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overview

Rekindling Joy in Medicine Through Thoughtful Communication: A Practical Guide

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Joy in medicine, or the loss of it, is a popular topic of conversation, even more so since the pandemic. Burnout in oncology is common and diminishes the satisfaction of practicing medicine. One of the challenges clinicians face is the way in which modern clinical practice takes us away from what we find most meaningful in our work: time with patients. Strategies like being kind, expressing gratitude, and using effective communication skills can establish more connection with our colleagues and our patients, and, in turn, result in a more joyful work environment. Creating space for more moments of feeling deep interconnectedness with patients and colleagues can rekindle feelings of joy in oncology practice. This article reviews the concepts of joy in medicine, the term *sacred moments*, and outlines practical strategies and communication skills that are effective in enhancing the patient-provider relationship.

INTRODUCTION: REKINDLING JOY STOKES THE EMBERS OF BURNOUT

> "A good life happens when you stop and are grateful for the ordinary moments that so many of us just steamroll over to try to find those extraordinary moments."—Brené Brown

The practice of oncology is full of complexities. Scientific advancements in detection, treatment, and technologies mean that we can partner with patients to provide exceptionally detailed, personalized care. This article examines the human side of personalized care delivery, the tools we use every day to connect with, and care for our patients. Modern medical practice often challenges our connection with patients, and we need an all hands on deck approach to repairing the aspects of work that bring the most meaning to oncology providers. Here, we provide context for our definition of joy in medicine, outline challenges to maintaining a joyful workplace, and propose considerations for individuals wanting to create more moments of feeling connected to patients and colleagues (Fig 1).

The Merriam-Webster Dictionary defines joy as to experience great pleasure or delight.[1] References to joy in medicine can be traced back to the Hippocratic Oath which states "May I long experience the joy of healing those who seek my help." The concept of cultivating joy in medicine has gained attention in recent years with books titled Recapturing Joy in Medicine and Finding Joy in Medicine, a podcast titled Joy in Medicine, and organizational focus on strategies to enhance joy in medicine including the American Medical Association and the Institute for Healthcare Improvement.[2,3] It is notable that the topic of rekindling, recapturing, or enhancing joy in medicine has become popular over the decade. A simple PubMed search reveals 1,800 publications on this topic since the 1940s and that most (1,300) have been published in the past decade and 50% of those since 2020 (Fig 2). The focus on rekindling joy undeniably correlates with the increasing prevalence of burnout among medical professionals. If burnout literally means to extinguish a flame, rekindling joy is to focus on strategies that stoke the embers of motivation and professional fulfillment.

When considering joy in oncology, the words pleasure and delight may not easily come to mind because their essence conjures a sense of playfulness, and cancer care often feels more serious. New York Times writer and columnist David Brooks makes a distinction about joy stating: "Happiness involves a victory for self. Joy involves the transcendence of self. Happiness comes from accomplishments. True joy is the present that life gives you as you give away your gifts."[4] The gifts clinicians have to give to patients include the gift of healing. Healing happens through understanding what is ailing the patient and offering treatments to relieve suffering. Clinicians can also give the gift of bearing witness to suffering; therapeutic presence can sometimes be the most powerful gift we have to offer in the face of serious, life-threatening illness. This joy is often experienced most acutely in the room with the patient, during shared moments of deep connection.

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PRACTICAL APPLICATION

- This practical guide reviews behaviors and skills that clinicians can adopt for partnering with patients during oncology visits and makes a case for applying them broadly to colleagues and teammates involved in clinical care.

A recent study on the concept of *sacred moments* provides a framework for describing the joy experienced in oncology care that arises through partnerships with patients. In the study, sacred moments were defined as brief periods of time in which people experience a deep interconnectedness that may possess spiritual qualities and emotions.[5] In our interpretation, sacred moments are spiritual in the sense that there is awe and wonder at witnessing the strength of the human spirit. They have been described as times when the patient or provider (or both) experienced a transient sense of being deeply interconnected as if time had stood still. After experiencing a sacred moment, one might feel a sense of joy, peace, gratitude, and empathy.[5] These moments can promote feelings of deep meaning and a sense of honor in caring for patients. If the fulfillment one feels after these moments motivates and sustains the clinician's desire to continue caring for patients, one might think of such moments as the equivalent to putting a log on a fire, stoking embers that are at risk for extinguishing. These moments might offer an antidote to the sense of low professional accomplishment that clinicians often experience as part of burnout.

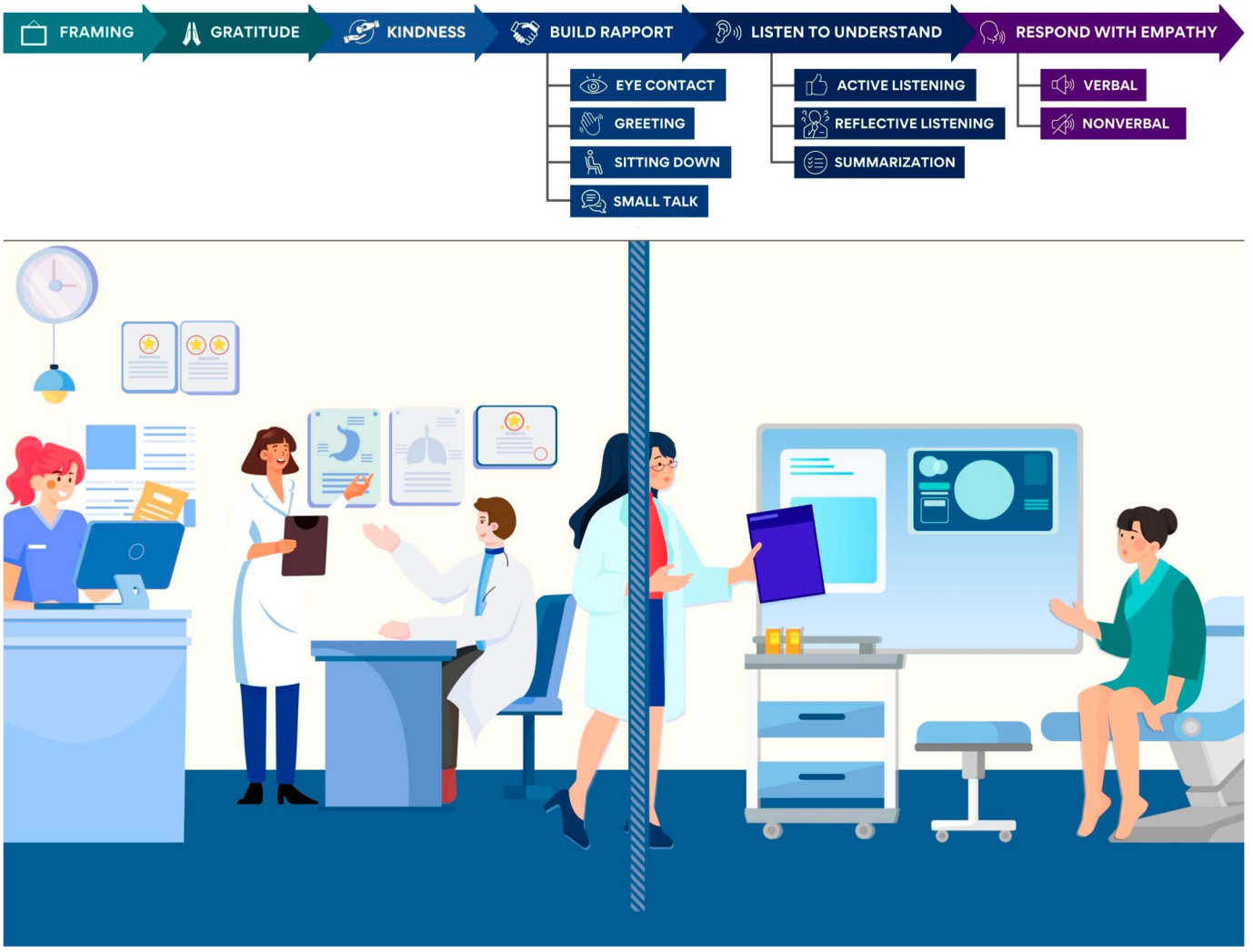

FIG 1. Strategies for creating conditions that allow for connection and thoughtful communication.

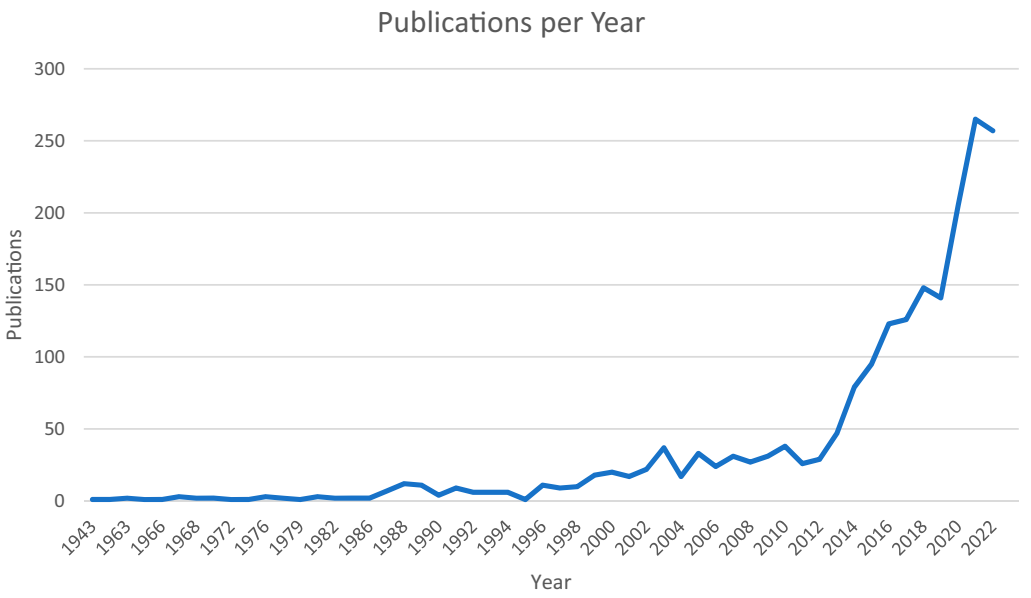

FIG 2. The number of PubMed publications per year matching the search term joy in medicine.

SACRED MOMENTS AS A SOURCE OF JOY

Sacred moments contain five elements: (1) an interconnectedness between patients and providers; (2) intense emotions and empathy; (3) a sense of awe and spirituality; (4) occurrence during conversations on the end-of-life or during moments in the clinical visit that seem relaxed and open; and (5) having profound meaning for the clinician and the patient.[5] Clinicians correlated these moments with a stronger therapeutic alliance and increased feelings of presence. Patients report that these moments occur when there was trust in the clinician and lead to an enhanced therapeutic relationship, greater satisfaction with that clinician, and better mental health outcomes.[6]

Enhancing communication skills such as listening and expressing empathy may increase the opportunity for sacred moments to arise, thereby leading to more fulfilling experiences, ultimately making the work more joyful. Structural and procedural barriers exist that exacerbate the challenge of making time for these moments. Despite these barriers, we will focus on solutions that are more readily within the control of the clinician and could be adopted while we wait for structural change.

Sample dialogue used throughout the text is derived from the author's (T.S.) experience and used to illustrate the concepts discussed in this study. An example of a sacred moment is recounted below.

> Physician: "I told a new mom she has metastatic breast cancer. I am amazed by how she handled herself. She maintained her composure, her optimism. She thanked me for letting her know, said she felt like this was what the results would show. I am reeling on the inside, full of thoughts about the future for her, and full of awe at her calm presence."

JOY IN MEDICINE IS THREATENED

Threats to joy in medicine come in many forms. Results of a Google search for loss of joy in medicine lists many articles discussing the problem of burnout in medicine. Burnout is an occupational syndrome of emotional exhaustion (EE), depersonalization (DP), and sense of low personal accomplishment (PA).[7] In a meta-analysis from 2019, pooled prevalence rates of oncologists showed that 32% had high EE; 24% had high DP; and 37% had low PA.[8] Similar findings have been reported among oncology fellows, physician's assistants, nurses, and pharmacists.[9-11] A study looking at themes of occupational and personal consequences of the pandemic on US oncologists found that COVID-19 exacerbated preexisting factors including external and internal factors contributing to burnout. External pressures include increased productivity expectations, high patient volumes, reimbursement issues, and administrative burdens. Internal pressures experienced by oncologists include the complexity of caring for patients with serious illness, addressing intricate treatment and psychosocial issues, a lack of balance between personal and professional demands, and lack of support from institutions to process grief and loss.[12]

The Stanford model of professional fulfillment characterizes three domains that, when optimized, best enhance professional fulfillment and, by proxy, mitigate burnout. The domains are thought to be of equal importance: (1) the efficiency of practice, (2) the culture of medicine, and (3) personal resilience. To address the threats to joy in medicine, health care systems and institutions must provide the scaffolding to ensure the practice environment is efficient and the workload demands are reasonable to allow all

clinicians to experience meaning in their interactions.[13] For instance, a study of 23 highly functional primary care practices found that effective and efficient models of care, such as shifting from physician-centric model of work distribution to a shared-care model that provides higher levels of clinical staff support, promote joy in the practice of medicine.[14]

The culture of medicine exacerbates the loss of joy by promoting endurance and exhaustion in the name of patient care. Working excessive hours, skipping meals or bathroom breaks, and missing major life events such as weddings and graduations are explained away as acceptable behavior because it is in service to the patients. With the pandemic came an onslaught of slogans stating health care workers are heroes, furthering the notion that clinicians are superhuman.[15] The concept can be exhilarating, yet it is partially based on fiction, and unfortunately, perpetuating this culture of exhaustion is not sustainable. The great resignation of health care workers across the nation is a testament to the fragility of the concept that health care workers are invincible. In 2021, 117,000 physicians resigned or retired, the largest group of some 334,000 health care workers to leave the profession.[16] This creates a quandary for the oncology workforce which is already strained by shortages. Oncology clinicians are human beings caring for other humans, challenged to handle the enormous expectations put on them to deliver cancer care. Institutional and systemic changes are needed to refine professional norms largely focused on self-sacrifice and a lack of vulnerability. Correcting systemic problems in the medical culture and refining ways of working are beyond the control of any one individual. Recent efforts such as ASCO's partnership with Vital Worklife and the Medical Society of Virginia to offer SafeHaven, a comprehensive offering of physician well-being resources, is an example of a novel investment in oncology workforce well-being at a national level.

The third domain of professional fulfillment is personal resilience. This may be somewhat of a misnomer as doctors score higher on resilience scales than other US workers.[17] Personal resilience refers to the individual *skills*, *behaviors*, *and attitudes* that contribute to physical, emotional, and professional well-being.[18] In a sense, this is what any one individual can modify or control on a consistent basis at work and at home. Therefore, addressing individual skills, behaviors, and attitudes such as learning and practicing effective communication skills could give clinicians more influence over the workplace. Actively adopting certain behaviors such as being kind, listening, and responding to emotions with empathy can create an environment that fosters collegiality and teamwork. This, in turn, can change the microculture of the clinical setting. When colleagues communicate clearly and treat one another with the utmost respect and generosity, the culture can change for the better and therefore enhance professional fulfillment.

CONSIDERATIONS: REKINDLING JOY BEFORE ENTERING THE ROOM

Joy and satisfaction in the workplace can be fostered by attitudes, behaviors, and communication skills practiced in the nonclinical spaces such as meetings, hallways, and workrooms. Anyone who has been on the receiving end of a spiteful comment will know how one difficult encounter can change the tone of the day. Similarly, a genuine, authentic compliment can induce feelings of happiness and make a day seem lighter and more fulfilled. In a recent *New England Journal of Medicine Catalyst* commentary "Finding Joy in Medicine: A Remedy for Challenging Times," the authors outline three practices to remedy burnout and provide a pathway to joy: framing, gratitude, and kindness.[19] These skills can be adopted by anyone on the oncology team and practiced in everyday settings not only between clinicians and patients. Culture is established through conversations and using framing, gratitude, and kindness can change culture by increasing the quality of relationships among colleagues. We will briefly review these practices below.

Framing can help overcome the tendency for humans to have a negativity bias. For example, a physician reviewing patient satisfaction scores may focus on a single negative comment rather than the positive comments. Framing helps overcome negativity bias by consciously reflecting on the situation and asking, "can I see this another way?" In this scenario, the question may be posed as "can I see the body of positive comments as a more accurate reflection of how patients feel about me?" Reflecting on this might help soften the reaction to negative input. Similarly, some physicians keep a feel-good file of thank you notes from patients and peers that they review periodically to help frame the positive impact they are having in the workplace.

Gratitude is the quality of being thankful. Gratitude includes being thankful for the things we often take for granted (eg, the security guard who always says good morning, the cleaning person who keeps the clinic space tidy, or the teammate who takes care of mundane tasks like peer-to-peer authorizations). Gratitude has health benefits including boosting mood, well-being, improving cardiovascular health, and increasing motivation to help others.[20] A study of 102 health care workers found those who kept a work-related gratitude diary had significantly lower depressive symptoms and perceived less stress compared with those who were assigned to writing in a work-related hassle diary or those assigned to not keeping a diary at all.[21] A recent study showed that expressions of gratitude buffered cardiovascular stress response among coworkers working on a stress-inducing task.[22] In workplace settings, expressing gratitude should be voluntary, allowed to be authentic, and built into recurring structures such as meetings and huddles.[19,20] Thanking staff for their hard

work and help at the end of a clinic is an easy way to express gratitude to teammates and allows for a few moments of goodwill before leaving the workplace.

Kindness is defined as doing something to help someone else. Many are called into oncology for the very purpose of helping someone else. The case of kindness in cancer care was made in a *Journal of Oncology Practice* article "Role of Kindness in Cancer Care," which outlines six types of kindness that can diffuse the negative impact a cancer diagnosis brings.[23]

Although lending kindness to patients facing a cancer diagnosis comes easily for many, less common is the recognition that kindness starts with oneself and when extended to all members of the team, reaps the most benefits. Recent data found that nearly one in four physicians suffers from frequent or intense feelings of imposter phenomenon (aka imposter syndrome), a psychological construct characterized by the persistent belief that one's success is undeserved rather than due to personal effort, skill, and ability. This leads to feelings of inadequacy and self-doubt despite objective proof of competence and achievement.[24] One skill to mitigate imposter phenomenon is self-compassion or the compassion individuals give to themselves in times of suffering. Although self-compassion has not been studied in oncology, it is gaining more attention for its use in the workplace.[25,26] Self-compassion is composed of three elements: self-kindness, a sense of common humanity, and mindfulness. Self-compassion can be taught and has been shown in randomized trials to improve outcomes in various populations.[27,28] In health care, there is preliminary evidence that suggests a mindfulness self-compassion intervention can reduce stress and improve compassion fatigue and resilience.[29,30] Self-compassion interventions could address the harsh negative reaction to one's perceived shortcomings that is common among those who may suffer periodically from imposter phenomenon.

CONSIDERATIONS: REKINDLING JOY WHILE IN THE ROOM

The tone of the visit is set by clinician's presence. Therapeutic presence is identified as a component of therapeutic effectiveness and requires eight attributes: being compassionate and empathic, respectful and nonjudgmental, genuine and authentic, trustworthy, fully present, valuing the intrinsic worth of the patient, being mindful of boundaries, and being emotionally resilient.[31,32] Presence can be established by having a mindful moment to prepare for entering the room and conveyed with nonverbal communication such as silence, eye contact, and avoiding distractions during the conversation.[33]

Essential communication skills in building the patient-provider partnership include creating rapport, allowing patients to share their story, listening to understand, and responding with empathy. Time in the room with patients is short.[34] Therefore, establishing rapport and a trusting relationship must happen very quickly in the course of the visit.

RAPPORT BUILDING

Oncology clinicians can build rapport in the first few minutes of the visit by making eye contact, in their greeting, by introducing themselves, and allowing the patient to introduce themselves and their loved ones. Sitting down is an important behavior in the clinic and in the hospital. Sitting at eye level with the patient lessens the hierarchy in the room and conveys to the patient that they have our full attention and that we have time for them. In the first few minutes of the encounter, it is critical to learn something about the patient's noncancer life (eg, where are they from, what kind of work do they do, what is their family situation). Small talk before big talk can help put a patient at ease. The Patient Dignity Question asks, "What do I need to know about you as a person to give you the best care possible?" and has been shown to help patients feel they are seen as whole persons and enhances clinician connectedness, respect, and empathy toward patients.[35] These few moments help to establish a bond, helping patients be known as a whole person rather than a person with a particular cancer or condition.

> Physician: "Tell me about yourself, what brings you joy in your life?"
>
> Patient: "Well, I like to go fishing and travel."
>
> Physician: "Please tell me more about that."
>
> Patient: "I really enjoy fishing with my sons. We used to go a lot when they were younger. Now we go once a year. That is an important weekend for me."

Rapport can be further built by giving the patient an opportunity to put on the table all the issues or concerns they are expecting to address during the visit. An example of this may be saying "I have reviewed your chart and know a lot about you. Before I start, I would like to know all the things you are hoping to cover today." This allows patients to present pressing questions and concerns at the beginning of the visit. Many of these concerns may be covered naturally during the visit and can help patients feel heard by allowing them to voice them up front.

> Physician: "It's so nice to meet you. I have reviewed your chart and spoke to your referring doctor and have a lot to cover. Before I do, what are all the things you are hoping to cover today?"
>
> Patient: "I don't know. I want to know if I will need to have my breast removed."
>
> Physician: "Ok, we will cover that, no problem. What else?"

Patient: "I want to know how long I will be out of work."

Physician: "We will cover that, too. What else?"

Patient: "I guess I really want to know if I'm going to die from this."

Physician: "That is an important question that we will certainly address. What else is on your mind?"

Patient: "That's it."

LISTENING TO UNDERSTAND

Listening facilitates understanding and listening without interruption promotes a therapeutic relationship.[36] Inviting and allowing patients to tell their stories without interruption can seem daunting to a busy physician or nurse. Studies show, however, that the time it takes for a patient to tell a story is not long. In one study, when doctors were instructed to listen without interruption, most patients talked for 2 minutes or less before taking a pause.[37] Unfortunately, other studies have demonstrated a decline in the time physicians allow patients to talk without interruption, with the most recent data published in 2019 showing an average time to interruption of 11 seconds.[38,39]

Listening skills can be broken down into two segments: active listening and reflective listening. Active listening includes the use of silence which can be bolstered by eye contact, head nods, and short verbal utterances that indicate listening such as hmm or go on. Reflective listening skills include echoing what the patient has said, requesting more information and summarizing in the clinician's own words. An example of an echo is if a patient says, "I've been struggling at home lately" and the clinician replies by repeating the word: struggling. This simple echo encourages the patient to say more about this. Echoing different words can emphasize curiosity about different parts of the phrase. The echo might be modified to state, struggling at *home*. Or perhaps there has been a change in condition recently, and the doctor or nurse wants to highlight this by echoing, struggling at home lately. These reflective statements demonstrate that the listener is paying attention and wants to know more.

Patient: "I'm just so grateful for my cancer."

Physician: "Grateful…"

Patient: "Well, before my cancer it was like I wanted to do something different, make changes, but after the cancer I realized I just needed to go for it. I've left my job and am volunteering at a museum and am so happy doing this."

Requesting is using phrases like "tell me more about…" to help draw out details of what the patient has already said. This open-ended statement allows the patient to determine what direction the story will take, may reveal what is on the patient's mind faster, and may help providers avoid assumptions. For instance, a patient might state, "I just want this to be over." Asking the patient to "tell me more about that" may allow the patient to disclose that they are worried about pain, worried about burdening a caregiver, or are thinking about something else entirely. Not assuming what this statement means and asking for the patient to say more about it can build a deeper relationship and avoid upsetting miscommunications.

Patient: "I wish I had planned more."

Physician: "Do you want to say more about that?"

Patient: "I wish I wrote a book "the girl's guide to metastatic breast cancer." I wish I had planned more for the end, but I didn't because it was too painful. I want to celebrate what I did do. I got to be a mom, got to discover the joy of being a mom and I feel like I've had some real success in my life which is that my son is a kind, lovable and caring human being, and he got to know me. When I look around my bedroom right now, I see all these mementos, special mom things like finger painted picture frames, things from baseball. I look at the photo of when I was first diagnosed. My son was 6 months old. We had portraits taken at JC Penny studio. We all sort of match as a family with what we are wearing. I remember being glad that I put those together. That was my first Mother's Day, and I thought it might be my last. That was 12 years ago. I don't know how I did it. I feel happy about that, I guess."

Summarizing is a very powerful tool that demonstrates to the patient that the listener has been paying attention and is trying to understand what is being said. Summarizing can be used by starting a sentence with "Let me see if I have this right…" or "Let me summarize what I've heard you say in my own words."

Physician: "So, if I'm hearing you correctly, you were doing fine until about three weeks ago when you noted this new pain in your abdomen. You tried different medications like tums and modified your diet but it's not getting better. And you're worried the cancer could be back because of the pain?"

Patient: "Exactly!"

RESPONDING WITH EMPATHY

Empathy as a communication skill has been shown to improve patient satisfaction, lowers anxiety and distress, improves self-efficacy, and improves clinical outcomes.[40] Recognizing and supporting emotion in encounters has been shown to improve the physician-patient relationship through establishing trust, improving patient satisfaction and compliance, and to save time.[40,41] In our careers, expressing empathy has often created sacred moments. Addressing emotional cues and providing verbal empathy can allow patients to feel seen and heard, and once that is

TABLE 1. Sample Phrases of Verbal Empathy Using the NURS Mnemonic

Description	Example
N, Name the emotion	"I think I can see how upsetting this is to you." "You seem sad as you are talking about this." "I heard you say you're frustrated."
U, Express acknowledgment that the emotional reaction is understood by the clinician	"Given what you've told me, I can see why you would feel this way."
R, Make a statement of respect for the patient's behaviors or actions, show appreciation for the patient, or acknowledge the difficulty of the patient's situation	"You seem to be handling this with grace." "Thank you for trusting me with this information." "You have a lot going on right now."
S, Supportive statements express how the clinician is able to align with the patient	"Let's see if we can make a plan together that feels right." "No matter what happens, I am here to support you."

established, the encounter can move on to discuss next steps and planning.

Empathy can be nonverbal and verbal. Nonverbal empathy includes body language such as leaning in to listen, making eye contact, or offering a touch on the shoulder or a tissue. Verbal empathy uses phrases to convey compassion. Verbal empathy can be more powerful than nonverbal empathy because when patients are experiencing strong emotions they may not recognize nonverbal cues but are able to hear words and therefore more easily receive and internalize empathy. Empathic statements can include Naming the emotion that is being expressed, expressing some level of Understanding about how the patient could feel that emotion, Respecting what the patient is going through, and lending Support in an authentic, relational way. A helpful mnemonic is NURS for four statements that give structure to lending verbal empathy.[42] Examples of empathic statements can be found in Table 1.

Verbal empathy is a powerful yet underutilized therapeutic tool. The frequency of empathic statements in oncology was studied by Pollak et al[43] who found, when given the opportunity, oncologists responded with verbal empathy only 22% of the time. Studies have shown physicians who expressed more empathy were evaluated more positively and had patients who reported higher levels of satisfaction and were more compliant with their doctor's advice.[44,45] Using empathic statements is a skill that can be taught and has demonstrated effectiveness in improving communication among oncologists with sustained improvements at 15 months.[46]

CONCLUSION: REKINDLING JOY BY LEARNING EFFECTIVE COMMUNICATION SKILLS

Partnering with patients through thoughtful communication is not only for clinicians who are naturally talented at communication or rate high in emotional intelligence. Training programs including courses offered by the Academy of Communication in Healthcare (ACH), Institute for Communication in Healthcare, and Vital Talk teach clinicians how to use communication skills in clinical encounters including those centering around serious news and end-of-life care. Teaching communication skills has been shown to improve patient satisfaction and improve physician burnout.[47,48]

Moments of feeling deeply connected have been described as profoundly meaningful for patients and clinicians alike. For clinicians, these moments serve as a reminder of why we chose oncology as a profession and supply fuel to the flames of burnout by making enhancing feelings of professional fulfillment. Partnering with patients through thoughtful communication can allow for more opportunity to experience these moments of deep interconnectedness, thus increasing feeling of joy in the practice of oncology.

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invited article

overview

Patient Advocates and Researchers as Partners in Cancer Research: A Winning Combination

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Inclusion of advocates as partners in research is now required by numerous international funding agencies. The role of advocates has expanded in recent years to include all areas of research, including basic cancer research, translational research, and clinical trial design and development. The involvement of advocates as partners in cancer research can be challenging for the advocate and for the researchers, but this collaboration is beneficial to all involved. Herein, we will define patient advocacy, explore advocate engagement, and share information on programs that train advocates and researchers to work together as partners.

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THE GROWTH OF PATIENT ADVOCACY

Patient engagement in research has grown significantly in the past 30 years,[1] primarily in the clinical research setting.[2] The roles of patient advocates in research vary from more limited involvement restricted to trial eligibility and feasibility to meet the requirements of funding agencies to engagement as patient partners at all levels of research. Some of the activities that advocates have engaged in are focus groups, grant reviews, steering committees, advisory committees, and clinical trial protocol review. These activities are being provided by several different stakeholders, including large private funding authorities, national organizations, government funded agencies, and pharmaceutical companies. Some of the national organizations in the United States include the National Cancer Institute Clinical Trials Network (NCTN) (which includes SWOG, the Alliance for Clinical Trials in Oncology, and ECOG-ACRIN Cancer Research Group and NRG Oncology), the Patient Centered Outcomes Research Institute (PCORI), the Department of Defense Peer Reviewed Cancer Research Program, the National Cancer Institute (NCI), the American Society of Clinical Oncology (ASCO),[3] and the US Food and Drug Administration (FDA). One example of the expanding roles of advocates is the NCI and the changes they have incorporated to enhance and expand the role of the advocates. Patient advocates have been engaged as partners with NCI cooperative groups since 2006, with changes in engagement and structure expanding in recent years.[4]

DEFINING A PATIENT ADVOCATE

Herein, we will define a patient advocate as a person with lived experience either as a patient with cancer/cancer survivor or an informal caregiver/carer of a person with cancer who is engaged in advancing something larger for themselves and their community, including increasing awareness, access to resources, and advancing research. This excludes paid professionals who are often referred to as patient advocates, because they are nurses or case managers who work to ensure that the patient is appropriately cared for in a system. There is little agreement on whether patient, partner, or patient partner is the most suitable term[5] to describe the engagement we are looking at. Another term that is used is that of a research advocate, which indicates that the patient advocate is involved with groups that influence the direction of the research.[6] This term is not being used universally in the literature, so we will use the term patient advocate.

DIFFERENTIATING TERMS FOR ENGAGEMENT

Engagement, participation, and involvement are all terms that are often used interchangeably in the literature about patient advocacy. The different terminologies used may be confusing as there is little consensus in the literature on the use of terms such as involvement, engagement, and patient-oriented research, raising the question of which definition should be considered most appropriate.[5] Here, we will use the following definition of engagement and will consider it equivalent to the international terms discussed below: The active, meaningful, and collaborative interaction between patient advocates and researchers across all stages of the research process.[7]

In the United States, we use the above definition. In Canada, the word patient engagement indicates that patients are partners in the research.[8] In the Netherlands, they use participation.[9] In the United Kingdom,

PRACTICAL APPLICATIONS

- Define who qualifies as a patient advocate.
- Differentiate between engagement and other forms of patient involvement.
- Discuss the benefits and challenges of partnering with and engaging patients.
- Demonstrate programs that are successful with training and evaluating their advocacy program.
- Future directions require standardization of definitions, training, and evaluation.

they differentiate between involvement which they define as patients and public involved as coinvestigators in research being carried out with or by members of the public, rather than to, about, or for them. In the United Kingdom, engagement is the dissemination of research knowledge to the public, and participation is when people take part in a study (patients provide data).[10] Engagement is often described as researchers doing research with patients, rather than for or on them, through integration of patients into the role of study team member.[11]

We will refer only to engagement where patient advocates are working as partners in research endeavors. We believe that patient advocates should be engaged in projects from conception to dissemination of the results spanning the spectrum of bench research to clinical trials.[12] Patient advocates have participated in focus groups, interviews, and time-limited roles and passive endorsements for both pharmaceutical companies and funded and funding agencies. We do not consider this engagement. Rather, this is participation and includes patients as clinical trial participants. Questions arise about defining what meaningful engagement is and how to measure it.[13]

In this review, we will discuss the use of patient advocates at all levels of research. The engagement of patient advocates in preclinical or basic cancer research is relatively new, but it is happening. The Patient-Centered Outcomes Research Institute and Cancer Grand Challenges require the engagement of patient advocates for their research funding programs.[14] Advocates can contribute at all steps in the process, and they can help formulate the research questions and identify patient concerns early in development of a research plan.[1] For clinical trial proposals, advocates can evaluate if a procedure or inclusion and exclusion criteria would be acceptable to patients. This may enable trials to move forward that are more acceptable to patients, more likely to recruit well and more meaningful for patients and their communities.[15]

REASONS PATIENT ADVOCATES BECOME ENGAGED

There are many reasons that patients and their caregivers become involved in advocacy. One major reason is a desire to help so that others may have an improved quality of life. Some of these include the opportunity to include the patient voice in the research process and the intellectual challenge[16] to add a human face and a sense of urgency to the research, to ensure that the patient is the focus of the research.[6]

> "Our experiences are all different but as a collective, we can share what works for the patient community, adding our thoughts to make sure it's relatable and relevant. Representation is important, it gives the patient voice a seat at the table and has shown that it's just as important as science. We have a PhD in experience–that offers a valuable opportunity to share in and guide the work being done"—Candace Henley, Patient Advocate[17]

Knowledge is power, and many patients find learning more about research progress in their disease and what is currently being investigated helpful for themselves and their loved ones.

BENEFITS OF ENGAGING PATIENT ADVOCATES AS PARTNERS

It has been reported in several studies that patient advocate engagement provided valuable contributions to research feasibility, acceptability, rigor, and relevance.[14] Engaging patients in research can increase its quality, and as health care providers integrate it into care, the quality of care will increase.[12] Engagement enables mutual learning, and the building of new skills, knowledge, and skills by patients increased understanding of basic science research and the broadening of researchers' perspectives, including an understanding of what is important to patients.[10,18] Patient partners can play an important role in disseminating research finding, which improves communication with the public and strengthens the research through trust of the research community, thereby increasing the impact of the patient voice.[6,15]

Engaging advocates early in the research process facilitates the design of more patient-centric clinical trials.[2] Engagement offers a mutual learning opportunity. Patient advocates can deepen their understanding of current research about their disease, and investigators can share their research results and become more effective scientific communicators. In addition, by interacting with patient advocates, investigators can grow their understanding of the priorities of those affected by the disease and focus their research on areas relevant to patients' needs.[15]

> "Collaboration between scientists and advocates is integral to making sure patients are represented in research and that their voices are heard. Many scientists find that collaboration with advocates strengthens their proposals by clarifying their goals and impact on patients. The relationship between

> advocates and scientists is mutually beneficial—as the advocates enrich ongoing research initiatives, they learn more about the latest scientific developments of their disease and future possibilities. Ultimately, both groups learn more about the other and develop an ongoing relationship characterized by a mutual respect and empathy."[19]

Engagement also offers advocates the opportunity to build new skills, knowledge, interests, and perspectives on their disease and the research enterprise. Some view patient engagement as a means of ensuring that research is patient-centered, useful, and trustworthy, leading to greater use and uptake of research results by the patient and the broader health care community.[20] Engagement fosters important discussions not only on what is important to patients but can inform the research on the appropriate questions to ask, methodology, and future research questions.[21] Patient advocate engagement increases trainee recruitment and retention as trainees have a greater appreciation of the purpose and impact of their research.[22] Engaging advocates may also enable a more ethical process in all phases of research. Overall, engagement encourages a sense of partnership between the advocate and the researcher, thereby increasing trust of the research community and ultimately increasing the trust of the patient community.[15,19]

CHALLENGES OF ENGAGEMENT

Challenges of engaging patient advocates at all stages of cancer research include a perceived lack of scientific knowledge, which may be frustrating for both advocates and researchers. Engaging patient advocates who are not trained in research presents a risk that they may feel ill equipped and lack confidence or understanding to voice their perspectives or concerns.[23]

Lauzon-Schnittka et al noted that patient advocates engaged in clinical trial development contributed to trial design by influencing inclusion or exclusion criteria; the designs selected, such as noninferiority designs, numbers and types of arms, and mixed methods; and decisions about assignment of participants. The advocates in some cases wanted more people in the study or interventions, which can lead to broader inclusion criteria; selection of designs, such as delayed start; or use of different participant assignment techniques, such as unequal random assignment.[8]

Another concern is that the same patients are recruited for engagement because the researchers may be familiar with them and have worked with them before.[20] Connections are important, and there are patient advocates who say yes when asked to participate and they are heavily relied on, which may result in a lack of diversity and opportunities for others. It is suggested that the patient advocates be pulled from the population being studied, although this comes with challenges, including finding individuals willing to participate.[18] It has been suggested by Perlmutter et al that developing a pipeline of patient advocates is important and that advocates are currently recruited on an ad hoc rather than systematic basis.[6] It is a challenge to ensure diversity within collaborations so that the interests of the well-educated White middle classes in rich countries do not dominate.[24] Greater diversity is needed in terms of age, class, sex, geography, ethnicity/race, immigration status, indigeneity, sexuality, and religion.[18]

There needs to be care in engaging advocates for research to avoid a tokenistic approach and attention paid to representation.[25,26] It has also been noted that there is a lack of measurement of meaningful engagement.[18] Largent et al[20] suggested that diversity can be increased by engaging more patient advocates to capture a wider variety of perspectives and experiences, by identifying and addressing obstacles or barriers to engagement, and determine which patients are presently engaged and assess their representativeness.

TRAINING AND EVALUATION

Engagement ensures that projects are relevant and valuable to the end users. There is broad agreement that the engagement of patient advocates should be meaningful, impactful, and measurable. The challenge is how to make the engagement of patient advocates in research more methodical and consistent[7] and how patient advocates are being engaged in research and how should they be engaged.[20] Questions arise about defining what meaningful engagement is and how to measure it.[13] Patient advocate engagement will be reduced to mere tokenism if patients are not capable of meaningfully contributing to the research enterprise because of a lack of preparation and training.[20]

Patient advocates are not always provided with the relevant resources to effectively contribute to the discussions.[27] Fox et al[15] found that most published evidence of patient engagement comes from clinical research; therefore, the benefits of patient advocate engagement in basic or translational research are unclear, and the current standing of patient advocate engagement overall is unclear.

The PCORI has trained advocates using voluntary training workshops, structured training interventions, and self-initiated training interventions.[28] A Canadian model for engagement is The Office for Patient Engagement in Research Activities (OPERA) in Ottawa that recommends ongoing education and training for both researchers and the advocates.[26] Table 1 demonstrates the processes used by several organizations in training and evaluating the effectiveness of patient advocates in research.

Effectiveness of engagement needs to be assessed by stakeholders in a structured manner to encourage constructive feedback of success and challenges in engagement.[23] Those skeptical of engagement want evidence of

TABLE 1. Formalized Cancer Patient Advocate Training Programs

Organization	Training Components	Evaluating Impact
AACR Scientist↔ Survivor Program	Meeting with scientific mentors Support to participate in poster sessions and networking at annual meeting	None noted
ASCO	Advocacy tools and resources including ASCO in Action, ASCO ACT Network videos, and podcasts Breaking down science for specific cancers Networking at the annual meeting	Advocate feedback on tools No. of advocates and advocacy organizations attending meetings
BMJ	Support for abstract submission Online presentations Peer review exercises	Cross-sectional survey to understand concerns and suggestions to improve the training materials and processes
Fight CRC	In-person training at academic centers Online modules throughout CRC continuum	Survey to advocates understanding research knowledge, skills, and confidence Survey to experts who have worked with advocates to understand strengths of the program, perceived impact, gaps, and satisfaction
FORCE	Self-paced, online educational course Expert-led webinars	Requests feedback from researchers who used patient input on impact of having advocates involved in their study
FOCR (Progress for Patients)	Online training modules to provide tools for advocates to communicate with drug researchers, developers, and regulators	Provide evaluation numbers for advocates who complete training to clarify research goals and refine questions in research process
PCORI	Patient Advocacy Executive review form Designed to be implemented for other organizations conducting clinical trials	Pre- and post-training survey data evaluating knowledge, confidence, skills, and self-efficacy
Research Advocacy Network	On-site training Customized workshops and webinars via online learning resources	Conduct evaluation of the effectiveness of advocate activities in basic, translational and clinical research

NOTE. Adapted from Garcia et al[3] with permission.

Abbreviations: AACR, American Association of Cancer Research; ASCO, American Society of Clinical Oncology; BMJ, British Medical Journal; Fight CRC, Fight Colorectal Cancer; FOCOR, Friends of Cancer Research; FORCE, Facing Hereditary Cancer Empowered; PCORI, Patient-Centered Outcomes Research Institute.

the costs, benefits, and risks before they become further engaged. Calls for measuring patient advocate effectiveness also raise questions about the effect on what and for whom.[29,30] Ideally, assessments should measure whether expectations were met by both the researcher and the patient advocate.[1]

INVOLVEMENT IN NATIONAL CLINICAL TRIAL DEVELOPMENT

Including patient advocates in the development of clinical trials is critical to the success of studies in terms of both effective patient accrual and communication of clinical meaningful outcomes to patients. In the NCI Cooperative Group Clinical Trials Network, now called the NCTN, there is a long history of engaging patient advocates across the clinical trial lifecycle and of incorporating feedback from patient advocates in the development and approval of clinical trial concepts.

In 2001, the Institute of Medicine published Crossing the Quality Chasm: A New Health System for the 21st Century to define priorities for improving the quality of health care in the United States.[31] A crucial outcome was recognition of the need for an increased emphasis on patient-centered care. In 2006, the NCI was establishing their own process for evaluating and prioritizing clinical trial concepts to be developed through the National Cooperative Group System. As a result, the NCI instituted disease-specific scientific steering committees composed of clinicians, biostatisticians, translational researchers, and patient advocates.[32] NCI Task Forces (TFs) also provided an initial forum for multidisciplinary discussion of concepts by disease-site experts before eventual submission to and evaluation by steering committees. Both TFs and steering committees created a demand for more training and support for patient advocates. In 2008, the NCI patient advocate steering committee (PASC) was formed. The PASC allowed for more interaction among the advocates participating on the NCI steering committees and TFs and provided an opportunity for defining roles and responsibilities. The priorities for the patient advocates were to bridge the gaps that exist among researchers, patients, and cancer communities. In the

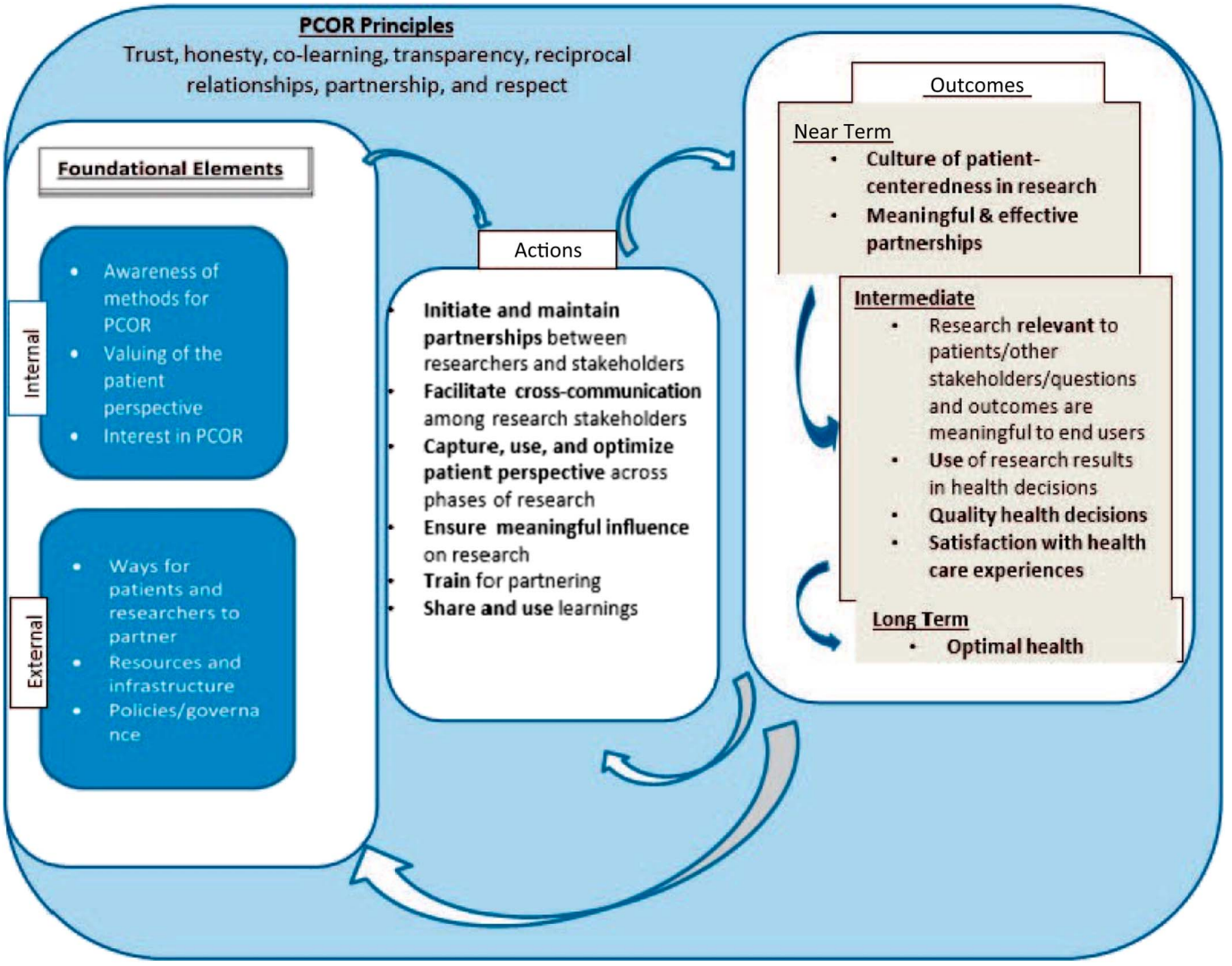

FIG 1. Conceptual model of PCOR. Reprinted from Frank et al[33] under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/3.0/us/). PCOR, patient-centered outcomes research.

setting of the steering committees and TFs, patient advocates are more focused on giving constructive feedback on research design, appropriate eligibility criteria, feasibility issues, barriers to patient participation, and ensuring that research outcomes are patient focused. Patient advocates on the steering committees review each of the clinical trial concepts and provide written critiques and critical questions to make certain that the study is patient centric. Recently, PASC developed an updated patient advocate template for the written critiques that includes questions addressing six domains: (1) importance of the concept; (2) design or schema; (3) risk, benefits, and burden; (4) eligibility (inclusion and exclusion criteria, including important implications on diversity and representativeness of consenting patients); (5) accrual feasibility; and (6) additional patient-centric comments.[32] Patient advocates provide their feedback during the steering committee conference call closed sessions and are equal voting members on the steering committees. Study concepts can be disapproved on the basis of the feedback of patient advocates and concerns about whether studies are feasible or patient centric. In addition to patient advocate involvement on NCI steering committees and TFs, NCTN groups which are responsible for the initial development of clinical trial concepts and conducting trials also work closely with patient advocates. Each NCTN group has numerous advocates working with disease-specific committees to provide advice on trial design and when the study is open, advocates disseminate information about the study, engage advocacy groups, and help publicize NCI trial findings. There is a true bidirectional

nature of engagement. Patient advocate engagement is multipartite and mutually beneficial for patients and clinical trialists.

PARTICIPATION IN EARLY-CAREER INVESTIGATOR TRAINING

Professional societies and national organizations engage patient advocates in educating early-career investigators. ASCO has patient representatives on the ASCO Cancer Research Committee and ASCO Expert Panels for guideline development. The American Association for Cancer Research (AACR) connects advocates with scientists at their Annual Meeting through the Scientist↔Survivor Program (SSP).[2] Both ASCO and AACR invite patient advocates to participate as faculty in their joint workshop, Methods in Clinical Cancer Research (MCCR) workshop, an important training opportunity for clinical oncology researchers. Patient advocates teach in the didactic sessions and participate in small group sessions where early-career investigators present their clinical trial proposals. The patient advocates provide guidance on how to make the studies more patient-centric. For example, advocates give feedback on the study design. Specifically, advocates provide insight into the impact of clinical trial participation for patients and their families, regarding the number and kinds of required procedures, such as biopsies, the logistics of treatment, barriers to patient participation, the side effects of treatment, and personal financial toxicity. This feedback can shape clinical trials and help junior investigators develop studies with higher patient participation and satisfaction. Having the opportunity to work directly with patient advocates early in their career is incredibly impactful for investigators. Such interaction cultivates an appreciation for the complexities of balancing what we want to learn in a study with the participation demands placed on the patient and their social network and emotional support system. The MCCR workshop empowers patient advocates to be partners throughout the research continuum by working with young clinical researchers in the initial development of their trials. The workshop also creates the opportunity for patient advocates to be a point of contact for studies, learn about their progress, and help disseminate the results. The bond forged between investigators and advocates can make clinical research both more meaningful and successful.

FUTURE DIRECTIONS

Patient advocates as partners with researchers in cancer research has been expanding, but challenges still exist. Some of the challenges can be alleviated if there is a universal definition of who is a patient advocate. The definition of engagement should be universal to eliminate tokenistic patient representation and clearly define what is considered engagement. Training advocates and researchers is necessary to eliminate the difficulties that each may feel working together. A reproducible standardized evaluation of the engagement will help with assessing the success or failure of this partnership. We have discussed successful initiatives for engagement and partnerships in cancer research. One example is from PCORI (Figure 1). PCORI has funded hundreds of projects that have patient advocates engaged in different ways from community forums, advisory panels, and coinvestigators on research. PCORI was created to fund comparative effectiveness research that compares the benefits and harms of clinical interventions in real-world settings, so engaging people who will receive those interventions is particularly salient.[33]

> "Effective patient engagement requires effort of both the researcher and the patient advocate; both must be committed to the process and communicate throughout the engagement. Patient engagement must not be about checking off a box on a form, with minimal contact after funding is secured. It is about making a difference to the way science is conducted, with urgency and value of the patient perspective and experience."[1]

The integration of patient advocates as partners has expanded in all areas of cancer research. The principles of reciprocal relationships, colearning, partnership, trust, transparency, and honesty[34] are necessary to ensure successful partnerships between patient advocates and researchers in all areas of cancer research.

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overview

Impact of Prior Authorization on Patient Access to Cancer Care

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Prior authorization (PA) is a type of utilization review that health insurers apply to control service delivery, payments, and reimbursements of health interventions. The original stated intent of PA was to ensure high-quality standards in treatment delivery while encouraging evidence-based and cost-effective therapeutic choices. However, as currently implemented in clinical practice, PA has been shown to affect the health workforce, adding administrative burden to authorize needed health interventions for patients and often requiring time-consuming peer-to-peer reviews to challenge initial denials. PA is presently required for a wide range of interventions, including supportive care medicines and other essential cancer care interventions. Patients who are denied coverage are commonly forced to receive second-choice options, including less effective or less tolerable options, or are exposed to financial toxicity because of substantial out-of-pocket expenditures, affecting patient-centric outcomes. The development of tools informed by national clinical guidelines to identify standard-of-care interventions for patients with specific cancer diagnoses and the implementation of evidence-based clinical pathways as part of quality improvement efforts of cancer centers have improved patient outcomes and may serve to establish new payment models for health insurers, thereby also reducing administrative burden and delays. The definition of a set of essential interventions and guidelines- or pathways-driven decisions could facilitate reimbursement decisions and thus reduce the need for PAs. Structural changes in how PA is applied and implemented, including a redefinition of its real need, are needed to optimize patient-centric outcomes and support high-quality care of patients with cancer.

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INTRODUCTION: PRIOR AUTHORIZATION IN HEALTH CARE

Utilization review is an established component of cost management in health care, broadly implemented to control service delivery, payments, and reimbursements.[1] Such services and treatments can include diagnostics, medications, and surgical procedures. When utilization review is required by health insurers before patients can receive services or treatments, it is called prior authorization (PA).[2,3] (Table 1) Stated goals of PA include screening for appropriateness and efficiency and reducing the overutilization of unnecessary services or medications, thereby reducing health care costs. Historically, one aim of PA has been to catalyze the uptake of generic drugs; when coupled with policies facilitating use of generic medications and biosimilars, utilization management may yield improved system sustainability by exerting downward price pressure on medications.[4] In an era of growing innovation, the rising costs of oncology care have been concerning for sustainability.[5] As a consequence, PA has been applied more broadly to a larger set of health interventions. Although such a process may be viewed as legitimately grounded in some respects, it places a significant burden on patients and health care providers, contributing to negative outcomes with further strains on the already-stressed health care workforce. Indeed, the PA process raises essential questions about the proper roles of insurers and health care providers in the care of oncology patients and everyday medical practice. This article focuses on the PA process in the United States, but the issues raised also illuminate some of the tradeoffs faced throughout the world in controlling health spending on the one hand and striving for optimal care of individuals facing cancer on the other hand.

PRIOR AUTHORIZATION IN CANCER CARE

Rationale for PA in Oncology: Improving Efficiency in Health Care Spending

The fast pace of innovation in oncology has not only brought improvements in patient outcomes but also increased costs and overuse of non–cost-effective therapies.[6] US health expenditure accounted for $4.3 trillion US dollars (USD) in 2021, that is, $12,914 USD per person, corresponding to 18.3% of gross domestic product.[7] Of such an expenditure, 5.33% is allocated to cancer care alone, that is, more than $200 USD billion annually ($16,346 USD pro capita). This is four times than those for patients treated for noncancer conditions.[8] Oncology drugs

PRACTICAL APPLICATIONS

- Prior authorization (PA) is a type of utilization review that health insurers use to make decisions on the coverage of health interventions for individual patients.
- PA has been originally introduced as a mechanism to rationalize health expenditures toward more affordable and evidence-based treatment choices, including to improve uptake of generics and biosimilars, reduce inappropriate use of off-label therapies, and reduce overuse of expensive medications outside of their intended use.
- PA is subject to insurers' review: Patients experiencing denials as the outcome of PA review may yield adverse health outcomes and financial toxicity, as receiving less effective therapy, therapy with higher risk for toxicity, and/or less optimal supportive care.
- PA is associated with adjunctive administrative burden for health care providers, including the need for peer-to-peer review, and leads to delays in access to care for patients.
- The harmonization of the PA process with national cancer treatment clinical guidelines could help rationalize and simplify the process and reduce costs and treatment delays.
- The establishment of a set of regularly updated, evidence-based essential interventions, the use of national guidelines to inform coverage decisions, a global rethinking of the proper scope of PA requirements, attention to administrative burden and costs, safeguards to protect against abuse of PA requirements, and better implementation science can reshape the PA process as it is applied now.

account for the largest spending of any specialty and exceed 15%-30% of the overall cancer budget.[9] PA has been touted as a way to encourage high-value and cost-efficient budget allocation in oncology.[10] When implemented in the context of treatment guidelines aligned with best practice, PA policies have the potential to increase the quality of cancer care.[1]

From the perspective of payers, the PA process gives health insurance companies a chance to review how necessary a medical treatment or medication may be.[11] Examples of medications that may require PA are those that have dangerous side effects, are harmful when combined with other drugs, are often misused or abused, or should be used only for certain health conditions.[12] Cost is an explicit factor to be considered, for example in the case of medical treatments that have lower cost but equally effective, alternatives available.[11] Step therapy is frequently also built into the PA process to prioritize more cost-effective options. When used judiciously, PA can minimize the use of overly toxic treatments and enhance adherence to established clinical guidelines. For instance, a retrospective analysis of more than 13,000 chemotherapy treatment requests (CTRs) submitted by oncologists for PA has been cited as an example of how a pathway-driven PA process may improve medical oncology quality.[13] In this study, 11.6% of requests were denied even after peer-to-peer review with a board-certified oncologist employed by the insurer: Denials concerned supportive care and antineoplastic agents in the same proportion. One third of denials were due to lack of compendia support, one quarter due to clinical criteria, and 22.8% for problems with dose/frequency. In 10.7% of cases, clinical tests did not support use. A difficulty in assessing this analysis is a lack of granular data on the clinical scenario, the source of guidelines/compendia used, and the outcomes of patients in whom CTRs were denied. Indeed, the implicit assumption in analyses of this type is that the health insurer's assessment is the gold standard for oncology care, which may not be the case always.

Rationale for PA in Oncology: Improving Quality of Cancer Care

Quality improvement can be achieved with the disengagement from low-value clinical interventions or overuse.[14,15] PA can serve as a firewall against the misuse of medical interventions and improve adherence to best practices. A key example is the use of granulocyte colony-stimulating factors (CSFs) in patients receiving chemotherapy. It is reported that up to 30%-50% of patients receiving high-risk regimens for febrile neutropenia are not put under the appropriate CSFs prophylaxis while 30%-40% are prophylaxed outside current indications.[16] In an attempt to rationalize the use of CSFs, a site-wide program initiative was implemented for patients with metastatic colorectal cancer receiving care at a multicenter oncology practice network.[17] The intervention included educational materials, appropriate nonuse recommendations, and PA requirements. The preimplementation versus postimplementation comparison showed that use of CSFs was significantly reduced from 13.5% to 4.5%, with no change in short-term mortality because of complications of neutropenia.[17] However, because of the multipronged intervention, it is unclear to what extent the PA component per se contributed to the reduction in CSF use or if implementation of consistent internal guidelines was instead the primary driver of the observed changes. Another study reported that inclusion of a CSF decision support tool as part of the PA process for women with breast cancer receiving chemotherapy resulted in higher alignment with clinical guidelines.[18] After implementation, a significant decrease in

TABLE 1. Overview of the Main Definitions and Procedures Used in Prior Authorizations by Health Insurances in the United States

Term	Definition
Utilization review	A process of evaluation of the care plan of a patient. It is intended to determine the medical necessity, taking into consideration the treatment standards for a certain health condition, the availability of alternative treatments, and the cost implications
Preauthorization (or prior authorization)	A type of utilization review that health insurances apply to control service delivery, payments, and reimbursements of health interventions
Denial	An adverse determination of a previous request for a health intervention through preauthorization
Peer-to-peer review	A process in which the requests for coverage for a health intervention are discussed between the ordering physician or advanced health provider and another physician employed by the health insurance. The intent of the peer review is to discuss the medical necessity and obtain an authorization or appeal of a request previously denied
Appeal	A request for a second review of the original coverage determination
Medicare Advantage Organizations	A private contractor that can give benefits for Medicare, including part D
Medicare Compendia	A set of authoritative sources for use in the determination of a medically accepted indication of health interventions used by Medicare as a reference to decide on coverage decisions. The National Comprehensive Cancer Network Drugs and Biologics Compendium is the source used by the Centers for Medicare & Medicaid Services to determine coverage for cancer interventions
Clinical pathways	Evidence-informed algorithms developed by multidisciplinary expert committees to define tasks and/or type and sequence of interventions that should encompass most of the clinical practices used in specific clinical scenarios

the proportion of patients with CSF use was observed in the intervention states (75%-69%) compared with no significant change in the nonintervention state (72%-71%), without an increase in the incidence of febrile neutropenia.

How Prior Authorization Is Conducted

PA is a multistep process. Common scenarios requiring almost automatic requirements for PA include advanced imaging, expensive medications (including supportive care treatments), indications where alternative, cheaper, and equally active treatments exist, drugs historically prescribed outside their on-label use, and drugs with cosmetic indications. Specific coverage determination is often not reached through initial submission of medical information to the insurer, resulting in denials. Insurers can communicate reasons for denials and provide the opportunity to request a peer-to-peer review (^Fig 1). The stated intention of peer-to-peer review is to provide an objective and transparent forum for the appealing health care provider, to critically review the evidence with their assigned peer, and to assess the appropriateness of the proposed intervention in relation to accepted standard of care. In some instances, the decision for denial can be appealed, resulting in a second review of the original coverage determination. Submissions for PA, the peer-to-peer reviews, and the appeals are time-intensive procedures. As such, PA and linked procedures are associated with extra administrative work for health providers, including physicians and advanced care providers. There have also been widespread complaints about the qualifications and expertise of assigned peer reviewers, leading to calls by the American Medical Association and other professional organizations to enforce standards for peer reviewers regarding specialty training and clinical experience.[19]

Potential Implications of PA Requirements on Patients' Access to Cancer Treatments

PA is a time-intensive procedure that can increase the workload of health providers and result in delayed access to treatments. A 2022 landmark survey of approximately 1,000 US physicians from the American Medical Association described physician-reported delays in the delivery of interventions requiring PA, with 82% of the respondents reporting they had experience of treatment abandonment as a result of a denial.[20] One third of responders claimed that the delays because of the PA had resulted in serious adverse events for patients, including hospitalization (25%) and life-threating events (19%). Two thirds of physicians reported that PA led to ineffective initial treatment owing to requirements for step therapy. In addition, 31% of respondents considered the criteria for PA rarely or never mirroring best clinical practice, perceiving most of the peer-to-peer review and appeals as avoidable if internal insurance guidelines were regularly reviewed by providers who are topic experts.[15,20] Seeking to understand the impact of PA requirements in oncology specifically, in 2022, ASCO conducted a survey[22] among ASCO members. Nearly all survey participants reported a patient who had experienced harm because of the PA process, including delays in treatment (96%) and diagnostic imaging (94%), being forced into second-choice therapy (93%), increased out-of-pocket costs (88%), denial of recommended therapy (87%), disease progression (80%), and even loss of life

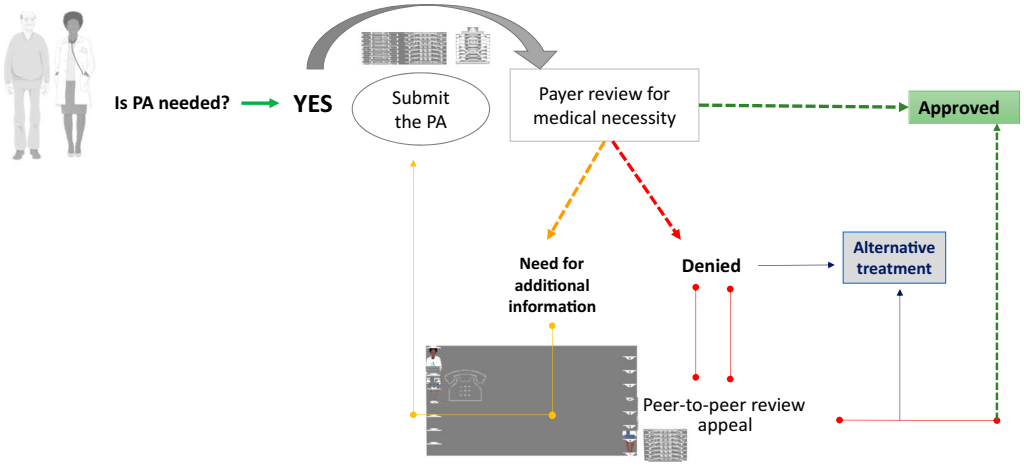

FIG 1. An overview of the current process of PA. PA, prior authorization.

(36%).[21] Ultimately, a potential detriment on overall survival was reported by 36% of the oncologists.[21]

Although very concerning, survey studies on the basis of provider self-report risk the potential for recall bias and have been criticized in this regard. There are relatively few studies in the oncology literature where access to detailed medical records was available to understand the nature of PA requests and denials. One such study conducted within a large US-based academic cancer center in Massachusetts from a cohort of patients with breast cancer reported that initial denials were received not only for antineoplastic agents but also for guideline-concordant use of supportive care medicines, such as CSFs and antiemetics, with extensive evidence supporting their use.[22] Delays could be as long as 14 days.[22] Notably, 13.6% of PA requests were for generic hormonal therapy used according to long-established standards of care. Overall, 97.5% PA requests were approved on the first request, suggesting that PA requirements added multiple layers of administrative complexity without any major impact on medication choice utilization. Another facility-based survey in the gynecology-oncology setting showed that PA was broadly requested for key interventions for cancer management such as imaging (54% of all PAs), supportive care medications (29%), and chemotherapy (17%).[23] Approvals occurred in 79%. Time to care delivery varied substantially, with a mean of 16 days and a broad range up to 98 days. As expected, patients whose requests were denied were forced into alternative options, with substantial changes in their previously recommended treatment plan.[23]

The often unpredictable variability in the decisions of insurers to cover certain procedures and denials can increase inequities in the delivery of cancer care. In addition, the additional workload and personnel requirements imposed by the PA process may deter providers from advocating for the best options for their patients. This is particularly of concern in less-resourced practice settings, which often serve the most vulnerable and historically underserved patients. Arguably, denial of PA is not a denial of treatment but of payment. Still, without insurance coverage, cancer treatments would be unaffordable to most patients. Indeed, it is estimated that 40%-50% of adults with a cancer history experience financial hardship.[24] When patients are denied high-value and important clinical procedures, they will often need to provide for their care with out-of-pocket expenditure, resulting in financial distress and risk of impoverishment.

Patients' perspectives. We explored the lived experience with PA from patients' perspectives and asked patients to share their stories, in conjunction with a long-standing patient advocate (L.K.), highlighting the implications on cancer care and capturing their emotions, when forced to change the treatment plan previously discussed with their providers (Table 2). Patients themselves experience vivid distress because of the intense efforts needed to advocate for their best care. The emotion reported is that of a fight against denials and of navigating many challenges to secure health insurer's approval. The experience of delays of life-saving treatment has been commonly reported, aggravated by the lack of transparency in the overall process of PA and the perception that who is making the decisions is not competent in the matter: deciding on the lives of people. Patients also underlined that not all patients are able to advocate for themselves through active efforts to have their treatments approved: Those who are too sick or those not experienced with insurance processes are left behind, leading to a chain of inequities, detrimental outcomes, and avoidable sorrow. "That's the last thing that I need as I fight for every minute of my life." "Patients deserve a medical system that works without patient intervention." "Insurance and ultimately cancer, won."

Potential Implications of PA Requirements on Patients' Access to Supportive and Palliative Care

At present, numerous supportive medicines require PA for coverage, even if broadly indicated in cancer management and frequently of low costs.[22,25,26] A notable trend in restricting

TABLE 2. Patients' Lived Experience on Pre-authorization

Patient Story	Narrative of Experience
Story 1	"While I've heard many different stories about how a prior authorization affects patients, I was living in blissful ignorance as to the mess that can ensue until a recent experience with getting a new **prior authorization for a** medication that I've been on for more than a year. This medication, **Capecitabine**, is an oral chemotherapy treatment for those of us with terminal cancer. Taking this medication is quite literally life or death for someone like me and the **psychological burden** of knowing that cancer could be growing out of control without medication can be extremely debilitating My private insurance company (through my husband's employer) requires that I use a specialty pharmacy that mails me my medication, for any medication taken long term. All of the pharmacy literature urges patients to use the website or application to refill medication. Dutifully, I went to the website to refill my prescription on 2/13 (a Monday) needing the meds the following Friday to start my next cycle. I get a call at 3:45 p.m. on Friday saying that a prior authorization was needed and so the medication can't be shipped and that the online system only checks for insurance paperwork needed at the time of mailing the medication Despite the fact that it was after the clinic closed at my doctor's office that Friday, I was able to get them to send in the paperwork to get the prior authorization via fax. The following week, **I began following up with everyone**. Took about a week for my doctor's office to discover that **they'd been using the wrong fax number**. Ironically, my insurance company kept sending back faxes saying that they needed more information, never mentioning it was the wrong number Once my doctor's office discovered that they'd been using the wrong fax number, my insurance company allowed one of the pharmacists to use the electronic prior authorization form and the information was received and processed within the time period allotted in my insurance contract. The pharmacy at my cancer center advanced me medication and my insurance company authorized the medication to be sent overnight and an extra dose ahead of the regular refill schedule, so I'd have medication on-hand The **burdens of living with a terminal cancer diagnosis** are many and varied. I already live in constant pain, have many side effects from the medication I'm on right now as well as the four other lines of treatment I've been on since 2017, take medication to manage depression and anxiety, have PTSD from all of the experiences thus far, see a variety of doctors and specialists and get regular bloodwork. **Being a forever patient is truly at least one full time job**. Adding on the trauma of knowing that I don't have the medication ie, quite literally keeping me alive and it can be just untenable. **"Patients deserve a medical system that works without patient intervention"**
Story 2	"My father passed away on March 28, 2022 after a long battle with Stage IV Oral Squamous Cell Carcinoma, which was overlooked by medical professionals and diagnosed in a very late stage. His form of cancer was very aggressive and progressed/further metastasized four times after initial diagnosis. I spent 3 years, from the time of diagnosis until his death, **waging a battle against cancer along with my Dad and unexpectedly, his own insurance company**. While my time should have been spent making memories in the final stages of my Dad's life, I spent that precious time advocating on behalf of my Dad. This cancer diagnosis felt like my own as it was trying to take something so precious. I advocated without hesitation, but at many points in time I thought about those who had no advocate. I saw them in the waiting room often. Knowing my father's experience, their **fate against cancer and equally against their insurance** was beyond worrisome While undergoing standard treatments, my Dad's cancer progressed again. In an effort to save his life, my Dad's oncologist switched gears and started a new regimen of zoledronic acid and pembrolizumab within just 6 days. We knew time was not on our side and while his oncologist set the expectation that he was unsure if/how my Dad's cancer would respond to this new treatment, we took the chance. Despite its aggressive nature, **2 doses of this new combination therapy stalled the progression of his cancer and visibly improved his quality of life** As infusions continued, each scan looked better than the last so I remained optimistic. While my Dad's cancer wasn't NED, we were inching closer to that milestone after each treatment. This continuation was necessary as stopping infusions could have caused it to come back with a vengeance. Based on his oncologist's medical expertise, and need for future treatment planning, he ordered a biopsy taken and sent it for genomic sequencing, analyzed through an FDA-approved test. I advocated on my Dad's behalf to get this test approved because his life absolutely depended on it. **After numerous denials, the nurse practitioner overseeing my Dad's care was scheduled for a peer-to-peer review** with insurance in order to get approval. The nurse practitioner called me immediately after the review concluded and quoted *"**physician admitted to him that he was not an oncologist and is unfamiliar with impact on genomic testing for cancer treatment** planning and therefore could not approve the test."* I was shocked. How is this a peer-to-peer review if the peer is not an oncology expert? Who decided that this physician (who lacked relevant experience and knowledge of genomic testing) was a suitable candidate to discuss the efficacy and medical necessity of the test? **My Dad's fate lay in the hands of someone who by his own admission didn't know the implications of the test**. My Dad's oncologist submitted a second request for the test to be approved and I called his insurance company many times questioning them as to why a physician insurance provider, not involved in his direct care, had greater oversight and influence over my Dad's health than my Dad's team of leading oncology experts. As we continued to contest the denial, scans showed that a new area was growing. While the rest of his body continued to respond favorably to his ongoing treatment, it was evident that his latest cancer development was resistant to the regiment. With no approval in sight, we ultimately gave up and opted for surgery on this new area in hopes that the cancer could be removed while still receiving pembrolizumab, as it continued to be effective in the rest of my Dad's body Following surgery, we marked 2 years on Keytruda. Then came yet another denial, this time for the very treatment keeping him alive. Insurance stated that the FDA and NCCN recommend a total treatment duration of 24 months for his diagnosis and my Dad had completed the recommended treatment cycle. Any future treatment was effectively denied. Despite a mountain of evidence supporting the efficacy in continued treatment **my Dad received 3 denials. The final letter was sent from an obstetrician-gynecologist**. Even pleas to the drug manufacturer were unsuccessful. I finally realized I could do no more **"Insurance and ultimately cancer, won"**

(Continued on following page)

TABLE 2. Patients' Lived Experience on Pre-authorization (Continued)

Patient Story	Narrative of Experience
Story 3	"I have had multiple experiences over my five years with metastatic colorectal cancer where pre-authorizations have either **limited my care or added a lot of extra effort and work** by my expert care team to provide me with their recommended care. One area where this has really become a challenge is in **scans**. I have disease in some organs that's only visible on CT scans and in other organs only visible on PET scans. Therefore, PET/CT is the only way to understand the full nature of my disease and at my center this combined scan is an option. However, my insurance will only approve one scan at a time. This includes **countless hours of my oncologist's team going through peer-to-peer reviews** and my going through my 'navigator' at the insurance company to try to resolve. Surprisingly, it is not always the less expensive scan, and it is **unclear** why sometimes when my team submitted for pre-authorization of a PET/CT the CT is approved and the PET is denied and other times the PET is approved, and the CT is denied. The insurance also does not require additional information from this chosen scan to justify the next scan. So, this preauthorization game does not at all relate to need or financial considerations, or any other logical rationale that I can tell, but rather that it is a policy, and therefore it is followed. What this has led to has been either needing to choose which portion of my disease we would like to see first or most often, and then filling in with the other scan on alternate dates or I have gotten one of the scans and as soon as it's completed, my team submits for the other scan, which then I get a week or two later. This two-step process not only can delay treatment decisions. It also adds **additional time toxicity** to my care of needing to go to the center multiple times to get the scan, scheduling, etc as well as more radiation exposure since the PET scan does include a low-resolution CT anyway. This also turns out to be more expensive for the insurance company as the scans are usually approved at different locations with different staff and adds additional common needs like bloodwork or accessing in my port that are therefore duplicated. While we've learned how to play this game over time, in the beginning **it was quite exhausting** to try to navigate and now **it's simply frustrating** that I as the patient and my team has to deal with all of this **extra complication for no reason**. And to think **all of this isn't actually to treat the cancer** but to understand what needs to be treated. The extra delays this has caused in terms of actually treating the cancer are quite **nerve wracking**. That's the last thing that I need as I fight for every minute of my life"

Abbreviations: FDA, the US Food and Drug Administration; NCCN, National Comprehensive Cancer Network; NED, no evidence of disease; PTSD, post-traumatic stress disorder.

the access to supportive care medicines has been reported for opioids, an essential treatment for neoplastic pain control.[27] In the period 2015-2021, the requirement for PA for two common formulations of long-acting opioids increased from no need for PA to 50% of Medicare prescription drug plans.[28] Additionally, many insurers reclassified four opioids of six available from lower tiers to tier 3 or specialty tier (ie, higher copayment requested) in Medicare part D coverage.[28] As a result, the out-of-pocket expenditure for optimal control of neoplastic pain increased up to four-fold. It is reported that such a restriction of the pain medications occurred in response to the opioid crisis in the United States; however, regulating cancer pain medications using the same tools as for opioids in the noncancer setting has had serious collateral consequences.[27,29] Denial of high-value drugs and supportive care management can increase the out-of-pocket expenditure and result in detriment for patients. Patients who are exposed to financial distress experience poorer quality of life and ultimately inferior survival outcomes.[30-32] Although evidence are limited on the impact of excluding supportive palliative care medicines from PA, we believe that a minimum set of essential interventions should be assured to all patients, with minimal administrative barriers.

Impact of PA Requirements on Health Care Providers and Health Systems

PA does not occur as an automated process but requires time and expertise from a highly skilled health workforce. It is reported that PA yields a substantial increase of the physicians' workload, corresponding to more than $68,000 USD time-equivalent per physician per year interacting with health plans, that is, $20 USD-$30 billion USD in the United States, annually.[33] Bingham et al created a time-driven activity-based model, estimating annual costs associated with obtaining PA for radiation treatment-related services[35] of $491,989 USD per institution.

Much of the dissatisfaction with the PA process is related to the time spent in supporting treatment decisions for patients, including peer-to-peer reviews and appeals. Physicians report frustration regarding the quality and flow of communications with insurers and the amount of documentation required.[35] Turnaround times for PA can widely vary. In the ASCO survey,[21] oncologists reported to have completed up to 50 PAs weekly, dedicating up to 40 hours every week. It is interesting to note that such an amount of time, 40-50 hours per week, corresponds to a full-time equivalent doctor's workload[36]: In substance, PA can double the average weekly workload. Bingham et al[34] estimated an overall time burden ranging from 92 to 95 minutes per PA event for radiation oncologists, when peer-to-peer discussion was required.

Half of the providers surveyed by ASCO had up to two staff in their practice dedicated to PA. Much of the bureaucratic hurdle was due to the burden of evidence requested to prove the clinical necessity of the interventions. The oncologist often perceived a lack of expertise of the authorization reviewers as a driver of denials and unsuccessful appeals and felt discouraged by the lack of transparency, especially on the criteria for coverage decisions.[21,35] Although some authorizations are smoothly managed and completed within 1 hour from the initial submission, escalation to peer-to-peer review occurs in a third of the

requests, and delays of ≥1 day occur in nearly a half of the cases.[21]

Oncology trainees are not spared: A survey circulated among medical physicians in training in the United States in 2019 showed that 70% of them were involved in some extent in the PA process.[35] The participation to this activity was associated with decreased enthusiasm for work and choice of the medical profession: Such a dissatisfaction was maximally reported by 83% of the medical oncology trainees.

In medical practice, dissatisfaction and challenges impeding the effective care delivery related to PA can result in clinician burnout and contribute to technology-induced and administrative burden-related distress.[37] Burnout is a substantial determinant of the workforce shortages, resulting in providers leaving oncology practice and changing their career paths.[38,39]

Taken together, the evidence suggests that while conceptualized to be a cost-containment and efficiency-improving procedure, PA is now a burden in terms of unfunded, adjunctive administrative labor. From a whole-health system perspective, the original intent appears to be ultimately corroded and possibly detrimental.

The Fundamental Question: Who Should Direct a Patient's Care and How Should Reimbursement Decisions Be Made?

One of the major problems exacerbated by the PA process is the fragmentation of patient-centered care. Rather than the locus of care centered on the patient, with shared decision making in concert with the oncology provider(s), many treatments and services must be precleared by insurers, each with their own policies and rules. Health insurers can formulate their own pathways for coverage decisions, although overarching regulations exist to govern their scope.[28] For example, the Medicare Advantage Organizations (MAOs) are private contractors that can give benefits for Medicare, including part D (drugs). In principle, MAOs should align with the initial criteria for service coverage set by Medicare. However, important divergences have been reported. In April 2022, the Office of Inspector General of the US Department of Health and Human Services issued a Report on the MAOs denials of procedures and medicines requested via PA.[40] The Inspector showed that MAOs had used decisional criteria beyond the Medicare coverage rules, putting adjunctive barriers to services that should not require extensive discussions. MAOs have requested adjunctive and unnecessary documentation to formulate their decisions to cover or not specific health interventions, restricting or delaying the access to cancer care while increasing the administrative burden for health providers.[40] The major determinants of inappropriate denials were errors during manual claims-processing reviews and system processing errors: 18% of all denials were about interventions meeting the Medicare rules for billing, which should have been covered.[40]

The PA system was ostensibly developed to optimize care delivery with a focus on noninferior, cost-effective options. However, the report of the Office of Inspector General portrays an alarming status quo: Insurance organizations have demanded unnecessary adjunctive workload for interventions of common practice and included in the basic services that Medicare has established on the basis of clinical relevance, impact, and cost-effectiveness. In short, given that insurance coverage is in many cases required for a patient to realistically access a treatment or service, insurers and MAOs are de facto governing the practice of medicine as it relates to individual patients. It can be debated if insurers are the most objective adjudicators because they have an inherent conflict of interest between optimizing revenues and supporting optimal patient care. In addition, there are controversies related to the choice of the adjudicators regarding their subject matter expertise, as well a relative lack of real-time oversight into internal reference guidelines adopted by insurers to make coverage determinations. Such variability in multiple critical decisional points generates more barriers and creates a mist of uncertainty, yielding frustration because of the arbitrary nature of some coverage requirements and the irreproducibility of final decisions. Finally, emerging reports of potential abuse including the use of automated algorithms to deny coverage of tests, medications, or treatments without true medical review only further erode trust between patients, health care providers, and insurers as to the true purpose of PA requirements.[41] The unpredictable or highly burdensome requirements for PA, in substance, can affect the clinical decision-making process and undermine the patient-doctor relationship.

BARRIERS, FACILITATORS, AND POTENTIAL SOLUTIONS

In the short term, health care providers can restructure systems to handle the current PA process more effectively, although it should be acknowledged that such efforts cost time and money. A pharmacy-based survey from 2022 reported that health benefits formulary management attitudes, differences in requirements between managed care organizations, and miscommunications seemed to drive many of the approval delays.[42] Additional determinants of delayed approvals have been reported in a recent, single-institution study with oral anticancer drugs.[43] A key factor that appeared to accelerate the time to approvals was the availability of a hospital-based specialty pharmacy. The proportion of patients who could eventually get treated within 7 days of prescription increased modestly from 47% versus 54% (adjusted odds ratio [aOR], 1.29; 95% CI, 1.00 to 1.68; $P = .05$) when the hospital-based specialty pharmacy was available. Although a positive study, it is important to note that despite the intervention, nearly half of adult oncology patients faced >1-week delays in medication approvals. Of note, a specialty pharmacy and dedicated

workforce to handle PA paperwork and other related services are not commonly available and not billable to insurers. As a result, although implementation of ad hoc services to manage PAs can be a short-term solution, a better long-term solution must be simplification of the process and reduction of the administrative burden. Reliance on specific services that only few centers can implement would yield to even more inequities in access to cancer care, with patients referred to smaller or less well-resourced centers left behind and systematically forced into second choices because of barriers imposed by the PA process. Solutions in this area should pursue simplification and efficiency first.

Specialty-Oriented, National Clinical Guidelines–Informed Tools Can Facilitate PA

A key driver of dissatisfaction is the burden for health providers to justify therapies and services broadly viewed as standard of care. A (sub)specialty-oriented, tool-based approach has the potential to support up-to-date, guideline-concordant care, while mitigating the problems associated with the frequent lack of disease specialists to review requests and reduce turnaround time to decisions.[35] Such an approach is concordant with the original intent of PA: to reduce the use of nonstandard interventions that can harm patients and assure efficiency in health expenditure. PA tools incorporating real-time decision support on the basis of the National Comprehensive Cancer Network Clinical (NCCN) Practice Guidelines in Oncology as the content for decision making have been piloted in one program of a large national payer.[44] The advantages of a structured tool-based approach for PA is in the data minimization to make the request and the transparent criteria for decision making, on the basis of national, most updated guidelines. The NCCN-based, pilot project for assisted PA reported a saving of $5.3 million USD for the state of Florida in 1 year, by aligning clinical decisions to best practices and requesting peer-to-peer review only in selected cases.[44] As with many policy prescriptions, the devil is in the details. Given the large number of insurance plans, there is the potential for such tool-based approaches to generate greater administrative burden if plans each use different decision tools and custom decision guidelines (^Fig 2).[45] As one oncologist has expressed, "If we're facing a situation where I have to use a different pathway based on whether my patient is a Blue Cross patient or an Aetna patient or Medicare Advantage patient, and each one of those has a different order set and different priority, that is going to create significant frustration and blowback from the oncology community."

Potential of Clinical Pathways to Facilitate PA

Clinical pathways are evidence-informed tools developed by multidisciplinary expert committees to define tasks and/or type and sequence of interventions that should encompass most of the clinical practice on the basis of a specific cancer type and stage.[46] It is well documented that adherence to best practices results in improved survival and quality of life for patients with cancer.[47] Alignment to common standards of treatment could improve efficiency and reduce discrepant decisions across decision makers. When clinical decisions are based on national treatment guidelines that are accepted by

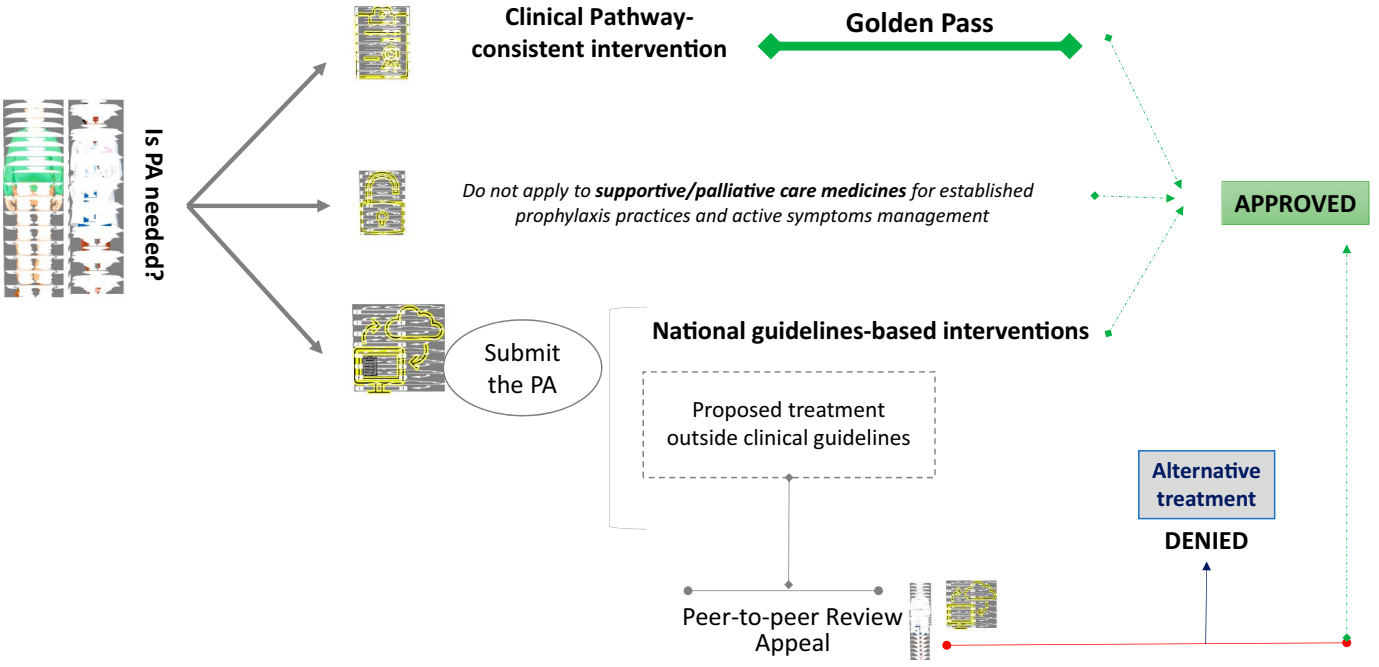

FIG 2. A proposed scheme for an evidence-informed next-generation PA process. PA, prior authorization.

Medicare as part of their compendia to inform reimbursement decisions, PA could be automatized and embedded in a transparent, web-based, consistent, and universal tool that should assist physicians in requesting cancer care interventions while assuring timely care delivery. In addition, with the widespread implementation of clinical pathways as quality enhancers at the institutional level, insurers should consider reducing the administrative burden when physicians can document that they navigated the pathways, instead of duplicating the efforts to align to institutional and then noninstitutional quality standards. Adherence-related metrics are broadly recognized as a key component of quality of care, with an acceptable threshold of ≥80% to state good quality.[48] This 80% threshold still provides space for patient-centered care and adjustment of the treatment plan according to patient preferences and comorbidities. Notably, the 80% threshold has been used by some health insurers, such as Blue Cross Blue Shield, to describe high pathways adherence.[49] Institutions with an adherence above such an established threshold of 80%, for example, may grant the benefit for a golden pass for facilitated preauthorization. A golden pass could bring benefits for high-quality institution to have their requests minimally scrutinized through preauthorization. Institutions may save workload and costs while investing in quality, and insurers would save costs.

Revisiting the Scope of PA

From multiple lines of evidence, it seems clear that tools supporting decision making on the basis of transparent criteria can enhance progress toward high-value care.[18] However, many groups have also demonstrated that implementation of internal clinical guidelines and pathways can deliver higher-quality care in the absence of coupled PA requirements.[50] In general, insurance-led PA efforts alone seem unlikely to deliver major benefits to patients, when not coupled with quality-oriented policy interventions. Accordingly, one could question if PA is truly needed in an era of rapid therapeutic advancements, institutional quality policies, and more attention toward sustainability.

The larger question at hand relates to the scope of PA, that is, what criteria should properly dictate where a particular treatment or service requires PA at all in the setting of oncologic care? Cost? Toxicity? Availability of generic or biosimilar substitutes? Evidence of overuse, misuse, or abuse? Just as importantly, what treatments or services should be *excluded* from PA requirements? Indeed, drastically restricting the scope of treatment or services subject to PA could go a long way in reducing negative impacts to patients, health care providers, and health care systems.

For supportive care medicines, we believe that a waiver of PA requirements should be granted because they are commonly requested when patients receive treatments with a moderate-to-high likelihood of adverse effects as prophylaxis or proactive treatments, making the timeliness a critical variable to minimize impact on quality of life. Where no misuse of supportive care medicines is well documented, insurers should not place barriers on their use. Supportive care drugs should be put under facilitated pathways for coverage without additional administrative requirements.

Experiences and Analogies From Other Countries' Experiences

Similarities in the PA process can be identified in countries outside the United States.[51] In Italy, a public fund covers antineoplastic treatments in the public setting. For some high-cost medicines, specific rules for prescription are in place to ensure the alignment with the on-label regulatory approvals. Although there is no formal PA process, providers must prove the appropriateness of their prescriptions for a set of drugs falling under a special monitoring scheme (commonly high-cost medicines) on the basis of an online registry.[52,53] These appropriateness registries enhance consistent prescription patterns while also help control the overall expenditure by informing value-based reimbursement models. Such an approach rhymes with the broader body of literature supporting quality improvement tools to enhance efficiency, especially if operationalized as consistent tools on the basis of consensus guidelines.

Policy Actions

ASCO has launched a campaign to urge the US Congress to pass PA reform.[54] ASCO's approach echoes the broad policy call to action of the American Medical Society on the basis of the need to define the appropriateness of PA, to deliver clinical validity and preserve continuity of care, enhance transparency in the process, and promote timely access to health service, including alternative billing strategies and exemptions for patients in need. In 2022, ASCO launched a campaign to endorse the passage of the Improving Seniors' Timely Access to Care Act to establish improved requirements and standards relating to PA processes under MAOs plans.[55] In September 2022, the US House of Representatives unanimously voiced the urgent need to facilitate access to health care, including cancer care, through efficient health policies aiming at reducing adverse impacts on patients deriving from unnecessary, non–evidence-based, and inappropriate bureaucratic procedures. The bill calls for an electronic authorization process. In addition, it calls the US Department of Health & Human Services to establish a process for real-time decisions for services that are part of the routine clinical practice. Such an item aims at facilitating clinical guidelines-driven or pathway-informed decisions. Approvals and denials are requested to be fully disclosed and reported to the Centers for Medicare & Medicaid Services to prompt review of the MAOs' decisions, encouraging these organizations to adopt evidence-based medical guidelines, developed, or adopted in consultation with physicians.

The Improving Seniors' Timely Access to Care Act has potential for broad impact on access to cancer care. Advocating to facilitate timely access to high-value cancer treatments is a policy and advocacy priority to ensure best care for all patients in need.

IMPLEMENTATION CHALLENGES AND FUTURE DIRECTIONS

The implementation phase of innovative and potentially transforming policies deserves strong efforts to turn commitment into impact. The implementation of the policy solutions outlined in the recently passed Access to Care Act and the ASCO agenda may present challenges at two levels.

First, there is a *structural* problem: The need to establish an online platform on the basis of common data standards, strong privacy data-sharing rules, and consistent web-based tools. It is critical to automatize a more efficient process: Health insurances manage PA and peer-to-peer review largely by phone and fax.[20] Yet, turning a fax-based procedure into an online form is not sufficient to streamline the process. Actions to tackle pragmatic issues, such as the need to manually input patient data to submit requests and lack of any linkage with the electronic medical records, can be instrumental. Moving online means thinking smart and approaching with innovative solutions, including prefilled fields and artificial intelligence support.

Then, there is an *ontology* question. Presently, PA appears closer to a chimera, with multiple layers of intentions and goals accumulated over the years that jeopardize the delivery of safest, effective, cost-effective health care. PA is still missing the opportunity to catalyze patient-relevant policy toward improved quality and sustainability. In the era of value-based health care, there is no excuse to restrict broad access to essential cancer care: Essential cancer interventions should be moved under facilitated reimbursement pathways,[56] as outlined in the *Cancer Moonshot* initiative[57] that aims at reducing cancer mortality through broadening equitable access to quality care. The challenge to cancer control, in substance, cannot disregard how patients access care.[58] In few words it means reducing bureaucracy, ending inefficiency, and delivering sustainable health impact. We would argue that in the current environment, there are insufficient barriers to imposing additional PA requirements under the assumption that PA policies save costs and reduce inappropriate care without negative consequences. By contrast, advocating to reduce PA requirements appears to require a higher burden of proof demonstrating evidence of harm and strong advocacy efforts.

Nevertheless, limitations of the evidence presented are acknowledged. The available data are mostly observational and derived from cross-sectional, survey-type studies. Better studies should be designed to capture and quantify the real impact of PA policies on patient outcomes and identify actionable barriers to result in renovated PA or alternative mechanisms to PA. Research approaches include the development of pragmatic clinical trials or ad hoc longitudinal policy case studies aiming at evaluating the impact of innovative PA and its alternatives on patient-centric outcomes.

In conclusion, the PA process for cancer management is a major barrier for the timely access to best care. The original role of PA to enhance efficiency, safeguard patients, and assure cost-savings appears nebulized in the complex world of its bureaucracy. In the short to medium term, a recent bill passed by the US House of Representatives has outlined specific policy goals to improve efficiency of the PA and to reduce nontransparent procedures. In the longer term, a fundamental reshaping of the PA process should be based on nationwide cancer control goals, as outlined by the *Cancer Moonshot* initiative, delivering equitable cancer care, through access to high-value essential cancer interventions while always keeping patients at the center.

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invited article

overview

Patient-Centered Care in the Management of Cancer During Pregnancy

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The management of cancer during pregnancy requires a patient-centered, multidisciplinary approach to balance maternal and fetal well-being given the rarity of this clinical scenario and lack of substantial data. Involvement of oncology and nononcology medical specialists and ethical, legal, and psychosocial supports, as needed, is instrumental in navigating the complexities of care for this patient population. Critical periods of fetal development and physiological changes in pregnancy must be considered when planning diagnostic and therapeutic approaches during pregnancy. The complexity of symptom recognition and interventional approaches contributes to diagnostic delays of cancers during pregnancy. Ultrasound and whole-body diffusion-weighted magnetic resonance imaging are safe throughout pregnancy. Surgery can be safely performed throughout pregnancy, with the early second trimester preferred for intra-abdominal surgery. Chemotherapy can be safely administered after 12-14 weeks of gestation until 1-3 weeks before the anticipated delivery. Most targeted and immunotherapeutic agents are contraindicated during pregnancy because of limited data. Pelvic radiation during pregnancy is absolutely contraindicated, while if radiation to the upper body is needed, administration should only be considered early in pregnancy. To ensure that the total cumulative fetal exposure to ionizing radiation does not exceed 100 mGy, early inclusion of the radiology team in the care plan is required. Closer prenatal monitoring is recommended for maternal and fetal treatment-related toxicities. Delivery before 37 weeks of gestation should be avoided if possible, and vaginal delivery is preferred unless obstetrically indicated or specific clinical scenarios. Postpartum, breastfeeding should be discussed, and the neonate should receive blood work to assess for acute toxicities with follow-up arranged for long-term monitoring.

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INTRODUCTION

A cancer diagnosis complicates approximately one in 1,000 pregnancies.[1-3] Delays in childbearing and growing rates of early-onset cancers have resulted in a rise in the incidence of cancer during pregnancy that is likely to continue for years to come.[1,4,5] Breast cancer, melanoma, hematologic malignancies, gynecologic cancers, and thyroid cancer are the most common types of cancers diagnosed during pregnancy in the United States.[1] The complexity of care and growing patient population support the need for greater evidence and guidance to inform the management of patients with cancer during pregnancy.

The authors of this study aim to use language inclusive of gender-diverse individuals. Terms such as women, patient, and individual are used as per the gender terminology from the evidence informing this document.

FRAMEWORK FOR PATIENT-CENTERED CARE

The diagnosis and treatment of cancer during pregnancy pose significant challenges as both maternal and fetal well-being must be considered. Optimizing maternal cancer outcome requires treatment that approximates standard diagnostic and therapeutic approaches that would be recommended for a nonpregnant patient. When treatment modifications are considered to avoid excess harm to the fetus or patient, including changes in timing or use of a particular treatment modality, it is critical to weigh potential risks to both the pregnant patient and the fetus while acknowledging the limitations of available evidence. This can pose medical and ethical challenges best addressed by a multidisciplinary care team with the most up-to-date knowledge of the cancer treatment options and fetal risks. When considering how to minimize fetal harm, understanding the patient's acceptance of risk to the fetus and options in this regard are critical. This discussion may be especially complicated by limited evidence regarding the risk of in utero exposure to newer drugs and modalities, as well as a paucity of the long-term outcomes data. Figure 1 outlines a framework to navigate these complexities.

Ethical and Legal Considerations

Treatment decisions for pregnant patients with cancer should center around patient preferences through

PRACTICAL APPLICATIONS

- Cancer care during pregnancy should approximate as closely as possible to the standard treatment for a nonpregnant patient with involvement of multidisciplinary supports, including both oncology and nononcology medical specialists and ethical, legal, and psychosocial supports, as needed.
- Ionizing radiation exposure to the fetus for diagnosis and radiotherapy, including use of radioactive agents, is to be limited to a cumulative dose of 100 mGy throughout the pregnancy.
- Risk of fetal harm with systematic therapy is greatest during the period of organogenesis; therefore, most chemotherapeutic agents can safely be administered after 12-14 weeks of gestation until 1-3 weeks before the anticipated delivery, although use of targeted therapy and immunotherapy during pregnancy is far more restricted.
- Surgery is ideally performed during the early second trimester, although surgery can be performed throughout the entirety of pregnancy when technically feasible with additional obstetric considerations.
- Closer prenatal monitoring is encouraged with routine biweekly fetal assessment during oncologic treatment with the goal of vaginal delivery, unless obstetrically indicated or particular clinical scenarios, after 37 weeks of gestation when possible.

shared decision making, individualized care plans, and guidance from multidisciplinary expert teams.[6] The complexity of caring for pregnant patients with cancer is exacerbated by the relative infrequency of cases and resulting limitations of both available literature and clinical experience. These limitations should be discussed in a transparent manner, adopting the ethical principles of treating rare diseases whereby limitations to traditional evidence-based medicine must be acknowledged and best available evidence in conjunction with clinical acumen must guide clinical decision making.[7]

A review of ethical principles relating to care of patients with cancer during pregnancy identifies patient autonomy as the primary guiding principle supporting shared decision making, centered on the patient's preferences, to facilitate informed decisions.[8] Balancing beneficence to the patient and the fetus is also a prominent theme. To uphold patient autonomy, recognition that fetal well-being may be dependent on maternal well-being is critical. However, patient wishes when balancing maternal and fetal well-being may position patient autonomy at odds with medical values, potentially jeopardizing the provider's duty of nonmaleficence and beneficence to the patient.[9] Thorough discussion is critical, including eliciting patient preferences in light of cancer prognosis and potential risks and benefits of treatment strategies for both patient and fetus. When treatment poses significant maternal and/or fetal risks, extensive multidisciplinary supports including psychosocial and ethical and legal counsel should be included throughout the decision-making process. The latter considerations have become increasingly complex in the United States since the 2022 Dobbs decision by the US Supreme Court overturning precedent set by *Roe v. Wade* (1973), resulting in decreased access to reproductive health care and potential prosecution of patients, their supporters, and clinicians for providing patient-centered reproductive care.[10]

Multidisciplinary Approach

Management of cancer during pregnancy requires a multidisciplinary team including oncology specialists (eg, medical oncologists, gynecological oncologists, surgical oncologists, hematologists, radiation oncologists, radiologists, and pathologists) and clinicians not routinely focused on cancer care, including maternal-fetal medicine specialists, neonatologists, pediatricians, obstetricians, anesthesiologists, clinical pharmacologists, ethical and legal advisors, and psychosocial providers (Fig 2). The Advisory Board on Cancer, Infertility and Pregnancy (ABCIP)[11] established in May 2021 offers an international online platform for physicians to request multidisciplinary consultations free of charge.[12] ABCIP operates under the International Network on Cancer, Infertility and Pregnancy and includes regional and national advisory boards in Belgium, The Netherlands, and Denmark with plans for expansion to Poland, Italy, and Spain-Ibero-America. An international board is available for physicians from regions without dedicated advisory boards. Recommendations from the respective advisory board are collated in a formal letter and returned within 4-7 days. Such international collaborative efforts, much like treatment of other rare diseases, may be instrumental in advancing cancer care during pregnancy.

Although multidisciplinary collaboration is recommended throughout the clinical decision-making process (Fig 1), team communication is particularly instrumental at particular junctures. During the diagnostic process, the pathologist should be informed of the patient's pregnancy because of the potential impact of the hyperestrogenic state on tissue morphology. We also encourage communication with the radiology team to provide an estimate of potential fetal radiation exposure and to identify potential modifications/shielding before imaging. Obstetrics, anesthesiology, and pain service teams should all confer to optimize perioperative management (eg, use of fetal monitoring, tocolytic agents, and postoperative pain management). Systemic treatment planning requires detailed discussion among oncology and obstetrics teams. Discussions with radiation oncologists and medical physicists to plan radiation therapy should be

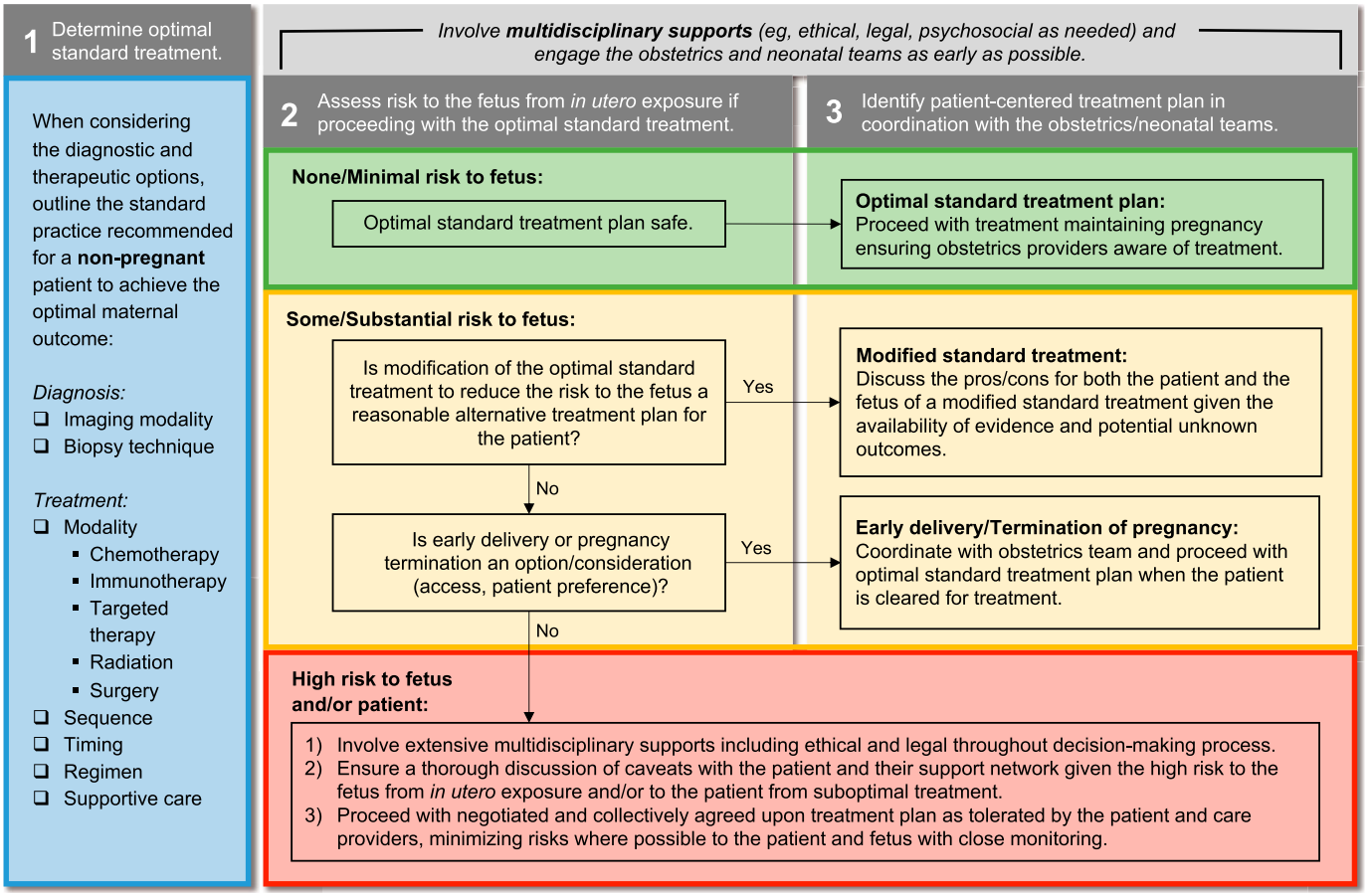

FIG 1. A multidisciplinary framework for management of cancer during pregnancy.

FIG 2. Multidisciplinary care team members to consider optimizing care of the pregnant patient with cancer.

initiated early to allow advance planning, particularly to optimize the timing of treatment and the potential need to develop shielding devices if radiation during pregnancy is considered. Psychosocial providers and resources are an integral component of care for this patient population given the substantial psychological burden of a young-onset cancer diagnosis, especially during pregnancy. Counseling is a critical opportunity to allow patients to openly discuss their concerns, potential outcomes, the impact on their loved ones, and planning for their futures. With the consent of the patient, loved ones and caregivers can be included in these discussions to ensure support from and for all parties.

A checklist of obstetric considerations for oncologists treating a pregnant patient with cancer is provided in Figure 3.

Fetal Development

Fetal risk from exposure to anticancer therapy is generally related to the gestational period. Therefore, structuring treatment decisions relative to the gestational timing of the pregnancy is optimal, and in contrast to historical practices,[14] preterm delivery is to be avoided whenever possible to prevent long-term neurodevelopmental effects and

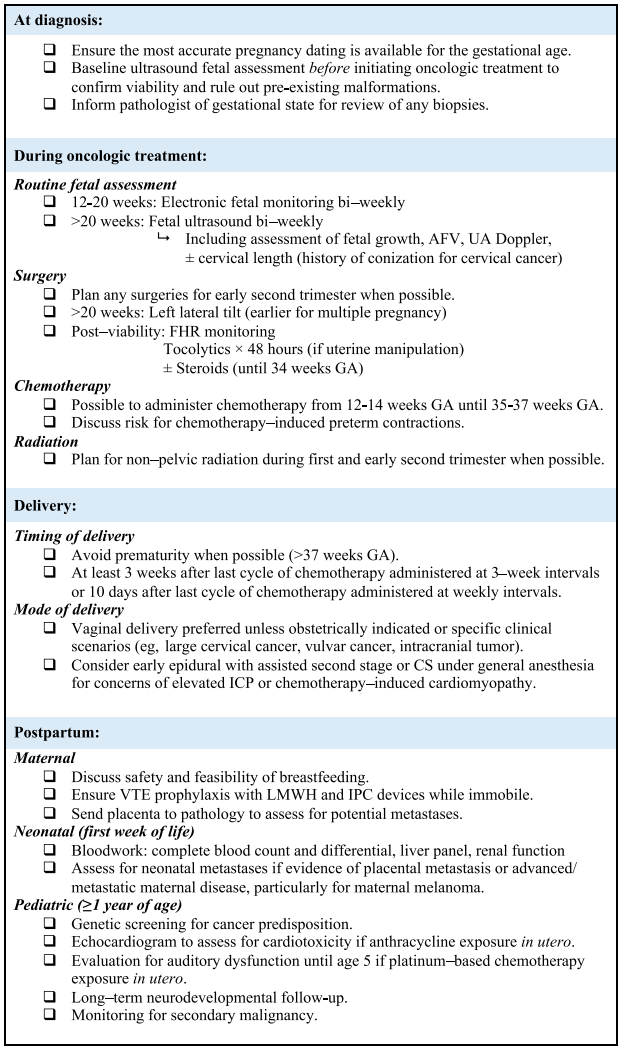

FIG 3. Obstetric considerations for oncologists treating pregnant patients with cancer. AFV, amniotic fluid volume; CS, cesarean section; FHR, fetal heart rate; GA, gestational age; ICP, intracranial pressure; IPC, intermittent pneumatic compression; LMWH, low molecular weight heparin; UA, uterine artery; VTE, venous thromboembolism. Adapted from Amant et al.[13]

immediate consequences of prematurity, including hematologic, metabolic, and cardiorespiratory compromises.[15,16] The predominant phases of fetal development are the embryonic period, during which organogenesis primarily occurs, and the fetal period, a period of growth until delivery (Fig 4).[18] Drug exposure during the first trimester (until 12-14 weeks of gestation) confers the highest risk of miscarriage and fetal malformation.[19] Chemotherapy exposure during the fetal period is most likely to affect fetal growth, specifically an increased risk of small for gestational age fetus and intrauterine growth restriction (IUGR).[20] Nonpelvic radiation is possible in some settings in the first trimester and early second trimester, with maximization of the distance from the radiation field to the fetus and minimization of radiation exposure to the fetus.[21]

Physiological Changes in Pregnancy

The anatomic and physiologic changes in pregnancy substantially affect the pharmacokinetic (PK) properties of medications administered. Changes in PK properties occur for chemotherapeutic agents, analgesia, and antithrombotic medications.[22] Collectively, PK changes outlined in Table 1 may lead to decreased exposure to many drugs during pregnancy.[22-25] The majority of the cardiovascular and renal changes occur within the first trimester while gastrointestinal and hepatic changes fluctuate throughout pregnancy.[26] These changes have been demonstrated for docetaxel, paclitaxel, doxorubicin, epirubicin, and cisplatin.[27-30] However, the magnitude of underexposure for these drugs cannot be reliably estimated given the existing data and models. Longer-term data correlating current protocols with disease progression and survival are required to better understand whether modifications to medication doses administered during pregnancy are warranted.

The placenta also plays a key role in determining the impact of systemic therapy on the fetus and, therefore, the risk threshold for administering the drug. Transplacental transfer of compounds primarily occurs by passive diffusion with some contribution from active transporters and placental drug-metabolizing enzymes.[31] Compounds in the maternal circulation with a low molecular weight (<500 Da) that are lipid-soluble, non–protein-bound, and nonionized can easily cross the placental barrier to the fetus via passive transport.[31] There is also greater transplacental passage of drugs that are substrates for active transporters, such as P-glycoprotein, multidrug-resistant proteins, and breast cancer–resistant protein.[32] Cytochrome P450 enzymes and uridine diphosphate glucuronosyltransferases have been detected in the placenta with variable concentrations depending on the gestational age.[31] Although there are very limited data describing transplacental passage of chemotherapeutic agents in humans,[32] mouse and baboon models have confirmed placental transport of chemotherapeutic agents consistent with these principles.[33-35]

In balancing maternal and fetal beneficence, specific cancer types and situations arising early in pregnancy warrant thorough discussion of pregnancy termination, in consideration of the patient's personal preferences, logistical concerns, and any regional legislative restrictions. These include situations in which maternal health will be harmed by delaying/modifying therapy, particularly when such a compromise would also impair fetal health, such as any advanced malignancy where maternal life is imminently at risk, as well as aggressive lymphomas, AML, ALL, ovarian cancer with peritoneal spread, and cervical cancer that is of advanced stage or node-positive at diagnosis.

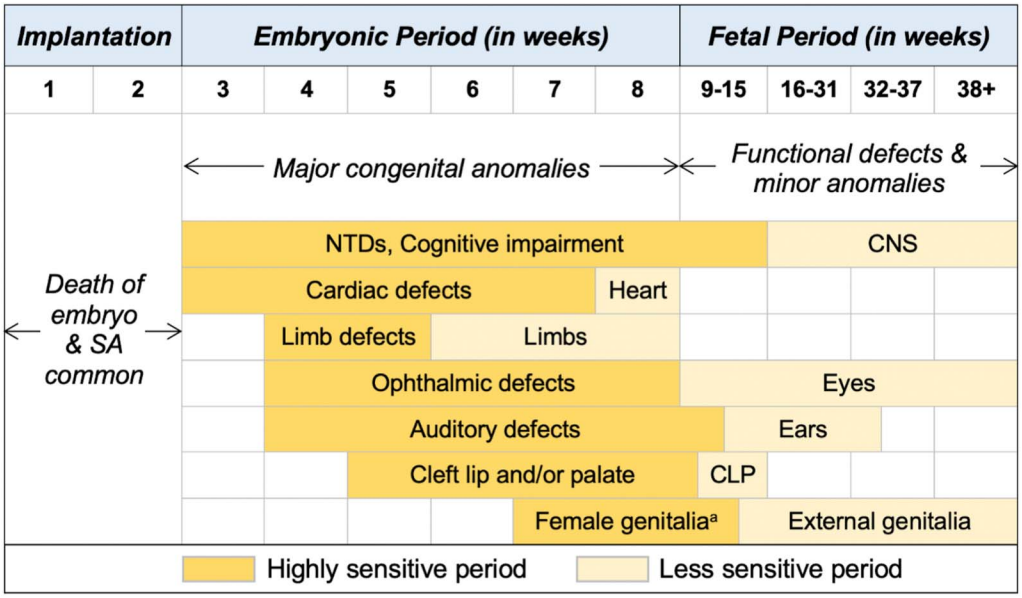

FIG 4. Critical periods in human fetal development. CLP, cleft lip and/or palate; NTD, neural tube defect; SA, spontaneous abortion. [a]Masculinization of female genitalia. Adapted from Moore et al.[17]

The recent Dobbs decision in the United States may have a detrimental effect on transparency when discussing treatment options, thus hindering a patient's ability to make an informed decision and diminishing their autonomy. Providers and patients may be reluctant or even unable to discuss options such as termination of pregnancy even when life-saving treatment cannot be delayed or where compromise in maternal survival because of a modified treatment plan is not acceptable to the patient. The need to obtain legal counsel may in some cases delay simply discussing this option, which could result in excess or unnecessary harm to the pregnant patient, the fetus, or both.

DIAGNOSTIC OPTIONS IN THE MANAGEMENT OF CANCER DURING PREGNANCY

During pregnancy, the patient's primary contact with health care providers are family physicians and obstetricians, the latter of whom are not as familiar with the presentation of nongynecologic cancers. Moreover, many cancer-related symptoms can mimic pregnancy symptoms (Table 2).[43] Collectively, these contribute to diagnostic delays of cancers during pregnancy, resulting in more advanced stage at diagnosis in some settings.[44,45]

TABLE 1. Summary of Physiological and Consequent PK Changes in Pregnancy

System	Gestational Changes	PK Impact
Cardiovascular	↑ Cardiac output ↑ Blood volume ↑ Total body water ↓ Serum albumin	↑ V_d of hydrophilic drugs ↓ C_{max} of hydrophilic drugs ↑ Free levels of protein-bound drugs
Renal	↑ Total body water ↑ Renal blood flow ↑ GFR	↑ Renal clearance
GI	↑ Delayed gastric emptying ↑ Gastric pH ↑ Small bowel transit time ↑ Nausea and vomiting	↓ C_{max} of orally administered drugs ↑ T_{max} of orally administered drugs ↓ Absorption of oral drugs
Hepatic	↑ Hepatic blood flow Altered enzyme activity	↑ Hepatic clearance Variable phase I metabolism

Abbreviations: C_{max}, maximum plasma concentration; GFR, glomerular filtration rate; PK, pharmacokinetic; T_{max}, time to maximum concentration; V_d, volume of distribution.

Imaging

The teratogenic effects of ionizing radiation restrict the imaging modalities considered safe during pregnancy. The total cumulative exposure to ionizing radiation during gestation must not exceed 100 mGy to limit deterministic effects, including fetal death, malformation, growth restriction, and long-term disability.[46,47] The former three occur primarily with exposure to ionizing radiation during organogenesis while the latter occurs during the fetal period.[46,47] The fetal radiation dose with whole-body (WB) positron emission tomography (PET) is approximately 10-50 mGy, and computed tomography (CT) varies from 0.01-0.66 mGy to 10-50 mGy for chest and pelvic imaging, respectively.[47] The stochastic effects, including long-term carcinogenesis and genetic defects, are dose-dependent such that there is no threshold.[47] Therefore, before staging, a multidisciplinary meeting with the radiologist and medical physicist is encouraged to ensure that only imaging required for decision making is pursued and to aim for single-step staging.[44,47,48]

Ultrasound and magnetic resonance imaging (MRI) are the only imaging options considered safe throughout all trimesters of pregnancy as they do not use ionizing radiation (Table 2). However, potential fetal risk from sustained temperature elevation still requires consideration, including restricting imaging to 30 minutes.[47,49,50] Fluorine-18-flurodeoxyglucose PET integrated with CT

TABLE 2. Cancer-Related Symptoms to be Aware of During Pregnancy

Cancer Type	Presenting Symptoms		Pregnancy Symptoms
Breast cancer[36]	Increased breast density and nodularity Skin changes Nipple discharge	≈	Hormonal and lactational changes in breast tissue
Hematologic malignancies[37,38]	Malaise	≈	Fatigue
	Shortness of breath	≈	Dyspnea of pregnancy
	Skin changes and pruritis	≈	Pruritus of pregnancy[a]
	Splenomegaly/hepatomegaly Abdominal or mediastinal mass	→	Obscured splenomegaly, hepatomegaly, or abdominal mass
	Cytopenia (anemia, thrombocytopenia)	≈	Dilutional anemia of pregnancy, gestational thrombocytopenia
Melanoma[39,40]	Change in existing nevus New and evolving lesion	→	Detection impeded by hyperpigmentation of pregnancy (ie, melasma/chloasma)
Cervical cancer[41,42]	Vaginal bleeding (particularly postcoital) Abnormal vaginal discharge	≈	Vaginal bleeding, cervical ectropion, and increased vaginal discharge

[a]Includes pruritic urticarial papules and plaques of pregnancy, cholestasis of pregnancy, prurigo gestationis, and pemphigoid gestationis.

(18FDG-PET/CT) is contraindicated during pregnancy because of the combined high ionizing radiation dose.[51] Therefore, WB diffusion-weighted MRI (WB-DWI-MRI) without contrast is the preferred imaging modality for cancer staging during pregnancy, if necessary.[21,52] If WB-DWI-MRI is unavailable for whole-body imaging, low-dose PET/CT can be considered after discussion with a medical physicist, or 18FDG-PET/CT can be performed with hydration and bladder catheterization.[48,53] Although there is increasing evidence supporting the use of WB-DWI-MRI for cancer staging,[52,54,55] and specifically for pulmonary lesions,[56] CT of the chest is still considered the standard imaging for suspected lung cancer or staging of cancers with high propensity for intrathoracic metastases.[57] The fetal effects of ionizing radiation are from direct exposure, with very minimal contribution from internal scatter.[58] Therefore, pelvic CT imaging is contraindicated throughout pregnancy, and abdominal shielding has no utility in reducing fetal exposure from nonpelvic imaging, although it may offer maternal reassurance.[51] MRI is preferred for abdominal and pelvic imaging.[44] When necessary, CT of the head, chest, and extremities can be performed.[47] Chest x-ray can also be considered.[47]

Contrast agents tend to have a low molecular weight and be hydrophilic, increasing transplacental passage to the fetus.[59] Gadolinium is contraindicated during pregnancy because of teratogenic risks.[60] If required, gadobenate dimeglumine and gadoterate meglumine are possible alternatives to gadolinium.[37,59] Iodinated contrast agents do not cause fetal malformations[59,61,62] but may cause neonatal hypothyroidism, so thyroid function testing should be pursued within the first week after delivery. For diagnosis of thyroid cancer, iodine-131 is contraindicated during pregnancy, and technetium-99m is the preferred radioisotope.[47] Pineapple juice has been used as a negative oral contrast agent with WB-DWI-MRI to visualize intra-abdominal lesions, most commonly for ovarian cancer.[53,63]

Biopsy

Pathologic diagnosis of some malignancies during pregnancy may be complicated by the hyperestrogenic state as this can influence tissue characteristics.[44] Consequently, a core needle or excisional biopsy to preserve tissue architecture is preferred to cytology from a fine-needle aspirate, although this may not always be feasible.[64] Moreover, because of changes in tissue, the pathologist must be informed of the pregnant state of the patient, particularly for melanoma, breast cancer, and cervical cancer. Regardless of gestational age, tissue and bone marrow biopsy should not be delayed.[21,37,53] Nonpelvic lymph node biopsies can be performed throughout pregnancy while pelvic lymph node dissection is limited to before 22 weeks of gestation (Fig 5).[53] For patients with breast cancer requiring sentinel lymph node mapping, radiation must be limited to a cumulative total of 5 mGy for the entire pregnancy.[47,65] Technetium-99m can be administered 2 hours before the surgical procedure, with <10% systemic circulation.[21] For fluorescence imaging, indocyanine green has minimal transplacental passage and appears safe in pregnancy,[66-68] while blue dyes are discouraged because of the risk of anaphylaxis.[69]

Cell-Free DNA

Noninvasive prenatal testing (NIPT) is a screening test for fetal aneuploidies that analyzes circulating cell-free DNA (cfDNA) in maternal plasma. The majority of the cfDNA is maternal, and a

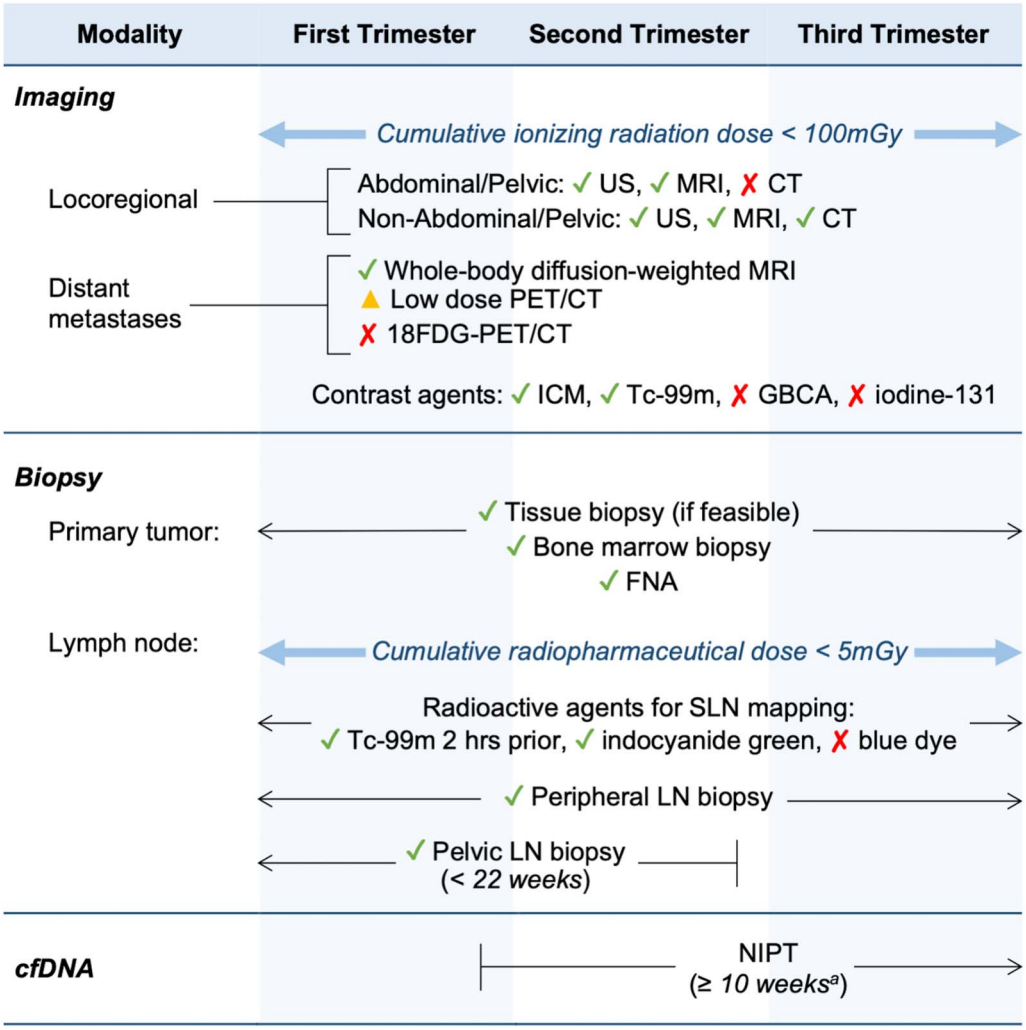

FIG 5. Diagnostic considerations. cfDNA, cell-free DNA; CT, computed tomography; FDG, fluorodeoxyglucose; FNA, fine-needle aspiration; GBCA, gadolinium-based contrast agent; ICM, iodinated contrast media; LN, lymph node; MRI, magnetic resonance imaging; NIPT, noninvasive prenatal testing; PET, positron emission tomography; SLN, sentinel lymph node; Tc-99m, technetium-99m; US, ultrasound. [a]Access to NIPT varies because of variations in reimbursement in the United States and guidelines in other countries that recommend testing after 12 weeks.

small proportion is fetal in origin.[70] Occult maternal malignancies have been known to cause false-positive results for NIPT.[71] For an initial NIPT concerning for maternal cancer, repeat testing and comparison with maternal tissue is recommended.[72] If results remain positive, the patient should be referred to a multidisciplinary team to evaluate for an occult malignancy, initially with WB-DWI-MRI and blood work. If the repeat NIPT is negative, a third NIPT can be done postpartum, and the placenta can be tested for mosaicism.[72] Because of these ambiguities, NIPT is not reliable for a woman with a known cancer during pregnancy.[73] In recent years, there has been greater attention to using maternal cfDNA to diagnose asymptomatic malignancies.[74] The impact of such early detection of cancer on outcomes and management requires greater investigation.[75]

TREATMENT OPTIONS AND TIMING IN THE MANAGEMENT OF CANCER DURING PREGNANCY

Surgery

Surgery can be safely performed during all trimesters of pregnancy. Early second trimester is the preferred time for surgery, particularly for intra-abdominal surgery to balance technical difficulty of maneuvering around the gravid uterus and potential risk of miscarriage in the first trimester.[53] Surgical intervention during pregnancy has been associated with a higher likelihood of preterm delivery.[76] Therefore, it is important to discuss this risk with the patient and consider potential steps to mitigate fetal morbidity after viability, including administration of steroids for lung maturity (Fig 6). Locoregional anesthesia is preferred to general

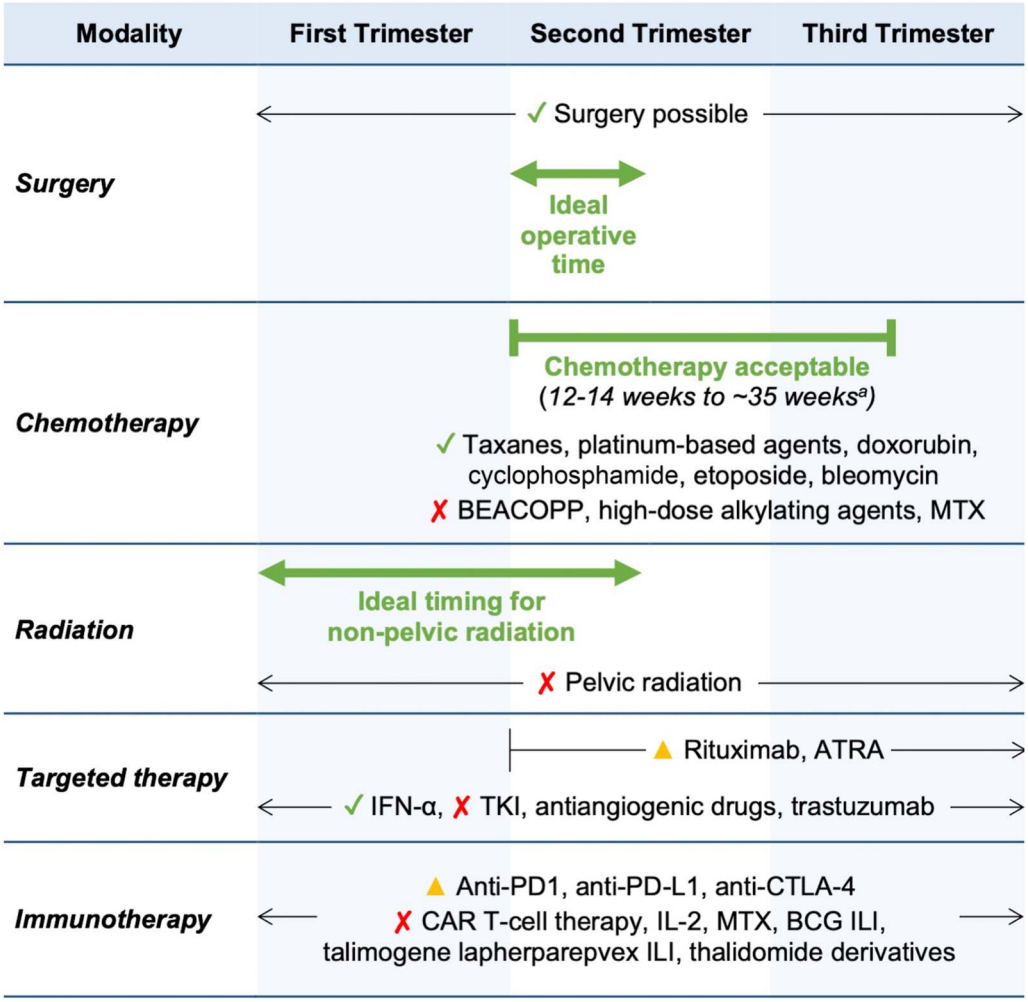

FIG 6. Therapeutic considerations. ATRA, all trans retinoic acid; BCG, bacille Calmette-Guerin; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CAR, chimeric antigen receptor; IFN-α, interferon-α; IL-2, interleukin-2; ILI, intralesional injection; MTX, methotrexate; TKI, tyrosine kinase inhibitor. [a]37 weeks of gestation acceptable for weekly chemotherapy regimen.

anesthesia whenever possible.[77] When considering a laparoscopic approach versus laparotomy, the following factors are to be considered: gestational age, experience of the surgeon, total anticipated procedure time (<90-120 minutes), and the feasibility of maintaining low intra-abdominal pressure (10-13 mmHg).[53] Intraoperative fetal heart rate (FHR) monitoring after viability should be discussed with the patient and the surgical, obstetrics, and neonatology teams to establish expectations of actions in case of intraoperative nonreassuring FHR. Postoperative fetal Doppler may also be preferred. Tocolytics may be considered for 48 hours postoperatively in the case of uterine manipulation during the surgery.[21,78] Given the limited analgesic options during pregnancy, consultation with the anesthesia team or any available specialized acute pain service is recommended for management of postoperative pain. The combination of surgery, immobility, malignancy, and pregnancy results in a highly prothrombotic state. Therefore, venous thromboembolism (VTE) prophylaxis with low molecular weight heparin (LMWH)[78] and an intermittent pneumatic compression device are critical considerations.

Chemotherapy

Generally, it is important to avoid delays in systemic cancer treatment when possible. Fortunately, the existing data and guidelines support the overall safety of many chemotherapeutic agents during pregnancy after 12-14 weeks of gestation and until the third trimester.[19,20,37,53,79-87] Most chemotherapeutic agents cross the placenta to the fetus in keeping with the drug properties previously outlined that facilitate transplacental passage. Consequently, exposure to chemotherapy is contraindicated before 12-14 weeks of

gestation to avoid the period of organogenesis when risk of fetal malformation and stillbirth is highest (Fig 6).[19,88] It is also recommended to avoid delivery at the hematologic nadir (ie, neutropenia and thrombocytopenia) from cytotoxic chemotherapy. Depending on the type and frequency of the regimen, chemotherapy is to be held 1-3 weeks before a high likelihood of spontaneous delivery (ie, 38-39 weeks of gestation) or a planned delivery, whichever is earliest.[89] Curative chemotherapy is not to be delayed to the postpartum period because of the negative impact on maternal prognosis. Fortunately, many conventional cytotoxic chemotherapy regimens for common cancers (ie, taxanes, platinum-based agents, doxorubicin, cyclophosphamide, etoposide, and bleomycin) are feasible with reasonable data for safety in pregnancy. Because of dose intensity, there are more limitations in treating hematologic malignancies,[32,37] and the following regimens and agents are contraindicated: BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), high-dose alkylating agents (eg, busulfan, cyclophosphamide, and melphalan), and methotrexate, necessitating compromises in treatment if a pregnancy is to be maintained.[32,37] Standard dosing on the basis of actual weight of the pregnant patient at the time of drug administration is recommended.[21]

Radiation Therapy

As detailed previously, fetal exposure to radiation overall is to be limited to a cumulative dose of 100 mGy throughout the entire pregnancy (Fig 6).[90] Radiation doses within a range of 50 mGy to 100 mGy have potential deterministic effects while doses <50 mGy have no suspected fetal impact.[51,91] Therefore, consultation with a medical physicist is instrumental for both imaging and radiation therapy to accurately estimate fetal exposure.[51,92,93] Pelvic radiation is contraindicated throughout pregnancy. Limited data suggest that radiation to the upper body, if needed, can be done without clear harm to the fetus during the first and early part of the second trimester when the distance from the field to the fetus can be maximized.[91] When necessary, patient-specific abdominal shielding using bridge construction and/or tertiary shield walls is recommended instead of lead aprons.[94] This poses notable challenges in designing appropriate shielding because of the changing position and size of the fetus, often requiring replacement throughout the pregnancy.[64] This highlights the need for early and frequent consultation with the radiation oncologist and medical physicist in the care plan.

Targeted Therapy

There are very limited data to guide administration of targeted agents during pregnancy. Given the lack of evidence, considering the properties of the different agents that may affect transplacental passage can guide decisions when assessing risk to the fetus. Tyrosine kinase inhibitors (TKIs) are mostly small molecules that can theoretically cross the placenta, although high rates of transplacental transfer have not been demonstrated.[95,96] The use of imatinib is controversial; although there are case reports of pregnancies occurring in the setting of imatinib use after the first trimester without clear harm to the fetus,[88,97] extreme caution should be exercised. Fortunately, the necessity of this TKI during pregnancy should be very rare given that chronic myeloid leukemia (CML) can often be observed for some time and gastrointestinal stromal tumor can usually be initially treated surgically or observed. The evidence is even more limited for the use of other TKIs in the latter trimesters.[98] Therefore, TKIs are currently contraindicated during pregnancy (Fig 6).

The target for monoclonal antibodies is particularly relevant when considering fetal risk for use during pregnancy. Trastuzumab targets human epidermal growth factor receptor 2 (HER2) for breast and gastric cancer.[99,100] HER2 is involved in organogenesis and expressed in fetal kidneys.[101-103] Trastuzumab use in pregnancy has been associated with anhydramnios/oligohydramnios and is, therefore, contraindicated throughout pregnancy.[88,104] Rituximab targets B lymphocytes and is primarily used to treat non-Hodgkin lymphoma. Use of rituximab after the first trimester for cancer and noncancer indications has not been associated with fetal malformations,[105,106] although there have been reports of cytopenia in the neonate that resolves within days or months.[107-109] Given the benefits of treatment, rituximab can be used with caution in the second and third trimesters.[82,98,110]

Antiangiogenic drugs, such as TKIs and monoclonal antibodies that target vascular endothelial factor, have been consistently shown to be teratogenic in animal models with limited data in humans.[88,98] Therefore, antiangiogenic agents are currently contraindicated in pregnancy.

All-trans retinoic acid (ATRA), also known as tretinoin, is a form of vitamin A primarily used to treat acute promyelocytic leukemia (APL), a high-risk leukemia typically arising in young adults.[111] ATRA crosses the placenta and has been shown in animal studies to be highly teratogenic[88,112,113] and, therefore, should be avoided during the first trimester.[111] Case reports of ATRA use during the second and third trimesters are more reassuring and therefore can be used cautiously to treat APL in pregnancy.[88] Optimal treatment of APL has a >90% cure rate with modern therapy of ATRA and arsenic.[111] However, arsenic is absolutely contraindicated throughout all trimesters of pregnancy because of risk of fetal malformation and fetal death.[114] Therefore, treatment of APL in pregnancy is restricted to more traditional agents consisting of ATRA and anthracycline during pregnancy with arsenic administered postpartum.[115,116] There are currently insufficient data regarding potential compromise for maternal outcomes.[115]

Interferon-α (IFN-α) is a pleiotropic cytokine used to treat various conditions including melanoma and select hematologic cancers.[117] Because of high molecular weight, there is very limited placental transfer of IFN-α.[98,118] Case reports of IFN-α monotherapy reveal no evidence of fetal malformations, including use during the first trimester.[88,119] Therefore, IFN-α can be used throughout pregnancy, particularly as an additional treatment option for patients with CML and essential thrombocytosis.[37]

Immunotherapy

There are currently very little data available on the use of immunotherapeutic agents during pregnancy. The maternal immune system undergoes changes in pregnancy to allow for maternal tolerance of the semiallogenic fetus, primarily by regulatory T cells (Tregs).[120] Consequently, agents that target various aspects of the immune system pose concerns. Immune checkpoint inhibitors (ICIs) act on proteins on the surface of Tregs, including PD-1 and its ligand PD-L1 as well as cytotoxic T-cell lymphocyte-4.[121] These proteins are expressed at the maternal-fetal interface and have a role in maintaining maternal tolerance of the fetus.[122] Therefore, use of ICIs during pregnancy is discouraged (Fig 6). The few case reports available detailing in utero exposure to ICIs indicate risk of IUGR and/or placental insufficiency and at least one case of potential immune-mediated hypothyroidism in the neonate, but no evidence of malformations.[123,124] Therefore, ICIs can be considered with caution if necessary for maternal benefit. Immunomodulatory drugs that are derivatives of thalidomide (ie, lenalidomide and pomalidomide) and methotrexate have well-documented teratogenic effects and are strictly contraindicated.[88,125] Chimeric antigen receptor T-cell therapy is absolutely contraindicated during pregnancy while additional forms of immunotherapy, such as recombinant interleukin-2 and intralesional vaccines (bacille Calmette-Guerin and talimogene laherparepvec), are generally contraindicated.[123]

Supportive Treatment

Many commonly used supportive medications also must be modified during pregnancy (Table 3). Consultation with a clinical pharmacologist is highly recommended. Analgesia is primarily limited to acetaminophen and opioids, as nonsteroidal anti-inflammatory drugs in high doses are contraindicated during pregnancy because of risk of premature closure of the ductus arteriosus and oligohydramnios.[18] For antiemesis, metoclopramide is routinely used throughout pregnancy. Because of concerns for potential malformations with use in the first trimester, ondansetron is only recommended in the second and third trimesters.[126] Antenatal corticosteroids, particularly dexamethasone and betamethasone which readily cross the placenta in their active form, may increase the risk of long-term behavioral and neurocognitive disorders in early childhood,[127] although the benefits for lung maturity in preterm neonates may offset these risks.[128,129] Steroids with lower placental transfer (ie, methylprednisolone, prednisolone, and hydrocortisone) may generally be preferred for the prevention of chemotherapy-induced nausea and vomiting during pregnancy, although data for this approach are limited.[130-132] For patients requiring anticoagulation, such as patients with CML with platelets >1,000 × 10^9/L and high-risk patients with myeloproliferative neoplasms, LMWH is the only available option.[37] Aspirin (acetylsalicylic acid) at a low dose of 81 mg daily can be considered for low-risk patients with myeloproliferative neoplasms.[37] Recent data in both chronic neutropenia and cancer treatment settings have suggested no clear harm from the use of granulocyte colony-stimulating factor during pregnancy, including pegylated formulations.[80,133,134] Therefore, growth factor can be used when necessary with close monitoring for neutropenia and associated complications during pregnancy, particularly in the peripartum period.

Supportive strategies (eg, indwelling venous catheters during chemotherapy administration, and opioid administration)

TABLE 3. Supportive Treatment Options

Category	Available Agents
Analgesia	Paracetamol Morphine Sufentanil Lidocaine Ketamine Tramadol (short-term use)
Antacid	Omeprazole Pantoprazole
Anticoagulant	LMWH
Antiemetic	Metoclopramide Ondansetron Granisetron
Antihistamine	Clemastine fumarate Diphenhydramine
Antimicrobial	Antibiotics: macrolides, cephalosporins, PCN, MTZ Antiviral: acyclovir, valacyclovir, famciclovir Antifungal: amphotericin B
Hematologic support	Erythropoietin G-CSF ASA[a]
Steroid	Methylprednisolone Prednisolone Hydrocortisone

NOTE. Adapted from Amant et al.[64]
Abbreviations: ASA, acetylsalicylic acid; G-CSF, granulocyte-colony stimulating factor; LMWH, low molecular weight heparin; MTZ, metronidazole; PCN, penicillin.
[a]Low dose (81 mg).

pose additional risks in pregnancy (eg, thrombosis and infection) that warrant consideration and discussion with the patient. Additional interventions, such as bone marrow transplant, are absolutely contraindicated during pregnancy.

OBSTETRIC AND NEONATAL ISSUES IN MULTIDISCIPLINARY MANAGEMENT

Prenatal Care

The obstetrical management of patients diagnosed with cancer during pregnancy has shifted notably in recent decades such that chemotherapy is more frequently administered during pregnancy, allowing for improved maternal survival outcomes and decreasing need for iatrogenic premature deliveries.[81] Pregnancy dating with ultrasonography is recommended to ensure the most accurate timing in gestation and for baseline fetal assessment before initiating oncologic treatment, particularly systemic therapy.[21] Biweekly ultrasound should be pursued to monitor fetal growth and amniotic fluid volume, including uterine artery Doppler because of risk of placental insufficiency associated with certain cancer types and treatments when administered.[13,64,135] Doppler ultrasound is also useful in identifying fetal anemia associated with chemotherapy-induced myelosuppression.[136] In patients with cervical cancer who have undergone conization, cervical length assessment is also required.[53,137] Vaginal progesterone should be added if the cervical length is <25 mm, and cervical cerclage can be considered if there is no evidence of residual disease.[53,138] The patient and oncology team should be aware of potential chemotherapy-induced contractions associated with platinum and non–platinum-alkylating agents and urgently notify the obstetric team if they occur.[81]

Timing of Delivery

Because of the associated high short- and long-term morbidity,[15,139] premature delivery should be avoided when possible with the goal being term delivery at >37 weeks of gestation. However, particular clinical situations, such as unstable patients or those with acute leukemia, intracranial tumors, or cervical cancer not responding to chemotherapy, may necessitate early delivery.[37,140] Clinical and ethical conundrums may arise when the optimal treatment for the patient's cancer entails the use of a treatment with limited safety data and/or clear risk to the fetus before the pregnancy reaching term.

When considering the timing of delivery, it is also important to avoid the nadir of maternal and fetal myelosuppression associated with chemotherapy whenever possible.[141,142] Identifying and proactively managing both maternal and neonatal cytopenia from chemotherapy-induced myelosuppression is critical. Ensuring an adequate interval between the last chemotherapy dose and delivery is also particularly important for deliveries <38 weeks of gestation as preterm neonates have inadequate liver function to metabolize many chemotherapeutic agents, which may lead to toxicities and complications in the neonate.[143]

Mode of Delivery

For the mode of delivery, vaginal delivery is preferred unless obstetrically indicated or for specific clinical scenarios.[53] For example, patients with unresected cervical cancer are recommended to have a cesarean section (CS) to avoid seeding at the episiotomy site during vaginal delivery or obstruction of the birth canal. Large cervical cancers warrant a corporeal uterine incision.[144-146] Simple or radical hysterectomy and pelvic lymphadenectomy, if complete excision was not done during pregnancy, can be done concurrently at the time of the CS in these patients.[53] Additionally, patients with vulvar cancer should be recommended to deliver by lower segment CS because of concerns for vulvar wound dehiscence.[53] Patients with intracranial tumors may be recommended to have an early epidural with assisted second stage of delivery or CS under general anesthesia because of concern for elevated intracranial pressure (ICP) with Valsalva.[147,148] Patients with bone metastases may have similar recommendations because of risk of long bone fractures during labor.[64] Patients at higher risk of thrombocytopenia because of cancer type or treatment should receive blood work before delivery to allow for timely intervention, including platelet transfusions if necessary to meet platelet targets for vaginal delivery (>20 to 30 $\times$ 10^9/L), CS (>50 $\times$ 10^9/L) and an epidural (>80 $\times$ 10^9/L).[149,150]

Postpartum Considerations

The placenta should be evaluated histologically for metastases by an informed pathologist, particularly for patients with melanoma.[151] Placental metastases necessitate reconsideration of maternal staging and additional evaluation of the neonate. During the postpartum period, careful consideration of the safety and feasibility of breastfeeding requires multidisciplinary discussion. Previous breast treatment, short interval since last chemotherapy cycle (ie, <3 weeks), or need to resume systemic therapy after delivery will often impede the patient's ability to breastfeed.[88,152,153] However, individualization is possible since estimated levels of taxanes and anthracyclines in breast milk are very low 2-3 days after administration.[154] Appropriate counseling given the societal pressures of breastfeeding is critical to ensure the patient feels supported.[155,156] VTE prophylaxis consisting of LMWH and ICP devices should also be considered as appropriate during this period.

Pediatric Assessment

During the first days of life, the neonate should have a complete blood count, liver panel, and renal function assessment to rule out cytopenia and other toxicity from in utero

exposures, particularly if <3 weeks after last chemotherapy cycle.[53] In the rare instance of placental metastases, the neonate should be referred to a pediatric oncologist for further follow-up to rule out fetal metastases.[151]

Children exposed to platinum-based chemotherapy in utero should be evaluated for auditory dysfunction within the first year and again 5 years thereafter.[89,157] In case of anthracycline exposure, an echocardiogram is recommended within the first year and then every 3 years until early adulthood to assess for potential risk of delayed cardiotoxicity.[158] For long term, these children should be monitored for secondary malignancies and neurodevelopmental disorders. Although current evidence does not indicate a higher rate of cancer among children exposed to chemotherapy in utero, there is a theoretical risk because of patterns observed among childhood cancer survivors.[159] Existing literature demonstrates adequate neurological and psychological development of children exposed to chemotherapy in utero with follow-up to age 9 years.[79,160,161] Independent of specific treatment, Full Scale IQ scores have been shown to be negatively affected by preterm birth, maternal death, and maternal education level.[160] In a separate study, children followed up to age 6 years after maternal demise were noted to have lower verbal IQ and visuospatial long-term memory scores.[162] There is a theoretical impact on fertility in children with in utero exposure to gonadotoxic agents, although studies with longer follow-up are required. Currently, there is no indication that secondary sexual characteristics are altered in children exposed to cancer drugs in utero.[163]

CONCLUSION

Caring for patients diagnosed with cancer during pregnancy poses multiple complex medical, ethical, legal, and psychosocial challenges. The inherent difficulty of balancing maternal and fetal well-being is complicated by the increasing number and modalities of treatment options, rarity of this clinical scenario, and lack of substantial data to inform patients about short- and long-term risks for themselves and the progeny. Further research including contributions to national and international registries for maternal and pediatric outcomes from cancer in pregnancy is necessary to expand our knowledge, especially given the high-quality data from randomized clinical trials that are usually impossible in this setting. Ultimately, multidisciplinary care that is patient-centered at each step along the care pathway is paramount to optimize the well-being of the patient and potential progeny, especially in a complex social and medicolegal environment.

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BREAST CANCER

Systemic Therapy in Older Patients With High-Risk Disease

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overview

Adjuvant systemic treatments for older patients with breast cancer require constant dose or schedule adjustments of standards established for younger ones. This is mainly due to frailty that increases according to age (40%-50% of signals in all comers after age 70 years) and remains difficult to spot or diagnose accurately and therefore is often overlooked. Older patients are at higher risk to develop side effects whether under chemotherapy, optimized endocrine treatment, or targeted therapies. Pharmacokinetic reflects poorly functional reserves that reduce with aging and is therefore misleading. The demonstration of significant long-term benefits provided by adjuvant treatments is challenged by life expectancy, driven by multimorbidity status that increases with age, competing with cancer outcome. When geriatric assessment is incorporated into the multidisciplinary team, treatment decision process shows 30%-50% changes, de-escalating initial age-agnostic treatment choices in two of three cases. Finally, expectations from treatment vary over the years: In older ones, although not being exclusive, there is a general shift of preference for protecting functionality, cognitive functions, and independence, as summarized in quality of life that many systemic adjuvant treatment may jeopardize. These provocative considerations show importance to pay more attention to expectations expressed by older patients to limit gaps between what is thought by health care professionals as right, often on the basis of dose intensity models strongly engrained in oncology and that older patients may assess counterintuitively differently. The most achieved molecular testing to identify high-risk luminal tumors should be combined with determinant geriatric factors to bring relevant global information in the adjuvant setting for older patients.

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GENERAL CONTEXT

Management of older patients with breast cancer raises many challenges. Representing the largest segment of the worldwide population, they should be the first target for treatment optimization. Ironically, specific data and guidance are missing from age 65 years, the official cutoff considered by regulators and developers to categorize older populations. New therapeutic strategies are still studied in younger adults, with fewer risks of development failure, ignoring two decades of debates that have stressed repeatedly the imperative need to change the rules of clinical research to match better with the epidemiological transition.[1-3] This emphasizes the artificial nature of many cancer guidelines established in a very controlled and selected younger population and then used improperly by direct extrapolation in older patients, taking poorly into account the competition of cancer with multimorbidity and frailty, all inflating in incidence with aging,[4,5] like through a distorting kaleidoscope. This also reinforces the value of all global efforts as those led by the Société Internationale d'OncoGériatrie (SIOG or the International Society of Geriatric Oncology) to publish updated summaries of the available evidence for the management of breast cancer in older patients,[6] setting recommendations according to the level of frailty.

In this context, the use of systemic treatments for localized breast cancer epitomizes one of the most relevant challenges faced by clinicians when treating older patients. These therapies are often associated with a narrow therapeutic ratio, as, for chemotherapy, the benefit of which may be undermined by a bad appraisal of frailty, potentially present in up to 40%-50% of all comers age 65-70 years and older, presenting with metastatic or early-stage breast cancer.[7,8] Most of these adjuvant treatments need a long follow-up to be able to observe an impact on disease relapse or survival, which may happen at a time point later than the estimated life expectancy of the individual. Discussion with a patient on such secondary prevention requires specific semantic skills and wording to make concrete and understandable the uncertainty of the benefit sought with adjuvant therapies as the difference between relative and absolute benefits easy to confuse for a lay audience. Finally, physicians and medical teams have to adapt to the changing perceptions of benefit and expectations with aging. Indeed, although this is not age-exclusive, younger patients often focus more on quantity of time because of social and family obligations. Older ones, marked by time flow and life experiences, are more in search for feeling safe, for maintaining control,

PRACTICAL APPLICATIONS

- Selecting appropriate systemic adjuvant treatment in older patients with breast cancer requires both assessing the risk of the disease and screening for frailty, with more in-depth geriatric assessment if screening is positive, to adjust regimens and schedules accordingly.
- Standards established in younger patients cannot be extrapolated easily to the treatment of older ones, especially regarding dose density, regimens with length exceeding 3 months, and the neoadjuvant approach opening to the postneoadjuvant rescue treatment strategy. Indeed, these three concepts fit in the dose intensity or dose-escalation concepts but may apply poorly to older ones.
- Although not age-exclusive, expectations from older patients differ from those expressed by younger ones. Older ones, marked by time flow and life experiences, are more in search for feeling safe, for maintaining control, independence, and cognitive functions, concepts that are very closely related to quality of life, to stay considered as a human being with a meaningful life.
- Older patients have been left behind from the development of the most achieved modern prognostic models using gene expression profiles for luminal breast cancer. As long as these age-agnostic molecular tests will not factor in essential information brought by geriatric assessment, especially competing risks for prognosis, their application to the most affected and growing population, patients who are 65 years and older, will remain very theoretical.

independence, and cognitive functions, concepts that are very closely related to quality of life, to stay considered as a human being with a meaningful life.[9,10] These essential individual aspects are best assessed through an extensive geriatric assessment evaluating the levels of frailty, intrinsic capacity, and resilience,[11] contributing to personalized medicine in older patients as much as the molecular portrait of any tumor sought in modern oncology to guide treatment.

DOSE INTENSITY AND FREQUENT NEED FOR ADJUSTMENT OF SYSTEMIC TREATMENTS

In older patients presenting with various tumors, including breast cancer, published data constantly show the frequent dose or schedule adjustments needed for cytotoxic agents, compared with official labels or standard schedules.[6,12,13] This is not limited to chemotherapy, and concerns optimized endocrine treatment[7,14] and targeted therapies.[15-17] This may seem in opposition to the historical concept of dose intensity described by Skipper,[18] overlapping with the maximum tolerated dose still broadly used for the development of new strategies, very anchored in the world of oncology where breast cancer has often served as an application model.[19,20]

For example, dose density is an important factor of success for adjuvant chemotherapy for early-stage breast cancer, irrespective of tumor phenotype, although the absolute effect is higher for endocrine-resistant disease than for luminal tumors. However, this may not easily apply to older people, given the increased risk of toxicity with such a schedule and the insufficient specific efficacy data, especially when translating into an almost provocative counterproductive effect after age 70 years according to subset analyses.[20]

This is also strongly and indirectly supported by the frequent (30%-40%) practical modification of the initial treatment plan created by the multidisciplinary team, as soon as some form of geriatric assessment is implemented into the treatment decision-making process, with then de-escalation occurring more often (two of three cases) than escalation.[21] Moreover, compared with standard schedules used in younger ones, this decrease in the intensity of systemic treatments in older ones, with a more frequent lower dose used up-front, apparently does not decrease treatment efficacy across different tumors, as shown in the Geriatric Assessment for Patients 70 years and older (GAP70+) cluster randomized study[22] or in other phase III trials.[23-25]

Data that are more recent and derived from the Hurria Older PatiEnts with Breast Cancer (HOPE) program tend to rebut this general consideration, especially for early-stage breast cancer, with inferior survival outcome when receiving relative dose intensity lower than 85% for adjuvant chemotherapy after age 65 years.[26] However, this may result merely from the well-known selection biases and lack of control found in prospective cohorts, missing the underlying creeping frailty that increases with age.

Another argument favoring a cautious approach of the concept of dose intensity in older ones is that pharmacokinetics poorly mirror functional reserves, failing to correlate with toxicity under similar physiological conditions. For instance, docetaxel pharmacokinetics show unaltered values in older patients with controlled renal and liver functions compared with younger ones while hematological toxicity is more frequent after age 65 years.[27] Indeed, pharmacokinetics cannot capture the decline of functional reserves, especially when they are collected along the first cycles of treatment, when the cumulative toxicity of chemotherapy on bone marrow has not yet reached its full impact, before being unveiled in later cycles. This may explain the crucial influence of the length of adjuvant chemotherapy for breast cancer on

the occurrence of serious side effects after age 65 years, holding the highest detrimental weight in the algorithm developed by the Cancer and Aging Research Group (CARG), CARG breast cancer (CARG-BC), with a 3-month threshold.[28]

Together with the retrospective works led on adjuvant trials for breast cancer run by the Cancer and Leukemia Group B (CALGB, now Alliance), these data should be a strong message of caution regarding the extrapolation of context of the benefits found in younger ones to older ones. They should remind all oncologists that, although chemotherapy may theoretically be active in older patients as in younger ones, it also brings more frequent and intense side effects.[29] If these occur, they may jeopardize all benefits sought with intervention, with no return to previous functional status and great cost on quality of life or even reaching rates of life-threatening events that would certainly be considered unacceptable in younger ones.

Practically, the more an adjuvant treatment may cause serious side effects, the more a significant and meaningful absolute benefit is necessary to envisage its use in older ones and the more a cautious adjustment of schedule, dose, and/or indication is needed on the basis of the level of frailty assessed. Algorithms, such as the Chemotherapy Risk Assessment Scale for High-age patients score[30] and the CARG general[31] or CARG-BC–specific[28] scores, may help estimate the risks of side effects of grade 3 and higher grade under chemotherapy. They may guide tailoring treatment intensity accordingly, as advocated by SIOG.[6] However, the reproducibility of these scores seems highly country-dependent, suggesting external factors,[32,33] so that they represent more a proof of concept of the role of factoring in the level of frailty in any treatment decision-making process for older ones than universal practical tools. They also highlight the challenges to implement in clinical practice frailty assessment and its two complementary concepts: intrinsic capacity and resilience.[11]

ADJUVANT SYSTEMIC TREATMENT AND HIGH-RISK DISEASE

Adjuvant systemic treatments for breast cancer vary greatly according to the tumor phenotype, which drives a large part of both the choice and the potential benefit of secondary prevention. From 0.5 to 1 cm tumor size, the two smaller categories, triple-negative breast cancer (TNBC, 10%) or tumors overexpressing the oncogene (HER2+; 10%), are generally considered at risk high enough, with most relapses occurring early (within 5 years) to sway the decision for adjuvant chemotherapy in older patients.[6,16,34] However, this general principle overlooks often the capital question of which chemotherapy should then be used in older ones.

Indeed, chemotherapy regimens most commonly used in younger adults, combining the two most important cytotoxic classes for breast cancer, anthracyclines and taxanes, have been poorly studied in older ones. The numbers of patients age 65 years and older enrolled in the clinical trials included in the successive meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group from Oxford are limited and very illustrative of the issue. They reach at best 10% of populations studied, and this worsens sharply with older age (<2% after age 70 years),[35,36] questioning the universal properties, said not differing with age, of the proportional advantages on recurrences brought by combinations of anthracyclines and taxanes. The general conclusions, valid in younger ones, minimize the length of such chemotherapy regimens in older ones, especially sequential schedules that can spread over 6-8 months[35] when a 3-month threshold has been identified as a key factor for the occurrence of serious side effects in the adjuvant setting after age 65 years.[28] In addition, the concurrent addition of anthracyclines to taxanes (eg, doxorubicin + docetaxel or doxorubicin + docetaxel + cyclophosphamide regimens), that gives the clearest reductions in recurrence compared with sequential administration (eg, three cycles of epirubicin + cyclophosphamide, followed by three cycles of docetaxel every 3 weeks),[36] is also at very high risk of toxicity, including life-threatening ones,[37] to be recommended in older ones, even with systematic granulocyte colony-stimulating factor as primary prophylaxis for febrile neutropenia.

Although there are no specific prospective data demonstrating that one should not consider anthracyclines and taxanes combinations in older patients, there are none available and adequately powered supporting their use in this population, except in a few limited and poorly defined subgroups, not representative of the standard old population. On the other hand, requiring longer period of treatment to be delivered, regimens combining anthracyclines and taxanes increase significantly the risks of side effects and of the exhaustion of functional reserves, leading to decompensation of the underlying, frequent (about 50%), and unknown frailty. This should make oncologists think carefully before embarking their older patients on such treatment.

Actually, the largest amount of data in the literature for adjuvant chemotherapy in older ones refer to the regimens of shorter duration than those used in younger ones, as four cycles of either docetaxel or doxorubicin combined with cyclophosphamide (docetaxel + cyclophosphamide and doxorubicin + cyclophosphamide, respectively).[6,38] Paclitaxel given once per week for 12 weeks is also listed in the regimens available by extrapolation of its use for HER2+ disease[6,16,39] (Table 1). One should avoid modified or subjectively attractive regimens, such as oral chemotherapy with capecitabine or docetaxel once per week 3 weeks out of 4, as demonstrated by the CALGB 49907

(Alliance) and ELderly Docetaxel Adjuvant trials, respectively.[40,41]

For HER2+ disease, the rule to combine 1 year of trastuzumab with chemotherapy, sequentially if using anthracyclines, prevails. However, in older ones, shorter (6 months) trastuzumab schedules,[16,42] regimens limiting cardiac toxicity,[16,43] or chemotherapy-free strategy[44] might be warranted, especially in vulnerable patients.[6,16] A successful attempt conducted in the metastatic setting to use a chemotherapy backbone with side effects milder than taxanes[15] suggests that metronomic cyclophosphamide could be an alternative for earlier stages.[6,16] Finally, the limited absolute benefit provided by the adjuvant use of the second anti-HER2 antibody pertuzumab in addition to trastuzumab must be weighed against the increased risk of diarrhea, being suitable only for fit and high-risk individuals.[6,16]

For TNBC, poly chemotherapy backbones with platinum salts have never been adequately studied in older patients. Combining further such backbone given dose dense with pembrolizumab, the KEYNOTE-522 regimen[45] shows a challenging safety profile, especially in real-life series.[46] Never studied appropriately in older ones, it is hard to believe it would be compatible with a rate of 50% of frailty present in all comers after age 70 years.[7,8] This clearly indicates the continuation of age discrimination with modern strategies, such as immunotherapy, while abbreviated and more tolerable regimens could be developed but do not fit well the escalation model used for new strategies development.

Of note, when choosing a neoadjuvant strategy and observing residual disease at surgery, the postneoadjuvant concept has raised a lot of interest making almost standard the neoadjuvant approach for HER2+ tumors and TNBC with a tumor size of 15-20 mm. However, very few old individuals were enrolled in the CREATE-X and KATHERINE trials, using capecitabine or trastuzumab emtansine as rescue treatments.[47,48] It calls for a cautious application of this fully developed neoadjuvant approach (ie, including postneoadjuvant strategy) that should be reserved mostly for fit older ones because of the risk of side effects under chemotherapy increasing with age. Indeed, older patients may reach surgery in worse conditions, mitigating the beneficial effects of the neoadjuvant approach, especially if the breast cancer is already operable. Adding presurgery and potential extended postsurgery chemotherapy, neoadjuvant strategy also increases the total length of treatment of localized breast cancer and, in doing so, toxicity. This advocates strongly for not embracing the increasing use of such strategy in older ones as much as in younger ones, once the disease has been categorized as TNBC or HER2+.

The most important challenge is certainly the choice of adjuvant systemic treatment for the largest group of older patients with breast cancer, those with luminal disease (80%), because of the delay of occurrence of relapse colliding with life expectancy that is strongly associated with frailty. Multimorbidity status competes with breast cancer for prognosis so that the presence of one or more significant comorbidities makes the latter the first cause of death,[49] requiring thorough hierarchy in treatment choices.

In these patients, the benefit of chemotherapy added to endocrine treatment remains a conundrum, diluting with time[40] and not really solved by refined selections on the basis of gene expression profiles. Most programs that have investigated genomic tools have not considered the older population or only in very limited subcategories contrasting blatantly with their real proportion in the disease presentation. The iconic noninferiority trials, Trial Assigning Individualized Options for Treatment (TAILORx)[50] and Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER),[51] have accrued hardly 10% of patients older than age 65 years while the trial Microarray In Node-negative (or 1-3 positive lymph node) Disease may Avoid ChemoTherapy (MINDACT) excluded those who are older than 70 years,[52] precluding any rational conclusion for the population most affected. In case of a high-risk recurrence score, adherence to chemotherapy may differ according to age. In TAILORx, of patients with a recurrence score above 25, only 5% were age 70 years and older. Some declined chemotherapy, and unfortunately, no follow-up will be available for valid interpretation.[53] Even the program Adjuvant Systemic Treatment for ER+ HER2– BC in women older than 70 years (ASTER 70s), the largest, inclusive, phase III superiority trial, presented at ASCO last year and conducted in nearly 2,000 women age specifically 70 years and older, failed to demonstrate a meaningful and significant benefit from chemotherapy added to endocrine treatment, when selecting patients at risk with the tumor genomic grade index.[8] These results holding true for any prespecified subgroup analysis including nodal (pN) status, they question the notion of treatment acceptability and the magnitude of potential benefit sought with such preventive treatments, such as chemotherapy or endocrine treatment. For instance, the literature on the minimum 3%-5% of absolute benefit supporting the use of adjuvant chemotherapy dates back to the early 2000s but included a very small number of patients older than 65 years,[54-56] questioning the reliability of such rates in the current epidemiological aging transition. The magnitude of benefit sought by older patients should be revisited, especially when the presence of dependants, an important factor influencing cares in older ones, was determinant for treatment choice in these works.[56]

So far, endocrine adjuvant treatment for 5 years should remain the mainstay of systemic adjuvant treatment in the older population with luminal breast cancer, irrespective of all other prognostic factors, with increasing interest for all new optimizing strategies as extended schedules and the use of inhibitors of cyclin D dependent kinases (CDK4/6i), especially

TABLE 1. Standards and Options for Adjuvant Systemic Treatment in Older Adults

Phenotype	Adjuvant Systemic Strategy
Triple-negative breast cancer	Chemotherapy is standard (from pT > 0.5 to 1 cm)
	Approved regimens
	Four TC once every 3 weeks + primary prophylaxis of neutropenia with G-CSF
	Four AC once every 3 weeks + primary prophylaxis of neutropenia with G-CSF
	Options
	Paclitaxel once per week × 12
	Neoadjuvant strategy (with or without postneoadjuvant capecitabine × six to eight cycles) in fit patients
	No supporting data
	Dose-dense regimens
	Chemotherapy regimens with sequential or concurrent use of anthracyclines and taxanes
	Poly chemotherapy regimens including platinum salts
	KEYNOTE-522 regimen (paclitaxel once per week × 12 + carboplatin, dose-dense AC, pembrolizumab)
HER2+ breast cancer	Chemotherapy is standard with 1-year trastuzumab (from pT > 0.5 to 1 cm), with endocrine treatment for 5 years if ER+ disease
	Approved chemotherapy regimens
	Four TC once every 3 weeks + primary prophylaxis of neutropenia with G-CSF + trastuzumab 1 year
	Paclitaxel once per week × 12 + trastuzumab 1 year
	Options
	Shorter duration (6 months) for trastuzumab
	Neoadjuvant strategy (with or without post neoadjuvant T-DM1 × 14 once every 3 weeks) in fit patients
	Trastuzumab without chemotherapy (especially if ER+ disease and frailty present)
	No supporting data
	Dose-dense regimens
	Chemotherapy regimens with sequential or concurrent use of anthracyclines and taxanes
Luminal breast cancer	Endocrine treatment alone for 5 years is standard
	Options
	Short (3-month) chemotherapy regimens once every 3 weeks (four TC, four AC + primary prophylaxis of neutropenia with G-CSF, or paclitaxel once per week × 12 in case of high-risk disease although poor evidence and guidance provided by gene expression profiles
	No supporting data
	Dose-dense chemotherapy
	Chemotherapy regimens with sequential or concurrent use of anthracyclines and taxanes

Abbreviations: AC, doxorubicin + cyclophosphamide; ER+, estrogen receptor–positive; G-CSF, granulocyte colony-stimulating factor; HER2+, HER2 3+ by immunohistochemistry and/or amplified by fluorescent in situ hybridization; pT, tumour size; TC, docetaxel + cyclophosphamide; T-DM1, trastuzumab emtansine.

as a substitute to chemotherapy (eg, EORTC 1745/EudraCT 2018-002553-30). Chemotherapy should stay in the list of options for high-risk situations, after geriatric assessment and an open discussion on the uncertainty and magnitude of absolute benefits, and side effects. Of note, this could also challenge the choice between a 3-month adjuvant chemotherapy with concentrated side effects and a 5-year adjuvant endocrine treatment with prolonged constraints. This would mirror the question of exclusive short adjuvant local radiotherapy (without endocrine treatment) versus exclusive

prolonged endocrine treatment (without radiotherapy), as investigated in the EUROPA trial, after breast conserving surgery for small and good prognosis tumors.[57]

FINAL CONSIDERATIONS

In clinical trials, there may be a large discrepancy of considerations on what matters the most between trialists and patients. When considering retrospectively the outcomes measured in a selection of published trials, patients and health professionals reached agreement on the primary end point in less than one third of the cases, questioning the relevance of the choice made by trialists to build the study design.[58] Furthermore, older patients may assess counterintuitively what health care professionals think as appropriate or justified. In the Age Gap Decision Tool cluster randomized program, the use of decision aids for supporting the choice of adjuvant chemotherapy or surgery had the reverse effect, almost halving the uptake of adjuvant chemotherapy or doubling the choices for primary endocrine treatment (*v* surgery).[59]

Given the high frequency of potential frailty in all comers with breast cancer after age 70 years (40% in ASTER 70s[8]), any modern optimized strategy for the adjuvant treatment of breast cancer should not solely rely on molecular prognosticators, regardless of promises. They should also factor in specific essential geriatric items, similar to what the PORTRET algorithm (from the prediction of outcome, risk of toxicity, and quality of life in older patients treated for breast cancer [the PORTRET] study) has shown feasible, mixing standard histopathological variables and others derived from the geriatric assessment, outperforming the English tool, Predict Breast Cancer.[60] Oncologists must learn reconciling the best information obtained from the tumor biology and from the patient in joined models to improve the discriminant power of these innovative tools adjusted to the growing and most affected aging population to reach the best medical decision and bring significant changes in attitudes.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Early-Stage Triple-Negative Breast Cancer Journey: Beginning, End, and Everything in Between

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Overview

Triple-negative breast cancer (TNBC) is a very heterogeneous and aggressive breast cancer subtype with a high risk of mortality, even if diagnosed early. The mainstay of early-stage breast cancer includes systemic chemotherapy and surgery, with or without radiation therapy. More recently, immunotherapy is approved to treat TNBC, but managing immune-rated adverse events while balancing efficacy is a challenge. The purpose of this review is to highlight the current treatment recommendations for early-stage TNBC and the management of immunotherapy toxicities.

INTRODUCTION

Triple-negative breast cancer (TNBC) accounts for approximately 10%-15% of breast cancer diagnoses and is defined by the absence of expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2).[1] The prevalence of TNBC is higher in *BRCA 1* mutation carriers, young women (50 years and younger), and African American women.[2-4] TNBC, including early-stage TNBC, remains the most challenging breast cancer subtype to treat given limited targeted therapies, resulting in relatively higher rates of relapse and greater risk of mortality.[5] The goal of upfront use of systemic therapy in nonmetastatic TNBC is to reduce the risk of distant recurrence and death. This review will highlight current practices in both the neoadjuvant and adjuvant settings to treat TNBC.

THE ROLE OF NEOADJUVANT THERAPY

Previously, preoperative and postoperative chemotherapies were established as equivalent in efficacy per the National Surgical Adjuvant Breast and Bowel Project Protocols (NSABP) B-18 and B-27.[6] Historically, the primary advantage of neoadjuvant chemotherapy (NAC) was the improvement of surgical outcomes by downstaging cancer in the breast and axillary lymph nodes. However, there is now a near-unanimous consensus for NAC as the preferred approach to treat stage II or III TNBC per the ASCO and St Gallen International Consensus Guidelines.[7,8] A complete pathologic response means to have no invasive residual disease in the breast or the lymph nodes after completing neoadjuvant therapy (ypT0 ypN0 or ypT0/is ypN0). The achievement of a pathologic complete response (pCR) after NAC is recognized as a marker for systemic therapy sensitivity. In addition, pCR is associated with improved long-term outcomes in TNBCs, both event-free survival (EFS) and overall survival (OS; EFS: hazard ratio [HR], 0.24; 95% CI, 0.18 to 0.33; OS: HR, 0.16; 95% CI, 0.11 to 0.25).[9-11] More recently, the degree of response has been evaluated and is called the residual cancer burden (RCB). RCB scores of RCB-0 (pCR) and RCB-1 (minimum residual disease) denote more favorable outcomes. RCB scores of RCB-2 and RCB-3 (extensive residual disease) are unfavorable scores, indicating a higher risk of recurrence.[12,13] Therefore, identifying and administrating effective preoperative chemotherapy may help improve TNBC outcomes as patients who do not achieve a pCR after neoadjuvant therapy might have the opportunity to receive additional adjuvant therapies to reduce the risk of recurrence.

NAC REGIMENS: WHERE DO WE STAND?

Intensity and Frequency of Chemotherapy Influence Response

Anthracycline- and taxane-based therapies remain the most active chemotherapeutic agents to treat TNBCs. The intensity and frequency of these regimens also influence responses. For example, every 2-week or dose-dense doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV reduced the risk of recurrence and death compared with conventional every 3-week dosing of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC).[14] In addition, the ECOG 1199 study demonstrated that once weekly paclitaxel 80 mg/m^2 improved disease-free survival (DFS; HR, 0.69; $P = .001$) and OS (HR, 0.69; $P = .019$) compared with

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PRACTICAL APPLICATIONS

- Triple-negative breast cancer (TNBC) remains the most challenging breast cancer subtype to treat because of its aggressive phenotype and limited treatment options.
- Neoadjuvant chemotherapy is the preferred approach to treat stage II or III TNBC.
- The addition of pembrolizumab to taxane-platinum–based chemotherapy followed by an anthracycline significantly increased pathologic complete response (pCR) rates and improved event-free survival in early-stage high-risk TNBC.
- Administering effective preoperative chemotherapy may help to improve TNBC outcomes as patients who do not achieve a pCR after neoadjuvant therapy might have the opportunity to tailor adjuvant therapies to reduce the risk of recurrence.
- Severe immune-related adverse events are rare but can be life-threatening. Recognizing and managing the side effects early may prevent death.

once every 3-weeks paclitaxel 175 mg/m^2 administration.[15] The current standard of care includes weekly paclitaxel or dose-dense paclitaxel as both have manageable side effect profiles and similar DFS and OS.

The Function of Platinum-Based Therapies in NAC

The addition of a platinum-based chemotherapy, such as carboplatin, to NAC regimens for TNBC has been studied in several randomized trials. Adding carboplatin to the paclitaxel- and anthracycline-based regimen increased the pCR rates in patients with TNBC.[16-18] GeparSixto was a randomized phase II study evaluating neoadjuvant carboplatin in patients with stage II or III TNBC and HER2-positive breast cancer. All participants received 18 weeks of chemotherapy with paclitaxel 80 mg/m^2 IV once weekly and non-pegylated liposomal doxorubicin 20 mg/m^2 IV once weekly. Patients with TNBC received simultaneous bevacizumab 15 mg/kg IV once every 3 weeks. Patients were randomly assigned to carboplatin AUC 1.5-2 mg/mL per min intravenously weekly (n = 296) versus no carboplatin (n = 299). The pCR rate was 53.2% with carboplatin versus 36.9% without carboplatin (P = .005) in patients with TNBC.[18] Notably, patients in GeparSixto who received carboplatin in addition to paclitaxel and nonpegylated liposomal doxorubicin had a significantly better 3-year DFS (HR, 0.56; 95% CI, 0.34 to 0.93; P = .024) and distant disease-free survival (DDFS; HR, 0.50; 95% CI, 0.29 to 0.86; P = .013).[19] Similarly, the BrighTNess trial, a phase III randomized study, evaluated the addition of the poly (ADP-ribose) polymerase (PARP) inhibitor veliparib (50 mg orally, twice daily) plus carboplatin AUC 6mg/mL/min IV once every 3 weeks for four cycles and paclitaxel 80 mg/m^2 intravenously once weekly for 12 doses (n = 316) versus carboplatin AUC 6mg/mL/min once every 3 weeks and paclitaxel 80 mg/m^2 once per week alone (n = 160) versus paclitaxel 80 mg/m^2 once weekly alone (n = 158) followed by AC every 2-3 weeks for four cycles for neoadjuvant treatment in stage II and III TNBC.[16] At the median follow-up of 4.5 years, the HR for the EFS was 0.63 (95% CI, 0.43 to 0.92; P = .02) for carboplatin plus veliparib with paclitaxel versus paclitaxel but 1.12 (95% CI, 0.72 to 1.72; P = .62) for carboplatin plus veliparib with paclitaxel versus carboplatin with paclitaxel.[20] The pCR rate increased in the carboplatin, paclitaxel, and veliparib group compared with the paclitaxel-alone group (168 [53%] of 316 patients *v* 49 [31%] of 158, P = .0001). There was no difference in the pCR rates between the two platinum therapy arms, demonstrating that the carboplatin improved the pCR and that veliparib did not contribute to the survival benefit. By contrast, the phase II CALGB40603 (Alliance) trial evaluated neoadjuvant carboplatin AUC 6 IV once every 3 weeks or bevacizumab 10 mg/kg once every 2 weeks added to once per week paclitaxel 80 mg/m^2 for 12 weeks followed by ddAC for four doses in patients with high-risk early-stage breast cancer.[17,21] One third of the patients were genomically identified as basal-like subtypes. This subtype had higher pCR rates when bevacizumab or carboplatin (54% *v* 41%, P = .0029; 60% *v* 44%, P = .0018) was added to standard NAC. In CALGB40603, pCR was associated with improved long-term outcomes when compared with minimum residual disease. However, CALGB40603 was not powered to assess the impact of carboplatin or bevacizumab on EFS or OS.[21] In both the GeparSixto and BrighTNess trials, patients without germline *BRCA1* and *BRCA2* mutations benefited more from the addition of carboplatin and those with germline *BRCA1* and *2* mutations showed superior response rates in both groups without much additive benefit from carboplatin.[16,22] In addition, the I-SPY Network reported increased pCR rates in the NAC investigational arm of veliparib 50 mg table by mouth twice a day plus carboplatin AUC 6 IV on weeks 1, 4, 7, and 10 followed by AC for four cycles compared with the control of paclitaxel 80 mg/m^2 IV once weekly followed by AC for four cycles in early stage HER2– breast cancers measuring at least 2.5 cm undergoing NAC of 51% versus 26% but increased toxicities in the investigational arm.[23] The most pivotal single-center, randomized phase III study conducted on the use of carboplatin was at Tata Memorial Hospital in Mumbai, India. Approximately 720 patients diagnosed with early-stage TNBC were evaluated. Patients were stratified by menopausal status. In the study, the addition of platinum-

based therapy with carboplatin AUC 2 once weekly and paclitaxel 100 mg/m^2 once per week for 8 weeks followed by four cycles of AC neoadjuvantly increased the pCR by 18.5% ($P < .001$), improved the EFS by 12.5% ($P = .004$), and had a higher OS rate of 11.2% ($P = .003$) in younger premenopausal women (50 years and younger).[24] There was no statistically significant improvement in pCR, EFS, or OS in women older than 50 years. The exact rationale for the significant interaction between age/menopausal status and carboplatin administration remains unclear. To date, to our knowledge, this is the only phase III study powered for EFS and OS that used platinum-based therapies in the NAC setting to treat TNBC. In summary, these studies demonstrated that the addition of carboplatin in NAC increased pCR rates in high-risk early-stage TNBCs and should be considered the standard of care in stage II or III high-risk early-stage TNBC (Fig 1). These data are encouraging for patients who may not be eligible for immune checkpoint inhibitors (ICPis) or have limited access to checkpoint inhibitors as platinum-based regimens in the NAC setting have demonstrated robust responses and improved survival. In general, weekly carboplatin administration may aid in adherence and minimize toxicities when compared with every 3-week carboplatin regimens. However, carboplatin does add additional side effects when combined with other chemotherapies such as myelosuppression, peripheral neuropathy, nausea, fatigue, alopecia, mucositis, nephrotoxicity, ototoxicity, infusion reactions, and electrolyte imbalance; therefore, personalizing therapy to account for comorbidities and functional status is important.

Chemoimmunotherapy Is the Standard of Care in Stage II and III TNBC

A new standard of care for high-risk early-stage TNBC was established with the US Food and Drug Administration (FDA) approval of pembrolizumab along with chemotherapy for high-risk early-stage TNBC in 2021.[25] Initially, the open-label, adaptively randomized, phase II I-SPY2 trial demonstrated that adding pembrolizumab to taxane-based chemotherapy followed by four cycles of AC significantly improved the pCR rate in TNBC (60% in the chemoimmunotherapy [CIT] arm *v* 22% in the chemotherapy arm, respectively).[26] In the phase III randomized KEYNOTE-522 trial, patients with previously untreated clinical or radiologic stage II or III (T1c N1-2 or T2-4 N1-3) TNBCs were randomly assigned 2:1 to receive neoadjuvant chemotherapy (NAC) with pembrolizumab versus placebo along with paclitaxel and carboplatin followed by anthracycline-based chemotherapy. After surgery, the patients received adjuvant pembrolizumab or placebo for up to nine cycles. Adjuvant capecitabine was not allowed. The addition of pembrolizumab to chemotherapy was associated with a significantly higher rates of pCR (64.8% in the CIT arm versus 51.2% in the chemotherapy-only arm).[27] In a subsequent interim analysis, CIT was associated with a significant improvement in EFS. The estimated EFS at 36 months was 84.5% in the CIT arm versus 76.8% in the chemotherapy-only arm (HR for an event or death was 0.63; 95% CI, 0.48 to 0.82; $P < .001$).[28] Interestingly, patients who achieved pCR in both arms had improved 3-year EFS rates at 94.4% with pembrolizumab and 92.5% with placebo (1.9% gain; HR, 0.73; 95% CI, 0.39 to 1.36). Conversely, the 3-year EFS rates for non-pCR patients were dismal in both arms, which were 67.4% with pembrolizumab and 56.8% with placebo (10.6% improvement; HR, 0.70; 95% CI, 0.52 to 0.95). Furthermore, the addition of pembrolizumab to chemotherapy shifted more tumors to lower RCB scores of 0 or 1, conferring a better prognosis. Tumors with RCB scores of 2 or III had worse outcomes in both groups, which may be an even more specific prognostic indicator than pCR versus non-pCR.[29] The RCB scoring system continues to be analyzed in clinical trials but is not used currently in clinical practices.

Although pembrolizumab is the only approved checkpoint inhibitor for the treatment of early-stage TNBC, several other checkpoint inhibitors, such as durvalumab,[30] cemiplimab,[31] and atezolizumab,[32] have been studied in combination with anthracycline-based NAC and showed similar promising results. In the phase III IMpassion031 study, the addition of atezolizumab 840 mg IV once every 2 weeks to nab-paclitaxel 125 mg/m^2 once per week for 12 weeks followed by ddAC for 8 weeks increased pCR rates to 58% in the CIT arm versus 41% in the chemotherapy-alone arm (rate difference 17%, 95% CI, 6 to 27, one-sided $P = .0044$).[32] In both the KEYNOTE 522 and IMpassion031 trials, both PD-L1–positive and PD-L1–negative patients had improvements in the pCR with the addition of checkpoint inhibitors to chemotherapy. The EFS data from Impassion031 are pending.[32] Despite a nonsignificant increase in the pCR rate in the phase II GeparNuevo trial, the addition of durvalumab to NAC was associated with a significant improvement in the 3-year invasive disease-free survival (iDFS), DDFS, and OS.[30] One critical factor among the studies is that the KEYNOTE-522 trial used carboplatin as part of the regimen, whereas IMpassion031 and GeparNuevo did not, which raised the question of whether carboplatins can be spared in some patients. In addition, pembrolizumab was also used postoperatively in KEYNOTE-522 but not in GeparNeuvo or the I-SPY network arms. These differences may contribute to the outcomes observed among the trials.

De-Escalation of Anthracycline-Based Therapies

Recently, there have been attempts to evaluate the nonanthracycline-based CIT regimens.

The NeoTRIP trial combined atezolizumab, carboplatin, and nab-paclitaxel and did not observe an improvement in the pCR rate in the CIT arm compared with the chemotherapy-only arm. EFS data are pending.[33] However, the single-arm,

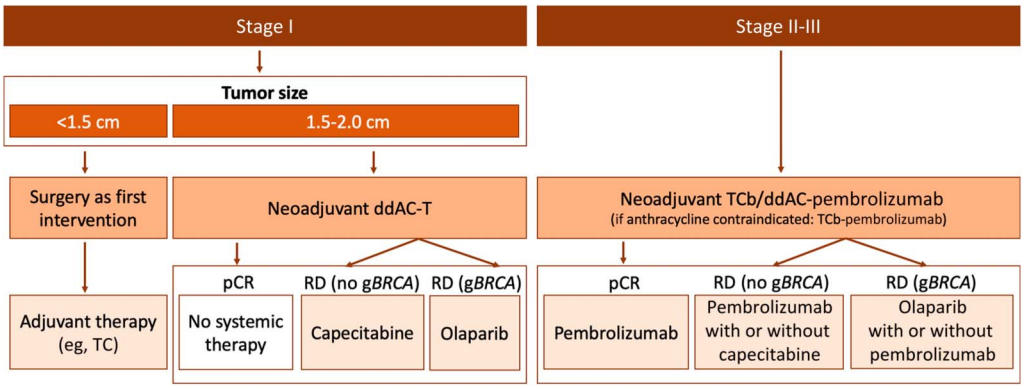

FIG 1. Treatment algorithm for early-stage triple-negative breast cancer. ddAC-T, dose-dense doxorubicin and cyclophosphamide followed by paclitaxel; g*BRCA*, germline *BRCA* mutation; pCR, pathologic complete response; RD, residual disease; TC, docetaxel and cyclophosphamide; TCb, paclitaxel and carboplatin.

multicenter, phase II NeoPACT study used a non-anthracycline-based CIT regimen including carboplatin AUC 6 IV, docetaxel 75 mg/m^2 IV, and pembrolizumab 200 mg IV in combination once every 21 days for six cycles. In this study, Sharma et. al[34] reported a pCR rate of 60% and a 2-year EFS of 88%, comparable to KEYNOTE-522. Although in an earlier stage of development, the combination of cemiplimab (a checkpoint inhibitor) with or without REGN 3767 (a lymphocyte-activation gene-3 inhibitor) along with paclitaxel followed by AC achieved a pCR rate of 53% in cemiplimab alone and 67% in cemiplimab/REGN 3767 compared with 29% in the standard AC-T chemotherapy-alone control arm without the use of adjuvant checkpoint inhibitors in the I-SPY network. In addition, RCB classes of 0 or 1 increased in the immune therapy arms compared with the nonimmune therapy control arm.[31,35] Neoadjuvant CIT is the standard of care for stage II or III TNBC. As the treatment paradigm for NAC continues to evolve for these early-stage high-risk TNBCs, escalation and de-escalation models will be important to tailor treatments for each individual. For the patients with stage I TNBC (T1a and T1b), taxane-based chemotherapy regimens, such as docetaxel and cyclophosphamide, remain the standard of care as those patients were not included in KEYNOTE 522 (Fig 1) and these small tumors often have a better prognosis.[36]

TAILORING POSTNEOADJUVANT THERAPY IN TNBC

NAC is indeed a standard option for most patients with early-stage TNBC as it allows for tailoring of adjuvant treatment under the premise that patients with residual breast cancer are at higher risk of cancer recurrence.[9] Historically, standard-of-care therapy without pCR was limited to observation until recent trials demonstrated a clinical benefit of adding adjuvant therapy in these cases. Initially, the benefit of this treatment approach was epitomized by the results of the CREATE-X trial as adjuvant treatment with capecitabine (1,250 mg/m^2 PO twice a day days 1-14, 6-8 cycles) improved OS of patients with TNBC and residual invasive disease after NAC when compared with observation (HR, 0.52; 95% CI, 0.39 to 0.90).[37] The ECOG-ACRIN EA1131 phase III trial attempted to challenge the role of adjuvant capecitabine against treatment with platinum agents (cisplatin or carboplatin) administered intravenously once every 3 weeks for four cycles.[38] The underlying hypothesis for this trial was that patients with residual basal-like TNBC (PAM50) could have improved iDFS when treated with platinums. The study was prematurely discontinued after an interim analysis observed that platinum agents were unlikely to show noninferiority or superiority to the standard capecitabine. The 3-year iDFS with basal subtype TNBC was 42% (95% CI, 30 to 53) versus 49% (95% CI, 39 to 59) with a HR of 1.06 for patients treated with platinum versus capecitabine, respectively. The overall substantially poor outcomes in this trial were likely a reflection of the underlying aggressive nature of basal-like TNBCs and higher-risk patients enrolled (at least 1 cm residual disease). For patient diagnosed with early-stage TNBC with residual disease, adjuvant capecitabine is highly recommended.

The Use of PARP Inhibitors in Early-Stage TNBC

PARP inhibitors such as talazoparib (ClinicalTrials.gov identifier: NCT03499353),[39] olaparib (GeparOla/ClinicalTrials.gov identifier: NCT02789332),[40] and veliparib (ClinicalTrials.gov identifier: NCT02032277; PMID: 29501363)[16] have been studied in the neoadjuvant setting.[39,41] Although these agents demonstrated activity in the neoadjuvant setting, none of these agents are currently used in phase III studies. Recently, the OlympiA trial further consolidated the benefit of tailored adjuvant therapy with the PARP inhibitor olaparib 300 mg twice a day for 1 year in patients with high-risk HER2-negative breast cancer and germline *BRCA 1* or *2* mutations.[42] Approximately 50% of patients received neoadjuvant therapy. Patients who did not achieve a pCR were eligible. Most tumors were classified as TNBC (82%). After a median follow-up of 2.5 years, the 3-year DDFS was 87.5% in the olaparib group and 80.4% in the placebo group (7.1% difference: 95% CI, 3.0 to 11.1). The HR for distant disease or death was 0.57 (99.5% CI, 0.39 to 0.83; $P < .001$).[43] On a second interim analysis for OS, olaparib significantly

improved outcomes compared with the placebo group (HR, 0.68; 98.5% CI, 0.47 to 0.97; $P = .009$).[43] In March 2022, olaparib was approved by the FDA for the adjuvant treatment of germline *BRCA 1* or 2 mutation carriers with high-risk HER2-negative BC who have been treated with neoadjuvant and/or adjuvant chemotherapy.

Careful review of the results from KEYNOTE-522 can shed light on the question regarding the tailoring of treatment with pembrolizumab in the adjuvant setting among nonresponders and responders to neoadjuvant CIT. In the KEYNOTE-522, EFS benefit in the pembrolizumab arm was also demonstrated for non-pCR patients, suggesting that a possible delayed activation of the adaptive immune system might improve clinical outcomes irrespective of pCR.[28] Similar findings were also noted in the phase II GeparNuevo trial, which combined durvalumab and chemotherapy only in the neoadjuvant setting and showed improvement in outcomes despite lack of significant improvement in pCR.[30] It should be emphasized that the magnitude of the treatment effect on continuation of adjuvant immune therapy on long-term clinical outcomes remains to be determined. Therefore, the risk-benefit ratio of adjuvant treatment with pembrolizumab should be carefully considered among pCR patients who experienced high-grade toxicities to NAC. On the basis of the available data, however, adjuvant pembrolizumab for pCR patients is advised (Fig 1).

The Alliance, an NCI cooperative group, has planned the OptimICE-pCR trial to evaluate the question whether the adjuvant ICPi can be safely omitted for patients with pCR. In addition, there are several recently completed trials evaluating the use of adjuvant immune therapy including SWOG S1418/BR006 (ClinicalTrials.gov identifier: NCT02954874) and OXEL (ClinicalTrials.gov identifier: NCT03487666). SWOG1418/BR006 is a phase III study to evaluate pembrolizumab as adjuvant therapy for TNBC with $\geq$1 cm of residual invasive cancer or positive lymph nodes (ypN1mi, ypN1-3) after NAC. Patients were randomly assigned to observation with standard of care compared with pembrolizumab IV every 3 weeks for 52 weeks. Adjuvant chemotherapy up to 24 weeks was allowed, and concurrent radiation to the affected breast or chest wall/regional lymph nodes was permitted. The OXEL study is a phase II open-label, randomized study evaluating nivolumab 360 mg IV once every 3 weeks $\times$ six cycles compared with capecitabine 1,250 mg/m^2 twice a day D1-D14 every 3 weeks $\times$ six cycles compared with nivolumab 360 mg IV every 3 weeks $\times$ six cycles and capecitabine 1,250 mg/m^2 twice a day D1-D14 every 3 weeks $\times$ six cycles combination in patients with TNBC with residual disease of 1.0 cm and/or node-positive disease after neoadjuvant therapy. The above studies will clarify the utility of adjuvant immune therapy in the absence of checkpoint inhibitors in the NAC setting. The next steps in the evolution of early-stage high-risk TNBC treatment paradigms are discussed in future directions.

IDENTIFICATION AND MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

ICPis, such as pembrolizumab, have been the most exciting development in the treatment of early- and advanced-stage TNBC. ICPi overall has a manageable safety profile. Most immune-related adverse events (irAEs) are mild and require close monitoring with continuation of ICPi therapy. However, the addition of pembrolizumab in the treatment of TNBC can lead to occasional serious and life-threatening irAEs, affecting various organ systems in the body.[44-46] Severe irAEs require early detection, prompt management, and discontinuation of ICPi. irAEs can be recognized and managed according to specific organ system–based toxicity. These toxicities range from cutaneous, GI, pulmonary, neurologic, nephrotoxic, endocrinopathies, hepatotoxic, cardiovascular, musculoskeletal, and hematologic toxicities.[44,47,48] The severity of these events is classified using the Common Terminology Criteria for Adverse Events (CTCAE) system developed by the National Cancer Institute (NCI). The common immune-related events are listed in this review. The exact mechanisms of these irAEs are not fully understood, but it is hypothesized that irAEs may be caused by autoimmunity and the enhancement of T-cell activation, resulting in the release of proinflammatory cytokines and infiltration of healthy tissue. Therefore, provider-patient education is warranted to detect and treat these adverse events early.

Endocrinopathies

Studies using ICPis in TNBC have reported on the incidence of endocrinopathies. The most reported endocrinopathy is thyroid dysfunction.[44] However, more serious endocrine irAEs include hypophysitis, immune-mediated diabetes mellitus, and adrenal insufficiency (AI). Identifying endocrinopathies can be challenging as patients often present with vague symptoms such as fatigue, headache, anxiety, tremor, and weight changes, which can also be attributed to chemotherapy agents concurrently administered. Identifying primary versus secondary endocrine dysfunction is often warranted to provide the most appropriate management.

Thyroid Dysregulation

The exact mechanism of thyroid dysregulation remains unclear; however, it is believed to be related to autoimmune thyroid destruction. In addition, patients with underlying untreated subclinical hyperthyroidism are at increased risk of developing thyroid-related irAEs. Clinical symptoms usually occur 3-6 weeks after the initiation of therapy and often start with a brief period of hyperthyroid and/or euthyroid state followed by longer-lasting hypothyroidism.[44,45]

When evaluating the thyroid axis, it is recommended to obtain thyroid-stimulating hormone (TSH) and free thyroxine serum levels to help identify primary versus secondary hypothyroidism. Patients with thyroid dysregulation often require permanent hormone replacement.

AI

AI is a rare irAE with only a 2% incidence. AI can result in acute life-threatening medical emergencies. Attentiveness to early warning signs/symptoms is necessary to avoid high mortality.,[44] Such adverse events have been reported as early as after a single dose of ICPi. In certain circumstances, hospitalization may be needed to correct electrolyte imbalance (hyponatremia, hyperkalemia), hypoglycemia, and shock. Steroid replacement and a prompt consult with an endocrinologist are advised.

CHECKPOINT INHIBITOR–ASSOCIATED DIABETES MELLITUS

Checkpoint inhibitor–associated diabetes mellitus is a relatively rare entity presenting as a new-onset hyperglycemia. It is associated with symptoms of polyuria, polydipsia, fatigue, and confusion. There is also the risk of life-threatening diabetic ketoacidosis that can result in coma or death.[48] Given the acuity and severity of these adverse events, hospitalization is often necessary.

IMMUNE-RELATED HYPOPHYSITIS

Hypophysitis can result in multiple hormonal imbalances, such as decreased levels of TSH, luteinizing hormone, follicle-stimulating hormone, and adrenocorticotropic hormone. Patients often present with fatigue, weakness, dizziness, nausea, headache, and visual impairment in the setting of pituitary enlargement.[44,45] In severe cases, hypophysitis can lead to loss of vision, decreased consciousness, and even coma. If suspected, a hormone assessment with laboratory test and an magnetic resonance imaging (MRI) of the brain are recommended for a diagnostic workup.

CUTANEOUS irAEs

Cutaneious toxicities range from a mild rash to an inflammatory dermatitis such as erythema multiforme. Rarely, patients can develop severe cutaneous adverse reactions that include Stevens-Johnson Syndrome or toxic epidermal necrolysis. Rash typically appears within the first 4 weeks of initiation of ICPi and is often the earliest observed irAEs.[45,46] It can be diffused or localized and can present in various forms (ie, maculopapular rash, pruritus, vitiligo, and psoriasis). The incidence of any-grade rash has been reported to be approximately 21% in CIT with a severe skin rash limited to only about 4% of patients. Management of this irAE includes topical steroids, systemic steroids, and a dermatology consultation.[45]

GI irAEs

GI irAEs are associated with ICPis including colitis, gastritis, and hepatitis.

Colitis

Colitis can present with diarrhea, abdominal cramps, and rectal bleeding, as well as fever and weight loss. Symptoms often occur within 6 weeks of the initiation of an ICPi when combined with chemotherapy. Mild cases can be managed with antidiarrheal, diet modification, and hydration. Moderate to severe cases may warrant endoscopy evaluation and treatment with corticosteroids and/or immune suppressants such as infliximab. In severe cases, bowel histology may mimic inflammatory bowel disease and warrant prompt hospitalization to avoid severe dehydration and sepsis.[48,49]

Gastritis

Gastritis may present with nausea, vomiting, epigastric pain, and dysphagia. Symptoms are often grade 1, can also present with diarrhea, and can be concurrently diagnosed with colitis. Supportive care practices are recommended. Endoscopy along with immunosuppressants may be warranted in severe cases.[48,49]

Hepatitis

Hepatitis is one of the most reported irAEs and mainly manifests as an increase in ALT and/or AST, with or without hyperbilirubinemia. Patients may be asymptomatic or present with loss of appetite, nausea, vomiting, or jaundice. Guidelines recommend extensive assessment of liver chemistries and screening for viral hepatitis as well as autoimmune liver damage. In addition, serial monitoring of liver function is necessary for early identification. ICPi-related hepatic toxicity often takes longer to resolve compared with other irAEs. Because of this, temporary or permanent suspension of ICPis may be required and treatment with high-dose steroids to alleviate the symptoms is often warranted. Of note, infliximab is contraindicated for the treatment of ICPi-related hepatitis because of an increased risk of hepatotoxic effects with infliximab therapy itself, and hence, mycophenolate mofetil or tacrolimus is used, if the patient is refractory to steroids.[48,50]

Musculoskeletal irAEs

Musculoskeletal irAEs can occur any time after the initiation of treatment of immune therapy. Presenting symptoms are fatigue, joint swelling, arthralgia, and myalgia.[48,51] Severe symptoms are associated with poor outcomes because of the negative effects on daily activity and quality of life. Most rheumatic irAEs respond to treatment with steroids; however, treatment with biologics may be needed in resistant cases.

Steroids are the agents used the most in the management of immune-related adverse events. There is growing concern

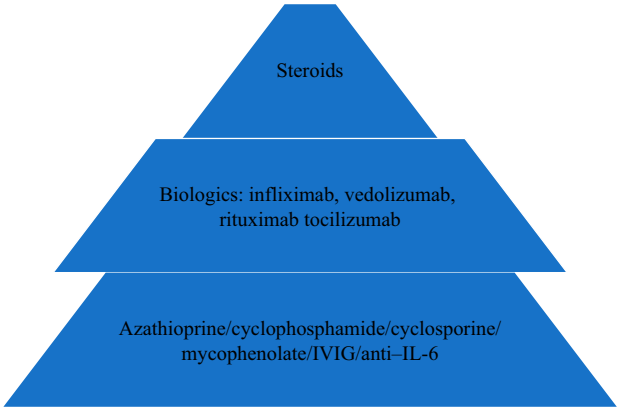

FIG 2. Treatment pyramid. Therapy options for moderate to severe immune-related adverse events in patients treated with immune checkpoint inhibitors (top to bottom). Moderate grade events can be managed with steroid. Severe events may warrant biologics, immune therapy, or combination therapy to mitigate symptoms. IL-6, interleukin-6; IVIG, intravenous immunoglobulin.

about acute and long-term toxicities resulting from dose and duration of steroid usage. Early recognition of steroid-related complications is important, and prophylactic agents to prevent opportunistic infections may be needed in select circumstances. GI prophylaxis with a daily antacid may be needed to reduce the risk of gastrointestinal discomfort while using steroids. Additionally, calcium and vitamin D replacement along with weight-earing exercise are encouraged to limit steroid-induced osteopenia while on prolonged steroids. When prescribing steroids, clinicians should take into consideration factors such as advanced age, immune status, and preexisting conditions like diabetes as these may increase the risk of steroid-induced complications.

ASCO has published updated guidelines on the management of immune-related adverse events in patients treated with ICPi therapy. Schneider et al[48] published detailed guidelines for the diagnosis and management of iRAEs by organ system. Some generalized recommendations on managing irAE along with certain commonly used agents are described here (Fig 2 and Table 1).

TABLE 1. General Recommendations on Immune-Related Adverse Events Management Arising From ICPi

Patients and caregivers should be educated about potential immune-related adverse events before initiating an ICPi
Any new symptom or laboratory/imaging abnormality should be carefully assessed for its association with an ICPi
ICPi therapy can generally be continued with close monitoring for most of the grade 1 toxicities. However, certain neurologic, hematologic, endocrinopathies, and cardiac toxicities will need special attention. A consultation with subspecialist is advised
ICPi therapy should be withheld for most grade 2 toxicities until the toxicity resolves or improves to a grade I toxicity
Corticosteroids at an initial dose of 0.5-1 mg/kg/d of prednisone or equivalent may be considered for grade II toxicities
Grade III toxicities necessitate interruption of ICPis, and high-dose corticosteroids (prednisone 1-2 mg/kg/d or equivalent) should be initiated. Corticosteroid taper should be gradual and administered over the course of 4-6 weeks
If the toxicity does not improve within 48-72 hours, use of other immunosuppressive agents like infliximab should be considered for certain toxicities
Grade IV toxicities often necessitate indefinite discontinuation, except for endocrinopathies that can be controlled with hormone replacement
A rechallenge of ICPis may be considered if a toxicity reverts to a grade 1 or resolves. Significant caution and close monitoring are required

NOTE. The total steroid dose can be administered once a day or split into a twice daily dose to adjust for tolerability.
Abbreviation: ICPi, immune checkpoint inhibitor.

FUTURE DIRECTIONS

There are many exciting developments in the use of NAC to treat TNBC. For example, antibody-drug conjugates (ADCs) are currently approved for second-line metastatic TNBC.[52,53] Multiple trials are ongoing to establish the efficacy of ADC with or without immune therapy in the neoadjuvant setting, such as sacituzumab govitecan (NeoSTAR, ClinicalTrials.gov identifier: NCT04230109)[54] and datopotamab deruxtecan (with or without durvalumab; I-SPY2, ClinicalTrials.gov identifier: NCT01042379).[55] Other exciting areas are the neoadjuvant use of cancer vaccines (ClinicalTrials.gov identifier: NCT04144023)[56] and oncolytic viral therapy (ClinicalTrials.gov identifier: NCT02779855) to target TNBCs.[57]

Using Biomarkers to Optimize Treatment in Early-Stage TNBC

A significant deficiency in NAC is the lack of adaptability and optimization of the treatment on the basis of response to therapy before surgery. Optimal modalities to predict early neoadjuvant therapy response are yet to be established. Multifeature MRI or diffusion coefficient in diffusion-weighted MRI to predict the pCR rate is currently under evaluation.[58,59] In addition, circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) are frequently incorporated in the current early-stage TNBC management in ongoing trials. Preliminary data suggest that detection of ctDNA and/or CTCs in patients with early-stage breast cancer after NAC is independently associated with a higher risk of disease recurrence.[60-62] Furthermore, the I-SPY 2 trial indicated that patients with TNBC are more likely to have positive ctDNA than other breast cancer subtypes before starting NAC (TNBC 86%, HER2+ 84%, hormone receptor–positive/HER2– 84%, $P < .01$).[60] In the realm of personalized adjuvant treatment, analysis of tumor tissue and/or tumor microenvironment of

TABLE 2. Selective Active Neoadjuvant and Adjuvant Trials for TNBC

Trial ID	Trial Phase No. (N)	Agents	Main Inclusion Criteria	Primary End Point
Chemotherapy trials				
NCT01752686 (POST-neoadjuvant study)	3 (587)	Carboplatin *v* observation	TNBC with residual disease after NAC with AC-docetaxel	DFS
NCT04437160	2 (286)	Epirubicin or pirarubicin + cyclophosphamide *v* observation	TNBC with residual disease after taxane- and platinum-based NAC	Recurrence-free survival
NCT03703427	2 (200)	Vinorelbine tartrate (oral) *v* capecitabine	TNBC or HER2+ with residual disease	DFS
Immune therapy trials				
NCT02954874	3 (1,155)	Pembrolizumab *v* observation	TNBC with residual disease after NAC Adjuvant chemotherapy was allowed	iDFS
NCT05163223 (Cornerstone001)	2 (146)	AST-301/rhuGM CSF + standard adjuvant therapy *v* control arm; placebo/rhuGM CSF + standard adjuvant therapy	HER2-low expression (IHC 1+ or 2+ and ISH–) and hormone receptor–negative breast cancer and residual disease after neoadjuvant treatment	2-Year iDFS
NCT03562637 (GLORIA)	3 (668)	Adagloxad simolenin+ OBI-821+ standard of care *v* standard of care	TNBC with residual disease or TNBC stage IIb-IIIC without neoadjuvant therapy Globo H IHC H-score ≥15	iDFS
NCT04674306	1 (40)	α-lactalbumin vaccine	TNBC with residual disease	MTD
NCT02826434	1b (22)	Adjuvant PVX-410 and durvalumab	HLA-A2+ patients with residual TNBC	DLT/safety
NCT03740893 (PHOENIX)	2 (81)	Olaparib, durvalumab, AZD6738	TNBC with residual disease	Changes in tissue-based biomarkers
NCT03487666 (OXEL)	Pilot study (45)	Nivolumab alone, capecitabine alone, or combination	TNBC with residual disease	Immune activation measured by changes of PIS at week 6
NCT04501523 (Apollo)	2 (460)	Tislelizumab + capecitabine × 1 year *v* capecitabine × 1 year capecitabine × 1 year	TNBC with residual disease and ctDNA+ TNBC with pCR and ctDNA+	5-year DFS
Antibody drug conjugate trials				
NCT05633654 (ASCENT-05)	3 (1,514)	Sacituzumab govitecan + pembrolizumab (eight cycles) *v* physician's choice (pembrolizumab or pembrolizumab + capecitabine)	TNBC with residual disease	iDFS
NCT05629585 (TROPION-Breast-03)	3 (1,075)	Datopotamab deruxtecan (DatoDXd) × 8 cycles with or without durvalumab ×9 cycles *v* investigator's choice (pembrolizumab, capecitabine, pembrolizumab + capecitabine)	TNBC with residual disease	iDFS
Biomarker-driven trials				
NCT05332561 (COGNITION-GUIDE)	2 (240)	Arm 1: Atezolizumab Arm 2: Inavolisib Arm 3: Ipatasertib Arm 4: Olaparib Arm 5: Sacituzumab govitecan Arm 6: Trastuzumab/pertuzumab	All subtypes with residual disease Arm 1: PDL1+, MSI-H, TMB-H or CD274 amp Arm 2: PIK3CA, hormone receptor–positive Arm 3: PI3K-AKT alteration except PIK3CA Arm 4: BRCA1/2 mutation (somatic or germline) Arm 5: TROP2+ Arm 6: HER2 exon 20 insertion or activating mutation	iDFS
NCT04849364 (PERSEVERE)	2 (197)	Arm 1: 1a: Talazoparib + capecitabine 1b: Atezolizumab + capecitabine 1c: Inavolisib + capecitabine —> atezolizumab 1d: Talazoparib + atezolizumab + capecitabine Arm 2 and 3: Treatment of physician's choice	TNBC with residual disease Arm 1 ctDNA+ genomic target+ 1a: DNA repair pathway 1b: Immunotherapy pathway 1c: PI3K Pathway 1d: DNA Repair + immunotherapy Arm 2 ctDNA+, no genomic target Arm 3 ctDNA–	2-year DFS

(Continued on following page)

TABLE 2. Selective Active Neoadjuvant and Adjuvant Trials for TNBC (Continued)

Trial ID	Trial Phase No. (N)	Agents	Main Inclusion Criteria	Primary End Point
NCT04434040 (ASPRIA)	2 (40)	Atezolizumab + sacituzumab govitecan × 6 cycles	TNBC with residual disease and ctDNA+	Rate of undetectable ctDNA rate after 18 weeks
NCT04501523 (Apollo)	2 (460)	Tislelizumab + capecitabine × 1 year *v* capecitabine × 1 year capecitabine × 1 year	TNBC with residual disease and ctDNA+ TNBC with pCR and ctDNA+	5-year DFS

NOTE. Table adapted from the review of ClinicalTrials.gov.

Abbreviations: AC, doxorubicin and cyclophosphamide; ctDNA, circulating tumor DNA; DFS, disease-free survival; DLT, dose-limiting toxicity; HER2, human epidermal growth factor receptor 2; HLA-A2+, human leukocyte antigen-A2; ID, identification; iDFS, invasive disease-free survival; IHC, immunohistochemistry; ISH, in situ hybridization; MSI-H, microsatellite instability-high; MTD, maximum tolerated dose; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response; PIS, peripheral immunoscore; rhuGM CSF, recombinant human granulocyte-macrophage colony-stimulating factor; TMB-H, tumor mutation burden-high; TNBC, triple-negative breast cancer.

residual or newly diagnosed tumor might eventually guide adjuvant treatment recommendations. Efforts are ongoing and are not ready for prime time. Schneider et al[63] reported results of a phase II trial (N = 193) of tumor tissue gene-directed therapies for the treatment of patients with residual TNBC. The estimated 2-year DFS for patients randomly assigned to the tumor-genomic matched approach was only 56.6% (95% CI, 0.45 to 0.70) compared with 62.4% (95% CI, 0.52 to 0.75) for patients randomly assigned to physician's choice (majority received capecitabine). Notwithstanding their potential predictive value, tumor analyses were limited by temporal and even spatial intratumor heterogeneity of breast tumors.[64] Liquid biopsies, including CTC and cell-free tumor DNA assessments, have long been studied as potential biomarkers of clinical utility for early-stage TNBC, but thus far, their value is largely prognostic.[65-69] These assays have been challenged by the need for both robust analytical and clinical validation before being declared as clinically useful in tailoring adjuvant treatments for patients with TNBC after neoadjuvant therapy. Currently, there are limited data available to guide the optimal therapy in postneoadjuvant therapy among the available standard-of-care options. The above biomarkers are to be further assessed by ongoing clinical trials.

Henceforth, tailoring of adjuvant treatments (optimization or intensification) for patients with residual TNBC will likely be equally guided by personalized approaches and new therapeutic strategies such as ADCs. The OptimICE-RD (ASCENT-05) is a large ongoing phase III study of 1,514 patients with residual TNBC (ClinicalTrials.gov identifier: NCT05633654), which will assess safety and efficacy of the addition of sacituzumab govitecan or capecitabine to pembrolizumab. In addition, TROPION-Breast-03, a study of Dato-DXd with or without durvalumab versus investigator's choice in patients with stage I-III TNBC without a pCR (ClinicalTrials.gov identifier: NCT05629585), will also evaluate the utility of adjuvant ADCs in high-risk TNBC. These trials will address an important area of an unmet need, the intensification of adjuvant treatment in patients with high-risk TNBC with newer targeted agents such as sacituzumab govitecan versus established agents such as capecitabine. There are ongoing efforts to evaluate combination immune therapies, targeted therapies, and vaccine trials for patients with TNBC with residual disease who are at highest risk of relapse (Table 2).

Conclusion

Despite current advances, TNBC remains the breast cancer subtype with the worse outcomes compared with estrogen receptor–positive and HER2-positive breast cancers, largely attributed to limited treatment options. Anthracycline- and taxane-based chemotherapy regimens remain the standard of care for high-risk TNBC, with the addition of ICPis for stage II and III TNBC. The careful management of immune-related adverse events is critical to avoiding severe life-threatening events. Several clinical questions around ICPi usage in TNBC remain unanswered, including the optimal pembrolizumab partner, continuation after pCR, and sequencing with capecitabine and PARP inhibitors. Finally, the continuous investigation of novel biomarkers and best-paired neoadjuvant and adjuvant therapies to optimize outcomes in high-risk tumors is needed.

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Not Too Little, Not Too Much: Optimizing More Versus Less Locoregional Treatment for Older Patients With Breast Cancer

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Overview

Although undertreatment of older women with aggressive breast cancers has been a concern for years, there is increasing recognition that some older women are overtreated, receiving therapies unlikely to improve survival or reduce morbidity. De-escalation of surgery may include breast-conserving surgery over mastectomy for appropriate candidates and omitting or reducing extent of axillary surgery. Appropriate patients to de-escalate surgery are those with early-stage breast cancer, favorable tumor characteristics, are clinically node-negative, and who may have other major health issues. De-escalation of radiation includes reducing treatment course length through hypofractionation and ultrahypofractionation regimens, reducing treatment volumes through partial breast irradiation, omission of radiation for select patients, and reducing radiation dose to normal tissues. Shared decision making, which aims to facilitate patients making decisions concordant with their values, can guide health care providers and patients through complicated decisions optimizing breast cancer care.

Over 77,000 women age 70 years or older in the United States are diagnosed with breast cancer annually. As the population ages, this figure will rise.[1] Women age 70 years or older account for 31% of diagnosed breast cancers, and given widespread mammography use in older women, the majority are diagnosed with stage I, estrogen receptor–positive (ER+)/human epidermal growth factor receptor 2–negative (HER2–) tumors.[2] Although undertreatment of older women with aggressive breast cancers has been a concern for years, there is increasing recognition that some older women with stage I, ER+, HER2– breast cancers are overtreated, receiving therapies unlikely to improve survival or reduce morbidity.

Studies have found that omitting radiation therapy after breast-conserving surgery and/or omitting axillary surgery in women age 70 years or older with stage I, ER+/HER2– breast cancer does not affect their survival when taking endocrine therapy.[3–6] While radiation therapy after lumpectomy may reduce local recurrence, the absolute risk reduction is <10% and takes years to achieve.[3,5] Thus, women age 70 years or older with stage I, ER+/HER2– face decisions regarding de-escalation or omission of parts of their locoregional therapy. More than 70% of women age 70 years or older with breast cancer undergo axillary surgery and receive radiation therapy.[7–11] Is this appropriate treatment or overtreatment? In thinking about patients who are best suited for de-escalation of axillary surgery or radiation therapy, this management pathway assumes compliance with endocrine therapy. Unfortunately, studies have demonstrated close to one-third of patients will have early discontinuation of endocrine therapy.[12–14] For older patients who are of higher risk for early endocrine therapy cessation, radiation gains importance in decreasing risk of locoregional recurrence.

As breast cancer care makes advances, individualized therapy should consider unique patient preferences, risk factors, and overall goals of care. These take precedence over uniform, generalized recommendations. There can be significant physician and patient discomfort with deviating from traditional treatment paradigms and when recommending de-escalation of locoregional care for the older patient with breast cancer. What is considered de-escalation? When is it appropriate? And how do we think about de-escalation of locoregional breast cancer care in the context of ongoing clinical trials and advances in therapies and technologies? The ensuing discussion will initially review de-escalation of surgery and radiation therapy and afterward provide an overview of the importance of shared decision making (SDM) in the care of older patients with breast cancer (Table 1).

SURGERY

De-escalation of surgery for patients with breast cancer refers to reducing the extent or invasiveness of surgical procedures while maintaining optimal clinical outcomes. The goal of de-escalation is to minimize the

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PRACTICAL APPLICATIONS

- Consider de-escalation of surgery for those patients with early-stage breast cancer, favorable tumor characteristics, are clinically node-negative, and who may have other major health issues.
- De-escalation of surgery entails decreasing the extent of surgery including offering breast conservation therapy over mastectomy for appropriate candidates, incorporating oncoplastic surgery techniques to increase patient eligibility for lumpectomy, and omitting or reducing extent of axillary surgery.
- De-escalation of radiation includes reducing treatment course length through hypofractionation and ultrahypofractionation regimens, reducing treatment volumes through partial breast irradiation, omission of radiation, and reducing radiation dose to normal tissues.
- Shared decision making, which aims to facilitate patients making decisions concordant with their values, can guide health care providers and patients through complicated decisions optimizing breast cancer care.

impact of surgery on a patient's physical and emotional well-being, without compromising the effectiveness of treatment.

De-escalation of surgery may be appropriate for patients who meet the following criteria:

1. Early-stage breast cancer: Patients with small, localized tumors are typically good candidates for breast-conserving surgery over mastectomy.
2. Favorable tumor characteristics: Patients whose tumors are hormone receptor–positive and HER2– may be good candidates for de-escalation of surgery. These tumors tend to be less aggressive and have a lower risk of recurrence, which may allow for less-invasive surgical procedures.
3. Clinically node-negative: Patients whose cancer has not spread to regional lymph nodes may be candidates for de-escalation of axillary surgery.
4. Other health issues: Patients who have other health issues may be more susceptible to complications from surgery, and de-escalation may be appropriate to reduce the risk of surgical complications and to balance the risks and benefits of breast cancer care.

Surgery for breast cancer may be de-escalated for the older patient in thinking about the appropriate extent of surgery in the breast and axilla. First, this can include removal of less breast tissue. The survival rates for patients with breast cancer who undergo lumpectomy versus mastectomy depend on the stage and aggressiveness of the cancer as well as the individual patient's overall health and other medical conditions. There is no significant difference in long-term survival rates between patients who undergo lumpectomy and those who undergo mastectomy for early-stage breast cancer. Lumpectomy with radiation therapy has been shown to be just as effective as mastectomy for treating early-stage breast cancer while allowing for breast preservation. Long-term follow-up of NSABP-06 found no significant difference in overall survival (OS) among women who underwent mastectomy and those who underwent lumpectomy with or without postoperative breast irradiation.[15] Additionally, for locally recurrent breast cancer after previous breast-conserving surgery, standard treatment historically has been mastectomy. However, there may be a role for repeat breast lumpectomy with radiation as studied in Radiation Therapy Oncology Group (RTOG) 1014 for select patients.[16] Furthermore, the Cancer and Leukemia Group B (CALGB) 9343 and PRIME II trials have demonstrated that patients who have early, low grade ER+ cancers can do well with surgery alone without adjuvant radiation.[3,4]

An older patient may also be able to consider oncoplastic reconstructive surgery after breast lumpectomy instead of mastectomy with postmastectomy reconstruction to de-escalate the extent of surgery in certain circumstances. Oncoplastic surgery involves combining breast cancer surgery with plastic surgery techniques to reshape and reconstruct the breast tissue, which can improve cosmetic outcomes while maintaining optimal clinical outcomes and allowing a greater proportion of patients to have breast conservation. Oncoplastic surgery may be used to achieve a more natural-looking breast shape after breast-conserving surgery. For example, in cases where a significant amount of breast tissue needs to be removed, oncoplastic techniques

TABLE 1. Recommendations for Clinical Practice in Locoregional Treatment of Older Patients With Breast Cancer

De-escalation of surgery	Offer breast conservation therapy over mastectomy for appropriate candidates Incorporate oncoplastic surgery techniques to increase patient eligibility for lumpectomy Omit or reduce extent of axillary surgery Consider whether appropriate to repeat breast conserving therapy for local recurrence
De-escalation of radiation	Reduce treatment course length with hypofractionation and ultrahypofractionation regimens Reduce treatment volumes through partial breast irradiation Consider appropriate patients for omission of radiation Reduce radiation dose to normal tissues
Shared decision making	Facilitates patients making decisions concordant with their values Guides health care providers and patients through complicated decisions

can be used to reshape the remaining tissue to maintain symmetry and contour. Oncoplastic surgery can minimize scarring and reduce the risk of complications in older patients with other medical conditions that may affect wound healing or increase the risk of infection. It can be a valuable option for older patients with breast cancer who desire both cancer removal and a good cosmetic outcome without necessitating a mastectomy. The specific techniques used depend on the patient's individual circumstances, including the size and location of the tumor, the amount of breast tissue to be removed, and the patient's overall health and preferences.

In addition to thinking about de-escalating the extent of surgery in the breast, de-escalation of surgery in the axilla is similarly important. In older patients with breast cancer, the omission of axillary surgery may be considered as a treatment option, particularly for those with early-stage disease and low risk of lymph node involvement. This is because axillary surgery, either in the form of sentinel lymph node biopsy (SLNB) or axillary lymph node dissection, can be associated with certain risks and complications, including lymphedema, numbness, and shoulder dysfunction. Several studies from Europe and North America have demonstrated no difference in breast cancer–specific mortality between undergoing axillary surgery versus no axillary surgery.[17–20] Furthermore, the International Breast Cancer Study Group trial 10-93 found that quality of life was significantly better in the group that avoided axillary surgery, and disease-free survival (DFS) and OS were similar for patients in the two arms of the trial.[6] The Society of Surgical Oncology's Choosing Wisely campaign now recommends that surgeons do not to routinely use sentinel lymph node surgery in women older than 70 years who have hormone receptor–positive breast cancer given this does not increase the risk of locoregional recurrence and has no adverse impact on mortality.[21,22]

De-escalation of surgery for breast cancer may be appropriate for certain patients with low-risk disease, where reducing the extent or invasiveness of surgical procedures can still maintain optimal clinical outcomes. However, the decision to de-escalate surgery should be made on a case-by-case basis, factoring in stage and grade of the tumor, the patient's age and overall health, and the presence of any comorbidities. The decision to de-escalate surgery is recommended to be made in consultation with a multidisciplinary team of breast cancer experts, including surgeons, medical oncologists, and radiation oncologists, who can help determine the optimal treatment plan for each patient on the basis of their individual circumstances.

RADIATION

Radiation therapy remains an integral component of breast conservation therapy for the majority of patients with early-stage invasive breast cancer.[23–26] In addition, regional nodal irradiation (RNI) improves cancer control outcomes for patients with axillary lymph node–positive or high-risk node-negative breast cancer.[27–29] However, our improved understanding of breast cancer biologic subtypes coupled with advances in diagnostic and therapeutic modalities has led to the recognition that there are likely subsets of patients who derive little benefit from adjuvant radiation therapy. De-escalation strategies include the following:

Reducing Radiation Treatment Course Length

Hypofractionation (HF) courses of whole breast irradiation (WBI) are now the standard of care. The data support HF courses for many patients undergoing RNI and postmastectomy radiation therapy (PMRT) as well. This reduces the treatment burden from 5 to 6.5 weeks down to 3 weeks or even less with ultrahypofractionation. HF refers to increasing the daily fraction size of radiation while simultaneously reducing the total number of fractions delivered and the total radiation dose delivered. Hypofractionated regimens are attractive in situations in which the radiosensitivity of the tumor cells is similar to the radiosensitivity of the surrounding normal tissues such that a higher dose per fraction can be delivered to obtain tumor control but a lower total dose delivered to reduce normal tissue toxicity.[30] The seminal UK START A and START B trials as well as the Canadian HF trial established that HF regimens result in similar cancer control outcomes with the same or reduced acute and late toxicities compared with conventionally fractionated radiation regimen.[31–36] The United Kingdom moved on with testing results of an ultrahypofractionated WBI regimen of 26 or 27 Gy in five once daily fractions (5.2 or 5.4 Gy/fraction) compared with HF WBI of 40 Gy in 15 fractions in the FAST-Forward trial in a group of women with fairly low-risk breast cancer (median age 60 years; 81% HR+/HER2–; median tumor size, 1.6 cm; 81% pN0; <25% received chemotherapy).[37] The United Kingdom has led to large studies investigating ultrahypofractionation, in which radiation is delivered to the whole breast in a total of five fractions. The UK FAST study randomly assigned women with early-stage breast cancer (pT1-2 pN0) to conventionally fractionated WBI (50 Gy/25 F) or to one of two experimental arms of either 30 Gy/5 F given once per week or 28.5 Gy/5 F given once per week such that all regimens were delivered over a total of 5 weeks (no tumor bed boost in any arm). The 10-year risk of ipsilateral breast events were similarly low across all groups (0.7% 50 Gy/25 F *v* 1.4% 30 Gy/5 F *v* 1.7% 28.5 Gy/5 F), but there were significantly worse normal tissue effects (eg, photographic changes in the breast, induration, edema) for 30 *v* 50 Gy but not for 28.5 *v* 50 Gy. Therefore, for patients with significant comorbidities or socioeconomic factors that preclude daily treatment, the 28.5 Gy in five fractions once per week is an acceptable alternative to conventionally fractionated WBI.[37]

The 26 Gy in five fraction regimen was much more tolerable, although there were still significantly higher rates of certain side effects, such as breast swelling, when compared with 40 Gy in 15 fractions. In addition, for patients requiring a tumor bed boost, this was delivered sequentially with an additional five to eight fractions, thereby increasing the course from 1 week to 2-2.5 weeks. Recent data from the Radiation Therapy Oncology Group 1005 study demonstrated that HF WBI of 40 Gy in 15 fractions with a concomitant boost to the tumor bed to a dose of 48 Gy in 15 fractions resulted in equivalent local control with similar acute toxicity, late toxicity, and cosmesis compared with WBI delivered with a sequential boost.[38] Thus, the RTOG 1005 regimen, which is delivered in 3 weeks, is an excellent option for high-risk patients requiring tumor bed boost.

HF regimens have also been used to deliver RNI and PMRT. In the START A and START B clinical trials, 8.3% and 14.6% of patients received hypofractionated PMRT.[31,32] In addition, Wang et al[39] performed a randomized noninferiority trial of HF PMRT (43.5 Gy in 15 fractions) compared with PMRT delivered as 50 Gy in 25 fractions in 810 patients with T3-4 and/or N2-N3 breast cancer and found noninferior local-regional control with HF PMRT. A recent meta-analysis of 25 trials involving almost 4,000 patients comparing efficacy and toxicity of hypofractionated versus conventionally fractionated PMRT showed no differences in local-regional recurrence, DFS, OS, or in any early or late toxicities between the groups.[40] The results of two recently completed randomized studies specifically comparing HF PMRT with conventionally fractionated PMRT in the reconstruction setting are highly anticipated.

Reducing Radiation Treatment Volumes

Partial breast irradiation. Most in-breast tumor occurrences are located within 1 cm of the original tumor bed.[41,42] This has led to numerous clinical trials comparing partial breast irradiation (PBI), which targets the tumor bed region with a margin of 1-2 cm, with WBI. All forms of PBI use HF, although some regimens are delivered twice per day with moderately large fractions (3.4-3.85 Gy $\times$ 10 fractions), while some are delivered daily with standard HF (2.67 Gy $\times$ 15 fractions) and others are given every other day with large fraction sizes (6 Gy per fraction $\times$ five fractions). Intraoperative radiation therapy delivers a single large dose (20-21 Gy) to the tumor bed with either low-dose photons or high-energy electrons.

The key APBI studies are summarized in Table 2. PBI should be considered as an alternative to WBI in the appropriate patient population, specifically patients who are 50 years or older with stage I, lymph node-negative (pT1 pN0), ER+/HER2– breast cancers. Across all techniques and fractionation schedules, it seems as though 10-year in-breast tumor recurrences are 2% or less when PBI (or WBI) is used in this patient population. Although there are no randomized studies that compare one PBI technique with another, it does seem that once daily PBI (30 Gy in five fractions given every other day or 40 Gy in 15 fractions given daily) is associated with low rates of acute and late toxicities and extremely high rates of favorable cosmesis.

Omission of Radiation Therapy

Biomarker-guided omission of radiation in hormone-sensitive breast cancer. While data support omission of radiation therapy in patients with ER+/HER2– breast cancer treated with lumpectomy and adjuvant endocrine therapy on the basis of age through the CALGB 9343 and PRIME II studies, recent focus has shifted to the use of genomic and immunohistochemistry-based biomarkers to help make these decisions with numerous ongoing prospective trials.[3,4] The recently reported LUMINA study was a single-arm prospective study that evaluated omission of radiation therapy in women age 55 years or older with grade 1-2 tumors that were $\leq$2 cm in size, surgical margins $\geq$1 mm, lymph node-negative, and had a low proliferative index (Ki67 $\leq$ 13.25%) and found that the 5-year risk of local-regional recurrence in the 727 patients enrolled was extremely low at 2.3%.[44]

Omission of radiation in HER2-positive breast cancer. Much of the de-escalation of radiation therapy has been focused on patients with ER+/HER2– disease. HER2+ breast cancers represent approximately 10%-15% of all breast cancers, and systemic therapy studies have demonstrated that patients with small node-negative tumors (pT1N0) have exceedingly low rates of local-regional and distant recurrences with de-escalation of systemic therapy.[45,46] For example, in the APT trial, patients who received lumpectomy with radiation therapy had <1% rate of in-breast recurrences.[47] This observation has led to a phase III randomized trial of postlumpectomy radiation versus omission of radiation in patients with pT1N0 HER2+ breast cancer treated with lumpectomy + axillary surgery and adjuvant chemotherapy with HER2-targeted therapy.

Reducing Radiation Dose to Normal Tissues

The entire field has shifted from a 2D anatomic landmark-based approach to design radiation fields toward 3D computed tomography (CT)–based radiation planning with improved delivery techniques such as 3DCRT using multileaf collimators to design fields,[48–50] prone breast radiation therapy,[51–56] inverse planned intensity–modulated radiation therapy, and volumetric modulated arc radiotherapy (RT), all of which have resulted in reduced treatment toxicities.[57,58] Respiratory gating with use of deep inspiration breath hold (DIBH) and improved image guidance during treatment delivery including real-time on-board

TABLE 2. Key Studies of De-Escalation Using HF and Ultrahypofractionation for Whole Breast Irradiation

Trial	Study Duration	N	Follow-Up (years)	XRT Dose	LR (%)
Whelan (OCOG)[16]	1993-1996	1,234	12	CF: 50 Gy/25 F	6.7
				HF: 42.56 Gy/16 F	6.2
START-A[12]	1999-2002	2,236	9.3	CF: 50 Gy/25 F/5 w	6.7
				HF: 41.6 Gy/13 F/5 w	5.6
				HF: 39 Gy/13 F/5 w	8.1
START-B[11]	1999-2001	2,215	10	CF: 50 Gy/25 F	5.2
				HF: 40 Gy/15 F	3.8
HYPO[43]	2009-2014	1,854	9	CF: 50 Gy/25 F	3.3
				HF: 40 Gy/15 F	3.0
FAST-Forward[17]	2011-2014	4,096	5.9	HF: 40 Gy/15 F	2.1
				UHF: 27 Gy/5 F	1.7
				UHF: 26 Gy/5 F	1.4

Abbreviations: CF, conventional fractionation; HF, hypofractionation; LR, local recurrence; N, number of patients; OCOG, Ontario Clinical Oncology Group; XRT, radiation.

imaging with cone beam CT capabilities further aid the field of radiation oncology to improve targeting and reduce radiation to normal tissue during treatment delivery.[43,59,60]

In Figure 1, a patient with a medially located lumpectomy cavity in the left breast underwent simulation in both the prone position and the supine position with use of DIBH because of concerns that the location of the lumpectomy cavity may result in a higher dose to the heart in the prone position. However, in this case in which contours for the target volumes (breast and lumpectomy cavity) and OARs were in place, the prone radiation plan resulted in lower mean heart dose (0.9 *v* 1.5 Gy) and substantially lower

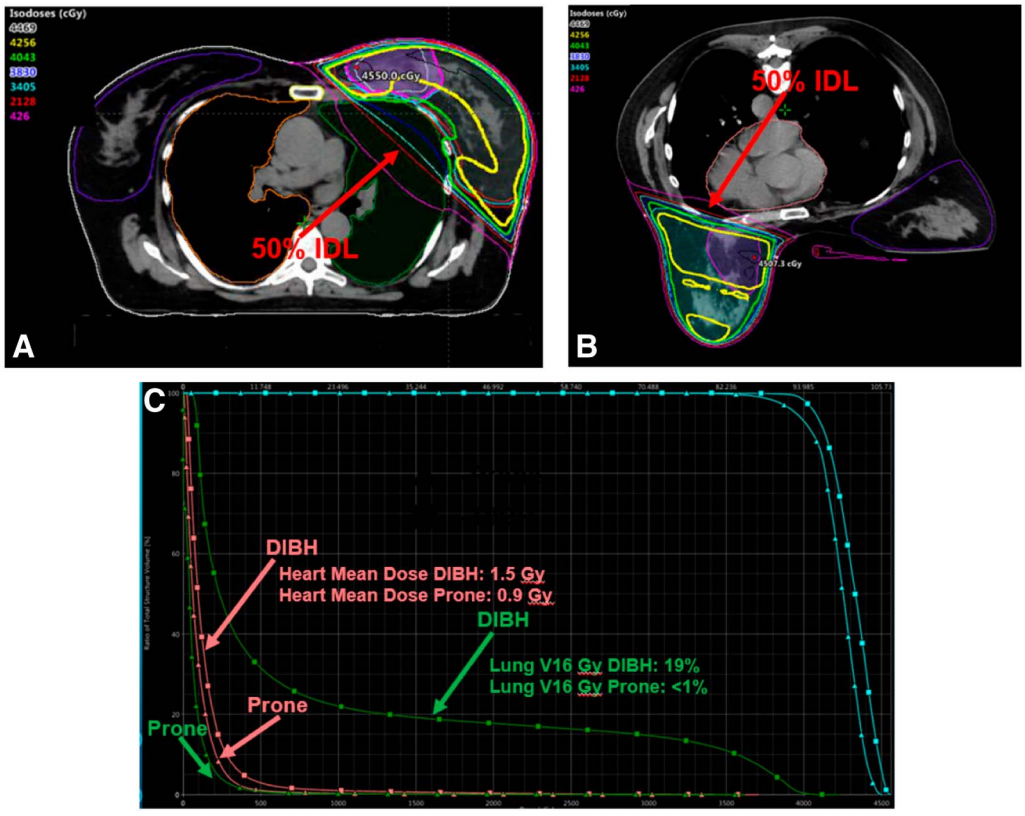

FIG 1. Individualizing radiation treatment technique. (A) This panel demonstrates radiation in the supine position with DIBH. (B) Same patient in the prone position. The 50% IDL is highlighted in the red arrow while the yellow and green curves represent the 100% and 95% IDL, respectively. (C) This panel demonstrates the dose-volume histogram. Curves with squares represent the DIBH radiation plan, and the curves with triangles are the prone radiation plan. DIBH, deep inspiration breath hold; IDL, isodose line.

volume of lung receiving ≥16 Gy (<1% prone *v* 19% DIBH) without compromising target volume coverage. This is an example of how RT approaches can be individualized to the patient and how modern radiation techniques and planning approaches can enable us to adequately cover our targets and reduce dose to normal tissues.

SDM

SDM, which aims to facilitate patients making decisions concordant with their values, can help to guide health care providers and patients through complicated decisions. It requires patients and providers to work together to select tests and treatments, with each party bringing different expertise to the decision-making process. Patients are responsible for sharing preferences while providers are responsible for informing patients of their treatment options and integrating relevant evidence-based information into the conversation.[61] SDM is particularly useful in the setting of multiple treatment options, when there is uncertainty regarding the evidence supporting a treatment or its outcomes, when there are both advantages and disadvantages that patients must weigh and when the decision is high impact as is the case for breast cancer treatment decision making for older women.[61] However, existing research demonstrates gaps in effective SDM with these women. Older women with breast cancer often report unmet informational needs, feel ill-prepared to communicate their preferences to their physicians, and feel uncomfortable asking their surgeons questions.[61] Furthermore, older women report being less likely to be given treatment choices, to engage in treatment decisions, and/or to be satisfied with treatment outcomes than younger women.[62] Many also have low knowledge of breast cancer survival and recurrence rates.[63] Yet, older women are increasingly interested in taking more active roles in treatment decisions, reporting that they would value educational materials to better understand their treatment options and to know what questions to ask.[64]

Decision aids (DAs) are educational tools that provide detailed, current information to guide patients through a deliberative process. Rather than replacing patient-physician interaction, they are intended to supplement the conversation.[65] They have been found to perform better than usual care with respect to improving patients' knowledge about risk perception and treatment outcomes, incorporating patients' preferences and values, and encouraging users to take a more active role in decision making without increasing anxiety. DAs also improve patient satisfaction with the decision-making process, possibly improving patient quality of life.[65]

A 2016 systematic review identified 23 individual breast cancer treatment DAs.[66] For this chapter, a literature review was performed for patient DAs for women with invasive breast cancer. Studies included were published since 2010 and included women age 65 years or older in the testing of the DA. Table 3 presents the 18 DAs identified. Six of the DAs focused on women age older than 65 years, two of which discussed RT and were only studied in Canadian women who had already chosen to undergo RT.[74,78] These DAs need to be tested among women facing this treatment decision. Another DA focused on SDM around cessation of surveillance mammography among women age 75 or older and encouraged older women to consider their tumor characteristics and life expectancy when deciding when to cease surveillance mammography.[80] Another study aimed to provide older women with information on their prognosis with and without breast cancer and with and without comorbidities.[73] Wyld et al[79] developed the Age Gap Decision Tool. This tool was developed for women age 70-99 years in the United Kingdom diagnosed with primary operable invasive breast cancer (T1-3, N0-1, M0). It considered a woman's age, tumor size, grade, ER and HER2 status, comorbidities and frailty to provide information on a woman's 2-year and 5-year OS, chance of breast cancer death, and chance of death from other causes if she is treated with (1) surgery plus endocrine therapy versus primary endocrine therapy and (2) surgery plus chemotherapy versus surgery alone. In a large cluster, RCT that included 1,339 women seen at 46 different breast units, use of the tool was associated with women having increased knowledge about treatments, more SDM, and with more women receiving primary endocrine therapy and fewer receiving chemotherapy (Table 2).[79]

Since there is a complex interplay between treatments that older women should consider when deciding on treatment, Schonberg et al[85] developed and pilot-tested a comprehensive DA for women age 70 or older with stage I, ER+/HER2– breast cancer. This DA was designed with low literacy principles, iteratively revised, and is on the preferred medium (paper) of older women. The DA encompasses surgical decisions (breast surgery and axillary surgery), the decision to proceed with RT, and endocrine therapy options. It also incorporates competing health issues into the decision process. In addition to the standard components of DAs, such as describing the health condition and the positive and negative features of treatment choices, the DA also includes a question prompt list since question prompt lists have been shown to increase patient knowledge, self-efficacy, identification of treatment preferences, and participation in decision making, especially among patients with cancer.[86] In a pilot pretest/post-test trial of 33 women, the DA improved women's knowledge of their treatment options and 97% would recommend it; the DA is available in the appendix of the article.[72]

Although DAs have been repeatedly shown to increase patient knowledge and reduce decisional conflict, successful integration requires engaging physicians in the process.

TABLE 3. Patient DAs for Older Women With Invasive Breast Cancer: Studies That Included Women Age Older Than 65 Years in Testing and Were Published Since 2010[a]

Reference	Participants	Decision	Methods	Results
Ager et al[67]	23 Australian women with history of stage I or II breast cancer; mean age, 58.6 (range, 43-67 years)	Contralateral prophylactic mastectomy	In-person interviews	The DA was found to be acceptable
Durand et al[68] (images of the DA in the article)	16 surgeons, 616 US women with stage I-IIIA breast cancer; mean age, 59.7 (±12.5 years)	Mastectomy *v* BCS	Three-arm RCT (Option Grid Text, Picture Option Grid [pictures + text], and usual care) with surgeon-level random assignment	Patients in Picture Option Grid arm had higher knowledge, improved decision process, lower decision regret, and more SDM compared with usual care. Patients in Option Grid text arm had higher decision process, better coordination of care, and more SDM compared with usual care arm
Freedman et al[80] (DA in the appendix)	21 US breast cancer survivors; median age, 78 (range, 75-92 years); 21 oncologists	Surveillance mammography	Observational cohort study of patients and survey of oncologists	Nearly all patients and clinicians would recommend the guide to others. Both previsit and postvisit patients reported strong intentions for surveillance mammography
Harwood et al[69] (images of the DA in the article)	Part 1: 28 Australian women with history of stage I/II breast cancer; mean age, 55 (range, 32-76 years) Part 2: Eight Australian women newly diagnosed with stage I/II breast cancer; mean age, 55 (range, 34-75 years)	Mastectomy *v* BCS; axillary dissection *v* sentinel node biopsy	Part 1: Qualitative Part 2: Observational cohort study	Part 1: Positive feedback on the DA Part 2: Too small but possible reduction in decisional conflict and possibly improved decisional satisfaction, knowledge, and choice
Hawley et al[70] (iCanDecide)	537 US women with stage I/II breast cancer; mean age 57 (±11 years; range, 21-84)	Locoregional and systemic treatment decision making	RCT: iCanDecide interactive and tailored website *v* iCanDecide static website[6]	Tailored DA associated with high-quality decisions and greater knowledge compared with nontailored DA. No differences in values-concordant treatment decisions by arm
Ke et al[82] (screenshots of the DA in the appendix)	15 Singaporean women with breast cancer who completed primary treatment (age range, 46-67 years); eight health care professionals	Breast cancer survivorship	Mixed methods	All patients found the final DA easy to navigate with sufficient interactivity
Lam et al[71]	276 Cantonese-speaking or Mandarin-speaking Chinese women in Hong Kong with stage 0-III breast cancer; mean age DA arm, 56.8 ± 10.8 years (mean age of controls, 54.6 ± 10.1 years)	BCS and RT, mastectomy, mastectomy and reconstruction	RCT:DA (take-home booklet) *v* standard information booklet (control condition)	Receipt of DA led to significantly lower decisional conflict scores, lower decision regret, and lower depression scores
Minami et al[72] (DA available in the appendix)	33 US women age 70 or older, with stage I, ER+, HER2– breast cancer; mean age, 74.7 ± 3.8 years	Mastectomy *v* BCS; lymph node surgery, RT, endocrine therapy	Pretest-post-test trial	Nearly all participants strongly agreed that the DA was helpful and that it prepared them for treatment decision making. Knowledge significantly improved after receiving the DA
Mühlbauer et al[73] (SPUPEO DA; images of DA in the article)	Part 1: 20 German women with history of early-stage ER+, HER2– breast cancer; mean age, 60 (range, 32-77 years) Part 2: 86 German women with history of early-stage ER+, HER2– breast cancer; mean age, 51 (range, 27-76 years)	Displayed age-based noncancer prognosis stratified by history of breast cancer and also by comorbidity for women 65-84 years	Part 1: focus groups Part 2: online survey	The DA was found to be helpful, informative, and interesting

(Continued on following page)

TABLE 3. Patient DAs for Older Women With Invasive Breast Cancer: Studies That Included Women Age Older Than 65 Years in Testing and Were Published Since 2010[a] (Continued)

Reference	Participants	Decision	Methods	Results
Neve et al[74] (images of the DA in the appendix)	40 Canadian women undergoing or had undergone whole breast RT with stage I/II ER+, HER2–, breast cancer; median age 72 (range, 65-86 years)	Adjuvant RT including WBRT, APBI, and omission of RT	Pretest-post-test trial	Decisional conflict decreased after using the DA, and nearly all stated the DA was useful for future patients
Raphael et al[83]. (BRASA DA)	Dutch women with T0-T3, N0, or N1 breast cancer facing a choice about RT; control group mean age 60.4 (±11.3 years), intervention group mean age, 62.8 (±12.6 years)	RT (boost/no boost, chest was RT, low-risk breast cancer)	Preintervention and postintervention trial	Knowledge increased with receipt of the DA, and fewer chose additional RT. There was no change in decisional conflict with DA
Savelberg et al[81] (images of the DA in the appendix)	84 Dutch women with stage I/II breast cancer; mean age, 61.1 (±9.9 years)	Surgical treatment	Observational cohort study	SDM was high as measured by CollaboRATE; 67% of patients used the DA at home
Sivell et al[75] (Bresdex)	62 women from the United Kingdom with stage I/II breast cancer; mean age, 53.3 (range, 29-80 years)	Designed to support surgical decision making	Observational cohort study	After receiving the DA, readiness to make a decision increased. There was no significant improvement in knowledge
Ter Stege et al[84] (borstreconstructie keuzehulp)	17 Dutch women with a history of making a decision about breast reconstruction (mean age, 51.3 [range 31-77 years]) and 40 health care professionals	Breast reconstruction after mastectomy	Semistructured qualitative interview with patients, survey of health care professionals	The DA was perceived to be informative, helpful, and easy to use
Tucholka et al[76]	227 US women with stage 0-III breast cancer; median age, 59 (range, 27-80 years)	Considering breast surgery	RCT: standard cancer websites (breastcancer.org) *v* health dialog DA	Receipt of the DA was associated with higher knowledge; both arms found the interventions helpful
Vodermaier et al[77]	111 German women with stage I-III ER+ breast cancer; mean age, 55.2 (±11.0 years)	Surgical and systemic treatment	RCT: a 20-minute decision board intervention plus an information brochure *v* usual care	Receipt of the DA was associated with less decisional conflict; no effect on anxiety, depressive symptoms, or quality of life
Wong et al[78] (images of the DA in the article)	Part 1: 16 Canadian women with stage I, ER+/PR+ breast cancer completed WBRT; median age, 77 (range, 71-84 years) Part 2: 36 Canadian women with stage I, ER+/PR+ breast cancer receiving WBRT; median age, 75 (range, 66-95 years)	Adjuvant radiation therapy	Part 1: qualitative Part 2: pretest-post-test study	All women thought the DA was helpful and informative. Patients experienced less decisional conflict and were more knowledgeable after using the DA
Wyld et al[79] (Age Gap Decision Tool)	1,339 UK women with T1-3, N0-1, M0, breast cancer; mean age, 78 (±6 years; range, 70-99)	Surgery plus ET *v* PET; surgery *v* surgery plus chemotherapy	Cluster RCT of two DAs (surgery and ET *v* PET; chemotherapy *v* no chemotherapy) *v* usual care; 46 breast units were randomly assigned	Use of DAs increased knowledge, facilitated SDM, and increased use of PET and decreased use of chemotherapy; no effect on global quality of life

Abbreviations: APBI, accelerated partial breast irradiation; BCS, breast-conserving surgery; DA, decision aid; ER+, estrogen receptor–positive; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2–negative; PET, primary endocrine therapy; PR+, progesterone receptor–positive; RCT, randomized controlled trial; RT, radiotherapy; SDM, shared decision making; WBRT, whole breast radiotherapy.

[a]If the age range of patients in the study was not reported, studies were included where the mean age plus the standard deviation was 65 years or older.

Qualitative studies have found that trust in one's surgeon is a key factor influencing older women's breast cancer treatment decisions,[63] but surgeons may overestimate older women's recurrence risk and the benefits of radiation therapy after breast-conserving surgery,[87] that surgeons may lack familiarity with recommendations to omit SLNB and the data supporting this recommendation, and that surgeons may lack the skills to engage older women in SDM.[88] Physicians in general tend to underestimate patient desire to participate in treatment decisions, especially for older adults, and are often incorrect when they attempt to infer patient treatment preferences.[89,90]

There thus remains much work to be done on SDM improvement with older patients with breast cancer. Physicians need training in SDM and DA use overall, but specific to this population is the need for tactful integration of patient health and life expectancy into treatment conversations. The relative risks and benefits of treatment (or omission of treatment), and the concepts of overtreatment and undertreatment in this patient population, require broaching the topic of remaining life expectancy.[91] Since the benefits of breast cancer treatments (ie, reduction of breast cancer morbidity and/or mortality) may take years to achieve, it is necessary to estimate if an older women is likely to live long enough on the basis of her overall health to have a chance of benefitting. The ePrognosis website provides risk calculators to help clinicians estimate older adults' mortality within the next 14 years (eg, the Lee-Schonberg index). Patients with a >50% risk of mortality during a specific time (eg, 10 years) are estimated to have a life expectancy less than that time since life expectancy is the median survival of a population.

Using the Lee-Schonberg index as a brief method for geriatric assessment, Mott et al[92] developed and pilot-tested a strategy for oncologists for de-escalating radiation therapy after breast-conserving surgery and for omitting SLNB. Their strategy considers whether a patient is a minimizer (tends to prefer a wait and see approach) versus a maximizer (tends to prefer taking action), estimates patients' health and overall prognosis using the Lee-Schonberg index, and provides tailored scripts for clinicians to explain why radiation therapy after breast-conserving surgery and SLNB may not be beneficial. The 22 oncologists (15 surgeons/eight radiation oncologists) who tested this strategy found it useful, particularly the assessment of patients' 10-year prognosis; however, some were concerned with patients seeing their overall prognosis while others felt it helped foster communication. Evidence-based strategies for oncologists to incorporate discussion of patient overall health and life expectancy in treatment decisions are much needed.

SDM around breast cancer treatment may also be challenging because these decisions often involve the preferences and values of patient family members in addition to those of patients themselves. An analysis of physician notes of patients older than 80 years diagnosed with breast cancer found that 71% had a family member present during consultation and that treatment decision making often occurred collaboratively between older women, their families, and physicians.[93] Clinicians may want to assess patient preferences for family involvement in decision making, welcome and involve family involvement when appropriate, and recognize that family involvement in the decision-making process may start before the initial visit and continue afterward.[94]

This discussion of SDM has focused on treatment decisions faced by older women with low-risk breast cancers; however, older women with more aggressive breast cancers also face many breast cancer treatment decisions (eg, chemotherapy, immunotherapy), and the approach to SDM should be similar. High-quality SDM for breast cancer treatment decisions in older women must consider the lag time to benefit from each treatment, whether the patient has adequate remaining life expectancy to have a chance of benefiting from the treatment, how the patients value the potential benefits and risks of each treatment, and the patient's preferences. The lag time to benefit is the time between when a treatment is given and the time to when improvement in breast cancer survival would be expected based on data from clinical trials.[95] If the patient's life expectancy because of their other health conditions is shorter than the lag time to benefit from the treatment, the patient will be very unlikely to benefit from the treatment. A formal geriatric assessment may also help inform oncologists and older women of their likelihood of benefiting from treatment and may inform SDM.[96]

The complexity of treatment options set by the current breast cancer literature requires physicians to be skilled in SDM communication. To engage older women in SDM, Mulley and Sepucha recommend a multistep approach that includes (1) inviting a patient to participate; (2) presenting the treatment options; (3) the benefits and harms of each treatment, (4) eliciting patient priorities, concerns, or decisional needs; (5) facilitating deliberation with involvement of trusted others; and (6) then implementing the shared decision.[97] The Agency for Healthcare Research and Quality has published example language for clinicians to use for these conversations.[98] For example, to invite patients to participate, a clinician may say "I want to go over all the options so we can find a path that works for you" and to elicit patients' values and preferences, a clinician may say "As you think about your options, what's important to you?" To facilitate deliberation, a clinician may ask older women to describe their understanding of their treatment options and to encourage these patients to take time to consider their options and to consult trusted family or friends.

While preferred decisional roles can run the gamut from passive to active in older patients with breast cancer,[99] nearly all older women regardless of their preferred decision-making role want treatment decisions to incorporate their values and preferences. Therefore, physicians need the skills to facilitate high-quality decisions. As the oncologic community continues to work toward tailored individualized breast cancer care, effective, feasible, sustainable interventions aimed at improving SDM in older adults are much needed.

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BREAST CANCER

Managing a Long and Winding Road: Estrogen Receptor–Positive Breast Cancer

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overview

We review key topics in the management of estrogen receptor (ER)–positive human epidermal growth factor receptor 2–negative breast cancer. The single biggest challenge in management of this disease is late relapse, and we review new methods for identifying which patients are at risk of late relapse and potential therapeutic approaches in clinical trials. CDK4/6 inhibitors have become a standard treatment option for high-risk patients in both the adjuvant setting and the first-line metastatic setting, and we review data on optimal treatment after progression on CDK4/6 inhibitors. Targeting the estrogen receptor remains the single most effective way of targeting the cancer, and we review the developments in new oral selective ER degraders that are becoming a standard of care in cancers with ESR1 mutations and potential future directions.

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INTRODUCTION

In this section, we review key current topics in the management of estrogen receptor–positive breast cancer. We review therapeutic options that may reduce the risk of late relapse, how to optimally use CDK4/6 inhibitors in the clinic, and how the new class of oral selective estrogen receptor downregulators (SERDs) is entering clinical practice with elacestrant for patients with advanced *ESR1*-mutant breast cancer.

LATE RECURRENCES IN ESTROGEN RECEPTOR–POSITIVE BREAST CANCER: WHAT ELSE CAN WE DO?

The most prevalent form of breast cancer is characterized by hormone receptor–positive tumor cells[1]; in modern terminology, we call it luminal breast cancer.[2] Approximately two of three patients are affected with this subtype that is characterized by relatively limited, but long-term, risk of recurrence.[3] More than half of all disease recurrences occur after 5 years of the initial diagnosis, and a life time trade-off of these late relapses for the rather limited early recurrence risk exists.[4,5] Currently, all disease recurrences that occur after 5 years are called late; however, most clinical trial databases end at 10 years, and with the exception of the Oxford group, very few firm data exist for truly long-term results, for example, 20 or 30 years after diagnosis.[6,7]

Interestingly, prognostic factors affecting long-term risk are tumor size and nodal status, which are classical prognosticators for breast cancer.[8] Despite all research efforts, it is still not exactly understood how late relapse works in terms of biology, particularly how the disease survives for prolonged periods including those of effective adjuvant anticancer treatment. The most likely concept is that breast cancer cells can undergo epithelial-mesenchymal transition,[9] escape from the primary tumor into the circulation,[10] even before diagnosis, and that some of these cells can undergo mesenchymal-epithelial transition again, and gain the ability to home in the bone marrow, most likely in the endosteal niche.[11] In that niche, subtle changes of the microenvironment equilibrium between stimulating and calming factors are probably decisive for the fate of these cells, resulting in either quiescence and dormancy or senescence and apoptosis.[12] However, a completely unresolved mystery is how these cells remember that they originally came from a large or node-positive tumor, given that these classical risk factors appear to remain risk factors for late relapse, that is, awakening of the dormant cells.

Since we have effective adjuvant therapies that reduce the risk of relapse for luminal breast cancer, the idea of extending treatment durations is in fact intriguing. Since the risk of recurrence persists for longer than 5 years, why not increase treatment durations accordingly? Since the risk of disease recurrence persists for a long term in luminal breast cancer, extending the risk-reducing adjuvant antihormonal therapies for 10 years or longer in theory makes sense.

Unfortunately, this compelling idea has its limitations: Cumulation of side effects (potentially outweighing any benefit) and loss of therapeutic efficacy are limiting this concept in clinical practice. Apparently, breast cancer (seemingly including its dormant stem cells) develops resistance mechanisms over time, and none of our contemporary endocrine therapies, as efficacious as they are, comes without sometimes substantial tolerability issues. The former can be overcome by changing drugs for intervention[13]; in an attempt to

PRACTICAL APPLICATIONS

- Adjuvant CDK4/6 inhibition, with abemaciclib, substantially reduces the risk of relapse and is a standard of care for patients with high-risk disease.
- Elacestrant is a new treatment option for patients with advanced breast cancer and *ESR1* mutations in circulating tumor DNA.
- Oral selective estrogen receptor degraders are in multiple clinical trials with the potential to become a future mainstay of endocrine therapy.
- Late relapse remains a key challenge of treating estrogen receptor–positive breast cancer, with more than half of relapses occurring 5 or more years since diagnosis.

address different targets, the latter is challenging to overcome in clinical practice.

Oral selective estrogen receptor modulators (SERMs), such as tamoxifen and aromatase inhibitors (AIs), are the mainstay of adjuvant endocrine therapy (ET), and both classes of drugs have been studied extensively with respect to extending treatment durations. The ATLAS and aTTom trials provided signals that 10 years of tamoxifen decreased the risk of recurrence but did not affect overall mortality unequivocally, and the extension resulted in an increase in endometrial cancer and pulmonary embolism.[14,15] In postmenopausal women, adding AIs after 5 years of tamoxifen yielded significant improvements in three large clinical trials,[16-18] but the situation is less clear if AIs are already used in the first quinquennium of adjuvant therapy—the respective extension trials showed controversial results (trial results summarized in Table 1).[20,22,24,26] In summary, for the majority of patients with luminal early breast cancer, 7 years of adjuvant endocrine treatment appears to yield the optimal benefit/harm relation.[25]

Another concept of reducing the risk of long-term disease recurrence is adding additional drugs. Interestingly, bone-targeted therapies, such as adjuvant bisphosphonates, have been shown to reduce recurrences and breast cancer mortality,[27] only in the postmenopausal setting.[28] In addition to favorably have an impact on bone health impairments,[29-31] which are among the important side effects of endocrine therapies, antiresorptive therapies can apparently parch the bone microenvironment,[32,33] and this may disadvantage the reactivation of dormants, eventually reducing overt bone metastases or distant disease relapse after secondary spread to other organs.[34] Recently, it was shown that even relatively short-term adjuvant treatment with the anti-RANK ligand antibody denosumab reduces breast cancer recurrence many years after stopping the therapy.[35]

Other classes of drugs that can be added to standard endocrine therapies are CDK4/6 inhibitors. In addition, these inhibitors of cyclin-dependent kinases 4 and 6 have been practice changing in metastatic breast cancer (mBC) and are currently considered the standard of care in combination with ET for the first- or second-line treatments of advanced hormone receptor–positive breast cancer.[36-44] However, for early breast cancer, the addition of CDK4/6i has yielded mixed results. Although two large adjuvant studies of adjuvant palbociclib were negative,[45,46] the addition of abemaciclib to standard ET increased disease-free survival of high-risk patients significantly.[47,48] Whether this benefit will also have an impact on late recurrences remains to be seen, but abemaciclib is also used in the currently recruiting ADAPTlate trial (ClinicalTrials.gov identifier: NCT04565054) to address this question. Results of the adjuvant ribociclib study (NATALEE; ClinicalTrials.gov identifier: NCT03701334) will be presented at the ASCO 2023 meeting.

Another evolution of luminal breast cancer treatment has been the development of agents addressing alternate growth pathways of hormone receptor–positive tumor cells. The inhibition of mTOR, PI3CA, and AKT has been demonstrated to be effective at least in the subgroups of patients with mBC[49-52]; however, whether these drugs can be used in the adjuvant setting remains unanswered, partly because of the nontrivial side effect profile. Some of the new oral SERDs have also demonstrated the activity in the advanced setting and are rapidly moved to the early breast cancer field in large clinical trials, for example, giredestrant (lidERA Breast Cancer, ClinicalTrials.gov identifier: NCT04961996), imlunestrant (EMBER-4, ClinicalTrials.gov identifier: NCT05514054), elacestrant, and camizestrant (CAMBRIA-1, CAMBRIA-2). Since these agents appear to be particularly effective in patients with ESR-1 mutations that are associated with resistance toward standard endocrine therapy[53] or even be able to prevent them, they appear to be promising candidates for future treatment standards.[54]

The main challenge in addressing late breast cancer relapses is the identification of who is actually at risk. None of the aforementioned interventions will likely be without side effects, and even putting the financial toxicity issue for society aside, it is highly unlikely that all relapse-free patients, for example, at 10 years of follow-up, will undergo an additional therapeutic intervention to tackle their residual risk, which is probably around 1% per year at that stage. Thus, identification of patients at risk is crucial.

So far, multigenomic tests have been developed to assess risk, mainly to assist in the clinical decision making

TABLE 1. Trials of Extended Adjuvant Endocrine Treatment

Trial	Endocrine Therapy Before Random Assignment	Randomized Treatment	No. Premenopausal/ Postmenopausal	Follow-Up, Months	Outcomes		Toxicity
					DFS	OS	
aTTom[15]	Tam 5 years	Nil Tam 5 years	6,953 pre/post	108	RR = 0.75 4% absolute at 7 years	0.86 ns 2% absolute at 7 years	More endometrial cancer and PE with longer TAM; less ischemic cardial events
ATLAS[14]	Tam 5 years	Nil Tam 5 years	6,846 pre/post	Approximately 120	RR = 0.75 3.7% absolute at 7 years	RR = 0.71 ns 2.8% absolute at 7 years	More endometrial cancer and PE with longer TAM; less ischemic cardial events
MA-17[19]	Tam 5 years	Placebo AI 5 years	5,187 post	80[a]	HR 0.58 4.9% absolute at 7 years	HR = 0.82 ns HR (N+ = 0.61)	More hormone-related side effects with AI
ABCSG-6a[17]	Tam 5 years[b]	Nil AI 3 years	856 post	62.3	HR = 0.53, $P = .03$ 3.4% absolute at 10 years	HR = 0.89 ns	More hot flushes, asthenia, somnolence
NSABP B-33[18]	Tam 5 years	Placebo AI 5 years	1,598 post stage II-III	30[a]	RR = 0.68 ns 2% absolute at 4 years	Not reported	More arthralgia, fatigue, bone pain, fractures (ns)
NSABP B-42[20]	AI 5 years Tam->AI 5 years	Placebo AI 5 years	3,923 post stage I-IIIA	82.2	HR = 0.85 ns 3.3% absolute at 7 years	HR = 1.15 ns	More arterial thrombembolic events after 2.5 years with AI; HR 1.85 (1.18 to 2.88)
MA-17R[21]	Tam->AI 5+ years	Placebo AI 5 years	1,918 post stage I-III	75.6	HR = 0.66 4% absolute	HR = 0.97 ns	More bone related toxic effects with longer AI
DATA[22]	Tam 2-3 years	AI 3 years AI 6 years	1,860 post stage I-III	49.2	HR = 0.79 ns 0.8% absolute at 5 years	HR = 0.91 ns	More osteopenia/osteoporosis and arthralgia with longer AI
GIM-4[23]	Tam 2-3 years	AI 2-3 years AI 5 years	2,056 post stage I-III	140.4	HR = 0.79 5% absolute at 12 years	HR = 0.77 4% absolute at 12 years	More osteoporosis arthralgia/ myalgia and cardio vascular events with longer AI (1% v <1%); Fractures reported similar
IDEAL[24]	5 years (AI 29%, Tam 12%, Tam-> AI 59%)	AI 2-3 years AI 5 years	1,824 post stage I-III	79.2	HR = 0.92 ns Second primaries HR = 0.39	HR = 1.04 ns	Reported similar
ABCSG-16[25]	5 years (AI 7%, Tam 51%, Tam-> AI 42%)	AI 2 years AI 5 years	3,484 post stage I-III	118	HR = 0.99 ns	HR = 1.02 ns	Significantly more bone fractures with longer AI

NOTE. Adapted from Huber (unpublished data).

Abbreviations: AI, aromatase inhibitor; DFS, disease-free survival; N+, node positive; ns, nonsignificant; OS, overall survival; PE, pulmonary embolism; RR, risk ratio; Tam, tamoxifen.

[a]Closed prematurely.

[b]Half of the patients had received Tam/aminoglutethimide combination for the first 2 years (within trial ABCSG-6).

whether patients with early luminal breast cancer should also receive adjuvant chemotherapy.[55] Several of these tests have also been applied for the late recurrence setting[56-59]; however, for the majority, this constituted merely an extrapolation of a test developed on data sets of the first 5 years to the extended setting. Only Breast Cancer Index has demonstrated some utility in predicting the benefit of extended treatment durations.[60-62]

More recently, technology has evolved to detect circulating tumor DNA in the blood of patients with cancer. In addition to early detection and treatment effect monitoring, this may be the future of identifying patients with early breast cancer who are clinically cured but biologically on the verge of disease recurrence; promising early results have been reported.[63-65] However, many questions remain unanswered at this point of time.[66,67] In addition to issues of technology, frequency of testing, and affordability, most

effective interventions must be defined—not least because of ethical and patients communication aspects. Once we tell a patient that she might be at increased risk to experience disease recurrence soon, we should also have something to offer to her—ideally a clinical trial with some type of intervention. The results of such translational-clinical research projects will have to be awaited, for example, from the TREAT trial (ClinicalTrials.gov identifier: NCT05512364).

The dream of the future is that we could change our target. Although we become reasonably effective in targeting proliferating tumor cells, we are still close to clueless on how to identify, measure, and address the issue of dormancy and quiescence.[68-71] Only when we decipher their mysteries, we will effectively be able to identify, prevent, and treat late disease recurrence. This future time point will mark the beginning of an era in which we might humbly start talking about cure of this disease.

USING CDK4/6 INHIBITORS IN EARLY-STAGE AND ADVANCED HORMONE RECEPTOR–POSITIVE BREAST CANCER

Advanced Breast Cancer

The addition of CDK4/6 inhibition to the first-line ET of patients with advanced breast cancer (ABC) is the standard for the vast majority of patients with advanced estrogen receptor (ER)–positive human epidermal growth factor receptor 2 (HER2)–negative breast cancer. Given the good tolerability of CDK4/6 inhibitors, advancing age and minor comorbidities should not be a reason to give ET alone, although patients with significant comorbidities or poor performance status may occasionally not be appropriate. All three clinical CDK4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) have the same effect on progression-free survival (PFS) and are all recommended by the guidelines in combination with an AI or fulvestrant in patients who relapse on adjuvant AI.[72,73] Although ribociclib improved overall survival in combination with AI,[39] with abemaciclib numerically improving survival, palbociclib did not appear to improve OS in the PALOMA-2 trial.[74] Overall survival was an underpowered secondary end point, and there was substantial cross-over to receive CDK4/6 inhibitor after progression, and a negative finding for PALOMA-2 is a distinct possibility. Potentially, there is a genuine difference between palbociclib and ribociclib/abemaciclib that is somehow not captured in the PFS readout. Indeed, palbociclib is a relatively less selective inhibitor of CDK4,[75] compared with CDK6, with CDK6 inhibition thought to possibly limit the activity because of CDK6 inhibition in the bone marrow resulting in toxicity. Abemaciclib also weakly inhibits CDK2,[76] which may enhance abemaciclib activity.

Selection of which inhibitor to use in clinical practice is a matter of physician choice, with the use of palbociclib plus AI since the PALOMA-2 OS readout. Abemaciclib has a higher incidence of diarrhea, fatigue, and thromboembolism.[77] Both ribociclib and palbociclib have a higher incidence of bone marrow suppression and neutropenia. Ribociclib has a higher incidence of nausea and liver function test abnormalities (compared with palbociclib in cross-trial comparison) and rarely QTc prolongation.[78] General clinical advice is to consider switching between CDK4/6 inhibitors if the patient develops side effects characteristic of one inhibitor and not the other.[72]

Biomarker Selection of Patients for Advanced CDK4/6 Therapy

Given the efficacy of CDK4/6 inhibitors and relatively good tolerance, a high level of evidence for a biomarker would be necessary to omit therapy. Rarely, biomarker subsets have relatively advanced evidence of true resistance to therapy, especially in cancers with *RB1* loss mutations/deletions[79] (approximately 2% of treatment-naive breast cancer) and cancers with a basal-like gene expression profile[80] (approximately 2% of treatment-naive breast cancer). However, establishing both biomarkers robustly is challenging in the clinic, for example, identifying cancers with homozygous *RB1* loss (would be resistant) instead of heterozygous loss (not resistant), and the guidelines do not recommend testing for these defects. Rare *FAT1* mutations may also signify true resistance, but with the same challenge of identifying true homozygous loss.[81]

Multiple markers of lower benefit from CDK4/6 inhibitors have been identified, including *BRCA2* germline mutations,[82] high *CCNE1* expression,[83] gene expression signatures of high E2F signaling,[83] and high interferon signaling.[84] None of these are generally considered clinically useful, as the activity of CDK4/6 inhibitors is lower but still present in the resistant groups. Postmarketing surveillance has demonstrated a low approximately 1%-2% rate of pneumonitis on all three CDK4/6 inhibitors,[85] and physicians should be alert to this possibility in patients with respiratory symptoms.

Therapy After Progression on CDK4/6 Inhibitor

A substantial evidence base is developing on treatments after progression on CDK4/6 inhibition. After progressing on AI plus CDK4/6 inhibitor, it is clear that single-agent ET is substantially less efficacious than after progression on AI. For example, in the CAPITELLO-291 study, the median PFS on fulvestrant alone was 2.6 months (95% CI, 2.0 to 3.5) with previous CDK4/6 inhibitor treatment and was 7.2 months (95% CI, 4.8 to 7.9) without previous CDK4/6 inhibitor treatment.[86] Single-agent ET must be used cautiously in patients post-CDK4/6 inhibition and largely reserved for patients with low-volume nonvisceral disease, strong ER expression, and long response to previous ET, as well as substantially older or patients with substantial comorbidities. The exception may be those with *ESR1* mutations in liquid biopsies at progression,[53] as discussed in the next section.

Substantial evidence suggests that PI3 kinase inhibition with alpelisib in patients with *PIK3CA* mutations[87] is active post-CDK4/6 inhibition, and AKT inhibition with capivasertib (not licensed at the time of writing) in patients with AKT1 pathway variants (*PIK3CA*/*AKT1*/*PTEN* mutations) is also active post-CDK4/6 inhibition. Generally, such combination therapy should be considered instead of single-agent ET post-CDK4/6 inhibition. There are little data on the activity of mTOR inhibition post-CDK4/6 inhibitor, but there is no scientific rational to expect lower activity of everolimus, and the use of everolimus in *PIK3CA* or *AKT* pathway wild-type patients is generally considered.

Limited data suggest that continuation of CDK4/6 inhibition and changing of ET partner are beneficial. The phase II MAINTAIN trial randomly assigned patients who had progressed on ET plus CDK4/6 inhibitor to exemestane or fulvestrant with or without ribociclib,[88] with improvement in PFS (HR, 0.56; 95% CI, 0.37 to 0.83; $P = .004$). However, the phase II PACE study did not observe a benefit for continuing palbociclib in a similar random assignment (HR, 1.11; $P = .62$).[89] Few patients in MAINTAIN had previous ribociclib, whereas 90.9% of patients in PACE had previous palbociclib, possibly providing an explanation for the difference between studies. As both studies are phase II studies, there remains no high-quality evidence to support continuing CDK4/6 inhibition after progression in clinical practice; although if this is done, a switch in CDK4/6 appears advisable. Abemaciclib in phase II trials also appears to have single-agent efficacy after progression on a different CDK4/6 inhibitor.[90] There is also evidence that switching ET backbone on molecular, but not clinical progression, may be beneficial. In the PADA-1 trial, patients on AI plus palbociclib who develop detectable *ESR1* (ER) mutations in circulating tumor DNA liquid biopsies before clinical progression had improved PFS when AI was switched to fulvestrant (HR, 0.61, $P = 0.0040$),[91] and this is being investigated further in the SERENA-6 trial (ClinicalTrials.gov identifier: NCT04964934).

Adjuvant CDK4/6 Inhibition

Two years of adjuvant abemaciclib, in addition to AI with or without ovarian suppression, has become the standard therapy for high-risk patients with ER-positive and HER2-negative breast cancer. The initial results of the MONARCH-E trial showed benefit from adjuvant abemaciclib (HR, 0.75), although the report was after only a median follow-up of 15.5 months, with very few patients having completed a full 2 years of follow-up.[92] A recent update, after 42 months, demonstrated a further strengthening of benefit with an invasive DFS at 4 years of 85.5% in the abemaciclib arm versus 78.6% (HR, 0.653; 95% CI, 0.567 to 0.753; $P < .0001$).[48] There was clear evidence of carryover benefit with piecemeal analysis in 1-2 years of follow-up where HR = 0.674 and in 3+ years (after completing abemaciclib) where HR = 0.602.

Follow-up at this time is immature, but the clear evidence for hangover benefit beyond stopping adjuvant abemaciclib and 6.9% absolute benefit at 4 years of follow-up clearly suggests that abemaciclib should be offered to all high-risk patients within the criteria of the trial (four or more positive lymph nodes or one to three lymph nodes with one of the following additional features: tumor >5 cm, grade 3 tumor, and Ki67 >20%). Translational research on the MONARCH-E trial is eagerly awaited, and so far it is clear that high proliferation cancers (Ki67 > 20%) and lower proliferation cancers (Ki67 ≤20%) derive the same relative benefit,[48] although cancers with high Ki67 derive greater absolute benefit because of the association with a higher risk of relapse.[48]

The adjuvant setting appears to draw a clear difference between palbociclib and abemaciclib. In marked contrast to MONARCH-E, there was no benefit from 2 years of adjuvant palbociclib in PALLAS (HR, 0.96; 95% CI, 0.81 to 1.14; $P = .65$).[45] Although perhaps differences in trial design (lower-risk patients in PALLAS) and compliance (42% of patients discontinued palbociclib before the planned 2 years) might explain some difference; by far, the most plausible difference is between the two drugs in this adjuvant setting. In the metastatic setting, abemaciclib has a higher single-agent response rate in heavily pretreated endocrine-resistant disease than palbociclib and ribociclib. Early relapses in the adjuvant setting are dominated by cancers with high proliferation, which are relatively insensitive to ET, potentially matching more single-agent data in the metastatic setting. Abemaciclib weakly inhibits CDK2,[76] which possibly explains the higher level of activity in endocrine-resistant cancers and might possibly provide a mechanistic understanding of the different activity seen in the adjuvant setting.

There are no data yet on the treatment of patients who relapse after adjuvant abemaciclib. In the absence of evidence, it would seem reasonable in clinical practice to offer CDK4/6 inhibition again in the metastatic setting for those with at least a gap of 24 months since completing abemaciclib, and this may extend less certainly to include those with at least a gap to 12 months. It is unlikely that patients who relapse on adjuvant abemaciclib, or within a year of stopping, could derive significant benefit from further CDK4/6 inhibition at the time of relapse.

SERDs in Breast Cancer: Where Do We Stand?

The majority of breast cancers express ER α, which has been widely and successfully prosecuted as a drug target, although various classes of endocrine therapies approved for the treatment of ER+ breast cancer exist (Fig 1).[93]

AIs, such as anastrozole, letrozole, and exemestane, block the conversion of androgens to estrogen, decreasing levels of circulating estradiol (E2) and therefore reducing the activation of ER. SERMs (ie, tamoxifen) exert their action by binding to intracellular ERs and competing with estrogen. SERDs, such as fulvestrant and others, will inhibit the transcription of ER-regulated genes by hampering the open chromatin conformation of the ER when binding to the receptor, destabilizing it, and causing impaired mobility, which will result in the downregulation and degradation of the receptor protein.[94]

Intramuscular administration of fulvestrant limits its dosing, prompting the development of orally administered alternatives. Furthermore, ET resistance is a significant limitation of luminal breast cancer treatments, as approximately 15%-30% of patients will present de novo resistance mechanisms and 30%-40% will acquire resistance during ET.[95,96]

One of the most recognized and studied molecular mechanisms of therapeutic resistance is the appearance of ESR1 mutations, leading to ligand-independent activity and promoting tumor growth plus resistance to ET. Prevalence of such mutations depends on the duration of ET and can be detected in 20%-40% of patients previously receiving AI for mBC. Mutation rates have been observed to be much lower in the case of recurrent breast cancer and <1% in ET-naive patients, hence suggesting the acquisition of ESR1 mutations during AI treatment in the metastatic setting.[97,98]

ESR1 mutations can be detected via noninvasive detection of circulating tumor DNA (ctDNA) in the patient's plasma. Clinical trials (such as the SoFEA trial) have already demonstrated significantly better PFS with the use of SERDs (fulvestrant) than with AIs (exemestane). Furthermore, currently evaluated strategies implementing the use of ctDNA to determine ESR1 mutations may result in the establishment of a new predictive biomarker with implications in decision making for ET selection (ie, PADA-1 trial).[91,99]

Another established ET resistance mechanism is the growth promoting PI3K-AKT-mTOR and RAS/RAF/MEK/ERK pathways, through which ER-mediated transcription without estradiol binding can be reactivated, driving ER signaling-independent resistance. In addition, mutations in the cyclin-dependent kinase 4/6 (CDK4/6) cyclin D1 axis will frequently appear in ER+ BC inducing inactivation of retinoblastoma protein and resulting in tumor progression through cell cycle.[13,102]

Current Data With SERDs

First-line treatment of patients with ER+ mBC has pivoted to the use of CDK4/6 inhibitors in combination with ET; however, some patients will develop resistance to this approach, frequently because of ESR1 mutations. Currently, novel oral SERDs are being explored in this setting. Novel SERDs are associated with a higher bioavailability in comparison with fulvestrant, leading to greater efficacy.[103] Furthermore, oral administration results in a more convenient approach, as opposed to intramuscular for fulvestrant. Recently, data from phase II and III clinical trials have been communicated, highlighting differences for some of the new oral SERDs in development.

The first oral SERD to demonstrate significant survival improvement over standard-of-care treatment was elacestrant in the open-label, international, phase III EMERALD trial. In this study, patients with ER+/HER2– ABC were randomly assigned to receive oral elacestrant or standard-of-care ET (fulvestrant, anastrozole, letrozole, or exemestane), with two primary end points: PFS in all population and PFS in patients harboring ESR1 mutation.

Of the 478 patients randomly assigned, 228 had ESR1-mutated tumors. Elacestrant significantly improved median PFS in comparison with SOC (HR, 0.70; $P = .002$). The PFS rates in all patients at 6 months and 12 months were 34.3% and 22.3%, respectively, with elacestrant, compared with 20.4% and 9.4%, with SOC (HR, 0.70; $P = .0018$). For patients with *ESR1* mutations, PFS rates at 6 months and 12 months were 40.8% and 26.8%, respectively, with elacestrant, compared with 19.1% and 8.2% at 6 months and 12 months, respectively, with SOC (HR, 0.55; $P = .0005$).[53] Most adverse events (AEs) were mild, and no grade 4 treatment-related AEs (TRAEs) were reported. The most common AEs observed with elacestrant were nausea (35.0%), fatigue (19.0%), and decreased appetite (14.8%); grade 3 and 4 AEs were reported in 27.0% of patients in the elacestrant arm versus 20.5% in the SOC arm.[53] On the basis of these data, US Food and Drug Administration granted approval to elacestrant for postmenopausal women with ER+, HER2-negative, ESR1-mutated ABC or mBC with disease progression following at least one line of ET. Determination of ESR1 mutations is required through liquid biopsy, which is an approved companion diagnostic tool.[53] In addition, longer duration of benefit on previous endocrine and CDK4/6 inhibitor benefit was associated with more pronounced elacestrant benefit.

Giredestrant is another oral SERD that has been investigated compared with ET (fulvestrant or an AI) in patients with HR-positive and HER2-negative ABC, progressing after one or two lines of previous systemic therapy. The primary end point (investigator-assessed PFS) was not met. There was a numerical improvement of PFS with giredestrant compared with ET (5.6 months *v* 5.4 months; HR, 0.81; $P = .1757$). Higher clinical benefit and objective response rates were reported with giredestrant. PFS benefit was reported to be more pronounced in patients with ESR1 mutations (HR, 0.60; $P = .0610$).[104]

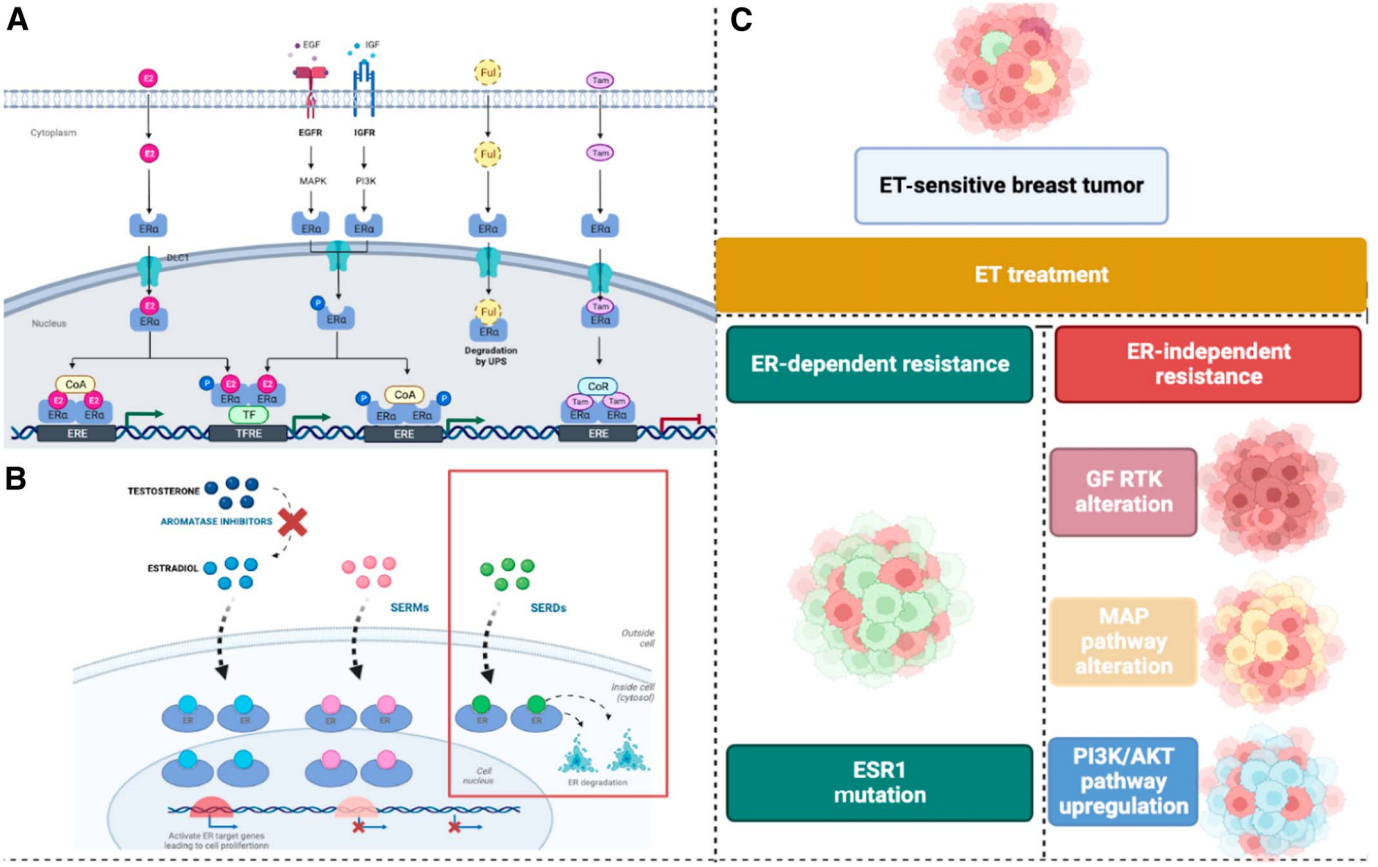

FIG 1. (A) Molecular pathways involved in ER functionality and the evolving mechanisms of resistance to ET. (B) Endocrine therapies and their mechanisms of action: AIs, SERMs, and SERDs. AIs block estrogen production through inhibition of androgen conversion to estrogens. SERMs inhibit the formation of the estrogen-ER complex. SERDs reduce the ability of translocation to the nucleus, thus inhibiting the transcription of ER-regulated genes and inducing the degradation of the ER-SERD complex consequently from impaired mobility. (C) ET resistance mechanisms upon ER dependence: ESR1 mutations will appear consequently after treatment with ET and mediate resistance through constitutive ER activity. ER-independent resistance is mediated via various mechanisms, such as mutations or amplifications of growth factor-driven RTKs (HER2, EGFR, and FGFR), alterations in MAPK pathway components (ie, KRAS, BRAF, MAP2K1, and NF1), and upregulation in the PI3K/AKT pathway. AI, aromatase inhibitor; AKT, protein kinase B; CDK, cyclin-dependent kinase; CoA, coactivator; CoR, coactivator receptor; E2, estradiol; EGFR, epidermal growth factor receptor; ER, estrogen receptor; ERE, estrogen response element; ERK, extracellular signal-regulated kinase; ESR1-mut, ESR1-mutant; ESR1-wt, ESR1 wild-type; ET, endocrine therapy; FGFR, fibroblast growth factor receptor; Ful, fulvestrant; GF RTK, growth factor-driven receptor tyrosine kinase; HER2, human epidermal growth factor receptor 2; IGF, insulin growth factor; MAPK, mitogen-activated protein kinase; MEK, meiotic chromosome-axis-associated kinase; mTOR, mammalian target of rapamycin; p, phosphate; PI3K, phosphoinositide 3-kinase; Rb, retinoblastoma; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; Tam, tamoxifen; TF, transcription factors; UPS, ubiquitin-proteasome system. Adapted from Lloyd et al[100] and Wang and Tang.[101]

A further oral SERD that demonstrated promising antitumor activity in initial phase I/II studies was amcenestrant. In the phase II AMEERA-3 trial, amcenestrant was compared with ET of physicians' choice in postmenopausal patients with HR-positive and HER2-negative ABC who had received ≤2 previous lines of ET and ≤1 previous chemotherapy or ≤1 targeted therapy for advanced disease. The study did not meet its primary end point, with the median PFS of 3.6 versus 3.7 months (HR, 1.051), and the development of amcenestrant was discontinued.[105]

Camizestrant is also a new oral SERD explored in the SERENA-2 trial: a phase II study in which 240 previously treated patients with HR-positive and HER2-negative ABC were randomly assigned to receive oral camizestrant at 75 or 150 mg once daily or fulvestrant with approximately one third of the patients having ESR1 mutations. Camizestrant demonstrated a statistically significant benefit in the median PFS at 75 mg and 150 mg, compared with fulvestrant (7.2, 7.7, and 3.7 months and adjusted HR, 0.58 and 0.67, respectively). In patients with ESR1 mutations, the median PFS with camizestrant 75 mg was 6.3 months and

9.2 months with camizestrant 150 mg while the PFS with fulvestrant was reported at 2.2 months (HR, 0.33 and 0.55, respectively). Regarding safety, grade 3 or above TRAEs occurred in 1.4% of patients receiving camizestrant 75 mg, 2.7% receiving camizestrant 150 mg, and 1.4% in those treated with fulvestrant.[106]

Tolerance of oral SERDs has generally been acceptable, with the most class-related frequent side effects being grade 1-2 nausea and fatigue. Arthralgia and hot flushes, common with AIs, have also been seen with some SERDs. For elacestrant, gastrointestinal toxicity has been reported as nausea, dyspepsia, and vomiting, although capsule formulation had a higher prevalence compared with tablets. Other toxicities of special interest are bradycardia, reported with camizestrant and giredestrant, and visual disturbance, only with camizestrant.[107,108]

Oral SERDs have demonstrated promising results in patients with ESR1 mutations. However, some tumors may lose sensitivity to ET by the activation of other pathways such as membrane receptors (HER2, EGFR, and FGFR), upregulation of oncogenic transduction (MAPK and PI3K/AKT), and dysregulation of the cell cycle through the cyclin D1/CDK4/6 pathway, hence the rationale for combinations with other targeted drugs.

Currently, oral SERDs are being studied in combination with CDK4/6 blockade in treatment-naive ABC where ESR1 mutations are less frequent (SERENA-4, ClinicalTrials.gov identifier: NCT04711252; persevERA, ClinicalTrials.gov identifier: NCT04546009). Other examples of combinations with targeted therapies are the EMBER clinical trial evaluating imlunestrant combined with alpelisib (ClinicalTrials.gov identifier: NCT04188548); the AKT inhibitor capivasertib is being combined with camizestrant in the SERENA-1 trial (ClinicalTrials.gov identifier: NCT03616587); camizestrant and imlunestrant are also being explored in combination with the mTOR inhibitor, everolimus, which acts as a downstream of the PI3K/AKT pathway.

Finally, these new ER-targeting agents are being evaluated in the window of opportunity (WoO) and neoadjuvant studies, allowing for in vivo activity evaluation, biomarker and pharmacodynamics change assessment, and prediction of their activity in the adjuvant setting.[109,110] ELIPSE (with elacestrant, ClinicalTrials.gov identifier: NCT04797728) SERENA-3 (camizestrant, ClinicalTrials.gov identifier: NCT04588298), and CooPERA (giredestrant, ClinicalTrials.gov identifier: NCT04436744) are some of the examples of WoO studies evaluating novel SERDs. Data from the CooPERA study have already demonstrated superior Ki67 reduction with 2 weeks of single-agent giredestrant versus anastrozole and have guided the development of studies in the adjuvant setting, such as the lidERA trial (ClinicalTrials.gov identifier: NCT04961996).

Liquid biopsy in the adjuvant and metastatic setting is an opportunity for the longitudinal collection of ctDNA, with early detecting of the emergence of ESR1 mutations, and guiding the design of studies where switching the treatment is prompted by the discovery of these mutations (SERENA-6, ClinicalTrials.gov identifier: NCT04964934).

FUTURE CONSIDERATIONS

We are witnessing the arrival of an improved drug class, resulting in an encouraging therapeutic strategy for patients with tumors expressing ESR1 mutations in the metastatic stage, as well as the dawn of the liquid biopsy era. Significant progress can be achieved by developing methods to identify patients whose tumors continue to have ER signaling in the metastatic stage, with greater precision than just identifying ESR1 mutations. This will enable the identification of individuals who are most likely to benefit from new therapies, a crucial step forward.

On the other hand, resistance to treatment may require several driver events to occur synergistically. In pretreated mBC, tumor heterogeneity suggests that genomic and nongenomic resistance drivers may emerge simultaneously during therapy. Therefore, further research is critical to understand the impact of these drivers on drug sensitivity.

The potential for next-generation SERDs to revolutionize the treatment of ER+ breast cancer is significant. As we continue to gather more clinical trial data, assessing the effectiveness and tolerability of these agents as ET backbones in monotherapy and in combinations will be essential to understand their impact on outcomes and identify where they fit into standard practice.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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BREAST CANCER

Advances in the Management of Menopausal Symptoms, Fertility Preservation, and Bone Health for Women With Breast Cancer on Endocrine Therapy

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overview

In patients with hormone receptor–positive early-stage breast cancer, adjuvant endocrine treatment administered for up to 5-10 years after diagnosis significantly reduces the risk of recurrence and death. However, this benefit comes with the cost of short- and long-term side effects that may negatively affect patients' quality of life (QoL) and treatment adherence. Among them, the prolonged estrogen suppression associated with the use of adjuvant endocrine therapy in both premenopausal and postmenopausal women can induce life-altering menopausal symptoms, including sexual dysfunction. Moreover, a decrease in bone mineral density and an increased risk of fractures should be carefully considered and prevented whenever indicated. For young women diagnosed with hormone receptor–positive breast cancer with unfulfilled childbearing plans, several challenges should be addressed to manage their fertility and pregnancy-related concerns. Proper counseling and proactive management of these issues are critical components of survivorship and should be pursued from diagnosis through the breast cancer care continuum. This study aims to provide an updated overview of the available approaches for improving the QoL of patients with breast cancer receiving estrogen deprivation therapy, focusing on advances in the management of menopausal symptoms, including sexual dysfunction, fertility preservation, and bone health.

INTRODUCTION

Hormone receptor–positive disease is the most common breast cancer subtype, and endocrine therapy is the mainstay of treatment. In early-stage breast cancer, adjuvant tamoxifen or an aromatase inhibitor (AI), in addition to ovarian function suppression (OFS) in premenopausal women, are associated with a significant reduction in the risk of recurrence and death.[1-3] However, this benefit comes with the cost of potentially distressing short- and long-term side effects that negatively affect patients' quality of life (QoL) and decrease treatment adherence.[4]

The acute toxicity of (neo)adjuvant chemotherapy is often reversible and generally lasts for a limited treatment period. By contrast, adjuvant endocrine therapy is administered for up to 10 years, during which side effects may be constant and, if untreated, irreversible.[5] While the expected benefits of endocrine therapy in reducing disease recurrence are well known, its undesirable side effects are underestimated and only sometimes optimally managed.[6] Nowadays, treating the physical and psychological effects of cancer and its therapy are considered critical components of survivorship care,[7] and not addressing these concerns can adversely affect treatment adherence. Proactive management of the symptoms and associated burden of endocrine therapy is a complex balance of tolerability, treatment adherence, and QoL.[4]

This study aims to review the available approaches for improving the QoL of patients with breast cancer who are receiving endocrine therapy, focusing on advances in the management of menopausal symptoms, including sexual dysfunction, fertility preservation (FP), and bone health.

HOT FLASHES AND GENITOURINARY SYNDROME OF MENOPAUSE

While antiestrogen therapy effectively reduces breast cancer risk in both the preventive and adjuvant settings, prolonged estrogen suppression below the normal postmenopausal range and estrogen receptor modulation can induce life-altering menopausal symptoms, such as hot flashes, vaginal dryness, and painful sex. Overlooking life-altering disruptions in sexual health and overall well-being influences treatment adherence and negates our efforts to improve oncologic outcomes.[4]

Vasomotor Symptoms

One of the hallmarks of estrogen suppression is the onset of hot flashes caused by a disruption in the

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PRACTICAL APPLICATIONS

- Addressing the physical and psychological effects of cancer and its treatment are critical components of survivorship care. For patients receiving adjuvant endocrine therapy, proper counseling and proactive management of treatment sequelae and their associated burden will improve patients' quality of life and optimize treatment adherence.
- Vasomotor symptoms are reported in more than 80% of women on antiestrogen therapy and are typically more severe in younger patients. Aside from behavioral modifications, clonidine, gabapentin, attenuated doses of antidepressants (serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors), and oxybutynin effectively decrease hot flash frequency and severity. However, treatment should take into account patient comorbidities and side effect profiles.
- Genitourinary syndrome of menopause can manifest as not only vaginal dryness but also increased infections, painful sex, and recurrent bladder infections. Treatment should include a discussion on reducing contact with potential irritants, regular use of a nonhormonal moisturizer, and an appropriate lubricant for sexual activity. Some patients may also benefit from vaginal dilators and pelvic floor physical therapy. Patients with severe disruptions in the genitourinary examination or nonresponsive to nonhormonal therapies should be offered low-dose vaginal estrogen or dehydroepiandrosterone after discussing the potential risks and benefits of treatment.
- Young women with breast cancer are at risk for infertility after receiving gonadotoxic chemotherapy. While endocrine therapy is not directly gonadotoxic, the time during which it is administered results in additional age-related declines in fertility. Options for fertility preservation should be discussed and offered before treatment to maximize opportunities for conception. It is reasonable for appropriately selected women to take a break from endocrine therapy after 18-30 months to try to conceive.
- Estrogen deprivation is a significant cause of reduced bone mineralization and increased risk of fractures. Hence, in patients with breast cancer receiving adjuvant endocrine therapy, proper attention to and monitoring of bone health is required. Whenever indicated, several strategies exist for preventing bone demineralization and reducing the risk of fractures in this setting.

hypothalamic perception of core body temperature. Hot flashes are common in women on endocrine therapy and are reported in 80% of women on tamoxifen and 93% with the addition of ovarian suppression. Hot flashes are typically more severe in younger patients and can negatively affect QoL.[4]

Aside from behavioral modifications such as exercise, avoiding triggers, and dressing in layers, randomized trials have shown cognitive behavioral therapy to be effective.[8] Data are mixed regarding the effectiveness of acupuncture.[9] Clonidine is a centrally acting alpha agonist that showed a 37% reduction in hot flashes but may lead to sleep disruption, dry mouth, and constipation.[10] Gabapentin is only effective at the 900 mg/d dose (300mg three times/day), which can induce significant sedation if not carefully tapered up.[11] Serotonin reuptake inhibitors (fluoxetine and paroxetine)[12,13] and serotonin-norepinephrine reuptake inhibitors (venlafaxine)[14] resulted in a more than 50% reduction in hot flashes, but side effects and concern for interaction with tamoxifen have limited their use.[15] Of note, sexual dysfunction symptoms, such as hypoactive desire and orgasm dysfunction, are prevalent in up to 80% of individuals taking antidepressants.[16] Oxybutynin (2.5 mg or 5 mg twice a day) was shown to significantly reduce hot flashes and improve QoL measures in a recent placebo-controlled trial and seems to be relatively well-tolerated. Side effects of oxybutynin during the 6-week course of the trial resembled those of other anticholinergics and include dry mouth, abdominal pain, and difficulty urinating.[17]

Genitourinary Syndrome of Menopause: Dryness and Atrophic Changes

The constellation of gynecologic sequelae ranging from dryness to recurrent urinary tract infections is termed genitourinary syndrome of menopause (GSM). Patient-reported dryness, itching, stinging, burning, and dysuria should alert the provider to the presence of atrophic changes to the mucosa of the vulva and the vagina. These hypoestrogenic effects may prompt women to apply a variety of over-the-counter topical therapies, including feminine washes, alcohol-based wipes, supermarket moisturizers, and other products with artificial fragrances. Patients should be counseled on the difference between moisturizers (to be used at regular intervals for treating GSM) and lubricants (PRN application), and encouraged to select their own lubricant while paying attention to potential offending ingredients. Silicone-based lubricants are preferred due to duration of action and less sticky, although water-based lubricants should be used with silicone non-compatible condoms or silicone devices.

The first step in mitigating the irritation and burning associated with GSM is minimizing exposure to potential irritants.

Patients should avoid potential offenders and start a vaginal moisturization regimen with a simple emollient such as single-ingredient organic coconut oil, which also has natural antimicrobial and antifungal properties[18]; however, it should not be used with condoms. A nonhormonal vaginal moisturizer with hyaluronic acid can be added once the burning symptoms abate, and these are available in creams, gels, and suppositories.[19] Vaginal moisturizers are intended to be used at least several times per week on a long-term basis. Patients should be counseled regarding the difference with lubricants, which have only short-term effectiveness for immediate sexual activity. Finally, patients should be encouraged to read labels and avoid products with artificial fragrances, parabens, petroleum, propylene glycol, and glycerin.[20]

Consistent use of a hyaluronic acid vaginal moisturizer can significantly improve symptoms of dryness, irritation, and painful sex.[19] However, prolonged estrogen deprivation can induce more dramatic changes in vaginal architecture, resulting in vaginal shortening, stenosis, and even a complete inability to participate in sexual activity. For these patients, adding low-dose vaginal hormones (either estradiol or dehydroepiandrosterone [DHEA]) can improve elasticity and promote collagen remodeling, especially if used with a vaginal dilator.[21]

The most effective treatment of GSM is vaginal estrogen, which promotes lactobacillus recolonization, increases vaginal blood flow, heightens sexual response, and improves mucosal thickness and elasticity.[21] However, previous pharmacokinetics studies of large (25 mcg given nightly for two weeks, then twice weekly) doses of vaginal estradiol applied to untreated atrophic mucosa found increased estradiol levels in the blood.[22] While usually short-lived, this potential for systemic absorption limits provider comfort with its use in women with a history of breast cancer. Notably, this absorption is less likely to occur with lower doses of commercially available vaginal estradiol tablets (4 mcg and 10 mcg nightly 1-2 times per week), along with the low-dose estrogen vaginal ring (2 mg estradiol delivering 7.5 mcg per 24 hours for 3 months).[23] Application to less atrophic mucosa after a period of nonhormonal moisturizer use may also further decrease the risk of absorption.

Overall, observational data have not suggested an increased risk of breast cancer recurrence with the use of vaginal estrogen.[24] However, a recent retrospective study of Danish patients treated for breast cancer between 1997 and 2004 suggested an association with breast cancer recurrence in a subset analysis limited to those on AIs.[25] Notably, treatment of this cohort predated the use of human epidermal growth factor receptor 2–targeted agents, when recurrence rates were higher, and potential confounders of recurrence, such as physical inactivity and body mass index, were not accounted for. Finally, the timing of recurrence was not defined, which is relevant since early recurrences are more likely to be attributed to residual disease than vaginal estrogen use.[26] Therefore, these data should be considered in the context of balancing an increased risk of recurrence due to noncompliance with endocrine therapy with a possible slight increase in recurrence risk with vaginal estrogen therapy (Fig 1).

For patients with external dyspareunia (pain with insertion), vaginal androgens are an additional adjunct that share some functions of vaginal estrogen but may better address persistent pain. The only US Food and Drug Administration (FDA)–approved androgen for vaginal use is an intravaginal tablet of 6.5 mg prasterone nightly or synthetic DHEA. DHEA is converted to either testosterone or dihydrotestosterone in the vulva and vagina and works similarly to vaginal estradiol while also targeting androgen-specific vulvovaginal receptors for pain. The active forms of testosterone are inactivated by glucuronidation before being eliminated through the circulation.[27] Prasterone's functioning through intracrinology may constitute a more palatable version of vaginal hormones for cancer care providers and patients with cancer. While the testosterone derivatives may be converted to estrogens by aromatase, a double-blind Alliance trial found that women on AIs experienced GSM symptom improvement without significantly increasing circulating estradiol.[28] In summary, vaginal DHEA or vaginal estrogen may be recommended to appropriately counseled patients who do not respond to nonhormonal therapies according to a 2018 American Society of Clinical Oncology Guideline Summary.[29]

Compounded vaginal testosterone is effective for the treatment of GSM. One study found that women treated with a very low dose (300 mcg nightly) for four weeks had serum estradiol levels that remained below the menopausal range cutoff (20 pg/mL).[30] However, there is not currently an FDA-approved version of vaginal testosterone. As with all compounded therapies, patients should be counseled that purity and efficacy are not monitored, and there is no government dosing regulation. The medical indication should be documented, and patients should be provided the financial disclosures of prescribers, pharmacists, and pharmacies. Furthermore, compounding pharmacists should provide written warnings of potential adverse effects, clearly stating that the preparation is not government-approved.[21,31]

GSM: Vaginal Stenosis and Levator Spasm

Untreated GSM may progress to vaginal shortening and narrowing, known as vaginal stenosis (VS). First described in women undergoing pelvic radiation, it has also been reported in women receiving estrogen-suppressing therapies and may manifest as the sensation of hitting a wall when intercourse is attempted. For example, in a South Florida sexual health after cancer program, approximately half of the women on

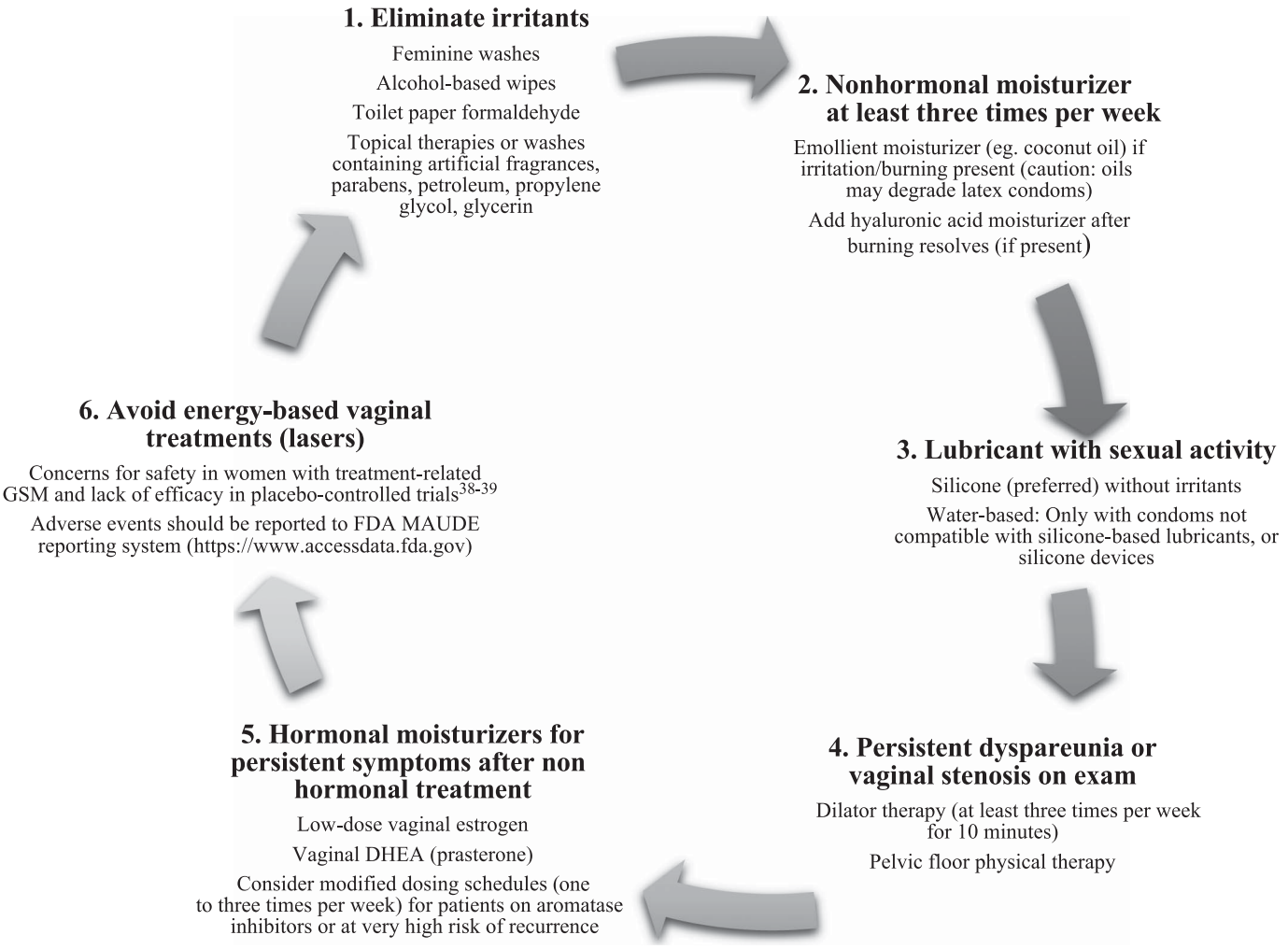

FIG 1. GSM treatment algorithm. FDA, US Food and Drug Administration; GSM, genitourinary syndrome of menopause.

antiestrogen therapy presenting for treatment of sexual dysfunction were found to have VS, making penetrative intercourse extremely painful and/or impossible.[32]

Patients who have experienced episodes of painful sexual activity may develop anticipatory anxiety, leading to pelvic floor muscle spasm during intimacy. For these patients, along with those found to have stenotic changes on examination, treating the atrophic mucosa with an appropriate moisturizer combined with dilator therapy improves elasticity and provides biofeedback during pelvic floor relaxation exercises. The effectiveness of consistent vaginal dilator use (three times per week for 10 minutes per session) has been reported in several studies.[33-35] However, patient adherence to a vaginal dilator regimen is low, with only half continuing use at 6 months.[36] Pelvic health physical therapists can be a critical resource for patients with pelvic floor muscle spasm or VS on pelvic examination. These specially trained physical therapists can work one-on-one with patients to develop a specialized treatment plan, including therapeutic exercise, manual therapy, dilator work, and biofeedback. Future initiatives should focus on improving provider and patient comfort with recommending and using dilators.[37]

Caution: Vaginal Lasers

Inadequate screening and treatment of women's sexual health disorders have fostered an environment where patients seek alternative therapies for treating GSM, some of which include the term vaginal rejuvenation. Intravaginal treatment with energy-based devices such as CO_2 and radioablative lasers is being marketed specifically to patients with breast cancer, but the lack of quality research demonstrating benefit and an ongoing concern for patient harm should dissuade clinicians from directing patients toward these therapies.

These procedures (currently not covered by insurance) were not shown to be effective in two sham-controlled

prospective trials. Eighty-five patients with GSM were randomly assigned to two treatments with a CO_2 laser or a sham laser therapy (where the device was inserted but not completely activated). There was no significant difference between the laser and the sham group with regard to patient-reported symptoms, vaginal health indices, QoL scores, or histologic comparisons.[38] A 2023 double-blind, sham-controlled trial of women on AIs randomly assigned to 5 monthly sessions of laser or sham laser therapy found similar results.[39] Furthermore, patients with cancer treatment-related severe GSM may be susceptible to abnormal healing after treatment with these devices designed to induce microscopic injury followed by collagen formation. Most of the commercially available devices were not FDA-approved to be used in the vagina but instead cleared for use through a fast-tracking program of the FDA known as 510(k), where manufacturers may register their devices without the FDA explicitly examining whether the devices are safe or even effective. In 2018, the FDA issued an advisory warning to consumers about bad actors promoting the unapproved, deceptive devices and described how numerous cases of vaginal burns, scarring, and chronic pain had been reported.[40] At least seven manufacturers were warned to cease advertising their products for an unapproved use. Patients who have experienced adverse events are encouraged to submit their experience to the FDA's Manufacturer and User Facility Device Experience (MAUDE) online database (https://www.accessdata.fda.gov).

FERTILITY PRESERVATION

Breast cancer is the most common malignancy diagnosed in women, and approximately 10% of new cases are diagnosed in women of reproductive age.[41] Unfortunately, many will not have realized or completed their family building plans at diagnosis. With survival rates reaching 90%, FP and family building are paramount.[42] Many women with cancer express their desire to have children, and the interruption or inability to do so causes significant distress. Existing guidelines recommend fertility counseling and FP referral for all individuals at risk for cancer-related infertility; however, overall utilization remains low.[43-45]

Treatment of breast cancer introduces several unique challenges regarding FP. The use of gonadotoxic chemotherapy can result in premature ovarian insufficiency, and the risk of negative reproductive impact increases with age. Alkylating agents are known to be highly gonadotoxic, but many other agents also carry some degree of risk; for newer agents, such as targeted therapies and immunotherapies, the reproductive risk is mostly unexplored.[46] Additionally, for women with hormone receptor–positive disease, the need for endocrine therapy for 5-10 years results in a reproductive hiatus, leading to an age-related decline in fertility.

Many women strongly desire and prefer having biological children, which emphasizes the need to discuss FP measures before initiating cancer treatment. Fortunately, several viable FP options exist for women diagnosed with breast cancer. The standard of care for FP before cancer treatment is assisted reproductive technologies (ART)—embryo cryopreservation and oocyte cryopreservation.[47] Both involve stimulation of the ovaries with injectable gonadotropins to recruit multiple follicles containing oocytes followed by oocyte retrieval (most commonly performed transvaginally). This process takes approximately two weeks and requires multiple visits for monitoring. Recent advances in ART have made FP more feasible for women with a new breast cancer diagnosis, including random start protocols, consecutive ovarian stimulation cycles (when feasible from an oncology perspective), and estrogen-lowering adjunctive agents.

While ovarian stimulation cycles are traditionally started based on menstrual cycle timing, random start protocols allow for the initiation of stimulation at any point during the menstrual cycle. This is of particular benefit in women for whom delaying gonadotoxic treatment for more than two weeks is not possible. Fortunately, outcomes of random start protocols are comparable with traditionally timed protocols, with the greatest difference being slightly longer periods of stimulation and higher doses of gonadotropins used.[48] While pursuing FP may slightly delay the initiation of cancer treatment in women with early-stage breast cancer, there is no difference in invasive disease-free survival (74 *v* 67%) or overall survival (84 *v* 81%) at 5 years.[49]

Consecutive ovarian stimulation cycles (ie, repeated stimulation of the ovaries over successive cycles) are safe and effective for FP in selected patients with breast cancer who may have lower ovarian reserve and oocyte yields by increasing the total number of oocytes retrieved without negatively affecting cancer treatment outcomes.[50]

One safety concern when performing ART for women with estrogen-sensitive breast cancer is the potential effect of the supraphysiologic estradiol levels reached during ovarian stimulation on tumor progression. Administration of AIs (letrozole) or selective estrogen receptor modulators (tamoxifen) in addition to stimulatory gonadotropins allows multifollicular development without a significant increase in estradiol levels. Use of these adjunctive agents during ovarian stimulation has resulted in comparable oocyte yield without increasing the risk of recurrence or compromising overall survival.[51,52]

There are additional benefits to using ART in women with hereditary breast cancer syndromes. Having embryos from ART allows for preimplantation genetic testing for monogenomic/single-gene defects (PGT-M) where cells sampled from fertilized embryos are tested for genetic mutations.[53]

This allows for the selection of embryos that do not carry mutations known to increase the risk of cancer. There is also evidence that *BRCA* carriers are at increased risk for diminished ovarian reserve (DOR), a loss of ovarian function that places them at increased risk of infertility even in the absence of gonadotoxic cancer treatment, although the association of *BRCA* pathogenic variants and DOR remains controversial.[54] The use of ART allows women with DOR to maximize their reproductive potential in a way they would not be able to with attempts at spontaneous conception. Finally, women with germline *BRCA* pathogenic variants are recommended to undergo risk-reducing bilateral salpingo oophorectomy between age 35 and 40 years for *BRCA1* carriers and between age 40 and 45 years for *BRCA2* carriers or after childbearing is complete; if they have cryopreserved eggs or embryos, they still have the opportunity to conceive without delaying surgery.[55]

There are women for whom ART is not an appropriate option, most commonly because of limited time or medical concerns. These women have alternative FP options that may be considered. Ovarian tissue cryopreservation (OTC; ie, the surgical removal of an ovary or ovarian tissue fragments typically completed via laparoscopy with cryopreservation of ovarian cortex and eventual reimplantation of this tissue) may be appropriate for women younger than 35 years who do not have time or do not wish to undergo ovarian stimulation. While OTC is no longer considered experimental and has resulted in approximately 200 births worldwide,[56] it is much less widely practiced than oocyte and/or embryo cryopreservation and should only be performed by providers with experience in this technique.[57-59]

Ovarian suppression is another option for minimizing the impact of chemotherapeutic agents on ovarian function and potentially also on fertility. Gonadotropin-releasing hormone (GnRH) agonists are used to decrease the release of gonadotropins from the pituitary gland, decreasing follicular development in the ovary. This causes the ovaries to become quiescent during gonadotoxic treatment and seems to reduce the risk of chemotherapy-induced premature ovarian insufficiency and to improve the rates of pregnancy after treatment completion.[60,61] While the use of GnRH agonists reduces the likelihood/risk of developing chemotherapy-induced premature ovarian failure in premenopausal women with breast cancer, for patients interested in FP, it should not be substituted for other methods of FP. The menstrual suppression that results from the use of GnRH agonists is an additional benefit, which reduces concerns regarding menstrual bleeding and anemia in the setting of chemotherapy-related bone marrow suppression. Patients who receive ovarian suppression with GnRH agonists during chemotherapy should be counseled on the high likelihood of the acute onset of side effects associated with hypoestrogenemia, including hot flashes, night sweats, changes in mood, insomnia, fatigue, diminished sexual interest, vaginal dryness, dyspareunia, and bone pain.

In patients who have completed cancer treatment resulting in infertility, several options exist for family building, including use of donor oocytes, donor embryos, or traditional adoption. However, these options do require investment of significant time, energy, and money and are not always widely available.

Historically, women with a history of breast cancer were advised not to become pregnant, but recent data have changed the paradigm for pregnancy after breast cancer. Available data show that in women who completed proper treatment and follow-up for breast cancer, pregnancy does not worsen oncologic outcomes,[62,63] even with a history of hormone receptor–positive disease[64,65] or in *BRCA* carriers.[66] Despite these outcome data, women with a history of breast cancer understandably express fear of recurrence in the context of stopping endocrine therapy for childbearing.[67] Fortunately, recent data from a large international trial (POSITIVE trial) showed that interrupting endocrine therapy after 18-30 months did not worsen short-term oncologic outcomes in women with a history of mostly stage I or II breast cancer. While the majority of women resumed endocrine therapy after conception attempts, 24% had not, raising concerns about compliance and longer-term safety.[68]

While breast cancer remains both common and likely to affect fertility in its survivors, significant advances in both cancer treatment and fertility treatment have made it more possible than ever for breast cancer survivors to build their families in various ways. Despite these advances, many significant barriers still exist. For example, there is inadequate psychological and decision support for women making choices about FP and the pursuit of pregnancy after cancer treatment. Finally, financial access to FP remains a formidable obstacle, with single cycles costing on average $8,000 US dollars (USD) for oocyte cryopreservation and $10,000 USD for embryo cryopreservation in the United States, plus the cost of medications, any desired genetic testing, long-term storage, and eventual embryo transfer. Currently, only 13 US states mandate insurance coverage of FP, making it a financial impossibility for many[69] (Fig 2). Only by addressing each of these barriers through research and policy can we ensure holistic, comprehensive care for all young women diagnosed with breast cancer.

BONE HEALTH

In women, the rate of bone loss increases with age, and estrogen deficiency is its primary cause.[70] Estrogen deprivation due to endocrine therapy in premenopausal and postmenopausal women with breast cancer accelerates

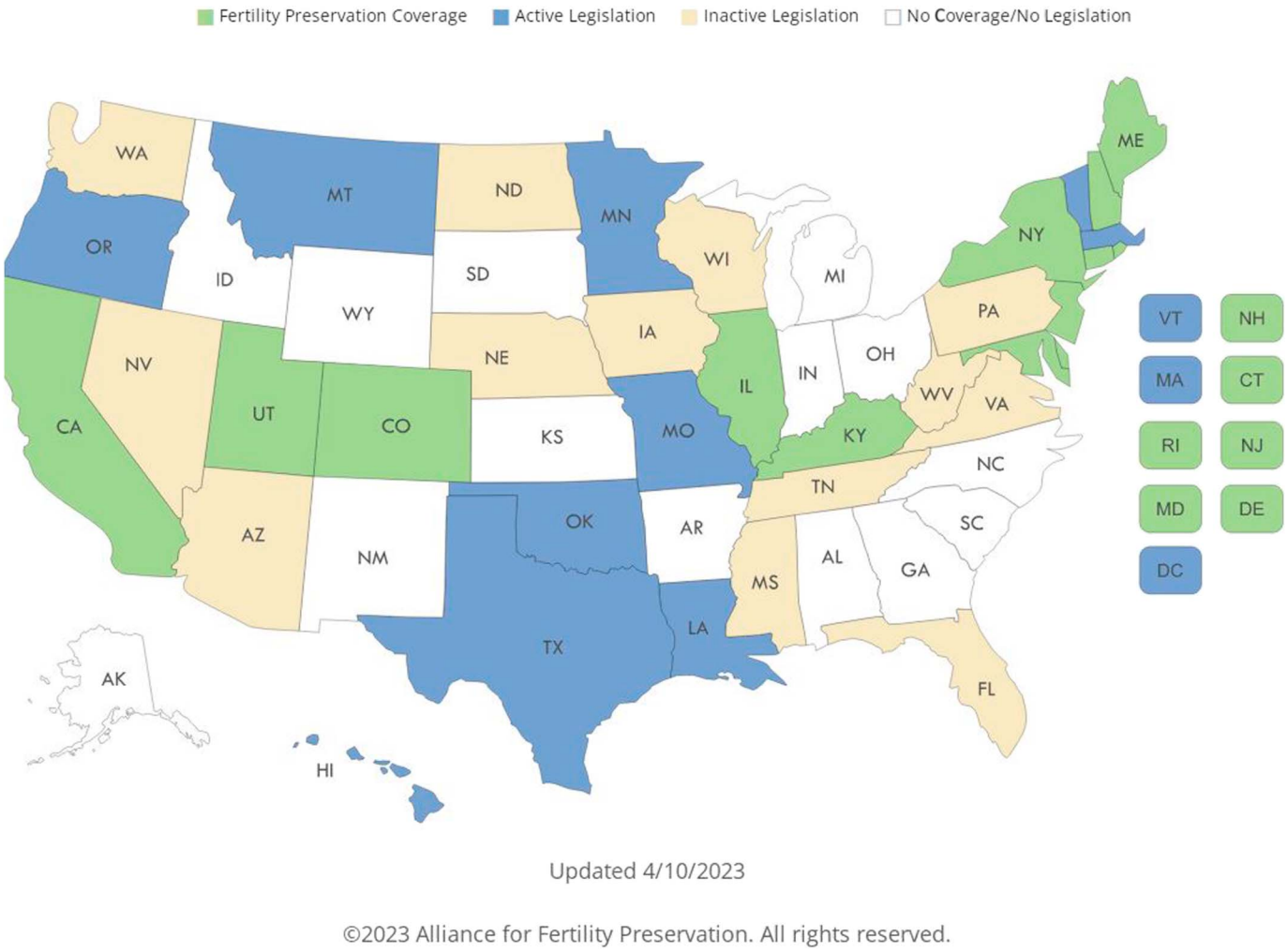

FIG 2. States covering fertility preservation for patients with cancer. Figure used with permission from the Alliance for Fertility Preservation https://www.allianceforfertilitypreservation.org/state-legislation/.

bone turnover, leading to decreased bone mineral density (BMD) and an increased risk of fractures.[71]

In premenopausal women, each available adjuvant endocrine treatment option (tamoxifen *v* tamoxifen plus OFS *v* AI plus OFS) increases bone loss.[72-74] While AI plus OFS results in the greatest decline in bone health (with an annual BMD loss of up to 11%), tamoxifen before menopause is associated with a decrease in BMD (up to 2% per year).[70] The effect of these therapies continues even after treatment discontinuation, leading to an increased proportion of patients with osteopenia and osteoporosis.

The influence of bone loss on fracture risk in women on estrogen suppression is understudied. The Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG-12) reported similar fracture rates in patients receiving OFS plus either AIs or TAM.[73] However, the results of the Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT) studies showed a higher number of fractures during adjuvant endocrine therapy with OFS plus AIs (7.7%) as compared with OFS plus tamoxifen (6.0%) or tamoxifen alone (5.3%).[75]

In postmenopausal women, AIs are associated with greater bone turnover, bone loss, and fracture risk compared with tamoxifen.[70] Two large metanalyses reported a 47% (odds ratio [OR], 1.47; 95% CI, 1.34 to 1.61)[76] and 35% (relative risk, 1.35; 95% CI, 1.21 to 1.51)[77] higher risk of fractures with AI than tamoxifen. Extended use of AIs beyond 5 years further increases the risk of fractures. In a recent meta-analysis, extended AIs were associated with a 34% (OR, 1.34; 95% CI, 1.16 to 1.55) higher risk of fractures compared with placebo or no treatment.[78]

Considering the major impact of adjuvant endocrine therapy on bone health, all patients should be clearly informed about the risk of bone loss and fractures before treatment initiation.[79] Optimal management of bone health in this setting

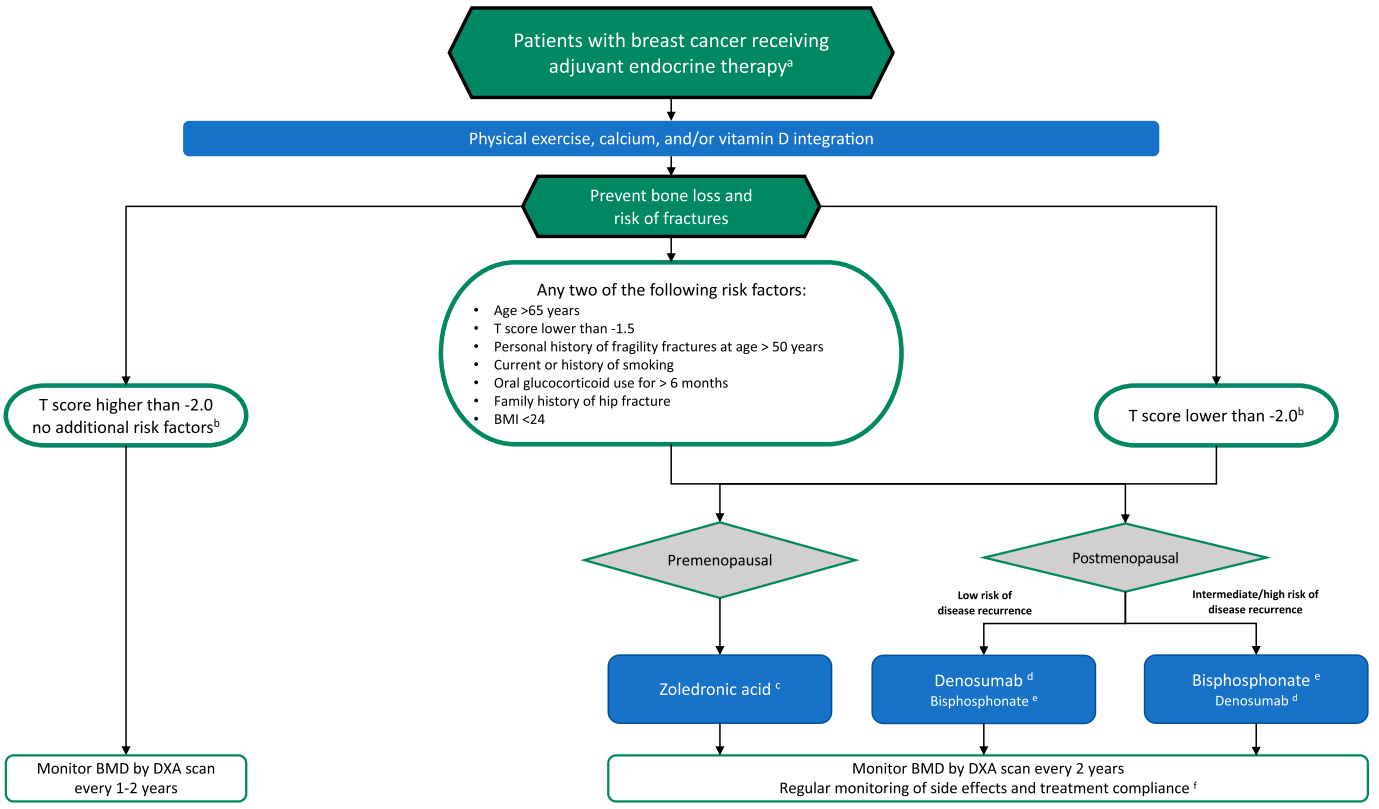

FIG 3. Algorithm for managing bone health in women receiving adjuvant endocrine therapy for breast cancer. [a]Include AIs, ovarian suppression therapy/oophorectomy (±tamoxifen or AIs), as well as tamoxifen alone in premenopausal patients. [b]Bone health can be measured by DXA, monitoring change in a patient's BMD with the T score that categorizes patients on the basis of standard deviations from the mean BMD of a healthy, young adult women. Generally, a 10% loss in BMD can be equated with one standard deviation drop in T score and can increase fracture risk by 2.6 times. The lowest T score from the spine and the hip should be used. [c]Preferred schedule of zoledronic acid: 4 mg intravenous every 6 months. [d]Preferred schedule of denosumab: 60 mg subcutaneously every 6 months (a bisphosphonate should be used on completion of denosumab therapy to prevent rebound osteoporosis). [e]Intravenous zoledronic acid every 6 months, weekly oral alendronate or risedronate, or daily oral ibandronate for the duration of endocrine treatment/for up to 5 years. [f]Regular dental care and attention to oral health are advisable to prevent possible osteonecrosis of the jaw. AI, aromatase inhibitor; BMD, bone mineral density; DXA, dual X-ray absorptiometry. Adapted from Coleman et al.[79]

includes a proper assessment of other risk factors for osteoporosis and the patient's BMD with a dual x-ray absorptiometry scan[80-82] at baseline and during adjuvant endocrine therapy (Fig 3).

Prevention and Management of Bone Loss

Limited evidence is available to counsel patients with breast cancer on the impact of calcium, vitamin D, and exercise to improve bone health. Nevertheless, a calcium-enriched diet, moderate resistance, weight-bearing exercise, and vitamin D uptake are recommended in all patients receiving treatments that may adversely affect bone health, such as adjuvant endocrine therapy.[79]

Bone-targeted agents (BTAs), such as bisphosphonates and denosumab, represent the most tested and widely applied pharmacological strategy to counteract bone loss in clinical practice. These agents inhibit bone resorption through a different mechanism of action. Osteoclasts ingest bisphosphonates through endocytosis during bone resorption, which leads to cell death through a cytotoxic effect for non–nitrogen-containing compounds (eg, clodronate) or a direct apoptotic effect for nitrogen-containing agents (eg, zoledronic acid, ibandronate, and pamidronate). Denosumab is a monoclonal antibody binding receptor activator of nuclear factor kappa B ligand (RANKL) that inhibits the binding of RANK with subsequent suppression of bone resorption.[79]

In premenopausal women receiving OFS plus AI versus tamoxifen with or without OFS, intravenous zoledronic acid (4 mg once every 3-6 months) is the only BTA effective in preventing BMD loss across several randomized trials (Table 1).[73,83,85] Moreover, its use seems to be associated with a reduction in the risk of fractures.[85] To our knowledge, to date, no randomized trials have investigated the use of oral bisphosphonates or denosumab in premenopausal women receiving adjuvant endocrine therapy.

TABLE 1. Largest (>1,000 patients) Randomized Trials on the Impact of Bone Antiresorptive Agents in Preventing Bone Loss and Fractures in Women With Early-Stage Breast Cancer (modified and updated from Waqas et al[70])

Study	Population, N	Intervention, n	Drug, Dose, Duration, and Route of Administration	Follow-Up	Mean BMD/T Score Change From Baseline	Fracture Data
Gnant et al[73] 2008 (ABSCG-12)	Stage I-II BC Adjuvant OFS + AI: 201 Adjuvant OFS + TAM: 203 Premenopausal: 100% Median age: 45 years N: 1,803 (N: 404 bone substudy)	Zoledronic acid (n = 205) *v* Controls (n = 199)	Zoledronic acid 4 mg, q6M for 3 years I.V.	60 months	LS: +4% *v* –6.3% TH: +3.9% *v* –4.1%	NR
Nuzzo et al[83] 2012 (HOBOE trial)[a]	Stage I-III BC Adjuvant AI: 66% Adjuvant OFS: 100% Median age: 50 years Premenopausal: 100% N: 459	AI + zoledronic acid (n = 154) *v* AI (n = 149) *v* TAM (n = 156)	Zoledronic acid 4 mg, q6M for 5 years I.V.	NR	LS: –0.27 (TAM) –0.57 (AI) +0.02 (Zol + AI)	NR
Coleman et al[84] 2013 (ZO-FAST trial)	Stage I-III BC Adjuvant AI: 100% Median age: 57 years Postmenopausal: 100% N: 1,065	Immediate—zoledronic acid (n = 532) *v* Delayed—zoledronic acid (n = 533)	Zoledronic acid 4 mg, q6M for 5 years, I.V.	60 months	LS: +4.3% *v* –5.4% ($P < .005$) TH: +1.6% *v* –4.2% ($P < .005$)	NR
Wilson et al[85] 2018 (AZURE trial, BIG 01/04)	Stage II-III BC Adjuvant AI (53.5%-57.5%) Median age: NR Premenopausal: 45% N: 3,359	Zoledronic acid (n = 1,681) *v* Controls (n = 1,678)	Zoledronic acid 4 mg, q4W × 6 4 mg, q3M × 8 4 mg, q6M × 5 Total 5 years I.V.	84 months	NR	5-year rate: 3.8% *v* 5.9% Time to first fracture: HR 0.69 (0.53 to 0.90), $P < .05$
Gnant et al[86]; Gnant et al[95] 2015, 2022 (ABCSG-18)	Stage I-III BC Adjuvant AI: 100% Median age: 64 years Postmenopausal: 100% N: 3,420	Denosumab (n = 1,711) *v* Controls (n = 1,709)	Denosumab 60 mg, q6M for 5 years S.C.	8 years	At 36 months: LS: +10.02% TH: +7.92% FN: +6.51% (adjusted $P < .005$)	Clinical fractures: 201 *v* 255 HR 0.76 (0.63 to 0.92), $P < .05$

Abbreviations: AI, aromatase inhibitors; BC, breast cancer; BMD, bone mass density; FN, femoral neck; HR, hazard ratio; I.V., intravenous; LS, lumbar spine; NR, not reported; OFS, ovarian function suppression; q3M, every 3 months; q6M, every 6 months; q4W, every 4 weeks; S.C., subcutaneous; TAM, tamoxifen; TH, total hip; Zol, zoledronic acid.

[a]Nuzzo et al[83] analysis included <1,000 patients, but it was performed in the context of the HOBOE trial with >1,000 patients.

In postmenopausal patients receiving AIs, several randomized trials demonstrated a benefit of both bisphosphonates (intravenous or oral formulations) and denosumab in preventing bone loss, while more limited evidence exists on their effect in reducing the risk of fractures (Table 1).[84,86,95] Dose schedules for patients on estrogen suppression are similar to those used for the management of osteoporosis in postmenopausal women.[88] Irrespective of age and BMD at baseline, denosumab (60 mg once every 6 months with adequate calcium and vitamin D supplementation) has the strongest evidence supporting its use in postmenopausal women receiving AIs, with a near 50% reduced risk of fractures both for patients with baseline T scores of –1 or higher (n = 1,872; HR, 0.44; 95% CI, 0.31 to 0.64) and for those with a T score of less than –1 (n = 1,548; HR, 0.57; 95% CI, 0.40 to 0.82).[86]

Anticancer Effect of BTAs

The rationale behind investigating BTAs as anticancer therapy relies on the established role that the bone microenvironment plays in the development of metastases.[89] In premenopausal women, the use of bisphosphonates as anticancer agent is controversial. There are currently no randomized trial data supporting the use of denosumab in this population (Table 2).[90-93] Both the ABCSG-12 and HOBOE trials reported a benefit with the addition of zoledronic acid to OFS as adjuvant endocrine therapy.[91,93] On the contrary, premenopausal women in the AZURE trial did not benefit from the addition of zoledronic acid to endocrine therapy.[92] In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, among the 4,616 women younger than 45 years, no benefit of bisphosphonates on bone recurrences was observed (RR, 1.00; 95% CI, 0.79 to 1.26).[94]

In postmenopausal women, many randomized trials sought to determine the potential anticancer effect of adjuvant oral or intravenous bisphosphonates (Table 2).[84,90,92,95-97] As shown by the EBCTCG meta-analysis, the use of bisphosphonates significantly reduced the risk of bone recurrences (RR, 0.83; 95% CI, 0.73 to 0.94) and breast cancer–specific mortality (RR, 0.91; 95% CI, 0.83 to 0.99).[94] Among the different bisphosphonates, a similar benefit was observed for clodronate (n = 5,053), zoledronic acid (n = 9,290), and ibandronate (n = 3,072), whereas there was no apparent effect in the smaller oral pamidronate group (n = 953). The beneficial effect of bisphosphonates was observed in all breast cancer subtypes.[94] The SWOG S0307 trial did not find a difference in disease outcomes between three different bisphosphonates given for 3 years: oral ibandronate (50 mg daily), oral clodronate (1,600 mg daily), or intravenous zoledronic acid (given monthly for 6 months and then every 3 months).[97] Hence, these are the preferred regimens to be considered for this purpose.[98]

Controversial data exist for the anticancer effect of denosumab (Table 2); while the ABCSG-18 trial showed a potential beneficial effect mostly in terms of DFS,[86,95] the D-CARE study that included patients with high-risk early-stage breast cancer did not show any effect.[96]

Bone Health: Practical Applications and Future Perspectives

In patients receiving endocrine therapy, proper management of bone health is a critical component of survivorship care.[99] Both prevention of treatment-induced bone loss and reduction in the risk of recurrence should be considered when counseling patients (Fig 2). The available types and dosing schedules of BTAs, as well as their toxicity profiles, including renal safety and risk of osteonecrosis of the jaw, should be discussed. However, osteonecrosis of the jaw is a rare event when using oral bisphosphonates or denosumab to prevent bone loss with 3- and 6-month schedules compared with more intensive treatments in patients with bone metastases.[100] In the main trials, the rates of osteonecrosis of the jaw ranged from <1% with clodronate, ibandronate, or 6-monthly zoledronic acid[91,97,101] to approximately 2%-5% with more intensive zoledronic acid or denosumab schedules.[96,102] For these reasons, an oral examination and preventive dentistry evaluation are recommended before starting therapy with BTA, and invasive dental procedures should be avoided during treatments.[79] Excretion of bisphosphonates occurs via the kidney, and both oral and intravenous formulations have warnings or contraindications regarding their use in patients with CrCl <30 mL/min (risedronate, ibandronate) or CrCl <35 mL/min (alendronate and zoledronic acid), mainly because of lack of data in patients enrolled in clinical trials with decreased renal function. However, when administered in accordance with the product characteristics (particularly regarding dose adjustments in patients with reduced renal function), bisphosphonates have not demonstrated additional renal toxicity, even in older patients.[103,104]

Notably, rebound osteolysis has been observed after the discontinuation of denosumab.[105] Although its pathophysiology remains uncertain, dormant osteoclast precursors may accumulate in the bone during treatment with denosumab and rapidly reactivate on drug discontinuation.[105] To date, there is no clear guidance on how to reduce the risk of rebound effect; small case series suggested that administration of zoledronic acid as two doses (6 and 12 months after the last denosumab injection) may help prevent the rebound effect and increased risk of fractures.[106]

Future research in the field should better address the impact of other potential breast cancer–related risk factors, including the bone safety profiles of newer targeted agents combined with endocrine therapy. Refined risk stratification

TABLE 2. Largest (>1,000 patients) Randomized Trials Studying Impact of Bone Antiresorptive Agents on Survival Outcomes in Women With Early-Stage Breast Cancer (modified and updated from Waqas et al[70])

Study	Population, N	Intervention, n	Drug, Dose, Duration, and Route of Administration	Follow-Up	Survival Data
Powles et al[90] 2002	Stage I-III BC Adjuvant TAM: 80% Median age: 52 years Premenopausal: 50% N: 1,069	Clodronate (n = 530) *v* Controls (n = 539)	Clodronate 1,600 mg/die for 2 years P.O.	5.5 years	5-year BMFS: 88.9% *v* 89.8% HR, 0.77; 95% CI, 0.56 to 1.08; *P* = .127
Coleman et al[84] 2013 (ZO-FAST trial)	Stage I-III BC Adjuvant AI: 100% Median age: 57 years Postmenopausal: 100% N: 1,065	Immediate—zoledronic acid (n = 532) *v* Delayed—zoledronic acid (n = 533)	Zoledronic acid 4 mg, q6M for 5 years I.V.	60 months	5-year DFS: HR, 0.66; 95% CI, 0.44 to 0.97; *P* = .037 5-year OS: 95.2% *v* 93.9% HR, 0.69; 95% CI, 0.42 to 1.14; *P* = .14
Gnant et al[91] 2015 (ABCSG-12)	Stage I-II BC Adjuvant AI: 50% Median age: 45 years Premenopausal: 100% N: 1,803	TAM (n = 450) *v* TAM + zoledronic acid (n = 450) *v* AI (n = 453) *v* AI + zoledronic acid (n = 450)	Zoledronic acid 4 mg, q6M for 3 years I.V.	94 months	94.4-month DFS: 88.4% (Zol) *v* 85.0% (no-Zol) HR, 0.77; 95% CI, 0.60 to 0.99; *P* = .042 94.4-month OS: HR, 0.66; 95% CI, 0.43 to 1.02; *P* = .064
Coleman et al[92] 2018 (AZURE trial)	Stage II-III BC Adjuvant AI (53.5%-57.5%) Median age: NA Premenopausal: 45% N: 3,359	Zoledronic acid (n = 1,681) *v* Controls (n = 1,678)	Zoledronic acid 4 mg, q4W ×6 4 mg, q3M ×8 4 mg, q6M ×5 Total 5 years I.V.	117 months	117-month DFS: HR, 0.94; 95% CI, 0.84 to 1.06; *P* = .340 In >5-year postmenopausal patients: HR, 0.82; 95% CI, 0.67 to 1.00 10-year OS: 69.0% *v* 64.6% HR, 0.92; 95% CI, 0.81 to 1.05; *P* = .24 In >5-year postmenopausal patients: HR, 0.84; 95% CI, 0.67 to 1.04
Coleman et al[96] 2020 (D-CARE)	Stage II-III BC Adjuvant AI: 54%-57% Adjuvant OFS: 12% Median age: 50 years Postmenopausal: 47% N: 4,509	Denosumab (n = 2,256) *v* Placebo (n = 2,253)	Denosumab 120 mg, q4W For 6 months than q6M for 5 years S.C.	60 months	5-year BMFS: HR, 0.97; 95% CI, 0.82 to 1.14; *P* = .70 5-year DRFS: HR, 1.06; 95% CI, 0.92 to 1.21; *P* = .41 5-year OS: HR, 1.03; 95% CI, 0.85 to 1.25; *P* = .76
Gralow et al[97] 2020 (SWOG S0307 trial)	Stage I-III BC Adjuvant ET: 75% Median age: 52.7 years Postmenopausal: N.R. N: 6,097	I.V.—zoledronic acid (n = 2,231) *v* O.S.—clodronate (n = 2,235) *v* O.S.—ibandronate (n = 1,552)	Zoledronic acid I.V. 4 mg q4W for 6 months, then q3M for 3 years Clodronate 1,600 mg/die P.O. for 3 years Ibandronate 50 mg/die P.O. for 3 years	60 months	5-year DFS: 88.3% (Zol) *v* 87.6% (Clo) *v* 87.4% (Iba), *P* = .49 5-y OS: 92.6% (Zol) *v* 92.4% (Clo) *v* 92.9% (Iba) *P* = .50

(Continued on following page)

TABLE 2. Largest (>1,000 patients) Randomized Trials Studying Impact of Bone Antiresorptive Agents on Survival Outcomes in Women With Early-Stage Breast Cancer (modified and updated from Waqas et al[70]) (Continued)

Study	Population, N	Intervention, n	Drug, Dose, Duration, and Route of Administration	Follow-Up	Survival Data
Gnant et al[95] 2022 (ABCSG-18)	Stage I-III BC Adjuvant AI: 100% Median age: 64 years Postmenopausal: 100% N: 3,425	Denosumab (n = 1,711) *v* Controls (n = 1,709)	Denosumab 60 mg, q6M for 5 years S.C.	8 years	9-year DFS: 79.4% *v* 75.9% HR, 0.83; 95% CI, 0.71 to 0.97; *P* = .016 8-year BMFS: HR, 0.81; 95% CI, 0.65 to 1.00; *P* = .047 8-year OS: HR, 0.80; 95% CI, 0.64 to 1.01; *P* = .065
Perrone et al[93] 2022[a] (HOBOE trial)	Stage I-III BC Adjuvant AI: 75% Adjuvant OFS: 100% Median age: 45 years Premenopausal: 100% N: 1,065	AI + zoledronic acid (n = 355) *v* AI (n = 356) *v* TAM (n = 354)	Zoledronic acid 4 mg, q6M for 5 years I.V.	8 years	8-year DFS: 22.9% (TAM) *v* 16.0% (AI) *v* 13.2% (Zol + AI) *P* = .001 Zol + AI *v* TAM: HR, 0.54; 95% CI, 0.38 to 0.78, *P* = .002 Zol + AI *v* AI: HR, 0.84; 95% CI, 0.57 to 1.24, *P* = .38 Death rate: 8.5% (TAM) *v* 6.2% (AI) *v* 5.6% (Zol + AI) *P* = .25

Abbreviations: AI, aromatase inhibitors; BC, breast cancer; BMFS, bone metastases-free survival; Clo, clodronate; DFS, disease-free survival; DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; I.V., intravenous; Iba, ibadronate; N.R., not reported; OFS, ovarian function suppression; OS, overall survival; P.O., per os; q3M, every 3 months; q6M, every 6 months; q4W, every 4 weeks; S.C., subcutaneous; TAM, tamoxifene; Zol, zoledronic acid.

[a]Perrone et al[93] presented at the 2022 Annual Conference of the Italian Association of Medical Oncology (AIOM).

would better inform clinical practice guidelines. In this regard, bone turnover biomarkers and new imaging techniques (such as high-resolution peripheral quantitative computed tomography) should be evaluated further.[107]

Anabolic bone drugs are not approved for use in this setting because of concerns of possible stimulation of cancer development and increased risk of recurrence.[99] Hence, at present, bisphosphonates and denosumab are the only BTAs used in clinical practice for patients receiving adjuvant endocrine therapy. Nevertheless, additional data are needed to better assess the role of BTAs in fracture prevention. Beyond their effect in patients undergoing endocrine therapy (as well as their role in the advanced setting in the presence of bone metastases), ongoing research is assessing the potential prophylactic effect of RANK/RANKL inhibition with denosumab in healthy carriers with a germline pathogenic variant in *BRCA* genes (ClinicalTrials.gov identifier: NCT04711109).

CONCLUSION

Patients with hormone receptor–positive early-stage breast cancer who report severe side effects from endocrine therapy are five times more likely to stop their prescribed medication, and 70% of them prematurely stop the treatment before 5 years.[108,109] Better addressing these QoL concerns, including menopausal symptoms, sexual dysfunction, FP, and bone health maintenance, can improve treatment compliance and therefore oncologic outcomes.

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EQUAL CONTRIBUTION

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Improving Quality of Life During Chemotherapy: Cannabinoids, Cryotherapy, and Scalp Cooling

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overview

There have been significant advances in the treatment of cancer in the past decade. However, patients continue to suffer from significant side effects of antineoplastic agents that greatly affect their quality of life (QOL), including chemotherapy-induced nausea and vomiting (CINV), chemotherapy-induced peripheral neuropathy (CIPN), and chemotherapy-induced alopecia (CIA). This review aims to provide an updated overview of emerging strategies for the management and prevention of these immediate and long-lasting side effects. The use of integrative medicine including cannabis continues to evolve in the realm of CINV and cancer-related anorexia. Although no pharmaceutical agent has been approved for the prevention of CIPN, cryotherapy, compression therapy and, more recently, cryocompression therapy have shown benefit in small trials, but there are concerns with tolerability especially related to cryotherapy. More data are necessary to determine an effective and tolerable option to prevent CIPN in large, randomized studies. Scalp cooling (SC), which has a similar mechanism to cryotherapy and compression therapy for CIPN prevention, has proven to be an effective and tolerable approach in randomized studies and has significantly limited CIA, an entity that definitively affects the QOL of patients living with cancer. Taken together, cannabis, cryotherapy, compression and cryocompression therapy, and SC all strive to improve the QOL of patients living with cancer by minimizing the side effects of chemotherapeutic agents.

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INTRODUCTION

Because of advances in early detection and novel therapies, patients with cancer are now living longer.[1] Unfortunately, most antineoplastic therapies have a substantial risk of both short-term and long-term adverse effects that could significantly diminish cancer survivors' quality of life (QOL). Many patients who receive chemotherapy experience a multitude of side effects, including but not limited to nausea, anorexia, pain, neuropathy, fatigue, alopecia, and sexual dysfunction. These side effects can persist even after completion of chemotherapy. This review provides an introduction to the prevention and treatment of several immediate side effects of chemotherapy such as chemotherapy-induced nausea and vomiting (CINV) and chemotherapy-induced alopecia (CIA) and discusses emerging strategies to prevent and treat chemotherapy-induced peripheral neuropathy (CIPN), which is often a long-lasting side effect of taxane-based chemotherapy.

INTEGRATIVE, COMPLEMENTARY, AND ALTERNATIVE MEDICINE

The National Center for Complementary and Integrative Health has defined integrative, complementary, and alternative medicine (ICAM) as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine."[2] The most recent Center for Disease Control study in the 2012 National Health Interview Survey found that one third of adults had used a form of ICAM during the past 12 months.[3] Among patients with cancer, the prevalence is even higher with almost half using a form of ICAM.[4] Herbs and supplements are the most common type of ICAM used by patients, and one, in particular, has grown in popularity—cannabis.

Historical Interest in Cannabis for Symptom Management

During the past few decades, there has been a growing interest in the use of phytocannabinoids, derived from the cannabis plant, to help with medical conditions. Two phytocannabinoids, in particular, have been studied extensively: tetrahydrocannabinol (THC) and cannabidiol (CBD). These agents were first derived from the cannabis plant (*Cannabis sativa* and *Cannabis indica*), and anthropologists have found evidence of their use over 2,000 years ago.[5,6] The medicinal use of cannabis grew in the 1800s and was even listed in the US Pharmacopoeia in 1850.[7] In the early 1900s, Mexican immigrants escaping the Mexican Revolution brought recreational cannabis to the United States. However, because of the growing stigma associated with its use, the Marijuana Tax Act was passed in 1937, making the cannabis plant illegal to grow.

PRACTICAL APPLICATIONS

- Chemotherapy-induced nausea and vomiting (CINV), peripheral neuropathy (PN), and alopecia significantly affect a patient's quality of life while undergoing treatment for cancer.
- Almost half of patients living with cancer report using some form of integrative, complementary, and alternative medicine.
- Cannabis use is implicated in improving CINV and cancer-related anorexia and might play a role in treating chemotherapy-induced PN.
- Cryotherapy, compression therapy, and cryocompression therapy may improve rates of PN in patients receiving chemotherapy via restricted blood flow to susceptible nerves.
- Scalp cooling offers an effective means of preventing chemotherapy-induced alopecia with minimal side effects and high rates of tolerability.

In the 1960s, there were a public resurgence in interest in recreational cannabis and, along with it, a growing interest in its use for medical conditions. However, in 1971, the United States classified cannabis as a schedule I drug within the Controlled Substances Act, indicating that cannabis had a high potential for abuse and no accepted medical indication. By the 1980s, among a paucity of medications for CINV, THC was found to have benefits for treating CINV and HIV/AIDS-induced anorexia, leading to Food and Drug Administration (FDA) approval of two synthetic forms of THC—dronabinol and nabilone. After FDA approval, in 1996, California became the first state to pass legislation making medical cannabis legal, and since then, 37 states and the District of Columbia have passed laws to legalize medical cannabis.[8] In December 2019, the US Congress passed legislation that removed hemp-derived CBD as a schedule I drug, permitting as it contains <0.3% THC. This change in legislation was based on the fact that CBD is not associated with cognitive and psychomimetic side effects and is considered safe with a low risk for abuse potential.[9] After this change in legislation, many states passed laws classifying hemp-derived CBD and THC as dietary supplements, which has led to further confusion regarding cannabis regulation in the United States.

The National Survey on Drug Use and Health indicates a growing use of cannabis by adult Americans from 10.4% in 2002 to 13.3% in 2015.[10] The Behavioral Risk Factor Surveillance System survey from 2016 and 2017 indicated current cannabis use of approximately 8% overall and, among individuals with cancer (nonskin cancer), rates ranging from 4.4% for those 55 years and older up to 23.7% in those age 18-23 years.[11] The National Health and Nutrition Examination Survey reported that 40.3% of patients with cancer had used cannabis in the past and that use of cannabis had increased from 9.3% to 12.3% from 2005 to 2014.[12] In states with legalized medical cannabis, use remains higher among patients with cancer as indicated by a study from Washington State, which found that 21% of patients surveyed had used cannabis in the past month.[13] This rate is similar to a 2018 cross-sectional analysis conducted in a community oncology office in Michigan, which found approximately one in five patients with cancer who were receiving chemotherapy used cannabis in the past 30 days.[14] Interestingly, the incidence was similar across those with early- versus advanced-stage cancer, but patients reporting cannabis use reported more pain, nausea, appetite issues, and anxiety on an electronic self-reported questionnaire than those who were not using cannabis.[14]

Mechanism of Action: Cannabis

While the rates of cannabis use in patients with cancer diagnoses continue to grow, research is growing about the potential benefits of cannabis although this has been limited because of the schedule I designation by the Drug Enforcement Administration. It is well established that THC and CBD work through the endocannabinoid system, with THC having a high affinity for cannabinoid receptors (CB1 and CB2). These G-protein–coupled receptors lead to decreased activation of neurotransmitters at the synapse in a retrograde signaling mechanism. CB1 receptors are found throughout the nervous system, whereas CB2 receptors are found primarily on immune cells. Although CBD has a lower affinity for the cannabinoid receptors, it appears to modulate signaling of anandamide, an endocannabinoid molecule, by increasing anandamide uptake or by decreasing its degradation, which then leads to increased activation of the endocannabinoid system. In addition, CBD appears to activate 5-HT1A and transient receptor potential subfamily V member receptors. It is thought that activation of 5-HT1A receptors in the dorsal raphe nucleus, which leads to release of 5-HT in terminal forebrain areas, may explain the antinausea effects of cannabis.[15] Growing data indicate that cannabis might have anti-inflammatory effects, which may relate to the presence of CB2 receptors on immune cells.[16,17] The variety of mechanisms through which THC and CBD exert their effects may explain the resultant different effects that THC and CBD have on different symptoms such as pain. Although the landscape has changed with regard to the use of legalized cannabis, the evidence for both the short- and long-term effects of cannabis and efficacy for specific indications has begun to emerge.

Cannabis for CINV and Anorexia

CINV has a significant impact on a patient's QOL while on treatment.[18] A review by the National Academies of Science, Engineering, and Medicine in 2017 concluded that, "there is conclusive or substantial evidence that cannabis or cannabinoids are effective" for chronic pain, CINV, and multiple sclerosis-related spasticity.[19] In a review by May and Glode,[20] the authors focused on the use of dronabinol, an orally active cannabis-based medication, which contains a synthetic version of THC. Although corticosteroids, serotonin receptor antagonists, and neurokinin receptor antagonists are well-known and effective antiemetics, dronabinol was approved by the FDA in 1985 for the treatment of CINV in patients who had failed conventional antiemetic treatments. One of the early studies from 1980 randomly assigned 55 patients to THC, prochlorperazine, or placebo and found that THC completely resolved nausea in 40 patients versus only eight with prochlorperazine and five with placebo.[21] Since that time, several clinical trials have been conducted.

One such randomized control study by Meiri et al[22] in 2007 included 64 patients receiving moderately to highly emetogenic chemotherapy who were randomly assigned to receive dronabinol, ondansetron, combination therapy, or placebo after initial prechemotherapy antiemetics on day 1. The trial found that the absence of nausea was similar between active treatment groups with 71% of patients free of nausea in the dronabinol group, 64% in the ondansetron group, and 53% in the combination group versus 15% in the placebo group ($P < .05$).[22] Nausea intensity and vomiting/retching rates were lowest in the dronabinol group.[22]

A systematic review by Tramèr et al[23] evaluated 1,366 patients within 30 randomized clinical trials who were treated with three different cannabis-based medications: oral nabilone, oral dronabinol, and intramuscular levonantradol. The review found cannabis-based medications to be more effective antiemetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride with a number needed to treat of six for complete control of nausea and a number needed to treat of eight for complete control of vomiting.[23] Notably, there were higher rates of beneficial side effects including sedation or drowsiness and euphoria as well as higher rates of harmful side effects including dizziness, dysphoria, depression, and hallucinations. Of note, this review was published in 2000 with articles from 1975 to 1996; thus, the comparison arms were either placebo or older CINV treatments.

More recent data assessing cannabis's role in CINV include a phase II clinical trial that compared the combination of THC:CBD and more modern antiemetic regimens. The trial demonstrated an improvement in complete response from 14% to 25% with the addition of THC:CBD to standard antiemetics.[24] Although nearly one third of patients experienced cannabis-related side effects, most commonly sedation, dizziness, and disorientation, 83% of participants still preferred cannabis to placebo.[24] A review by Allan et al[25] identified seven randomized controlled trials assessing the role of medical cannabis in CINV, found a number needed to treat of three, and concluded reasonable evidence for improvement in nausea and vomiting symptoms.

Although clinically both dronabinol and nabilone are recommended for CINV resistant to standard treatments by ASCO and National Comprehensive Cancer Network (NCCN), more randomized controlled trials incorporating modern antiemetic regimens are needed.[26,27]

Similar to CINV, cancer-related anorexia remains a prevalent and distressing symptom for patients living with cancer. In a systematic review by Razmovski-Naumovski et al,[28] five studies of medicinal cannabis interventions (dronabinol, nabilone, and cannabis extract) compared with either placebo (n = 4) or megestrol acetate (n = 1) were analyzed. The efficacy of dronabinol was demonstrated in one of five trials with patients experiencing improvement and enhancement in chemosensory perception and other secondary outcomes such as taste of food and premeal appetite compared with placebo.[29]

Cannabis for Pain

Initial preliminary clinical research has indicated the potential benefits of THC and CBD for pain. Most studies analyzing the use of cannabis in pain have looked at nabiximols and found a benefit for chronic pain. Notably, nabiximols, an oral spray containing THC and CBD, has been approved in Europe and Canada for the treatment of nausea and vomiting as well as spasticity and pain. A systematic review and meta-analysis by Whiting et al,[30] which looked at randomized clinical trials of cannabis use for numerous indications including CINV and chronic pain, found moderate-quality evidence for the use of cannabis for the treatment of chronic pain and spasticity, with a 41% increase in reporting a 30% or greater improvement in pain among reviewed studies. One randomized, placebo-controlled study evaluated the effect of oromucosal Sativex (THC:CBD) on neuropathic pain of different etiologies. The trial reported a 22% reduction in the primary outcome of pain intensity scores after a 5-week treatment period.[31]

Only one study thus far has evaluated the use of phytocannabinoids for CIPN.[32] In this crossover study, 16 patients were provided nabiximols (THC 2.7 mg:CBD 2.5 mg) spray or placebo and instructed to start with one spray and then increase by one to two sprays per day until they reached a dose that helped their pain without exceeding 12 sprays per

day over approximately 4 weeks and, after a 2-week washout period, switched arms. Although the primary outcome was not met in this small study, five patients did have a >2-point reduction in pain with a number needed to treat of five. A review by the Cochrane Library sought to assess the efficacy, tolerability, and safety of cannabis-based medicines for chronic neuropathic pain, including CIPN. The review found that although cannabis-based medicines may improve pain relief when compared with placebo, the quality of the data was rated very low to moderate, and there was moderate-quality evidence that more people dropped out because of adverse events with cannabis-based medicines compared with placebo. Overall, the review noted that there was no high-quality evidence to suggest value of cannabis-based medicine in the treatment of chronic neuropathic pain.[33] The evidence was limited by short study duration and relatively small sample sizes. In another systematic review by Nugent et al,[34] investigators found low-strength evidence for cannabis in the relief of neuropathic pain across 27 chronic pain trials. These reviews stand in stark contrast to the findings of systemic reviews of Boychuk et al[35] and Lynch et al,[36] which found cannabis-based medicines to be effective and well-tolerated in chronic neuropathic pain, although notably both excluded malignancy-associated neuropathic pain. More recently, an Israeli team of investigators conducted a retrospective analysis looking at the effect of cannabis on oxaliplatin-induced peripheral neuropathy (PN) in 768 patients treated with oxaliplatin and 5-fluorouracil–based combinations for gastrointestinal malignancies.[37] Waissengrin et al[37] found a significant difference in grade 2-3 CIPN in cannabis-exposed patients versus controls (15.3% *v* 27.9%, respectively; $P < .001$). Interestingly, the authors further suggested a protective effect of cannabis given higher rates of neuropathy-spared patients among those treated with cannabis first compared with those treated with oxaliplatin first (75% *v* 46.2%; $P < .001$).[37] Importantly, although cannabis continues to be explored as an option for prevention of CIPN, duloxetine remains the only agent that has appropriate evidence to support its use in the treatment of patients with established and painful CIPN.[38]

Although the evidence is still lacking with respect to the use of cannabis-based medicines, all reviews have articulated the need for high-quality clinical studies to adequately answer this question, and this conclusion was echoed at the recent NCI-sponsored symposium on cannabis.[39]

PREVENTION OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

CIPN is a severe dose-limiting toxicity of many commonly used chemotherapy agents, including taxanes, platinum-based drugs, and vinca alkaloids, and newer more targeted drugs such as antibody-drug conjugates, including ado-trastuzumab emtansine. PN is a common side effect with the incidence of about 30%-40% in patients treated with any neurotoxic chemotherapy and up to 73% in those treated with taxanes specifically. CIPN can present with a wide range of symptoms and severity and can substantially affect QOL.[40,41]

CIPN is caused by neurotoxic effects on neurons, with sensory symptoms tending to be greater than motor or autonomic symptoms.[41] Damage to the dorsal root ganglion neurons and their axons leads to features such as acral pain and paresthesias as well as dysesthesia, allodynia, and hyperalgesia.[42] In general, CIPN occurs in a dose-dependent manner with symptoms typically beginning during the first 2 months of treatment, progressing while chemotherapy continues and then stabilizing after treatment is completed. There are drug-specific features such as the acute neurotoxicity of oxaliplatin, which includes cold sensitivity and muscle cramping and normally peaks within 2-3 days after each dose.[38] On the other end of the spectrum lays the phenomenon referred to as coasting whereby the neuropathy associated with cisplatin treatment worsens after discontinuation of the drug.[41] In addition, paclitaxel causes a pain syndrome, classically in a truncal/hip distribution, that occurs in the days following each dose, and while previously described as arthralgias or myalgias, newer data suggest that these symptoms are instead a manifestation of acute neuropathy.[38,43,44] Although symptoms vary greatly, CIPN has a profound impact on QOL and can limit patients' daily functioning and motor activities with symptoms persisting for years after treatment.[45,46] Importantly, CIPN can affect cancer outcomes given the need to dose reduce or even hold certain chemotherapeutic agents, which may ultimately result in inferior survival.

For many years, investigators have sought out approaches to prevent CIPN without much success. At present, mitigation of CIPN primarily focuses on dose modification to prevent worsening CIPN once symptoms become apparent. ASCO has recently updated their guidelines for the prevention of CIPN and reconfirmed that no agents are recommended for the prevention of CIPN.[38] Similarly, the European Society for Medical Oncology (ESMO) has established guidelines which confirm that no pharmacologic agent exists to prevent CIPN.[42]

Although no pharmacologic agent has yet been established for the prevention of CIPN, the ASCO and ESMO CIPN guidelines note several nonpharmacological interventions, including compression therapy, cryotherapy, and exercise for the prevention of CIPN.[38,42] However, given that current data originate from small studies, no recommendation can be made on the utility of such interventions in clinical practice

although there is emerging interest in these approaches, which we aim to review here and summarize in Table 1.

Cryotherapy for Prevention of CIPN

Some studies have suggested that cryotherapy may reduce the occurrence of CIPN, especially in those patients receiving taxane-based chemotherapy. The hypothesized rationale for the neuroprotective effect of limb hypothermia in CIPN invokes cold-induced vasoconstriction, which leads to reduced exposure of peripheral nerves to the neurotoxic chemotherapeutic agent. The first suggestion of efficacy for this method came from a retrospective exploratory analysis conducted by Eckhoff et al[47] of 1,725 Danish patients with breast cancer (BC). Although 34% of patients included in the study reported PN during treatment, the odds ratio (OR) of PN was significantly reduced in those patients who wore frozen gloves or socks during treatment. The study found that 40% of the patients, who received cryotherapy with the intention of decreasing onycholysis, had a 44% reduction in subsequent neuropathy, compared with patients who had not received the cryotherapy ($P < .0001$).[47] In a prospective, self-controlled trial by Hanai et al,[48] 36 patients with BC, receiving treatment with once-weekly paclitaxel, wore frozen gloves on the dominant hand for 90 minutes during treatment. The incidence of objective CIPN, measured by the monofilament test, and subjective CIPN at a cumulative dose of 960 mg/m^2 of paclitaxel was significantly lower on the intervention side than on the control side (hand: tactile sensitivity = 27.8% *v* 80.6%, OR = 20.00, 95% CI = 3.20 to 828.96, $P < .001$; foot: tactile sensitivity = 25.0% *v* 63.9%, OR = infinite, 95% CI = 3.32 to infinite, $P < .001$).[48] Importantly, no patient dropped out because of cold intolerance.

In a larger study by Beijers et al,[49] 180 patients were randomly assigned to either wear frozen gloves on both hands or not wear frozen gloves. Patients were treated with oxaliplatin, docetaxel, or paclitaxel for mostly colorectal cancer or BC. Notably, 31 patients (34%) discontinued the intervention of frozen gloves because of discomfort. Intention-to-treat analyses showed no important differences in reported CIPN on the basis of the European Organization for the Research and Treatment of Cancer Quality of Life (EORTC QLQ) CIPN20 subscale. Although there was no difference reported on the CIPN20 scores, which may be attributed to the fact that lower extremities were not treated with cryotherapy, researchers found a clinically relevant decrease in tingling in fingers/hands and less trouble in opening a jar or bottle because of loss of strength in those who adhered to frozen glove treatment than in those in the control group.[49]

Although there are several trials of cryotherapy, which are encouraging, these studies are retrospective, underpowered, and uncontrolled or used an unblinded self-control (ie, opposite limbs) group and thereby subject to placebo effects.[47,48,56,57] In addition, although the feasibility of cryotherapy is there, many studies exhibit poor compliance or discontinuation because of discomfort.[58] The effectiveness of ice/gel packs and frozen gloves may furthermore be limited because of steep cooling gradients, nonuniform cooling, and the inability to adjust the temperature in the case of intolerance.

Cryotherapy Using a Continuous-Flow Cooling Device (without or with cyclic compression for prevention of CIPN)

Given that many patients are unable to tolerate cryotherapy using frozen gloves/socks, continuous-flow cooling devices offer easier implementation and better tolerance. These devices provide a constant low temperature over the duration of treatment, with the rationale being that continuous flow cooling has been shown to be superior to crushed iced for musculoskeletal injuries or postoperative pain.[59,60] In an internally controlled pilot study by Sundar et al,[50] 20 patients with BC underwent cryotherapy via continuous-flow limb hypothermia of one limb for a duration of 3 hours while receiving paclitaxel. The noncooled side served as the control. The study found that there was a mild improvement in nerve conduction studies (NCSs) at 6 months in the cooled limb compared with the contralateral untreated limb. Importantly, in comparison with frozen gloves, the treatment was well tolerated without dropout. The authors found a significant correlation between the amount of skin cooling and motor nerve amplitude preservation at 6 months ($P < .0005$) using NCSs for measurement.[55]

Compression Therapy for CIPN Prevention

Interestingly, compression therapy may also offer an effective means of preventing CIPN via similar mechanisms of restricted blood flow to susceptible nerves. In a self-controlled study by Tsuyuki et al,[51] patients with BC receiving nab-paclitaxel wore two surgical gloves, one size too small, on their dominant hand and no gloves on their nondominant, control hand. The study found that compression gloves resulted in lower rates of sensory and motor peripheral neuropathies in the protected hands versus control hands (sensory neuropathy 21.4% *v* 76.1%; motor neuropathy 26.2% *v* 57.1%) using the common terminology criteria for adverse events (CTCAE) and Patient Neurotoxicity Questionnaire.[56] Given the subjective nature of reporting neuropathy, a subsequent double-blind, phase II trial assessed the effectiveness of the same procedure, surgical glove compression for the prevention of paclitaxel-induced PN, by having patients don two gloves, both one size too small, on the one hand (intervention side) versus two normal sized gloves on the other hand (control side).[61] Forty-nine patients were evaluated, and there was no significant difference in sensory or motor neuropathy between the study and control sides.[61]

TABLE 1. Trials for Prevention of Chemotherapy-Induced Peripheral Neuropathy[1]

Intervention	Control	Authors	Trial Design	No.	Chemotherapy Agent	End Point and Results	Tolerance of Intervention
Cryotherapy—FG or socks worn for decreasing onycholysis	None	Eckhoff et al[47]	Retrospective exploratory analysis, controlled	1,725	Docetaxel	CIPN incidence; OR, 0.56; 95% CI, 0.38 to 0.81	NA
Cryotherapy—FG on the dominant hand	Nondominant hand without gloves	Hanai et al[48]	Prospective, nonrandomized, self-controlled	36	Paclitaxel	CIPN incidence; hand: 27.8% *v* 80.6%, $P < .001$; foot: 25.0% *v* 63.9%, $P < .001$	No discontinuations because of cold intolerance
Cryotherapy—FG	No FG	Beijers et al[49]	Randomized, controlled	180	Oxaliplatin, docetaxel, or paclitaxel	EORTC QLQ-CIPN20 subscales; no difference in subscales, reduced tingling in fingers/hands (β, –10.20; 95% CI, –3.94 to –3.14; $P = .005$), and less trouble in opening a jar or bottle because of loss of strength in hands (β, –6.97; 95% CI, –13.53 to –0.40; $P = .04$) in the FG group compared with the control group	31 (34%) patients discontinued frozen gloves, mainly because of discomfort
Cryotherapy—continuous-flow cooling device	None	Sundar et al[50]	Prospective nonrandomized pilot study	20	Paclitaxel	SNAP amplitude change; –19.9% *v* –25.8% ($P = .16$); there was correlation between the degree of skin cooling and motor amplitude preservation ($P < .0005$)	No discontinuations because of cold intolerance; one patient required one intracycle thermoregulator temperature increase of 1°C toward the end of a hypothermia session
Compression therapy—two SGs one size too small on the dominant hand	Nondominant hand	Tsuyuki et al[51]	Prospective, nonrandomized, self-controlled	43	Nab-paclitaxel	Rates of CTCAE grade 2 or higher sensory and motor peripheral neuropathies were significantly lower for SG-protected hands than for control hands; sensory neuropathy 21.4% *v* 76.1%; motor neuropathy 26.2% *v* 57.1%	No discontinuations because of intolerance

(Continued on following page)

TABLE 1. Trials for Prevention of Chemotherapy-Induced Peripheral Neuropathy[1] (Continued)

Intervention	Control	Authors	Trial Design	No.	Chemotherapy Agent	End Point and Results	Tolerance of Intervention
Cryotherapy—FG and socks *v* compression therapy compression garments to upper and lower extremities 15-30 mmHg	Loose gloves and socks	Accordino et al[52]	Randomized, controlled phase IIb, adaptive sequential design	63	Nab-paclitaxel, paclitaxel, or docetaxel	Change in FACT-NTX; success, defined as a <5-point decrease from baseline in the FACT-NTX at 12 weeks, occurred in 64.7% of patients treated with compression and 41.1% of patients treated with cryotherapy and placebo	Adherence to study garments (worn ≥80% of infusions) occurred in 72.7.% of patients treated with compression, compared with 35.0% of patients treated with cryotherapy
Cryotherapy—FG *v*, compression therapy—two gloves one size too small of the dominant hand	Non-dominant hand	Michel et al[53]	Randomized, controlled	122	Nab-paclitaxel	Rates of CTCAE grade 2 or higher sensory neuropathy; cooling: 25% *v* 46%; *P* = .0008; compression: 23% *v* 39%; *P* = .0016 with similar efficacy (no significant difference was found: *P* = .7303)	NA
Cryocompression therapy	Continuous-flow cooling and controls with no hypothermia	Bandla et al[54]	Prospective nonrandomized, controlled	13	Paclitaxel or docetaxel	NCS motor amplitude change; NCS_{3m} cryocompression *v* NCS_{3m} control: ankle stimulation: 8.1% ± 21.4%, *P* = .004; below fibula head stimulation: 12.7% ± 25.6%, *P* = .0008; above fibula head stimulation: 9.4% ± 24.3%, *P* = .002	One patient required an intracycle temperature increase
Exercise	Chemotherapy without exercise	Kleckner et al[55]	Randomized, controlled	355	Taxane-, platinum-, or vinca alkaloid–based chemotherapy	CIPN symptom scale (0-10); hot/coldness in hands/feet (–0.46 units; *P* = .045) and numbness and tingling (–0.42 units; *P* = .061)	NA

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; CTCAE, Common Terminology Criteria for Adverse Events; EORTC QLQ-CIPN20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN twenty-item scale; FACT-NTX, Functional Assessment of Cancer Therapy Neurotoxicity; FG, frozen glove; NA, not available; NCS, nerve conduction study; OR, odds ratio; SG, surgical glove; SNAP, sensory nerve action potential.

In a recently completed randomized, phase IIB adaptive sequential selection trial that compared cryotherapy (frozen gloves/socks), compression therapy (compression garments 20-30 mmHg on upper and lower extremities), and placebo (loose gloves/socks), compression therapy had the highest probability of success in a future randomized phase III trial. There were 64 patients randomly assigned in triplets (n = 20 cryotherapy, n = 22 compression, n = 22 placebo), and the stopping criterion was met after the 17th triplet (n = 51) had been evaluated for the primary end point. Success, defined as a <5-point decrease from baseline in the Functional Assessment of Cancer Therapy Neurotoxicity at 12 weeks, occurred in 64.7% of patients treated with compression and 41.1% of patients treated with cryotherapy and placebo. Adherence to study garments (worn ≥80% of infusions) occurred in 82.4% of patients treated with compression, compared with 29.4% of patients treated with cryotherapy. In this pilot study, compression was the most effective and tolerable intervention, whereas cryotherapy was not successful likely related to poor tolerability, suggesting the need for future studies.[52]

Recently, at ESMO 2022, the POLAR trial by Michel et al[53] randomly assigned 122 patients with BC to either cooling via frozen glove or compression via two surgical gloves, one-size smaller than tight-fitting size, of the dominant hand while receiving taxane-based therapy. No intervention was performed on the other hand. Cooling and compression were both highly effective in prevention of grade ≥2 CIPN using the CTCAE (cooling: 25% *v* 46%, *P* = .0008; compression: 23% *v* 39%, *P* = .0016) and showed similar efficacy.[59]

Cryocompression Therapy for CIPN Prevention

More recently, cryocompression therapy has been investigated as a tolerable approach with the goal of enhancing the depth of cooling by adding dynamic pressure to cooling to improve efficacy. The nonpainful sensory input of dynamic pressure is thought to inhibit pain sensation via the gate control theory of pain. Sundar et al[50] who had previously researched continuous-flow cooling devices in a pilot study conducted a proof-of-concept study using cryocompression limb wraps on all four limbs in 13 patients receiving taxane chemotherapy.[62] Cryocompression was administered at 16°C with a cyclic pressure of 5-15 mmHg. In comparison with retrospective data collected by the same group, the study found that cryocompression achieved significantly greater skin temperature reductions compared with continuous-flow cooling and control ($P < .0001$) while also illustrating an improvement in NCS compared with the controls who showed significant deterioration at 3 months.[62] The authors postulated that the ability to achieve lower temperatures led to improved efficacy in mitigating neurotoxicity.

SWOG 2205 (ICE COMPRESS) is a recently launched randomized phase III, cooperative group trial to evaluate the aforementioned modalities with 1:1:1 random assignment of patients scheduled to receive taxane-based therapy to either limb cryocompression continuous compression or low cyclic compression, all using a novel Paxman limb cooling compression system. The study aims to enroll almost 800 patients and hopes to elucidate the most effective and tolerable CIPN prevention strategy.[63]

Exercise for CIPN Prevention

In addition to cryotherapy and compression therapy, exercise has been studied as a mechanism for preventing CIPN and is postulated to prevent and treat CIPN through changes in inflammation and sensory pathways in the brain.[64,65] In a randomized study of 355 patients, 79% with BC, patients were randomly assigned to either chemotherapy alone or chemotherapy plus Exercise for Cancer Patients (EXCAP), a 6-week, moderate-intensity, at-home walking, and resistance exercise program.[55] The trial showed that exercise significantly reduced CIPN symptoms, on a scale of 0-10, of hot/coldness in hands/feet (–0.46 units; *P* = .045) and did not significantly reduce numbness and tingling (–0.42 units; *P* = .061) compared with the control group.[55]

While at this time, approved pharmacologic agents are lacking for the prevention of CIPN, researchers continue to explore nonpharmacologic interventions including cryotherapy, cryocompression therapy, and exercise-based programs. More randomized controlled studies are needed with larger patient populations given that these options remain as promising, yet understudied solutions.

PREVENTING HAIR LOSS: SCALP COOLING FOR ALL?

Chemotherapeutic agents used for cancer treatment introduce many adverse effects, with hair loss being one of the most devastating toxicities. Alopecia can greatly reduce QOL and negatively affect body image for patients with BC, many of whom consider hair loss to be the most traumatic aspect of chemotherapy treatment.[66,67] This fear can negatively affect outcomes with BC treatment as up to 8% of patients with BC decline chemotherapy to avoid hair loss.[68] In many cases, a head scarf or a wig can be used; however, these can be costly and uncomfortable, especially for those experiencing hot flashes during chemotherapy. Although CIA is often considered to be temporary, in rare cases, it can be permanent.[69] Prevention of alopecia can help to improve QOL of patients receiving chemotherapy and may allow patients to accept a therapy with potential curative or survival benefits.

Methods for Scalp Cooling

Several different methods of prevention have been explored in the realm of CIA. Methods include machine-based and manual scalp cooling (SC), intravenous administration of ammonium trichloro (dioxoethylene-O,O') tellurate (AS101), immunomodulatory tellurium, and topical application of vitamin D3.[70-73]

Of these potential treatments, only SC has demonstrated measured success in preventing alopecia because of chemotherapy.[69,74-76] Importantly, although SC has been used for decades in Europe, it was not until 2015 that the DigniCap received FDA approval as the first machine-based SC device in the United States. Similar to cryotherapy for CIPN, SC is thought to prevent hair loss through vasoconstriction, which reduces blood perfusion and substantially decreases the amount of chemotherapy taken up into follicular cells. Cold temperatures also reduce cellular metabolic activity, which lessens the effects of cytotoxic chemotherapeutic agents on follicular cells.[77,78]

SC can be achieved through different techniques; one such method includes manual cooling caps, such as Penguin Cold Caps, Chemo Cold Caps, and Arctic Cold Caps, which require chilling/freezing in an ice chest and frequent changes throughout treatment to maintain the cool temperature of the scalp. This method can be very labor-intensive and provoke anxiety to maintain a constant cool temperature. An alternative technique uses an automatic, machine-based cooling system consisting of a fitted cap connected to a device that circulates coolant throughout the cap and gradually cools the scalp to a preset fixed temperature throughout treatment. The two FDA-approved machine-based systems currently available are DigniCap (Dignitana, Dallas, TX) and the Paxman Scalp Cooling System (Paxman Coolers Limited, Huddersfield, UK).[79]

Regardless of the specific device, it is recommended that SC start 30 minutes before treatment and continue for the duration of the treatment. Postcooling times are highly variable, depending on the institution and manufacturer. In a recent prospective trial, Komen et al[80] demonstrated that extending the duration of postcooling from 90 minutes to 150 minutes in patients receiving adjuvant 5-fluorouacil, epirubicin, and cyclophosphamide chemotherapy did not significantly improve hair preservation as measured by need to wear a hair covering, but did result in less evidence of grade 2 and 3 alopecia. In this study, SC was well tolerated with only 3% of patients stopping because of intolerance.

Efficacy of SC in the Prevention of CIA

SC's efficacy depends on many factors, including chemotherapy regimen, dose, dose interval, hair type, correct cap size, race/ethnicity, SC temperature, postcooling time, and SC system.[81] Most studies assessing SC use the WHO Criteria for hair loss to grade alopecia. Hair loss grading is rated from grade 0 (no significant hair loss) through grade 4 (nonreversible alopecia). Success of SC is generally defined as the patient not requiring a wig.

In the pivotal prospective cohort trial by Rugo et al,[82] 106 patients with stage I or II BC across five US medical centers receiving adjuvant or neoadjuvant chemotherapy regimens received SC using the DigniCap device compared with 16 who did not. Among these patients, hair loss of 50% or less was seen in 66% of women compared with the control group where all participants experienced significant hair loss.[81] Importantly, although the trial did not include anthracycline (AC)-based regimens, several combination regimens, including docetaxel and cyclophosphamide and docetaxel and carboplatin with human epidermal growth factor receptor 2–targeted therapy, were included.

Although SC has been shown to be effective in patients receiving taxane-based regimens, the technology is not nearly effective at preventing alopecia in patients receiving AC-based regimens.[83] In a randomized multicentered control trial of SC versus control, Nangia et al[82] demonstrated a success rate of only 16% in those receiving AC-based chemotherapy (95% CI, 4 to 46) versus 59% in those receiving taxanes (95% CI, 27 to 84). Across seven sites in the United States, 182 patients who were undergoing chemotherapy with taxane, AC, or both were randomly assigned to SC using the Paxman device or a control group of no SC (without sham placebo). Alopecia assessments were conducted using CTCAE v4.0. The team found that patients who underwent SC had <50% hair loss after completion of treatment compared with the control group. QOL assessments were completed at baseline and after four cycles of chemotherapy using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EQRTC-QLQ-C30), Hospital Anxiety and Depression Scale, and Body Image Scale (BIS). There was no effect on QOL measurements although the trial was stopped early for superiority, and the power of detecting a difference in end points might have been affected.[83] Possible explanations for this observation could include the heterogeneity of chemotherapy regimens received, the timing of interviews, and, most importantly, variability in patient expectations after prestudy education.

In a large study of 1,411 patients across 28 Dutch hospitals, van Den Hurk et al[76] analyzed data from the Dutch Scalp Cooling Registry. The analysis found that 50% of the 1,411 scalp-cooled patients wore no head covering during the last SC session. Although results were most promising for those receiving single-agent taxanes with 84%-91% of patients receiving single-agent low-dose taxanes wearing no head covering, results were less promising for those receiving TAC (docetaxel, doxorubicin, and cyclophosphamide) with only 8% of those patients wearing no head covering at least treatment.[75] The team identified patients of older age as having less chance of satisfactory results and attributed this to aged skin having a diminished cold-induced vasoconstriction. They also identified differences in those with non–West-European-type hair perhaps attributed to lower maximum tolerable chemotherapeutic dose and higher toxicity rates.[75]

Despite SC's promising results with many different treatment regimens, data continue to be lacking regarding the efficacy of SC in the African American population. Data suggest that hair thickness can prevent the scalp's skin temperature from reaching the temperature goal, perhaps resulting in lower effectiveness in African American women.[84] Dilawari et al[85] conducted a phase II feasibility trial looking at African American patients with stage I-III BC receiving at least four cycles of nonanthracycline (NAC) or anthracycline (AC)-based regimens. Modified Dean Scale scores were used to assess the alopecia rate and the Chemotherapy Alopecia Distress Scale (CADS) to measure patient distress. The trial was closed early because of lack of efficacy, with success seen in only one of 15 patients, most of whom had grade 3 alopecia. The regimen did not affect the efficacy of SC or CADS.[84] Although SC can prevent CIA, hair texture affects its efficacy. Further studies are needed to determine whether a different approach in hair preparation before cold cap application may make a difference.

Although machine-based SC represents a promising option, Rice et al[86] looked at the efficacy of hair preservation using a manual Penguin cold cap in 97 evaluable patients with early-stage BC receiving various types of chemotherapy. The manual cold caps prevented CIA in 61% of patients overall with efficacy varying on the basis of the regimen with improved success for those receiving shorter, NAC-based regimens.[86]

SC's Impact on QOL

In the same prospective, multicenter study that led to FDA approval of the DigniCap device, Rugo et al[81] assessed SC's effect on QOL in patients with BC. The study found improvement in three of five QOL measurements one month after completion of chemotherapy. Women in the SC group felt less upset about losing their hair and were less dissatisfied with their bodies compared with women in the control group.[82]

van den Hurk et al[87] conducted a prospective multicenter study looking at the effect of SC on the well-being of patients with BC. The study included 98 of possible 266 patients across 13 hospitals who used the Paxman SC device. Multiple questionnaires including EORTC-QLQ-30, EORTC-QLQ-BR23 (breast cancer–specific module), and the BIS were each assessed at 3 weeks and 6 months after the last chemotherapy cycle. The results showed effectiveness of SC in 52% of patients receiving it and a trend toward higher scores in overall well-being, including QOL and body image, in those successfully scalp-cooled patients compared with those who were unsuccessfully scalp-cooled. Investigators identified a correlation between unsuccessful SC and significantly more complaints about alopecia.[87]

Practical Considerations When Using SC

Overall, SC is effective in the reduction or prevention of alopecia with many chemotherapeutic regimens for patients with BC. It is now the standard of care and has been recommended by the NCCN, ESMO, and Cancer Australia.

SC is reasonably well-tolerated by patients with minimal to no adverse events. The most common adverse events include headache, dizziness, pruritus, chills, nausea, and skin ulceration.[82,83,86] Supportive measures such as anti-anxiety or pain medications can also improve tolerability and thus improve efficacy. An important side effect to be aware of includes cold thermal injury, which, although likely an infrequent event, may result in mild persistent alopecia.[88] One concern related to the potential for development of scalp metastasis has been shown to be unfounded on the basis of low rates of scalp metastases regardless of SC without an apparent increase in those who received SC.[89]

To achieve the optimal outcome, a collaborative effort is required from medical and nursing professionals and patients. When implementing SC, every institution should consider issues such as cost, chair time, cap fitting, patient expectations, and the need for educational materials for both patients and families.

Cost continues to be one of the most important issues for patients. The cost of SC treatment is different according to the type of system being used and the number of chemotherapy cycles. In general, the cost is estimated to be somewhere between $1,500 in US dollars (USD) and $3,000 USD. As on January 1, 2022, the US Center of Medicare and Medicaid has reassigned the repayment for SC for Medicare claims filed with 0662T CPT code. The national average Medicare payment is currently $1,850.50 USD. Although patients may consider using flexible spending accounts for payment, there are also nonprofit organizations such as Hair To Stay, which helps subsidize the cost of SC in addition to raising awareness and providing information on SC to patients.[90]

In addition to cost, implementing a SC workflow according to institutional guidelines is key. Many institutions are using a precooling time while patients are receiving premedications, and some have developed a separate area for the post-cooling time. In the setting of manual cold caps, patients can continue with the postcooling time outside of the institute, which is an advantage compared with the Paxman and DigniCap SC devices.

Future Research Involving SC

To date, most studies in SC have focused on preventing hair loss and improving QOL in patients undergoing treatment for early-stage BC. Data about the efficacy of SC in patients with BC undergoing treatment for metastatic disease using novel therapies such as newer

antibody drug conjugates are not well known, despite rates of alopecia ranging from 37% with trastuzumab deruxtecan to 46% with sacituzumab govitecan.[54,91] Currently, there is an rrongoing prospective, controlled, nonrandomized trial (ClinicalTrials.gov identifier: NCT04986579) using the Paxman Scalp Cooling device, looking at the efficacy and QOL of SC when using trastuzumab, sacituzumab, and eribulin in the metastatic setting.[92]

There is hope that the use of supportive care therapies such as SC will not only help improve the patient experience of receiving anticancer therapies but also improve overall efficacy outcomes by increasing the number of patients who successfully complete recommended systemic therapy for their disease.

CONCLUSIONS

Although we continue to make great strides in improving survival across oncologic fields, we must match these strides with improvements in QOL. This review has focused on some of the progress that has been made with the use of SC for CIA, which has proven to be quite effective with taxane-based chemotherapy and cannabis-based medications for CINV. Small studies have illustrated that compression, cryotherapy, and cryocompression devices may further improve QOL by preventing CIPN although larger studies are needed to solidify this finding. Overall, there have been significant advances in managing the symptomatic burden of chemotherapy in patients living with cancer, but more research is needed to continue this trajectory.

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Aligning Germline Cancer Predisposition With Tumor-Based Next-Generation Sequencing for Modern Oncology Diagnosis, Interception, and Therapeutic Development

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overview

In the era of precision medicine, genomic interrogation for identification of both germline and somatic genetic alterations has become increasingly important. While such germline testing was usually undertaken via a phenotype-driven single-gene approach, with the advent of next-generation sequencing (NGS) technologies, the widespread utilization of multigene panels, often agnostic of cancer phenotype, has become a commonplace in many different cancer types. At the same time, somatic tumor testing in oncology performed for the purpose of guiding therapeutic decisions for targeted therapies has also rapidly expanded, recently starting to incorporate not just patients with recurrent or metastatic cancer but even patients with early-stage disease. An integrated approach may be the best approach for the optimal management of patients with different cancers. The lack of complete congruence between germline and somatic NGS tests does not minimize the power or importance of either, but highlights the need to understand their limitations so as not to overlook an important finding or omission. NGS tests built to more uniformly and comprehensively evaluate both the germline and tumor simultaneously are urgently required and are in development. In this article, we discuss approaches to somatic and germline analyses in patients with cancer and the knowledge gained from integration of tumor-normal sequencing. We also detail strategies for the incorporation of genomic analysis into oncology care delivery models and the important emergence of poly(ADP-ribose) polymerase and other DNA Damage Response inhibitors in the clinic for patients with cancer with germline and somatic *BRCA1* and *BRCA2* mutations.

INTRODUCTION

In the era of precision medicine, genomic interrogation for identification of both germline and somatic genetic alterations has become increasingly important. Traditionally, the purpose of germline genetic cancer risk assessment has been to identify individuals at an increased risk for an inherited cancer who could benefit from tailored cancer surveillance and risk-reducing measures, as well as testing of at-risk family members.[1] While such germline testing was usually undertaken via a phenotype-driven single-gene approach, with the advent of next-generation sequencing (NGS) technologies, the widespread utilization of multigene panels, often agnostic of cancer phenotype, has become a commonplace in many different cancer types.[2-4] At the same time, somatic tumor testing in oncology performed for the purpose of guiding therapeutic decisions for targeted therapies has also rapidly expanded, recently starting to incorporate not just patients with recurrent or metastatic cancer but even patients with early-stage disease.[5,6] For example, the NCI-MATCH trial demonstrated the feasibility of pan-cancer tumor testing at a large scale with identification of actionable mutations for genotype-targeted treatments in both the clinical and research settings.[7] Notably, germline testing and tumor testing were traditionally performed independently, often by different specialists (ie, geneticists versus medical oncologists); however, we are beginning to recognize that an integrated approach may be the best approach for the optimal management of patients with different cancers.[8]

APPROACHES TO SOMATIC AND GERMLINE ANALYSES IN ONCOLOGY PATIENTS

Approaches to germline and somatic genomic analyses differ across institutions. Understanding the benefits and limitations of each approach is important (Fig 1; adapted from the study by Liu and Stadler[8]). If tumor-only assessment is undertaken, tumor sequencing will result in the identification of both somatic (acquired) and germline (inherited) genomic variants. As discussed in more detail later, tumor-only assessment has the potential of uncovering inherited risk

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PRACTICAL APPLICATIONS

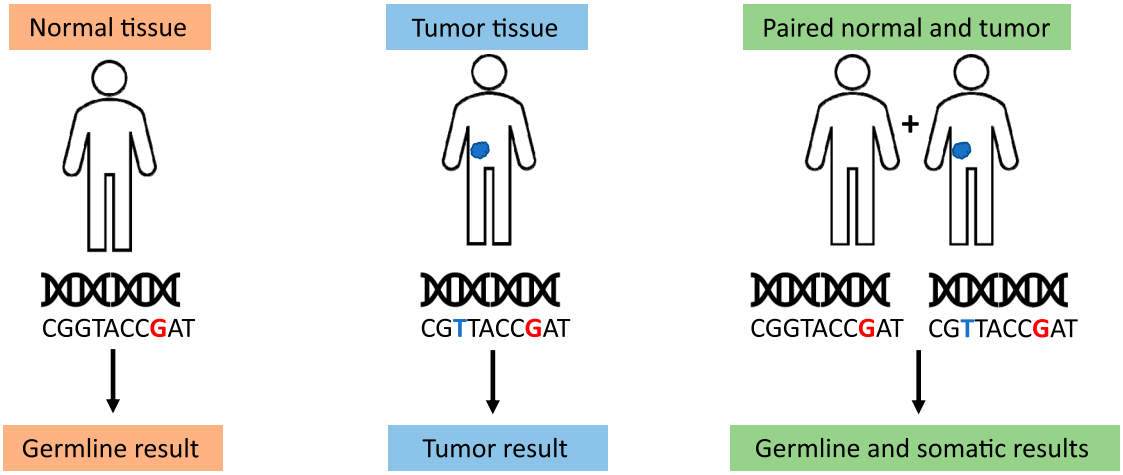
- While germline testing was usually undertaken via a phenotype-driven single-gene approach, with the advent of next-generation sequencing (NGS) technologies, the widespread utilization of multigene panels, often agnostic of cancer phenotype, has become a commonplace in many different cancer types.
- At the same time, somatic tumor testing in oncology performed for the purpose of guiding therapeutic decisions for targeted therapies has also rapidly expanded, recently starting to incorporate not just patients with recurrent or metastatic cancer but even patients with early-stage disease.
- An integrated approach may be the best approach for the optimal management of patients with different cancers.
- The lack of complete congruence between germline and somatic NGS tests does not minimize the power or importance of either, but highlights the need to understand their limitations so as not to overlook an important finding or omission.
- NGS tests built to more uniformly and comprehensively evaluate both the germline and tumor simultaneously are urgently required and are in development.

variants, yet, at the same time, it should not be a replacement test for germline analysis. In parallel tumor-normal sequencing, simultaneous sequencing of both normal and tumor tissues results in the ability to directly discriminate germline versus somatic alterations usually performed through subtracting out of germline variants from somatic variants. As such, only somatic variants are generally reported under the tumor assessment, but direct analysis of the germline with clinical return of results is possible with necessary informed consent procedures and pretest genetic counseling. Limitations of this technology are increased costs of sequencing of both normal and tumor DNA, need for genetic consent and pretest counseling, and molecular pathologist(s) designated as specialists in the curation and interpretation of both somatic and germline findings.[8] If somatic-only variants are reported and the germline is not directly interrogated, the subtracted-out germline findings may be of significant clinical importance, potentially with direct therapeutic implications, and may be missed. Many institutions have undertaken tumor testing and germline genetic testing using separate platforms often involving different commercial laboratories. This approach has the benefit of ensuring that all treatment relevant alterations in the tumor are identified, whether germline or somatic, yet also ensure that if the patient meets germline genetic testing criteria, the needed germline assessment is also performed. Disadvantages of such separate tumor and germline assessments are limited ability to assess whether a germline variant is a driver of the cancer and difficulty in assessing cases of somatic mosaicism or clonal hematopoiesis (CH).

KNOWLEDGE GAINED FROM INTEGRATION OF TUMOR-NORMAL SEQUENCING

Integrated tumor-germline analysis may help to inform whether a tumor is driven by the germline findings or whether the germline variant is simply an incidental observation. For example, in a recent assessment by Srinivasan et al[9] of >17,000 patients undergoing parallel-tumor normal sequencing, the dependency of the tumors on pathogenic germline variants was dictated by both tumor lineage and gene penetrance. Specifically, somatic biallelic inactivation, namely, either a somatic mutation or loss of heterozygosity in the gene or gene region implicated by the germline event, was identified in 40% of all patients with cancer harboring a germline pathogenic variant. Higher rates of biallelic inactivation, at 65%, were observed in patients with germline pathogenic variants in high-penetrance genes, with an increase to 85% when assessment was limited to tumor types known to be associated with the germline cancer risk variant. Beyond an increased understanding of oncogenesis, these results might also have therapeutic implications. For example, in patients with *BRCA1/2* germline variants, initial evidence suggests that poly (ADP-ribose) polymerase (PARP) inhibitor sensitivity may be linked to biallelic inactivation and tumor lineage, whereas in non–BRCA-associated cancer types, tumor pathogenesis appeared to be independent of the mutant *BRCA1/2* alteration.[10] As such, pathogenic germline variants may inform somatic alterations, helping to optimize genotype-directed therapies, yet at the same time, certainly not all patients with high-penetrance germline variants demonstrate biallelic inactivation, highlighting the complexity of selecting genotype-directed therapies.

Beyond traditional sequencing for genetic variants, tumor molecular phenotype or tumor signature as assessed by somatic tumor profiling may also be important. Traditionally, the hallmark of Lynch syndrome, a well-described high-penetrance cancer predisposition syndrome, has been associated with tumors exhibiting microsatellite instability (MSI). Interestingly, tumor-germline integration has helped to better understand this syndrome helping to optimize patient management. In a study of MSI in the pan-cancer population of >15,000 patients undergoing parallel tumor-normal sequencing, Lynch syndrome was identified in 16.3% of



Pros	Assess inherited risk Cancer screening Counseling for families Reproductive planning	Inform diagnosis and prognosis Guide therapeutic decisions for targeted therapies Assess MSI for immunotherapies	Differentiation and integration of germline *v* somatic variants Guides therapy Allows genetic counseling, screening, and reproductive planning
Cons	Limited to patients who meet guidelines Testing difficulties (eg, clonal hematopoiesis and mosaicism)	Inability to distinguish somatic *v* germline variants Inadequate surrogate for direct germline testing Need for further genetic testing and potential delays in care	Increased costs and resources, particularly related to genetic consents and counseling Specialized curation and interpretation by molecular pathologist

FIG 1. Pros and cons of tumor-only versus paired tumor-normal genetic testing.[8] This figure depicts the results of germline, tumor, and paired tumor-normal sequencing and displays how paired sequencing allows the differentiation of germline (red) versus somatic (blue) results. MSI, microsatellite instability.

high-frequency MSI tumors, 1.9% of MSI-indeterminate tumors, and 0.3% of microsatellite-stable (MSS) tumors.[11] Notably, among patients with Lynch syndrome, 50% had tumors other than the canonical colorectal and endometrial cancers, with 45% of these patients not meeting clinical criteria for germline testing on the basis of personal/family history. As such, the presence of MSI in the tumor helped to direct germline testing. On the other hand, Lynch syndrome was present in some patients even with an MSS tumor. In fact, the 0.3% prevalence of Lynch syndrome in this cohort was equivalent to the estimated prevalence of Lynch syndrome in the general population (1 in 270 individuals). In these patients, the cancer diagnosis was not driven by the Lynch syndrome, and the associated response to the immune checkpoint blockade on the basis of MSI status would not be expected in these patients. More recently, Ranganathan et al observed that even in patients with Lynch syndrome and colorectal cancer, the classic tumor associated with Lynch syndrome, 11% of colorectal tumors were MSS, predominantly consisting of the lower-penetrance *PMS2* and *MSH6* germline carriers (Ranganathan et al). Beyond MSI, other tumor phenotypes such as an ultra-hypermutated phenotype or homologous recombination deficiency (HRD) signature may help to point to the underlying presence of germline alterations in DNA polymerase genes (*POLE, POLD1*) genes or *BRCA1/2* and associated genes, respectively.

Increased understanding of both the somatic and germline landscapes in an individual patient with cancer can help differentiate germline alterations from CH, also referred to a CH of indeterminate potential or somatic mosaicism. When germline analysis using the standard source of blood for normal DNA analysis is used, DNA alterations may represent not just germline findings but also potential mosaic alterations or somatic alterations present in the hematopoietic lineages only, namely, CH.[12] CH alterations, a fairly common finding both in patients with cancer and associated with advancing age, smoking, and radiation therapy, may carry a potential risk factor for hematologic malignancies and for cardiovascular disease risk.[13] Germline analysis alone is often unable to distinguish germline variants from CH even when variant allele fraction is assessed. The resulting misinterpretation of a CH variant such as a *TP53* alteration for a germline finding has significant clinical management implications. Although variants in *TP53* because of CH imply an increased risk for hematologic malignancies, the pan-cancer risks and high-risk surveillance recommendations are dramatically different in Li-Fraumeni syndrome, the condition associated with germline TP53

alterations. Somatic mosaicism refers to the presence of a variant in some but not all cells of an individual and may be present at varying levels in different tissues.[14] The presence of a somatic pathogenic variant in the APC gene in all cells of the colon, but at decreased frequency (<50%) in the blood, may lead to a clinical diagnosis of Familial Adenomatous Polyposis. Matched tumor analysis may help inform the blood DNA–derived variant as being CH or mosaic in etiology.[12] A CH variant would not be expected to be present in tumor DNA, whereas a variant detected at lower levels in the blood but present at a higher frequency in the tumor may represent a mosaic finding. Although further confirmation analysis may be needed, matched tumor-normal analysis greatly helps with this evaluation.[12]

INCORPORATION OF GENOMIC ANALYSIS INTO ONCOLOGY CARE DELIVERY MODELS

Although no one model is perfect, it has become apparent that better integration of germline and somatic genomic findings is needed. This is inclusive of using novel care delivery models within oncology, wherein both germline assessment and somatic assessment are initiated promptly at cancer diagnosis. This is paramount given the increasing evidence for the therapeutic implications of germline finding in oncology.[15] Barriers to referral and access to genetics clinics for standard genetic testing are a commonplace, with well-documented underutilization of germline testing even in cancers such as ovarian cancer, wherein universal germline testing has been recommended by ASCO, the US Preventive Services Task Force, and National Comprehensive Cancer Network.[16-19] Moreover, existing disparities in cancer treatment and outcomes may be even further exacerbated if genomic molecular assessments are not implemented using standard procedures across all populations.[19] While precision medicine in oncology has revolutionized our field, increased flexibility with modification of existing care delivery pathways will ensure that all patients have equal access to these dramatic advancements.

TUMOR SEQUENCING TO RULE OUT INHERITED CANCER PREDISPOSITION

Tumor testing with NGS has become standard practice for patients with advanced cancer.[20,21] The overarching goal of NGS testing is to uncover potential drug targets. This often includes US Food and Drug Administration (FDA)–approved targeted therapies and molecules being tested in trials. The ASCO guidelines support testing for patients with advanced solid tumors and now several tumor types in the earlier curative settings.[22] Since the backbone of genetic variability in the tumor is shaped by the host patient's own unique blueprint, it should be of no surprise that somatic tumor testing can uncover important, risk-conferring, germline variants. Although the likelihood of identifying a germline variant is clearly affected by the disease type and the patient's personal and family history, previous data have shown that 4.3%-16% of patients undergoing NGS for tumor testing were found to harbor a germline variant, with many having not met guidelines for germline testing.[23-30] Properly identifying patients with a germline mutation is clinically relevant as it may open additional targeted therapy options for the patient and may highlight an increased risk of malignancy for the patient and related family members. Therefore, ASCO supports disclosing medically relevant incidental germline findings arising from somatic testing to patients who wish to receive this information.[31]

Although providers must be cognizant of the implications of uncovering germline mutations in the context of tumor testing, it is crucial to reinforce that this is not a replacement test or even an adequate surrogate. There are two scenarios centered around risk-conferring genes that may be clinically challenging. First, a somatic NGS test may not identify a germline mutation in a risk-conferring gene carried by the patient. Second, the somatic test may highlight a somatic mutation in a risk-conferring gene that simply arose during the development of the cancer. With regard to the latter, mutations seen in risk-conferring genes may represent stochastic somatic mutations in a patient with an inherited wild-type allele or, as previously mentioned, may represent CH rather than an inherited event.[32] When identified in a tumor test, the variant allele frequency (VAF) can be helpful in determining the likelihood that the mutation was inherited, rather than acquired. Previous work has shown that mutations with the VAF frequency between 40%-60% were very commonly found to be germline in origin, with the notable exception of *TP53* and *APC* mutations.[33-35] While mutations outside this range should never preclude germline testing when clinically appropriate, using VAF can be another tool in identifying germline carriers, especially when a patient's personal or family history is uninformative. Current guidelines support talking to the patient about germline testing when a risk-conferring variant is detected, even when the patient's personal and/or family history are not suggestive of a hereditary cancer syndrome.[31] Thus, it is important that the ordering provider actively considers this possibility across the risk-conferring variants with close attention to pathogenicity. As outlined below, a tumor test's definition of pathogenicity does not always match the germline test's definition for conferring risk.

Of equal importance, germline cancer risk-conferring mutations can be missed on tumor testing. The frequency of missed mutations is not insignificant, with previous data demonstrating a range of 8.1%-18.3%.[36,37] The reasons for this are multifactorial, but clearly include differences between somatic and germline testing assays and the downstream bioinformatic processes. There are many commercially available somatic tests, many of which have

differences in the mutations that can be detected and which mutations are ultimately selected as candidates to be listed on the summary report. The number of genes and variants tested is variable across testing platforms, and obviously less comprehensive tumor somatic tests will not detect all cancer risk-conferring variants. Another reason for not identifying a germline mutation on a tumor test is related to differences in the chemistry of sequencing. Many somatic tumor tests are not designed to detect important structural alterations, including small deletions or duplications. In addition, some germline mutations are missed because of informatic processing by somatic laboratories. For example, although somatic laboratories may be able to detect mutations in the *PMS2* gene within regions of homology with the *PMS2CL* pseudogene, in some instances, those mutations are filtered off the clinical report. Relying on these tumors to exhibit MSI may miss individuals with Lynch syndrome as previous studies have shown an enrichment of MSS tumors in individuals with germline *PMS2* mutations.[38] Furthermore, some mutations that are almost exclusively germline in origin (eg, *MITF* p.E318K) are filtered off using some somatic test results, even in the absence of a paired normal test, because they may be less likely to be driving cancer growth. Finally, some mutations are not highlighted because of differences in the interpretation of pathogenicity between somatic and germline laboratories. Germline mutations causative of high-risk cancer syndromes, including Lynch syndrome, have been listed on the variants of unknown significance page of somatic test results, which may be buried deep within the final report. A pathogenic mutation on a tumor NGS test is meant to uncover drug targets, whereas uncovering risk-conferring germline mutations is an incidental finding. For the latter, we recommend evaluating the pathogenicity of all variants in a germline setting using a quality germline database (eg, ClinVar).

Not identifying a germline variant has two potential significant consequences for the patient. The first centers on the evolving intersection of somatic and germline mutations as important drug targets. Mutations in the DNA-repair pathway appear to predict benefit for therapeutic inhibition of PARP.[39-49] The degree of benefit appears to depend on the disease type, gene mutated, and whether the mutation is germline or somatic in origin. PARP inhibitors are FDA-approved for ovarian cancer, breast cancer, prostate cancer, and pancreatic cancer. Although somatic mutations across DNA repair genes predict some degree of benefit (and even FDA-approved for prostate cancer), the most robust activity across disease types appears to be seen in patients with germline mutations in *BRCA1* or *BRCA2*.[50] More recently, the HIF-2alpha inhibitor, belzutifan, has been FDA-approved for patients with renal cell cancer who carry germline mutations in VHL.[51] The activity of this drug, and others in the class, is still undergoing investigation for patients with somatic *VHL* mutations. The second consequence of missing germline variants is having the opportunity to optimally address the risk for malignancy in the affected patient and at-risk relatives. The benefit to at-risk relatives is both obvious and potentially substantial in terms of scope and significance. The early days of tumor NGS were usually confined to patients with refractory metastatic disease, making the implications of uncovering a hereditary cancer syndrome less impactful for the patient. As tumor NGS testing moves into earlier disease settings, the potential to also affect the index patient's screening and risk reduction for additional primary cancers begins to increase as well.

EMERGENCE OF PARP INHIBITORS IN THE CLINIC

The added importance of both somatic and germline profiling lies in molecular matching with rational antitumor therapies.[52] The FDA approval of PARP inhibitors in patients with advanced ovarian cancer harboring deleterious or suspected deleterious germline *BRCA* mutations after $\geq$3 previous lines of chemotherapy represented the first proof-of-concept for exploiting a synthetic lethal approach in the clinic.[53] This is especially important given that 10% to 15% of ovarian cancer cases in the United States are due to germline or somatic *BRCA1/2* mutations. After the approval of olaparib, three other PARP inhibitors rucaparib, niraparib, and talazoparib have since obtained FDA approval in different indications in patients with ovarian, breast, prostate, and pancreatic cancer in different settings.[54] Although PARP inhibitors have successfully shifted therapeutic paradigms in cancers harboring HRD, drug resistance is nearly inevitable, leading to eventual disease progression. PARP inhibitor resistance is complex and multifactorial, including different underlying mechanisms such as the restoration of HR repair, replication stress, and other diverse mechanisms.

Given the success of PARP inhibitors, the DNA damage response (DDR) therapeutic landscape has rapidly expanded, in part facilitated by the discovery of novel precision targets enabled by cancer genome sequencing and modern CRISPR technologies.[54] Beyond PARP inhibitors, there are now multiple agents targeting the DDR pathway, including ATR, WEE1, ATM, DNA-PK, CHK1/2, POLQ, PKMYT1, USP1, and PARG inhibitors that are in clinical testing. There is also a myriad of DDR clinical candidates in preclinical testing, including ALC1, FEN1, MRN, MLH1/2, APEX2, CIP2A, DNA nucleases, and many more. Many of these agents are particularly effective in DDR biomarker–driven tumors, which provides a molecularly based patient selection strategy to optimize and guide their clinical development. Such predictive biomarkers of response are critical to the success of the different DDR agents, as evidenced by

the biomarker-driven FDA approval of PARP inhibitors in cancers with *BRCA1/2* and other mutations.

GOING BEYOND BRCA1/2-ASSOCIATED TUMOR TYPES

A key question now is how to expand the approval of PARP inhibitors beyond the traditional hereditary breast ovarian cancer (HBOC) types (ie, breast, ovarian, prostate, and pancreatic cancers), where the phenotypic and therapeutic relevance of *BRCA1/2* mutations remains poorly defined in most cancer types. Jonsson et al[10] showed that in 2.7% and 1.8% of patients with advanced-stage cancer and germline pathogenic or somatic loss-of-function alterations in *BRCA1/2*, respectively, selective pressure for biallelic inactivation, zygosity-dependent phenotype penetrance, and sensitivity to PARP inhibitors was only observed in HBOC tumors. In addition, among patients with non–BRCA-associated cancer types, most carriers of these *BRCA1/2* mutation types had evidence for tumor pathogenesis that was independent of *BRCA1/2* mutations. Overall, although it is evident that *BRCA1/2* mutations represent indispensable founding events for certain cancers, they are likely biologically neutral in other cancer types, suggesting a difference predominantly driven by tumor lineage. This, in turn, has important implications for disease pathogenesis, screening, clinical trial design, and therapeutic decision making.

A recent trial of the PARP inhibitor talazoparib and the PD-L1 inhibitor sought to address the question if such a PARP inhibitor–based combination is effective in patients with pathogenic *BRCA1/2* mutations, regardless of the tumor type.[55] In this pan-cancer tumor-agnostic phase 2b nonrandomized controlled trial, 200 patients at 42 institutions in nine countries with advanced *BRCA1/2*-altered or ATM-altered solid tumors were enrolled into two respective parallel cohorts. Interestingly, neither the *BRCA1/2* nor *ATM* mutation cohort met the prespecified target of an objective response rate of 40% across cancer types. Durable clinical activity was observed in patients with BRCA1/2-associated tumor types (eg, ovarian, breast, prostate, and pancreatic cancers), rather than those with non–BRCA-associated cancer types. A notable exception was patients with *BRCA1/2*-altered advanced uterine leiomyosarcoma (uLMS), who had prolonged responses to treatment.

In the BRCA1/2 cohort, 119 patients had BRCA1/2-associated tumor types (defined as breast, ovarian, prostate, and pancreatic cancers), whereas 40 patients had non–BRCA1/2-associated cancer types.[55] Within this BRCA1/2 cohort, the ORR was 30.3% for BRCA1/2-associated tumor types versus 15.0% for patients with non–BRCA1/2-associated tumor types, including three of three responses in patients with advanced uLMS. In an exploratory analysis, patients with uLMS were combined with the patients with BRCA1/2-associated tumor types to form one subset of patients, defined collectively as *BRCA1/2*-dependent cancer types. In the *BRCA1/2*-dependent versus non–*BRCA1/2*-dependent groups, ORRs were 32.0% versus 8.1%, the median DOR was 12.5 months versus 5.8 months, and the median PFS was 5.3 months versus 1.9 months, respectively. The ORRs were 40.0% versus 9.7% in patients with blinded independent central review (BICR)–assessed measurable disease, respectively. Overall, these findings suggest that a pan-cancer, tumor-agnostic approach with this PARP inhibitor combination is not an optimal clinical strategy for treating patients with *BRCA1/2*-altered tumors.

In the clinic, there have been anecdotal reports of PARP inhibitor activity in non–*BRCA1/2*-associated tumors, such as urothelial, biliary tract, and small cell lung cancers, and other tumors.[53] However, in general, none have led to sufficient success in larger suitably powered clinical trials to warrant FDA drug approval in specific subsets of patients. For example, on the basis of the findings that DDR and DNA repair gene mutations were associated with improved outcomes to platinum-based chemotherapy in metastatic urothelial cancer,[56] several studies have been undertaken to evaluate the efficacy of PARP inhibitors in metastatic urothelial carcinoma. This included a phase II trial of rucaparib in patients with advanced urothelial cancer who progressed on one or two lines of systemic therapy.[57] This study enrolled patients with both HRR-deficient and HRR-proficient tumors. However, the study was terminated after preliminary review by an independent data monitoring committee did not show adequate objective response rate and met the criteria for study discontinuation. Additional studies evaluating the efficacy of PARP inhibitors in a cohort of urothelial cancers that is selected for HRR deficiency are ongoing.

Another trial is ATLANTIS, which is a multicenter, umbrella trial in the United Kingdom that screened patients with advanced urothelial cancer for biomarkers while receiving first-line chemotherapy.[58] Patients were eligible to participate in multiple phase II studies evaluating targeted agents as maintenance therapy in biomarker-defined subgroups. The trial showed that maintenance therapy with the PARP inhibitor rucaparib extended progression-free survival in a cohort of patients with DNA repair deficiency, biomarker-positive metastatic urothelial cancer, defined as 10% or greater genome-wide loss of heterozygosity; alteration in any of 15 different genes associated with DNA repair; or *BRCA1/2* germline alteration. However, rucaparib did not significantly improve the secondary end point of overall survival. Patients were randomly assigned 1:1 to receive maintenance treatment within 10 weeks of completion of chemotherapy with either rucaparib at 600 mg twice daily or placebo until disease progression. The study was shut down after 40 patients were recruited for two reasons: the COVID pandemic and data from the JAVELIN Bladder 100 trial

showing a survival advantage for avelumab immunotherapy in this treatment setting. Treatment with rucaparib achieved a median progression-free survival of 35.3 weeks versus 15.1 weeks with placebo. For the secondary end point of overall survival, median overall survival was not reached in the rucaparib arm versus 72.3 weeks in the placebo arm, but this difference was not statistically significant.

The BAYOU trial enrolled treatment-naive, platinum-ineligible patients with metastatic urothelial cancer.[59] They were randomly assigned 1:1 to first-line treatment with durvalumab plus olaparib or durvalumab plus placebo. The BAYOU trial assessed the combination of olaparib and durvalumab, but did not improve progression-free survival in previously untreated, platinum-ineligible patients with metastatic urothelial cancer compared with durvalumab plus placebo, missing the primary end point of the trial. This trial used the FoundationOne assay to test tumor samples for aberrations in 15 HRR genes: *ATM*, *BARD1*, *CHEK1*, *PALB2*, *RAD51C*, *BRCA1*, *BRIP1*, *CHEK2*, *PPP2R2A*, *RAD51D*, *BRCA2*, *CDK12*, *FANCL*, *RAD51B*, and *RAD54L*, with HRR mutations found in seven of the 15 genes analyzed. The *BRCA2* mutation was found in 4.6% of all tumors and in 22.6% of the HRR-mutated subgroup.

An alternative strategy currently being explored clinically is the use of DDR agents beyond PARP inhibitors, such as WEE1 or ATR inhibitors.[54] For example, with the WEE1 inhibitor adavosertib, a confirmed partial response was observed in a patient with head and neck squamous cell cancer (HNSCC) harboring a *BRCA1* mutation.[60] With ATR inhibitors, early RECIST responses have been observed in *BRCA1/2*-mutated patients with melanoma and HNSCC.[61] Given that PARP binding to Chk1 at stalled replication forks is necessary for S-phase checkpoint activation and following these preliminary observations of anecdotal monotherapy antitumor activity with WEE1 and ATR inhibitors in patients with *BRCA1/2* mutations, PARP inhibitor combinatorial approaches should also be considered in the future.

CONCLUSIONS

In summary, as tumor NGS becomes a more commonplace, it is important to understand the potential implications for uncovering germline mutations. Specifically, we recommend providers pursue germline testing for patients with mutations in a cancer risk-conferring gene that could explain the patient's personal/family history or if the mutation VAF is near 50% allele frequency even if their personal/family history does not support testing. We also recommend offering germline testing to all patients who meet current established guidelines for testing even in the absence of a mutation in a risk-conferring gene on a tumor NGS test. The lack of complete congruence between germline and somatic NGS tests does not minimize the power or importance of either, but highlights the need to understand the limitations so as not to overlook an important finding or omission. NGS tests built to more uniformly and comprehensively evaluate both the germline and tumor simultaneously are urgently required and are in development.

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Team-Based Care in Oncology: The Impact of the Advanced Practice Provider

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overview

Integration of APPs into care teams affects quality and safety for the oncology patient. Learn the best practices and understand the concepts of onboarding, orientation, mentorship, scope of practice, and top of license. Review how productivity and other incentive programs can be adapted to integrate APPs and focus on team-based metrics.

INTRODUCTION

The incorporation of Advanced Practice Providers (APPs) into the care of the oncology patient has been transformational to team-based care. APPs provide care and services that would otherwise require a physician to complete. Physicians Assistants (PAs) and Advanced Practice Registered Nurses (APRNs) were developed in the United States in the mid-1960s to address physician shortages and expand access to health care. Since that time, APPs have entered practice in all disciplines and specialties. Despite more than 50 years since their creation, there remains a considerable amount of misunderstanding and questions around how to recruit, onboard, orient, and team with APPs so that they function at the top of their license and train within a full scope of practice.

ASCO has committed substantial resources in exploring the oncology workforce and the delivery of high-quality, patient-centered, team-based care.[1-4] The team approach in oncology has become a necessity as our health care system and cancer treatment have grown ever more complicated. To successfully address the needs of oncology patients, a well-integrated approach is required. This relies on the skills and competencies of many committed interprofessional team members, including APPs.[5-9] Describing the oncology workforce, including the role of the APP, has been a commitment from ASCO for several decades. The body of work developed by ASCO has found that APPs are positioned to provide care to oncology patients who would traditionally require physician time and effort. Collaboration with physicians to provide patient evaluations, diagnostic workup, consultation, patient management, systemic therapy ordering, toxicity management, patient education, and the delivery of survivorship care is one of the defining hallmarks of the APP. The APP research completed by ASCO reflects some common themes including the following: there is more work required for patients in oncology than can be performed by physicians alone; APPs are recognized by both patients and physicians as integral members of the team; and a well-coordinated team is required for the delivery of high-quality care across the cancer care continuum.[4,10-14]

APP INSIGHTS—ASCO'S ONGOING WORK

Although APPs are an integral part of the oncology care team, there remains a need to explore their role and scope of practice. In addition to the research that has been completed, ASCO has committed significant resources to further define and describe the APP. The ASCO Clinical Practice Committee's APP Task Force is charged with helping all oncology health care professionals better understand the important role that APPs play in oncology care teams in practices and clinics. This Task Force is dedicated to developing tools, resources, and educational opportunities to support oncology APPs and the team members working alongside them. The APP Task Force was established in June 2019 and comprises APPs, clinic administrators, and physicians from various practice settings and geographic locations across the United States. The Task Force's diverse membership brings together a wide array of perspectives to advance its important work.

This Task Force builds on some of the team-based care work led by ASCO's now-sunset Workforce Advisory Group (WAG), which focused on broader oncology workforce issues. The WAG developed and launched one of the first large-scale surveys of oncology APPs in 2018 and a subsequent contribution to *JCO Oncology Practice*.[11] This work helped ASCO and other organizations more clearly understand the role of the APP and the benefits of appropriately integrating APPs into a collaborative team-based oncology practice model to promote high-quality cancer care.[15,16]

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PRACTICAL APPLICATIONS

- Advanced Practice Providers (APPs) are critical members of the oncology care team that affect access, quality, and safety of care.
- Integration of APPs into practice requires an intentional effort around onboarding, orientation, and mentorship.
- Scope of practice and top of license are concepts that are critical to understand to fully engage APPs in oncology care teams.

Since its inception, the Task Force has developed an APP onboarding and practice guide to help provide basic guidance, comprehensive integration of new team members, and best practices for onboarding APPs into an oncology practice. This guide is meant to supplement a practice's current onboarding processes. The Task Force has developed a designated webpage that can serve as a user-friendly clearinghouse for APP and team-based oncology care information and resources currently available from ASCO. In addition, The Task Force has created ASCO Education podcast episodes on APPs 101," covering a wide array of topics, including what and who APPs are in today's oncology practice, their role and responsibilities, understanding their full scope of practice, and how to foster positive and beneficial working relationships between APPs and physicians. The taskforce has completed the following podcasts to provide insights into the APP: Episode 1: What and Who Are APPs? Episode 2: PAs and APRNs in Oncology, Episode 3: APP's Scope of Practice, and Episode 4: APPs in Oncology. Additional podcasts are planned to explore other areas of interest such as APPs in rural oncology practices.

EDUCATION AND TRAINING

Although the educational preparation of Nurse Practitioners (NPs) and PAs differs, their role within the cancer care team and at the bedside is analogous. Both NP educational preparation and PA educational preparation are at the graduate level. NPs acquire their Bachelor of Science in Nursing first and become licensed Registered Nurses (RNs). Many NPs work as RNs before becoming an NP. To become an NP, they complete a specific population-focused (eg, Family, Women's Health, etc) NP training program, which includes didactic and clinical practicum coursework. NPs must pass a board certification examination within their population focus and acquire their license to practice as a NP within that population focus.

Most PAs hold a baccalaureate degree before pursuing their educational preparation as a PA. Many PA training programs require as part of their prerequisites that a prospective PA student has hands-on clinical experience before acceptance into a PA training program. PAs are trained in the medical model, and most are trained as generalists as opposed to having a specific population focus. PA training includes didactic and clinical rotation coursework. On completion of their training, PAs must also pass a board certification examination (which spans the focus of their education as generalists) and acquire their license to practice as a PA.

APP BASICS FOR CLINICAL INTEGRATION

Before integrating APPs into the clinical team, it is important to understand several basic concepts. These include onboarding, orientation, scope of practice, and physician mentorship. With this basic knowledge, it will provide clarity on how the APP can be most effectively empowered and supported to serve the patient and partner with physicians.

The term onboarding refers to the initial time that an APP is brought into and introduced to the team. The APP entering oncology practice should have an onboarding process and commitment from the practice to ensure that they obtain the necessary medical knowledge and patient care knowledge and understand team workflows, team members, roles, responsibilities, and national guidelines. This investment enables the APP to assume care of the oncology patient in a team-based care model.

Unlike onboarding, the orientation is a much longer period where the APP is assigned a mentor and given a schedule that will be focused on a deep understanding of the details of the practice and how care is delivered. This can include assigned reading, e-learning, conferences, training on medical procedures, and any required credentialing and privilege processes. This is a much deeper dive than onboarding and requires a sustained commitment over several months to ensure that the APP will be effectively integrated into the practice.

The role of the physician and other experienced APPs in a team-based oncology model is to share best practices and collaborate on patient care by serving as a mentor for the new APP. Although APPs are trained across a broad range of general medical practices and/or populations, they require specialized knowledge in oncology that is specific to the practice and the individual team. This role of mentorship is critical in the successful formation of teams and is a necessary commitment to support APPs in team-based oncology practice.

SCOPE OF PRACTICE

Scope of practice is a critically important concept to understand. This sets the entire framework for how an APP can function in the team. Unlike physicians, the APP scope of practice can vary significantly from state to state. The scope

of practice is the statutory and regulatory standards that define what clinical activity is permitted, authority is granted, and physician collaboration is required. Team-based practice in oncology requires each health care provider to practice at the fullest scope to enhance patient safety and quality of care. Understanding the scope of practice will empower the physician and APP to work synergistically.

It is important for each licensed professional to be familiar with and understand the practice act for each state in which they are licensed. It is particularly important to be vigilant about differences in practice acts when providing medical care across state lines, especially if that care is provided within the same medical practice. For example, if a clinic has sites in two cities that span a state border, who can deliver a particular medical service and how that service is to be delivered may be different within each state.

When the care team includes NPs and PAs, the American Academy of Nurse Practitioners and the American Academy of Physician Associates are helpful resources for state-related information in addition to a state's practice act. State practice acts may vary widely in how they are written, and practicing clinicians need to have a working knowledge of the provisions of the practice act for each state in which they are licensed. Some states may include laundry lists of permitted clinical activities, whereas other states focus on the language of the practice act on restricted clinical activities. State practice acts, nursing boards, physician assistant boards, and medical boards can provide additional insight into the degree of autonomous practice permitted by the practice act and the conditions that must be met for the autonomous practice to be authorized.

TOP OF LICENSE: EMPOWERING THE TEAM AND SERVING THE PATIENT

With the complexity of oncology care, sharing and appropriately distributing the growing volume of tasks required to safely care for the patient is important for optimizing efficiency. A key tenet of this is top of license practice. Top of license means that each member of the team performs routine activities that should use the full extent of their education, training, experience, and competency to deliver the best possible care to the patient.[17] This typically results in the most cost-effective structuring of the team while ensuring that the patient's and caregiver's needs are being met by the appropriate member of the team.[8] To optimize top of license practice, it is important to remember the scope of practice of each individual of the patient's cancer care team. Scope of practice is shaped by the following: federal law (in some cases), state laws and regulations, facility or institutional policy, clinical privileges granted to a provider by a facility, and, at times, payer policy with the final determination occurring at the practice level.[18]

APP VISIT MODELS: SHARED OR INDEPENDENT

APPs are highly educated individuals who enhance organizational ability to provide cost-efficient and quality care through a multidisciplinary approach to hematologic and oncologic patient-centric care. Many health care institutions struggle with best practices and optimal APP utilization, particularly in specialty care.[19] Definition of care team roles, coordinated onboarding and orientation, departmental education regarding the APP scope of practice, and identification of practice models all can improve optimization efforts for APP integration.[19] There are several different types of practice models that exist within health care settings. The two most common visit types in the various models are independent versus shared visits. The terminology is confusing as both visit types still involve collaborative work between physicians and APPs given the complexity of this specialty; this can differ significantly from practice models implemented in primary care settings.[11]

Independent or supervised wrap models have physicians initially see patients and formulate a plan of care and then alternate future visits with the APP depending on medical complexity of the visit.[11] APPs have their own roster or template of patients, and all providers bill independently in this model. Shared visit models involve physicians often seeing patients on the same calendar day as APPs. When completing shared visits, APPs and physicians often work off the same templates in the clinic setting. Providers may use split/shared billing or independent billing procedures in this model. It should be noted that independent models in a collaborative setting are reported to increase APP satisfaction rates and visit volumes per provider compared with shared-only visit models.[11]

Although care team models affect return on investment for APPs, practice environments can also enhance or inhibit success of APPs in the clinical setting. Positive characteristics that may facilitate top of scope practice include encouragement of autonomy and positive APP-physician relationships.[20] Through an integrative review, barriers to effective APP practice models included the following: poor administrative and physician relationships with APPs, physician opposition to independent practice models, policy restrictions on APP practice, and lack of understanding of the APP role.[20] All the above influence advanced practice outcomes and should be considered when expanding the provider workforce.

APP SCRIBES—THERE IS A BETTER WAY

Provider burnout is at an all-time high; data entry and documentation in the electronic medical record (EMR) are two contributing factors.[21-23] Several studies have cited increased documentation times versus the delivery of patient care resulting in dissatisfaction of their role, which may be partially responsible for the growing number of

physicians leaving medicine overall.[23] Unfortunately, oncologists are at higher risk of burnout compared with other specialties because of complicated history and treatment plans, which may shift documentation work to others in the care team.[22] While APPs may assist with documentation, one should question if it is the best use of their role. Consideration of clinical needs, scope of medically trained individuals, improving access, and cost of resources should be used to inform decisions.

Misunderstanding the APP role is often a costly mistake and misuse of talent. APPs are highly trained clinicians who can assist in medical decision making and are recognized by Centers for Medicare & Medicaid services as billing providers. Their contributions can mitigate physician burnout in hematology and oncology in other ways such as triaging patients, managing toxicity or sick visits, offloading follow-up visits, procedures such as bone marrows, completing benign hematology consultations, and covering infusion units. Therefore, the use of APPs as scribes is an inefficient use of their skillset both clinically and financially.[21] Scribes are a part of the care team that specializes in the following: prepare medical history from charts, document patient-clinician encounters in real time, and prepare pending orders in the EMR for clinicians.[21] Several studies increasingly recommend scribes because of documented improved workplace satisfaction, decreased screen time for providers, and increased and enhanced quality patient facing time.[22] Medical practices appropriately using scribes were also able to increase volumes of patients per day because of efficiencies in workflow.[22] Both APPs and scribes are important roles that can support medical practices in a variety of ways to boost patient and teammate satisfaction. Ultimately, roles should align with training and will prove to be cost-effective if aligned with top of license and full scope of practice.

DEFINING AND MEASURING CARE TEAM DELIVERY

Thoughtfully and purposefully defining care team delivery at the practice level is critically important. To empower care team delivery and recognize the contributions of the entire care team it is key for practices to (1) establish buy-in from the administrative and clinical enterprises and (2) create compensation models that are flexible and transparent.[24,25]

To establish buy-in, practices should establish committees consisting of multidisciplinary and interprofessional team members to optimize team-based care and develop team-based compensation models. Efforts to optimize ambulatory APP collaborative practice have shown to increase APP clinical productivity and increase time that APPs are working at the top of their license without affecting physician-generated relative value units (RVUs) or patient satisfaction.[26] Having participation of all team members in shaping care delivery will make it clear that team-based care is a valued priority while empowering them to directly contribute to compensation model development. Committees can be tasked with identifying the service categories to be included in compensation models and determining the importance of each service and the metrics by which they will be measured.[24] In addition, committees should be tasked with identifying benefits and incentives beyond financial compensation to engage employees. Incentives such as increased flexibility in provider work schedules (working remotely) or increased protected time to pursue work-related activities that provide the most meaning can provide motivation greater than financial compensation alone.[27] Finally, the committees will be key in ensuring alignment of values between the center, team, provider, and patient.

To ensure that compensation models are fair and transparent, it will be vital to have an ongoing process for the evaluation. The chosen productivity goals, value metrics, provider success in meeting benchmarks, and the overall impact of the compensation models will need ongoing evaluation and revision. As noted previously, productivity metrics can be challenging to attribute in collaborative practice. However, opportunities to leverage the EMR to improve the tracking of APP clinical productivity and practice efficiency have been successful and provided transparency in data reporting, identifying or validating requests for additional staffing, and assessing performance expectations.[28] In addition to measuring quality-of-care metrics, novel strategies using the EMR to identify and track nonrevenue generating activities such as patient phone calls, prescription refills, and previous authorizations will be important to develop. Objective metrics are needed for recognition of the entire interdisciplinary team. The success of the compensation models and efforts to improve team-based care can and should be assessed through employee retention data and ongoing monitoring of employee satisfaction with work-life integration.

FINANCIAL INCENTIVES AND CARE DELIVERY

The complexity of oncologic care requires the expertise of multiple disciplines practicing within a team-based model of care delivery. Each team must manage numerous interdependent tasks to achieve the common goal of providing the best care for each patient. Teams must leverage the expertise of each professional discipline and use their unique background and training to successfully meet the shared goals of team-based care.[29] However, as the management of patients living with cancer has changed to team-based, so has the reimbursement models from payers prompting organizations to reconsider the provider compensation and incentive models. Importantly, as the health care landscapes change from a volume-based (fee for service) model to a value-based model, it will be vital to have

compensation and incentive models for providers that reflect the team-based practice of oncology.

Ideally, the goal of compensation and incentives will be to encourage the highest quality of care for the greatest number of patients. It will be important for compensation models to reflect the goals of the health system and align with the values of the workforce. Within the oncology team, the compensation models should encourage collaboration among team members working toward the shared goal of patient-centered care. Well-designed compensation models should acknowledge the individual's productivity and contributions to quality of care while also recognizing that the collective success of the team should be rewarded. To successfully accomplish these goals, compensation models will need to balance the incentives tied to productivity and the incentives related to quality of care and influencing the behavior of the provider and the team.[30] This will require deliberate work of providers, administrators, and practice leadership to (1) identify and establish the work performed by the clinical team, (2) rank the importance of the work, and (3) develop a compensation model that reflects the organization goals.[24] When properly aligned, each member of the team will be incentivized to achieve maximal results for their patients and the team. Importantly, individuals should have a sense of control over their ability to meet compensation goals and contribute to the success of other members of the team.

MISALIGNMENT OF INCENTIVES

When compensation models do not align with the goals and values of the individual, team, or health system, there is significant risk to the entire health care enterprise. When the values of an individual do not align with the goals of the compensation model, they may be at risk of suffering from moral distress, decreased engagement at work, or simply leaving the institution entirely. In addition, when compensation models too heavily favor productivity metrics, individuals and teams may be more focused on increasing the episodes of care and procedures and be less focused on improving the quality or value of care delivered.[31]

Within the team context, compensation models that heavily focus on individual metrics (especially productivity) are at risk of creating competition between team members to increase their individual productivity. This requires detailed attention when examining compensation models that include collaborative practice between physicians, NPs, and PAs. For example, standardized work RVUs have the benefit of providing a value for a level of care independent of the provider providing the care.[32] When an independent visit model is used in collaborative practice, this is less of an issue. However, shared visit models and incident to billing are often used in oncology and result in RVUs being attributed to the physician alone. This results in the time and effort of the APP being hidden.[11] The limitations of RVU metrics for APPs are further challenged in the surgical oncology setting where services provided by an APP during the perioperative period are hidden in the overall global surgical package.

Group or team goals may help encourage collaboration among team members. However, there is also the risk that individuals may sense lack of control related to their role and ability to meet incentive metrics, which can lead to further frustration and potentially burnout. For APPs, they might not have control over their schedule and might have to rely on their collaborating physician(s) to establish practice volumes and referral patterns. There may also be scope of practice limitations that affect collaborative practice and the ability of APPs to work to the top of their degree and training. Not only will this affect their ability to meet productivity targets but may also lead to increased rates of APP or oncologist burnout.[33,34] There is a significant amount of time that the clinical team dedicates to providing care for patients that is not revenue-generating (phone calls, patient education, coordination of care, treatment planning, etc).[35] Much of this work is often delegated to APPs and other nonphysician members of the team. If compensation models are not able to account for nonrevenue-generating activities, the value and contributions of APPs will be significantly under-represented. The APP value to patient experience, safety, and quality will be overlooked.

COLLABORATION NOT COMPETITION

No compensation and incentive model will be perfect, and institutions should be tasked with establishing a deliberate process for ongoing evaluation of the selected model. Ideally, compensation models will include incentives that reflect the mission of the center such as clinical productivity, quality of care, citizenship, and, when applicable, research, education, and administrative responsibilities. As noted previously, there are challenges with using individual RVU metrics for APPs. One possible solution would be to establish RVU goals for the individual and the clinical team as a whole.[36] This would ensure not only some degree of responsibility and ownership of individual productivity but also recognizing the contribution to clinical productivity that may not be reflected in individual RVUs. The individual goal and team goal could be weighted (60% individual and 40% team for example) to reflect an overall productivity score. This would enable an incentive in support of the individual and encouraging productivity of highly functioning teams. In addition, by distributing productivity metrics between individual and team goals, there would be less of a focus on extremely high levels of individual production and institutions would be conveying a message that they value hard work but in a more modern team-based environment.[37]

Although productivity-based compensation incentives remain the most common and heavily weighted form of compensation, quality-of-care metrics have been successfully incorporated in oncology.[38] One large integrated health care system reported their experience with developing a matrixed incentive plan in their division of hematology-oncology on the basis of clinical productivity (50%), patient-center goals (10%), academic goals (10%), quality measures (20%), and overall performance of the health system (10%).[38] They noted that providers responded well to the quality measures outcomes, but interestingly, the other variables were met with variable success. Within a team-based care delivery system, the use of quality metrics to help guide compensation for providers is likely to require work of the entire team to achieve the selected metric. For example, a compensation model that used the ASCO Quality Oncology Practice Initiative core measures related to documentation and monitoring of oral chemotherapy would rely on multiple members of the oncology team to be sucessful.[39] In addition, although select metrics may be attributable to an individual for a given visit (such as documentation of oral chemotherapy plan), other metrics may be more longitudinal in nature (medication adherence assessed and addressed) in which both the APP and the physician may contribute to the success in quality care. In addition, because of the nature of the quality metrics, there will be opportunities for the team to identify problematic areas in clinical care to improve practice efficiency and workflows that encourage teamwork and collaboration.

CONCLUSION

The creation of the APP more than 50 years ago continues to have a profound impact on the health care system in the United States. Although APPs have moved into every aspect of patient care, there remains a need for better understanding of these professionals, their role, integration into clinical practice, models of care, and incentives that recognize the work of the team. ASCO has contributed to exploring the APP workforce in oncology and understanding the collaborative relationship between physicians, APRNs, and PAs. It is clear that team-based care is required for providing safe, timely, and quality care of the individual with cancer. Patients benefit from this collaboration and when the entire team works at the highest levels. Ongoing exploration and refinement of models of care, incentives, and collaboration with APPs will enhance and empower care teams.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Implementing Innovation: Informatics-Based Technologies to Improve Care Delivery and Clinical Research

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Overview

Improving technology has promised to improved health care delivery and the lives of patients. The realized benefits of technology, however, are delayed or less than anticipated. Three recent technology initiatives are reviewed: the Clinical Trials Rapid Activation Consortium (CTRAC), minimal Common Oncology Data Elements (mCODE), and electronic Patient-Reported Outcomes. Each initiative is at a different stage of maturity but promises to improve the delivery of cancer care. CTRAC is an ambitious initiative funded by the National Cancer Institute (NCI) to develop processes across multiple NCI-supported cancer centers to facilitate the development of centralized electronic health record (EHR) treatment plans. Facilitating interoperability of treatment regimens has the potential to improve sharing between centers and decrease the time to begin clinical trials. The mCODE initiative began in 2019 and is currently Standard for Trial Use version 2. This data standard provides an abstraction layer on top of EHR data and has been implemented across more than 60 organizations. Patient-reported outcomes have been shown to improve patient care in numerous studies. Best practices for how to leverage these in an oncology practice continue to evolve. These three examples show how innovative has diffused into practice and evolved cancer care delivery and highlight a movement toward patient-centered data and interoperability.

INTRODUCTION

The practice of oncology has seen a steady stream of technological advances over the past several decades, including tracking quality metrics, the concept of the Learning Healthcare System, CancerLinQ, and others.[1-3] These improvements in health care delivery have come as a direct result of the increasing adoption of electronic health records (EHRs). Here, we focus on three contemporary informatics-based initiatives that have the potential to continue transforming how oncologists provide care to patients with care: minimal Common Oncology Data Elements (mCODE),[4] Clinical Trials Rapid Activation Consortium (CTRAC), and electronic Patient-Reported Outcomes (ePROs). Here, we describe the current state of these three practice innovations.

The EHR has its roots in the 1960s when medical facilities first began using computers to store patient data.[5] However, it was not until the late 1990s and early 2000s that the widespread use of EHRs in health care became a reality. Several factors, including increasing consumer demand for access to health information and advances in information technology, have driven the growth of the EHR. However, one of the most significant drivers of EHR adoption has been government policy.

The first major policy effort to promote the use of EHRs in the United States was the Health Insurance Portability and Accountability Act (HIPAA) of 1996.[6] HIPAA established national standards for the privacy and security of patient health information, making it possible for health information to be shared electronically between providers and patients. In 2004, the Office of the National Coordinator for Health Information Technology was established to promote the widespread use of health IT, including EHRs.

The American Recovery and Reinvestment Act (ARRA) of 2009 marked a turning point in adopting EHRs in the United States. ARRA provided funding for the implementation of EHRs and incentivized providers to adopt them through the Medicare and Medicaid EHR incentive programs.[7] As a result of these incentives, the use of EHRs in the United States increased dramatically over the next several years.[8]

The adoption of EHRs has promised opportunities to further leverage technology to improve cancer care delivery. CTRAC, mCODE, and ePROs are three examples of initiatives building on this information technology infrastructure.

CTRAC AND PROTOCOL INTEROPERABILITY

The construction of treatment plans in the EHR can greatly support quality care delivery through standardization. Although efficient for standard-of-care

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PRACTICAL APPLICATIONS

- The Clinical Trials Rapid Activation Consortium project aims to provide a method to electronically share cancer treatment protocols between organizations.
- Released in 2019, minimal Common Oncology Data Elements is a data abstraction layer that leverages Fast Healthcare Interoperability Resources and currently implemented at more than sixty institutions.
- Electronic Patient-Reported Outcomes have been shown to improve outcomes in oncology care, but key challenges with these systems are alert fatigue, management of false positives, and identification and deployment of effective response strategies.

treatment, EHR treatment plans for clinical trials must be built uniquely for each participating site within its own instance of the EHR. To address this current costly, complex, and inefficient paradigm, the University of Texas MD Anderson Cancer Center (MD Anderson) has served as the coordinating site for the CTRAC, one of the consortia funded by the National Cancer Institute (NCI) to develop processes across multiple NCI-supported cancer centers to facilitate the development of centralized EHR treatment plan builds that can be deployed at multiple institutions. Here, we describe the inefficiencies of the current process, challenges underlying the necessity of repetitive builds, and work underway to enable our vision of a single build that can be shared across multiple sites.

EHR build components consist of medication builds and treatment plan builds; they require configurations for novel medications, numerous ancillary procedures, and research finance requirements. For example, each investigational medication may consist of multiple electronic medication records (ERXs), and each ERX in Epic (the most deployed EHR among large cancer centers) has hundreds of configurable fields. Each clinical trial may also require multiple treatment plans to implement different arms, cohorts, or phases of the study. In the current state, EHR treatment plans for clinical trials must be built uniquely for each instance of an EHR. Differences in workflow, standard operating procedures, and medication formularies, and the lack of standardization for site-specific procedures and laboratories all contribute to differences in workflow.

These problems are amplified in precision medicine studies with numerous arms. For example, the NCI-MATCH Precision Medicine Cancer Trial boasts 37 arms and is active at nearly 1,100 sites according to ECOG-ACRIN. If each site activated all arms, >40,000 EHR treatment plan builds could potentially be needed to support this single important study.[9] Compounding these costly inefficiencies, many studies and treatment plan builds may not be used because of a small eligible patient population, early study terminations, or changes in development priorities.

How We Currently Build Clinical Trial Treatment Plans in EHRs

The EHR build of research protocols follows a similar multistep process at most sites (Fig 1) that includes (1) clinical content extraction, (2) construction of build documents, (3) EHR build by technical teams, and (4) validation by clinical team.

This process requires participation from site investigators, pharmacists, research staff, and EHR technical teams. It often also requires frequent back and forth between these teams and with the study sponsors. We outline some of challenges that often consume resources and delay protocol activation here.

First, there is lack of standardization and structure for the provision of clinical content. Information can be represented to various degree of completeness in numerous protocol and ancillary documents, including the protocol text, study calendar, pharmacy manual, laboratory manual, investigative brochure, and other appendices. Second, clinical decisions are almost always needed by site investigators and clinical personnel before technical build. For example, although some studies include recommendations for antiemetics, many studies are silent about their use. Thus, sites may need to make decisions about whether to include antiemetics as premedication and, if used, which antiemetics is to be included. Decisions are also needed when several permissive choices are available. For example, if the protocol states that drug ABC123 can be diluted in D5W or NS to a final concentration between 1 mg/mL and 5 mg/mL and a final volume of 100 mL or 250 mL is recommended, site clinical or investigational pharmacist will need to make decision about diluent and volume before technical build. Finally, most clinical trials are written in a task-oriented manner specifying a task and when it needs to be performed. EHR builds are oriented to cycle day structure specifying what tasks are to be performed during a specific patient encounter necessitating a pivot that can be laborious.

Key Challenges Facing Centralization of EHR Builds

Lack of standardization in how protocols are written and local differences in formularies, practices, roles, workflows, and policies are challenges for an efficient centralized EHR build process. These differences proliferated as site implementation of EHR often tailored to legacy processes. CTRAC cataloged relevant challenges by comparing builds

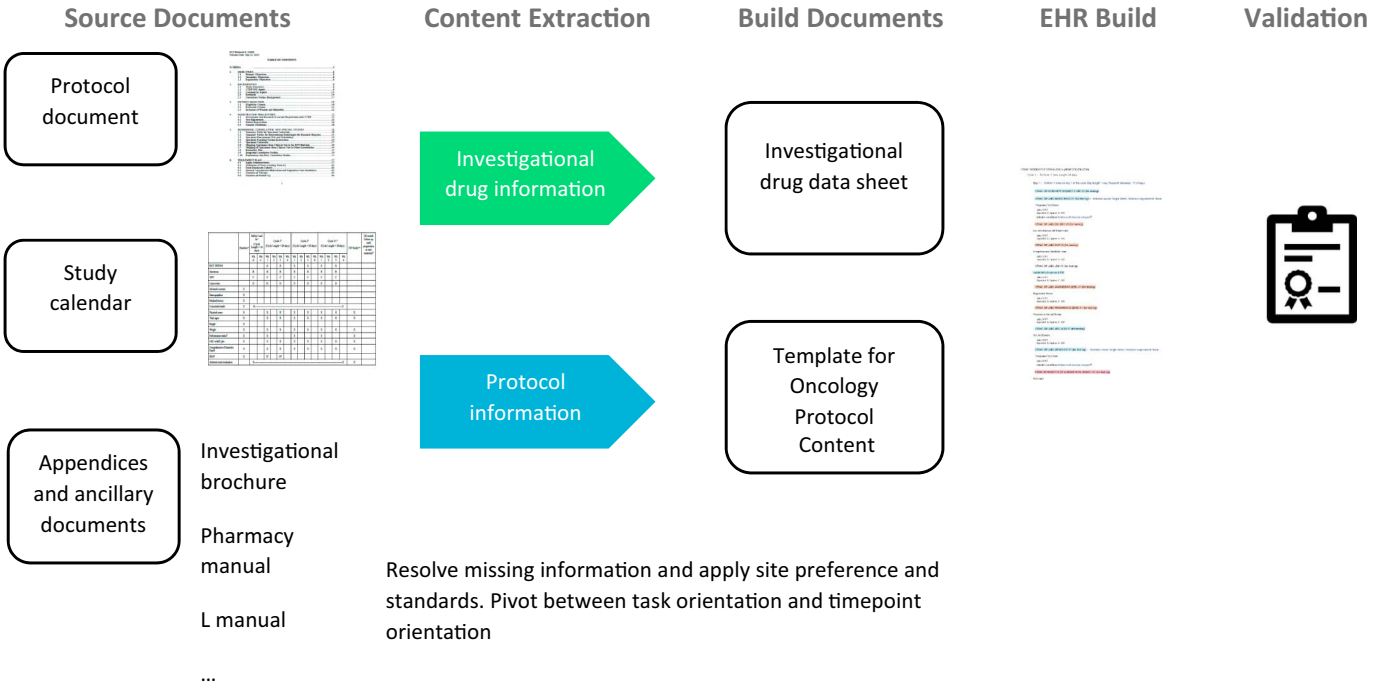

FIG 1. Clinical Trials Rapid Activation Consortium current state: EHR build process repeated at each site. EHR, electronic health record.

and build processes across its member sites and is working on solutions to enable centralized build.

Clinical content extraction. CTRAC developed standardized processes and tools for the extraction of both investigational drug information and clinical protocol information. Missing or incomplete information is clarified centrally by CTRAC or protocol sponsor. Subsequently, build documents are completed before technical build.

Heterogeneity in site formularies, practices, roles, and workflows. Protocol tasks can be generally categorized as protocol-specific or general tasks. Protocol-specific tasks, such as delivery of investigational medication, are generally fully specified by the protocol and allow little to no variation from site to site. General tasks are often supportive and may contain high degree of variation from site to site. Examples include antiemetic or hypersensitivity orders. We developed a library of standardized tasks along with specifications what each task must accomplish. Site can specify how it will accomplish the task conforming to CTRAC specifications and site policy by building groups of orders that can be called upon by a master protocol build. These building blocks act as a translation layer and a documentation layer for site clinic decisions, such as how a site handles antiemetics or hypersensitivity (Fig 2).

Progress to date and future directions. Using the methodology outline discussed here, CTRAC has completed successful proof of concept. We successfully built protocols using CTRAC standards, exported them into packages, and subsequently imported them at member sites. Although we have iteratively refined the process, most sites still need to do substantial adjustments to the build after import. Causes for postimport adjustments include the following:

1. Rigid site standards for style, wording, and naming.
2. Heterogeneity in what sites include in their treatment plan builds. For example, some sites perform certain categories of tasks outside of EHR treatment plan workflow.
3. Site preference in the sequence of how orders are presented.

With substantial progress, the work of CTRAC will continue under the newly expanded, NCI-supported, pilot EHR consortium and will work to innovate and create solutions with the goal of delivering more tailored builds that will further decrease the work of protocol activation. Our goal is to create a seamless process from protocol authoring, centralized build, and delivery of builds conforming to site needs in a speedy and efficient process.

mCODE AND DATA INTEROPERABILITY

The mCODE project began in 2018 with a working group within American Society of Clinical Oncology (ASCO). The group of informaticians worked with two use cases to conceive and propose a set of minimal set of data elements to describe patients with cancer and their journey from diagnosis to treatment. The ambitious goal was that this set

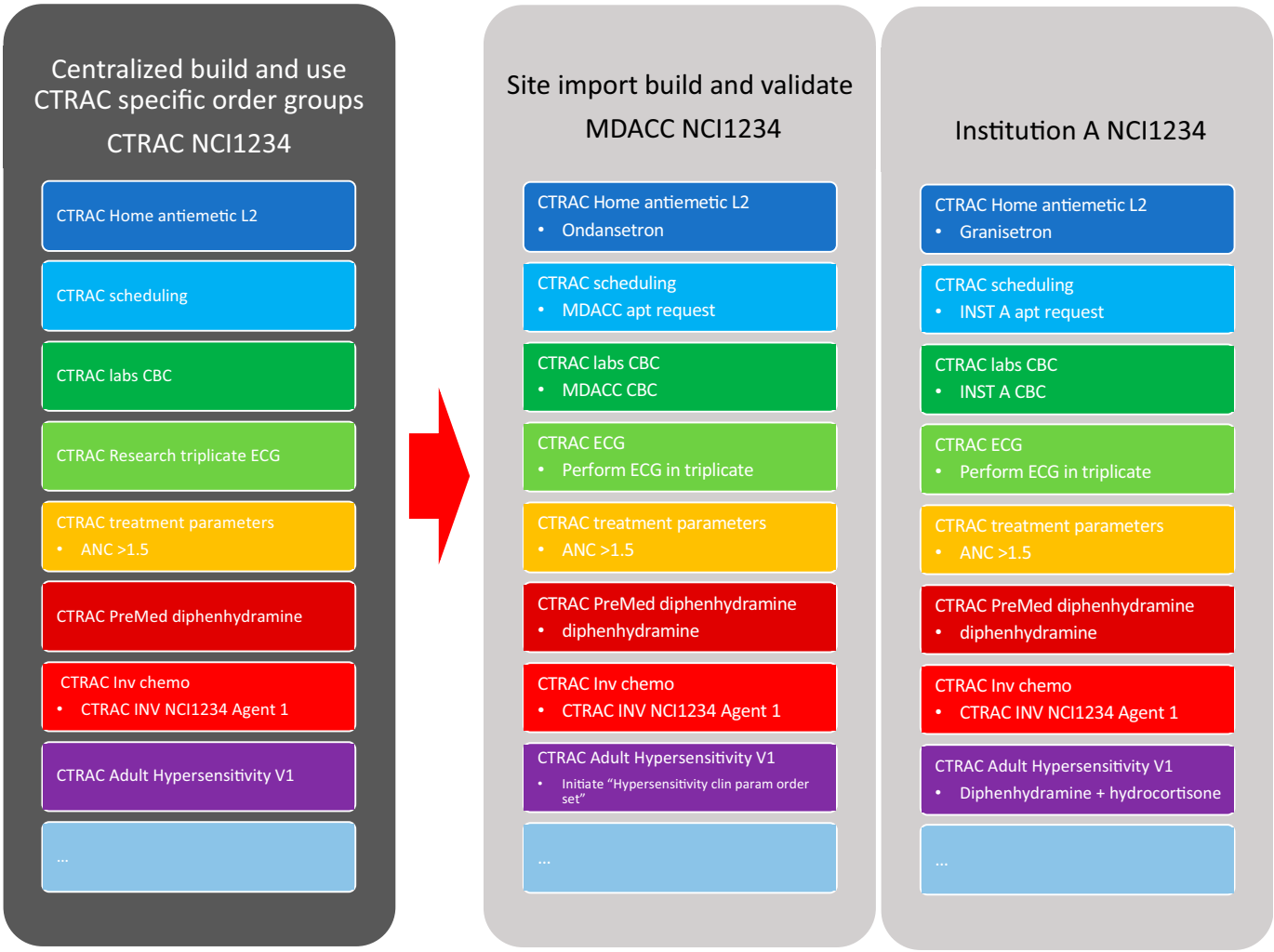

FIG 2. CTRAC use of order groups as translation layer across clinical sites. ANC, absolute neutrophil count; CBC, complete blood count; CTRAC, Clinical Trials Rapid Activation Consortium; INST, institution; INV, investigational; MDACC, MD Anderson Cancer Center.

of data elements would be an interoperable layer sitting above the EHR.

The initial public release of mCODE occurred at the 2019 ASCO Annual Meeting.[10] This was considered version 0.9 and contained 73 data elements across six domains: patient, disease, laboratory results/vitals, genomics, treatment, and outcomes. The governance of the mCODE project transitioned early from ASCO to the mCODE Executive Committee (EC). The EC is composed of four to seven entities, each entitled to appoint one representative and one alternate. The EC is chaired by the ASCO representative. EC members are voting unless they decide to be nonvoting members. The current EC members are ASCO, Alliance Foundation of the Alliance for Clinical Trials in Oncology (Alliance), the MITRE Corporation (MITRE), American Society for Radiation Oncology (ASTRO), and the Society of Surgical Oncology (SSO).

The mCODE EC formed the mCODE Technology Review Group (TRG) to manage the mCODE data dictionary. The TRG worked closely with the MITRE Corporation to respond to public comments and comments from the Heath Level 7 (HL7) community, and on March 18, 2020, Standard for Trial Use version 1 (STU1) was released.

Although the TRG largely focuses on maintaining the data dictionary, CodeX was created as a member-driven HL7 Fast Healthcare Interoperability (FHIR) Accelerator.[11] CodeX has the vision to collect patient data once and reuse those data to enable a range of critical workflows. CodeX currently supports six active community projects that use mCODE: Cancer Registry Reporting, EHR Endpoints for Cancer Clinical Trials (ICAREdata), Integrated Trial Matching for Cancer Patients and Providers, mCODE++ Extraction, Radiation Therapy Treatment Data for Cancer, and Prior Authorization in Oncology. Several other projects are planned.

Organizations also find implementation support through the Community of Practice (CoP).[12] The CoP holds monthly meetings highlighting mCODE implementations and providing a venue for organizations to ask questions and learn from one another.

The mCODE ecosystem relies on implementors to provide feedback, which is used to evolve the mCODE data dictionary. For example, the mCODE Standard for Trial Use version 2 (STU2) was released on January 18, 2022, and contained significant changes expanding the representation of radiation oncology concepts.

Today mCODE is implemented at more than 60 institutions across several countries. The data standard is currently STU2, and changes for the next version are being actively considered. Furthermore, the project has garnered interest from other groups with similar problems. Cardiology has begun to create a CardX group, for instance, on the basis of lessons learned from the mCODE project.[13]

Implementing ePROs in Real-World Oncology Practice

The growing body of evidence supporting the benefits of using patient-reported outcomes (PROs) in oncology settings has led to substantial interest in the implementation of PROs into routine practice. Studies have shown that systematic symptom assessment using PROs is better at capturing patients' symptoms and experience than clinical assessment.[14] Furthermore, their utilization to facilitate clinic assessments[15-17] or to remotely monitor patients during treatment[18-21] has been associated with improved outcomes in multiple studies. PROs can be administered using a variety of approaches ranging from paper-based forms through phone-based systems to fully integrated EHR-based systems with interactive capabilities and self-management support. Currently, the two main use cases in routine oncology practice are to support real-time assessment by a clinician during a scheduled visit or to facilitate remote monitoring during treatment. Although the evidence base on the benefits of using PROs in oncology care has grown substantially over the past decade, experience with implementation into real-world oncology practice has been limited, albeit accelerating.

EVIDENCE FOR UTILIZATION OF PROS IN ONCOLOGY

Most of the early studies in oncology focused on using PROs to support patient-clinician communication regarding quality of life and symptom management. Multiple randomized trials showed that the routine use of PROs before an outpatient oncology visit helps to identify key symptom concerns and improve quality of communication without negatively affecting visit duration.[15-17]

The ambulatory nature of oncology practice coupled with the high symptom needs between visits to the cancer center sparked interest in using PROs to facilitate the remote monitoring of patients during treatment. There have now been several randomized studies that have evaluated remote monitoring using PROs in the oncology setting.[18-24] The majority of these studies have focused on patients with solid tumors undergoing systemic treatment using a variety of PROs administered at different frequencies ranging from daily to every few weeks either by phone or electronically. Compliance with reporting has generally been high in these mostly proof-of-concept studies, as has been acceptability to both patients and providers. These studies have consistently shown that remote monitoring improves symptom control and quality of life. Two of the studies showed improvement in survival.[25,26] A key finding from one of the studies was the importance of having a robust response system with dedicated roles to manage symptom alerts, as opposed to leaving the response to the discretion of the treating team.[23] Only two of these studies examined the impact on health system outcomes, such as emergency department (ED) visits and hospitalizations. In one individually randomized study, there were fewer ED visits in patients with advanced cancer randomly assigned to remote monitoring.[18] However, in a pragmatic cluster RCT in early-stage breast cancer, there was no difference in ED visits or hospitalizations in the intervention arm.[24] Therefore, although it is clear that remote monitoring of patients with cancer improves patient outcomes, the impact on health system outcomes is less clear.

REAL-WORLD EXPERIENCE

A number of institutions and health systems have worked on integration of PROs, including electronic PROs into routine practice.

To Facilitate Clinic Assessment

The longest experience with the utilization of PROs in routine practice in the oncology setting has been in the province of Ontario, Canada. Ontario has a universal health system with standards for cancer care set by the provincial cancer agency Cancer Care Ontario. The Cancer Care Ontario implementation started with a quality improvement project focusing on improving symptom control in patients with lung cancer but led to province wide rollout starting in 2008. The focus of this implementation was on utilization of the Edmonton Symptom Assessment System (ESAS) PRO before clinic visits to facilitate patient-clinician communication. Although there was a provincial mandate for implementation, the approach to institution-level implementation was left at the discretion of the institution. Some centers did mostly paper-based implementation, but several did a successful integration into their electronic medical record (EMR) with features for trending and addition of other questions or symptom measures (Fig 3).[27] Monitoring of uptake focused on screening rates, and chart audits showed challenges with response to symptoms, which may have

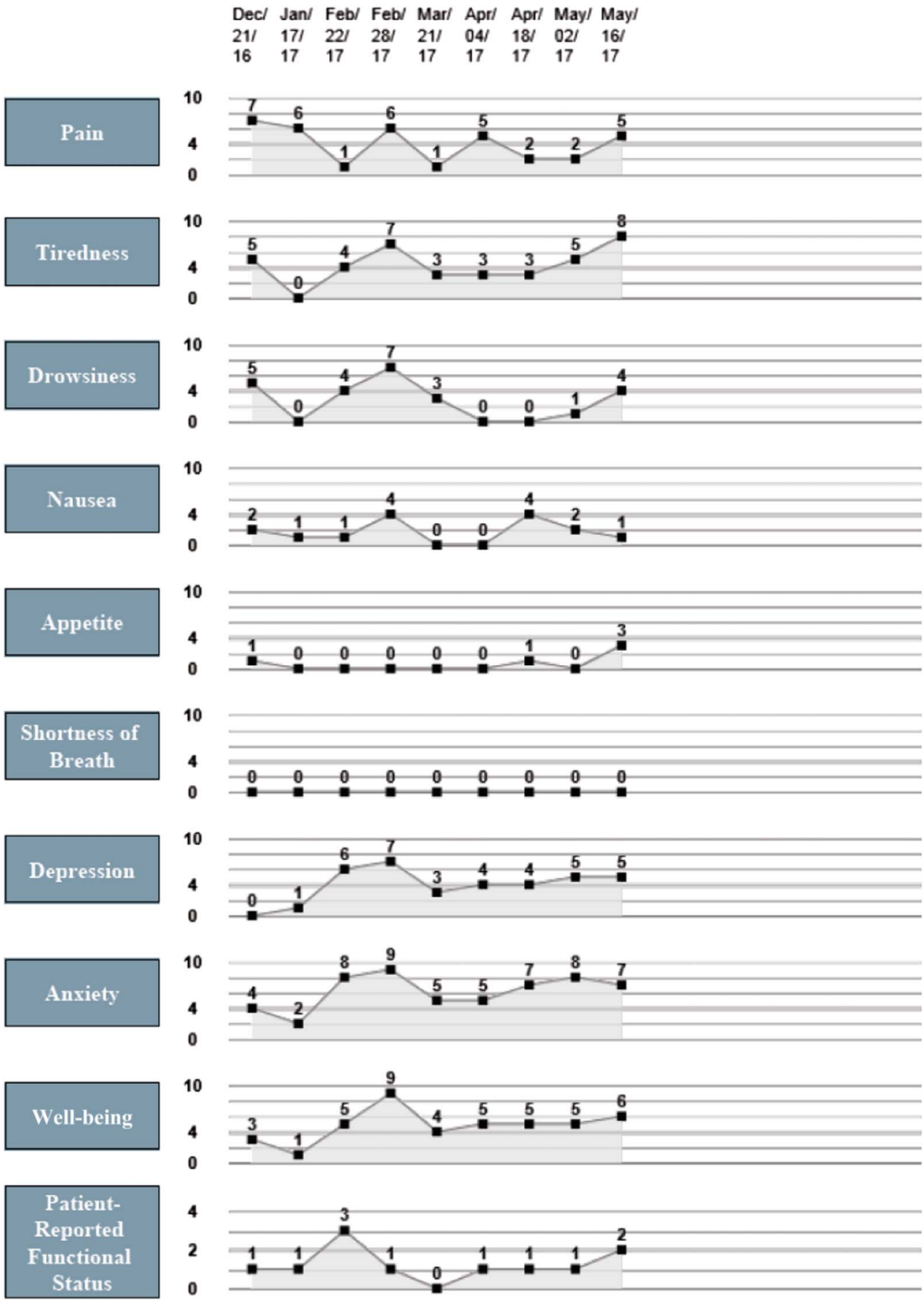

FIG 3. Example of patient-reported outcome integration into the electronic health record.

negative impact on patient engagement ("why am I filling this out if no one is looking at it"). Key learnings from the Cancer Care Ontario experience were the importance of clinician engagement and the need to pay attention to sustainability after initial implementation as compliance with screening can decrease with time.

Remote Monitoring

Published experience with implementation of remote monitoring in routine oncology practice is growing.[28-30] Some of the groups have used vendor-based applications,[28,29] whereas the SIMPRO consortium[30] is focusing on developing an

EHR-based solution in partnership with the EHR vendor. The target population in the majority of these implementations consists of patients initiating systemic therapy; the SIMPRO group has also included patients after surgery. The reported experience thus far has focused on recruitment, retention, frequency of alerting, and early barriers. The recruitment rates appear reasonable, but retention has been quite variable with one practice reporting an 88% retention rate at 6 months,[29] whereas another system-wide implementation reported 52% at approximately 3 months.[28] The available reports suggest that generated alerts are manageable, but technical, practice-level, and patient-level barriers impede uptake and sustainability.

At present, there is limited information on the system-level outcomes of PRO integration into routine practice. Data from Ontario have shown that province-wide ESAS implementation has been associated with improved system outcomes,[31] but formal financial analyses are lacking. Patient- or system-level impact of remote monitoring in real-world settings is not yet known and should be evaluated as part of the ongoing implementation efforts.

PLANNING FOR A SUCCESSFUL IMPLEMENTATION: KEY IMPLEMENTATION CONSIDERATIONS

On the basis of the experiences reported thus far, there are a number of implementation considerations that practices or health systems need to consider when implementing ePROs. Although leadership buy-in and conducive reimbursement models are essential to ensure appropriate resources for implementation, the biggest challenges, to date, to successful adoption are effective clinical integration, EMR integration, and sustainability beyond initial implementation. Systematic reviews of strategies to support ePRO implementation that include nononcology settings are emerging.[32]

Clinical Integration

The importance of response to PROs cannot be underestimated, and patient disengagement can occur if patients perceive that no one is looking at this. It is essential to engage clinical teams early to clearly articulate the objectives and potential benefits and to codesign the PRO collection and response process with the clinical team. The process should be designed to meet the needs of patients and fit the clinical resources. Identifying clinical champions has been shown to be a key component of an effective implementation strategy.[33] Importantly, practices should consider and define workflows following PRO completion. This includes developing algorithms and guidelines to support the response, training and education of clinicians, and assigning dedicated time to do this work. As the sophistication of the ePRO collection systems has increased over time, there are opportunities for automation and self-management support on some of the platforms, but a live clinician is still needed for management of more severe symptoms or to support patients with low self-efficacy.

PRO Selection—Tool and System

Many different validated PROs are available ranging from broad symptom screening tools, such as ESAS, to disease-specific ones, such as the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP). The advantages of a broad PRO, such as ESAS, are that it can work across multiple settings and can be a good screening tool, but it may not be specific enough for a certain clinical scenario which may affect patient and clinician adoption. Another key consideration is the response burden, especially if multiple PROs are being considered for a particular patient. It is important to establish a governance process for PRO selection that considers the local context early in the implementation process.[34] The PROs can either be integrated into the existing EMR or come as part of stand-alone systems. Either approach has pros and cons.

Supporting Adoption

Like any complex intervention, implementation of PROs requires implementation support in the form of project management and ongoing audits of uptake and response. Planning for staff turnover with ongoing education and training at the time of joining a practice is also a key consideration.

Equity Considerations

A concern with implementation of ePROs is the risk of not reaching certain patient populations, such as patients without access to an appropriate device or Internet, those with low digital health literacy, those who are not primary English speakers, or older patients. Interestingly, the data suggest that age or low digital literacy may not be as much of a barrier, as was previously considered.[18] Regardless, access needs to be considered at the design phase and may vary depending on local context and the population served by the practice or system. Several of the PROs have been validated in other languages. Giving patients a choice (electronic completion versus via the phone) is also important. In the PRO-TECT trial of 52 community practices across the United States of which 26 were cluster randomized to remote monitoring, approximately one third of patients chose automated telephone-based administration rather than the web-based system.[22]

DISCUSSION

Here, three initiatives have been highlighted to show examples of innovation currently being implemented in cancer care deliver. CTRAC offers the potential to transform how treatment protocols are electronically shared. This has the opportunity to transform the currently siloed process of translating a narrative treatment protocol to electronic form. Although complexities such as local drug preference,

treatment plan format, and underlying EHR are not fully solved, the progress of this initiative offers hope that the burden of translating and transcribing treatment protocols will soon be reduced. A primary benefit of CTRAC is for multisite clinical trials. If successful, CTRAC may offer sites the opportunity to download an electronic version of the treatment protocol into the site's EHR, thus decreasing both local build resources and potentially decreasing activation time.

The mCODE project has seen incredible adoption since its announcement at the 2019 ASCO Annual Meeting. One key to the project's success is the focus on being the minimal set of clinical data elements to describe patients with cancer and their journey through the cancer care continuum. Additionally, mCODE has created an ecosystem to support implementers through CodeX and the Community of Practice. This setting not only provides benefits to new mCODE adopters but also facilitates feedback to the mCODE Technology Review Group on which portions of the data dictionary may need to be expanded to accommodate new use cases. mCODE also focuses on integrating with other national and international data standards while providing specialty-specific expertise in areas, such as cancer staging and tumor genomics.

There is strong evidence for the use of PROs in oncology settings, but real-world implementation is underway. Attention to key implementation considerations, especially early focus on clinical integration, has the potential to improve adoption at the practice level. Future studies of real-world implementation should focus on testing of implementation strategies and evaluation of impact on patient- and system-level outcomes.

Additional EHR elements, wearable data, and other parameters may integrate ePROs to identify and predict adverse outcomes prompting early intervention. With substantial interest to move more care into the home, PROs may also help facilitate the hospital@home model for patients who would otherwise have been managed in the inpatient setting. Key challenges with these systems are alert fatigue, management of false positives, and identification and deployment of effective response strategies.

CONCLUSION

There are several exciting evolving opportunities for data standards such as mCODE, interoperable clinical trial protocols such as CTRAC, and implementation of ePROs into routine oncology care. Each of these initiatives is rooted in fundamental clinical informatics principles. The success of these highlighted initiatives is, however, based largely on a shared process. First, identify key problems and opportunities in the field of oncology. Second, bring stakeholders together to discuss approaches to address the given problem. Next, implement one or more solutions and share the results with the community. Finally, learn from each other and continue to refine the solutions while decreasing implementation burden for future organizations. This approach can be leveraged by other informatics projects aiming to implement innovation in cancer care delivery.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Molecular Profiling in Neuro-Oncology: Where We Are, Where We're Heading, and How We Ensure Everyone Can Come Along

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Overview

Advances in molecular profiling have led to improved understanding of glioma heterogeneity. Results have been used to inform diagnostic classification and targeted treatment strategies. Validation of these tests is necessary in the development of biomarkers that can aid in treatment decision, allowing for personalized medicine in neuro-oncologic diseases. Although not all populations have benefitted equally from awareness of and access to testing, opportunities arise regarding incorporating this testing into the standard of care for patients with glioma.

BACKGROUND

Over the last decade, there have been major advances in our ability to profile tumors molecularly with next-generation sequencing and DNA methylation analysis.[1,2] These techniques have significantly improved our understanding of the major molecular drivers in brain tumors and the identification of novel tumor types.[1,3,4] They provide the opportunity to improve the classification and diagnosis of brain tumors and identify potential targeted therapies. Nonetheless, to date, these advances have not translated into better outcomes for most patients.[5,6]

2021 WHO CLASSIFICATION OF CNS TUMORS

Undoubtedly the most important role of molecular profiling in brain tumors currently is the classification of these tumors. Beginning with the 2016 WHO CNS Tumor Classification update,[7] and expanded in the 2021 WHO CNS Tumor Classification,[8] molecular profiling now plays a crucial role in the diagnosis and classification of brain tumors (Fig 1).

Diffuse gliomas are now separated into adult-type and pediatric-type with different biology and molecular drivers.[8] Adult-type gliomas have been condensed into just three types (isocitrate dehydrogenase [*IDH*]–mutated astrocytomas and oligodendrogliomas, and *IDH* wild-type glioblastomas).[8] Glioblastomas now include not only tumors with the classical histologic findings of necrosis and microvascular proliferation but also tumors without these findings but with *TERT* promoter mutation, epidermal growth factor receptor (EGFR) amplification, or gain of chromosome 7 and loss of chromosome 10 (molecular glioblastomas).[8] For pediatric-type diffuse gliomas, there is differentiation into low-grade tumors, such as those with MAP kinase alterations, and high-grade gliomas with H3K27M alterations and infantile hemispheric gliomas, which are often associated with fusions, offering potential targets for therapies.[9]

Molecular classification of medulloblastomas also allows the identification of good prognostic groups with WNT alterations that may allow for reduction in radiotherapy dose and potential neurotoxicity and groups that have alterations in the sonic hedgehog pathway that may respond to smoothened inhibitors.[10] In contrast, those patients in other groups have a much poorer prognosis and require aggressive therapy.[8,10,11]

DNA methylation profiling enables quantitative interrogation of selected methylation sites across the genome, offering high-throughput capabilities.[2,12,13] It has improved the classification of brain tumors and allowed the identification of several previously unknown tumor types. Although it is currently not widely available, it offers the potential for a relatively cost-effective method to diagnose brain tumors, providing O^6-methylguanine–DNA methyltransferase (MGMT) methylation status and copy number information. Methylation of the MGMT promoter and silencing of the gene are predictive of improved response to alkylating chemotherapy (temozolomide and lomustine) in patients with glioblastoma.[14,15] MGMT promoter methylation status is being used increasingly to stratify patients in glioblastoma clinical trials and select patients without MGMT promoter methylation for trials omitting temozolomide, allowing the agent under investigation to be used at full dose or to avoid immunosuppression.[16]

The improved classification of CNS tumors with molecular profiling allows for better understanding of the

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PRACTICAL APPLICATIONS

- Molecular profiling plays a critical role in diagnosis, classification, and outcomes of brain tumors.
- The greatest advances have been seen in children, allowing targeted therapy for SEGA in tuberous sclerosis, low-grade glioma, and plexiform neurofibroma.
- Methylation of O^6-methylguanine–DNA methyltransferase promoter enzyme is predictive of improved response to alkylating chemotherapy in patients with glioblastoma and is being used to stratify patients in clinical trials.
- Developing a predictive biomarker for widespread use in patients with glioma requires validation.
- Improving access and awareness of advanced molecular testing will broaden understanding regarding the spectrum of diseases in patients with various elements of diversity.

prognosis and optimal therapy for patients.[9,17] It also allows more homogeneous populations of patients to be enrolled into clinical trials, facilitating the evaluation of novel therapies, and increases the potential for identifying more molecular targets for therapy. However, there is now a much greater requirement for neuropathology laboratories to have access to adequate molecular testing and to provide the results in a timely manner. There is also the need for payors to be educated on the importance of these tests and provide appropriate reimbursement.

THERAPY ON THE BASIS OF MOLECULAR PROFILING

Although there has been major progress in understanding the molecular pathogenesis of brain tumors, these advances have only recently started to be translated into improved outcomes for patients, primarily in the pediatric population.

Therapy for systemic cancers has been effective with agents able to achieve therapeutic concentrations against well-validated therapeutic targets. For many brain tumors, targets are often not well-validated and there are uncertain ability of the agents to cross the blood-brain barrier (BBB) and achieve adequate concentrations in tumor and uncertain information regarding the ability of these agents to adequately inhibit the targeted pathways.[6] Other challenges to developing effective molecular therapies include the poorly predictive preclinical models, the limited number of agents under development that can effectively cross the BBB, redundancy of signaling pathways, tumor heterogeneity and plasticity of cellular states, the relative rarity of easy targets, such as *BRAFV600E* mutations and fusions, the poorly organized and funded infrastructure for early phase (phase I and surgical window of opportunity) clinical trials in neuro-oncology, the need for improved response criteria and trial design, and the relative lack of funding and interest from the pharmaceutical industry.[6]

Despite these challenges, there has been some recent progress (Table 1). In adults, the combination of dabrafenib (RAF inhibitor) and trametinib (MEK inhibitor) produced durable responses in 32% of *BRAFV600E*-mutated glioblastomas and 69% of lower-grade gliomas and contributed to the US Food and Drug Administration approval of the combination for all solid tumors in 2022.[18] Single-agent vemurafenib (BRAF inhibitor) produced a lower 25% objective response rate (ORR) and a 5.5-month median progression-free survival (PFS) in *BRAFV600E*-mutated gliomas.[19] Retrospective studies have also shown similar benefits.[36] In adults, durable response rates of 30% have been observed with larotrectinib for neurotrophic tyrosine receptor kinase fusion–positive brain tumors,[20] 20.7% with erdafitinib for high-grade gliomas with fibroblast growth factor receptor mutations or fusions,[21] and 20% with dordaviprone (ONC201), a dopamine receptor D2 inhibitor and ClpP agonist, in H3K27M-mutated diffuse midline gliomas.[22,23] In IDH-mutated gliomas, several IDH inhibitors have shown prolonged stabilization of disease and vorasidenib has shown response rates of up to 40%.[24-28,37,38]

However, the greatest advances have been seen in children. The first targeted therapy that received regulatory approval for brain tumors was the mammalian target of rapamycin inhibitor everolimus for subependymal giant cell astrocytoma associated with tuberous sclerosis.[29] A durable response rate of 35% was observed and associated with a reduction in seizure frequency. The combination of dabrafenib and trametinib has produced a response rate of 25% in children with recurrent low-grade gliomas with *BRAFV600E* mutations[30] and increased responses and prolonged progression-free survival compared with standard chemotherapy with newly diagnosed low-grade gliomas with these mutations (an ORR of 47% and a median PFS of 20.1 months with dabrafenib/trametinib *v* an ORR of 11% and a median PFS of 7.4 months with chemotherapy).[30] MEK inhibitors, such as selumetinib,[31,39] and type 2 RAF inhibitors, such as tovorafenib (day 101), also show high response rates in children with low-grade gliomas, including those with BRAF-KIAA fusions. Infants with hemispheric gliomas often have fusions, and responses have been seen with a variety of agents.[40] Dordaviprone (ONC201) has also shown activity in children with H3K27M-mutated midline gliomas,[32] and encouraging responses have been observed with GD2 CAR-T-cell therapy for these tumors.[33] Selumetinib has also shown encouraging activity for malignant plexiform neurofibromas.[34]

General Changes in Nomenclature

Use of Arabic numerals (1, 2, 3, 4) rather than Roman numerals (I/II/III/IV)

Not Otherwise Specified (NOS) indicates that the molecular and/or immunohistochemical testing needed to precisely classify a particular CNS tumor by the new scheme is not available.

Not Elsewhere Classified (NEC) refers to cases in which advanced molecular testing was done, but still failed to classify the tumor.

Adult-Type Diffuse Gliomas

- Astrocytomas, IDH-mutant
- Oligodendrogliomas, IDH-mutant, 1p/19q codeleted
- Glioblastoma, IDH wild-type

Pediatric-Type Diffuse Gliomas

Pediatric-Type Diffuse Low-Grade Gliomas

- Diffuse astrocytomas, MYB- or MYB-L1–altered
- Angiocentric glioma
- Polymorphous low-grade neuroepithelial tumor of the young
- Diffuse low-grade glioma, MAPK pathway–altered

Pediatric-Type Diffuse High-Grade Gliomas

- Diffuse midline gliomas, H3K27-altered
- Diffuse hemispheric gliomas, H3G34-mutant
- Diffuse pediatric-type high-grade glioma, H3 wild-type and IDH wild-type
- Infant-type hemispheric glioma

Circumscribed Astrocytic Gliomas

- Pilocytic astrocytoma
- High-grade astrocytoma with piloid features
- Pleomorphic xanthoastrocytoma
- Subependymal giant cell astrocytoma
- Chordoid glioma
- Astroblastoma, *MN1*–altered

Glioneuronal and Neuronal Tumors

- Ganglioglioma
- Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma
- Dysembryoplastic neuroepithelial tumor
- Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters
- Papillary glioneuronal tumor
- Rosette-forming glioneuronal tumor
- Myxoid glioneuronal tumor
- Diffuse leptomeningeal glioneuronal tumor
- Gangliocytoma
- Multinodular and vacuolating neuronal tumor
- Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
- Central neurocytoma
- Extraventricular neurocytoma
- Cerebellar liponeurocytoma

Ependymal Tumors

- Supratentorial ependymoma
- Supratentorial ependymoma, *ZFTA* fusion–positive
- Supratentorial ependymoma, *YAP1* fusion–positive
- Posterior fossa ependymoma
- Posterior fossa ependymoma, group PFA
- Posterior fossa ependymoma, group PFB
- Spinal ependymoma
- Spinal ependymoma, *MYCN*-amplified
- Myxopapillary ependymoma
- Subependymoma

FIG 1. Major changes on the basis of the 2021 WHO CNS Tumor Classification of Glial Tumors.[8,9] H3, histone H3; *IDH*, isocitrate dehydrogenase; MAPK, mitogen-activated protein kinase; *MN1*, MN1 proto-oncogene transcriptional regulator; *MYB*, MYB proto-oncogene transcription factor; *MYCN*, MYCN proto-oncogene, bHLH transcription factor; *YAP1*, yes1-associated transcriptional regulator; *ZFTA*, zinc finger translocation–associated.

TABLE 1. Table Summarizing Molecular Targets Responding to Therapy

Molecular Target	Agent	Activity (ORR)	Reference
Adults			
BRAFV600E	Vemurafenib	25%	19
BRAFV600E	Dabrafenib/trametinib	32% GBM; 69% LGG	18
NTRK	Larotrectinib	30%	20
FGFR mutation/FGFRTACC fusion	Erdafitinib	20.9%	21
H3K27M	Dordaviprone (ONC201)	20%	22,23
IDH	Ivosidenib, vorasidenib Olutasidenib, BAY 1436032 Safusidenib	5%-40%	24-28
Children			
TSC1/2	Everolimus	35%	29
BRAFV600E	Dabrafenib/trametinib	25%-47%	30,35
BRAF/KIAA fusion	Selumetinib	35%-40%	31
BRAF/KIAA fusion	Tovorafenib	64%[a]	
H3K27M	Dordaviprone (ONC201)		32
H3K27M	GD2 CAR-T cell	50%	33
NF1	Selumetinib	70%	34

Abbreviations: CAR, chimeric antigen receptor; GBM, glioblastoma; LGG, low-grade glioma; ORR, objective response rate.
[a]Not yet published in peer review journal.

These recent examples of activity with targeted molecular therapies suggest that despite the concerns regarding tumor heterogeneity, plasticity of cellular states, and redundancy of signaling pathways, in small subsets of brain tumors, targeting of oncogenic drivers can be effective. Whether targeting of the more common molecular drivers involving the EGFR, the cyclin-dependent kinase (CDK) 4/6 pathway, and the phosphatidylinositol-3-kinase (PI3kinase) pathways will be effective remains to be seen. Trials with targeted therapies against these pathways, for example, abemaciclib for glioblastomas with CDKN2A/B loss, buparlisib for tumors with PI3K activation, and numerous agents against EGFR, have been ineffective. Paxalisib, a pI3 kinase inhibitor, did not graduate to stage 2 in GBM Agile, although the patients in that trial were not specifically selected for PI3 kinase pathway activation. Newer agents against EGFR directed at the molecular alterations specific for glioblastomas with good BBB penetration such as BDX1535 and ERAS-801 are in clinical trials. Whether they will be more effective remains to be determined. In addition, progress in evaluating sensitive and reliable blood and cerebrospinal fluid biomarkers will help with less invasive profiling of tumors and the selection and monitoring of molecular therapies.[41]

ESTABLISHING PREDICTIVE BIOMARKERS IN NEURO-ONCOLOGY

Predictive biomarkers, also known as treatment selection biomarkers, typically represent some characteristics related to the study drug's mechanism of action. Successful identification and deployment of predictive biomarkers are crucial toward the goal of precision oncology as its central tenet lies in delivering the right cancer therapy to the right patients at the right time. However, to date, few molecular changes detected in brain tumors have risen to the level of being clinically useful. The reasons for the paucity of clinically useful biomarkers in neuro-oncology are multifaceted. In this section, we highlight several methodological challenges associated with identifying predictive biomarkers. Using examples in neuro-oncology, we first underscore the need for well-validated and reproducible biomarker assays for routine clinical use. Second, we illustrate some difficulties arising from evaluating the predictive value of a biomarker on the basis of data collected from previous randomized clinical trials (RCTs). Although these discussions are framed primarily around predictive biomarkers, many methodological principles apply generally to other types of biomarkers (diagnostic and prognostic biomarkers).

Biomarker Assay Validity and Reproducibility

Uncertainty around the performance characteristics of the biomarker assay can pose significant challenges in clinical implementation. In a newly diagnosed glioblastoma, for example, *MGMT* promotor methylation status has emerged as a biomarker for prognosis and for predicting response to alkylating agents, such as temozolomide and

lomustine.[14,42,43] Although *MGMT* status has been used in clinical trials for some time, the implementation of this biomarker in clinical practice is challenging. One reason is that there is currently no consensus regarding the best assay to evaluate *MGMT* methylation status. The use of different assay methods has led to discordant *MGMT* results in some patients, leading to ambiguous treatment recommendations.[44,45] A study by Lassman et al[46] analyzed the concordance of *MGMT* methylation results between local and central laboratories using tissue specimens collected from a randomized phase III trial RTOG 3508 and found that the interlaboratory concordance was only 61%. At present, several assays are in use to determine *MGMT* promoter methylation status in patient samples. A comprehensive review of the various methods is beyond the scope of this article; readers are referred to a review by Weller et al.[47]

Another considerable limitation is the lack of standard cutoff values for determining *MGMT* status from quantitative methods, such as methylation and expression assays. A group of investigators conducted an international survey regarding the use of *MGMT* assays in 25 countries. The survey results revealed that there is considerable variability with respect to the assays used and the cutoff values for *MGMT* methylation status.[48] Considering the potential of this biomarker in treatment decisions in clinical trials and routine practice for glioblastoma, there is a pressing need for an international consensus guideline to standardize the *MGMT* methylation assay and define a reliable cutoff for clinical deployment. Furthermore, appropriate quality measures need to be established to ensure comparable assay results across different laboratories.

Challenges in Evaluating The Predictive Value of A Biomarker On The Basis of Completed Clinical Trials

Modern clinical trials frequently evaluate the predictive value of a biomarker for an experimental therapy using previously completed RCTs of the experimental therapy vs. the standard treatment, where the biomarker status is ascertained on patients with available biologic specimens but not used to direct therapies on the trial.[49-51] Simon et al[52] designated these types of biomarker studies as prospective-retrospective (P-R) studies to distinguish them from nonexperimental observational biomarker studies. A prime example of a prospective-retrospective predictive biomarker study is the one by Hegi et al, which examined *MGMT* promoter methylation status in a subset of patients with available tissue specimens and assay results in the practice setting trial EORTC/NCIC 22981/26981, which compared radiotherapy + temozolomide versus radiotherapy alone for newly diagnosed glioblastoma.[14,42] The investigators reported that there was a statistically significant survival benefit from temozolomide in the *MGMT*-methylated subgroup (P = .007), but this benefit did not reach statistical significance in the *MGMT*-unmethylated subgroup (P = .06). On the basis of these observations, they concluded that *patients with glioblastoma containing a methylated MGMT promoter benefited from temozolomide, whereas those who did not have a methylated MGMT promoter did not have such a benefit*.

It is important to note that in these retrospective evaluations of predictive biomarkers, the parent treatment trial is powered to discern a clinically meaningful treatment effect for all trial patients (regardless of their biomarker status). Consequently, the statistical power to detect treatment benefit from the experimental therapy in a biomarker-defined subgroup is limited because of the reduced sample size. This issue of low power is especially exacerbated in the biomarker subgroup that is not expected to derive benefit from the experimental therapy or to derive a much lesser degree of benefit, compared with the other biomarker subgroup. In a study by Hegi et al, the consequence of the reduced sample size and resultant uncertainty around the benefit from temozolomide were reflected in the wide confidence interval for the treatment hazard ratio in the *MGMT*-unmethylated subgroup (hazard ratio [HR], 0.69; 95% CI, 0.47 to 1.02). Of note, failure to demonstrate a statistically significant treatment benefit in a biomarker subgroup does not imply the lack of benefit in that subgroup since P values are highly influenced by the sample size and number of observed events. Relatedly, achieving statistical significance in one biomarker subgroup but not in the other is not sufficient to establish the predictive value of a biomarker. As such, the data presented by Hegi et al do not lend conclusive evidence for *MGMT* methylation as a predictive biomarker for benefit from temozolomide in patients with glioblastoma. In fact, among *MGMT*-unmethylated patients, PFS was significantly improved with temozolomide (HR, 0.62; 95% CI, 0.42 to 0.92). With further clinical follow-up, a subsequent analysis reported a statistically significant survival benefit in *MGMT*-unmethylated patients (HR, 0.6; 95% CI, 0.4 to 0.8).[43]

This example underscores the challenges associated with establishing the predictive value of a biomarker using data from completed clinical trials. Retrospective evaluations of the predictive value of a biomarker frequently lack adequate statistical power to reliably discern a treatment effect, especially in the biomarker subgroup that is not expected to respond to the experimental therapy. In this setting, of critical relevance are the biomarker subgroup–specific treatment hazard ratio estimates and their confidence intervals, the width of which reflects the certainty that one should place around the estimated treatment benefit. Specifically, when the confidence interval around a treatment hazard ratio is too wide in a biomarker subgroup, it would be impossible to make a definitive conclusion about

whether patients in that subgroup benefit from the experimental therapy. In turn, the clinical utility of the predictive biomarker cannot be confidently established. Possible solutions to this problem include pooling data from similar trials or increasing the clinical follow-up of the trial to obtain more events although the latter may be infeasible if the parent trial has been terminated. Furthermore, biologic insights into the biomarker and mechanism of action of the study agent from preclinical and clinical studies may increase confidence on the predictive value of the biomarker.

LEVELING THE PLAYING FIELD: ADDRESSING RACIAL, GEOGRAPHIC, AND SOCIOECONOMIC DISPARITIES IN IMPLEMENTATION OF BRAIN TUMOR DIAGNOSTICS

Nearly universally fatal, there are more than 13,000 new cases of glioblastoma identified annually. Typically affecting men more than women age 55-65 years, aggressive multimodal treatment leads to an average survival of 2 years.[53] On the basis of SEER data, incidence of glioma is highest in non-Hispanic White (NHW) populations and has been associated with increased socioeconomic status.[54,55] Similar to other reports, Ostrom et al[54] found that NHW populations have reduced overall survival compared with other racial and ethnic groups after diagnosis of glioblastoma. Black patients, Hispanic patients, and patients with lower socioeconomic status have been found to have increased risk of non–glioblastoma-related mortality. Death from other cancer, cardiac, and cerebrovascular events is reported disproportionately in these populations.[56]

Limited reporting of race and ethnicity in glioblastoma-related clinical trials has led to an incomplete understanding of the impact of treatment and outcomes in varied populations.[57] Although it is believed that nearly 15% and 13% of patients with cancer are Black and Hispanic, these populations typically are under-represented in clinical trials at 6% collectively.[58] There are several challenges leading to poor enrollment in clinical trials, including stringent eligibility criteria, geographic distribution of access to trials, inefficient activation processes, limited consumer-friendly information, and an inadequate pipeline of novel therapies.[53] Barriers to clinical trial enrollment span the clinical care pathway from diagnosis to end of life. Issues of unconscious bias, cultural barriers, cost, healthy literacy, transportation, insurance, and patient/physician factors perpetuate these disparities including lack of advanced molecular testing on tumor tissue and limited pathologic interpretation.[59,60]

Testing Disparities

Advanced molecular testing has provided deeper understanding as to the heterogeneity in high-grade glioma and is less likely to be offered to certain groups and often underutilized in clinical decision making.[61] While some patients are being offered testing up front to stratify clinical trial enrollment, others are using the results to determine treatment strategies after first or second recurrence. Understanding of promoter methylation status of MGMT is often an inclusion criterion in clinical trials, which aids in decision making regarding elderly and frail populations who may not tolerate multimodal treatment.[5] The importance of this nuance has reached the threshold to allow inclusion in National Comprehensive Cancer Network guidelines in the treatment of glioblastoma.[62]

Chukwueke et al found that patients with newly diagnosed glioblastoma who were from lower socioeconomic status, uninsured or insured through Medicaid, were less likely to receive MGMT testing.[63] Patients from these backgrounds are also noted to frequently present later in the course of disease with larger tumors, incomplete resection, and are less frequently recipients of multimodal therapy ultimately leading to reduction in survival.[64] Similarly, patients who were diagnosed at community hospitals were less likely to receive advanced testing and multimodal care. The authors note that despite the increasing incidence of testing across the United States, the populations with varied elements of diversity continued to experience disparity in testing frequency.[63] Data to direct the clinical management were also underutilized with undertreatment of populations that could have benefited from temozolomide.

Opportunities for Improvement

Limitations in referral for advanced testing in diverse populations have led to an incomplete understanding in the spectrum of diseases. The US Food and Drug Administration published guidelines in 2020 to enhance clinical trial diversity including broadening eligibility criteria and adopting enrollment and retention practices that enhance inclusiveness.[65] Efforts to reduce disparities in diagnostics are multilayered, ranging from governmental and institutional policies to individual provider behavior and patient education. As testing becomes more widely available, increased coverage by insurers is essential. While patient assistance programs are available, the addition of this recommendation to National Comprehensive Cancer Network guidelines should lead to consideration of advanced testing becoming standard of care.[62] Patient education through advocacy groups and community engagement can help raise awareness among patients and caregivers regarding the relevance and importance of the additional information this testing provides.[59] In addition to provision of resource for advanced testing as part of the protocol, behavior modification in care teams to offer advanced testing to all patients is necessary to attempt to bridge this gap.

CONCLUSION

Advances in molecular profiling have introduced a growing number of biomarkers in neuro-oncology. Comprehensive characterization of molecular alterations in brain tumors has the potential to provide more accurate disease classification, risk stratification, and tailored treatments for individual patients. The future of molecular profiling in neuro-oncology, particularly concerning the utility of treatment selection biomarkers, will depend on the availability of robust biomarker assays and effective therapeutic options to allow tailored treatment choices for individual patients. Although a burgeoning field, opportunities remain for validation of testing and improved awareness and accessibility for widespread use. Failure to pursue molecular profiling not only contributes to disparate understanding of the spectrum of diseases and populations affected but also perpetuates disparities in treatment and outcome.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Immune Resistance Mechanisms and the Road to Personalized Immunotherapy

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overview

Despite decades of clinical and preclinical studies, the markers and mechanisms of resistance to cancer immunotherapy, particularly immune checkpoint blockade (ICB), remain elusive. In this review, we address the current clinical challenges regarding ICB treatment by examining the underlying cellular and molecular contributors to resistance and newly developed agents to target them. Furthermore, we discuss emerging computational tools to consolidate genomic data and provide examples of how these tools can guide clinical decision making in the context of immuno-oncology. Finally, we examine the shortcomings and clinical limitations of current predictive biomarkers of response to ICB treatment and provide details on next-generation biomarker research, including prospective genomic profiling on the basis of known biomarkers and personalized immunotherapy.

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Since its implementation over a decade ago,[1] immunotherapy has quickly ascended through the ranks of approval to join radiotherapy, chemotherapy, and surgery as a mainstay in oncologic treatment. However, clinical trials have repeatedly shown that only a subset of patients respond to immunotherapy.[2] As such, extensive research work has gone into understanding the factors governing the balance between response and resistance, with efforts yielding a complex network of viable treatment targets. Here, we summarize the current thought regarding cancer cell–intrinsic and cancer cell–extrinsic resistance mechanisms to immune checkpoint blockade (ICB).

MECHANISMS OF RESISTANCE TO ICB

Tumor-Intrinsic Resistance

Lack of tumor immunogenicity. Like any other immunotherapy, response to ICB is contingent on immune cell recognition of tumor cells. To evade immune recognition, cancer cells can develop mechanisms to effectively disguise themselves and avoid CD8-mediated killing. Many of such mechanisms rely on the alteration or downregulation of the HLA antigen presentation complex, a group of proteins required for adaptive immune clearing of pathogens and differentiating between self and non-self cells.[3] Cancer cells hijack this system and cause HLA downregulation through mechanisms that include genetic silencing via NF-kB dysregulation,[4] epigenetic alteration by hypermethylation and deacetylation of the HLA promoter,[5,6] post-transcriptional silencing by noncoding microRNAs[7], and translational suppression through the downregulation of chaperone proteins,[8] resulting in immune evasion. Genetic mutations in the HLA complex are also common in tumors, with one of the most important being a mutation in the b2-microglobulin (B2M) subunit. B2M plays a critical physiologic role in immune surveillance and regulation,[9] and its loss has been shown to reduce folding and transport of HLA to the cell surface,[10] resulting in acquired resistance to ICB.[9]

After intact and functional antigen presentation machinery, the next hurdle that immunotherapeutic strategies face is the ability to discriminate between normal tissue and cancer cells. This process relies heavily on neoantigens or antigens generated by mutations expressed only in tumor cells.[11] Response to ICB is intrinsically tied to neoantigen load,[12,13] but methods of accurately quantifying antigenicity remain elusive. For years, tumor mutational burden (TMB), or the composite of all tumors' mutations, was pursued as a surrogate of tumor antigenicity, with a low TMB having been thought to confer resistance to ICB. However, those ventures have yielded highly discrepant results, with an elevated TMB having been detected in both ICB-responsive and nonresponsive patients.[14,15] Recent evidence suggests that resistance to ICB could instead be related to a low tumor *neoantigen* burden (TNB), but techniques designed to assay and enhance TNB are still in their early stages.[16-18] One strategy of promoting neoantigen cross-presentation to overcome resistance to ICB is the combination of radiotherapy and immunotherapy treatment, under the guiding principle that radiation-induced cell death releases neoantigens, which can then be used to prime T cells and initiate a specific and systemic antitumor immune response.[19-21] As immunotherapy advances into the next generation, identification of tumor neoantigens will undoubtedly be a

PRACTICAL APPLICATIONS

- A systematic approach to understanding the underlying cellular and molecular contributors to resistance in ICB treatment.
- Analysis of novel clinically actionable targets of resistance currently in clinical and preclinical trials.
- Examination of emerging computational tools to analyze vast genomic data and the power they hold in guiding clinical decision making.
- An overview of the clinical shortcomings of historical biomarkers of response such as PD-L1 expression and tumor mutational burden.
- Discussion of next-generation biomarker research including prospective genomic profiling on the basis of known biomarkers and personalized immunotherapy.

driving force in the development of novel immunotherapeutic approaches such as personalized neoantigen peptides and mRNA vaccines and novel cell therapy targeting these neoantigens.[22]

Aberrations in the IFNg/JAK/STAT pathway. Cancer cells have also devised ways to avoid immune-mediated killing by crippling critical immune response pathways. For example, the interferon-gamma (IFNg)/janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling axis is one of the primary pathways in mediating resistance to ICB. Under normal physiologic conditions, the JAK/STAT cascade is activated by cytokines and growth factors and plays a vital role in hematopoiesis, immune fitness, tissue repair, inflammation, and apoptosis.[23] Because effective immunotherapy relies on the production of IFNg by activated T cells and the subsequent JAK/STAT-mediated upregulation of genes involved in antitumor immune responses,[24] the role of this pathway is magnified in the context of ICB resistance. As anticipated, mutations in interferon (IFN) receptors have been linked to poorer treatment outcomes and have been shown to confer resistance to ICB. For example, Gao et al[25] found that ICB nonresponsive tumors were enriched for specific mutations in the IFNg receptor genes *IFNGR1* and *IFNGR2*. To demonstrate the causality of this relationship, the group then performed an IFNGR1 shRNA knockdown in the B16/BL16 melanoma cell line and found that IFNGR1-deficient tumors had an impaired response to anti-CTLA4 treatment in vivo.[25] Similarly, JAK mutations have also been implicated in resistance to ICB. JAK signaling has been widely known to contribute to T-cell chemotaxis, and targeted inhibition has been shown to dimmish T-cell recruitment by reducing expression of the chemokine CXCL10.[26] Moreover, in a genome-wide analysis of four patients who demonstrated acquired resistance to anti-PD1 therapy, two were found to harbor JAK1/2 loss-of-function mutations with significantly decreased sensitivity to IFN signaling.[27] Importantly, these JAK-deficient tumor cells were found to be clonally selected for from baseline to progression, suggesting a critical role for JAK activity in mediating resistance to ICB. On the other hand, hyperactive JAK also contributes to treatment resistance and JAK inhibition has also been shown to attenuate the response to ICB,[28-30] suggesting that more work will need to be performed to determine the exact contexts in which JAK inhibition is clinically beneficial.

The role of the STAT family of proteins in mediating response to ICB is even more ambiguous. Although currently considered oncogenes, STATs are essential for the transfer of information for dozens of immunostimulatory cytokines, including IFNs, interleukins (ILs), and colony-stimulating factors (CSFs).[31] The dichotomous effect of STAT signaling lies in the promiscuous and pleiotropic nature of this family of proteins, with some groups reporting a robust antitumor effect of STAT activity while others describing a more nefarious role in STAT function. For example, analyses of the cancer genome atlas (TCGA) database have suggested that PD-L1 expression is intrinsically regulated by STAT3 activity.[32-34] As such, overexpression of STAT3 may result in response to ICB. However, STAT3 activity has been shown to downregulate MHCII expression on dendritic cells and CD4 T cells while simultaneously promoting the development and maturation of regulatory T cells (Tregs) and myeloid-derived suppressive cells (MDSCs), two immunosuppressive cell types.[35,36] Clinical trials testing the efficacy of STAT inhibition in combination with ICB are currently ongoing.[37] Although these complex interactions seem to illustrate highly variant effects of the IFN/JAK/STAT pathway in different cell types, it is clear that this foundational signaling pathway plays an important role in regulating the response to ICB treatment.

Alterations to RAF and RAS. Another commonly mutated pathway contributing to cancer progression is the RAS/RAF signaling axis. RAF signaling in tumors has been shown to contribute to immune tolerance and evasion by both downregulating MHCI[38] and upregulating PD-L1 expression.[39] RAF mutations, particularly BRAF, have proven to be particularly significant in the progression and treatment of melanoma. Approximately 50% of melanomas harbor a BRAF mutation, and abhorrent BRAF signaling has been correlated with a more aggressive tumor phenotype.[40] Several clinical trials have explored the efficacy of BRAF and MEK inhibition in combination with ICB because of the paradoxical immune activation and sensitization by BRAF inhibitors in mouse models.[41] Initial results of these trials showed improved clinical activity

with a manageable safety profile,[42] leading to the Food and Drug Administration (FDA) approval of the combination of vemurafenib, cobimetinib, and atezolizumab for BRAF-mutant melanoma. In addition, a recently completed phase I/II clinical trial assessed the efficacy of the combination of durvalumab and trametinib on patients with metastatic colorectal cancer and found a clinical benefit in the growth of lung metastases.[43] Similar clinical trials exploring MEK-induced immunotherapy resistance are currently ongoing.[44] Once thought of as an undruggable target, trials such as these provide great rationale and optimism for combinatorial ICB approaches in aggressive RAF-mutant tumors.

Meanwhile, RAS is a molecular target of therapy that oncologists have gravitated toward since it was first isolated from the sarcoma-inducing virus MSV in the 1960s.[45] RAS has been shown to induce expression of PD-L1,[46] promote the conversion of conventional T cells into Tregs,[47] and prevent T lymphocyte intratumoral infiltration,[48] prompting the clinical investigation of its inhibition in combination with ICB. In a syngeneic murine model of colon cancer,[48] the RAS G12C inhibitor combined with anti–PD-1 therapy led to enhanced T-cell tumor infiltration, activation, and killing. In fact, the combination of these agents is currently the subject of an ongoing clinical trial (ClinicalTrials.gov identifier: NCT04185883), with preliminary results showing a tolerable toxicity profile and improved response rates after treatment with the KRAS inhibitor sotorasib in combination with pembrolizumab over sotorasib alone.[49]

Abnormal phosphatidylinositol 3-Kinase and PTEN. Cancer cells also frequently mutate to usurp control of the phosphatidylinositol 3-kinase (PI3K) signaling cascade involving PI3K, protein kinase B (AKT), and mammalian target of rapamycin to promote unrestricted cell survival.[50] However, the development of targeted therapies against different elements of this pathway has thus far yielded underwhelming results. As these molecular targets not only play an active role in cancer but also are important in homeostasis, targeted inhibition has proven to be difficult and when inhibition is achieved, compensatory resistance mechanisms are commonly observed.[51,52]

Although their direct cytotoxic activities have been disappointing, recent evidence has shown that various targeted agents of the PI3K signaling axis have a dual immunostimulatory effect on the tumor microenvironment (TME). For instance, pan-PI3K inhibition has been shown to provide a survival benefit in preclinical models by enhancing CD8 T-cell infiltration into the tumor,[53] and AKT inhibitors have been found to enhance tumor immunosurveillance by selectively inhibiting Tregs.[54] Meanwhile, loss-of-function mutations in PTEN, a negative regulator of the PI3K pathway, are associated with increased production of immunosuppressive cytokines including IL-6 and IL-10[53] and increased expression of PD-L1.[55] These observations suggest a synergistic effect between PI3K inhibition and immunotherapy, and indeed, the combination of PI3K inhibition and ICB in preclinical mouse models has been shown to augment effector T-cell function through Treg inhibition, promote memory CD8 T-cell differentiation, and elicit a strong and durable inhibition of tumor growth.[56] Clinical trials aimed at validating this relationship are currently underway.[57] This growing body of data provides yet another lens to view intrinsic resistance to ICB and identifies molecular mediators that can augment response to immunotherapeutic modalities.

Tumor-Extrinsic Resistance

Adaptative immunity Tregs. Resistance to ICB poses a complex clinical problem primarily because it is a multicompartmental phenomenon mediated by several different cellular populations (Fig 1). One such population is Tregs. Perhaps the most prominent and extensively characterized immune population within the TME, Tregs are a subpopulation of CD4 T cells that normally play an important role in autoimmunity, homeostasis, and self-tolerance by inhibiting the activation and differentiation of CD4 and CD8 effector T cells.[58] In the context of cancer, Tregs exhibit strong immunosuppressive activity and function to inhibit antitumor immunity and promote tumor immune evasion.[59]

Treg function is governed primarily by the regulatory transcription factor FoxP3, a known promoter of immunosuppression, and the production of various anti-inflammatory signaling molecules including IL-10,[60,61] a cytokine necessary for Treg maturation.[62] IL-10 plays a central role in controlling inflammatory processes and maintaining peripheral tolerance.[63] In cancer, however, IL-10 attenuates the antitumor immune response by downregulating MHCII on antigen-presenting cells[64] and decreasing the production of proinflammatory cytokines such as IL-2, TNFa, and IFNg.[65,66] Indeed, IL-10 levels have been correlated with poorer clinical outcomes in multiple disease types[67,68] and improved immune activation after IL-10 signaling inhibition has been observed in both virus- and tumor-derived preclinical models.[69,70]

Another mechanism by which Tregs suppress immune activation is by monopolizing the available IL-2 in the TME. Because of its role in the survival, proliferation, and differentiation of activated T and NK cells,[71] IL-2 has become a hallmark of immune stimulation. To our knowledge, exogenous high-dose IL-2 treatment was even the first approved cancer immunotherapy.[72] However, Tregs are also heavily dependent on IL-2 for maturation[73] and constitutively express the high-affinity IL-2 receptor subunits CD25, CD122, and CD132, allowing them to consume IL-2 more efficiently than conventional T cells.[74] Furthermore, FoxP3 has been

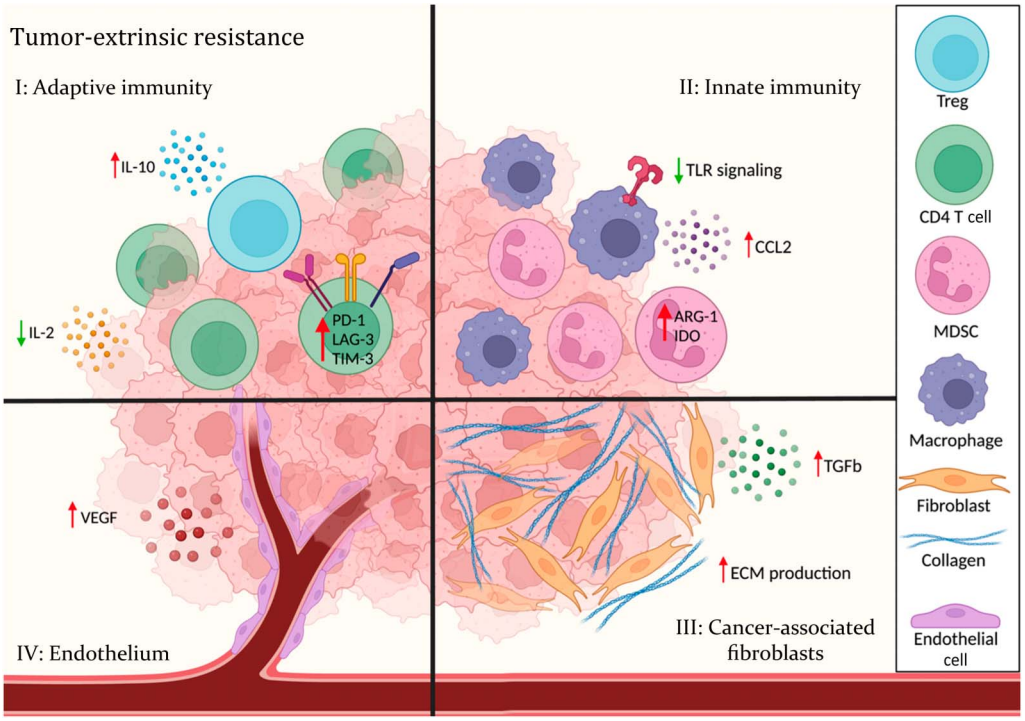

FIG 1. Mechanisms of tumor-extrinsic and cell-mediated resistance to ICB therapy. ARG-1, arginase-1; CCL2, chemokine ligand 2; ECM, extracellular matrix; ICB, immune checkpoint blockade; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; LAG-3, lymphocyte-activation gene 3; MDSC, myeloid-derived suppressive cell; TGFb, transforming growth factor b; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TLR, toll-like receptor; VEGF, vascular endothelial growth factor.

shown to attenuate factors needed for Treg-mediated IL-2 production,[75,76] meaning that Tregs lack the self-sufficiency to meet their own high IL-2 demand. The sum of these effects is the sequestration of IL-2 by Tregs in the TME, leading to a deprivation of IL-2 from effector T cells and resulting in an inadequate antitumor immune response.[77]

T-cell exhaustion. T-cell exhaustion is broadly defined as a state of T-cell differentiation distinct from effector or memory T cells and is marked by dysfunction and apoptosis because of chronic antigen stimulation.[78] This process is partly mediated by the temporal expression of inhibitory receptors, many of which have been shown to prolong and maintain immune stimulation when selectively targeted in combination settings. Although PD-L1 inhibition is critical for overcoming exhaustion, it may be overshadowed by other mediators of exhaustion. For example, T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) is an inhibitory receptor expressed on the surface of CD4, CD8, and NK cells that signal to impede T-cell receptor (TCR)-mediated activation and reduce degranulation and cytotoxicity in CTLs.[79,80] Clinically, TIGIT inhibition in combination with ICB has been shown to enhance the proliferation and functionality of antigen-specific, tumor-educated CD8 T cells and improve response over ICB alone.[81] T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) is a related coinhibitory protein expressed by the most terminally dysfunctional subset of CD8+ tumor-infiltrating lymphocytes (TILs).[82] In preclinical models, dual TIM-3 and PD-1 inhibition was also found to have a substantial synergistic effect on CD8 T-cell activity and tumor regression,[82] leading to the opening of several clinical trials testing the synergy between TIM-3 antagonization and ICB.[83,84] Finally, because of its role in autoimmunity and immune homeostasis, lymphocyte activation gene 3 (LAG-3) has garnered significant clinical and preclinical attention as a promising immunotherapeutic target. LAG-3 is an inhibitory receptor expressed on the surface of activated T lymphocytes, which has been shown to interfere with the binding of major histocompatibility complex II (MHCII) to the TCR[85] and prevent CD3-mediated cytokine release.[86] More recent work has demonstrated significant cooperation between targeted inhibition of LAG-3 and the blockade of immune checkpoints PD-1 and cytotoxic T-cell lymphocyte-4 (CTLA-4).[87,88] In fact, anti–LAG-3 relatlimab in combination with nivolumab has been recently approved for frontline treatment of advanced melanoma.[89] Although the details and complexities of the molecular mechanisms dictating T-cell exhaustion are still being elucidated, it is now undeniable that sustained T-cell activation is a required criterion for response to ICB, and the identification of tumor-reactive T cells and novel agonistic targets using genomic analyses[90] may be clinically useful in meeting that precondition.

Innate immunity tumor-associated macrophages. The innate immune system and cells of myeloid lineage have also been implicated in mediating resistance to checkpoint inhibitors immunotherapies.[91,92] One such cell type is tumor-associated macrophages (TAMs). Similar to conventional

macrophages, TAMs are phagocytes that proliferate in their site of action (the tumor) and contribute to the coordination of an immune response. Unlike conventional macrophages, TAMs express cytokines and chemokines that can suppress antitumor immunity and promote tumor progression.[93] Subsets of TAMs are now regarded as a negatively prognostic marker in response to therapy,[94] and several strategies to improve antitumor immunity by targeting or modulating TAMs are being developed. These strategies include blocking the recruitment of TAMs, repolarization of TAMs into an immunostimulatory phenotype, and upregulating antigen presentation machinery that can stimulate CTL activation.[93] For instance, the chemokine chemokine ligand 2 (CCL2) and toll-like receptor 8 have become the subject of multiple clinical trials to suppress macrophage accumulation in tumors and repolarize TAMs toward a proinflammatory phenotype, respectively.[93] Preclinical results have demonstrated that inhibition of these two signaling axes may operate synergistically with ICB therapy,[95,96] prompting further investigation of these combinations as viable treatment modalities.

MDSCs. Another mediator of immunosuppression and treatment resistance is MDSCs. MDSCs are a heterogeneous subpopulation of immature myeloid cells with a significant capacity to inhibit T and NK cell effector functions.[97] Clinically, their accumulation has been associated with disease progression and recurrence,[98] and their activity is correlated with diminished responses to immunotherapies.[99] MDSC-mediated immunosuppression is unique in that it is related to their metabolism.[100] For example, MDSCs express high levels of ARG1, an essential enzyme that catalyzes the conversion of L-arginine to L-ornithine as part of the urea cycle. Because L-arginine is a necessary molecule for T-cell proliferation, the increased consumption of L-arginine by MDSC-expressed ARG1 leads to cell cycle arrest and apoptosis in TILs.[101] Similarly, MDSCs produce elevated levels of the enzyme indoleamine 2,3-dioxygenase (IDO), which degrades and depletes L-tryptophan, starving T cells of another essential amino acid and promoting their differentiation into a Treg phenotype.[102,103] To counteract this effect, tadalafil (a small molecule inhibitor of MDSC function) and entinostat (a class I histone deacetylase inhibitor) have been shown to reduce ARG1 and IDO expression and demonstrated early signs of preclinical and clinical promise in combination with anti-PD1.[104] MDSC frequency and activity have also been targeted using an interesting strategy to leverage the population's immature nature. Recent evidence has shown that ATRA, a vitamin A derivative and approved drug for acute promyelocytic anemia, can bind to the retinoic acid receptor on MDSCs and force their maturation and differentiation into benign dendritic cells or monocytes.[105] In multiple clinical trials, ATRA administration has been shown to deplete MDSCs and improve the adaptive antitumor immune response in combination with immunotherapy.[106,107]

Cancer-associated fibroblasts. Perhaps the most abundant cell type in TME, stromal fibroblasts have been shown to play a protective role in cancer and have recently become a target of inhibition in relieving treatment resistance. Cancer-associated fibroblasts (CAFs) arise from quiescent tissue-resident myofibroblasts that migrate to the tumor where they adopt a transcriptionally and metabolically active phenotype and produce growth factors and cytokines that promote angiogenesis and immune evasion.[108,109] CAFs primarily enact their immune regulation through the production of transforming growth factor b (TGFb), a pleiotropic and immunosuppressive cytokine that functions in normal wound healing, extracellular matrix (ECM) remodeling, and immune cell differentiation.[110] TGFb downregulates MHCII on dendritic cells,[111] reduces CD8 T-cell activation and infiltration, and confers resistance to ICB.[112] CAFs have also been shown to recruit immunosuppressive myeloid populations through the secretion of CCL2[113] and express inhibitory receptors such as TIM-3, LAG-3, PD-1, and CTLA-4 to inhibit T-cell proliferation.[114] Finally, although simplistic, CAFs can prevent T-cell–mediated killing of tumor cells through the excessive deposition of ECM and the construction of a collagen network that serves as a physical barrier to CTL infiltration.[115]

These broad-spectrum mechanisms of suppression, coupled with the significant effects on tumor progression, have led to the development of novel therapeutic approaches aimed at inhibiting the activity of intratumoral fibroblasts. Such newly generated anti-CAF therapies have focused primarily on the targeted depletion of fibroblasts in the TME. For instance, one study demonstrated that administering a DNA-based vaccine specifically targeting stromal cells in the TME induced immune-mediated killing of CAFs and increased the bioavailability of chemotherapeutic drugs intratumorally.[116] More contemporary studies have shown that CAF-specific CAR-T-cell therapy can boost host immunity and arrest cancer growth in highly desmoplastic tumors.[117,118] Several clinical trials testing the efficacy of anti-CAF treatments alone or in combination with ICB[119] are underway, providing a new, potentially transformative treatment option for patients with fibroblast-rich tumors. Of note, recent preclinical studies have also shown that the newly developed FAP-41BB and FAP-CD40 bispecific antibodies can specifically activate intratumoral T cells while reducing toxicity and enhancing the therapeutic index when delivered systemically,[120,121] suggesting a potential role for CAFs and the tumor stroma as a scaffold for T lymphocyte activation.

Endothelium. The final major cellular composition of the TME is the endothelium. Once larger than a few cubic millimeters, solid tumors must establish blood supply to

meet their high energy and nutrient demands. However, the resulting vascular network is immature, disorganized, thin-walled, and prone to leaks.[122] This poorly constructed endothelium has many protumorigenic qualities, including promoting immune evasion and resistance to immunotherapy. In fact, endothelial cells of the tumor vasculature have been shown to induce CD8 T-cell apoptosis,[123] prevent T-cell adhesion and lymphocyte extravasation,[124] and polarize immune cells toward an anti-inflammatory phenotype.[125] Interestingly, preclinical studies have shown that vascular endothelial growth factor–modulating monoclonal antibodies (eg, Bevacizumab) can have a transient vessel normalization effect,[126] suggestive of a window of opportunity wherein the tumor is adequately perfused and can allow for improved delivery of immunotherapeutic agents and enhanced infiltration of antitumor immune cells. In light of these effects, the combination of antiangiogenesis and immunotherapy treatment is currently being tested in a wide range of clinical trials, with five such combinations already receiving FDA approval.[127] A comprehensive review of all completed and ongoing clinical trials incorporating immune checkpoint inhibition can be found here.[128]

TOOLS AND TECHNOLOGIES

Since the completion of the Human Genome Project in 2003,[129] technological advancements have made genome-wide sequencing techniques exponentially more accessible and cost-effective,[130] creating opportunity in the field of bioinformatics and the study of molecular drivers of cancer. However, the allure of whole genomic and transcriptomic sequencing is accompanied by an almost incomprehensible amount of data, and as this enormous amount of data continues to grow, more efficient, accurate, and informative methods for analyzing such data sets become progressively more imminent.[131] Here, we present novel data analysis and collection techniques developed to improve the acquisition of genomic data and discuss their potential in guiding treatment decisions (Fig 2).

Multiomics

Cellular deconvolution. The fundamental challenge facing the interpretation and extrapolation of bulk RNA sequencing data is its inherently conglomerate nature. Broad-spectrum analyses must use some approximation technique to identify and isolate specific cell types within the TME—without such a technique, it would be impossible to trace a given gene expression signal back to its cell of origin. COnfident DEconvolution For All Cell Subsets (CODEFACS) is one such deconvolving algorithm developed by Wang et al[132] that works by analyzing bulk gene expression data sets of tumor samples together with a training data set composed of estimated cellular abundances and expression profiles. CODEFACS then uses a heuristic algorithm to predict the cellular composition and maximize the number of expressed genes in each cell type across samples. The eventual output of CODEFACs is twofold: a three-dimensional gene expression matrix for which each entry represents the predicted expression of a gene in a given cell type in a specific sample and a two-dimensional matrix of confidence scores ranging from [0,1] representing the level of confidence between each gene/cell type association.[132] The creators of CODEFACS also developed a statistical framework referred to as ligand–receptor interactions between cell subsets that takes the output of CODEFACS and predicts likely cell-to-cell interactions within bulk genomic data sets by cross-referencing overexpressed receptor-ligand pairs with a database containing all plausible ligand-receptor interactions between any two cell types.[132] The results from an analysis such as this allow for the prioritization and interrogation of specific cell-to-cell interactions within the TME, a powerful tool in the field of precision oncology.

Spatial transcriptomics. Another emerging and promising technique in bioinformatics is that of spatial transcriptomics and the study of cellular gene expression patterns relative to each other and to a position in space. The notion that cellular function is irrevocably tied to spatial organization in complex tissues is not novel—imaging-based spatial techniques have been widely used to demonstrate this idea for many years.[133,134] However, the process of sequencing a cell's genome and confining it to a two-dimensional position with high spatial resolution has only recently become feasible.[135] To date, one of the most innovative techniques of spatial transcriptomics relies on single-cell sequencing of spatially barcoded tissue. In their work, Rodriques et al[136] developed a technique for transferring tissue sections to a surface precoated with 10-μm DNA-barcoded beads with known positions. The entire tissue section is subsequently sequenced, and, once the DNA barcodes are identified, the entire spatial transcriptome can be reconstructed. This revolutionary technique paves the way for the study of chromatin states, epigenetic changes, gene expression, and protein activity for thousands of genes in multiple regions of a tumor. To date, this and similar techniques have been used to identify transcriptional drivers of metastasis[137] and map the expression of tumor suppressor genes within the tumor.[138] As intratumoral heterogeneity is a known mediator of resistance and poses a significant challenge for oncologic treatment,[139-141] spatial genomic techniques such as this may aid in determining responsiveness to targeted treatments, identify prognostic factors, and guide clinical decision making.[142]

Proteomics. When considering sequencing options in a clinical setting, it becomes important to emphasize that it is not genetic mutations but the manifestation of those mutations that controls tumorigenesis. As such, the proteome, or the collection of a cell's translated proteins, has emerged

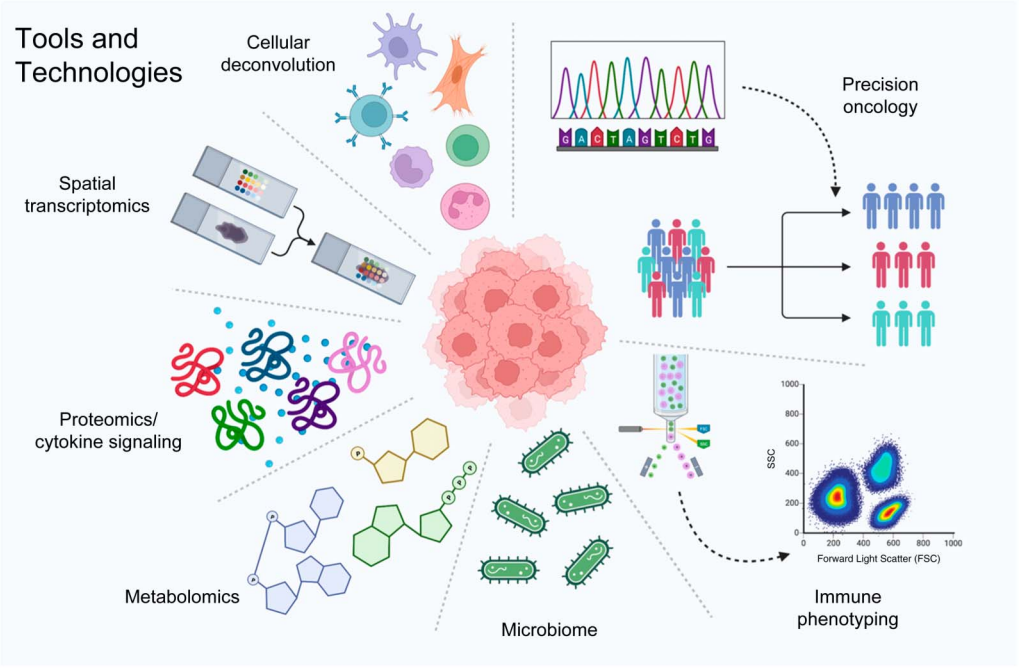

FIG 2. Current methods of omics data acquisition and computational analysis. FSC, forward light scatter; SSC, side light scatter.

as an important diagnostic and prognostic tool in many different tumor types.[143] Nucleic acids, particularly DNA, have the advantage of being thermally stable, readily amplified, and sequenced directly.[144] However, genomic sequencing approaches do not provide definitive information on a given cell's functional or activation state. Proteins, on the other hand, not only are widely accessible in solid tissues and liquids such as blood and CSF but also provide direct insight into many important biologic processes ranging from cell-cell communication to immune diversity and intratumoral heterogeneity.[145]

Recent advancements have allowed for proteomic analyses at the single-cell level, with the most commonly used methods involving antibody-based techniques.[145] For instance, antibodies conjugated to fluorophores (flow cytometry) or rare metal isotopes (mass cytometry) can be used to stain an isolated population of cells. These kinds of approaches have been widely adopted in clinical settings with applications in tumor diagnosis, tumor progression, and immunophenotyping as biomarkers of response to ICB.[146-148] However, these modalities are limited by the spectral overlap and the number of identifiable proteins in the case of flow cytometry and by throughput and sensitivity in the case of mass spectrometry.[149,150] Antibodies conjugated to enzymes, as in enzyme-linked immunosorbent assay and enzyme-linked immunosorbent spot assays, have also been used widely as a sensitive method of detecting proteins of a cell's secretome. Meanwhile, more contemporary methods can accurately quantify proteins in biologic samples even at the whole proteome level using amino acid isotope-labeling[151,152] or chemical-labeling techniques.[153-155] Although revolutionary, these novel techniques and reagents are expensive and make the large-scale implementation of these methods financially implausible. To address the high cost, researchers have developed a novel quantitative method called data-independent acquisition (DIA) that does not require expensive isotopic labels and instead relies on large-scale mass spectrometry (MS) data and protein identification to compare the signal strength of associated peptides and perform a relative quantification.[156] DIA has already made a significant clinical impact as a diagnostic tool by generating protein signatures capable of determining histologic subtypes and tissue of origin in complicated clinical scenarios such as cancers of unknown primary.[157] Techniques such as these are becoming increasingly prevalent in clinical settings and provide an attractive option for studies involving large cohorts, continuous tissue collection, and large-scale analyses such as the National Cancer Institute (NCI)'s Clinical Proteomic Tumor Analysis Consortium project.[158]

Metabolomics. Cancer cells are widely accepted to have a significantly altered metabolism, so much so that reprograming of cellular metabolism has even become one of the hallmarks of cancer.[159] However, the significance of differences in metabolite prevalence and the identification of specific products and byproducts of metabolic pathways have only recently become the topic of exploration.

In practice, circulating and intracellular metabolites are most commonly assayed using MS or nuclear magnetic resonance spectroscopy.[160] These techniques have allowed for the characterization of the most prominent metabolic pathways

to cancer maintenance and growth. For instance, while it has long been known that cancer cells display a heightened glycolytic activity compared with their nonmalignant counterparts,[161] recent studies have identified metabolites such as lactate, pyruvate, hydroxybutyrate, acetate, glutamine, and fatty acids as important catabolic and anabolic barometers of a tumor's energy requirement and biosynthetic demand.[162] To date, such novel metabolomic analyses have been used in diagnostic and prognostic settings,[163] in the grading of tumors,[164] and as biomarkers in response to treatment, including in immunotherapy.[165]

However, metabolomic analyses not only are useful in characterizing the metabolism of the tumor itself but can also be used to assess the dynamic immune-related changes that ensue after immunotherapy. The idea of using dynamic changes in metabolism as a surrogate to the antitumor immune response is a novel area of cancer research with two important advantages: (1) favorable sensitivity and specificity for metabolomic analyses in predicting clinical outcomes[163,164] and (2) biospecimens can be easily and noninvasively collected using blood or urine samples. For instance, proinflammatory cell types such as M1 macrophages, activated dendritic cells, NK cells, and effector T cells preferentially rely on glycolysis to meet their energy needs and produce elevated levels of lactate as a byproduct.[160,166,167] Meanwhile, regulatory populations such as M2 macrophages, MDSCs, and Tregs have a predilection toward fatty acid oxidation to support their functionality.[168,169] Interestingly, as effector T cells differentiate into memory T cells and then into an exhausted phenotype, they become increasingly more reliant on fatty acid oxidation and less dependent on glucose uptake,[170,171] providing a rationale for the use of glycolysis and fatty acid oxidation as biomarkers of response to ICB therapies. In fact, clinically relevant metabolomic signatures are currently being pursued as a correlative factor of clinical outcomes in multiple ongoing clinical trials.[160]

Predictive Signaling

Cytokine signals. Emerging roles for genomic data go beyond characterizing gene expression patterns of a given cell at a single point in time and instead predict how those expression patterns may change in response to an external stimulus, such as cytokine signaling.[172] However, predicting the changes in cellular activity and transcription following cytokine activation remains a significant challenge because of their inherent redundant and pleiotropic properties. To address some of the current shortcomings in cytokine signaling analysis, Jiang et al[172] developed a program called CytoSig, a predictive model of cytokine signaling interactions derived from existing transcriptomic databases. This novel model has particular advantages in that it is more effective at capturing ambiguous cell types buried in large data sets and can identify cytokine target genes even if they are only transiently expressed.[172] Technological developments such as this have allowed for the characterization of specific immune subpopulations[173] and the assessment of the spatial architecture of the TME[174] and illustrate how vast genomic databases can be leveraged into informative predictive models with many clinical and preclinical uses.

Microbiome signals. Another rapidly growing area of interest is the signaling interactions between tumor cells and the microbiome in the TME. Once overlooked, recent evidence has found that the tumor microbiome can be a potent modulator of the host antitumor immune response and induce differential gene expression in tumor cells.[175,176] It has long been known that bacteria have a significant presence in the TME—it is common practice to remove bacterial reads from RNA-seq and whole genome sequencing (WGS) of tumor samples.[177] However, in response to recent advancements and a more complete understanding of the TME, human tumor sequencing data are now being reanalyzed to retroactively include once filtered-out reads from the local tumor microbiome. The results indicate a role for microbial organisms in both prognosis and disease progression. For example, Poore et al[178] recently constructed a comprehensive pan-cancer microbiome data set derived from 18,116 WGS and RNA-seq samples within the TCGA cohort. Using this data set, the authors were able to discriminate between healthy, cancer-free, and cancer-harboring patients using only plasma-derived, cell-free microbial nucleic acids. Moreover, they showed widespread associations between diverse cancer types and specific microbiota, illustrating the diagnostic potential for microbiome sequencing. Building on this analysis, Hermida et al[177] used the same curated data set to demonstrate that microbial abundances predict prognosis, clinical outcome, and response to treatment in a subset of tumor types.

Precision Oncology

Computational approaches. As the trove of genomic data continues to accumulate and novel techniques continue to be developed, it becomes pertinent to consider where the fields of bioinformatics and big data go from here. What does a meaningful and actionable application of predictive genomic analysis look like? Today's algorithms are becoming more and more effective at providing prognoses and identifying clinically targetable molecules. Still, next-generation models will undoubtedly aim not only to predict response to treatment but also to anticipate mutations, identify mechanisms of resistance, and help guide physicians in determining and adjusting treatment regimens. Such is the goal of precision oncology.

In a recent proof-of-concept study by Ahmadi et al,[179] the authors developed a novel computational model called

MadHitter that analyzes large amounts of single-cell RNA sequencing data to identify the optimal combination of treatment targets for a given tumor sample. To make their results more clinically relevant, the group confined their analysis to cell surface proteins minimally expressed in normal tissues. Implementing these criteria allowed for the identification of molecules that can be selectively and precisely targeted by a variety of techniques, including CAR-T-cell therapy and immunoglobulin-chemotoxin conjugates, while minimizing toxicity to adjacent normal tissue. The results found that simultaneous targeting of up to four genetic targets identified by single-cell RNA sequencing was sufficient to kill at least 80% of tumor cells while sparing more than 90% of normal tissue in most disease types.[179] Combinatorial chemotherapy targeting different tumor growth mechanisms is a well-known and extensively studied aspect of cancer treatment, and with completed clinical trials demonstrating the feasibility of harvesting, sequencing, and analyzing genomic data fast enough to inform treatment decisions,[180,181] this study paves the way for robust clinical uses of genomic data. While future treatment modalities will likely use high-resolution single-cell genomic techniques such as this in tandem with systemic immune profiling, spatial analyses, and imaging modalities, this initial report demonstrates the feasibility of the personalized oncology approach in clinical care.

Attempts to implement these tools into clinical practice are already being made. For example, in a recently published study, Lee et al[182] established a framework known as synthetic lethality and rescue-mediated precision oncology via the transcriptome (SELECT) that aims to identify the most effective therapeutic drugs for a given patient on the basis of the tumor transcriptome. This computational strategy's innovativeness and novelty lie in its dependence not on the raw expression of genetic targets, but instead on specific genetic interactions subclassified into two groups: synthetic lethal interactions, wherein the simultaneous activation of two genes reduces a cancer cell's viability (as in PARP inactivation in BRCA-mutated breast malignancies[183]), and synthetic rescue (SR) interactions, defined as a change in the expression of a gene that reduces the fitness of a cancer cell, but for which viability is rescued by a concomitant alteration in a second gene (as in the rescue of Myc alterations by BCL2 activation in lymphomas[184]). The feasibility and application of this algorithm were tested by retroactively analyzing genomic data from previously published trials involving immune checkpoint inhibitors (PD-1/PD-L1 and CTLA-4) in multiple disease types. Using 21 previously published data sets and 1,021 patient samples, the group demonstrated a strong predictive power for SELECT, and specifically SR interactions, in response to treatment and overall survival.[182] The group then applied this framework to the results of the WINTHER trial, a landmark clinical trial and, to our knowledge, the first of its kind to treat patients on the basis of molecular targets identified by either genomic (WGS) or transcriptomic (RNA-seq) analysis. The study reported that SELECT would have recommended a different drug from the one prescribed in 94% of the cases, and the authors estimate that if SELECT guided treatment, 65% of patients would have responded to treatment as compared with the 27% reported in the trial, suggesting that although genomic and transcriptomic analyses do positively influence treatment decisions, SELECT and other models like it can further improve on this foundation. Of note, a recent follow-up paper has shown the predictive power of this approach on approximately 20 new additional targeted and ICB unseen (not trained on) patient cohorts.[185] Although still in their infancy, studies such as this one are making it increasingly more apparent that precision medicine tools have the potential to transform the field of personalized oncology.

BIOMARKERS OF RESPONSE

The most well-documented and problematic feature of ICB is that it is not equally beneficial to all patients. On an indication level, ICB response levels vary considerably across different cancer types. Response rates remain highly variable, and the biologic underpinnings of that variation are still poorly understood. Fortunately, in most cases, clinicians do not need an exact understanding of the mechanisms of these divergent responses; they need a more accurate way of predicting them. The emergence of the above computational and applied techniques has now allowed for comprehensive analysis of the molecular composition of both the tumor and the immune system and provides new avenues for deciphering which patients may derive benefit from ICB before the initiation of treatment. Here, we discuss the current obstacles and optimism in biomarkers of response to ICB treatment.

Shortcomings of the Past

Despite immense research and clinical efforts, PD-L1 remains the only reliable molecular marker of response to ICB treatment and the only one approved by the FDA as a companion diagnostic before initiating ICB therapy. As the most prominent mediator of immunosuppression, several diagnostic assays have been developed to establish a therapeutic PD-L1 threshold and stratify patients by predicted responsiveness.[186] Still, published results have shown that PD-L1 expression remains an incomplete and imperfect marker on its own. In a retrospective study of 45 FDA approvals of clinical trials incorporating ICB, PD-L1 expression was found to be predictive in only 28.9% of cases (53.3% were not predictive, and 17.8% were not tested), suggesting that PD-L1 as a univariate prognostic factor has significant limitations and illustrating the need for additional predictive biomarkers independent of PD-L1 status.

Meanwhile, the genetic basis for predictive biomarkers of response to ICB has historically been tied to tumor antigenicity and TMB. In preclinical models, TMB correlates with an increased probability of displaying neoantigens on the HLA molecules, eliciting CD8+ T-cell–dependent immune responses and tumor cell lysis.[2] Published clinical studies revealed a positive association between TMB and response to ICB in various disease types,[187-189] including a retrospective meta-analysis of 27 cancer subtypes that demonstrated a positive linear regression between ICB response rates and the logarithmic transformation of TMB.[190] An essential and positively prognostic genetic process that underlies neoantigen formation and TMB is microsatellite instability (MSI). MSI results from dysfunctional or deficient mismatch repair machinery, leading to the clustering of thousands of consecutive mutations along microsatellite regions.[191] Tumors that demonstrate deficiencies in MMR (MSI-high) have been shown to have improved responses to ICB treatment. For instance, in a Phase II clinical trial evaluating ICB among patients with heavily pretreated metastatic colorectal carcinoma, the objective response rate was 40% in MSI-high patients as compared with 0% in MSI-stable patients.[192] Since then, MSI-high patients have shown improved response to ICB in prostate, pancreatic, thyroid, neuroendocrine, endometrial, gastroesophageal, and biliary cancers,[193] prompting accelerated approval of pembrolizumab as second-line therapy for MMR-deficient solid malignancies. Pembrolizumab is also approved for the treatment of adult and pediatric patients with advanced solid tumors classified as TMB-high ($\geq$10 mutations/Mb) as determined by the FoundationOne CDx assay. However, similar to PD-L1, significant limitations apply to the use of TMB as a predictive biomarker because of outliers on both sides of the cutoff (responders in TMB-low and nonresponders in TMB-high populations).[194]

Finally, the most extensively studied cellular markers of response to ICB are TILs. As a correlate, the density, location, and proximity of T lymphocytes to cancer cells within the tumor have been shown to predict response to ICB in various cancer types.[195] Previous studies have attempted to quantify this effect by establishing a scoring system on the basis of the quantification cytotoxic and memory T-cell populations within tumoral cores (referred to as Immunoscore) to differentiate between immunologically hot and cold tumors.[196] Indeed, the Immunoscore has demonstrated improved accuracy in predicting prognosis and recurrence compared with MSI status or TNM staging.[197,198] By extension, tumors lacking T-cell infiltration have been shown to confer resistance, allowing them to evade immune detection and destruction. On the surface, TIL quantification seems like a promising and worthwhile potential biomarker. It is important to note, however, that pathologic analysis and the harvesting of a tissue biopsy require an invasive procedure and are not possible in all patients, highlighting the need for a surrogate marker that can reflect the composition of the tumor and be collected less invasively. Collectively, the significant limitations of even the most promising biomarkers to date illustrate the profound need for innovative identification and testing methods.

Challenges of the Present

As cancer research enters the next generation of biomarker identification and testing, several important and inescapable challenges have become increasingly apparent. Perhaps the most acute challenge is the lack of actionable markers of resistance mechanisms to guide combination immunotherapy selection. Although extensive preclinical work has identified several therapeutic targets for combination with ICB, very few have demonstrated a clinical benefit in randomized clinical trials in a nonselected patient population. This is likely due to the inter- and intrapatient variation within and among histologic cancer types. For instance, in a study of patients with metastatic melanoma, it was reported that 26% of tumors were homogenously positive for PD-L1 expression, 22% were homogenously negative for PD-L1 expression, and (most importantly) 52% of patients showed significant heterogeneity in PD-L1 expression between primary melanoma sites, locoregional disease, and distant metastases,[199] highlighting the magnitude of variation within a given tumor type (and even within the same patient) and underscoring the limitations of current biomarker testing in predicting clinical outcomes.

The degree of intratumoral heterogeneity and the diversity of subclonal cancer cells within a tumor are now also known to be significant barriers to the interpretation of predictive biomarkers.[200] Because tissue-based biopsies do not necessarily represent the entire tumor, predictive analyses reliant on pathologically harvested samples are often susceptible to sampling bias. In a study of patients with non–small-cell lung cancer, subclonal neoantigen heterogeneity was found to confer a poorer response to ICB and the neoantigen burden of subclonal populations, rather than the neoantigen burden of the tumor writ large, was more predictive of this worse clinical outcome.[201] Another important consideration in the context of biomarkers is the effect of host immunity. Factors such as baseline PD-L1 expression,[199] HLA allele polymorphism,[202] and TCR diversity[203] have been shown to contribute to ICB response rates and need to be normalized and controlled for in any effective predictive analysis.

To combat these challenges, considerable work has been performed to identify novel biomarkers that can give a more accurate representation of disease at the level of the

individual patient. One such marker gaining popularity in clinical practice is circulating tumor DNA (ctDNA). Plasma ctDNA is cell-free circulating DNA segments with previously characterized genetic, epigenetic, and chromosomal alterations corresponding to a specific cancer subtype.[204] The recent development of novel analytic platforms for ctDNA detection has generated considerable optimism that this class of biomarkers may be sensitive and specific enough to noninvasively monitor tumor growth and response to treatment.[205] Indeed, because of its ability to both profile and characterize molecular features of the tumor and serve as a surrogate for disease burden and tumor progression,[206] ctDNA has come to be known as the liquid biopsy. For example, using paired tumor and peripheral blood whole exome sequencing, a recent study in patients with advanced solid tumors treated with ICB found that a decrease in mean ctDNA concentration was highly correlated with improved clinical outcome independent of the tumor type, TMB, or PD-L1 status.[207] ctDNA monitoring has also been used to detect microscopic residual disease after curative-intent chemotherapy or surgical resection,[208] highlighting the broad clinical applications for ctDNA-based surveillance in improving patient response rates.

Promises of the Future

The unavoidable reality of biomarker research for immunotherapy is this: tumor immunobiology is far too complicated to be accurately defined at a univariate level. It is exceedingly unlikely that any single parameter will ever be predictive enough for a given disease type or treatment modality. The ideal biomarker (or collection thereof) must therefore be multifaceted and multivariable, taking into consideration individualized factors to identify patients who are most likely to derive benefit from ICB and limiting exposure and toxicity while simultaneously suggesting resistance to guide combination strategies. The ideal biomarker possesses another essential quality: it can be isolated and analyzed noninvasively.

The problem with mining previously published databases to find this optimal predictive combination is twofold: (1) the development and implementation of multivariate combinatorial biomarker algorithms quickly become a titanic mathematical undertaking and (2) most of today's immuno-oncologic clinical trials do not include considerations for upfront, prospective tumor characterization by genetic sequencing. To address these shortcomings, the immunoMATCH (iMATCH) central platform has been proposed, and the iMATCH pilot study (also referred to as the Biomarker-Stratified CaboZantinib and NivOlumab trial) has been developed and, to our knowledge, activated as the first of its kind to *prospectively* stratify participants into treatment cohorts on the basis of the expression of predefined biomarkers (ClinicalTrials.gov identifier: NCT05136196). The ultimate goal of this study is to initiate several independent trials with standardized biomarker testing to study mechanisms of response and resistance in distinct biologic

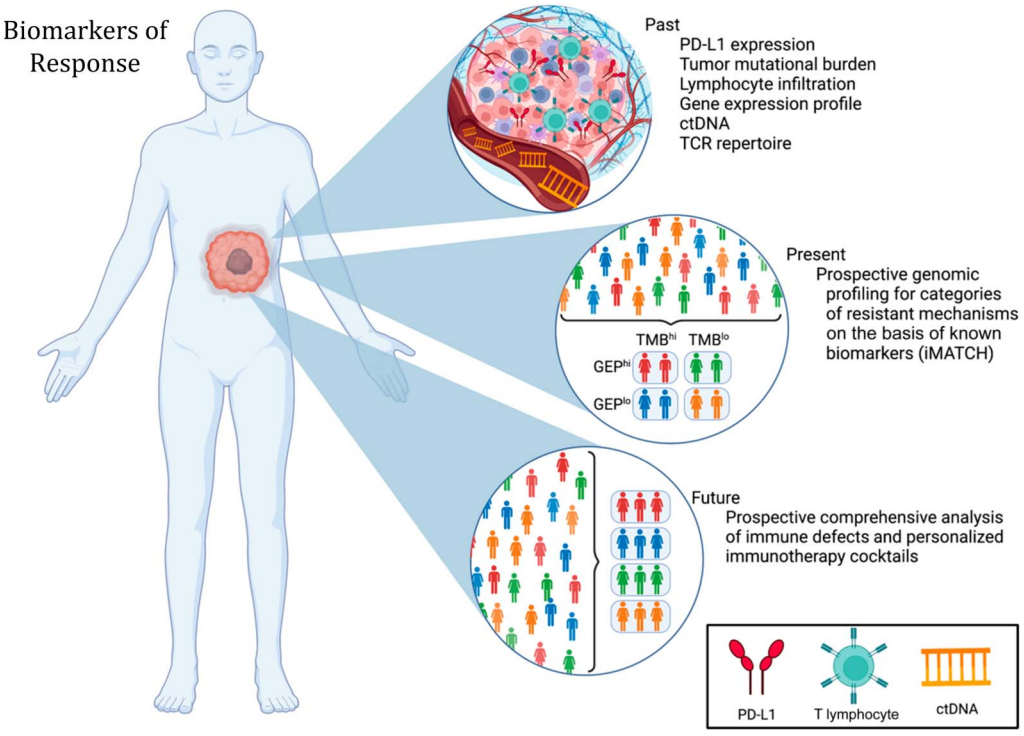

FIG 3. Evolution of biomarkers for the development of next-generation personalized immunotherapy. ctDNA, circulating tumor DNA; GEP, gene expression profile; iMATCH, immunoMATCH; TCR, T-cell receptor; TMB, tumor mutational burden.

subgroups of resistance mechanisms. To meet this end, patients will simultaneously undergo whole-exome sequencing to calculate TMB and identify treatable targets and a gene expression profiling analysis to generate a tumor inflammation score (an 18-panel gene set to quantify the immunogenicity of a patient's tumor). Patients will then be stratified by biomarker status into TMB-high (≥10 mutations/Mb) and TMB-low and gene expression profile-high (≥6) and gene expression profile-low subgroups to determine the course of treatment (Southwest Oncology Group S2101). It is believed that the robustness of these two parameters in combination can help overcome the variation of immune resistance to ICB between patients and facilitate the clinical development of combination immunotherapy (Fig 3).

Finally, what may well be the last frontier in biomarker research is the discovery of a marker that is predictive, prognostic, *and* therapeutic. One such intriguing and encouraging potential biomarker has recently made its way onto the scene. In their work, Lucca et al[209] analyze paired transcriptome and TCRαβ repertoire of both circulating and tumor-infiltrating T cells from matched tumor and blood samples in patients with metastatic melanoma at the single-cell level. They found that a small subset of clonally expanded T cells within the TME have sister clones (ie, clones with matching TCR sequences) that can be found in the periphery.[209] Using genetic profiling analyses, the group demonstrated that the degree of cytotoxicity of circulating TILs is reflective of the cytotoxicity of the tumor infiltrate and shows a positive correlation between the frequency of circulating TILs and a reduced metastatic burden,[209,210] providing a basis for the longitudinal monitoring of the antitumor immune response in situations where tumor biopsies are unfeasible. However, the presence of circulating tumor-specific T cells serves as more than just a biomarker of response and a means of viewing the immune environment of the TME. This subset of T cells can also be harnessed and invigorated with therapeutic intent. Once identified, these cells can theoretically be isolated, expanded, and reintroduced into the patient as a kind of pseudo-chimeric antigen receptor (CAR)-T-cell therapy wherein all the TCR expression and antigen priming are performed endogenously. Although this kind of technology is years away from any meaningful clinical impact, the rationale for this revolutionary personalized medicine has now been established.

CONCLUSION

Despite the challenges, immunotherapy remains the only treatment modality capable of eliciting a durable response resistant to dissemination and recurrence. As such, it naturally serves as a highly exciting launching pad in the search for novel combinations to increase its efficacy and better identify the patients most likely to benefit.

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points of view

overview

High Cost of Chimeric Antigen Receptor T-Cells: Challenges and Solutions

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Chimeric antigen receptor (CAR) T-cells are a cellular immunotherapy with remarkable efficacy in treating multiple hematologic malignancies but they are associated with extremely high prices that are, for many countries, prohibitively expensive. As their use increases both for hematologic malignancies and other indications, and large numbers of new cellular therapies are developed, novel approaches will be needed both to reduce the cost of therapy, and to pay for them. We review the many factors that lead to the high cost of CAR T-cells and offer proposals for reform.

Advances in harnessing the immune system to treat cancer have defined the past decade of progress in oncology. Chimeric antigen receptor (CAR) T-cells are a type of cellular immunotherapy created by extracting and then genetically modifying a patient's T cells to target surface markers on—and thereby attack—malignant cells. CAR T-cells have demonstrated remarkable efficacy in treating multiple hematologic malignancies, including B-cell ALL (B-ALL), multiple subtypes of lymphoma (including the two most common types, diffuse large B-cell lymphoma [DLBCL] and follicular lymphoma), and multiple myeloma. In DLBCL, for example, trials indicate that CAR T-cells offer the possibility of cure to approximately 30%-35% of patients who would previously have had no curative therapeutic option available to them,[1] and we now have evidence that CAR T-cells can persist in vivo to maintain remissions for more than a decade.[2]

Since the first CAR T-cell therapy was approved by the US Food and Drug Administration in 2017—tisagenlecleucel (tisa-cel) for the treatment of B-ALL[3]—there are now six CAR T-cell therapies approved in the United States for the treatment of hematologic malignancies (Table 1; Fig 1).[6,7] Additionally, numerous cellular therapies, including not just CAR T-cells but also CAR-natural killer (NK) cells and CAR macrophages (among others), are being investigated across more than 500 clinical trials for a variety of malignancies,[8,9] including solid tumors such as pancreatic cancer and glioma[10] and nonmalignant conditions such as lupus and heart disease.[11,12]

However, cancer therapies are useful only to those who can access them.[13] Drug prices both in the United States and globally have increased substantially over the past two decades,[14] with the median launch price for cancer drugs in the United States now over $155,000 US dollars (USD) per year.[15] Cellular and gene therapies are among the most expensive therapies on the market.[16,17] Improving both local and global access to cancer therapies must be a priority if we want to improve cancer outcomes worldwide.[6,18] Yet, cellular therapies come with numerous logistical barriers in addition to their high cost,[6,19] including coverage limitations and insurance-required prior authorizations, lack of or delayed referrals to tertiary centers, manufacturing constraints and delays, and misperceptions around eligibility. As we sit on the precipice of a cellular therapy revolution in oncology, the high cost of CAR T-cell therapies—typically over $400,000 USD and sometimes over $1 million USD per patient[20,21]—and their logistical challenges raise concerns about their affordability and access for patients, payers, and health care systems both in the United States and globally.

Over time, increasingly disparate access to cancer therapies around the world may further exacerbate already stark inequalities in cancer outcomes.[13,22,23] Furthermore, the financial burden of CAR T-cell therapy may strain health care budgets, forcing governments and insurers to make tough decisions regarding resource allocation and coverage of different products.[24] We review the challenges of CAR T-cell pricing and evaluate the viability of various avenues for reform, including price negotiation, health technology assessment (HTA) and cost-effectiveness analyses, scientific advances such as novel CAR or costimulatory constructs and off-the-shelf allogeneic CAR T-cells, and innovative manufacturing approaches. We also consider different payment models for these high-cost therapies.

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PRACTICAL APPLICATIONS

- Chimeric antigen receptor (CAR) T-cells are revolutionizing the care of many hematologic malignancies by offering an effective treatment to patients with ALL, lymphoma, and myeloma.
- However, the high cost of CAR T-cells means that uptake is limited to countries, health systems, payers, and individuals who can afford them—and a cancer treatment is only effective if a patient can access that treatment.
- Price negotiation—such as through the Inflation Reduction Act—offers a key opportunity to reduce the prices of CAR T-cells by more closely aligning them with the value that they offer patients.
- Furthermore, increasing transparency and reducing the price of the bundle of care negotiated between hospitals and insurers also has the potential to substantially affect the total cost of administering CAR T-cells.
- Autologous CAR T-cells are costly to produce because of their patient-specific nature and complex manufacturing process—novel approaches to manufacturing such as allogeneic CAR T-cells may reduce manufacturing costs.

FACTORS CONTRIBUTING TO HIGH MANUFACTURING COSTS OF CAR T-CELLS

The manufacturing and administration costs of CAR T-cell therapy represent one component of their high prices. The multistep process to manufacture CAR T-cells includes leukapheresis to obtain T cells, subsequent genetic engineering using viral vectors (or nonviral methods) to introduce CAR expression, and the expansion of modified T cells in a controlled environment.[25,26] Each of these steps can require sophisticated equipment, skilled labor, and strict quality control measures. Production costs are higher for local cell manufacturing facilities that produce trial products (compared with commercial manufacturers making cellular therapies at scale) as the reagents and lentiviral vectors, which are typically tied to each product or group of products, remain expensive.[27]

The patient-tailored nature of autologous CAR T-cell therapy raises the cost of production. Patient-specific features also impose additional logistical expenses relating to the apheresis process, cryopreservation, transportation of patient-derived cells to specialized manufacturing facilities, and the subsequent shipment of the final therapeutic product back to the clinical site. This also contributes to research and development (R&D) costs as the costs of running cellular therapy clinical trials are likely to be greater than those of small molecule therapies,[28] although it is difficult to quantify by how much.

So far, the development of many CAR T-cell products has followed a similar trajectory. In many cases, products with promising early-phase data launched by universities and/or small biotech companies have been bought by major pharmaceutical companies, who have then conducted the late-phase clinical trials and commercialized the products at scale. For example, Novartis entered into a R&D alliance with the University of Pennsylvania to develop tisagenlecleucel.[29]

PRICE VERSUS COST

Once a patient is deemed eligible for CAR T-cell therapy, the patient's insurer must then approve an entire bundle of care to enable T-cell collection and manufacturing to begin. This bundle typically includes all related patient care from collection through a specified postinfusion landmark, inclusive of expected and unexpected, inpatient and outpatient care. The price for this bundle is confidentially negotiated between the hospital and the insurer, and then a price is also confidentially negotiated with the CAR T-cell manufacturer.[30-32] Notably, the insurance approval process can take up to 2-3 weeks, exclusive of time for additional contracting between the medical center and the insurer.

Although many stakeholders, including pharmaceutical companies, argue that the extraordinary price of CAR T-cells reflects their high manufacturing cost, in fact, a large proportion of the price charged to payers represents profit for manufacturers, as suggested (but not definitively proven) by the high revenues of cell therapy manufacturers combined with their high margins across portfolios, and the collective interest in the biotech and pharma industries in cell therapies.[33] The high price charged by manufacturers is compounded by the fact that CAR T-cells are also billed as a bundle or procedure similar to stem-cell transplantation.

Definitive publicly available data about the true cost of manufacturing autologous CAR T-cells are sparse because of commercial confidentiality. University of Pennsylvania CAR T-cell pioneer Carl June suggested in 2012 that CAR T-cells cost about $20,000 USD per patient to manufacturer and that he expected this cost to decline when the product was manufactured at scale.[29] One study found that high-quality anti-CD19 CAR T-cells could be made using an automated system for approximately $35,107 USD per patient.[27] An academic group in Spain sells their product for ~€89,000, implying that their manufacturing costs are lower than this amount.[34,35] For companies manufacturing at scale, this cost may even have decreased over the past 5 years as companies may have made manufacturing processes more efficient as volume has expanded with more indications, and more centers deliver these products.

TABLE 1. List Prices of FDA-Approved CAR T-Cell Products

Generic Name	Brand Name	Approved Indication	Approval Date	Approved via Accelerated Approval	Acronym for Pivotal Trial	List Price in March 2023 (WAC, USD)
Tisagenlecleucel (tisa-cel)	Kymriah	R/R pediatric and young adult (<25) B-cell ALL	August 30, 2017	No	ELIANA	$543,828
		R/R adult DLBCL, HGBL, transformed DLBCL	May 1, 2018	No	JULIET	$427,048
		R/R FL	May 27, 2022	Yes	ELARA	$427,048
Axicabtagene ciloleucel (axi-cel)	Yescarta	R/R DLBCL	October 18, 2017	No	ZUMA-1	$424,000
		R/R FL	April 2, 2021	Yes	ZUMA-5	$424,000
Lisocabtagene maraleucel (liso-cel)	Breyanzi	R/R DLBCL, HGBL, transformed DLBCL, PMBL, FL grade 3B	February 5, 2021	No	TRANSCEND-NHL-001	$447,227
Brexucabtagene autoleucel (brexu-cel)	Tecartus	R/R MCL	July 24, 2020	Yes	ZUMA-2	$424,000
		Adult R/R B-cell ALL	October 1, 2021	No	ZUMA-3	$424,000
Idecabtagene vicleucel (ide-cel)	Abecma	R/R MM	March 26, 2021	No	KarMMa	$457,255
Ciltacabtagene autoleucel (cilta-cel)	Carvykti	R/R MM	February 28, 2022	No	CARTITUDE-1	$465,000

NOTE. List prices (WACs) include rebates and other confidential discounts, but these discounts are typically modest for oncology products (on average 2%).[4] Source: FDA Cellular and Gene Therapy Products website, Office of Tissues and Advanced Therapies and Red Book (Micromedex).
Abbreviations: CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FDA, US Food and Drug Administration; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma; MCL, mantle-cell lymphoma; MM, multiple myeloma; PMBL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory; USD, US dollars; WAC, wholesale acquisition cost.

If manufacturing costs represent a small component of high list prices for CAR T-cells, the opportunity to make the greatest impact on prices would be to decrease the difference between the cost of production and the price paid by the payer for the product. Of course, the reality of this calculation—the difference between the total amount paid by payers, list price, and production cost—is more complex because of the involvement of different entities in payment negotiations and agreements (eg, hospitals, public and private payers, and intermediaries). The common counterargument against negotiating lower drug prices is that these margins are needed to drive R&D. However, there are important assumptions underlying that counterargument that may not hold up to scrutiny. For example, at least for CAR-T treatments marketed thus far, substantial public funding helped support their discovery, and large companies entered later in the development process.[36] Large pharmaceutical companies spend more on marketing, administration, and stock buybacks than they do on R&D.[37] Furthermore, it is well demonstrated that there is no association between the price of a cancer therapy and the magnitude of benefit it offers to patients.[38]

HEALTH TECHNOLOGY ASSESSMENT AND DRUG PRICE NEGOTIATION

The United States pays substantially more for new therapeutics than other industrialized countries.[14] Achieving fair prices for brand name drugs is accomplished most effectively around the globe through two main mechanisms: HTAs that incorporate cost-effectiveness analysis or other assessment of a drug's value to inform price negotiation and, typically after some period of market exclusivity, entrance of direct competition from generic or biosimilar manufacturers.[39]

HTAs investigate the value of novel therapeutics and help government payers decide which therapies to reimburse and how much to offer, given the therapy's clinical value. They do this by reviewing the evidence supporting a novel agent to evaluate its incremental benefits over current standard-of-care therapies. When these assessments are subsequently used as the basis for negotiation, they are combined with a drug's proposed price to determine an incremental cost-effectiveness ratio—the amount of money it costs to deliver benefits, which can be expressed using

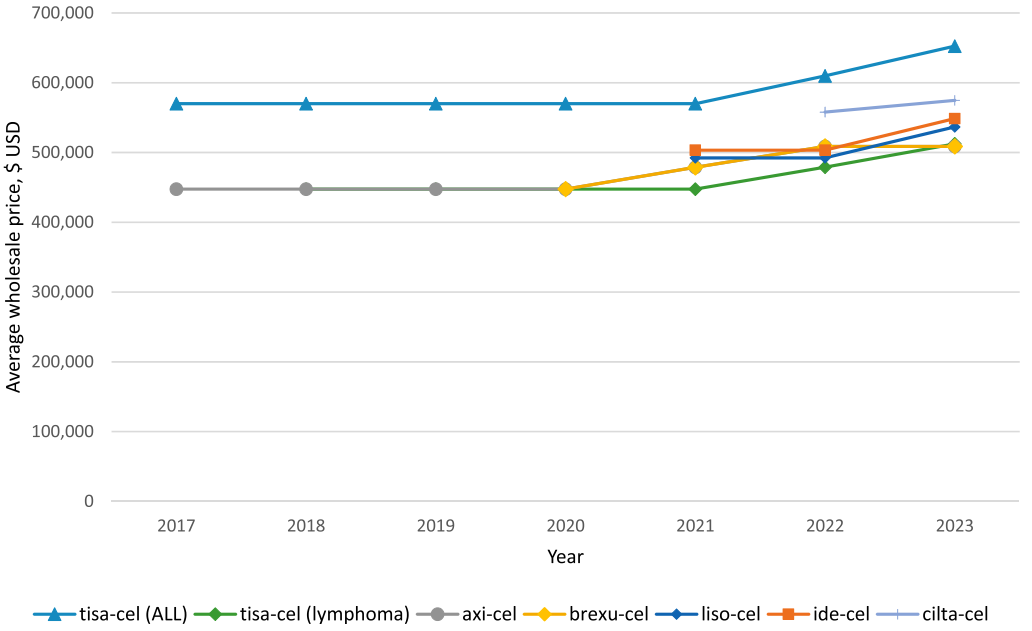

FIG 1. Prices of FDA-approved CAR T-cell products in the United States (AWP, USD). Source: Red Book (Micromedex). Average wholesale price is the price that manufacturers charge pharmacies while WAC (also known as the list price) is the price that manufacturers charge wholesalers (excluding any discounts). The AWP is generally approximately 20% higher than the WAC.[5] AWP is used in this figure as historical data are available for the AWP in the Red Book. ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; FDA, US Food and Drug Administration; USD, US dollars; WAC, wholesale acquisition cost.

standard measurements such as the quality-adjusted life year (QALY).[40,41,42] Through this process, the goal is to ensure that therapies offering only marginal value are less expensive than those offering larger benefits. Some countries use a willingness-to-pay threshold to enable comparisons across different disease types, essentially saying that they are only willing to fund therapies that cost less than a certain amount per QALY. For example, the United Kingdom's HTA agency, the National Institute for Health and Care Excellence, uses a threshold of £30,000.[43] To date, HTAs have made mixed recommendations on CAR T-cells, leading to differences in reimbursement and access across different countries.[44]

Although the United States does not have an HTA body,[45] the 2022 Inflation Reduction Act for the first time will enable the Secretary of the Department of Health and Human Services to negotiate the prices of certain expensive drugs in Medicare.[46] Negotiation is limited to a small number of drugs and biologics that have been on the market for a set period of time (9 years for small molecules and 13 years for biologics) and have no generic or biosimilar competition. Drugs with only a single rare disease indication and plasma-derived products (defined as a biological product that is derived from human whole blood or plasma) are excluded from negotiation. It remains to be seen whether this clause will exclude cellular therapies from negotiation since they are indeed derived from human whole blood. Another provision in the Inflation Reduction Act that could help curb price increases is the inflationary rebates, designed to prevent companies from increasing prices year-on-year beyond inflation.[47]

Given that commercially available CAR T-cell products are currently protected by multiple patents, it is difficult to predict the duration of market exclusivity for cellular therapies. Furthermore, because autologous CAR T-cells are manufactured from a patient's own cells, most patents for CAR T-cell products relate to viral vectors and manufacturing processes. Lack of clarity about the duration of protection means that it is also not yet clear whether cellular therapies will be subject to a vibrant competitive market from biosimilars.[48,49]

Negotiating Billing Agreements Between Hospitals and Payers

An additional and under-reported opportunity to reduce the price of CAR T-cells lies in reducing the total cost of the delivery of cellular therapies to patients. Because of the complexity of delivering cellular therapies, medical centers enter elaborate, multistep negotiations with payers to pay for the entire package of care, typically in a bundle. Treating a patient with a CAR T-cell therapy generally requires (1) procedural and laboratory pretesting (eg, echocardiography and pulmonary function testing), (2) suitability review by physicians and social workers, (3) placement of an apheresis catheter (typically under a local anesthetic), (4) leukapheresis, (5) CAR T-cell production and return shipment to the medical center, (6) treatment with lymphodepleting chemotherapy, (7) treatment with CAR T-cell therapy, (8) response assessments (eg, in lymphoma with fluorodeoxyglucose-positron emission tomography scans, or in ALL with bone marrow biopsy plus flow cytometry), and (9) recovery from toxicities (discussed below). Only step 5 is included in the product list prices in Table 1. Exact quantification of the costs of each step is challenging because of the confidentiality of reimbursement agreements between payers and hospitals, but it has been reported that

reimbursement of a bundle of these items may be in excess of $1-1.5 million USD, inclusive of the CAR T-cell product charge.[20,30-32,50-52] This series of studies found a wide range of total health care costs associated with CAR T-cell therapy, suggesting that these costs are underestimated in some analyses, and the wide variation reflects the methodological challenges associated with estimating these total costs.

Although centers may accept a smaller amount as reimbursement of the requested charges, part of hospitals' justification for these high bundled prices stems from their concern that they can lose large sums of money when treating patients on Medicare or Medicaid with CAR T-cell therapies. That is, often the amount paid by Medicare or Medicaid is less than the total cost of care for a patient receiving CAR T-cells. For example, in fiscal year 2022, inpatient hospital reimbursements by Medicare for CAR T-cell products were calculated on an episodic basis using a Medicare Severity Diagnosis Related Groups base payment rate adjusted for factors such as hospital geography and augmented by a new technology add-on payment and outlier payments.[52] Even with such payment adjustments, Medicare reimbursement for CAR T-cell products often failed to cover total hospital costs, which can incentivize centers to balance the books via charges to private payers.[21] Increased transparency in this area is greatly needed and could potentially build on recent policies designed to increase disclosure of hospital markups.[53,54]

STRATEGIES TO REDUCE THE PRODUCTION AND ADMINISTRATION COSTS OF CAR T-CELLS

Given that many of the aforementioned costs of CAR T-cells relate to their personalized nature, one emerging cost-saving approach is the use of allogeneic CAR T-cell products. Such products would be derived from healthy donors rather than the patient, which could reduce the manufacturing time and costs associated with autologous CAR T-cell therapy.[55] The primary concerns with this approach are the potential for graft-versus-host disease and, until recently, modest demonstrated efficacy of allogeneic products.[56] However, several allogeneic CAR T-cell products are currently in clinical development, with more promising early efficacy results than previous iterations of allogeneic products.[57,58] In December 2022, the first allogeneic cellular therapy received European Medicines Agency approval: tabelecleucel targeting the oncogenic Epstein-Barr Virus (EBV) in patients with post-transplant lymphoproliferative disease (EBV + PTLD).[59] Allogeneic CAR-NK cells, which are also under development, have a reduced risk of graft-versus-host disease than allogeneic CAR T-cells because of their lack of need for activation, shorter lifespan, and lower potency than T-cells.[60]

Innovative manufacturing approaches may also help reduce the cost of CAR T-cell therapy, such as closed-system manufacturing, which limits contamination risk and reduces the need for cleanroom facilities.[27,61] The use of serum-free or xeno-free culture media could reduce the reliance on expensive components derived from animals. Supply chain automation, from leukapheresis to CAR T-cell infusion, can help minimize the potential for human error, improve efficiency, and reduce labor costs. Automated cell processing systems, such as the CliniMACS Prodigy,[62] and more rapid production methods, such as Novartis' T-Charge,[63,64] could streamline the manufacturing process and reduce the time required for CAR T-cell production.

Decentralized manufacturing—the production of CAR T-cells at or near the point of care, currently undertaken by many university laboratories as part of clinical trials—may be able to reduce costs associated with transportation and storage. This approach may also help alleviate the logistical challenges associated with autologous therapies, such as the need for cryopreservation, strict chain-of-custody procedures, and stringent shipping requirements.

The bundled prices negotiated between hospitals and payers represent an often under-reported element of the cost of CAR T-cells. Such costs could be minimized by increasing the proportion of patients who receive CAR T-cells as outpatients, as well as reducing the frequency of complications. For example, if cytokine release syndrome or immune effector cell–associated neurological syndrome could be prevented, this may reduce the need for tocilizumab and/or intensive care unit admission for such severe adverse events. Another example is the cost-intensive need for prolonged supportive transfusions and growth factor support for patients with post-CAR-T cytopenias.[65,66] For example, use of biosimilar filgrastim can help manage post-CAR-T cytopenias. Reduced toxicity may also be achieved through novel CAR T-cell costimulatory domain constructs that may offer the possibility of T-cell expansion without the same degree of cytokine release or neurotoxicity, but the potential impact of these strategies on cost-effectiveness has yet to be formally assessed.

Assessing the Value of CAR T-Cell Therapies

To assess the relative value of novel therapeutic approaches, economic analyses are needed from HTA agencies, companies (often conducted via consulting agencies), and decision scientists. These often come in the form of cost-effectiveness analyses, in which different approaches are compared to determine which offers the best value for money. The most common cost-effectiveness analyses are conducted from the societal and health sector (eg, third party payer) perspectives, which often include budget impact analyses that consider the ramifications of the added costs on a health system. The key outcome measure used to make decisions in cost-effectiveness analyses is the incremental cost-effectiveness ratio, which is useful for comparing the difference between two approaches against a willingness-to-pay threshold.[67,68]

Cost-effectiveness analyses of CAR T-cell therapies have shown a wide variety of results, ranging from incremental cost-effectiveness ratios that would be considered cost-effective in many jurisdictions, to high incremental cost-effectiveness ratios that are nowhere near being cost-effective (Table 2). Many of these analyses have been limited by the fact that all CAR T-cell therapies were initially approved using single-arm clinical trials, which means that the comparisons inherent to cost-effectiveness analyses are hampered by the challenges of cross-trial comparison and the use of synthetic or historical control arms.[74] Similarly, the need to extrapolate treatment effects over time horizons longer than clinical trials poses important challenges and introduces considerable uncertainty for these novel therapies.[75]

Recently, the first three randomized controlled trials of CAR T-cell therapies—ZUMA-7, TRANSFORM, and BELINDA, all testing the use of CAR T-cells against autologous stem cell transplant in the second-line setting for DLBCL[1]—were published, leading to multiple cost-effectiveness analyses using this randomized data. The first three studies demonstrated cost-effectiveness over salvage chemotherapy with autologous stem-cell transplantation,[69,70,72] but the two most recent reported that CAR T-cell therapy was not cost-effective.[71,73] As shown in Table 2, one cost-effectiveness analysis has industry funding and editorial contribution; these types of studies must be interpreted with caution as industry-led cost-effectiveness analyses are more likely to report favorable results than independently-conducted analyses.[76-78]

Discrepancies in results across cost-effectiveness analyses pose a challenge in decision making. The modeled outcomes of therapies given subsequently to CAR T-cells or autologous transplantation (ie, outcomes in response to third- and fourth-line therapies and beyond) have the largest impact on the cost-effectiveness outcomes as the costs applied in the second-line therapies are very similar across the models. Other factors such as quality of life and risk of death, both while on therapy and for long-term survivors (eg, does a cured patient return to perfect quality of life?) can also influence outcomes and are based on very limited available data. By comparing various cost-effectiveness analyses, policymakers and clinicians can make informed decisions about the value of CAR T-cell therapy relative to other treatment options.

One challenge with assessing the cost-effectiveness of CAR T-cell therapy is that it may often be compared with other therapies that are already disproportionately expensive, which could make it more likely to appear cost-effective even when prices remain high.[67]

Another important consideration in assessing the value of CAR T-cell therapy is the potential for cure compared with more conventional treatments. Although some patients may achieve long-term remission or cure with CAR T-cell therapy, others may not respond or may experience relapse. Although CAR T-cells seem to offer a cure to some patients with ALL and DLBCL,[79] it is difficult to know whether they are curative in other lymphoma subtypes, and it seems unlikely that they offer a substantial proportion of myeloma patients cure. Whether patients are cured by CAR T-cells has a large impact on their subsequent life experience, but developing a better understanding of their long-term quality of life is essential to determining the treatment's value in all cases. Although CAR T-cell therapy can cause potentially life-threatening adverse events, such as cytopenias and neurotoxicity, patients who achieve long-term remission or cure may experience substantial improvements in quality of life compared with those who continue to receive conventional treatments.[80]

In children, the value of CAR T-cell therapy is particularly dependent on long-term outcomes, including cure and quality of life. If pediatric patients are cured, the benefit they gain, as measured by QALYs, will be substantial over the course of their life, which can result in improved cost-effectiveness—such as has been calculated for tisagenlecleucel in pediatric ALL.[81]

PAYMENT MODELS FOR HIGH-COST THERAPIES

Even if many of the above approaches combine to reduce the price of CAR T-cells, the cost may still be high, and innovative payment models may be required to meet remaining financial challenges.[17,82] These models aim to ensure that patients have access to life-saving treatments while mitigating the financial burden on patients and health care systems.

One potential approach to help ensure that payers only pay for treatments that provide meaningful clinical benefits is outcome-based payments, which tie the cost of a therapy to its effectiveness, with payments being contingent on the achievement of specific clinical outcomes. For example, a payer may only reimburse the full cost of a CAR T-cell therapy if the patient achieves a predefined treatment response or remains in remission for a certain period of time. As some patients initially respond to CAR T-cell therapy but then rapidly progress, it is important to ensure that the outcome measure being used reflects true clinical effectiveness.[83] Although there was some initial enthusiasm for outcome-based pricing approaches in CAR T-cells, especially in Europe,[83] current payment approaches in the United States largely do not take outcomes into account.[52] It can be difficult for payers and manufacturers to reach agreement regarding the appropriate outcome, time horizon, and adjudication approaches.[84] Outcome-based pricing models can also be complex and costly for payers and hospitals to administer. Another challenge is how to account for beneficiaries who may change insurance providers or lose their insurance coverage.

CAR T-cell payment models could borrow elements from previous models developed to pay for high-cost therapies.

TABLE 2. Comparison of Different Cost-Effectiveness Analyses of CAR T-Cells for Second-Line DLBCL

	Choe et al[69]	Kambhampati et al[70]	Kelkar et al[71]	Perales et al[72]	Vijenthira et al[73]
Perspective	US health care sector and societal	US health care sector	US health care sector	US third-party commercial payer	Canadian and US payers
Model type	Partitioned survival model	Markov	Microsimulation	Partitioned survival model	Markov
Funding	Independent	Independent	Independent	Industry	Independent
Health states	PFS/EFS, progression, death	PFS/EFS, progression, death	PFS/EFS, progression, death	PFS/EFS, progression, death	PFS/EFS, progression, death
Model population	High-risk DLBCL	High-risk or all DLBCL	High-risk DLBCL	High-risk DLBCL	All DLBCL (from first-line)
Second-line data	ZUMA-7 and BELINDA	ZUMA-7	ZUMA-7 and TRANSFORM	ZUMA-7	ZUMA-7 and TRANSFORM
Drug prices source	REDBOOK	REDBOOK	VA FSS	REDBOOK	CADTH and REDBOOK
WTP threshold (USD)	$150,000/QALY	$100,000/QALY and $150,000/QALY	$200,000/QALY	$150,000/QALY	$150,000/QALY (CAD and USD)
Cycle length, month	1	1	1	1	1
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime
Extrapolation	Standard parametric modeling	Modeled 2- and 5-year EFS from historical data	Mixture cure modeling with cure at 5 years	Mixture cure modeling with cure at 5 years	Parametric modeling with cure at 5 years
≥5 year SMR in remission	ASCT: NR CAR-T: 1.09	ASCT: 2.2 CAR-T: 1.4	ASCT: 1 CAR-T: 1	ASCT: NR CAR-T: NR	ASCT: 1.4 CAR-T: 1.2
≥5 year HSUV in remission	ASCT: 0.83 CAR-T: 0.83	ASCT: 1.0 CAR-T: 1.0	ASCT: 0.70 CAR-T: 0.70	ASCT: 0.673 CAR-T: 0.823	ASCT: 0.830 CAR-T: 0.830
Crossover costs	Yes	Yes	Yes	No	No
Lines of therapy	Up to third line	Up to third line	Up to fifth line	Up to seventh line	Up to third line
Axi-cel base-case ICER (USD)	$99,101/QALY	$93,547/QALY	$684,225/QALY	$66,381/QALY	$309,813/QALY
Costs year	2021	2021	2022	2021	2021
Is second line axi-cel cost-effective?	Yes	Yes	No	Yes	No

NOTE. This table was adapted from Kelkar et al[71] with permission from the authors.

Abbreviations: ASCT, autologous stem-cell transplantation; CAD, Canadian dollars; CADTH, Canadian Agency for Drugs and Technologies in Health; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; NR, not reported; PFS, progression-free survival; QALY, quality-adjusted life-years; SMR, standardized mortality ratio; USD, US dollars; WTP, willingness-to-pay.

In the mid-2010s, the Louisiana Medicaid program and the Australian health care system pioneered the use of a fixed-fee, subscription model to pay for expensive but curative hepatitis C antivirals.[85,86] In this example, the payer pays a fixed price per year for access to the treatment that does not vary with its use. This approach may prove less appealing to manufacturers of cellular therapies with higher manufacturing costs than small molecule drugs, for which the actual amount of drug produced has a much smaller impact on the profit margin. Alternatively, it could lead to a subscription model that is prohibitively expensive.

Nonexclusive licensing agreements, especially by universities and academics receiving public funding, could democratize access to transformative discoveries and in turn encourage competition.[82] Licensing agreements could also contain requirements for future pricing strategies. Just as Moderna's agreement with the United States compelled it to supply its COVID-19 vaccines preferentially to the United States, a licensing agreement at the time of public research investment could compel a manufacturer to contain prices below a certain threshold.

Because cellular and gene therapies are so expensive, health insurers have trialled new payment schemes that outsource initial payments to specialty pharmacies in a role in some ways analogous to pharmacy benefits managers. This third party—the specialty pharmacy—can help manage both high costs and the actuarial risk associated with them. For example, specialty pharmacies such as Accredo

have initiated systems in which they pay a manufacturer upfront for its gene therapy, and the specialty pharmacy is, in turn, reimbursed by a patient's health plan over time with both the rate and time period subject to negotiation.[87,88]

CONCLUSION

CAR T-cell therapies have demonstrated remarkable clinical outcomes in certain patients with cancer with otherwise limited treatment options. However, the high costs present a major obstacle for patients, health care providers, and payers. To ensure a fair price for CAR T-cell therapies and increase access to these potentially life-saving therapies, a multipronged combination of strategies is needed, including price negotiation, innovative manufacturing approaches, and the implementation of alternative payment models. Addressing these extremely high prices would help to ensure that CAR T-cell therapies are accessible to patients who may benefit from them, without placing an unsustainable burden on health care systems.

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Novel Immunotherapeutics: Perspectives on Checkpoints, Bispecifics, and Vaccines in Development

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Overview

Over the past decade, the advent of molecular techniques and deeper understanding of the tumor microenvironment (TME) have enabled the development of a multitude of immunotherapy targets and approaches. Despite the revolutionary advancement in immunotherapy, treatment resistance remains a challenge leading to decreased response rate in a significant proportion of patients. As such, there has recently been an evolving focus to enhance efficacy, durability, and toxicity profiles of immunotherapy. Although immune checkpoint inhibitors have revolutionized cancer treatment with many already-approved antibodies and several others in the pipeline, bispecific antibodies build on their success in an attempt to deliver an even more potent immune response against tumor cells. On the other hand, vaccines comprise the oldest and most versatile form of immunotherapy. Peptide and nucleic acid vaccines are relatively simple to manufacture compared with oncolytic virus–based vaccines, whereas the dendritic cell vaccines are the most complex, requiring autologous cell culture. Nevertheless, a crucial question in the development of cancer vaccines is the choice of antigen whereby shared and patient-private antigen approaches are currently being pursued. There is hope that cancer vaccines will join the repertoire of successful novel immunotherapeutics in the market. Better insights into the impact of immunotherapy on effector T cells and other immune cell populations in the TME shall be a major priority across the immune-oncology discipline and can help identify predictive biomarkers to evaluate response to treatment and identify patients who would most likely benefit from immunotherapy.

INTRODUCTION

Over the past decade, the advent of molecular techniques and deeper understanding of the tumor microenvironment (TME) have enabled the development of a multitude of immunotherapy targets and approaches. Despite the revolutionary advancement in immunotherapy, treatment resistance remains a challenge leading to decreased response rate in a significant proportion of patients. Immune checkpoints are essential regulators of the immune system that can inhibit the T-cell receptor signaling pathway, thus promoting self-tolerance.[1] In 2011, ipilimumab was the first immune checkpoint inhibitor (CPI) that received US Food and Drug Administration (FDA) regulatory approval.[2] Since then, several CPIs have been approved with a continuously expanding spectrum of clinical indications. Although immune CPIs have revolutionized cancer treatment with many already-approved antibodies and several others in the pipeline, bispecific antibodies build on their success in an attempt to deliver an even more potent immune response against tumor cells by simultaneously binding two independent epitopes.[3] The field of cancer immunotherapy has been steadily growing with multitargeted approaches that exceed checkpoint inhibition to engage the various facets of the immune system.

Although vaccines were the first agents devised in an attempt at stimulating the immune system, their application as cancer immunotherapeutics has remained limited to date. Prophylactic vaccines, such as those protecting against human papilloma virus (HPV) and hepatitis B virus (HBV), are considered cancer vaccines that prevent HPV- and HBV-related malignancies. This is different from therapeutic vaccines that actively target tumor cells with therapeutic intent, whereby several platforms are underway, including cell-based, nucleic acid–based, peptide-based, and virus-based cancer vaccines, all of which carry promising potential in the field of immunotherapeutics.[4]

Cancer immunotherapeutics have been at the forefront of revolutionary advances in the field of immuno-oncology (Table 1). With the long-term remission provided by CPIs, on the one hand, and the promising results of bispecific antibodies and cancer vaccines, on the other hand, better understanding of these novel immunotherapeutic approaches ensues. In this chapter, we aim at providing an overview of advances in immunotherapeutics while focusing on their emerging game-changing role in cancer treatment.

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PRACTICAL APPLICATIONS

- Despite the revolutionary advancements in immunotherapeutics and the incorporation of several checkpoint inhibitors (CPIs) in the standard practice, treatment resistance remains a challenge, leading to a decreased response rate in a significant proportion of patients.
- With evolving focus to enhance efficacy, durability, and toxicity profiles of CPIs, several other promising immune checkpoints are being studied in cancer treatment
- Although CPIs have revolutionized cancer treatment with many antibodies already-approved and several others in the pipeline, other immunotherapeutic approaches, including bispecific antibodies and cancer vaccines, are needed to deliver an even more potent immune response against tumor cells.
- More efforts are now put in investigating combinatorial approaches to improve clinical outcomes.
- Clinical trials that incorporate immune profiling of baseline tumor specimens are needed for deeper understanding of the relationship between the immune tumor microenvironment and response to treatment, resistance, and micrometastases.

INSIGHT INTO NOVEL IMMUNE CPIs

To enhance the benefit from CPIs in cancer treatment, there has recently been an evolving focus on identifying and targeting alternative novel immune checkpoints.[5]

Lymphocyte Activation Gene-3

Lymphocyte activation gene-3 (LAG-3) is a surface molecule on T cells that is related to a cluster of differentiation, CD4. It is expressed on the cell membrane of tumor-infiltrating lymphocytes, on activated CD4+ and CD8+ T cells, and on regulatory T cells.[6] LAG-3 binds to major histocompatibility complex class II on antigen-presenting cells (APC) with a great affinity that inhibits the binding of CD4 and T-cell receptor (TCR) and results in inhibition of the TCR signaling pathway. In addition, LAG-3 crosslinks with CD3, which can impair T-cell proliferation and cytokine secretion by inhibition of influx of calcium. LAG-3 has a unique cytoplasmic tail as compared with other immune checkpoints, which further supports its unique molecular characteristics and role.[7-9] Moreover, dual genetic knockdown of LAG-3 and PD-1 in murine melanoma models was associated with decreased tumor growth and improved overall survival (OS) of mice. This suggested LAG-3 as a potential target for overcoming resistance of single-agent immune-checkpoint inhibitor (ICI).[5] In addition, both LAG-3 and cytotoxic T-cell lymphocyte-4 (CTLA-4) can inhibit the TCR signaling pathway and result in tumor immune tolerance. An interesting recent finding was an increased expression of LAG-3 in tumor-infiltrating lymphocytes after treatment with ipilimumab, a CTLA-4 antibody.[10] Several clinical trials that investigate the use of a combination of ICIs targeting LAG-3, PD-1, and/or CTLA-4 are ongoing.[5,10,11]

Targeting LAG-3 results in an enhanced TCR signaling pathway, thus inhibiting the suppression of regulatory T cells. The immunomodulatory role of LAG-3 dates back to 2006 when LAG-3Ig fusion protein was used to induce an antitumor immune response. This was followed by studies that investigated its role in renal cell carcinoma, metastatic breast cancer, and melanoma.[12-14] Antibodies against LAG-3 can release the brake against the immune response targeting melanoma tumor cells. Relatlimab is the first anti-LAG-3 antibody that is under current investigation in more than 12 clinical trials in multiple tumors.[15,16]

The landmark RELATIVITY-047 trial studied the combination of relatlimab and nivolumab as compared with single-agent nivolumab for untreated advanced melanoma. This trial included 714 patients with treatment-naïve metastatic melanoma. They were randomly assigned to receive relatlimab (160 mg) and nivolumab (480 mg) once every 4 weeks or to nivolumab (480 mg) once every 4 weeks. The median progression-free survival (PFS) was 10.1 months for the combination group, which was significantly greater than that of the nivolumab group of 4.6 months ($P = .0055$). Interestingly, this improved PFS was not dependent on the expression of neither LAG-3 nor PD-L1.[17,18] At a median follow-up of 19.3 months presented at the ASCO 2022 plenary series, the PFS slightly increased to 10.2 months, as compared with 4.6 months for the combination and single-agent groups, respectively.[19] This study led to FDA approval of nivolumab-relatlimab combination on March 18, 2022, for patients with previously untreated advanced melanoma.[20] The combination is now being studied in treatment-naïve patients with advanced melanoma and active brain metastases.[21]

Following the results of RELATIVITY-047, a similar study combined relatlimab and nivolumab in the neoadjuvant setting, which enabled investigators to evaluate treatment efficacy after surgical resection. Twenty-nine patients with stage IIIB-IV resectable melanoma were enrolled in this study, and 59% of patients had complete response (CR).[22] The results from the addition of relatlimab to the CPI backbone in melanoma have led to further ongoing trials that study anti–LAG-3 therapy combinations. The phase II PLATforM trial (ClinicalTrials.gov identifier: NCT03484923) studies LaG-525 in combination with spartalizumab, which is a monoclonal antibody against PD-1.[23] There are also

TABLE 1. Approved and Most Promising Immunotherapy Agents Currently at Various Phases of Clinical Development

Agent	Target	Indication/Type of Cancer	Phase	Clinical Trial No.
Checkpoint inhibitors				
Ipilimumab	CTLA-4	Melanoma, renal cell carcinoma, colorectal cancer, HCC, NSCLC, malignant pleural mesothelioma, esophageal cancer	Approved	>380 active CTs
Tremelimumab	CTLA-4	HCC, NSCLC	Approved	>200 active CTs
Nivolumab	PD-1	Melanoma, NSCLC malignant pleural mesothelioma, renal cell carcinoma, Hodgkin lymphoma, SCCHN, urothelial carcinoma, colorectal cancer, HCC, esophageal cancer, gastric cancer	Approved	>900 active CTs
Pembrolizumab	PD-1	Melanoma, NSCLC, Hodgkin lymphoma, PMBCL, urothelial carcinoma, MSI-H or dMMR, CRC, gastric cancer, esophageal cancer, cervical cancer, HCC, MCC, RCC, endometrial carcinoma, TMB-H, cSCC, TNBC	Approved	>1,000 active CTs
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma, basal cell carcinoma, NSCLC	Approved	>80 active CTs
Durvalumab	PD-L1	NSCLC, HCC, extensive-stage SCLC, biliary tract cancer	Approved	>400 active CTs
Atezolizumab	PD-L1	NSCLC, SCLC, HCC, melanoma, alveolar soft part sarcoma	Approved	>400 active CTs
Avelumab	PD-L1	Merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma	Approved	>100 active CTs
Relatlimab	LAG-3	Metastatic melanoma (in combination with nivolumab)	Approved	>40 active CTs
Fianlimab	LAG-3	Melanoma	III	NCT05608291
				NCT05352672
		NSCLC	II/III	NCT05785767
Sabatolimab	TIM-3	Myelodysplastic syndrome, myelomonocytic chronic leukemia	III	NCT04266301
Tiragolumab	TIGIT	NSCLC	III	NCT04294810
				NCT04513925
				NCT04619797
		SCLC	III	NCT04665856
				NCT04256421
		Esophageal cancer	III	NCT04543617
				NCT04540211
Ociperlimab	TIGIT	NSCLC	III	NCT04746924
				NCT05791097
				NCT04866017
Domvanalimab	TIGIT	NSCLC		NCT05211895
				NCT05502237
				NCT04736173
		Gastrointestinal adenocarcinoma	III	NCT05568095
Vibostolimab	TIGIT	Melanoma	III	NCT05665595
		NSCLC	III	NCT04738487
				NCT05298423
				NCT05226598
		SCLC	III	NCT05224141
COM701	PVRIG	Various types of cancers	I	NCT03667716
			I	NCT04354246
			I/II	NCT04570839
Monalizumab	NKG2A	SCCHN	III	NCT04590963
		NSCLC	III	NCT05221840

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TABLE 1. Approved and Most Promising Immunotherapy Agents Currently at Various Phases of Clinical Development (Continued)

Agent	Target	Indication/Type of Cancer	Phase	Clinical Trial No.
Oleclumab	CD73	NSCLC	III	NCT05221840
Inupadenant	A2aR	Solid tumors	I	NCT05117177
		Lung, head and neck cancer, melanoma	I/II	NCT05060432
		NSCLC	II	NCT05403385
Bispecific antibodies				
Amivantamab	c-Met/EGFR	NSCLC with EGFR exon 20 insertion mutations	Approved	NCT04599712
		NSCLC	III	NCT05388669
			III	NCT04538664
			III	NCT04487080
			III	NCT04988295
KN026	HER2/HER2	Gastric cancer	II/III	NCT05427383
Zanidatamab	HER2/HER2	Gastroesophageal cancers	III	NCT05152147
			III	NCT05615818
Zenocutuzumab	HER2/HER3	NRG1-harboring tumors	II	NCT05588609
			II	NCT02912949
KN046	PD-L1/CTLA-4	Non–small-cell lung cancer	III	NCT04474119
			II/III	NCT05001724
		Pancreatic adenocarcinoma	III	NCT05149326
Cadonilimab	PD-L1/CTLA-4	Nasopharyngeal cancer	III	NCT05587374
Tebotelimab	PD-1/LAG-3	Gastroesophageal cancer	II/III	NCT04082364
Blinatumomab	CD3/CD19	B-cell malignancy	Approved	8 active CTs
Tebentafusp	CD3/gp100	Uveal melanoma	Approved	7 active CTs
		Advanced melanoma	II/III	NCT05549297
Teclistamab	CD3/BCMA	Multiple myeloma	III	NCT05243797
				NCT05552222
				NCT05572515
				NCT05083169
BRiTE	CD3/EGFRvIII	Glioblastoma	I	NCT04903795
RO6958688	CD3/CEA	Solid tumors	I	NCT02650713
			I	NCT02324257
		NSCLC	I/II	NCT03337698
AFM24	CD16/EGFR	EGFR-expressing cancers	I/II	NCT04259450
				NCT05109442
				NCT05099549
Catumaxomab	CD3/EpCAM	Gastric cancer	III	NCT04222114

Product/Agent	Antigen/Target	Type of Cancer	Phase	Clinical Trial No.
Vaccines				
Dendritic Cell Vaccines				
Sipuleucel-T	PAP	Prostate cancer	Approved	
AV-GBM-1	Irradiated TICs	Glioblastoma	III	NCT05100641

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TABLE 1. Approved and Most Promising Immunotherapy Agents Currently at Various Phases of Clinical Development (Continued)

Product/Agent	Antigen/Target	Type of Cancer	Phase	Clinical Trial No.
PEP-DC	Designed peptides	NSCLC pancreatic adenocarcinoma	I	NCT05195619
			I	NCT04627246
OC-DC/PEP-DC	Oxidized tumor lysate/designed peptides	Ovarian cancer	I	NCT05714306
DCVAC-OvCa	Allogeneic tumor cells	Ovarian cancer	II	NCT04834544
DNA vaccines				
VGX-3100	E6/E7 HPV oncogenes	HPV-positive tumors	II	NCT03603808
GX-188E	E6/E7 HPV oncogenes	HNSC	II	NCT05286060
				NCT05280457
		Cervical cancer	I/II	NCT03444376
pTVG-HP/ pTVG-AR	PAP/AR	Prostate cancer	II	NCT04090528
RNA vaccines				
BNT111	NY-ESO-1, tyrosinase, MAGE-A3, TPTE	Melanoma	II	NCT04526899
			I	NCT02410733
BNT112	5 prostate antigens	Prostate cancer	I/II	NCT04382898
BNT113	E6/E7 HPV oncogenes	HPV-positive tumors	II	NCT04534205
			I/II	NCT03418480
BNT122	Up to 20 neoantigens	Colorectal cancer	II	NCT04486378
mRNA-4157	Up to 34 neoantigens	Melanoma	II	NCT03897881
		Solid tumors	I	NCT03313778
Peptide vaccines				
NeoVax	Up to 20 neoantigens	Melanoma	I	NCT04930783
				NCT03929029
		Kidney cancer	I	NCT02950766
		Ovarian cancer	I	NCT04024878
		Lymphocytic leukemia	I	NCT03219450
		Glioblastoma	I	NCT02287428
		Follicular lymphoma	I	NCT03361852
iNeo-Vac-P01	Up to 20 neoantigens	Pancreatic cancer	I	NCT04810910
		Advanced solid tumors	I	NCT03662815
				NCT04864379
		Esophageal cancer	I	NCT05307835
HSPPC-96	HSPPC-96 bound to tumor-associated peptides	Liver cancer	II/III	NCT04206254
		Glioma	II	NCT03650257
KRAS peptide vaccine	KRAS	NSCLC	I	NCT05254184
		Pancreatic cancer	I	NCT05013216
		Colorectal cancer, pancreatic cancer	I	NCT04117087
SurVaxM	Peptide that mimics amino acids 53-67	Glioblastoma	I	NCT04978727
			II	NCT05163080
			II	NCT04013672
			II	NCT02455557

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TABLE 1. Approved and Most Promising Immunotherapy Agents Currently at Various Phases of Clinical Development (Continued)

Product/Agent	Antigen/Target	Type of Cancer	Phase	Clinical Trial No.
Virus-based vaccines				
T-VEC	Produces antigen on tumor cell lysis	Melanoma	Approved	24 active CTs
OH2	Produces antigen on tumor cell lysis	Melanoma, colorectal, gastrointestinal, liver, pancreatic, bladder, and central nervous system cancers	I and I/II	10 active CTs
PVS-RIPO	CD155	Breast cancer	I	NCT03564782
		Glioma, glioblastoma	II	NCT02986178
			II	NCT03043391
			II	NCT04479241
		Bladder	I/II	NCT04690699
		Melanoma	II	NCT04577807
PROSTVAC		Prostate cancer	II	NCT02772562
			I/II	NCT02933255
			II	NCT02649855
			II	NCT03315871

NOTE. For products that are currently approved or at phase III clinical trials, earlier phases of clinical development are not outlined. Only active clinical trials are listed.

Abbreviations: BCMA, B-cell maturation antigen; CRC, colorectal carcinoma; cSCC, cutaneous squamous cell carcinoma; CTs, clinical trials; CTLA-4, cytotoxic T-cell lymphocyte-4; DCVAC-OvCa, different approach for ovarian cancer; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; GI, gastrointestinal; HCC, hepatocellular carcinoma; HNSC, head and neck squamous cell carcinoma; NSCLC, non–small-cell lung cancer; HPV, human papilloma virus; HSPPC-96, heat shock protein peptide complex 96; MCC, Merkel cell carcinoma; MSI-H, microsatellite instability-high; NRG1, Neuregulin 1; OC-DC, oxidized tumor cell lysate; PAP, prostatic acid phosphatase; PEP-DC, peptide loaded dendritic cell; PMBCL, primary mediastinal large B-cell lymphoma; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; SCLC, small-cell lung cancer; TICs, tumor-initiating cells; TMB-H, tumor mutational burden-high; TNBC, triple-negative breast cancer; T-VEC, talimogene laherparepvec.

around 50 studies that are currently ongoing to evaluate the role of anti–LAG-3 antibodies added to other CPIs.[24]

T-Cell Immunoglobulin and Mucin Domain–Containing Protein-3

T-Cell immunoglobulin and mucin (TIM-3), also referred to as hepatitis A virus cellular receptor 2 (HAVCR2), is a type I transmembrane protein, which is encoded by the HAVCR2 gene. Its extracellular domain consists of the N-terminal immunoglobulin variable (IgV) domain located at the distal end of the membrane followed by the membrane mucin domain that contains an O-linked glycosylation potential. It is expressed in CD4+ and CD8+ T cells, regulatory T cells, natural killer cells, dendritic cells, and Th17 cells.[25,26] When compared with other immune checkpoints, TIM-3 binds to a wider spectrum of ligands on normal and malignant cells, including galectin 9, phosphatidylserine carcinoembryonic antigen–related cell adhesion molecule 1 (CEACAM1), and high mobility group protein B1 (HMGB1).[27] Similar to LAG-3, stimulation of TIM-3 by its ligands promotes T-cell exhaustion, which entails failure of T cells to proliferate and exert their usual effector functions, including cytokine release and cytotoxicity.[28,29] There are several ongoing clinical trials for the combination of CPIs that include antibodies against TIM-3 in solid tumors.[30-32]

A phase I/II study by Curigliano et al investigated sabatolimab, an anti–TIM-3 antibody, with or without spartalizumab, an anti–PD-1 antibody. This study enrolled 219 patients with advanced solid tumors, 86 of whom received combination therapy. No response was observed in patients receiving sabatolimab, but five patients receiving combination therapy had partial response, one of whom had malignant perianal melanoma. The authors suggested that combining sabatolimab with spartalizumab showed enhanced antitumor activity.[32] Another phase II trial (ClinicalTrials.gov identifier: NCT02608268) investigated the combination of sabatolimab and spartalizumab in patients with non–small-cell lung cancer and melanoma.[33] In addition, a phase I/II trial NCT04370704 is studying the combination of antibodies against PD-1 (INCMGA00012), LAG-3 (INCAGN02385), and TIM-3 (INCAGN02390) in selected tumors.[34] Another ongoing trial is comparing dostarlimab (TSR-022), a PD-1 inhibitor, with combination therapy of TIM-3 inhibitor, cobolimab, and dostarlimab in melanoma.[35]

T-Cell Immunoglobulin and Immunoreceptor Tyrosine–Based Inhibitory Motif Domain

T-Cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains (TIGIT) is a 244-amino acid transmembrane glycoprotein with an extracellular IgV domain, a transmembrane domain, and cytoplasmic tail that includes the immunoreceptor tyrosine–based inhibitory motif (ITIM) and an immunoglobulin tail tyrosine–like phosphorylation motif.[36] To our knowledge, TIGIT was first introduced by Yu et al[36] as a suppressor of T-cell activation. It is expressed on regulatory and memory T cells and natural killer (NK) cells. TIGIT binds with two main ligands, C155 and CD112, and competes with their other counterparts, namely, CD266 and CD96, thus exerting an immunosuppressive effect on T cells. CD266 delivers a positive costimulatory signaling pathway, whereas TIGIT delivers inhibitory signals.[37] Moreover, the ligation of TIGIT can result in inhibition of natural killer cells cytotoxicity through its ITIM cytoplasmic domain in human and mice models.[37]

The above data emphasized that dual inhibition of PD-1 and TIGIT is a promising combination option of CPIs for melanoma that is refractory to anti–PD-1. The first-in-human phase I study on antibody against TIGIT was conducted by Niu et al[38] and recently published. Vibostolimab, an antibody against TIGIT, showed an improved antitumor activity when combined with pembrolizumab, an anti–PD-1 antibody, with an acceptable toxicity profile in patients with solid tumors. In a phase I/II study, neoadjuvant vibostolimab plus pembrolizumab resulted in numerically higher objective response, event-free survival, and recurrence-free survival as compared with gebasaxturev plus pembrolizumab or pembrolizumab alone. The 18-month event-free survival was 85%, 70%, and 78%, respectively.[39] There are more than six antibodies targeting TIGIT that are being studied in solid tumors, including MK-7684, which is a candidate anti-TIGIT drug developed by Merck, and etigilimab (OMP-313 M32), which is a humanized monoclonal antibody that blocks TIGIT from binding CD155.[40,41] Another anti-TIGIT candidate is tiragolumab (MTIG7192A, RG-6058), which also hinders its interaction with CD155. There are two clinical trials that involve tiragolumab, namely, NCT02794571 and NCT03563716.[40]

Other Promising Immune Checkpoints

With evolving focus to enhance efficacy, durability, and toxicity profiles of CPIs, several other promising immune checkpoints are being studied in cancer treatment. Similar to TIGIT, poliovirus receptor–related immunoglobulin-containing domain (PVRIG or CD112R) also binds to CD112 and mediates comparable effects. PVRIG was first described in 2016[42] and is expressed primarily on NK and CD8+ T cells with mostly effector and memory phenotype. Activation enhances PVRIG expression on CD4+ and CD8+ T cells.[42] COM701 is a monoclonal antibody that binds to PVRIG and inhibits its interaction with CD112. Its effect, in combination with nivolumab, against advanced tumors is underway in phase I and I/II studies. Preliminary results suggest an acceptable safety profile and a promising potential therapeutic benefit.[43] It is also being investigated in combination with TIGIT inhibitors (ClinicalTrials.gov identifiers: NCT04354246, NCT04570839).[44,45]

Natural killer group protein 2A (NKG2A) is a receptor present in approximately 50% of NK cells and to a smaller extent on NKT of CD8+ T cells.[46,47] Preclinical models showed that activation by its ligand HLA-E causes a cascade of events that suppress NK and CD8+ T-cell effector function, whereas its blockade promotes antitumor immunity.[46] Monalizumab, a humanized monoclonal antibody against NKG2A, is being investigated in clinical trials with encouraging results. In addition to a phase I trial that supported its safety as monotherapy,[48] several phase III clinical trials that investigate monalizumab in combination with other CPIs in a variety of malignancies, including squamous cell carcinoma of the head and neck and non–small-cell lung cancer, are currently ongoing.[49,50]

ATP catabolism is mediated by CD73, an enzyme that is found in healthy tissue but is overexpressed in the TME, on myeloid-derived suppressor cells, tumor-associated macrophages, Tregs, exhausted T cells, and tumor cells.[51,52] Targeting CD73 and the adenosine receptors is, therefore, expected to reverse the cascade of events that lead to immunosuppression. Oleclumab, an anti-CD73 antibody, has already been shown to be well tolerated as a monotherapy in one phase I clinical trial.[53] A phase III clinical trial in patients with non–small-cell lung cancer (NSCLC) compares the combination of durvalumab/oleclumab or durvalumab/monalizumab with the combination of durvalumab/placebo. In parallel, inupadenant, an A2aR antagonist, is also under investigation in phase I, I/II, and II trials.[54,55]

BISPECIFIC ANTIBODIES

BsAbs Binding Two Tumor Antigens

Amivantamab is an FDA-approved BsAb that targets and disrupts epidermal growth factor receptor (EGFR) and MET signaling. Through this binding, amivantamab promotes targeting of tumor cells for destruction by immune effector cells, such as NK cells, by antibody-dependent cellular cytotoxicity. FDA granted accelerated approval for on May 21, 2021, for metastatic NSCLC, whose tumors harbor EGFR exon 20 insertion mutations.[56] Amivantamab is currently being investigated as monotherapy in a variety of clinical trials for salivary gland cancer, hepatocellular carcinoma, and gastroesophageal cancer.[57] On the other hand, KN026 is an antihuman epidermal growth factor receptor 2 (HER2) bispecific antibody that was produced from the structural coupling of trastuzumab and pertuzumab,[58] two

approved monoclonal antibodies for the treatment of HER2-positive cancer. Pertuzumab is, so far, only approved in combination with trastuzumab for the treatment of breast cancer, whereas trastuzumab is also approved for gastric and gastroesophageal cancers.[59] Clinical trials for single-agent KN026 have focused on the approved indications of trastuzumab and pertuzumab, in addition to combination with chemotherapy, and results from completed studies indicate that KN026 seems to be well-tolerated.[60,61]

Similarly, zanidatamab targets the same domains as trastuzumab and pertuzumab[62] and is being investigated for the same indications as KN026, in addition to biliary tract cancer and colorectal cancer. Importantly, there is an active phase III clinical trial (ClinicalTrials.gov identifier: NCT05152147) that compares zanidatamab plus chemotherapy with the standard of care, trastuzumab plus chemotherapy, as first-line treatment for patients with advanced/metastatic HER2-positive gastroesophageal adenocarcinoma.[63] This study also looks at the addition of a PD-1 inhibitor, tislelizumab, to the regimen. In parallel, zanidatamab is also being developed as an antibody drug conjugate, with the cytotoxic drug (N-acyl sulfonamide auristatin), and is currently at a phase I clinical trial (ClinicalTrials.gov identifier: NCT03821233).[64] Zenocutuzumab is an anti-HER2 and anti-HER3 BsAb developed specifically for tumors with Neuregulin 1 (NRG1) rearrangements, which are recurrent oncogenic drivers in solid tumors.[65] NRG1 binds to HER3, leading to heterodimerization with other HER/ERBB kinases, increased downstream signaling, and enhanced tumorigenesis. With results from single-patient experimental protocols[65] and a phase I clinical trial (ClinicalTrials.gov identifier: NCT03321981) showing promise, zenocutuzumab is also being investigated in ongoing phase II clinical trials.[66]

BsAbs Blocking Two Immune Checkpoints

KN046 is a recombinant humanized PD-L1/CTLA-4 BsAb that is currently investigated in multiple clinical studies, mostly phase II, for a wide range of indications with promising results.[67] Importantly, in two phase III clinical trials, KN046 is combined with first-line chemotherapy, namely, carboplatin and paclitaxel for NSCLC and gemcitabine and nab-paclitaxel for pancreatic ductal adenocarcinoma.[68] AK104, or cadonilimab, is a human tetravalent anti–PD-1/CTLA 4BsAb that was recently granted conditional approval in China for patients with relapsed or metastatic cervical cancer who have progressed on or after platinum-based chemotherapy.[69] Its investigation is underway for a range of solid tumors, including cervical cancer, lung cancer, gastric/gastroesophageal junction cancer, and liver cancer.[69]

BsAbs targeting PD-1 and other immune checkpoints are also ongoing. For example, an ongoing trial NCT03708328 studies a bispecific antibody R07121661 that targets both PD-1 and TIM-3 in metastatic melanoma and non–small-cell lung cancer.[70,71] Another trial NCT04140500 studies RO7247669, which is a BsAb against both LAG-3 and PD-1 in solid tumors refractory to previous therapy.[72] Concurrent inhibition of PD-1 and LAG-3 is explored with tebotelimab, or MGD013, a BsAb constructed from combining nivolumab and relatlimab.[73] Tebotelimab is being investigated in a phase II/III clinical trial for gastric and gastroesophageal cancers in combination with an anti-HER2 antibody.[26]

Bispecific T-Cell Engagers

This group of BsAbs binds simultaneously to T cells, through CD3, and tumor cells, through a tumor-specific antigen, thus directing the cytotoxic potential of immune cells onto tumor cells. Blinatumomab, for example, is a bispecific T-cell engager (BiTE) that binds to CD3 to engage T cells and CD19 to direct cytotoxicity to B cells. It was the first BiTE to gain FDA approval whereby it was approved in 2014 for relapsed or refractory B-cell precursor ALL.[74] Several clinical trials that combine blinatumomab with other drugs are ongoing in an effort to expand its clinical indications.[75]

Another BiTE, tebentafusp, was FDA-approved on January 25, 2022, for HLA-A*02:01–positive patients with unresectable or metastatic uveal melanoma. It is a bispecific gp100 peptide-HLA–directed CD3 T-cell engager, which continues to be investigated in clinical trials for other types of melanomas and solid cancers among patients who test positive for HLA-A*02:01. Teclistamab is a BiTE that binds to CD3 on T cells and to B-cell maturation antigen, which is expressed on the surface of multiple myeloma cells and some healthy B-lineage cells.[76] It was approved on October 25, 2022, for relapsed or refractory multiple myeloma after at least four lines of therapy and is currently in clinical trials for different combination regimens.[77]

Recently, a bispecific antibody was designed to engage CD3 on T cells and EGFR variant III (EGFRvIII) on tumor cells, and EGFRvIII is frequently expressed by glioblastoma cells while sparing healthy tissue, which makes it an attractive target for brain tumors.[78,79] This novel T-cell engager is referred to as a brain bispecific T-cell engager, BRiTE, and is the subject of several ongoing phase I clinical trials.[80]

RO6958688 recognizes CEA and CD3e and induces T-cell–mediated killing of CEA-overexpressing tumors. RO6958688 showed an acceptable safety profile in phase I clinical trials (ClinicalTrials.gov identifiers: NCT02650713, NCT02324257), and it is currently under investigation in a NSCLC phase I/II trial (ClinicalTrials.gov identifier: NCT03337698).[81] In addition to T-cell engagers, an innate cell engager was recently developed, namely, AFM24, which binds to EGFR on tumor cells and CD16 on NK cells and macrophages. In preclinical models, AFM24 was shown to be potent and effective in antibody-dependent cell-mediated

cytotoxicity via NK cells and cellular phagocytosis via macrophages.[82] AFM24 is currently under investigation in phase I/II clinical trials, alone or in combination with other immunotherapy agents.[83]

Engagement of NK cells, dendritic cells, and macrophages can also occur through the constant fragment (Fc) of antibodies. This was put into play with catumaxomab rat-mouse hybrid antibody with specificity against epithelial cell adhesion molecule and CD3. With its ability to bind innate cells as well, catumaxomab was described as being trifunctional. Although it was approved in Europe on April 20, 2009, catumaxomab was voluntarily withdrawn in 2013 for commercial reasons. It was recently reconsidered for investigation in China for its potential immunotherapeutic benefit through ongoing clinical trials for urothelial and gastric cancers.[84]

CANCER VACCINES

The advent of vaccines has introduced a promising cell-based therapeutic approach by triggering tumor antigen–specific cellular immune responses.[85,86] In this section, we will provide insight into the main cancer vaccines, namely, dendritic cell vaccines, nucleic acid vaccines, peptide vaccines, and virus-based vaccines.

Dendritic Cell Vaccines

In 2010, a dendritic cell–based vaccine, sipuleucel-T, was successfully used to treat prostate cancer, which proved the viability of cancer vaccines and created excitement in the field of cancer vaccines.[87] A major obstacle in developing other dendritic cell vaccines was the requirement for autologous dendritic cells, usually monocyte-derived, which need to be isolated and differentiated, thus significantly adding to the complexity of manufacturing. Nevertheless, a lot of progress has been made in cancer vaccines to date, particularly with the development of vaccine technology in the era of COVID-19 pandemic, which brought vaccines back to public focus.[85] So much so, a personalized vaccine, namely AV-GBM-1, which consists of autologous dendritic cells pulsed with autologous tumor antigens, was associated with promising 15-month OS in patients with newly diagnosed glioblastoma.[88]

More advanced approaches are targeting patient-specific neoantigens, which require experimental data from patient tumor samples and sophisticated algorithms for prioritization of the targets.[89] These neoantigens are delivered to the dendritic cells as long-chain peptides (ClinicalTrials.gov identifiers: NCT04147078, NCT04627246, NCT05195619).[90] To compare and combine the advantages of using oxidized tumor cell lysate and predesigned peptides for the manufacturing of dendritic cell vaccines, a phase I/II clinical trial on ovarian cancer is using peptide-loaded dendritic cells (PEP-DCs) in one arm and oxidized tumor cell lysate–loaded (OC-DC) followed by peptide-loaded DCs in the other (ClinicalTrials.gov identifier: NCT05714306).[91] Importantly, after exposure to the tumor lysate DC vaccine, a new set of peptides will be designed, on the basis of immunogenicity changes that are observed. Therefore, the contribution of each step of the vaccination will be measured and compared separately.[92]

In a different approach for ovarian cancer (DCVAC-OvCa), allogeneic tumor cells (from OV-90 and SK-OV-3 cell lines) killed by high hydrostatic pressure are used as a source of multiple tumor-associated antigens (TAAs) for loading onto autologous DCs.[93,94] This strategy provides off-the-shelf material for the preparation of dendritic cells but may lack the specificity of personalized antigens. Nevertheless, it has shown acceptable safety and promising efficacy in phase II clinical trials[94,95] and continues to be investigated (ClinicalTrials.gov identifier: NCT04834544).[96] A similar approach had been used for prostate cancer, which reached phase III clinical trials, yet did not show increased OS.[97]

Nucleic Acid Vaccines

There are several advantages for nucleic acid vaccines: amenability to the inclusion of many antigens, ability to induce both, humoral and cellular immune responses, feasibility, safety, and cost-effectiveness. However, their therapeutic potential has been modest to date.[98] The most advanced DNA vaccine in terms of clinical development is VGX-3100, which targets E6 and E7 oncogenes of HPV-16 and HPV-18 strains. This has reached phase III but is not yet able to secure regulatory approval. GX-188E, which targets the same genes as VGX-3100, has also shown promising results in phase II trials.[99,100] pTVG-HP, a plasmid DNA vaccine, produced in E. coli, that encodes the complementary DNA for human prostatic acid phosphatase had shown modest results.[101,102] Considered more immunogenic, RNA vaccines have recently gained more attention. For example, BNT111, a liposomal RNA vaccine, targets four nonmutated TAAs (NY-ESO-1, tyrosinase, MAGE-A3, and TPTE) that are prevalent in melanoma and has shown impressive preliminary results in an ongoing phase I trial.[103] More recent cancer vaccine approaches have focused on targeting neoantigens from individual tumor mutations, which are unique to cancer cells. mRNA-4157/V940 is a novel mRNA-based personalized cancer vaccine that encodes up to 34 patient-specific tumor neoantigens. In addition to encoding the target antigens, these vaccines also convey adjuvant properties that amplify the immune response. KEYNOTE-942 trial assessed the efficacy of mRNA-4157/V940 in patients with resected stage IIIB/IIIC/IIID and IV melanoma in combination with standard-of-care pembrolizumab. The vaccine was administered every 3 weeks for a total of nine doses, and pembrolizumab was administered every 3 weeks for up to 18 cycles. At 18 months, the relapse-free survival was 78.6% for the combination arm and 62.2% for the pembrolizumab arm, thus corresponding to a 44% reduction in the risk of

recurrence or death. Treatment-related and serious adverse events were mild and comparable between the two arms.[104]

Peptide Vaccines

NeoVax is a long-peptide vaccine, used with polyinosinic-polycytidylic (poly-ICLC) as adjuvant, that targets up to 20 personal neoantigens per patient.[105] It has shown very promising results in a phase I clinical trial in patients with melanoma. Long-term persistence of neoantigen-specific T-cell responses was reported, with some neoantigen-specific T cells exhibiting a memory phenotype. Phase I melanoma studies with NeoVax in combination with other therapies continue for lymphocytic leukemia, follicular lymphoma, glioblastoma, and kidney and ovarian cancers. Similarly, iNeo-Vac-P01, which was developed in China, also uses up to 20 neoantigen peptides and showed very promising results in patients with pancreatic cancer.[106]

Heat shock protein peptide complex 96 (HSPPC-96), which is purified from patient tumors, has received a lot of attention as a personalized multivalent therapeutic vaccine. In contrast to NeoVax and iNeo-Vac-P01, HSPPC-96 does not require determination a priori and synthesis of peptide targets as these are agnostically isolated, bound to gp96, from the tumor. HSPPC-96 has exhibited a safe profile in treating a variety of malignancies including recurrent and newly diagnosed glioblastoma.[107-109] After withdrawal in Europe in 2009 by the Committee for Medicinal Products for Human Use, it re-entered clinical trials in phase II/III for liver cancer (ClinicalTrials.gov identifier: NCT04206254) and in phase II, in combination with temozolomide for glioblastoma (ClinicalTrials.gov identifier: NCT03650257).[110,111]

KRAS, the most frequently mutated oncogene, has been at the core of many drug development efforts. Recently, a vaccine was developed, composed of long peptides corresponding to six common mKRAS mutations, namely, G12D, G12R, G12V, G12A, G12C, and G13D, mixed with poly-ICLC adjuvant. Three phase I trials are currently recruiting patients, one of which uses KRAS peptide vaccine prophylactically in patients with high risk for developing pancreatic cancer. KRAS vaccine is being studied in combination with nivolumab and ipilimumab for NSCLC and colorectal and pancreatic cancers.[112]

On the other hand, survivin is an important oncogene for promoting glioblastoma tumor proliferation.[113] SurVaxM (SVN53-67/M57-KLH) contains a synthetic long peptide mimic that spans amino acids 53 through 67 of the human survivin protein sequence. The amino acid alteration in this peptide (M57) leads to enhanced binding of the core survivin epitope to HLA-A*0201 molecules.[114,115] Results from a phase II clinical trial for glioblastoma, where it was used in combination with temozolomide, showed that it was very well tolerated and increased progression-free survival.[116]

Virus-Based Vaccines

Oncolytic viruses are attractive as immunotherapeutic agents, as the lysis of tumor cells leads to the release of tumor-derived antigen that can be taken up by APC, thus amplifying the antitumor immune response.

Talimogene laherparepvec (T-VEC) is a genetically modified herpes simplex virus (HSV)-1 engineered to replicate within tumors and to produce the immune stimulatory protein granulocyte-macrophage colony-stimulating factor. Approved in 2015, it is indicated for the treatment of recurrent injectable but nonresectable melanoma skin lesions.[117] The phase III clinical trial, on which the approval was based, had shown a 31.5% response rate with a 16.9% CR. Furthermore, additional data showed substantially more positive results with a response rate of up to 88.5% and a CR of rate up to 61.5%.[118] T-VEC is still actively being investigated in multiple clinical trials for various indications, including sarcoma, hepatocellular carcinoma, and pancreatic and breast cancers, and for combinations with other drugs, primarily CPIs.[119]

In a more recent approach, OH2 is a novel oncolytic virus derived through genetic modifications of HSV-2. It is currently under investigation in multiple phase I and II clinical trials for melanoma and colorectal, gastrointestinal, liver, pancreatic, bladder, and central nervous system cancers.[120] PVS-RIPO is a recombinant, live attenuated, nonpathogenic oncolytic poliovirus, in which the internal ribosomal entry site (IRES) is replaced with the IRES from human rhinovirus type 2 (HRV2), with potential antineoplastic activity. On intratumoral administration of PVS-RIPO, the poliovirus is selectively taken up by and replicates in tumor cells expressing CD155 (poliovirus receptor, PVR, or NECL5) eventually causing tumor cell lysis.[121] CD155, an oncofetal cell adhesion molecule and tumor antigen, is ectopically expressed in certain cancers, including glioblastoma multiforme, and plays an important role in tumor cell migration, invasion, and metastasis. Because of the heterologous HRV2 IRES in this recombinant virus, PVS-RIPO only propagates in susceptible, nonneuronal cells.[122,123] In a phase I clinical trial in patients with malignant glioma, the absence of neurovirulent potential of PVS-RIPO was confirmed with an improved survival rate compared with historical controls.[124] There are more ongoing trials with PVS-RIPO in phase I and II for various indications including glioblastoma, melanoma, and breast and bladder cancers, some of which combine it with a CPI.[125]

PROSTVAC is a recombinant vaccine composed of a heterologous prime-boost regimen using two different live poxviral-based vectors: PROSTVAC-V, a recombinant vaccinia virus (rilimogene galvacirepvec), and PROSTVAC-F, a recombinant fowlpox virus (rilimogene glafolivec). Both vectors contain transgenes for human prostate-specific antigen and three costimulatory molecules for T cells (B7-1, ICAM-1, and LFA-3) to enhance immune activation.

Although PROSTVAC was shown to be safe and well tolerated, it did not show an OS benefit in metastatic castration-resistant prostate cancer.[126] Combination therapies of PROSTVAC, either with nivolumab (ClinicalTrials.gov identifier: NCT02933255) or with a human fusion protein that combines a monoclonal antibody against PD-L1 and the soluble extracellular domain of transforming growth factor-β (TGF-β) receptor II, which acts as a TGF-β trap (ClinicalTrials.gov identifier: NCT03315871), are currently being explored in clinical trials.[127,128]

FUTURE PERSPECTIVE: FROM TUMOR GENOMICS TO IMMUNOGENICITY

The advent of molecular techniques, including next-generation sequencing and discovery of germline mutations, further widened the scope and complexity of genetic mutations involved in tumorigenesis.[129] An effective antitumor immune response requires recognition of tumor antigens by immune cells followed by a mounted immune-mediated tumor cell killing. It has been proposed that tumors that do not benefit from CPIs have low immunogenicity, thus having a limited antitumor T-cell response.[130] High mutation rate is associated with a greater chance in producing mutant proteins that act as neoantigens, thus increasing the tumor cell immunogenicity. This was supported by data whereby mutational burden (TMB) was associated with the efficacy of the anti–PD-1 antibody pembrolizumab.[130,131] For example, compared with other tumors, cutaneous melanoma belongs to tumors with the highest tumor mutation burden, which, in turn, is linked to high melanocytes exposure to ultraviolet radiation and accumulated mutations.[132-134] On the other hand, in rare types of melanoma, namely, acral, uveal, and mucosal melanoma, the TMB is generally lower with a lower response to CPIs. The fact that noncutaneous melanoma has much fewer mutations than cutaneous melanoma and, at the same time, is less responsive to immunotherapy further supports the close connection between TMB and tumor immunogenicity.[135] Despite the clinical efficacy of immunotherapy reported to date, the majority of patients develop resistance and the overall outcome for patients remains generally unsatisfactory. There has been a recent trend to incorporate tumor immune profiling into the design of clinical trials to correlate it with response to treatment.[136,137] Deeper understanding of the relationship between the immune TME and response to treatment, resistance, and micrometastases by analyzing baseline tumor specimens can help in the development of novel approaches to enhance the antitumor immune response.

Conclusions

Despite the revolutionary advances in immunotherapeutics, treatment resistance remains a challenge leading to decreased response rate in a significant proportion of patients. As such, there has recently been an evolving focus to enhance efficacy, durability, and toxicity profiles of immunotherapy. Although CPIs have revolutionized cancer treatment with many already-approved antibodies and several others in the pipeline, other immunotherapeutic approaches, including bispecific antibodies and cancer vaccines, build on their success in an attempt to deliver an even more potent immune response against tumor cells. Moreover, there are several ongoing trials for the combination of immunotherapeutic approaches to enhance their efficacy, yet at the expense of potential toxicity. With the long-term remission provided by CPIs, on the one hand, and the promising results of bispecific antibodies and cancer vaccines, on the other hand, better understanding of these novel immunotherapeutic approaches ensues. More clinical trials that incorporate immune profiling of baseline tumor specimens are needed for deeper understanding of the relationship between the immune TME and response to treatment, resistance, and micrometastases.

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Artificial Intelligence in Clinical Oncology: From Data to Digital Pathology and Treatment

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overview

Recently, a wide spectrum of artificial intelligence (AI)–based applications in the broader categories of digital pathology, biomarker development, and treatment have been explored. In the domain of digital pathology, these have included novel analytical strategies for realizing new information derived from standard histology to guide treatment selection and biomarker development to predict treatment selection and response. In therapeutics, these have included AI-driven drug target discovery, drug design and repurposing, combination regimen optimization, modulated dosing, and beyond. Given the continued advances that are emerging, it is important to develop workflows that seamlessly combine the various segments of AI innovation to comprehensively augment the diagnostic and interventional arsenal of the clinical oncology community. To overcome challenges that remain with regard to the ideation, validation, and deployment of AI in clinical oncology, recommendations toward bringing this workflow to fruition are also provided from clinical, engineering, implementation, and health care economics considerations. Ultimately, this work proposes frameworks that can potentially integrate these domains toward the sustainable adoption of practice-changing AI by the clinical oncology community to drive improved patient outcomes.

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INTRODUCTION

Artificial intelligence (AI) is being widely explored for diverse applications in clinical oncology. Initial key work affected a broad spectrum of clinical indications including ophthalmology, radiology, dermatology, and others.[1-8] From this foundational work, broader capabilities emerged, such as digital pathology, biomarker development, treatment, and beyond. For example, the initial emergence of AI and its application to medicine were based on multiple large-scale studies pertaining to AI-based pathology as a means of supporting clinician-driven risk prediction and diagnosis.[9-18] As a specific example, this has been promising when deep learning (DL) has been paired with conventionally acquired histology toward the differentiation between primary and metastatic tumors and positive lymph node detection.[19,20] With regard to biomarker development, AI has been applied toward immune checkpoint inhibition, prediction of recurrence, ovarian cancer, and many other domains.[21-25] With regard to drug discovery and development, AI has also demonstrated promising advances. For example, target identification and the design of novel therapies for multiple disease indications are being widely explored.[26-28] These and other studies have introduced the potential of markedly increasing the speed with which drug candidates can be selected and prioritized for validation and downstream clinical trials to reduce the costs and time needed to advance new therapies toward late-stage development.[29] Importantly, additional work has shown that to truly position AI as a platform for optimizing cancer treatment, recognizing its role across the full therapeutic spectrum, from discovery (eg, new drug design or repurposing) to development (eg, combination regimen design) to dosing, is critical. Therefore, seamlessly integrating these segments has also been proposed as a strategy toward AI-augmented intervention in oncology.[30] Beyond the potential observed across these aforementioned aspects of clinical oncology, other areas of development, from data infrastructures, the type of data needed (eg, environmental factors, genomic profiles, family history, etc), matching patients to appropriate trials, and other indications, may incorporate AI.[31] Importantly, a plethora of studies have advanced to clinical trials across the globe, utilizing AI to enhance cancer screening/diagnosis and predict treatment outcomes. These studies rely on digital pathology, radiology, and genomic data to optimize the design of combination regimens and determine appropriate dosing of chemotherapy and immunotherapy (Table 1).[32-34] As the trial outcomes continue to be realized, if AI will ultimately change practice in oncology, a number of factors that extend far beyond technology and data will need to be explored. These include behavioral and implementation sciences, health care economics, reimbursement, and beyond. Therefore, in addition to highlighting promising technical advances in AI for clinical oncology, this work

PRACTICAL APPLICATIONS

- In early studies, artificial intelligence (AI) has demonstrated promise toward supporting and augmenting clinician-driven cancer diagnosis and prognosis; an example includes the emergence of digital pathology.
- With regard to cancer treatment, AI has also demonstrated promise in reducing timescales needed for drug/target discovery, the ability to personalize drug regimen design, and modulating drug dosing.
- Large-scale validation is still needed for diagnostic, prognostic, and therapeutic applications of AI, among other potential use cases.
- Potentially actionable frameworks for the seamless integration of AI into clinical workflows are proposed.
- Challenges remain with regard to the logistics of harnessing AI to empower practice-changing outcomes in clinical oncology. Outside of technical validation, a number of additional disciplines that span implementation sciences, health care economics, and other considerations are proposed.

also provides an outline of challenges that are already being or will be confronted by the continued advancement of AI in oncology. In addition, this work provides recommendations moving forward which may play a helpful role in integrating AI-based solutions into clinical workflows, with an aim of ultimately harnessing unprecedented predictive and interventional outcomes at scale.[35-37] We also convey the importance of deep collaboration across a multitude of disciplines to achieve real-world impact, demonstrate quantifiable value to health care systems, and achieve eventual adoption.

AI ADVANCES IN CANCER PATHOLOGY AND DIGITAL BIOMARKER DEVELOPMENT

Conventional cancer diagnosis and prognosis have included the use of standard pathology and other approaches.[38] These approaches have played a critical role in facilitating AI validation and beyond. This section will examine the role that AI has played in recent studies toward the continued validation of digital pathology as a prognostic platform and digital biomarker development.

DL in Cancer Pathology for Digital Biomarker Development

The identification of new molecular biomarkers to enable tailored cancer treatment options remains an enduring challenge and objective in the application of AI toward oncology. However, the limited availability of molecular assays, cost, and lengthy turnaround time hamper the practicality of unique biomarker findings. To accelerate the development of actionable biomarkers, DL methods are now being explored for advanced histology analysis of tumor cells to include inference of molecular features,[39-41] mutation prediction,[18,42,43] survival prediction,[44,45] and end-to-end prediction of therapy response.[32,46-48] Through these features, the aim is to harness DL to assign patients to optimal therapy regimes faster and more precisely compared with standard care. The implementation of DL-based genotyping in clinical workflows serves a dual purpose. First, DL biomarkers can be used to prescreen patients before conducting genetic testing. Second, these biomarkers could potentially replace the current methods of definitive testing, provided they demonstrate higher test performance than current methods. At present, challenges include the need for large-scale, prospective clinical validation of the DL systems to confirm the clinical impact of candidate biomarkers.[32]

Developing Biomarkers with Tumor Vasculature Imaging

To address these challenges, a number of studies have been conducted with promising outcomes toward the realization of imaging-based biomarker. In one such study, a tumor vasculature-based biomarker was developed. The tumor microenvironment comprises several critical elements, including the tumor vasculature, which can significantly affect invasiveness, metastatic potential, and resistance to therapeutic interventions. Several studies highlight the correlation between the twisted nature of vessels and its ability to counteract metastasis formation. Hence, quantitative vessel tortuosity (QVT) is being validated as a new imaging biomarker to predict the response and outcome prognosis of patients. In this study, 507 patients with non–small-cell lung cancer (NSCLC) treated with immune checkpoint inhibitor (ICI) therapies were analyzed for association between baseline and delta QVT features to their response to ICI therapies and overall survival (OS). This study was conducted using small cohort sizes for both training and test sets in a retrospective fashion. It was noted that there was insufficient tissue for analysis. As such, the correlation was derived with a small subset of cases. The investigators have noted that further prospective clinical validation is required. However, this study represented a promising step forward for digital biomarker development.[49]

Digital Pathology of Collagen Fibers for Breast Cancer Treatment Prediction

In another study, the digital pathology of collagen fibers was assessed and correlated with breast cancer outcomes. In invasive breast cancer, the interaction between tumor cells and surrounding extracellular matrix (ECM) can potentially predict metastatic outcomes. Specifically, because collagen is the most abundant protein in the ECM, it

TABLE 1. Clinical Trials Evaluating Artificial Intelligence in Clinical Oncology

Study Type	Condition	Description	Clinicaltrials.gov Identifier
Observational	Breast cancer	Breast cancer screening with an AI platform for mammography (AI-STREAM)	NCT05024591
Observational	Breast cancer	AI-driven breast cancer screening	NCT05650086
Observational	Lung cancer	I3LUNG: A framework for data-driven lung cancer management	NCT05537922
Observational	Lung cancer	Real-world data to drive lung cancer treatment (APOLLO11)	NCT05550961
Observational	Lung cancer	Integrating AI and radiomics for nodule stratification	NCT05375591
Observational	Head/neck cancer	Recurrence analysis with AI	NCT04086849
Observational	Ovarian cancer	AI-based risk assessment and biomarker development	NCT05161949
Observational	Prostate cancer	AI-based MRI analysis for prostate cancer classification	NCT04765150
Observational	Bladder cancer	Combining endoscopy with AI to enhance tumor detection	NCT05415631
Observational	Pancreatic cancer	Pancreatic cancer screening with AI (ESPRIT-AI)	NCT04743479
Observational	Leukemia	Deep learning and digitalized blood smears for leukemia diagnosis (BELUGA)	NCT04466059
Observational	Solid/blood cancers	AI-guided quality-of-life management postimmunotherapy	NCT05626764
Interventional	Liver cancer	AI-guided lesion detection	NCT03151564
Interventional	Breast cancer	Neural network–guided combination regimen development	NCT05177432
Interventional	Gastric cancer	AI-optimized regimen design and dosing	NCT05381038
Interventional	GI cancers	Combination therapy regimen optimization with AI	NCT04611035
Interventional	Glioma	Optimization of combination regimens with AI	NCT05532397
Interventional	Sarcoma/melanoma	Pinpointing unforeseen drug interactions in combination therapy	NCT04986748
Interventional	Solid tumors	AI-guided dynamic dosing in immunotherapy	NCT05175235
Interventional	Solid tumors	Modulating combination therapy dosing with AI	NCT04522284
Interventional	Neuro-oncology	Personalized digital therapeutics for neuro-oncology patients	NCT04848935
Interventional	Breast cancer	AI versus in-person breast cancer genetic counseling	NCT04354675
Interventional	Head/neck cancer	AI-based adaptive radiotherapy	NCT05081531

NOTE. A summary of observational and interventional studies pertaining to a broad spectrum of clinical oncology studies is shown.
Abbreviation: AI, artificial intelligence.

has been widely studied using second harmonic generation (SHG)–based microscopy or laser scanning microscopy (LSM). These studies previously showed that stiff and aligned collagen fibers were indicative of microinvasion sites by breast cancer cells and that collagen fiber analysis could potentially predict breast cancer prognosis. Unfortunately, neither SHG-based microscopy nor LSM is commonly used in clinical practice. To address this barrier, digital pathology was explored using standard hematoxylin & eosin (H&E) staining without the need for any additional specialized collagen staining or complex imaging approaches. The organization of collagen fibers from routine H&E slides were analyzed and investigated for association with disease-free survival outcome measure, with promising findings. Of note, the team noted that a small data set was used because of restricted inclusion criteria, which may be suboptimally representative of the entire population. However, these and other studies serve as important proof-of-concept validation toward downstream prospective studies.[50]

Addressing DL Accuracy and Enhancing the Reliability of Digital Pathology

Histology images are generally used by pathologists to examine and identify characteristics to categorize tumor subtypes, assess prognosis, and potentially predict response to treatments. With the emergence of digital histology, DL can be applied to identify more subtle but specific features, illuminating substantially more information from traditional histology to potentially determine clinical biomarkers, gene expression patterns, survival outcomes, and pathogenic mutations. To support this promising avenue of innovation, the Cancer Genome Atlas (TCGA) represents a substantial digital histology collection and has played a crucial role in developing DL-based histology models. It contains more than 10,000 digital slide images obtained from 24 different types of tumors and also includes relevant clinical, genomic, and radiomic data. The TCGA is among the largest biorepositories of its kind and has provided a valuable resource for researchers

to access and analyze cancer tissue samples for their studies, and its large collection of data has been crucial in advancing cancer research. Recent developments have made promising advances toward overcoming previously observed challenges and realization of widespread digital pathology usage in clinical oncology. For example, the preparation of histological specimens for digital imaging has traditionally involved multiple steps that can introduce variations in resulting images. Fixation, staining, and digitization methods can all contribute to unique site-specific digital histology signatures. Additionally, biological differences between patients that were treated across different centers can also affect histologic characteristics of tumors. Despite using color normalization and augmentation methods across sites to reduce site detection, there is significant variation in the histological features of cancer samples across different tissue submitting sites in TCGA, which can be detected by DL methods. This site-specific digital histology signature can lead to overfitting of digital histology models to site-level characteristics, resulting in biased accuracy of feature prediction. Therefore, these site-specific signatures must be considered to ensure equitable DL application and accurate predictions in cancer research.

Numerous approaches have been taken to reduce bias and improve trustworthiness in identifying patient specifics to achieve equity with DL models.[51] For example, a recent study characterized the heterogeneity between clinical and digital imaging in TCGA for more than 3,000 patients with six cancer subtypes. A quadratic programming approach was used to ensure that models are not trained and validated on samples from the same site.[53] The study recommended a set of best practices for DL studies on histology using TCGA or other data sets on the basis of the combination of multiple hospital sites.[53] First, the study described that outcomes of interest should be reported across included sites to assess the potential impact of site-specific signatures on accuracy. Second, knowledge regarding the distribution of outcomes on both training and testing sites can enable the accurate assessment of model performance. It was subsequently suggested that the area under the receiver operating characteristic (AUROC) curve is an uninformative marker for heavily imbalanced data sets and that the precision recall curve, or F1 score, may be more informative. Therefore, if outcomes of interest vary significantly across sites, it may be necessary for further validation at individual institutions before implementing the models to ensure that biases learned from institutional staining patterns do not affect the results.

The study analyzed the basic demographics and tumor-specific factors for six major solid tumor types (breast, colorectal, lung adenocarcinoma renal clear cell and lung squamous cell carcinoma, and head and neck squamous cell carcinoma) and found that multiple clinical features vary by site for all tested tumor subtypes. To predict tissue submitting sites, the study trained a DL convolutional neural network on the basis of Xception architecture[52] and used threefold cross-validation stratified by site to calculate the one versus rest AUROC for accuracy assessment. The study implemented preserved site cross-validation, optimally stratifying for k-fold cross-validation while also isolating each site to an individual k-fold by using convex optimization/quadratic programming to produce perfect stratification in 55% (32 of 58) of outcomes tested. This preserved site cross-validation represents a promising tool for identifying features that are unlikely to survive external validation testing—an important foundation for DL-based improvements in reliability of digital pathology as clinically actionable platforms for biomarker development and disease prognostication.[53]

AI ADVANCES IN CLINICAL CANCER TREATMENT

In the field of cancer treatment, the terms drug discovery and drug development are often used interchangeably, but they are different segments of the interventional pipeline. Seamless integration matters to ensure that drugs are used individually and in combination properly. In addition, diagnostic-guided modulation of treatment (eg, pharmacologic/radiation dosing) can subsequently be realized. This section will highlight the use of AI across the spectrum of drug discovery through development and dosing and outline a framework to combine these capabilities toward the potential of optimized clinical cancer treatment, guided by AI-augmented diagnostic and biomarker development capabilities (Fig 1).

Harnessing AI to Design and Discover Novel Therapies

AI has been widely explored as a catalyst to accelerate the discovery and design of new targets and drugs. For example, a recent study described the successful integration of AlphaFold, an AI-based protein structure prediction system, with two AI-driven drug discovery platforms. These included PandaOmics and Chemistry42, resulting in the identification of a new hit molecule against a novel target involved in the treatment of hepatocellular carcinoma.

The molecule was identified in a time- and cost-efficient manner within 30 days, starting from the selection of the protein target, identification of the CDK20 hit molecule, compound synthesis, and biological testing. Chemistry42 generated the molecules on the basis of the protein structure predicted by AlphaFold, and the selected molecules were then synthesized and tested in biological assays. Overall, this study demonstrates the effectiveness of integrating AlphaFold into AI-powered drug discovery pipelines.[54]

Addressing Cancer Therapy Regimen Design With AI

In standard medical practice, combination therapies are commonly prescribed, but for patients with chemotherapy-resistant conditions, these treatments often lead to low response rates. Additionally, these approaches are largely

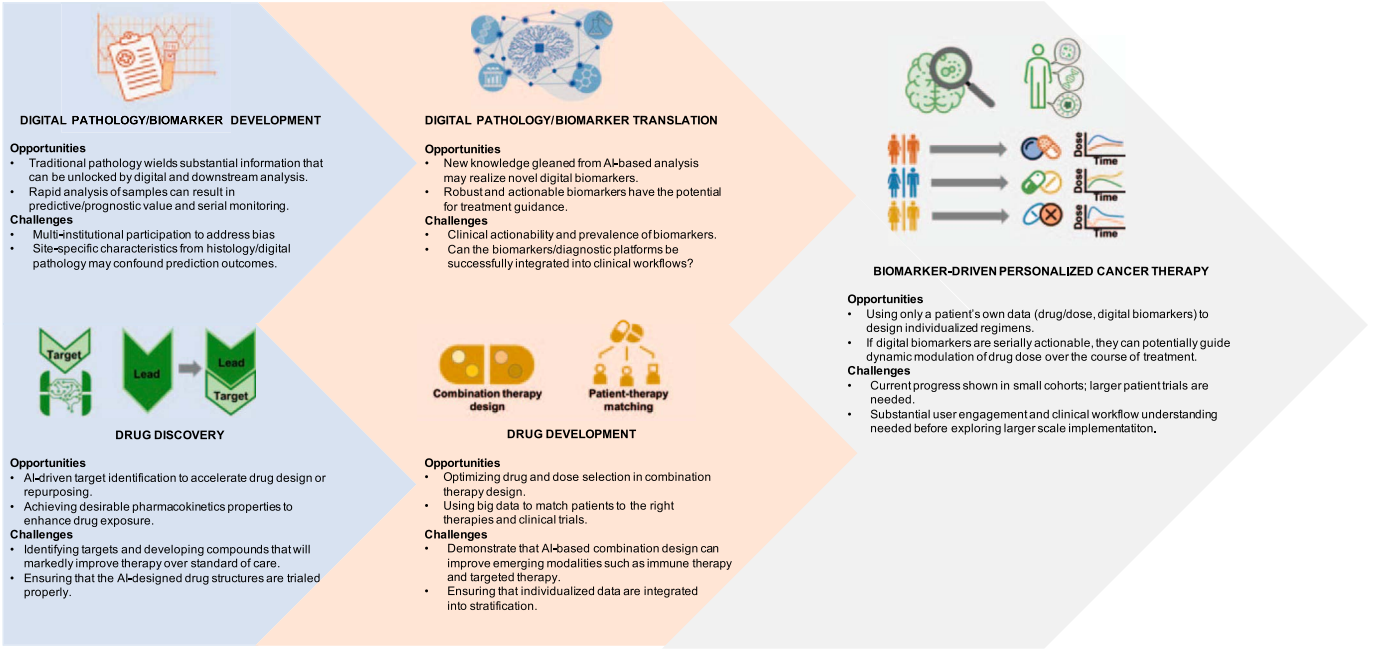

FIG 1. Technology workflow: Harnessing digital platforms to personalize treatment. This technology-centric workflow discusses opportunities and challenges in applying AI toward digital pathology, drug discovery/development, and dynamic drug dosing. AI, artificial intelligence.

based on population-level responses, ignoring interpatient heterogeneity. To address this challenge, the quadratic phenotypic optimization platform (QPOP) was developed.[55] Contrary to purely computational methods, QPOP combines prospective laboratory experimentation with optimization analysis to design patient-specific drug combination, followed by the validation of efficacy through ex vivo testing of biopsied tumor samples. As opposed to existing ex vivo drug testing that relies on single drug sensitivity, QPOP uses an orthogonal array composite design that plates drugs in a specific format to markedly reduce experimental data points from extraordinarily large parameter spaces. QPOP ideally maps individualized and unforeseen drug-drug interactions and ranks drug combinations for individual patients. A prospective study was conducted with 71 patients (75 samples) with relapsed or refractory non-Hodgkin lymphoma (RR-NHL) whose biopsies were subjected to ex vivo testing using a panel of 12 drugs with known efficacy against NHL. For 67 of 75 patient samples, individualized QPOP reports were generated within a clinically actionable timeframe within a median of 6 days from sample collection to report generation. Five of the 17 treated patients achieved complete responses using QPOP, a promising proof-of-concept study toward future large-scale validation studies.[55]

In another study, an image-based single-cell functional precision medicine (scFPM) platform was used for drug profiling of patient biopsies with singe-cell resolution. This enabled the direct quantification of drug effects.[56] scFPM platform-based ex vivo drug efficacy was identified using high-content microscopy and image analysis for patient population with progression-free survival (PFS) ratio of $\geq$1.3 as an outcome measure. Like QPOP, this method does not require population-scale data or indirect reference to genomic data for the design of treatment strategies. A prospective trial, Extended Analysis for Leukemia and Lymphoma Treatment (EXALT; NCT03096821), was conducted for 143 patients with advanced aggressive hematologic cancers who exhausted all standard therapy lines. Fifty-six of 143 patients were treated according to scFPM with 54% of patients demonstrating $\geq$1.3-fold improved PFS. The median time taken from sampling to scFPM report generation was about 5 (1-33) days.[56]

Addressing Cancer Therapy Dosing With AI

In an important previous study, evolutionary game theory was proposed to model physician therapy and cancer cell resistance strategies. In this scenario, the physician aims to guide cancer cells to better treatment outcomes over traditional treatment protocols. Specifically, the physician can rationally anticipate future events by applying game theory. The cancer cells cannot anticipate or adapt to future events and only have the ability to respond to current or past events through evolution of resistance strategies. This approach addresses a key barrier confronted by traditional treatment strategies, where the continuous application of the same regimen on the basis of maximum tolerated dose alone yields short-term success but does not anticipate the long-term evolutionary characteristics of the tumor. Hence, game theory emphasizes that cancer cells continuously evolve to

generate adaptive responses to treatments and similarly physicians should adopt more dynamic treatment protocols and modulate therapies accordingly. This study also highlights the potential need to expand cancer treatment protocols toward defining the goal of the treatment to maximize cancer cell extinction or the time to progression and include a resistance management plan to exploit evolution-based approaches to delay or suppress resistant phenotype proliferation. In this work, game theory has also been explored in understanding glucose membrane transporters such as GLUT1 production in cancer cells and its correlation with rapid proliferation and metastatic potential.[57] Game theory–based studies have also advanced to clinical trials, with a recent outcome revealing a 47% reduction from standard dosing and a markedly increased time to progression compared with standard care.[58]

Harnessing CURATE.AI to Dynamically Modulate Cancer Treatment Dosing

Cancer therapy, particularly chemotherapy, is often given at fixed and high doses. Although these doses have been established through properly powered, randomized controlled trials (RCTs), there can be a subset of patients where high/fixed drug dosing may result in a suboptimal response or nonresponse to treatment and high toxicity. Broadly speaking, patients who do not respond or stop responding to each line of therapy are then moved to other lines of treatment until they run out of options. Unfortunately, among the aforementioned subset of patients, this may also result in the misperception that therapy cannot work for certain patients. To address this challenge, the CURATE.AI platform was developed. CURATE.AI is an AI-based optimization platform that aims to pinpoint optimal doses at the right time for each patient. CURATE.AI uses only a patient's own data to manage only their own care. It does not use population data to treat individuals. CURATE.AI has previously shown that optimal dosing may be dynamic, meaning the dose needs to be modulated or changed during the course of treatment.[59-61] CURATE.AI implementation prospectively calibrates each patient by providing each patient with modulated *inputs*. These inputs include varied drug doses (all within clinically accepted safe ranges). *Outputs*, which can include quantifiable measures of efficacy and safety which correspond with each of these varied doses, are measured. Outputs can include carcinoembryonic antigen (CEA, used for colorectal and other cancers), other biomarkers that indicate cancer progression including images (computed tomography [CT], magnetic resonance imaging [MRI], and ultrasound), liquid biopsies, and markers for toxicity (liver health, kidney health, white blood cell numbers, etc). On the basis of the aforementioned calibration, CURATE.AI relates the drug dosing to treatment efficacy and safety using a quadratic algebraic series which was previously discovered via neural networks. Solving for this series constructs a two-dimensional or three-dimensional profile, which we referred to as a Digital Avatar, which then identifies the right doses to optimize treatment outcomes. This map may evolve/change over time during the course of treatment. This allows us to identify doses as treatment proceeds that can sustain optimal care. Of note, CURATE.AI does not require the use of big data, genomics, or pharmacokinetics. A CURATE.AI-centric workflow is shown in Figure 2. Instead, CURATE.AI is implemented through the use of small data sets that are carefully acquired through prospective calibration of patient response. However, approaches such as CURATE.AI can be complementary to big data or genomic approaches (eg, precision medicine) in that the initial drugs used for treatment can be selected on the basis of patient's genomic profiles. Therefore, in parallel with AI-based diagnostic approaches or the development of predictive algorithms which may require big data sets, interventional AI platforms can potentially improve treatment outcomes over standard care using small data, which are both important areas for further validation.

PRECISE CURATE.AI (ClinicalTrials.gov identifier: NCT04522284), a phase I single-arm (treatment), two-center, pilot clinical trial, was recently conducted to assess the logistical and technical feasibility of a larger RCT with CURATE.AI. Regimens covered in this study included XELOX (oxaliplatin and capecitabine), XELIRI (irinotecan and capecitabine), and single-agent capecitabine. Tumor markers used included CEA, CA125, and ctDNA (an experimental marker in the study). Individualized patient digital avatars (akin to a digital twin) were successfully constructed via CURATE.AI. Capecitabine doses were reduced on average by 19.4% ± 13.71% compared with what would have traditionally be given as standard-of-care dosing for these patients. Additional outcomes included the timely delivery of dosing recommendation (100%), clinically significant dose changes (100%), and patient adherence to the prescribed doses (independent if the dose was recommended by CURATE.AI or a medical team alone; 80%).[62] It is important to note that CURATE.AI does not aim to lower the dose to all patients with cancer. Instead, the impetus for its assessment is to potentially find more responders to treatment and provide bespoke dosing for patients who can optimize efficacy and/or prolong the period the patient is responsive to the treatment. These doses may be lower than the conventional doses that are traditionally used.[62,63] Moving forward, additional clinical trials harnessing the use of platforms such as QPOP and CURATE.AI have been launched to address other indications such as breast cancer (ClinicalTrials.gov identifier: NCT05177432), GI cancers (ClinicalTrials.gov identifier: NCT04611035), glioma (ClinicalTrials.gov identifier: NCT05532397), and sarcoma/melanoma (ClinicalTrials.gov identifier: NCT04986748), as well as modulated dosing in immunotherapy for solid tumors

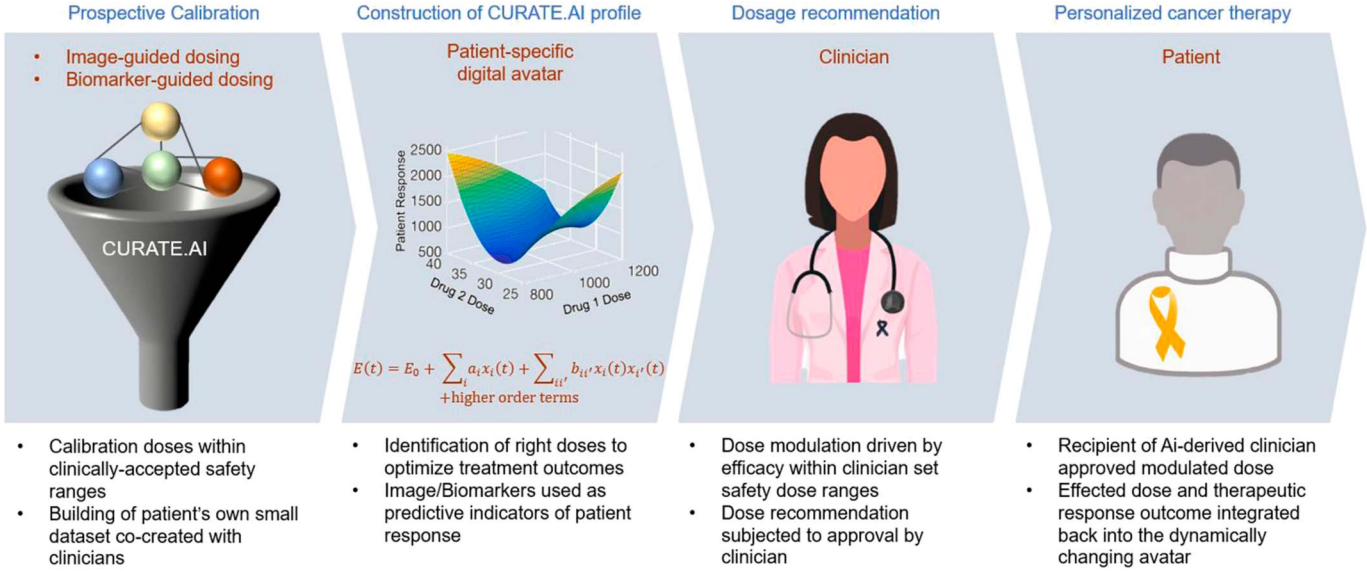

FIG 2. CURATE.AI workflow: Clinical implementation of dynamic dosing. This workflow harnesses clinician-guided, prospective calibration of patient dosing (input) and biomarker outcomes (output) to construct a digital avatar. This avatar is subsequently used to dynamically modulate cancer therapy dosing. AI, artificial intelligence.

(ClinicalTrials.gov identifier: NCT05175235), multiple myeloma (ClinicalTrials.gov identifier: NCT03759093), digital therapeutics for neuro-oncology patients (ClinicalTrials.gov identifier: NCT04848935), and an integrated regimen and dose optimization trial for gastric cancer (ClinicalTrials.gov identifier: NCT05381038). In parallel to collecting clinical outcomes additional information is gathered on the implementation aspects including physicians' perceptions.[64]

AI IN CLINICAL ONCOLOGY: A USE CASE OF INTEGRATED DATA FRAMEWORKS

Predictive algorithms have the potential to revolutionize the health care industry, especially in the field of oncology, by improving patient outcomes and optimizing treatments. However, it is essential to demonstrate the effectiveness and safety of AI-based models for clinical decision support (CDS) in oncology. Several key aspects must be considered to successfully implement AI-based models. These include the quality, source, storage, and sharing of data; the accuracy and trustworthiness of chosen models; ethical considerations and patient involvement in the use of predictive models; and the legal implications related to the use of patient data. Transparency and open communication between patients and health care providers are crucial to building trust and promoting patient-centered care. Novel data-driven trial designs need to balance progress with security while ensuring that patients' privacy and autonomy are protected. By addressing these challenges, AI-based models can be powerful tools for improving the quality of care and patient outcomes in oncology. A subsequently described international use case outlines key considerations for the integration of AI into clinical workflows.

The I3LUNG Use Case: Recommendations for Design, Methodology, and Infrastructure for Integrating AI Into Clinical Oncology Workflows

To successfully integrate AI into a clinical oncology workflow, it is crucial to develop and validate a platform that can (1) aid physicians through CDS by offering readily accessible predictive models, (2) equip patients with personalized codecision-making platforms, and (3) ensure secure access to generated data for further research purposes by using a continuum learning process. An example of such a project is the recently described EU-backed (Horizon Europe) I3LUNG Project: Integrative science, Intelligent data platform for Individualized LUNG cancer care with Immunotherapy.[64] I3LUNG aims to individualize treatment in patients with advanced non–small-cell lung cancer (aNSCLC) treated with immunotherapy. The study is international and multicentered and combines retrospective, observational, and prospective validation. The main objective of this study is to investigate the usefulness of heterogeneous data sources and the effectiveness of big data for individualized prediction for patients with NSCLC treated with immunotherapy (IO). The study uses AI-based tools to improve survival and quality of life, minimize or prevent undue toxicity, and promote efficient resource allocation by investigating the omics role by personalizing diagnostics. The final product of the project aims to yield a novel, integrated, AI-assisted data storage and CDS platform for IO-based therapy in NSCLC,

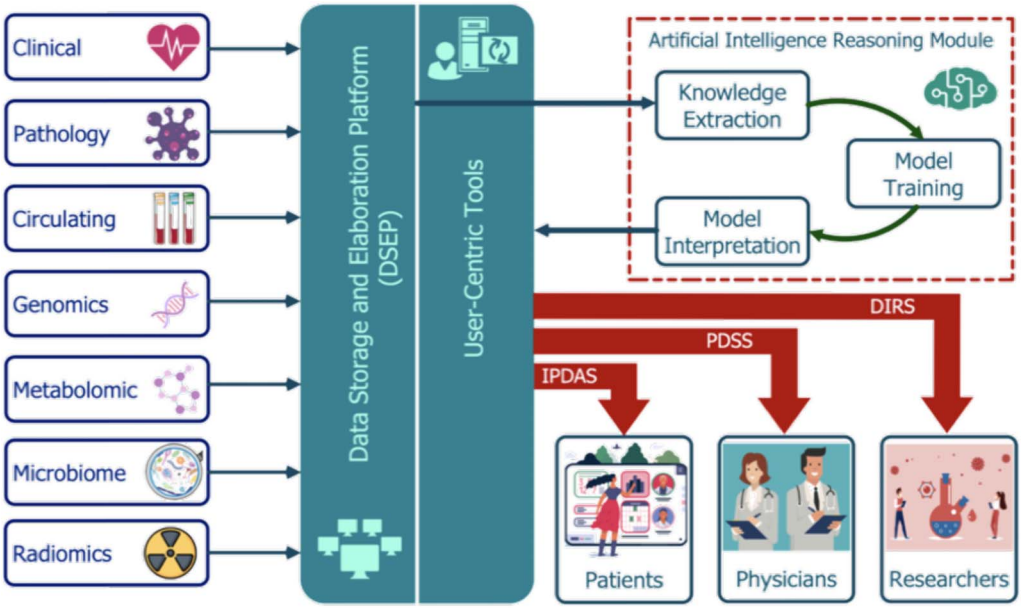

FIG 3. Data use case workflow: An integrated data framework for the I3LUNG platform use case. This use case demonstrates an integrative, omics-driven strategy to drive personalized CDS for immunotherapy toward NSCLC that is accessible and economically sustainable for health care systems and patients. AI, artificial intelligence; CDS, clinical decision support; DIRS, a tool that allows the researchers to easily access data about patients with NSCLC to be used in future clinical studies[64]; IPDAS, tools aimed at patient-physicians' shared decisions on treatment, giving information about NSCLC treatments and on the AI techniques used for prediction; ML, machine learning; NSCLC, non–small-cell lung cancer; PDSS, element to provide physicians with patients' individualized predictive model library, integrating the available data and ML algorithms for NSCLC.

ensuring easy access and cost-effective use by health care providers and patients. A data-centric workflow illustrating the I3LUNG use case is shown in Figure 3.

Framework Design and Data Collection

Fully integrating AI tools into real-world clinical oncology workflows requires the engagement of a highly multidisciplinary team, which includes medical doctors, AI experts, bioengineers, experts in ethics research, behavioral scientists and user engagement experts, psychologists, legal experts, data managers, designers and health economists, and reimbursement specialists, and patients themselves, among others. This is critical in an effort to ensure that the many users of such platforms,[65] which can span clinicians through patients and caregivers, are adequately engaged during development and implementation processes. Initiatives such as I3LUNG, the work of the Institute for Digital Medicine (WisDM), and other international stakeholders reflect the importance of deep collaboration required to empower studies that have the potential to change clinical practice.

In parallel, the development of effective AI predictive models in clinical oncology research is heavily dependent on the availability of large data sets. Therefore, multicenter studies and data are critical to generate the necessary big data for training and validating AI models. Although AI can analyze already available retrospective data from blood examinations; CT, PET, and MRI scans; and pathological slides, among others, acquiring prospective data, including multiomics data sets, will also be critical for further AI development and validation. For example, personalized multiomics data can shed previously unforeseen insights into the molecular mechanisms of cancer, potentially improving the way that treatments are designed, developed, or dosed.[66]

As an example, I3LUNG will use retrospective clinical data from CT and PET scans, digital histological diagnosis, and PDL1 slides at diagnosis from 2000 patients with NSCLC to develop retrospective (R-model) predictive models. The platform will subsequently enroll two cohorts: (1) 2,000 patients with prospective NSCLC treated with first-line IO, collecting real-world data, digital slides (both histology at diagnosis and PD-L1 slides), and CT and PET scans to validate the R-model and (2) 200 patients with NSCLC with a sufficient period of follow-up. Data collected will be similar to the previous cohorts and also include personalized bioomics analyses (eg, genomics, transcriptomics, circulating immune profiling, single-cell analysis, metabolomics, and microbiome). Prospectively collecting these omics data sets

will validate previously developed predictive models coupled with prospective trial validation and will further establish the importance of these data sets in refining the model. These models will then be integrated into the final I3LUNG platform for NSCLC CDS for downstream medical device clearance submissions.

Cross-Institutional Data Harmonization Storage

Importantly, this infrastructure will also enable data harmonization across partner institutions (six European Union [EU] cancer centers and centers in the United States and Israel). This harmonization will further support model refining and the establishment of a cross-institutional omics data dictionary. Data storage for such an initiative is envisioned to involve a collaborative, shared data platform that uses compressed binary files and a multimodel database structure capable of handling various types of data. Therefore, the I3LUNG platform has been designed to enable aggregation, compression, encryption, storage, processing, and transport of data while maintaining embedded security and privacy protections. It will support multiscale data and other semantic domains such as quality of life and behavioral measurements, which is envisioned to advance patient-specific treatment. Data included in the platform should be a multiscale and anonymized with possible future bidirectional data exchange. A multi-institutional data sharing workflow to enable predictive analytics is shown in Figure 4.

Creation of Predictive Models and Integration of Multimodal Data

The I3LUNG use case and our envisioned frameworks for AI-enhanced digital pathology, drug discovery, and cancer treatment collectively illustrate the importance of reconciling multiple classes of data as a foundation for AI-based CDS in clinical oncology. This will in turn enable new insights that were previously precluded because of limitations brought on by insurmountable amounts of clinical information. Therefore, multimodal data integration using machine learning (ML) and DL continue to gain traction in clinical oncology research.[67-69] Two recent studies[70,71] have shown that incorporating ML to integrate data of various modalities, including CT scans, digitalized PD-L1 slides, and genomics, can enhance the accuracy of predicting the effectiveness of immunotherapy in NSCLC and also aid in risk stratification of high-grade serous ovarian cancer.

CHALLENGES AND OPPORTUNITIES OF AI-BASED ONCOLOGY APPLICATIONS

Before the widespread and sustained application of AI in clinical oncology, a number of challenges and opportunities remain. These challenges span several domains, ranging from the need for continued technical validation to legal/ethical implications, as well as data infrastructure, regulatory, and economic considerations.

Technical Challenges of AI in Clinical Oncology

There are many potential applications of AI in clinical cancer diagnosis, treatment, and monitoring. The body of work in this space has been substantial and continues to gain traction. However, before the clinical implementation of AI at scale, a number of challenges remain. At the heart of these challenges is clinical validation, where clear pathways that span well-designed preclinical studies through adequately controlled RCTs continue to be needed. Recently, multiple AI-based oncology platforms have received regulatory clearance.[72] A number of clinical trials from pilot through RCT are also underway. Continued momentum in these domains will be needed to avoid the associated challenge of Pilotitis, where studies are unable to progress beyond small-scale clinical studies, which preclude the derivation of clinically actionable findings.[73]

With regard to challenges in the diagnostics space, with AI-enhanced imaging as a use case, there remains a continued need to achieve a scale of validation such that AI can be reliably integrated into clinical workflows. Progress has certainly been made, as demonstrated by a plethora of recent studies. However, factors such as trust, clinician confidence in AI-based recommendations, and AI performance that can empower the clinical community to markedly enhance clinical practice over standard care remain to be seen at scale across health care systems, regions, and indications.

With regard to biomarker development and predictive/personalized matching of patients to therapies, the clinical concordance of AI-derived predictions of matching molecular alterations to drug selection also need further validation. Although studies have illuminated the potential to achieve improved outcomes in objective response rate, PFS, OS, and other end points, the potential of tapping into AI to further improve these outcomes remains. Although molecular alteration and biomarker-driven drug selection have yielded promising results, a substantial number of patients do not respond favorably to treatment on the basis of these approaches. As discussed in this work, there are other factors such as drug-dose optimization that may be explored to bridge this gap, but they will need to be further validated.

There are also challenges confronting AI-based cancer therapy. The first is the concept that AI-driven drug discovery alone will optimize patient treatment. It is clear that the field has accelerated drug target identification, new drug design, and repurposing. AI also led to an emergency use authorization of an AI-predicted, repurposed drug during the COVID-19 pandemic within the span of approximately 8 months of initial identification.[74] However, beyond AI-designed compounds, implementing a comprehensive workflow that ensures that these compounds are properly stewarded during the subsequent development process will be important for AI to realize its full potential toward

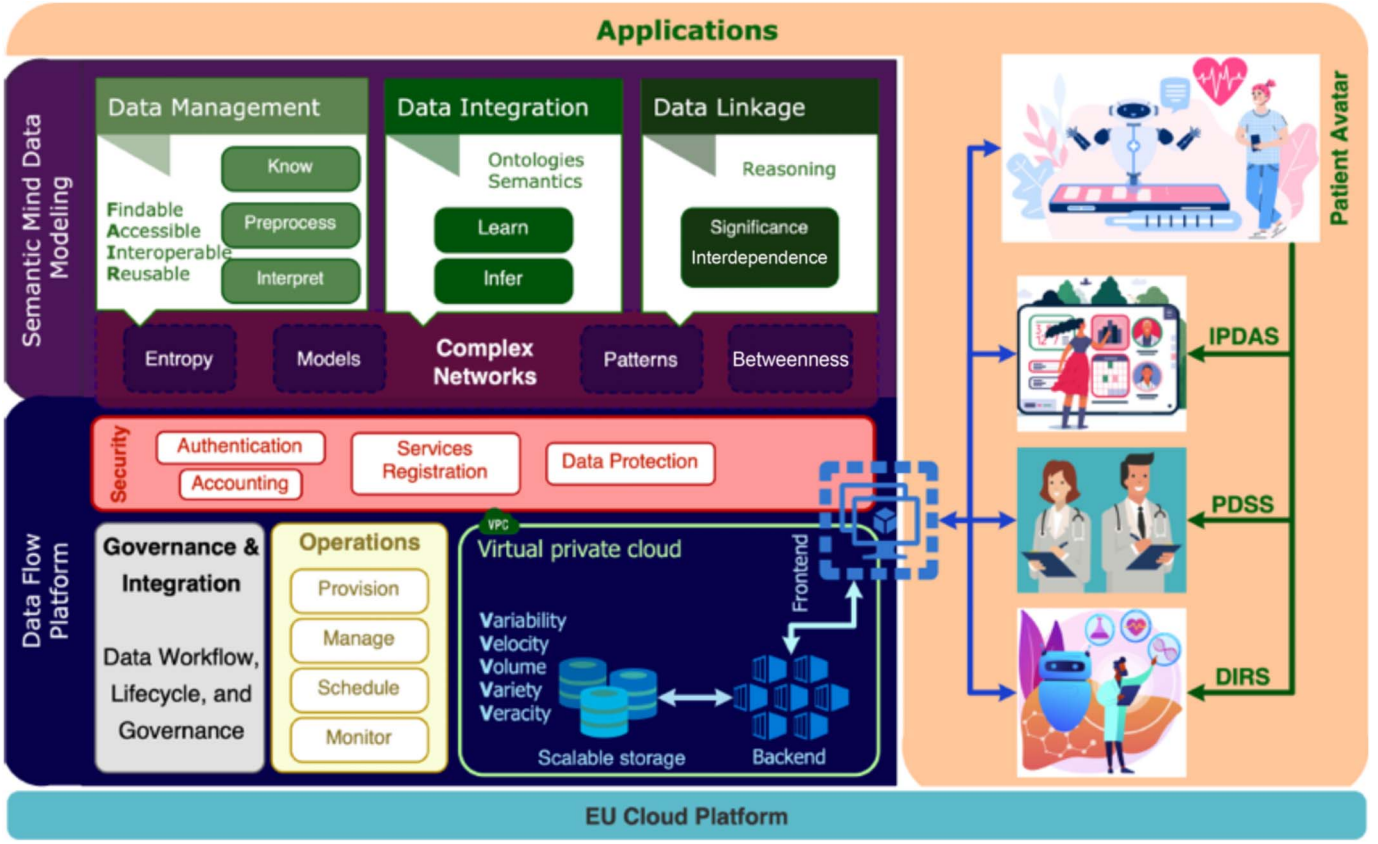

FIG 4. Predictive analytics data workflow: A multi-institutional data sharing platform for predictive AI analytics. To support international collaboration in platforms such as I3LUNG, a platform has been created to drive data harmonization and safe storage and access. AI, artificial intelligence; DIRS, a tool that allows the researchers to easily access data about patients with NSCLC to be used in future clinical studies64; IPDAS, tools aimed at patient-physicians' shared decisions on treatment, giving information about NSCLC treatments and on the AI techniques used for prediction; PDSS, element to provide physicians with patients' individualized predictive model library, integrating the available data and maching learning algorithms for non–small-cell lung cancer.

changing practice in cancer treatment. AI has reimagined how drug combinations can be designed, finding unforeseen drug interactions that have increased therapeutic efficacy compared with traditional mechanism-of-action–based combination design. However, there are substantial operational challenges to overcoming convention if mechanism independence will be integrated into common practice across the drug development through CDS domains, where mechanism of action (MOA)-based drug selection is a cornerstone of current workflows. To support the further validation of these and other AI-enabled advances, reimagining and innovating clinical trial design, adequate user engagement in the development of new clinical workflows, and other considerations will need to be addressed.[75,76] These have been discussed as part of the proposed therapeutic, data, and CDS workflows illustrated in this work.

Trustworthy AI

The complexity of ML and DL models can potentially affect their interpretability. This can in turn complicate CDS. To make these models more usable, recent efforts have harnessed post hoc explainable AI (XAI). XAI aims to make models accountable, interpretable, transparent, explainable, and trustworthy, targeting models that are not interpretable by design.[77] The goals of XAI methods are to produce more explainable models while maintaining high learning performance, enabling humans to understand, trust, and manage the emerging generation of AI partners. In oncology research, different post hoc XAI approaches are used, such as feature relevance explanation techniques like SHAP[78] and saliency maps,[79] which help explain predictions for DL models. Generative methods may also provide opportunities to create explanation-embedded visualizations of clinical states in images.[80] Despite relevant studies on XAI in oncology,[25,81,82] a significant development in the field of XAI in medicine is expected in the next few years to enhance the transparency, accountability, and trustworthiness of AI in health care.

Legal and Ethical Considerations of AI in Clinical Oncology

The use of AI in clinical research raises a number of ethical and legal questions that need to be addressed. One of the main concerns is the protection of patient privacy as vast

amounts of potentially sensitive patient data can be collected. Another consideration is data vulnerability to cyberattacks. Therefore, strict privacy policies and measures against data theft are essential. Additional considerations, ranging from data ownership to patient access to their own data, will require further consideration and debate.[83]

Health Care Economics of AI in Clinical Oncology

The sustainable deployment of clinical AI will require substantial infrastructural considerations to address the aforementioned data storage, sharing, and safety requirements. The training of AI may require new procedures in the types of tests and data we require from each patient. The implementation of AI in CDS may also change the landscape of drug-patient matching, dosing, and other factors. Therefore, the previously noted innovation in clinical trial design will also need to further consider whether the health and economic benefits of using these tools outweigh the additional implementation costs. Therefore, how AI will affect actuary modeling, quality of life (QoL), and other patient outcomes will need to be addressed.[84]

Regulatory Considerations of AI in Clinical Oncology

A number of challenges are shared by both the diagnostic and intervention spaces. When using population-based data to train models for diagnosis or CDS, the generalizability of approaches across patient populations will need to be carefully considered. Additional challenges pertain to whether relevant infrastructures (eg, data security, clinical laboratory, software/computing, etc) are in place to support new workflows. However, a number of guidelines and recommendations through the collective effort of an international community of regulatory agencies are being released, which should aid in the advancement of new platforms into clinical practice.[85-91]

Opportunities for AI in Clinical Oncology

Aside from these challenges, there remain substantial opportunities for AI to positively affect the delivery of evidence-based oncology care. At the heart of the AI oncology community interface is the potential of empowering the clinical community to accessibly improve patient outcomes. After the early and continued promise of AI-assisted image and biomarker development for potentially enhanced prognostic capabilities, the promise of improved treatment selection over standard care for more patients may greatly enhance clinical practice and save lives. AI-guided drug regimen selection and dynamic dose modulation has, in early studies, revealed the potential of improving the practice of CDS to find more responders to treatment and optimize the development of drug combinations, among other outcomes. For these opportunities to take shape at scale and to change the practice of clinical oncology more work remains across a broad spectrum of disciplines.

RECOMMENDATIONS FOR THE DEVELOPMENT OF AI SOLUTIONS FOR CLINICAL ONCOLOGY

Here, we propose a series of recommendations for the disciplined development of AI-based platforms for diagnostic and therapeutic applications. It is important to note that the categories and recommendations are not exhaustive, and AI platform developers are encouraged to consider additional factors that can support safe and rigorous technology development to enable accessible solutions to reach patients at scale. In addition, many of these recommendations may not need to be addressed chronologically. Some may also be applicable across multiple or all stages of development.

Ideation

- A critical first step is to comprehensively assess the intended use for the solution. Can conventionally acquired data (eg, histology, clinical records) drive AI development and training to enable actionable CDS?
- Aside from ensuring the solution addresses an unmet clinical need, it is critical to note who the core user(s) is/are and if data infrastructures are in place to support deployment.
- It is important to assess if the originality of the proposed solutions, supporting infrastructure, and data sharing practices have the potential of advancing practice at scale.

Validation

- The data used for model training/validation and recruited trial participant population should be representative of the downstream user population to reduce prediction bias. In addition, the model training/validation and clinical validation studies should sufficiently address the objectives needed for regulatory approvals/clearances to meet clinical implementation guidelines.
- External validation, validation with cohort from different institutions, is highly recommended to test models generalizability and should become a norm.
- User engagement studies should be considered as part of the workflow validation process. The health economics of the solutions will also be critical to demonstrate value to the health care system and users.
- Clinical trial design innovation should be strongly considered and subsequently explored.

Implementation

- The AI solution should properly consider clinical practice norms and other requirements (eg, time required for execution per user).
- Infrastructural requirements and other applicable operations considerations should be considered early on in the development process so that the AI platform can be practically integrated into clinical workflows.

- User feedback should be considered as part of early trial designs to better inform downstream implementation.

Adoption

- How does the AI developer intend to sustain the use of the solution in a health care system with regard to data infrastructure and sharing?
- When considering the user of the AI solution, what steps have been taken to address implementation sciences, user interface, and experience (UX/UI) that can support user engagement with the solution?
- Can payer considerations/engagement be addressed early on in the development process to avoid downstream challenges with reimbursement?

CONCLUDING REMARKS

At present, the potential role of AI in driving digital pathology, biomarker development, and treatment outcomes for patients is being explored using a broad spectrum of applications. As the validation of AI-based platforms continues, early and frequent consideration of the end user, which could be the doctor, nurse, pharmacist, allied health, patient, caregiver, or a combination of these stakeholders and others, along with implementation and adoption considerations will be essential. As the field continues to progress, the seamless integration of AI-based solutions across the entire health care workflow will serve as a vital catalyst toward AI-enabled change in clinical oncology practice.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Rise of Antibody-Drug Conjugates: The Present and Future

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overview

Antibody-drug conjugates (ADCs) embody a simple, but elegant, vision for cancer therapy—the delivery of a potent cytotoxic agent to tumor cells with minimal damage to normal cells—so-called smart chemo. Although there were significant challenges in achieving this milestone culminating in the first Food and Drug Administration approval in 2000, subsequent advancements in technology have led to rapid drug development with regulatory approvals for ADCs targeting a variety of tumor types. The most successful application for solid tumors has been in breast cancer, with ADCs becoming the standard of care across traditional human epidermal growth factor receptor 2 (HER2)+, hormone receptor+ (HR+) and triple-negative disease subtypes. Moreover, the improved features and gains in potency with the development of ADCs have expanded the treatment-eligible population to those with low/heterogeneous expression of the target antigen on the tumor with trastuzumab deruxtecan or in the case of sacituzumab govitecan, agnostic to target expression. Despite their antibody-directed homing, these novel agents come with their share of toxicities obligating appropriate patient selection and vigilant monitoring while on treatment. As more ADCs are included in the treatment armamentarium, mechanisms of resistance need to be studied and understood for optimal sequencing. Modifying the payload to use immune-stimulating agents or combination therapies with immunotherapy and other effective targeted therapies may further extend the utility of these agents in the treatment of solid tumors.

INTRODUCTION

Antibody-drug conjugates (ADCs) are a rapidly emerging class of therapeutic agents that combine the target specificity of a monoclonal antibody (mAb) with the lethality of cytotoxic cellular poison. With ongoing advancements in drug engineering and fresh biologic insight into mechanisms of drug action, the ADC field is still early in its evolution. Despite this, there are over a 100 new ADCs in clinical trials encompassing a wide variety of tumor types. This explosion of interest is, in part, due to the spectacular success in the past 5 years, particularly in some highly treatment-refractory diseases. This review will provide a brief overview on ADC design and mechanism of action, highlighting ADCs currently in use for breast and urothelial cancer (UC) where some of the most significant clinical advancements have been achieved. The toxicity profile of these agents, development of resistance, and the potential of combination therapies with ADCs will be explored.

HISTORY OF ADC DEVELOPMENT

The idea of targeted chemotherapy was conceptualized by a German scientist, Paul Ehrlich, over a century ago. His magic bullet would target a cytotoxin to intended structures in unwanted cells but spare healthy tissues.[1] The structures were later conceptualized to be cell surface antigens to attract antibodies that could grant the desired target specificity. Ehrlich also coined the term chemotherapy, where he proposed to use chemicals to kill the pathogenic cells. Early progress in the development of chemotherapy included generation of some cellular toxins that might be too potent and toxic to administer without a targeted approach. Inception of the hybridoma technology for generation of mAbs[2] helped realize Ehrlich's vision with the first ADC trials underway in the 1980s.[3-5] The first approved ADC was gemtuzumab ozogamicin[6] in 2000, where a CD33 antibody is conjugated to an antitumor antibiotic, calicheamicin.[7] Growing understanding of the ADC mechanism of action and technological breakthroughs have heralded the approvals of over a dozen ADCs, including two on the basis of trastuzumab backbone, an antibody against human epidermal growth factor receptor 2 (HER2).

ADC DESIGN

The fundamental components of an ADC are a mAb directed against a tumor-associated antigen, a cytotoxic agent called payload, and a connecting linker. Each component and their interactions play crucial roles in determining the efficacy and toxicity profiles of an ADC.

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PRACTICAL APPLICATIONS

- The fundamental components of an antibody-drug conjugate (ADC) include an antibody, a linker, and a payload, and the choice and construction determine the clinical characteristics of the ADC.
- Recent drug development has focused on altering linker chemistry and tapping into novel cytotoxic payloads to generate high-potency ADCs that have dramatically improved outcomes, especially in breast cancer.
- Some novel ADCs demonstrate clinical efficacy regardless of the level of tumor antigen expression, enabling the treatment of tumors with heterogeneous expression of the target.
- Most ADCs are associated with unique toxicities, such as pneumonitis/interstitial lung disease, and ocular or skin toxicities that warrant careful monitoring and mitigation strategies.
- The next wave of agents looking to build on the success of ADCs include immune-stimulating antibody conjugates, engineered toxin bodies, and radioligand conjugates that aim to improve therapeutic index while minimizing toxicity.

Antibody Moiety

The antibody moiety of an ADC dictates its plasma circulation duration, immunogenicity, immune functions, and target specificity. Current ADCs are predominantly based on immunoglobulin G (IgG), particularly IgG1. IgG1 offers a long serum half-life and strong Fc-mediated immune functions, including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity.[8] Murine antibodies in the early ADCs have been replaced with chimeric or humanized antibodies to minimize immunogenic side effects.[9] Selection of a suitable target antigen has also proven to be instrumental in modulating the specificity and processing of an ADC. An ideal target should exclusively, or preferentially, be expressed at high levels on the surface of tumor cells and not on normal cells. HER2 and trophoblast cell surface antigen 2 (TROP2) are two such targets being used for ADC development in breast cancer (BC) because of their overexpression on tumor cell surfaces[10,11] while sparing normal tissue.

Linkers

A linker's function is to ensure that the payload remains bound to the antibody during circulation but is released at the tumor site. Linkers can be cleavable or noncleavable.[8] Cleavable linkers release the payload on reduction, proteolysis, or hydrolysis because of tumor cell–associated factors (eg, proteases or pH), but noncleavable linkers require complete lysosomal degradation for the payload release. Of the three ADCs approved for BC, ado-trastuzumab emtansine (T-DM1) is the only one with a noncleavable linker,[12] which provides stability to the ADC during circulation and might contribute to a better safety profile compared with other trastuzumab-based ADCs. However, the noncleavable linker may also hinder the potential for bystander killing, wherein payload is released into the tumor microenvironment (TME) and can kill antigen-less cancer cells or even cancer-supporting cells.[13]

Cytotoxic Payloads

Payloads are the chemotherapeutic agents that exert cytotoxic effects on the tumor cells targeted by the ADCs. These are commonly microtubule binding or DNA damage (DNA cleavage or alkylation)-inducing agents. Because of advances in linker conjugation chemistry and our understanding of the ADC mechanism of action in vivo, an increasing breadth of anticancer agents are now being incorporated in newer ADC designs. Among all the newer payloads, however, the most effective have been topoisomerase I (Topo 1) inhibitors including camptothecin derivatives. Fam-trastuzumab deruxtecan (T-DXd) is an anti-HER2 ADC on the basis of an exatecan derivative,[14] and sacituzumab govitecan (SG) is an anti-TROP2 ADC that uses SN-38 (the active metabolite of irinotecan) as its payload.[15] Both ADCs have high drug to antibody ratios (DARs), which can enhance ADC efficacy in vivo given low hepatic clearance.[16] In the case of T-DXd, the membrane permeable deruxtecan is also proficient at diffusing to neighboring cells to exert a bystander effect. This characteristic is integral to the activity in HER2-low or HER2-heterogeneous tumors. Continuous progress is moving the field forward toward the development of more powerful ADCs with varied payloads[17,18] including even nonchemotherapeutic[19] payloads like immune-stimulating agents,[20] while improving the therapeutic window and decreasing systemic side effects to healthy cells.

MECHANISM OF ADC ACTION

The primary antitumor action of ADCs is via targeting of the cytotoxic payload to the tumor cells. On binding of the mAb to the target antigen, the ADC is internalized into the tumor cell. The eventual linker breakdown promotes intracellular release of the payload, where it exerts its microtubule- or DNA-damaging effects.[16] The process of antibody binding and internalization may be subject to further pharmacologic manipulation or enhancement. For instance, recent work has highlighted the potential to increase antigen availability through the use of statin[21] or increase internalization and

lysosomal sorting through the use of kinase inhibitors.[22] These and other studies highlight the multistep process to ADC-mediated killing, which may be enhanced through such drug combinations and may also prove to be relevant to drug resistance.

In addition to the canonical payload release mechanism of drug action, the antibody moiety can exert anticancer effects in a payload-independent manner. The binding of the antibody to its target antigen can disrupt the antigen's downstream function by preventing interaction with its binding partners[23] or promoting its degradation.[24] Furthermore, ADC antitumor action can also be mediated through antibody-dependent activation of immune response including ADCC,[25] such as trastuzumab. Indeed, some of these particular effects may be insufficient as a single agent but provide critical support to the chemotherapy combination akin to how trastuzumab combines with chemotherapy to realize synergistic antitumor effects.

TOXICITIES OF ADCs APPROVED FOR BC AND UC

A major goal of ADCs is to achieve high specificity and low toxicity, beyond the capability of traditional chemotherapeutic agents that lack tumor selectivity.[26] However, despite nuanced drug development strategies, important toxicities exist in clinical practice for approved ADCs. While the toxicities are often attributed to the payload, the target antibody and linker have important implications in determining the implicated organs of observed adverse reactions.[26] Key trial data for ADCs approved for BC and UC and the toxicities associated with them are discussed below. The most common treatment-related adverse events (TRAEs) with these ADCs and the clinical monitoring recommended during treatment are included in Tables 1 and 2, respectively.

T-DM1

T-DM1 is an ADC composed of the mAb trastuzumab, the cytotoxic payload maytansine (DM1), and a nonreducible thioether linker MCC (4-[*N*-maleimidomethyl] cyclohexane-1-carboxylate).[27] The use of a stable noncleavable linker maximizes the therapeutic index of DM1 by minimizing the systemic exposure to free DM1 and improving exposure to T-DM1.[28]

T-DM1 was the first ADC that was granted regulatory approval for solid tumors; it was Food and Drug Administration (FDA)–approved for the treatment of HER2-positive metastatic breast cancer (MBC) on the basis of results from the EMILIA trial.[29] It now has expanded use as an adjuvant therapy for residual disease in early-stage HER2-positive BC after neoadjuvant therapy, on the basis of KATHERINE trial data.[30]

The EMILIA trial also reported a superior toxicity profile associated with T-DM1 compared with capecitabine plus lapatinib (40.7% *v* 57% ≥grade 3 events). The rate of ≥grade 3 adverse events (AEs) was 41% in patients treated with T-DM1, the most common being thrombocytopenia (13%) and elevated serum concentrations of aspartate aminotransferase (4%) and alanine aminotransferase (3%; Table 1).[29]

TABLE 1. TRAEs of Antibody-Drug Conjugates

Drug	Antibody/Payload	Cancer Type	Most Common TRAEs	
			All Grade	TRAEs ≥ Grade 3
T-DXd (*DESTINY-Breast03*, *DESTINY-Breast04*)	Trastuzumab (anti-HER2)/deruxtecan	Breast, colorectal, gastric, non–small-cell lung cancers	Nausea (77%, 73%), vomiting (52%, 34%), alopecia (40%, 38%), anemia (37%, 33%), constipation (37%, 21%), fatigue (31%, 48%)	Neutropenia (16%, 14%), anemia (9%, 8%), platelet count decreased (8%, 5%), nausea (7%, 5%), fatigue (6%, 8%)
EV (*EV-301*)	Anti–nectin-4/MMAE	Urothelial carcinoma	Alopecia (45%), peripheral sensory neuropathy (34%), pruritus (32%), fatigue (31%), decreased appetite (31%)	Maculopapular rash (7%), fatigue (6%), decreased neutrophil count (6%)
T-DM1 (*EMILIA*, *KATHERINE*)	Trastuzumab (anti-HER2)/DM1	Breast cancer	Nausea (39%, 42%), fatigue (35%, 50%), thrombocytopenia (28%, 29%), elevated AST (22%, 28%)	Thrombocytopenia (13%, 4%), elevated AST (4%, 0.5%), ALT (3%, 0.4%)
SG (*ASCENT*, *TROPICS-02*)	Anti-TROP2/SN-38	Breast, urothelial carcinoma	Neutropenia (63%, 70%), diarrhea (59%, 57%), nausea (57%, 55%), alopecia (46%, 46%), fatigue (45%, 37%), anemia (34%, 34%)	Neutropenia (51%, 51%), diarrhea (10%, 9%), anemia (8%, 6%), febrile neutropenia (6%, 5%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transferase; EV, enfortumab vedotin; HER2, human epidermal growth factor receptor 2; MMAE, monomethyl auristatin E; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TRAEs, treatment-related adverse events; TROP2, trophoblast cell surface antigen 2.

TABLE 2. Precautions, Baseline Investigations, and Monitoring for T-DXd, EV, and T-DM1

Drug	Precautions	Baseline Investigations	Monitoring During Treatment and Prophylactic Measures
T-DXd	Pneumonitis, ILD, history of drug-induced pneumonitis Symptomatic or history of congestive heart failure	Assessment of LVEF	Assessment of LVEF clinically as indicated, consider regular assessment throughout Regular assessment of respiratory symptoms (cough, dyspnea, fever)
EV	Hyperglycemia (increased risk in baseline hyperglycemia, BMI > 30) Pre-existing peripheral neuropathy	Assessment of glycemic control (consider HbA1C)	Glucose monitoring Consider ocular prophylaxis with artificial tears Clinical assessment of neuropathy
T-DM1	Pneumonitis, ILD, history of drug-induced pneumonitis Symptomatic or history of congestive heart failure	Assessment of LVEF	Assessment of LVEF as clinically indicated, consider regular assessment throughout Platelet count Liver enzymes Regular assessment of respiratory symptoms (cough, dyspnea, fever)

Abbreviations: EV, enfortumab vedotin; HbA1C, hemoglobin A1C; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Trastuzumab and T-DM1 bind to FcγRIIa on megakaryocyte progenitors, but only T-DM1 is associated with thrombocytopenia, indicating that this toxicity is due to DM1 or its metabolite lys-SMCC-DM1.[26] For most patients, the first occurrence of grade 3 or 4 thrombocytopenia was observed during the first two cycles of T-DM1 treatment and, with appropriate dose modifications, did not result in treatment discontinuation.[29] Interestingly, the incidence of thrombocytopenia after treatment with T-DM1 has been reported to be higher in Asians than White patients, with grade 3 events in 45% and 12%, respectively.[26] Although rare, studies have reported left ventricular dysfunction and the appearance of interstitial lung disease (ILD) associated with the use of TDM-1.[31] Careful patient monitoring is required throughout treatment in an effort to prevent more serious toxicity, and baseline assessment of left ventricular ejection fraction (LVEF) is recommended (Table 2).

T-DXd

Fam-T-DXd is a novel ADC with a humanized HER2 antibody with the same sequence as trastuzumab, covalently linked to a Topo I inhibitor (DXd). This ADC was designed with several unique features: (1) a potent payload DXd; (2) a novel linker that permits a high DAR of 8, with reduced hydrophobicity; (3) a tumor-selective cleavable linker susceptible to lysosomal proteases in the tumor; (4) short systemic half-life to avoid systemic exposure; and (5) bystander effect caused by the high membrane permeability of DXd that enables its diffusion out of tumor cells to exert its cytotoxic effects in the TME.[32]

The FDA granted accelerated approval for T-DXd in December 2019, on the basis of the efficacy in pretreated HER2-positive MBC in DESTINY-Breast01.[33] The DESTINY-Breast03 study demonstrated an unprecedented 1.5-year improvement in median progression-free survival (PFS) with T-DXd compared with T-DM1 in predominantly second-line HER2+ MBC (25.1 *v* 7.2 months; hazard ratio [HR], 0.28; $P = 7.8 \times 10^{-22}$), earning T-DXd a confirmatory FDA approval in this patient population.[34,35] Furthermore, the DESTINY-Breast04 trial in patients with pretreated HER2-low (HER2 immunohistochemistry [IHC]1+ or HER2 IHC2+/in-situ hybridization) MBC demonstrated the superiority of T-DXd over TPC with improved median progression-free survival (HR, 0.50; $P < .0001$) and overall survival (OS; HR, 0.64; $P = .0010$).[36] T-DXd received FDA approval in HER2-low MBC on August 5, 2022, expanding the pool of patients with MBC eligible for treatment with this HER2-targeted ADC.[37]

In DESTINY-Breast01, the most common of these TRAEs associated with T-DXd were decreased neutrophil count (21%), anemia (9%), nausea (8%), and fatigue (6%). Of note, 14% of patients receiving T-DXd had ILD related to the receipt of the study drug, resulting in death among 2% (four patients) of patients. Just three patients experienced decreased LVEF (1.6%), with only one patient (0.5%) experiencing grade 3 severity, suggesting that cardiac toxicity is infrequently observed with this anti-HER2 ADC.[38]

In DESTINY-Breast03, a phase III study comparing T-DXd with T-DM1 in metastatic HER2-positive BC (Table 1), AEs were similar to those in DESTINY-Breast01 and drug-related ILD or pneumonitis occurred in 15% of patients treated with T-DXd, with no grade 4 or 5 ILD/pneumonitis events. Proactive monitoring, early diagnosis, and management were thought to have contributed to the lack of grade 4 or 5 events in this large trial.[39] Nausea and fatigue were also the most common drug-related AEs reported on the DESTINY-04 trial,[36] and a two- to three-drug prophylactic antiemetic regimen (5 Hydroxytryptamine 3, steroid ± neurokinin-1) is recommended for all patients receiving T-DXd.[40]

Drug-related ILD is an important toxicity that must be considered in patient selection and monitoring throughout

treatment with T-DXd. Of note, there seems to be increased risk with the use of T-DXd in the management of HER2-mutated non–small-cell lung cancer, with 26% of patients experiencing drug-related ILD in DESTINY-Lung01.[41] Patients with pre-existing or suspected ILD or pneumonitis should not be offered this therapy and were excluded from DESTINY-Breast01 and subsequent clinical trials investigating T-DXd.[38,42] If ILD is suspected during treatment, consultation with a pulmonologist is recommended, along with high-resolution computed tomography, testing of pulmonary function, and monitoring of oxygen saturations[38,42] (Table 3). Systemic glucocorticoids may be indicated, and further treatment with T-DXd may be contraindicated depending on the severity of toxicity.[38,42]

ENFORTUMAB VEDOTIN

Enfortumab vedotin (EV) is an ADC with proven survival benefits in the treatment of UCs.[43] EV consists of a fully human mAb specific for nectin-4, a cell adhesion molecule, and monomethyl auristatin E (MMAE), an agent that disrupts microtubule formation.[44] EV received accelerated FDA approval in 2019 and regular approval in July 2021, after the publication of EV-301.[45] EV-301 was a global phase III trial, which showed significantly prolonged survival with EV compared with standard chemotherapy in patients with advanced urothelial carcinoma who had previously received platinum-based treatment and an immune checkpoint inhibitor (ICI; HR, 0.70; 95% CI, 0.56 to 0.89).[43]

In EV-301, TRAEs of grade 3 or higher occurred in 51% of patients who received EV, which was similar to the chemotherapy control arm. The most common of these events included maculopapular rash (7%), fatigue (6%), and decreased neutrophil count (6%).[43] Skin reactions and peripheral neuropathy were the most frequent TRAEs of special interest, occurring in 44% and 46% of patients, respectively. The majority of peripheral neuropathy events were grade 1 and 2 sensory events, but they were identified as the TRAE most commonly leading to drug interruption, withdrawal, or dose reduction. This AE appears to accumulate with time and has both motor and sensory components.[43]

Postmarketing reports of severe and fatal cutaneous adverse reactions, including Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with the use of EV.[46] Most commonly, these serious cutaneous toxicities occur during the first cycles of treatment, and therefore, careful initial monitoring with early drug interruption is recommended[47] (Table 3). In cases of severe (grade 3 or higher) dermatologic events, treatment should be withheld and referral for specialized dermatologic care should be considered. In confirmed cases of SJS or TEN, treatment with EV should be permanently discontinued. Mild skin reactions can be managed with supportive care, including topical corticosteroids and oral antihistamines, and treatment may be continued.[47] The role of oral steroids is unproven.

The precise mechanism for SJS or TEN with the use of EV remains unknown, but both the nectin-4–directed antibody and MMAE payload have been implicated. Nectin-4 is expressed in the skin, where it is involved in cell–cell adhesion[47] and may be a case where the target is not specific enough to tumor cells only. In skin biopsies of patients taken 7 days after treatment, EV has been shown to localize to healthy tissues including epidermis, epithelium, and sweat glands.[47]

In EV-301, treatment-related hyperglycemia occurred in 6% of patients, occurring more frequently in patients with hyperglycemia at baseline or with a BMI of 30 or higher,[43] and glucose monitoring is helpful. Ocular toxicities, including dry eyes, blurred vision, and keratitis, have been reported.[48] Artificial tears may be used prophylactically, treatment should be interrupted for ≥grade 3 toxicity, and consultation with ophthalmology is recommended for consideration of additional therapy, including ophthalmic topical steroids[48] (Table 3).

EV has also been investigated in a phase II study of EV plus pembrolizumab in previously untreated UC.[49] No new safety signals were reported in combination with PD-1 therapy; the toxicity profile was similar to that of EV and pembrolizumab monotherapy. However, AEs were more frequent than those with EV monotherapy. This combination is being evaluated further in a phase III study (Table 4). An ongoing clinical trial, EV-202, is investigating the efficacy of EV in the treatment of breast, lung, head and neck, and gastroesophageal cancers, all of which have been shown to express nectin-4[59] (ClinicalTrials.gov identifier: NCT04225117). Overall, EV should not be considered more toxic than chemotherapy in the treatment of UC. Rather, it has a distinct toxicity profile that requires education and awareness.

DISITAMAB VEDOTIN (RC48)

Disitamab vedotin (DV) also has MMAE as its payload but targets HER2 rather than nectin-4 (as is the case with EV).[60] It is licensed in China for advanced UC and has a single-agent response rate of over 50% in a cohort of 107 patients with HER2 positivity. ≥Grade 3 AEs occurred in 58% of patients, the most common of which were hypoesthesia (23%) and neutropenia (14%).[60] Skin toxicity appears less than that seen with EV. The differences in toxicity profile compared with EV are likely due to the distribution of the target as the payload is the same. Larger randomized trials with DV are ongoing.

TABLE 3. Management Recommendations for Important ADC Toxicities

Toxicity (*ADC*)	Severity	Management of Toxicity
Skin reactions (*EV*)	Suspected SJS or TEN	Immediately withhold EV and refer to specialized care Permanently discontinue in confirmed cases
	Grade 2	Withhold until ≤grade 1 Consider referral to specialized care Consider dose reduction if rechallenging after grade 2 toxicity
Hyperglycemia (*EV*)	Blood glucose >13.9 mmol/L (>250 mg/dL)	Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL) Resume treatment at the same dose
Peripheral neuropathy (*EV*)	Grade 2	Withhold until ≤grade 1 For first occurrence, resume treatment at the same dose level. Consider dose reduction for rechallenge after recurrences
	Grade ≥3	Permanently discontinue
Pneumonitis (*trastuzumab deruxtecan*, *trastuzumab emtansine*)	Grade ≥2	Referral to pulmonary, CT thorax, PFT if pneumonitis/ILD suspected Permanently discontinue
Ocular toxicity (*EV*)	Grade ≥2	Consider referral to specialized care Consider topical ophthalmic corticosteroids

Abbreviations: ADC, antibody-drug conjugate; CT, computed tomography; EV, enfortumab vedotin; ILD, interstitial lung disease; PFT, phenylalanine mustard, fluorouracil, tamoxifen; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

SACITUZUMAB GOVITECAN

SG consists of a humanized mAB specific for TROP2 linked to SN-38, the active metabolite of the Topo I inhibitor irinotecan.[15] This conjugation is achieved using a hydrolyzable, proprietary linker, CL2A, which allows for delivery of SN-38 inside tumor cells expressing TROP2. CL2A linker also allows for release of SN-38 into the nearby TME, resulting in a bystander effect killing adjacent tumor cells. SG is linked with high DAR.[15] SG has FDA approval for the treatment of metastatic triple-negative breast cancer (TNBC) and metastatic UC and most recently for the treatment of hormone receptor+ (HR+)/HER2– MBC.[61-63]

ASCENT was a phase III study comparing SG with physician's choice chemotherapy in patients with TNBC who had received two or more previous systemic therapies for metastatic disease. SG was found to improve PFS (HR, 0.41; 95% CI, 0.32 to 0.52) and OS (HR, 0.48; 95% CI, 0.38 to 0.59) compared with single-agent chemotherapy.[64] In this trial, the most common TRAEs of any grade were neutropenia (63%, ≥grade 3—51%), diarrhea (59%, ≥grade 3—10%), nausea (57%), alopecia (46%), fatigue (45%), and anemia (34%, ≥grade 3—8%); see Table 1. Febrile neutropenia was also observed (≥grade 3—6%). Low frequencies of rash (9%, any grade), ocular toxicity effects (5%; all grade 1), and neuropathy (1% ≥grade 2) were reported.[64]

TROPICS-02 randomly assigned patients with HR+/HER2– MBC 1:1 to receive SG or TPC.[65] SG demonstrated statistically significant and clinically meaningful improvements in PFS (HR, 0.66; $P < .0003$) and OS (HR, 0.79; $P = .02$) over TPC.[66] The safety profile in TROPICS-02 was consistent with previous studies (Table 1).

TROPHY-U-01 was a phase II study investigating SG in the treatment of metastatic UC in patients who experienced disease progression after platinum-based chemotherapy and ICI therapy. This study reported a very similar toxicity profile to that observed in ASCENT. There was again a low rate of TRAE involving skin (6%), ocular disorders (4%), and peripheral neuropathy (4%).[67]

There has been rapid development of ADCs in the treatment of other solid tumors as well, with promising activity compared with conventional cytotoxic chemotherapy. Tisotumab vedotin (targeting human tissue factor) is already a standard treatment for advanced cervical cancer,[68] and mirvetuximab soravtansine (targeting FRα) received FDA approval recently for FRα-expressing recurrent epithelial ovarian cancer/fallopian tube cancer/primary peritoneal carcinoma,[69] expanding the treatment options for these patients.

The therapeutic success with novel ADCs in relapsed disease is prompting their evaluation in earlier lines of treatment including the curative setting (Table 4). However, with the use of potent cytotoxic agents and imperfect mechanisms of targeting tumor cells, toxicity is an important consideration while using these agents. Patient selection and careful monitoring continue to be critical components in prescribing systemic therapy, with attention to the unique toxicities associated with these novel agents.

TABLE 4. Select Ongoing Trials With ADC Combinations

ADC	ADC Target	Trial ID (name)	Phase	Combination Therapy	Patient Population	Clinical Trial Data (if applicable)
ADC + IO combinations						
T-DM1	HER2	NCT04740918 (KATE3)	III	Atezolizumab (anti–PD-L1 antibody)	HER2-positive and PD-L1+ MBC	
		NCT04873362 (ASTEFANIA)	III	Atezolizumab (anti–PD-L1 antibody)	HER2+ BC with residual disease after NAC	
		NCT02924883 (KATE2)	II	Atezolizumab (anti–PD-L1 antibody)	HER2-positive MBC	mPFS: HR, 0.082, $P = .33$,[50] atezolizumab arm: 8.2 months, placebo arm: 6.8 months Treatment-related SAEs: atezolizumab arm: 19%, placebo arm: 3%
		NCT02605915	Ib	Atezolizumab (anti–PD-L1 antibody)	HER2-positive BC	
		NCT03032107	I	Pembrolizumab (anti–PD-1 antibody)	1-2L metastatic HER2+ MBC	ORR (N = 20): 20%[51] mPFS: 9.6 months G3 AEs: 20% Pneumonitis: 20% (n = 4; G2 = 3, G3 = 1)
T-DXd	HER2	NCT04538742 (DESTINY Breast-07)	Ib/II	Durvalumab (anti–PD-1 antibody)	1L metastatic HER2+ MBC	
		NCT04556773 (DESTINY Breast-08)	Ib/II	Durvalumab (anti–PD-1 antibody) + paclitaxel	1-2L metastatic HER2-low MBC	
		NCT03742102 (BEGONIA)	Ib/II	Durvalumab (anti–PD-1 antibody)	1L HER2-low TNBC	ORR (n = 12): 66.7%[52] (regardless of PD-L1 expression) G3/4 AE (n = 21): 38.1%, pneumonitis: two cases
		NCT03523572	Ib	Nivolumab (anti–PD-1 antibody)	≥2L HER2+ MBC	ORR (n = 32): 65.6%[53] mPFS: 11.6 months, no benefit with addition of nivolumab to T-DXd, adjudicated ILD/pneumonitis[a]: 14.6%
		NCT03523572	Ib	Nivolumab (anti–PD-1 antibody)	≥2L HER2-low MBC	ORR (n = 16): 50%[53] mPFS: 7.0 months, adjudicated ILD/pneumonitis[a]: 14.6%
		NCT04042701 (KEYNOTE KN-797)	I	Pembrolizumab (anti–PD-1 antibody)	HER2+ MBC (treated with previous T-DM1) and HER2-low MBC	
SG	TROP2	NCT04468061 (Sacı-IO TNBC)	II	Pembrolizumab (anti–PD-1 antibody)	1L mTNBC, PD-L1–negative	
		NCT04448886 (Sacı-IO hormone receptor+)	II	Pembrolizumab (anti–PD-1 antibody)	1-2L hormone receptor+/HER2– MBC	
		NCT05633654 (ASCENT-05)	III	Pembrolizumab (anti–PD-1 antibody)	TNBC with residual disease after NAC	
		NCT04434040 (ASPRIA)	II	Atezolizumab (anti–PD-L1 antibody)	TNBC with residual disease after NAC	
		NCT03971409 (InCITe)	II	Avelumab (anti–PD-1 antibody)	Metastatic TNBC	
		NCT04863885	I/II	Ipilimumab (anti-CTLA4 antibody) + nivolumab (anti–PD-1 antibody)	1L cisplatin-ineligible metastatic UC	Phase I results: ORR: 66.6% (4/6 evaluable –1 CR, 3 PR)[54] DLTs: G3 skin rash (n = 2), G3 pneumonitis (n = 1) RP2D: 8 mg/kg SG IV D1, 8 q3 weeks + 3 mg/kg Ipi IV q3 weeks + 1 mg/kg nivo IV q3 weeks

(Continued on following page)

TABLE 4. Select Ongoing Trials With ADC Combinations (Continued)

ADC	ADC Target	Trial ID (name)	Phase	Combination Therapy	Patient Population	Clinical Trial Data (if applicable)
Dato-DXd	TROP2	NCT05629585 (TROPION Breast03)	III	Durvalumab (anti–PD-1 antibody)	TNBC with residual disease after NAC	
		NCT03742102 (BEGONIA)	Ib/II	Durvalumab (anti–PD-1 antibody)	1L mTNBC	Phase I results: ORR: 74% (regardless of PD-L1 expression),[55] no DLTs Common AEs: Stomatitis, alopecia, no ILD/pneumonitis
Ladiratuzumab vedotin	LIV-1	NCT03310957 (KEYNOTE 721)	I/II	Pembrolizumab (anti–PD-1 antibody)	1L mTNBC; PD-L1 CPS <10	ORR (ITT): 35%[56] ORR (de novo): 69%
BDC-1001[a]	HER2	NCT04278144	I/II	Nivolumab (anti–PD-1 antibody)	HER2-expressing advanced solid tumors	DLTs, AEs, irAEs, MTD, ORR
EV	Nectin-4	NCT05524545 (ASPEN-07)	I	Evorpacept (CD-47 blocker)	UC after PD on previous platinum and checkpoint inhibitor	DLTs, AEs
		NCT05239624 (EV-ECLIPSE)	II	Pembrolizumab (anti–PD-1 antibody)	1L locally advanced or node-positive UC	pCR
		NCT04223856 (EV-302)	III	Pembrolizumab (anti–PD-1 antibody)	1L locally advanced/metastatic UC	PFS, OS
		NCT03924895 (EV-303)	III	Pembrolizumab (anti–PD-1 antibody) + cystectomy	Nonmetastatic muscle invasive bladder cancer eligible for radical cystectomy + pelvic LN dissection	EFS
		NCT04700124 (KEYNOTE-B15/EV-304)	III	Pembrolizumab (anti–PD-1 antibody)	Perioperative setting in muscle invasive bladder cancer	EFS
		NCT04960709 (VOLGA)	III	Durvalumab (anti–PD-1 antibody) and tremelimumab (anti-CTLA-4 antibody)	Muscle invasive bladder cancer suitable for neoadjuvant therapy	pCR, EFS
Disitamab vedotin	HER2	NCT05302284	III	Toripalimab (anti–PD-1 antibody)	HER2-expressing LA/metastatic UC	PFS, OS
ADC + anti-HER2 therapy combinations						
T-DM1	HER2	NCT03975647 (HER2CLIMB-02)	III	Tucatinib (HER2-specific TKI)	2L metastatic HER2+ MBC	
		NCT04457596 (CompassHER2 RD)	III	Tucatinib (HER2-specific TKI)	HER2+ BC with residual disease after NAC	
		NCT05372614	I/II	Neratinib (pan HER kinase inhibitor)	Solid tumors with HER2 alterations	
		NCT05388149	II	Neratinib (pan HER kinase inhibitor)	HER2+ BC receiving adjuvant T-DM1 (two to six cycles) with evidence of MRD	
T-DXd	HER2	NCT04538742 (DESTINY Breast-07)	Ib/II	Pertuzumab (anti-HER2 antibody)	1L metastatic HER2+ MBC	uORR[57] T-DXd (n = 23): 87% T-DXd + pertuzumab (n = 22): 82%
		NCT04784715 (DESTINY Breast-09)	III	Pertuzumab (anti-HER2 antibody)	1L metastatic HER2+ MBC	
		NCT04539938 (HER2CLIMB-04)	II	Tucatinib (HER2-specific TKI)	>2L HER2+ MBC	
ADC + PARP inhibitor combinations						
SG	TROP2	NCT04039230	I/II	Talazoparib (PARP inhibitor)	≥2L mTNBC	Continuous dosing (n = 7)[58]: four DLTs, ORR: 29% (2/7) Staggered dosing (n = 20): no DLTs; ORR: 45% (9/20)
Dato-DXd	TROP2	NCT04644068 (PETRA)	I/II	AZD5305 (PARP 1 inhibitor)	Advanced solid tumors including MBC	

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TABLE 4. Select Ongoing Trials With ADC Combinations (Continued)

ADC	ADC Target	Trial ID (name)	Phase	Combination Therapy	Patient Population	Clinical Trial Data (if applicable)
ADC + other targeted therapy combinations						
T-DXd	HER2	NCT04556773 (DESTINY Breast-08)	Ib/II	Capivasertib (AKT inhibitor)	1-2L metastatic HER2-low MBC	
				Anastrozole (NSAI)	1-2L metastatic HER2-low MBC	
				Fulvestrant (SERD)	1-2L metastatic HER2-low MBC	
		NCT04553770 (TALENT)	II	Anastrozole (NSAI)	Hormone receptor+/HER2-low (neoadjuvant setting)	
		NCT04704661 (DASH)	I	AZD6738 (ATR inhibitor)	Advanced solid tumors with HER2 expression	
SG	TROP2	NCT05143229 (ASSET)	I	Alpelisib (a specific PI3K inhibitor)	≥2L HER2– MBC	
		NCT05006794	I	GS9716 (Mcl-1 antagonist)	Advanced solid tumors including TNBC	
Patritumab deruxtecan	HER3	NCT05569811 (VALENTINE)	II	Endocrine therapy	High-risk hormone receptor+/HER2– BC neoadjuvant	
EV	Nectin 4	NCT04963153	I	Erdafitinib (FGFR inhibitor)	Metastatic UC with FGFR2/3 genetic alterations	

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; ATR, ataxia telangiectasia and Rad3-related; BC, breast cancer; CPS, combined positive score; CR, complete response; CTLA4, cytotoxic T-lymphocyte-associated protein 4; Dato-DX, datopotamab deruxtecan; DLT, dose-limiting toxicity; EFS, event-free survival; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; G, grade; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ILD, interstitial lung disease; irAE, immune-related adverse events; ISAC, immune-stimulating antibody conjugate; ITT, intent-to-treat; LA, locally advanced; LN, lymph node; MBC, metastatic breast cancer; Mcl-1, myeloid leukemia cell differentiation protein -1; mPFS, median progression-free survival; MRD, minimal residual disease; MTD, maximum tolerated dose; mTNBC, metastatic triple negative breast cancer; NAC, neoadjuvant chemotherapy; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PARP, poly ADP-ribose polymerase; pCR, pathologic complete response; PD, progressive disease; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PR, partial response; RP2D, recommended phase 2 dose; SAE, serious adverse event; SERD, selective estrogen receptor degrader; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; TLR, toll-like receptors; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen 2; UC, urothelial cancer; uORR, unconfirmed overall response rate.
[a]ISAC consisting of an anti-HER2 monoclonal antibody conjugated to a TLR 7/8 dual agonist.

RESISTANCE TO ADC THERAPY

The advent of ADCs for the treatment of metastatic cancers over the past decade has significantly improved outcomes across different solid tumors. Nevertheless, patients on these therapies eventually experience disease progression, likely because of resistance. As ADCs are a relatively new class of drugs in oncology, the mechanisms of resistance are not fully elucidated.

Resistance may be related to the components of ADCs including altered target cell surface expression or gene mutation, upregulation of drug efflux transporters to offset payload toxicity, changes in trafficking of the ADC and internalization rates, or simple payload resistance. Some of these are discussed below with the relevant preclinical and clinical findings.

Target Modulation

Target downregulation is a common resistance mechanism; for example, HER2 downregulation is well known to lead to T-DM1 resistance in HER2+ disease.[70,71] In a neoadjuvant trial of T-DM1 + pertuzumab in HER2+ BC, there was a significant association between HER2 heterogeneity (defined as HER2 positivity by FISH in 5%-50% of tumor cells or an area of tumor that tested HER2-negative in multiple core biopsies) and lack of pCR after dual HER2-targeted therapy; none of the patients with HER2 heterogeneity achieved a pCR, in contrast to a 55% pCR rate in patients without HER2 heterogeneous tumors.[72] On the other hand, T-DXd, a next-generation ADC, has significant activity in tumors classified as HER2-low, likely because of a prominent bystander activity. However, data from DAISY revealed that a high percentage of HER2 IHC 0 tumor cells and their spatial distribution relative to HER2+ cells negatively affected response to T-DXd.[73]

Although SG outperformed chemotherapy in low–TROP2 expression settings, patients with low expression had reduced response rates (22%) versus those with medium/high expression in tumors (39%-44%).[74] A three-case autopsy series from patients treated with SG also demonstrated that there was no TROP2 expression detected (mRNA and protein) in one patient who experienced rapid progression, suggesting primary resistance.[75]

Lack of access to the target antigen can also promote resistance to ADCs. The presence of the HER3 ligand neuregulin that promotes HER2-HER3 dimerization diminished

the efficacy of T-DM1 in vitro, and combining T-DM1 with pertuzumab alleviated this inhibitory effect.[76]

Drug Efflux Transporters and Defects in Internalization and Trafficking

Upregulation of genes encoding multidrug resistance proteins (MDR) that promote DM1 efflux have been reported in-T-DM1–resistant cell lines.[77,78] Inhibiting the activity of multidrug resistance–associated protein 1 (MRP1), MRP2 and MDR1 reversed the resistance to T-DM1.

T-DM1 is dependent on lysosomal trafficking for intracellular release of the cytotoxic payload. In T-DM1–resistant gastric cancer cells, trastuzumab-ADCs were internalized into caveolin-coated vesicles/endosomes instead of colocalizing to lysosomes.[79] This cell line was also cross-resistant to an auristatin-based ADC with a noncleavable maleimide linker because of its inability to degrade the antibody in the endosomes and enable payload release. This resistance could be overcome by replacing the linker with protease cleavable linker. Thus, the modular nature of the ADCs can be exploited to generate new ADCs by swapping individual components with different functional properties to bypass resistance.

Mutations That Affect Payload Sensitivity or Antigen Binding

Whole-exome sequencing of tumor tissue from pre-SG treatment and postprogression autopsy tumor lesions identified mutually exclusive somatic mutations in *TOP1* (gene encoding topoisomerase I) and *TACSTD2* (gene encoding TROP2) in distinct lesions from the same patient.[75] TOP1 is a target of the SN-38 payload, and the $TOP1^{E418K}$ mutation prevents binding of the payload to TOP1, leading to resistance. The $TACSTD2^{T256R}$ encodes a protein that alters TROP2 binding to the antibody in SG, leading to resistance to SG. Furthermore, the mutant protein is mislocalized from the plasma membrane to the cytosol. Whether these mutations will be a frequent source of resistance to SG in the clinic remains to be seen.

Thus, diverse and numerous mechanisms likely account for the observed resistance to current ADCs in clinical use. The sequential use of ADCs with distinct mechanisms of action may offer a solution to overcoming resistance, but strong clinical trial translational work will be required to guide optimal sequencing. In addition, combinations of ADCs with other anticancer therapies can also potentially evade resistance or even overcome resistance.

COMBINATIONS WITH ADCs

Anti-HER2 Therapies

Combination of anti-HER2 ADCs and other HER2 agents that target a different epitope or function of HER2 to further improve outcomes has been explored. Although preclinical data showed synergistic activity for the T-DM1 + pertuzumab combination,[76] this was not seen in the MARIANNE trial where the addition of pertuzumab to T-DM1 did not improve PFS (stratified HR, 0.91; 97.5% CI, 0.73 to 1.13).[80] In DESTINY Breast-07, T-DXd is being combined with pertuzumab, immunotherapy, endocrine therapy, and other targeted agents. Other ADCs currently under evaluation with HER2-targeting agents are listed in Table 4.

Immunotherapy Agents

The multifaceted mechanism of action of ADCs also includes the engagement of immune effector cells with the goal of eliciting antitumor immunity.[16] This may manifest itself as the ADCC effects of the tumor-specific antibody in the ADC and direct interaction of the ADC with immune cells to modify their function.[81] In a mouse model, T-DXd + anti–PD-1 antibody was more active than T-DXd alone, potentially because of increased T-cell activity and upregulated PD-L1 expression induced by T-DXd.[82] These data formed the basis for the randomized trial of T-DM1/placebo + atezolizumab in HER2+ MBC (KATE-2) and the phase 1 trial of T-DXd with nivolumab. Disappointingly, neither trial showed significant improvement in efficacy with the combination over HER2-ADC alone.[50,53] Results from trials with ICI in TNBC suggest that setting and the line of therapy are important in BC, and there are ongoing trials in earlier lines of therapy (Table 4). On the other hand, preliminary results from T-DXd + nivolumab in HER2-expressing advanced UC reported an ORR of 37% and a medium duration of response of 13.1 months.[83]

The cytotoxic activity of Topo I inhibitors like SN-38 (payload in SG) results in the release of tumor-associated antigens into the circulation, which may upregulate PD-L1 expression on tumors and further prime the antitumor immune response. Topo I inhibitors can also alter tumor immune landscape by reducing Tregs and augmenting MHC class I–mediated tumor antigen presentation.[84] Hence, the TROP2 ADCs are under clinical investigation in combination with ICIs in TNBC (Table 4).

A phase 1 trial of SG with EV is ongoing in advanced/metastatic UC that has progressed on previous ICI therapy (ClinicalTrials.gov identifier: NCT04724018).

PARP Inhibitors

ADCs with Topo I inhibitors may be synergistic with poly ADP-ribose polymerase (PARP) inhibitors since the latter block resolution of TOP1 cleavage complexes induced by Topo I inhibitors, thus exposing the inability of remaining pathways to repair DNA damage. Unfortunately, early clinical trials exploring combinations with standard Topo I inhibitors, such as irinotecan and topotecan, were hampered by dose-limiting myelosuppression.[85,86] Preclinical models that used a temporal separation of SG and PARPi treatment demonstrated

the synergy of the combination.[58] Subsequently, a phase 1b study in TNBC revealed that staggered dosing of SG with talazoparib was well tolerated without DLTs and resulted in preliminary clinical activity.[58] Translational studies in pre- and on-treatment biopsies confirmed target inhibition. Thus, utilization of alternate dosing schedules may permit the use of promising ADC drug combinations to enhance efficacy/overcome resistance while minimizing toxicities.

CONCLUSION

It is not an understatement that the use of ADCs is revolutionizing the treatment of solid tumors, especially HER2+ BC, delaying progression and prolonging survival in one of the most aggressive subtypes of the disease. These successes have encouraged the evaluation of ADCs across a spectrum of cancers expressing a variety of tumor antigens. Advances in linker chemistry, antibody technology, and the use of potent drugs have enabled targeting of tumors regardless of the level of antigen expression, thus extending the benefit of these agents to a broader pool of patients. However, the use of these novel ADCs is associated with unique toxicities and mandates vigilance and careful monitoring of patients and continuous education on mitigation strategies. A vital practical consideration is the appropriate sequencing of these different ADCs during the course of a patient's treatment, and there are a handful of ongoing trials addressing this issue.

Understanding the mechanisms of resistance to ADC therapy and overcoming them using combination strategies or new agents are imperative. Harnessing the power of the immune system to ADC development and generating molecules that target immune cells and other components of the TME are already underway. Probody drug conjugates, immune-stimulating antibody conjugates, engineered toxin bodies, radioligand conjugates, and so on comprise the new wave of molecules in clinical development, seeking to improve efficacy and circumvent the drawbacks with existing ADCs while maintaining an acceptable safety profile.

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Expanding the Benefit: Dabrafenib/Trametinib as Tissue-Agnostic Therapy for *BRAF* V600E–Positive Adult and Pediatric Solid Tumors

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Overview

The recent US Food and Drug Administration (FDA) approval of the dabrafenib/trametinib combination as a tissue-agnostic treatment for solid tumors with *BRAF* V600E mutation is the result of more than 20 years of extensive research into *BRAF* mutations in human cancer, the underlying biological mechanisms that drive *BRAF*-mediated tumor growth, and the clinical testing and refinement of selective RAF and MEK kinase inhibitors. Such approval marks a significant achievement in the field of oncology and represents a major step forward in our ability to treat cancer. Early evidence supported the use of dabrafenib/trametinib combination in melanoma, non–small-cell lung cancer, and anaplastic thyroid cancer. Furthermore, data from basket trials have demonstrated consistently good response rates in various tumors, including biliary tract cancer, low-grade glioma, high-grade glioma, hairy cell leukemia, and multiple other malignancies, which has been the basis for FDA approval of a tissue-agnostic indication in adult and pediatric patients with *BRAF* V600E–positive solid tumors. From a clinical standpoint, our review delves into the efficacy of the dabrafenib/trametinib combination for *BRAF* V600E–positive tumors: examining the underlying rationale for its use, evaluating the latest evidence on its potential benefits, and discussing the possible associated adverse effects and strategies to minimize their impact. Additionally, we explore potential resistance mechanisms and future landscape of BRAF-targeted therapies.

INTRODUCTION

Genome-driven precision oncology has revolutionized the landscape of management in multiple solid tumors. With the evolving advances in next-generation sequencing technologies, the molecular heterogeneity of cancers has become apparent. Advances also led to identifying several potentially actionable oncogenic driver mutations and developing drugs that can act on them, which ushered in the era of precision oncology.[1] One of the most promising therapeutic targets is the *BRAF* proto-oncogene. *BRAF* alterations, including *BRAF* V600E, are not uncommon in cancer and can lead to ligand-independent activation of the MAPK pathway.[2,3] This results in uncontrolled phosphorylation of downstream MEK and ERK, eventually leading to unregulated cell growth and differentiation as part of oncogenesis (Fig 1).[4-6] BRAF can be targeted by BRAF inhibitors, which results in the cessation of the aberrant activation signal. Downstream MEK can also be inhibited using targeted treatment options that have demonstrated clinical benefit in different patient populations.[7,8] Currently, three BRAF plus MEK combinations are approved by the US Food and Drug Administration (FDA) for treatment of melanoma harboring *BRAF* V600 mutations: vemurafenib/cobimetinib, dabrafenib/trametinib, and encorafenib/binimetinib. In addition, the dabrafenib/trametinib combination is approved for anaplastic thyroid cancer and non–small-cell lung cancer (NSCLC) with *BRAF* V600 mutations. More recently, the combination of the BRAF inhibitor, dabrafenib, and the MEK inhibitor, trametinib, has been approved for *BRAF* V600E–altered unresectable and metastatic solid tumors with the exception of colorectal cancer.[9] This approval for a tissue-agnostic indication was based on evidence from several adult and pediatric studies (ROAR basket trial, NCI-MATCH trial, and Study X2101), demonstrating efficacy in different tumor types.[10-17,75] From a clinical standpoint, our review delves into the efficacy of the dabrafenib/trametinib combination for *BRAF* V600E–positive solid tumors: examining the underlying rationale for its use, evaluating the latest evidence on its potential benefits, and discussing the possible associated adverse effects and strategies to minimize their impact. Additionally, we explore potential resistance mechanisms and future landscape of *BRAF*-targeted therapies.

RATIONALE BEHIND COMBINATION

Despite the efficacy of BRAF inhibition monotherapy (eg, vemurafenib, dabrafenib, and encorafenib), durable clinical benefit is limited, and most patients will eventually progress.[18,19] In addition, BRAF inhibitor

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PRACTICAL APPLICATIONS

- Combining the BRAF inhibitor, dabrafenib, and the MEK inhibitor, trametinib, has been practice changing in managing *BRAF* V600–mutated cancers.
- Early evidence supported using dabrafenib and trametinib in *BRAF* V600–positive melanoma and non–small-cell lung cancer. However, data from basket trials have demonstrated consistent responses in various tumors harboring *BRAF* V600 mutation, including anaplastic thyroid carcinoma, biliary tract cancer, hairy cell leukemia, low-grade glioma, high-grade glioma, and multiple other rare cancers.
- Dabrafenib and trametinib combination is currently approved for all solid tumors with *BRAF* V600E mutations, regardless of tissue of origin (except colorectal cancer).
- Understanding the adverse event profile of dabrafenib and trametinib and possible strategies to mitigate these toxicities is important.

monotherapy has been associated with paradoxical activation of the MAPK pathway, which has been linked to progression of cancer and various side effects, including the development of secondary skin cancers.[20,21] Therefore, a combination with MEK inhibitors was explored and has currently emerged as the standard of care.

The idea behind the combined targeting of different molecules in a cellular pathway is not new and has long been practiced at different levels.[22] The same concept applies to dual inhibition of upstream BRAF and downstream MEK, which can lead to a synergistic effect ending the aberrant oncogenic signal (Fig 1). Although the most feared issue with drug combinations is added toxicities, the toxicity profile shown with the dabrafenib and trametinib combination was quite manageable, and in some cases, the combination could even prevent BRAF inhibitor monotherapy-related complications. Even with a high proportion of patients experiencing any-grade toxicity, most are limited to grade 1 and grade 2 events, and even grade 3 events can resolve with appropriate management. So far, the combination of dabrafenib and trametinib has demonstrated good response rates in different tumor types harboring *BRAF* V600E (Fig 2), which was the basis for FDA drug approvals.

CURRENT INDICATIONS FOR DABRAFENIB AND TRAMETINIB

Currently, the FDA approves the use of dabrafenib and trametinib combination in patients with melanoma, NSCLC, anaplastic thyroid carcinoma, and low-grade glioma (pediatrics) who have *BRAF* V600E–mutated metastatic disease (also V600K in lung cancer, unresectable disease and early disease with nodal involvement in melanoma, and locally advanced disease in anaplastic thyroid carcinoma).

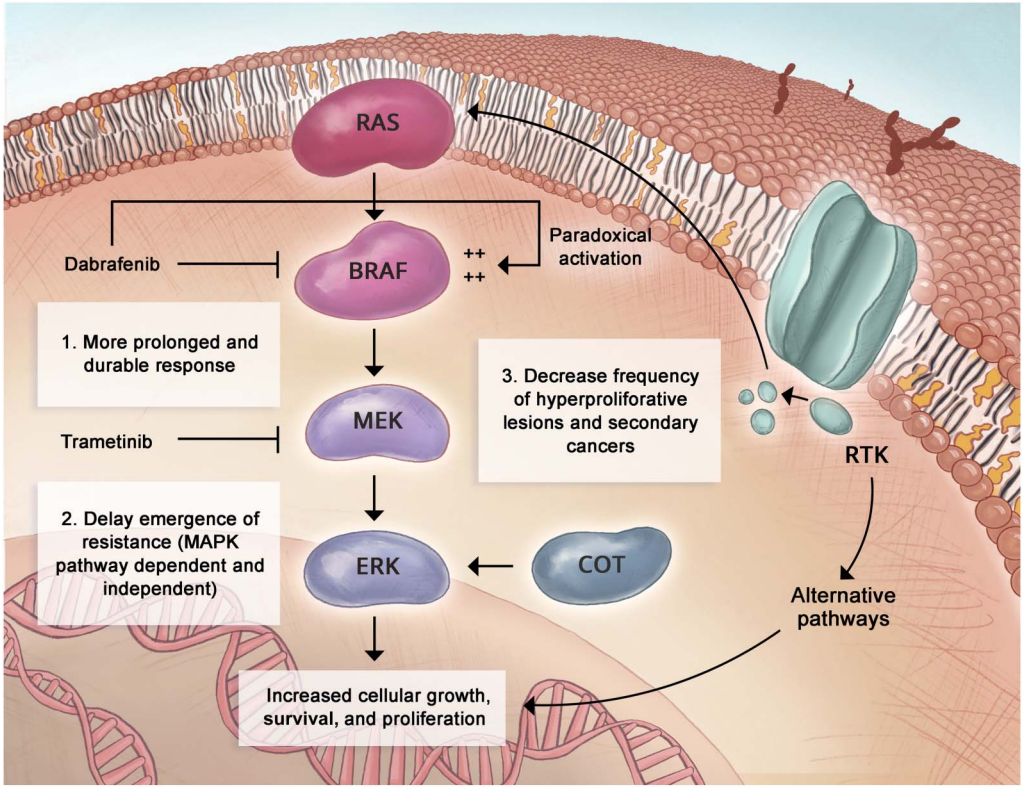

FIG 1. BRAF pathway and rationale for combination therapy. RAF isoforms, including BRAF, are activated through interaction between small G protein and N-terminal, which leads to phosphorylation of MEK and downstream ERK eventually resulting in cell survival. A serine/threonine protein kinase, COT/Tpl2, is indispensable for extracellular signal–regulated kinase (ERK) activation. Combination of BRAF inhibitor, dabrafenib, and MEK inhibitor, trametinib, leads to more prolonged and durable response, delays emergence of resistance, and decreases frequency of hyperproliferative lesions compared with monotherapy BRAF inhibition alone. MEK, mitogen-activated protein kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RTK, receptor tyrosine kinase.

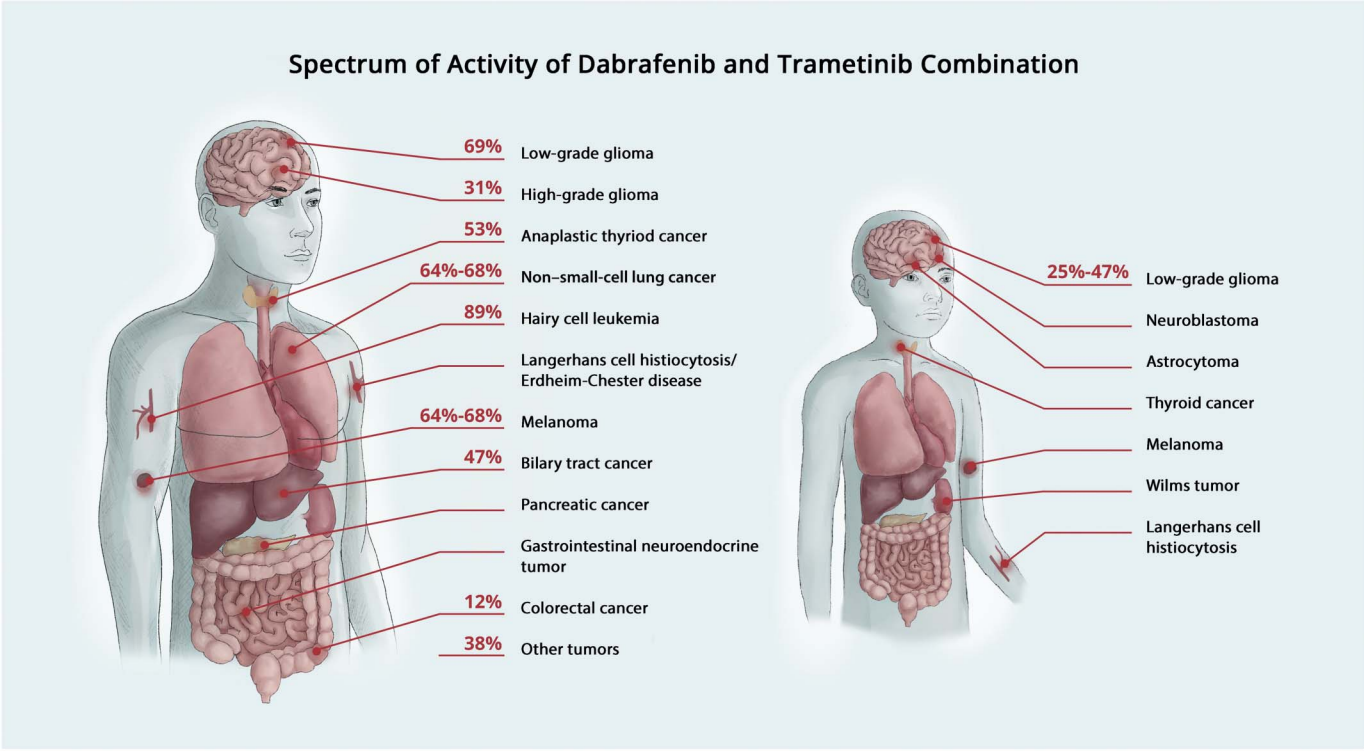

FIG 2. The depth and breadth of dabrafenib plus trametinib use in cancer. Response rates of dabrafenib plus trametinib from multiple clinical trials in different tumor types are shown. Other tumor types with anecdotal evidence of BRAF plus MEK inhibitor activity from a literature review are also shown.

In addition to these tissue-specific indications, the current FDA label also includes the treatment of adult and pediatric patients with unresectable or metastatic solid tumors who have *BRAF* V600E mutation in a tissue-agnostic indication (Table 1).[23]

Use in Melanoma

More than 50% of patients with malignant melanoma harbor *BRAF* oncogenic alterations (approximately half are V600E).[3,24,25] Evidence on the efficacy of dabrafenib and trametinib combination in patients with metastatic and unresectable melanoma is supported by data from three randomized controlled trials (COMBI-v, COMBI-d, and COMBI-MB; Table 2). The COMBI-v (ClinicalTrials.gov identifier: NCT01597908) was a phase III trial that randomly assigned patients with unresectable or metastatic V600E/K-altered melanoma to receive either the combination of dabrafenib and trametinib or vemurafenib monotherapy. The trial demonstrated improved progression-free survival (PFS) and overall survival (OS) in patients randomly

TABLE 1. Current US Food and Drug Administration Indications for the Dabrafenib and Trametinib Combination

Indication	Setting	Population	Alteration	Age	Approval Type
Melanoma	Advanced	Unresectable or metastatic disease	*BRAF* V600E or V600K	Not specified	Regular approval
Melanoma	Adjuvant	After complete resection in patients with nodal involvement	*BRAF* V600E or V600K	Not specified	Regular approval
NSCLC	Advanced	Metastatic disease	*BRAF* V600E	Not specified	Regular approval
Anaplastic thyroid carcinoma	Advanced	Locally advanced or metastatic disease and no satisfactory locoregional treatment options	*BRAF* V600E	Not specified	Regular approval
Low-grade glioma (pediatrics)	Advanced	Low-grade glioma that requires systemic therapy	*BRAF* V600E	≥1 year	Regular approval
All solid tumors	Advanced	Unresectable or metastatic disease after progression on previous treatment and no satisfactory alternative treatment options	*BRAF* V600E	Adult and pediatric patients 6 years and older	Accelerated approval

Abbreviation: NSCLC, non–small-cell lung cancer.

assigned to the combination arm compared with patients in the vemurafenib arm (median, 11.4 months *v* 7.3 months for PFS; and median, not reached *v* 17.2 months for OS). The objective response rate (ORR) was also higher in the combination group compared with the vemurafenib group (64% *v* 51%).[26] Another phase III trial (COMBI-d; ClinicalTrials.gov identifier: NCT01584648) randomly assigned patients with unresectable or metastatic V600E/K-altered melanoma to receive either the combination of dabrafenib and trametinib or dabrafenib plus placebo. Results showed longer PFS (median, 9.3 months *v* 8.8 months) and higher ORR (68% *v* 55%), although the median OS was not reached in both groups.[27,28] Both trials reported a lower incidence of secondary skin cancer in the combination group.[26-28] The third trial (COMBI-MB; ClinicalTrials.gov identifier: NCT02039947) was a phase II trial that included patients with metastatic melanoma to the brain and *BRAF* V600 mutations. Four cohorts were included in this trial: Cohorts A and B included patients with V600E mutation and asymptomatic brain disease that was subject (cohort B) or not subject (cohort A) to previous local therapy. Cohort C included patients with other *BRAF* mutations (V600D/K/R) and asymptomatic brain disease that was not previously treated. Cohort D included patients with brain disease irrespective of mutation type or local therapy. Responses were seen across different cohorts (lowest in cohort C and highest in cohort D), and the side effect profile was tolerable.[29]

Use in the adjuvant setting is supported by evidence from the phase III randomized controlled trial (COMBI-AD; ClinicalTrials.gov identifier: NCT01682083), which compared the use of the combination with placebo in patients with stage 3 *BRAF* V600E/K-altered melanoma after curative intent surgery. Data from this trial showed a lower risk of recurrence in patients in the combination arm compared with patients who received placebo (37% *v* 57%). The median recurrence-free survival was not reached in the combination arm and was 16.6 months in the placebo arm, and OS was not reached in both groups.[30]

Use in Non–Small-Cell Lung Cancer

BRAF mutations are present in nearly 1%-5% of patients with NSCLC (including 50% *BRAF* V600).[3,31] Evidence supporting the use of dabrafenib and trametinib combination in lung cancer stems from the phase II trial BRF113928 (ClinicalTrials.gov identifier: NCT01336634; Table 2). In this study, patients with pretreated metastatic NSCLC who harbored *BRAF* V600E mutation received either dabrafenib monotherapy (cohort A) or dabrafenib and trametinib combination (cohort B). In the same trial, a treatment-naïve patient cohort was included (cohort C) and received dabrafenib and trametinib combination. The ORR was 64%, 68%, and 33% in cohorts C, B, and A, respectively, demonstrating a favorability of the combination in treatment-naïve and pretreated patients. PFS was also higher in cohorts B and C (median, 10.2 months and 10.8 months) compared with cohort A (median, 5.5 months), and so was OS (median, 17.3 months, 18.2 months, and 12.6 months in cohorts C, B, and A, respectively). With a tolerable safety profile, this trial established the efficacy of the combination in NSCLC, which led to its FDA approval.[32-35]

Use in Anaplastic Thyroid Carcinoma

BRAF mutations are estimated to be present in 20%-50% of patients with anaplastic thyroid carcinoma.[36-39] Evidence of combination efficacy in anaplastic thyroid carcinoma came from the Rare Oncology Agnostic Research (ROAR) trial (BRF117019; ClinicalTrials.gov identifier: NCT02034110). ROAR was a basket trial that explored the use of dabrafenib/trametinib combination in multiple tumor types (Table 2).[10-14,75] FDA approval was based on an ORR of 61% in 23 patients with anaplastic thyroid carcinoma who were evaluable for response at the time of initial data cutoff. The complete and partial response rates were 4% and 57%, respectively. The response duration was at least 6 months in 64% of responding patients.[40] These data were very promising, considering the poor prognosis of anaplastic thyroid cancer. Recently, an updated analysis that included the full enrollment of 36 patients and around 4 years of additional study follow-up showed that investigator-assessed responses were observed in 56% of patients, with 50% of responders still in response at 12 months. The median OS was 15 months, with the 12-month OS rate of 52% being notable given the historic median OS of <6 months. This updated analysis confirmed the definitive benefit of dabrafenib plus trametinib in anaplastic thyroid carcinoma at long-term follow-up.[10,11]

Use in Biliary Tract Cancer

Around 5%-7% of patients with biliary tract cancer harbor *BRAF* alterations.[41,42] In 43 patients included in the ROAR trial with *BRAF* V600E–mutated biliary tract cancer (Table 2), there were very promising results in the form of a response rate of 47% (investigator-assessed response rate, 51%). Besides, 35% had a stable disease, which expands the proportion of patients who derived clinical benefit to 81%. The median duration of response was 9 months; with nearly 59% of responding patients having ongoing responses beyond 6 months, and 9% with ongoing responses at data cutoff.[13]

Use in Glioma

BRAF V600 mutations are present in nearly 5%-15% of patients with low-grade glioma and 3% of patients with glioblastoma.[3,43] In the ROAR trial, 45 patients with high-grade glioma (including 31 with glioblastoma) and 13 with low-grade glioma were included (Table 2). The ORR reported by the independent review committee was 31% and 69% in patients with high-grade and low-grade glioma, respectively. Interestingly, complete responses were seen in

TABLE 2. Summary of Clinical Trials of Dabrafenib (D) Plus Trametinib (T)

		PFS (mo)		OS (mo)		ORR	
Trial	**Disease/Cohort**	**Intervention**	**Control (if available)**	**Intervention**	**Control (if available)**	**Intervention**	**Control (if available)**
COMBI-d	Advanced melanoma	D plus T	D plus placebo	D plus T	D plus placebo	D plus T	D plus placebo
		9.3	8.8	NR	NR	68%	55%
COMBI-v	Advanced melanoma	D plus T	Vemurafenib	D plus T	Vemurafenib	D plus T	Vemurafenib
		11.4	7.3	NR	17.2	64%	51%
COMBI-MB	Melanoma with brain metastasis	D plus T		D plus T		D plus T	
	Cohort A[a]	5.6		10.8		58%	
	Cohort B[b]	7.2		24.3		56%	
	Cohort C[c]	4.2		10.1		44%	
	Cohort D[d]	5.5		11.5		65%	
COMBI-AD	Stage III melanoma (adjuvant)	D plus T	Placebo	D plus T	Placebo	D plus T	Placebo
		NR	16.6	NR	NR	37%[e]	57%[e]
Study BRF113928	Metastatic NSCLC[f]	D plus T		D plus T		D plus T	
	Cohort B[g]	10.2		18.2		68%	
	Cohort C[h]	10.8		17.3		64%	
ROAR trial	Multiple cancers	D plus T		D plus T		D plus T	
	ATC	5.5		14.5		53%	
	BTC	9		14		47%	
	LGG	14		NR		69%	
	HGG	4.5		17.6		31%	
	HCL	NR		NR		89%	
NCI-MATCH	Multiple cancers	D plus T		D plus T		D plus T	
		11.4		28.6		38%[i]	
Study X2101	Pediatrics	D plus T		D plus T		D plus T	
	LGG cohort	36.9				25%	

Abbreviations: ATC, anaplastic thyroid carcinoma; BTC, biliary tract cancer; D, dabrafenib; HCL, hairy cell leukemia; HGG, high-grade glioma; LGG, low-grade glioma; NR, no response; NSCLC, non–small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T, trametinib.

[a]Asymptomatic patients with *BRAF* V600E mutation who had no previous local brain therapy.

[b]Asymptomatic patients with *BRAF* V600E mutation who had previous local therapy.

[c]Asymptomatic patients with *BRAF* V600D/K/R mutations who had no previous local brain therapy.

[d]Symptomatic disease regardless of local therapy or mutation subtype.

[e]Recurrence rate.

[f]Cohort A received dabrafenib monotherapy.

[g]Previously treated.

[h]Treatment naïve.

[i]Responses seen in seven different tumor types.

three patients with high-grade glioma and one with low-grade glioma. In a post hoc analysis of the high-grade glioma cohort, ORR increased to 50% in patients age 18-39 years with a median PFS of 18.5 months and median OS of 45.2 months, which showed the relatively better clinical benefit in the adolescent and young adult population who conventionally have poor outcomes than the pediatric or older adult population. The median duration of response was 13.6 months in patients with high-grade glioma, and the median PFS was 4.5 months. In low-grade glioma, the median duration of response was 27.5 months, and the median PFS was not reached. The median OS was 17.6 months and not reached in the high-grade and low-grade cohorts, respectively.[14]

In the pediatric patient population, data supportive of using dabrafenib plus trametinib were demonstrated in the TADPOLE trial (Study CDRB436G2201; ClinicalTrials.gov identifier: NCT02684058).[23] The phase II/III randomized trial included pediatric patients with high-grade glioma and low-grade glioma who require systemic therapy. Compared with patients in the control arm who received carboplatin plus vincristine in the low-grade glioma cohort (n = 37), patients on dabrafenib plus trametinib (n = 73) showed higher ORR (46.6% *v* 10.8%) and longer median PFS (20.1 months *v* 7.4). On the basis of these promising results, FDA recently approved dabrafenib plus trametinib for treatment of pediatric patients with low-grade glioma who require systemic therapy.[23,44] This marks the first FDA approval of a systemic treatment for first-line therapy of children diagnosed with low-grade glioma harboring a *BRAF* V600E mutation. Additionally, the FDA granted approval for novel oral formulations of both medications that are appropriate for patients with difficulty in swallowing pills.[45] Similar to the TADPOLE trial, Study X2101 in the pediatric patient population (ClinicalTrials.gov identifier: NCT02124772) evaluated trametinib alone or in combination with dabrafenib in pediatric patients with *BRAF* V600–mutated solid tumors including low-grade glioma (Table 2). The multicenter, open-label, multicohort trial recruited pediatric patients with refractory or recurrent solid tumors. Encouraging data were reported in patients with low-grade glioma (n = 47) who received combination therapy, where a response rate of 25% was seen with a median PFS of 36.9 months.[9,16,17]

Use in *BRAF* V600E Mutation–Positive Unresectable or Metastatic Solid Tumors

Data on dabrafenib/trametinib combination efficacy in other tumor types originated from three basket trials (ROAR, NCI-MATCH, and Study X2101) that included a heterogeneous group of patients with multiple cancer diagnoses.[9,15-17,23] The ROAR trial (BRF117019 study; ClinicalTrials.gov identifier: NCT02034110) included adult patients with *BRAF* V600E mutation–positive tumors, such as high-grade glioma, low-grade glioma, biliary tract cancer, adenocarcinoma of the small intestine, GI stromal tumor, and anaplastic thyroid cancer. Arm H of the NCI-MATCH study (EAY131-H; ClinicalTrials.gov identifier: NCT02465060) included patients with *BRAF* V600E–mutated tumors, excluding melanoma, thyroid, and colorectal cancer. The study enrolled adult patients with various types of solid tumors, such as gastrointestinal tumors, lung tumors, gynecologic or peritoneal tumors, CNS tumors, and ameloblastoma of the mandible. In a pooled analysis of 131 patients with multiple tumor types specified in ROAR and NCI-MATCH (90% pretreated), responses were seen in multiple tumor types (Table 3).[15,23] Study X2101 reported promising data in pediatric patients with low-grade glioma while results from other cohorts are still awaited.[9,16,17]

Data in Hematological Malignancies and Histiocytic Neoplasms

Beyond solid tumors, *BRAF* alterations (primarily V600E) are observed in more than 90% of patients with hairy cell leukemia.[14,46] Data from ROAR also supported the use of the dabrafenib/trametinib combination in this patient population (Table 2). In 55 patients with *BRAF* V600E–mutated hairy cell leukemia, the investigator-assessed ORR was 89%.

TABLE 3. Pooled Data From ROAR and NCI-MATCH Expanding the Benefit of Dabrafenib/Trametinib for *BRAF* V600E Solid Tumors

Diagnosis	No.	ORR (%)	Duration of Response (mo)
Biliary tract cancer	48	46	1.8
High-grade glioma	48	33	3.9
Glioblastoma	32	25	3.9
Anaplastic pleomorphic xanthoastrocytoma	6	67	6
Anaplastic astrocytoma	5	20	15
Astroblastoma	2	100	15
Undifferentiated	1	100	6
Anaplastic ganglioglioma	1	0	NA
Anaplastic oligodendroglioma	1	0	NA
Low-grade glioma	14	50	6
Astrocytoma	4	50	7
Ganglioglioma	4	50	6
Pleomorphic xanthoastrocytoma	2	50	6
Pilocytic astrocytoma	2	0	NA
Choroid plexus papilloma	1	100	29
Gangliocytoma/ganglioglioma	1	100	18
Low-grade serous ovarian carcinoma	5	80	12
Adenocarcinoma small intestine	4	50	7
Adenocarcinoma pancreas	3	0	NA
Mixed ductal/adenoneuroendocrine carcinoma	2	0	NA
Neuroendocrine carcinoma of the colon	2	0	NA
Ameloblastoma of the mandible	1	100	30
Combined small-cell squamous carcinoma of the lung	1	100	5
Mucinous papillary serous adenocarcinoma of the peritoneum	1	100	8
Adenocarcinoma of the anus	1	0	NA
GIST	1	0	NA

Abbreviations: GIST, GI stromal tumor; NA, not available; ORR, objective response rate.

Responding patients remained event-free for at least 24 months. Complete remission was reported in 65.5% of patients (including nine patients with no minimal residual disease).[14] In addition to hairy cell leukemia, dabrafenib is listed in National Comprehensive Cancer Network guidelines for Erdheim-Chester disease or Langerhans cell histiocytosis harboring *BRAF* V600 mutation, and trametinib is listed for patients with MAP kinase pathway mutations, no detectable mutation, or no available testing. The combination has been reported anecdotally in a case that demonstrated a sustained response in a patient with *BRAF* V600E–positive Langerhans cell histiocytosis.[47,48]

FDA TISSUE-AGNOSTIC APPROVAL AND BEYOND

On the basis of these data showing efficacy in more than 20 tumor types, dabrafenib plus trametinib was indicated as combination in adult and pediatric patients with advanced solid tumors that harbor *BRAF* V600E mutation.[9,23,49] The exception is patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition by activation of the EGFR pathway.[23,50] Hence, adding EGFR monoclonal antibodies to BRAF/MEK combination has shown salutary effects. For example, encorafenib in combination with cetuximab is currently approved for colorectal cancer harboring *BRAF* V600 alteration.[51] Interestingly, recent data have also shown that the BRAF plus MEK combination might still be effective in patients with colorectal cancer by adding with a third therapeutic drug other than an EGFR pathway inhibitor. For example, a recent phase II trial (ClinicalTrials.gov identifier: NCT03668431) provided evidence on the efficacy of dabrafenib/trametinib combination when an anti–PD-1 antibody (spartalizumab) was added, leading to a confirmed response rate of 24.3%.[52]

DRUG ADMINISTRATION AND DOSAGE

Adults

The recommended doses of dabrafenib and trametinib are 150 mg (twice daily) and 2 mg (once daily). Both drugs should be given at least 1 hour before or 2 hours after the last meal.[23,50]

Pediatrics

The recommended doses of dabrafenib and trametinib should be based on body weight. The dose would be 75 mg/1 mg, 100 mg/1.5 mg, and 150 mg/2 mg in patients with a weight of 26-37 kg, 38-50 kg, and ≥51 kg, respectively. The drugs should be given orally twice daily for dabrafenib and once daily for trametinib.[23,50]

Oral Suspension

The recommended dosage for dabrafenib tablets for oral suspension is based on body weight ranging from 20 mg twice daily for a patient weighing 8-9 kg to 150 mg twice daily for patients >51 kg. The recommended dosage for trametinib for oral solution is based on body weight ranging from 6 mL (0.3 mg once daily) for a patient with

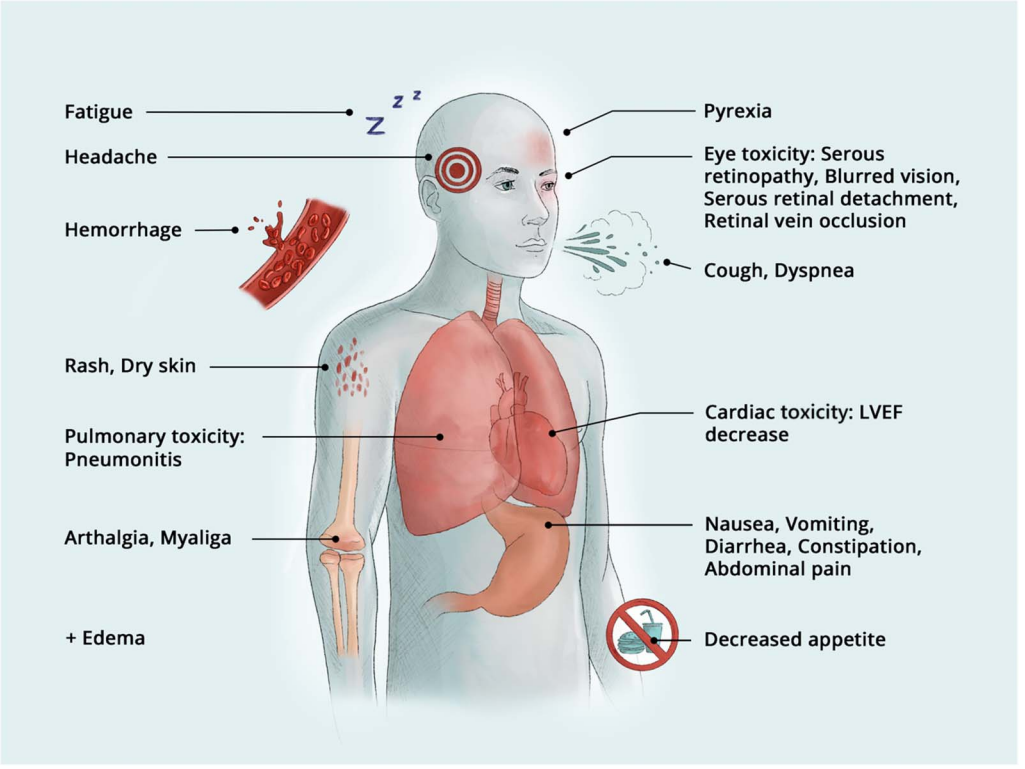

FIG 3. Common side effects of dabrafenib and trametinib. LVEF, left ventricular ejection fraction.

TABLE 4. Management of Select Adverse Events in Patients Receiving D Plus T[6,23,50,55]

Side Effect	General Management	D Plus T Use
Pyrexia	Use antipyretics (eg, acetaminophen) as appropriate A limited burst of corticosteroids may be used after 3 days (eg, prednisone 10 mg once daily for 5 days) No recommended sepsis routine workup unless localizing symptoms or other symptoms suggestive of infection exist	100.4-104°F (38-40°C) Withhold D plus T until fever resolves. Resume at same or lower dose >105°F (40.5°C) OR pyrexia complicated by rigors, hypotension, dehydration, or renal failure Withhold D plus T until fever resolves for at least 24 hours Resume at lower dose or permanently discontinue
Skin toxicities (including rash, photosensitivity, and secondary skin cancers)	Use emollients, antihistamines, and analgesics to alleviate symptoms A short course of corticosteroids may be tried in patients with persistent symptoms Dermatologic consultation before and during therapy may be helpful. Any suspicious lesions should be removed and evaluated Patient education about photosensitivity reactions. Use sunblock with high sun protection factor and UV protective clothing. Avoid UV-A exposure if possible	Intolerable grade 2 OR grade 3-4 Withhold D plus T for up to 3 weeks. Resume at lower dose If not improved, permanently discontinue Severe cutaneous adverse reactions Permanently discontinue
Noncutaneous RAS mutation–positive new primary		Permanently discontinue D
Cardiomyopathy	Assess LVEF before starting D plus T and reassess 1 month after starting therapy and regularly each 2-3 months thereafter	Asymptomatic ≥10% decrease in LVEF Withhold T for 4 weeks Resume at lower dose If not improved, permanently discontinue Symptomatic cardiomyopathy OR decrease >20% from baseline Permanently discontinue T Withhold D. Resume at lower dose. If not improved, permanently discontinue
Elevated liver enzymes	Measure liver enzymes before starting therapy and monthly afterward	Persistent or recurrent grade 2 (and any grade ≥3) events. Withhold D plus T Resume at lower dose OR same dose If not improved, permanently discontinue
Ocular toxicities	Active surveillance including ophthalmologic consultation while on therapy Patient education and instruction to promptly report any abnormal visual manifestations Some ocular toxicities (eg, iritis and uveitis) may benefit from local steroids and mydriatic eye drops	RPED Withhold T for 3 weeks Resume at lower dose If not improved, permanently discontinue or resume at lower dose Uveitis, including iritis and iridocyclitis Withhold D for up to 6 weeks If improved to grade 0-1, resume at same or lower dose If not improved, permanently discontinue RVO Permanently discontinue T
Hemorrhage	Manage hemorrhagic events with supportive care including blood transfusion as appropriate	Grade 3 Withhold T Resume at lower dose If not improved, permanently discontinue Grade 4 Permanently discontinue T
Venous thromboembolism	Provide supportive care as appropriate	Uncomplicated Withhold T for 3 weeks Resume at lower dose If not improved, permanently discontinue Life-threatening Permanently discontinue T
Interstitial lung disease	Active surveillance including consultation with pulmonologist as appropriate Patient education and instruction to promptly report any pulmonary manifestations	Permanently discontinue

Abbreviations: D, dabrafenib; LVEF, left ventricular ejection fraction; RPED, retinal pigment epithelial detachments; RVO, retinal vein occlusion; T, trametinib.

8 kg to 40 mL (2 mg once daily) for a patient over 51 kg.[23]

SIDE EFFECTS AND MANAGEMENT OF ADVERSE EVENTS

The combination of dabrafenib and trametinib can lead to high rates of adverse events, given the added toxicity of each drug. In a recent meta-analysis, the incidence of any grade toxicity was 95%, with 43% of patients having grade 3 or higher events. Dose reductions were reported in 28% of patients, and toxicities led to treatment discontinuation in 24% of participants.[53] The most common adverse events are pyrexia, chills, fatigue, rash, dry skin, headache, arthralgia, myalgia, cough, dyspnea, nausea, vomiting, diarrhea, constipation, abdominal pain, decreased appetite, edema, hemorrhage, and paronychia (in pediatrics; Fig 3).[23,50] Evidence shows that those side effects, and corresponding dose reductions or interruptions, become less frequent after 6 months of treatment,[54] which highlights the importance of understanding possible management strategies that would prevent treatment cessation because of toxicity (Table 4). Managing adverse effects can be quite challenging, given the overlapping profile of possible toxicities. However, the general rule of thumb is to try to prevent those toxicities, and if they happen to try to resume with dose reductions after toxicities resolve unless they are serious enough, which would warrant treatment discontinuation (Fig 4).

RESISTANCE MECHANISMS

After initial response to BRAF/MEK inhibition, some patients will eventually develop secondary resistance which can be driven by MAPK pathway–dependent or MAPK pathway–independent alterations. For example, *NRAS* mutations can lead to upstream activation of BRAF and paradoxical activation of MAPK pathway via CRAF dimerization. Some non-*BRAF* V600 alterations, for example, *BRAF* fusions, have been also linked to BRAF inhibitor resistance by escaping selective inhibition. Other pathway alterations in *MEK*, *ERK*, and *COT* have been shown to contribute to the possible resistance to BRAF inhibitors. MAPK-independent resistance can originate from overexpression or upregulation of receptor tyrosine kinases and upregulated PI3K/AKT pathway.[56,57] Apart from MAPK-mediated resistance, various other resistance mechanisms such as CRAF, ARAF, MET, and the P13K/AKT/mTOR pathway exist, among other intricate pathways. The VEM-PLUS study analysis to investigate the effectiveness and safety of vemurafenib monotherapy and its combination with targeted therapies (sorafenib, crizotinib, or everolimus) or carboplatin plus paclitaxel in treating advanced solid tumors with *BRAF V600* mutations revealed no significant differences in the duration of OS or PFS between vemurafenib monotherapy and combination treatments.[58] This shows that combining BRAF inhibitors with other agents (beyond BRAF plus MEK) may be quite challenging.

BEYOND DABRAFENIB PLUS TRAMETINIB IN ADVANCED SETTING

Although current evidence supports the use of dabrafenib plus trametinib in patients with advanced cancers, more data on use in other disease settings are currently awaited. For example, there is at least some evidence from the COMBI-AD trial (ClinicalTrials.gov identifier: NCT01682083) to suggest a survival benefit in patients with melanoma in the adjuvant setting.[30] Moreover, there are data in the neoadjuvant setting from the NeoCombi trial (ClinicalTrials.gov identifier: NCT01972347) demonstrating complete responses in nearly half of included patients.[59] Use in anaplastic thyroid carcinoma is currently also tested in the neoadjuvant setting in the ANAPLASTIC-NEO study (ClinicalTrials.gov identifier: NCT04739566).[60] Triplet combinations with immunotherapy have been tested and provided evidence on the efficacy of dabrafenib/trametinib/anti–PD-1 combinations in colorectal cancer.[52,61] Other disease indications and other triplet combinations, for example, with anti-EGFR, are also being explored in clinical trials.[57] Aside from dabrafenib/trametinib, other combinations for BRAF/MEK inhibitors are also being explored in the same context.[2]

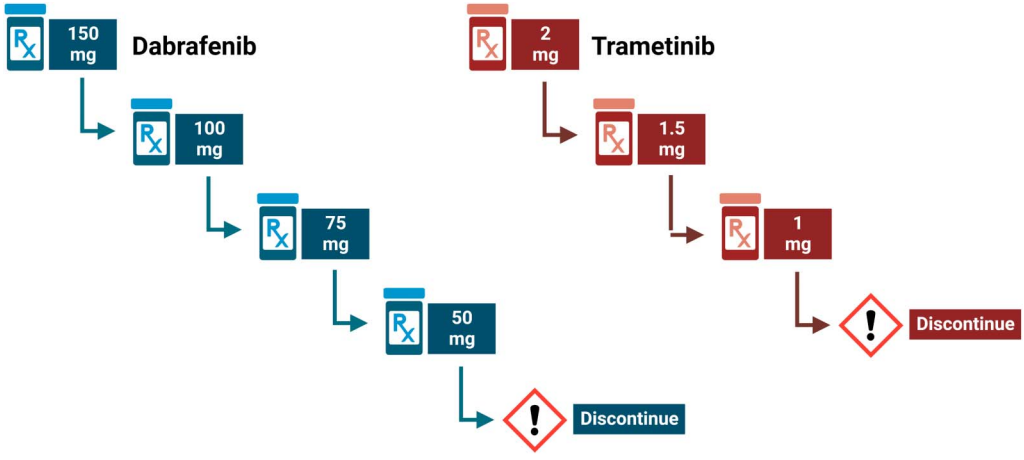

FIG 4. Dose reductions in dabrafenib and trametinib.

For example, vemurafenib plus cobimetinib is currently approved in patients with advanced melanoma on the basis of data from the coBRIM trial (ClinicalTrials.gov identifier: NCT01689519).[62-64] Similarly, encorafenib plus binimetinib is currently approved in patients with advanced melanoma on the basis of data from the COLUMBUS trial (ClinicalTrials.gov identifier: NCT01909453).[65-67] In addition to those combinations, more novel drugs are being explored in therapeutic drug development field as well. Those include novel brain penetrant BRAF inhibitors, BRAF paradox breakers, BRAF dimer inhibitors using an allosteric site, BRAF selective degraders, and mutant-selective degradation by BRAF-targeting proteolysis targeting chimeras (PROTACS).[2,68-74]

CONCLUSIONS

Dabrafenib and trametinib combination has transformed clinical care in *BRAF* V600E–altered cancers by providing an additional option for biomarker-driven therapy in patients with multiple tumor types, especially rare cancers. *BRAF* V600E alterations across solid tumors add to the tissue agnostic precision medicine list of targetable alterations that include neurotrophic tyrosine receptor kinase (NTRK) fusion, microsatellite instability-high phenotype, high tumor mutational burden (≥10 mutations/megabase), and rearranged during transfection (RET) fusions. Evidence supporting the efficacy of dabrafenib/trametinib is substantial in multiple tumor types, including melanoma, NSCLC, anaplastic thyroid cancer, biliary tract cancer, high-grade glioma, low-grade glioma, pediatric cancers, and other tumor types. To ensure that patients with *BRAF* V600E solid tumors who could potentially benefit from dabrafenib plus trametinib are identified, it will be essential to identify these alterations by comprehensive genomic testing.

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Equitable Access to Clinical Trials: How Do We Achieve It?

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overview

The mismatch between the study populations participating in oncology clinical trials and the composition of the targeted cancer population requires urgent amelioration. Regulatory requirements can mandate that trial sponsors enroll diverse study populations and ensure that regulatory revue prioritizes equity and inclusivity. A variety of projects directed at increasing accrual of underserved populations to oncology clinical trials emphasize best practices: broadened eligibility requirements for trials, simplification of trial procedures, community outreach through patient navigators, decentralization of clinical trial procedures and institution of telehealth, and funding to offset costs of travel and lodging. Substantial improvement will require major changes in culture in the educational and professional practice, research, and regulatory communities and will require major increases in public, corporate, and philanthropic funding.

Clinical trials are pivotal for testing novel drugs and establishing new standard-of-care treatments for patients with cancer. The advent of immunotherapy and cellular therapy and the broad use of sequencing techniques allowing the identification of subpopulations more likely to respond to targeted agents have led to an impressive change in the oncology treatment landscape[1] and a decrease in cancer-related mortality.[2] However, there is a noticeable mismatch between populations participating in trials and real-world oncology patients.[3] Data generalizability is jeopardized by the unequal representation of certain groups (ie, racial minorities, elderly, females, patients living in rural areas, and patients with comorbidities, such as HIV, hepatitis, autoimmune disorders, cirrhosis, and renal dysfunction). Thus, the effectiveness of drugs for groups under-represented in pivotal oncology trials is either extrapolated or assessed retrospectively using institutional cohorts or national databases, which is limited by biases and incomplete information.[4-7] Similarly, unequal participation in early-phase cancer clinical trials affects the effective delivery of potentially efficacious investigational therapies to patients with cancer without other available treatment options.[8-14]

Previous reports have extensively summarized barriers affecting access to clinical trials at the patient level (distrust, unawareness, financial status, geography, social support, and logistics issues), provider level (lack of awareness, lack of research workforce, innate bias), study level (restrictive inclusion criteria, complex processes with multiple study visits), and institutional level (deficient screening and trial matching, lack of periodic institutional self-assessments).[15] Equitable access to participation in oncology clinical trials is a crucial step to improve health equity through access to care.[16] Consequently, efforts have focused on identifying and developing tools, resources, and programs to overcome some of these barriers.[17] However, as we face a high-priority, public health problem, there is an urgent need to implement interventions with nationwide outreach. This review focuses on projects and interventions aimed at increasing diversity in the access to cancer clinical trials at regional and national levels.

DIVERSITY IN CANCER CLINICAL TRIALS—US FOOD AND DRUG ADMINISTRATION ONCOLOGY CENTER OF EXCELLENCE PROJECT EQUITY

The US Food and Drug Administration (FDA) has had a long-standing policy recommending that clinical trial sponsors implement measures that help enroll members of historically under-represented populations on the basis of demographic and clinical characteristics.[18-21] Drugs should be evaluated in populations for which they are intended to be used in clinical practice once approved. Enrolling diverse study populations in clinical trials, in a representative fashion, helps improve study results generalizability. In addition, it allows members of all populations to contribute to scientific and clinical discoveries related to the drug under investigation and the disease under study and offers the opportunity for early access to potentially efficacious investigational therapies. A clinical trial may provide the best patient care option for those with serious or life-threatening diseases like

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PRACTICE APPLICATIONS

- Study populations for cancer clinical trials do not match the composition of targeted populations for cancer therapies.
- A variety of changes to clinical trial requirements can improve the accrual of patients from underserved populations to cancer clinical trials.
- Linguistic and culturally appropriate patient navigators and simplification of clinical trial procedures, including the use of telehealth, constitute best practices to increase diversity in clinical trial accrual.
- Increased equity and diversity in cancer clinical trials will require substantial changes in oncology culture and will require major investment in appropriate personnel and education.

cancer, many of whom do not have effective approved therapies. Thus, the FDA Oncology Center of Excellence launched Project Equity,[22] a public health initiative aimed at addressing disparities in cancer trials intended to support marketing applications.

Racial and ethnic minorities and older adults have historically been under-represented in cancer research, including clinical trials submitted to the FDA as part of oncology drug development and approval.[11,23,24] The many barriers to clinical trial participation include failure to invite members of racial and ethnic minority populations and older adults to participate in clinical trials, because of bias, socioeconomic factors, and other factors.[25] Gender identity information is not currently routinely collected in cancer trials submitted to the FDA[26]; thus, the extent to which sexual and gender minority patients with cancer are enrolled in oncology clinical trials remains unknown. Geographic location may also be a significant barrier to clinical trial access particularly for those who reside in rural parts of the country and patients living in health professional shortage areas lacking access to large cancer centers.[27,28] In the United States, a study reported that 38%-52% of patients with commonly diagnosed cancer types have commute times longer than an hour to participate in clinical trials, with longer travel times for those residing in Central United States.[28] Geographic accessibility disproportionally affects racial minority groups, with lower rates of clinical trial participation among Black patients living in rural than urban areas.[27] Improving clinical trial accessibility in rural areas is crucial as worse clinical outcomes of patients living in rural areas compared with urban areas dissipate when disparities in access to clinical trials are uniform.[27]

Consequently, the evidence base generated to support the safe and effective use of medical products might have limited external validity, particularly when certain clinical characteristics occur more commonly in the excluded populations. In addition to missing an opportunity to learn about drug effects in a population more reflective of the diversity of patients likely to use the approved drug, the lack of participant diversity can also curtail collection of data that could provide insight on how the disease manifests across the population. Project Equity aims to facilitate improvement in the clinical trial participation rates by focusing on historically under-represented populations in oncology trials on the basis of demographic characteristics, such as race, ethnicity, sex, age, gender, and geographic location.

Project Equity objectives are met through three focus areas: outreach and engagement, policy development, and regulatory science research. Through outreach and engagement efforts with stakeholders (ie, the pharmaceutical and biotechnology industry, patient advocacy, academia), Project Equity provides a regulatory perspective on initiatives to promote health equity and diversity in clinical research, oncology drug development, and regulatory policy. Project Equity priorities are informed by and may be developed and adapted in response to these stakeholder interactions. Inclusive enrollment practices intended to improve diversity in clinical trials can include measures such as designing trials that maximize inclusivity while maintaining patient safety. Broadening eligibility criteria at the outset of a clinical development program, on the basis of known and unknown safety assumptions, may be coupled with re-examination of the need for the previously necessary restrictive criteria as more data accumulate over time. Strategies that enrich for select populations or that allow for extending trial accrual to ensure that a representative population is enrolled may also improve study participant diversity. Additional measures to improve clinical trial diversity can include decreasing the burden of trial recruitment and trial participation by decentralizing some or all aspects of the clinical trial to community settings with fewer access barriers. Decreasing the frequency of study visits could improve clinical trial retention, particularly for those clinical trial participants who face resource barriers. Addressing known barriers (eg, financial reimbursement for travel and lodging); implementing public outreach, education, community engagement, and strategic site selection; and providing language access to participants with limited English language proficiency can also reduce barriers.[21]

Project Equity policy initiatives involve facilitating the integration of an inclusive approach in the review practices of FDA oncology staff. For example, FDA oncology review templates have been revised to ensure that the FDA review process consistently considers representativeness of study

populations enrolled in trials that support approval of oncology medical products. In addition, Project Equity has fostered more comprehensive descriptions of the study population demographic characteristics in oncology product labeling to promote transparency regarding populations enrolled in trials that support drug approval. Project Equity also provides technical assistance on various policy and legislative efforts that support enrollment of underrepresented and special populations in clinical trials. Of note, a major focus of Project Equity policy measures has been ensuring that diversity and inclusion are prioritized as highly as other aspects of drug development during clinical development. This position was outlined previously in a published framework for integrating diversity in the clinical and operational strategy for drug development.[29] On the basis of this framework, the FDA issued a draft guidance for industry on *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials*.[30] The draft guidance provides recommendations to sponsors developing medical products on developing Race and Ethnicity Diversity Plans to enroll representative numbers of participants from underrepresented racial and ethnic populations in the United States, such as Black or African American patients, Hispanic/Latino patients, Indigenous and Native American patients, Asian patients, Native Hawaiian and Other Pacific Islander patients, and other persons of color in clinical trials. The draft guidance outlines the types of medical products for which a diversity plan is recommended, timelines and processes for submitting a diversity plan, and the recommended plan content. While this guidance focuses on racial and ethnic minorities, the FDA encourages the application of these principles to other under-represented populations.

In December 2022, the Food and Drug Omnibus Reform Act of 2022 (FDORA) was enacted, as part of the Consolidated Appropriations Act, 2023.[31] It contains provisions codifying the principles of the draft guidance on Diversity Plans by requiring drug and medical device sponsors to submit Diversity Action Plans for pivotal trials to include sex and age groups. Under FDORA, drug sponsors are required to submit a Diversity Action Plan to FDA, not later than the date on which sponsors submit protocols for the phase III or other pivotal trial. The plan should include goals for enrollment and supporting rationale and an explanation of how the sponsor intends to meet those goals. FDA policy emphasizes implementation of inclusive practices early in clinical development as these measures are likely more effective when the evidence base that informs subsequent clinical trials derives from a diverse population. Despite best efforts, when the planned diversity goals are not achieved, trials conducted once a drug is marketed may provide opportunities in some case to evaluate new therapies in diverse populations.

A plan of action to enroll and retain diverse participants requires a multipronged approach that includes clinical considerations such as broadening eligibility criteria and should also incorporate operational measures and strategies that foster such engagement and collaboration with key stakeholders including global regulatory authorities and community cancer centers. The plan of action includes investment in infrastructure to collect data that will inform understanding of the population receiving care,[32] improve enrollment performance at clinical sites, and sustain community engagement. In addition to site location and access considerations (eg, language assistance for persons with limited English proficiency, reasonable modifications for persons with disabilities, etc), sponsors should consider measures that help reduce potentially burdensome elements of clinical trial design and conduct (eg, reducing the number and frequency of study-related procedures, permitting use of local laboratory/imaging facilities and telehealth, etc).

Clinical trials provide patients the opportunity to access potentially promising investigational treatments, which may be especially important when standard treatment options provide limited benefit or no standard treatments exist. For patients with serious and life-threatening diseases, such as cancer, quick access is important. Policies that improve access are critical to address inequities for historically underserved and under-represented populations.

ENSURING ACCESS TO PRECISION MEDICINE TRIALS FOR UNDER-REPRESENTED POPULATIONS: THE ETCTN CATCH-UP.2020 PROGRAM

Access to quality care including clinical trials leading to paradigm-changing treatments is critical for cancer care and equity in society. Clinical trial participation has been associated with longer 1-year survival in specific cancer types, such as acute myeloid leukemia, prostate, lung, and pancreatic cancers.[33] A report from the SWOG Cancer Research Network suggested that access to clinical trials may bridge the urban and rural divide in cancer care. In line with the FDA policy that acknowledges that the primary aim of phase I trials is to find early evidence of effectiveness, American Society of Clinical Oncology (ASCO) reaffirms its position that phase I trials provide trial participants potential clinical benefit including improved quality of life and psychological and direct medical benefit.[34,35] Disproportionate access to high-quality cancer care, including access to novel therapies through early-phase clinical trials among racial/ethnic minorities and socioeconomically disadvantaged and geographically isolated members of our society, continues to exist. In fact, disparities are worsening in early-phase clinical trial participation among patients from racial and ethnic minority groups.[36]

CATCH-UP.2020: CREATE ACCESS TO TARGETED CANCER THERAPY FOR UNDERSERVED POPULATIONS

In September 2020, the National Cancer Institute's (NCI) Experimental Therapeutics Clinical Trial Network (ETCTN) awarded CATCH-UP.2020, a congressionally budgeted administrative supplement to NCI P30 Cancer Center Support Grants, to 8 NCI-designated cancer centers that were not network members to provide enhanced access to targeted cancer therapy for minority/underserved populations. This 1-year grant, launched during the height of the COVID-19 pandemic, required each site to accrue 24 patients with 50% from underserved populations. Over 18 months (including necessary ramp-up time to set up infrastructure and activate studies), 246 patients were accrued by CATCH-UP centers, including 127 from racial and ethnic, rural, socioeconomic, and Health Professional Shortage Areas (HPSA) under-represented populations, as recently reported.[37] This report will focus on best practices adopted to address barriers in accrual to ETCTN trials in CATCH-UP.2020.

STRATEGIES TO ENHANCE ACCESS AND ACCRUAL TO ETCTN TRIALS IN UNDER-REPRESENTED POPULATIONS

ETCTN clinical trials include phase I, phase I/II, or phase II trials associated with challenges inherent to early-phase trials such as slot availability and enrollment pauses for dose-escalation safety reviews. Sites developed and implemented program-based, investigator-based, and patient-based strategies, some of which were adopted across CATCH-UP sites, whereas others were site-specific.

Program-Based Approaches

Cancer center catchment area demographics, common and uncommon cancers, and gaps in clinical trial portfolio were considered in trial selection. Sites that implemented programmatic changes for rapid activation (such as priority or expedited review by protocol review committees) and increase in number of trials resulted in increased access and accrual. A change in culture was associated with invitation to trial participation to patients from under-represented populations that were historically not offered trials. Less complicated ETCTN trials were opened in community and outreach sites, bringing them closer to patients. Program leaders sought additional funding from cancer centers, local government, and philanthropic resources to offset high-cost research-related procedures such as tumor biopsies and histologic testing where grant funding was insufficient. Progress reports from each site were presented during a monthly virtual conference. NCI program leaders assisted in addressing trial-related questions, and the sites exchanged best practices. Clinical and nonclinical linguistically appropriate patient navigators were successfully used by several sites. By contrast, the bulk screening of genomics studies on patients with cancer for identification of patients did not prove to be an effective strategy.

Investigator-Based Approaches

Each site had a program leader with early-phase research experience and an outreach investigator as a coleader. Disease-Focused Clinical Investigators (DFCI) were selected as local principal investigators (PIs) with effort included in the grant budget to encourage ownership. In each site, one or two early career DFCI were paired with mentors with expertise in drug development. Academic PIs built strong relationship with PIs in community and outreach sites. Investigators prioritized accrual of patients from under-represented populations to ETCTN trials. Training and education of research staff in clinical trial conduct and engagement of under-represented populations were provided by the lead academic organizations.

Patient-Based Approaches

To increase public awareness of this program, many CATCH-UP sites held press releases and outreach events emphasizing the importance of clinical trial participation and the need to promote equity in access. Patient advocacy groups were engaged to understand barriers to accrual to ETCTN. Telehealth was used to prescreen patients, and, in some sites, e-consenting was performed. Financial counseling was offered to patients.

Inadequate access to electronic devices and connectivity by patients, rigidity of trial requirements, initial lack of clarity of e-consenting guidelines, and changes in requirement for practitioners to practice medicine outside the state where they are licensed contributed to underutilization of telehealth. For some trials with complicated study procedures, patients continued to travel long distances. Although industry-sponsored trials often provide travel vouchers, only a couple of CATCH-UP.2020 sites were able to offer full or even partial reimbursement for patients' travel expenses.

Lessons Learned

The successful accrual of large numbers of patients from underserved populations to complex NCI-sponsored early-phase clinical trials despite the COVID-19 pandemic highlights important resource requiring features of future equity-/inclusion-focused clinical trial enhancement programs. These include dedicated clinical investigators compensated for the additional effort required; community-based patient navigators, outreach coordinators, and educators dedicated to the clinical trial mission; novel approaches to longer-distance accrual including telemedicine and the engagement of community oncology treatment centers; and ability to compensate patients and families for the additional expenses involved in participating in high-impact clinical trials.

ADDITIONAL INITIATIVES TO INCREASE ENROLLMENT AMONG UNDER-REPRESENTED POPULATIONS

Educational Modules and Programs for Staff Members

The Association of Community Cancer Centers (ACCC) in collaborating with ASCO supported the assessment of two independent interventions across multiple sites in the United States, including 50-65 academic centers, hospital/health systems, and private practices: Just Ask and Site Self-Assessments. Just Ask included an online training program containing five electronic modules developed using a curriculum offered by the Duke Cancer Institute, followed by evaluations and peer-to-peer discussions. These modules could be completed independently in a timeframe of 60-90 minutes. This training program aimed to address implicit bias among research team members, including study investigators, enrolling clinical staff members, and nonresearch staff members engaging in clinical trials at 50 sites in the country. With over 90% of enrollees completing the training modules and evaluations and an increase in knowledge scores that was sustained over 6 weeks, Just Ask successfully facilitated the process of asking patients about their interest in clinical trials and decreasing implicit bias in this population.[25] Cancer sites conducting research should be encouraged to implement this intervention once a publicly available version becomes available.

Another ongoing initiative launched by the Bristol Myers Squibb Foundation in partnership with Virginia Commonwealth University and the American Association for Cancer Research has focused on increasing diversity in the oncology research workforce by training a new generation of researchers to develop research skills along with a deep sense of community engagement. The educational program Robert A. Winn Diversity in Clinical Trials Program is offered to medical students and early-career investigators from minority groups committed to increasing diversity in clinical trials.[38] The expectation of the program is to train researchers, which will expand the number of community-based sites in the country and diversity in clinical trials.

Site Self-Assessments

Another intervention supported by ASCO-ACCC is a Site Self-Assessment intervention, which used a Plan-Do-Study-Act strategy to assess site performances and identify strategies to overcome deficiencies in the screening process. The first part of the intervention aimed to collect performance measure data. For this, participant sites had to track the number of patients screened, offered, and enrolled in clinical trials by race/ethnicity across 65 sites in the country. In the second part, 36 questions with Likert scale options were used to evaluate opportunities for improvement in several domains. Although the majority of participants identified opportunities for improvement and up to 63% of participants agreed that collecting data of performance measure would increase diversity, most participating sites were unable to provide data in the first part of this intervention. This study reinforced the importance of conducting self-assessment evaluations as a tool to identify strategies to increase the enrollment of under-represented populations.[39] Importantly, it evidenced the urgent need for a standardized, screening tool that could substitute our current screening practices entailing manual review of charts to identify trial participants.

Implementation of a Geriatric Assessment Tool

Adults older than 70 years have been under-represented in cancer clinical trials. Despite constituting 42% of the total cancer population, only 24% of participants in clinical trials are 70 years or older.[40] Historically, several clinical trials have excluded older patients on the basis of an age cutoff rather than a comprehensive functional and cognitive assessment. A study reported that clinical trials were more often discussed with patients with breast cancer younger than 65 years.[41] This might result from unconscious biases or concerns of poor tolerability in this population.[40] Although screening tools should not substitute geriatric assessments, these could serve to discriminate patients who do not require a full assessment and to follow up elderly patients participating in clinical trials.[42] Several geriatric assessment tools have been validated, and most consist of self-administered questionnaires on paper forms. Recently, an electronic geriatric assessment embedded in a data capture system and offered to elderly patients using tablets showed feasibility in a multi-institutional study,[43,44] with 81% of completion rates without help. Notably, 28% of patients were non-Hispanic Black patients. As this tool was only available in English, only 6% of participants identified as Hispanic patients.[43] The implementation of electronic geriatric tools is a promising intervention that could increase the enrollment of elderly patients, and the validation of the tool could allow expansion to other under-represented groups.

Reimbursement Programs

Most clinical trials, and more specifically early-phase studies, may incur additional out-of-pocket costs, leading to financial burden. In a survey among 230 patients enrolled in phase I clinical trials, nearly half of the participants reported unanticipated costs, generally not related to medical care. Financial burden was more prominent among Hispanics and non-Whites.[45] Logistic and financial burden, mainly associated with longer commutes, was identified as an important barrier for participation in clinical trials in a qualitative study. Decentralization of study activities, including treatment, laboratory, or follow-up visits to facilities in their communities, and financial assistance were strategies proposed by participants of this study.[46] An intervention to reimburse travel and lodging expenses among participants in cancer clinical trials who expressed concerns about nonmedical costs at baseline was conducted in a single institution in Massachusetts and

showed improvements in travel-related concerns over time, which was encouraging. However, there were no improvements in general financial well-being, which highlighted the need for a more comprehensive program.[47] This led to further collaboration and an ongoing study supported by the Lazarex Foundation with the Cancer Prevention and Research Institute of Texas to evaluate the effectiveness of a financial reimbursement program aimed to enhance the representation of racial minorities in therapeutic clinical trials by supporting expenses associated with study participation including transportation, lodging, parking, meals, and/or childcare costs across three institutions in the United States.[48]

Moving Equitable Access to Clinical Trials Forward

The experiences summarized here provide reasons to be optimistic and simultaneously remain sobering. Well-funded, intentional projects can facilitate enrollment of populations that face innate racism, structural barriers, and historical distrust and populations for which clinical trial enrollment involves treatment at long distances from academic medical centers. Each of the demonstration projects described here received resources from public and philanthropic funding. They illustrate the importance of several principles that can drive or facilitate enrollment of underserved populations to clinical trials:

1. Regulatory expectations of inclusion and congruence of the constitution of clinical trial cohorts with the targeted treatment population
2. Active change of culture in the research community, which requires education of all personnel interfacing with patients and families
3. Broadened eligibility requirements for trials
4. Simplification of trial procedures to minimize patient travel and inconvenience
5. Community outreach through cultural and linguistically appropriate advocacy groups, patient navigators, and study coordinators
6. Increased use of telehealth and decentralization of clinical trial procedures; facilitation of the delivery of clinical trial procedures at local sites
7. Funding to offset travel costs and lodging. This may require a change in IRB and other regulatory culture in terms of what is considered coercive
8. Each of these principles require significant funding

Although some of these principles appear concrete and can be easily implemented if funding is available, the necessary changes in culture require long-term commitment and willingness among educators, administrators, and practitioners. While many efforts may be bottom-up, locally developed and funded, public-private partnerships to incentivize and enable the necessary changes in culture and practice will be needed for larger impact on our national cancer research infrastructure. An inclusive, diverse clinical trial patient population will lead to cancer treatments that will be feasible across communities.

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New Opportunities for Minimizing Toxicity in Rectal Cancer Management

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overview

Advances in multimodal management of locally advanced rectal cancer (LARC), consisting of preoperative chemotherapy and/or radiotherapy followed by surgery with or without adjuvant chemotherapy, have improved local disease control and patient survival but are associated with significant risk for acute and long-term morbidity. Recently published trials, evaluating treatment dose intensification via the addition of preoperative induction or consolidation chemotherapy (total neoadjuvant therapy [TNT]), have demonstrated improved tumor response rates while maintaining acceptable toxicity. In addition, TNT has led to an increased number of patients achieving a clinical complete response and thus eligible to pursue a nonoperative, organ-preserving, watch and wait approach, thereby avoiding toxicities associated with surgery, such as bowel dysfunction and stoma-related complications. Ongoing trials using immune checkpoint inhibitors in patients with mismatch repair-deficient tumors suggest that this subgroup of patients with LARC could potentially be treated with immunotherapy alone, sparing them the toxicity associated with preoperative treatment and surgery. However, the majority of rectal cancers are mismatch repair-proficient and less responsive to immune checkpoint inhibitors and require multimodal management. The synergy noted in preclinical studies between immunotherapy and radiotherapy on immunogenic tumor cell death has led to the design of ongoing clinical trials that explore the benefit of combining radiotherapy, chemotherapy, and immunotherapy (mainly of immune checkpoint inhibitors) and aim to increase the number of patients eligible for organ preservation.

INTRODUCTION

During the past decades, improvements in the diagnosis and treatment of locally advanced rectal cancer (LARC) have led to improved local control and survival.[1] Currently, the standard of care for LARC includes multimodality treatment with radiotherapy, chemotherapy, and surgery.[2,3] Preoperative management includes the administration short-course radiotherapy (SCRT) or long-course chemoradiotherapy (CRT) which may be proceeded or followed by chemotherapy (total neoadjuvant therapy [TNT]). Surgical options include a sphincter-preserving low anterior resection (LAR) with partial or total mesorectal excision (TME), depending on the distal distance of the rectal cancer from the upper part of the anal sphincters or an abdominoperineal resection (APR) with a resultant permanent colostomy.[4]

Although successful in controlling locoregional disease, this multimodality treatment approach is associated with significant risk for short- and long-term morbidity and a decline in patient's quality of life (QoL).[5-8] For example, the LAR procedure has been associated with a substantial risk for acute and chronic anastomotic complications[5,9] and long-term bowel dysfunction,[10] such as urgency, fecal incontinence, clustering, and frequent bowel movements known as the LAR syndrome (LARS).[11] After an APR, perineal wound infection and delayed closure are not uncommon.[12,13] Furthermore, a permanent colostomy has been associated with a negative effect on patient's body image and well-being.[14] In addition, urogenital and sexual dysfunction issues are often reported after curative rectal cancer surgery.[15] Neoadjuvant radiotherapy further increases the rates of toxicity noted with surgery alone including (1) postoperative perineal complications,[16] (2) LARS,[17-19] and (3) sexual dysfunction.[15,20] Similarly, the addition of induction or consolidation systemic chemotherapy therapy (often including oxaliplatin) to neoadjuvant radiotherapy increases the risk of chemotherapy-related toxicity, such as neurotoxicity.[21]

In this review, we discuss therapeutic treatment options for patients with LARC that have the potential to minimize toxicity including the watch and wait (WW) approach and the evolving role of radiotherapy and immunotherapy in LARC management.

WW AFTER TNT

Until recently, the standard of care for LARC consisted of neoadjuvant CRT, which induces tumor downsizing and thereby increases the chance of radical resection,

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PRACTICAL APPLICATIONS

- Total neoadjuvant therapy results in excellent oncological outcomes, with current evidence favoring consolidation over induction chemotherapy.
- Local regrowth in patients after a WW approach may be resected with negative margins in most cases but may compromise sphincter preservation.
- Improved techniques facilitate dose escalation, and doses above 70 Gy may result in increased organ preservation rates.
- Combining immunotherapy and chemoradiotherapy may enhance tumor response and improve organ preservation rates in microsatellite-stable/mismatch repair-proficient patients.
- Neoadjuvant immune therapy demonstrates great promise in the management of MSI-H/mismatch repair-deficient locally advanced rectal cancer and may allow for omission of chemotherapy, radiation, and surgery.

followed by surgery according to the TME principles. This strategy minimized the rates of local recurrences below 10% at 5 years.[22,23] For intermediate-risk tumors in whom downsizing may not be required, SCRT followed by immediate surgery can be considered. Using SCRT in this cohort of patients may be beneficial because SCRT leads to lower early toxicity and similar rates of postoperative complications, late toxicity, health-related QoL, and anorectal and sexual function compared with CRT.[24-28] In addition, SCRT leads to noninferior oncological outcomes compared with CRT.[29] However, several studies demonstrate higher rates of complete response post-CRT compared with post-SCRT even if the interval between completion of SCRT and surgery is prolonged.[29-32] Still, prolongation of this waiting period is seemingly safe as, according to the results of the Stockholm III trial, the chances of radical resection and the risk of postoperative complications are not compromised.[33]

Unfortunately, distant metastases (DM) remain a problem, with 5-year disease-free survival (DFS) rates of about 65% for patients with LARC.[34] The beneficial effect of postoperative adjuvant chemotherapy (aCT) in rectal cancer is limited, especially after CRT.[34] This could be due, in part, to the poor compliance to chemotherapy after major surgery and the possible outgrowth of micrometastatic disease in the time interval between diagnosis and commencement of aCT. Thus, introducing chemotherapy before surgery, in the form of TNT, may improve compliance and efficacy.

According to the National Comprehensive Cancer Network (NCCN) guidelines, TNT is the preferred neoadjuvant treatment modality for most patients with LARC[3] including those with (1) T_3N_{any} lesions with clear mesorectal fascia (MRF) by magnetic resonance imaging (MRI), (2) $T_{1\text{-}2}N_{1\text{-}2}$ lesions, (3) T_3N_{any} lesions with involved or threatened CRM by MRI, and (4) T_4N_{any} lesions with locally unresectable disease or who are medically inoperable. However, the European Society of Medical Oncology (ESMO) guidelines for neoadjuvant treatment differ as they use preoperative MRI to identify risk factors to distinguish between intermediate disease ($cT_{3a/b}$ [very low, levators clear, MRF clear] or $cT_{3a/b}$ in mid or high rectum with $cN_{1\text{-}2}$ [not extranodal, no extramural venous invasion]) and locally advanced disease (>cT_{3b}, extramural venous invasion+ or threatened MRF on MRI).[2] According to ESMO, preoperative radiotherapy, either CRT or SCRT, for patients with intermediate disease is not routinely advised on the basis of the fact that the local recurrence risk should be low if a good-quality TME is performed.[35,36] For patients with a high local recurrence risk, CRT is recommended, whereas for patients with an added risk for DM, TNT is advised.[2] Although these guidelines are designed to risk-stratify and identify patients suitable for TNT, it is important to recognize that there will be cases that on the basis of patient comorbidities, patient preference (sphincter preservation, organ preservation, avoidance of CRT, etc), and tumor location (upper *v* lower) where the decision to pursue TNT versus conventional CRT or up-front surgery will be best made at the multidisciplinary team level, taking all factors into consideration.

The first report on TNT, published in 2006,[37] demonstrated that the addition of capecitabine and oxaliplatin (CAPOX) before the commencement of CRT resulted in a 24% pathological complete response (pCR) rate which was superior to the 15% pCR achieved with standard fluorouracil (FU)–based CRT.[38] The GCR3 randomized phase II trial demonstrated noninferiority regarding pCR rates, increased compliance, and improved toxicity profile with induction CAPOX, followed by CRT and surgery compared with CRT plus surgery.[39] During that time, the group from Memorial Sloan Kettering Cancer Center (MSKCC) gradually altered their treatment paradigm for patients with LARC and noted that approximately 36% of patients treated with TNT were able to achieve a clinical response (CR), defined as either a pCR or a clinical complete response (cCR).[40] The MSKCC group subsequently reported on a larger sample size with 36% CR rate in patients who received TNT compared with 21% CR rate in patients receiving standard CRT.[41] A recent pooled analysis of patients receiving TNT demonstrated that pCR rate for patients undergoing TNT was 22.4%.[42] In addition, a meta-analysis of studies comparing TNT with CRT demonstrated a pCR rate of 29.9% in the TNT group versus 14.9% in the CRT.[43]

The superiority of TNT with respect to pCR rates has recently been confirmed by phase III clinical trials (Tables 1 and 2). The RAPIDO trial, which compared SCRT, followed by consolidation chemotherapy consisting of either six cycles of CAPOX or nine cycles of FOLFOX4 and surgery (TNT arm) with CRT, followed by surgery with or without aCT, demonstrated that patients in the TNT arm achieved higher pCR rates and lower 3- and 5-year DM rates.[21,44] However, the 5-year locoregional recurrence rate was higher in the TNT arm when compared with the CRT arm (10.2% *v* 6.1%).[44] Whether this difference will be confirmed in other studies remains to be determined. The PRODIGE 23 study, which compared induction chemotherapy consisting of six cycles of FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and fluorouracil), followed by CRT plus surgery with CRT followed by surgery and aCT, demonstrated higher pCR rates, improved 3-year DFS, and lower DM rates in the TNT arm.[45] The results from the CAO/AIO/ARO-12 trial, a study comparing three cycles of induction mFOLFOX6 (modified scheme with fluorouracil, leucovorin, and oxaliplatin) followed by CRT to CRT (with oxaliplatin in both arms) followed by three cycles of consolidation mFOLFOX6, demonstrated that consolidation resulted in better pCR rates when compared with induction chemotherapy.[46] However, 3-year DFS, toxicity, QoL, and stool incontinence were similar between the two groups.[47] The STELLAR study, which compared SCRT followed by four cycles of CAPOX, surgery, and adjuvant two cycles of CAPOX with CRT, followed by surgery and adjuvant six cycles of CAPOX, demonstrated better CR rates and overall survival (OS) in the TNT group compared with the CRT group, but similar 3-year DFS.[48] Of note, the Polish Study, which compared SCRT, followed by three cycles of FOLFOX4 and surgery with CRT (including oxaliplatin) and surgery, failed to demonstrate a significant difference in pCR rates and 3-year DFS.[49] Currently, it is not clear if the better pCR outcomes noted with consolidation are due to the prolonged time interval between TNT completion and surgery or the effect of the chemotherapy itself since it has been demonstrated that waiting more than 10-11 weeks after CRT completion does not improve pCR rates.[50,51]

The recently published Organ Preservation for Rectal Adenocarcinoma (OPRA) trial, a prospective, randomized phase II trial, demonstrated a 3-year DFS of 76% for both consolidation- and induction-based TNT which was similar to historical controls treated with CRT, surgery, and aCT.[52] In addition, organ preservation was achieved in 50% of the entire cohort. The secondary aim of the OPRA trial was to compare consolidation versus induction chemotherapy approaches with respect to organ preservation. In total, 225 patients demonstrating a cCR or near clinical complete response (ncCR; 76% in the consolidation *v* 71% in the induction group) were offered a standardized WW approach. As in the CAO/AIO/ARO-12 trial that demonstrated the superiority of consolidation over induction chemotherapy on the basis of pCR rates, the OPRA trial noted organ preservation to be more likely with the consolidation versus the induction chemotherapy approach (53% *v* 41% respectively).[52]

It appears that one of the first descriptions of what we currently refer to as WW was a case report published in 1929 highlighting significant tumor downsizing and symptom resolution in a patient with rectal cancer treated with radiation therapy alone and careful follow-up.[53] In 2004, to our knowledge, Habr-Gama et al[54] were the first to demonstrate in a group of carefully selected patients who achieved a cCR after CRT and adhered to a very strict follow-up regimen equivalent to 5-year OS and DFS (100% and 92%, respectively) to patients who had undergone surgery after CRT and experienced a pCR. Subsequent reports from multiple international centers[55-59] and a meta-analysis[60] confirmed that patients classified as cCR who pursued a WW approach had similar OS and DFS to patients treated with surgery after CRT. Furthermore, a recent meta-analysis of individual patient data[61] and an analysis of the International WW Database,[62] a multicenter, multinational database that contains data on patients with cCR managed with a WW protocol,[63] demonstrated a 5-year OS ranging between 84.6% and 87%.

Although not uniformly accepted as standard of care, the NCCN guidelines suggest that the WW approach may be considered in centers with experienced multidisciplinary teams[3] after a careful discussion with the patient about their risk tolerance and need for adherence to an extended surveillance program. Reservations with pursuing a WW approach include current limitations with detecting residual disease[64-66] and concerns with leaving behind occult residual disease after the completion of CRT or TNT that may ultimately go on to present as local tumor regrowth. The local regrowth rates in patients who experience a cCR after CRT and pursue WW range from 21.6% to 24.9% at 3-years- follow-up[61,67] and approximately 28% at 5-year follow-up,[61] with the majority occurring within the first 3 years of follow-up (93.4%-96.1%).[61,67] However, the percentage of patients with a local regrowth who can undergo a salvage operation is high (82.5%-95.4%),[60,61,67,68] with the majority achieving an R_0 resection (approximately 79%).[61,67] Furthermore, through conditional survival analyses, it appears that the longer the patient sustains a cCR (ie, the longer they do not develop a local regrowth), the greater the probability of remaining local regrowth free during future follow-up.[69] Another perceived limitation with the WW approach has been the concern for the development of DM. However, the DM rates for patients classified as cCR who pursue WW range between 6.8% and 9.1% at 3-year follow-up[61,62,67] and 10.7% at 5-year follow-up,[69,70] with 71.8% to 78.6% of the DM occurring within the first 3

TABLE 1. Management of Patients Receiving TNT in Phase III Clinical Trials

Study	INCT	SCRT or CRT	CNCT	aCT
RAPIDO[21,44]	NA	Five times × 5 Gy over a maximum of 8 days	Six cycles of CAPOX: (1) capecitabine 1,000 mg/m^2 orally twice per day on days 1-14 and (2) oxaliplatin 130 mg/m^2 IV on day 1, with a chemotherapy-free interval between days 15 and 21 OR nine cycles of FOLFOX4: (1) oxaliplatin 85 mg/m^2 IV on day 1; (2) leucovorin (folinic acid) 200 mg/m^2 IV on days 1 and 2; (3) bolus FU 400 mg/m^2 IV; and (4) FU 600 mg/m^2 IV for 22 hours on days 1 and 2, with a chemotherapy-free interval between days 3 and 14	NA
PRODIGE 23[45]	Six cycles of FOLFIRINOX: (1) oxaliplatin 85 mg/m^2 delivered as 2-hour IV infusion; (2) leucovorin (folinic acid) 400 mg/m^2 delivered as 2-hour IV infusion followed by (3) irinotecan 180 mg/m^2 as a 90-minute IV infusion; and (4) FU 2,400 mg/m^2 continuous IV infusion over 46 hours every 14 days	50 Gy over 5 weeks (2 Gy five times/wk, with a reduction of fields after 44 Gy) and capecitabine 800 mg/m^2 oral twice daily for 5 days/wk	NA	Six cycles of mFOLFOX6: (1) oxaliplatin 85 mg/m^2 given as 2-hour IV infusion; (2) leucovorin (folinic acid) 400 mg/m^2 given as 2-hour IV infusion and followed by (3) FU 400 mg/m^2 given as an IV bolus; and (4) FU 2,4000 mg/m^2 over 46 hours every 14 days OR four cycles of capecitabine 1,250 mg/m^2 twice daily orally on days 1-14 every 21 days
CAO/AIO/ARO-12[46-47,a]	Three cycles of (1) oxaliplatin 100 mg/m^2 delivered as a 2-hour IV infusion; (2) leucovorin (folinic acid) 400 mg/m^2 delivered as a 2-hour IV infusion followed by (3) FU 2,400 mg/m^2 delivered as a continuous infusion over 46 hours repeated on days 1, 15, and 29 for a total of three cycles	50.4 Gy in 28 fractions and continuous infusion of (1) FU 250 mg/m^2 on days 1-14 and days 22-35; (2) oxaliplatin 50 mg/m^2 2-hour IV infusion on days 1, 8, 22, and 29 of radiotherapy	Three cycles of (1) oxaliplatin 100 mg/m^2 delivered as a 2-hour IV infusion; (2) leucovorin (folinic acid) 400 mg/m^2 delivered as a 2-hour IV infusion followed by (3) FU 2,400 mg/m^2 delivered as a continuous infusion over 46 hours repeated on days 57, 71, and 85 for a total of three cycle	NA
STELLAR[48]	NA	Five times × 5 Gy	Four cycles of CAPOX: (1) oxaliplatin 130 mg/m^2 once a day on day 1 and (2) capecitabine 1,000 mg/m^2 twice/d from day 1 to day 14, 7-14 days after the completion of radiotherapy	Two cycles of CAPOX: (1) oxaliplatin 130 mg/m^2 once a day on day 1 and (2) capecitabine 1,000 mg/m^2 twice/d from day 1 to day 14, 7-14 days after the completion of radiotherapy
Polish III[49]		Five times × 5 Gy	Three cycles of FOLFOX4	
OPRA[52,a]	Eight cycles of FOLFOX: (1) oxaliplatin 85 mg/m^2 delivered as IV infusion; (2) leucovorin (folinic acid) 400 mg/m^2 delivered as IV infusion followed by (3) FU 400 mg/m^2 IV push; and (4) FU 2,400 mg/m^2 over 46-48 hours by continuous infusion on a 14-day cycle OR five cycles of CAPOX: (1) oxaliplatin 130 mg/m^2 on day 1 and (2) capecitabine 1,000 mg/m^2 twice a day on days 1-14 repeated on a 21 day cycle	45 Gy in 1.8 Gy over 25 fractions to regional pelvic nodes 50-56 Gy delivered at the primary tumor either as simultaneous integrated boost and/or a sequential boost AND capecitabine 825 mg/m^2 twice a day orally OR FU 225 mg/m^2/d delivered as a continuous infusion during radiotherapy	Eight cycles of FOLFOX: (1) oxaliplatin 85 mg/m^2 delivered as an IV infusion; (2) leucovorin (folinic acid) 400 mg/m^2 delivered as an IV infusion followed by (3) FU 400 mg/m^2 IV push; and (4) FU 2,400 mg/m^2 over 46-48 hours by continuous infusion on a 14-day cycle OR five cycles of CAPOX: (1) oxaliplatin 130 mg/m^2 on day 1 and (2) capecitabine 1,000 mg/m^2 twice a day on days 1-14 repeated on a 21 day cycle	NA

Abbreviations: aCT, adjuvant chemotherapy; CAPOX, capecitabine and oxaliplatin; CNCT, consolidation chemotherapy; CRT, chemoradiotherapy; d, day; FOLFOX, fluorouracil and oxaliplatin; FU, fluorouracil; INCT, induction chemotherapy; IV, intravenously; NA, not applicable; OPRA, Organ Preservation for Rectal Adenocarcinoma; SCRT, short-course radiotherapy.

[a]CAO/AIO/ARO-12 and OPRA compared INCT with CNCT. Patients received either INCT or CNCT, not both.

years of follow-up.[67,70] Since approximately 2%-9%[38,71] of patients who achieve a pCR after CRT and undergo surgery develop a DM at 5-year follow-up, the added risk for DM development in patients pursuing a WW approach may be minimal.

Overall, it appears that current results with a WW approach in patients experiencing a cCR seem acceptable. However, the decision to pursue WW should be shared between the physician and the patient fully informed of the fact that the opportunity for cure may be lost even if a cCR is achieved. Further improvements to WW may be achieved with research dedicated to (1) increasing cCR rates; (2) identifying ncCR patients who will not convert to cCR; (3) identifying cCR patients likely to develop a local regrowth; (4) clarifying the potential role of circulating tumor DNA (ctDNA) to detect persistent disease; (5) overcoming the paucity of long-term outcome data, particularly in younger patients; (6) identifying failure patterns other than endoluminal; (7) accurately capturing QoL in this unique population; and (8) minimizing the burden of surveillance and inequalities in care delivery with a WW approach.

ncCR Conversion to cCR

It appears that patients who experience a ncCR (Table 3) do not fare as well since organ preservation is feasible in only 52% of patients classified as ncCR compared with 79% classified as cCR at 3-year follow-up.[73] Because patients experiencing a ncCR represent a heterogeneous population, half of whom do not progress to cCR, pursuing a WW approach in this population exposes those ultimately requiring an operation to the risks associated with delayed surgery including inferior quality of the mesorectal excision,[74] increased pelvic fibrosis,[51] compromised sphincter preservation,[75] and need for perineal reconstruction.[76] This heterogeneity highlights the urgent need for research dedicated to improving our ability to identify ncCR patients unlikely to achieve a cCR.

cCR and Local Regrowth Development

Similarly, early identification and resection of cCR patients with an increased tendency to develop a local regrowth could potentially benefit this subset of cCR patients since the development of a local regrowth is associated with a decreased likelihood of achieving organ preservation. In fact, in the OPRA trial, patients who underwent surgery after initial restaging had a numerically higher, albeit statistically not significant, rate of sphincter preservation compared with patients who underwent surgery after a local regrowth (55% *v* 44% respectively).[52] Furthermore, two meta-analyses of patients with distally located rectal cancers classified as cCR after CRT who pursued WW demonstrate that in approximately 55% of salvage procedures performed for local regrowth, an APR was required.[61,67]

ctDNA

ctDNA, a marker of residual micrometastatic disease, has recently been demonstrated to identify a subset of patients with colon cancer who would benefit from aCT on the basis of their postoperative ctDNA levels.[77] Although not yet proven, ctDNA may also increase risk stratification and management of patients with LARC. Measurement of ctDNA levels pretreatment and after completion of CRT/TNT may help determine eligibility and improve surveillance of patients pursuing a WW approach. However, the current literature exploring the utility of ctDNA in LARC management remains scarce.[78,79]

Early Age at Onset and WW

The implementation of WW in patients with early age-at-onset rectal cancer should be further investigated, especially given the increasing number of cases noted worldwide.[80-82] Although an analysis demonstrated that patients younger or older than 50 years managed with WW after cCR did not differ in terms of local regrowth and DM rates after 3-year follow-up,[83] long-term follow-up data in this young population with an anticipated long lifespan are needed to accurately assess the long-term incidence of local regrowth and DM and local effects of TNT on pelvic fibrosis and function.

Patterns of Failure

Although after 3 years of follow-up most of the local regrowths appear to be luminal,[62] concerns exist regarding pelvic/regional failures that may become evident with long-term follow-up. These concerns arise from the observation that the rate of downstaging may be greater in the primary tumor than in the regional lymph nodes (LNs).[84,85] In addition, a prospective pathological analysis of patients with LARC undergoing CRT demonstrated that approximately 18% of LNs are located in the region above the current standard field of external beam radiation therapy (EBRT), suggesting that a fraction of LN in patients pursuing a WW approach after TNT will have only been treated with systemic chemotherapy and not EBRT.[86] Long-term results on patterns of failure (either pathological confirmation on those who undergo surgery or serial imaging demonstrating progressive growth) after a WW approach could potentially lead to modifications in the radiotherapy target volumes.

QoL

In addition to achieving good oncological outcomes, a parallel goal of the WW approach is the improvement of patients' QoL. Although the literature is limited, it appears that one third of patients who follow a WW approach report symptoms consistent with a LARS, despite not undergoing surgery, a finding that highlights the late effects of radiation therapy to the rectum and pelvic floor musculature.[87,88] The development of a validated instrument that accurately

TABLE 2. Oncological Outcomes of TNT Clinical Trials

Study	pCR Rates	CR Rates	3-Year DFS	3-Year OS	5-Year OS	3-Year DM Rates	5-Year DM Rates	5-Year LRF	5-Year DrTF	3-Year LRR	5-Year LRR	3-Year DMFS
RAPIDO[21,44]	TNT: 28%[b]			TNT: 89.1%	TNT: 81.7%	TNT: 20%[b]	TNT: 23%[b]	TNT: 11.7%[b]	TNT: 27.8%[b]		TNT: 10.2%[b]	
	CRT: 14%			CRT: 88.8%	CRT: 80.2%	CRT: 26.8%	CRT: 30.4%	CRT: 8.1%	CRT: 34%		CRT: 6.1%	
PRODIGE-23[45]	TNT: 28%		TNT: 76%[b]	TNT: 91%						TNT: 4%		TNT: 79%
	CRT: 12%		CRT: 69%	CRT: 88%						CRT: 6%		CRT: 72%
CAO/AIO/ARO-12[46,47,a]	INCT: 17%		INCT: 73%	INCT: 92%		INCT: 18%				INCT: 6%		
	CNCT: 25%		CNCT: 73%	CNCT: 92%		CNCT: 16%				CNCT: 5%		
STELLAR[48]		TNT: 21.8%[b]	TNT: 64.5%	TNT: 86.5%[b]						TNT: 8.4%		TNT: 77.1%
		CRT: 12.3%	CRT: 62.3%	CRT: 75.1%						CRT: 11%		CRT: 75.3%
Polish III[49]	TNT: 16%		TNT: 53%	TNT: 73%		TNT: 22%						
	CRT: 12%		CRT: 52%	CRT: 65%		CRT: 21%						
OPRA[52,a]			INCT: 76%									INCT: 84%
			CNCT: 76%									CNCT: 82%

Abbreviations: CNCT, consolidation chemotherapy; CR, complete response, defined as the sum of pCR and sustained clinical complete response (cCR); CRT, neoadjuvant chemoradiotherapy; DFS, disease-free survival; DM, distant metastases; DMFS, distant metastases–free survival; DrTF, disease-related treatment failure; INCT, induction chemotherapy; LRF, locoregional failure; LRR, locoregional recurrence rate; OPRA, Organ Preservation for Rectal Adenocarcinoma; OS, overall survival; pCR, pathologic complete response; TNT, total neoadjuvant therapy.

[a]CAO/AIO/ARO-12 and OPRA compared INCT with CNCT. Patients received either INCT or CNCT not both.

[b]Statistically significant results.

TABLE 3. Criteria for Patient Classification as cCR, ncCR, and iCR According to the International Consensus Recommendations[72]

Modality	cCR[a]	ncCR	iCR
DRE	Absence of palpable tumor material	Presence of small and smooth regular irregularities	The presence of a palpable tumor mass
Endoscopy	No residual tumor material or only a small erythematous ulcer or a scar	Presence of small and smooth regular irregularities, including residual ulcer or small mucosal modules or minor mucosal abnormalities, with mild persisting erythema of the scar	Presence of a visible macroscopic tumor
MRI[b]	Substantial downsizing with no observable residual tumor material or residual fibrosis only (with limited signal on DWI), sometimes associated with residual wall thickening because of edema, no suspicious lymph nodes	Obvious downstaging with residual fibrosis but heterogeneous or irregular aspects and signal regression or regression of lymph nodes with no malignant enhancement features, but with a size of >5 mm	Patients not fulfilling criteria for cCR nor ncCR

Abbreviations: cCR, complete clinical response; DRE, digital rectal examination; DWI, diffusion-weighted imaging; iCR, incomplete clinical response; MRI, magnetic resonance imaging; ncCR, near complete clinical response.

[a]All criteria including DRE, endoscopy, and MRI should be fulfilled to define a cCR.

[b]Gadolinium contrast medium is no longer compulsory for MRI conducted with the aim of defining a cCR.

measures sexual, bowel, and urinary dysfunctional issues after a nonoperative WW approach is needed to accurately capture the QoL in this unique patient population.[72]

Burden of Surveillance and Equity in Care

The current follow-up regimen of the WW approach (Table 4) translates into 16 outpatient visits over the course of at least 60 months, assuming optimal coordination of single-day scheduling of all five assessment modalities (carcinoembryonic antigen, digital rectal examination, MRI, endoscopy, and computed tomography).[72] This intensive follow-up regimen may be challenging to adhere to and highlights the need to carefully advise patients and families of the long-term commitment of time and resources required to be compliant with a WW surveillance approach. The fact that different sectors of our patient population may not have the resources to support this follow-up regimen suggests that a WW approach may potentially propagate the existing disparities in the treatment of LARC. Thus, research on the feasibility of the WW approach in areas that are limited in resources should be pursued and encouraged.

ADVANCES IN RADIOTHERAPY

Radiotherapy Dose Escalation

In the past, radiotherapy dose escalation was considered impossible because of technical constraints and fear of grave toxicity. However, in the past decades, the technique of external beam radiotherapy for rectal cancer has emerged, and it has been shown that high doses of radiotherapy increase the number of patients achieving a pCR or cCR.[89] In addition, the conventional three- or four-field technique, leading to a large high-dose volume, has been replaced by intensity-modulated radiotherapy or volumetric-modulated arc therapy, which allows for a more conformal coverage of the target volume. The introduction of image-guided radiotherapy enables further reduction of the required safety margins. Novel radiotherapy techniques, such as magnetic ressonance (MR)-guided radiotherapy, facilitate daily delineation of the target volume with adaptation of the dose distribution. This may permit a 30% reduction of the high-dose volume, a gain which facilitates dose escalation allowing for higher response rates. The smaller treatment margins and better visibility of the pelvic anatomy may therefore enhance sparing of the sphincter complex and pelvic floor musculature.[90,91]

The recently published phase III randomized controlled OPERA trial demonstrated a 3-year organ preservation rate of 81% after a contact x-ray brachytherapy boost (3 × 30 Gy combined with 45 Gy CRT) in early- and intermediate-stage rectal cancers.[92] The effects of contact x-ray brachytherapy boost on LARC are currently investigated in the OPAXX study, where ncCR patients after SCRT or CRT are randomly assigned to receive either contact therapy boost or undergo prolonged observation with local excision, if needed.[93]

Although radiotherapy dose escalation holds great promise for organ preservation, its long-term toxicity remains a concern since the high radiation doses delivered to the tumor and adjacent bowel wall increase the risk of long-term toxicity.[94] In the aforementioned OPERA trial, despite the lack of late grade 3-5 toxicities, 19% of the patients reported major LARS at 1-year follow-up and 63% experienced late grade 1-2 rectal bleeding caused by telangiectasia.[92] Similarly, late proctitis and bleeding complications were observed in the HERBERT trial which evaluated high-dose rate endorectal brachytherapy boost post-EBRT in the elderly patients.[95] In addition, the RECTAL-BOOST trial, a randomized phase II trial comparing external radiation boost before CRT, followed by TME with standard CRT, followed by TME, demonstrated that patients in the boost group reported worse global health, physical role, and social functioning compared with the standard CRT group at 3 and

TABLE 4. Projected Follow-Up Schedule of a Patient After WW According to the International Consensus Recommendations[72]

Years Post-Treatment Completion	Month 3	Month 6	Month 9	Month 12
Year 1	CEA DRE[a] Endoscopy[a] Pelvic MRI[a]	CEA DRE[a] Endoscopy[a] Pelvic MRI[a] Chest and/or abdominal CT	CEA DRE[a] Endoscopy[a] Pelvic MRI[a]	CEA DRE[a] Endoscopy[a] Pelvic MRI[a] Chest and/or abdominal CT
Year 2	CEA DRE[a] Endoscopy[a] Pelvic MRI[a]	CEA DRE[a] Endoscopy[a] Pelvic MRI[a]	CEA DRE[a] Endoscopy[a] Pelvic MRI[a]	CEA DRE[a] Endoscopy[a] Pelvic MRI[a] Chest and/or abdominal CT
Year 3	CEA	CEA DRE Endoscopy Pelvic MRI	CEA	CEA DRE Endoscopy Pelvic MRI Chest and/or abdominal CT
Year 4		CEA DRE Endoscopy Pelvic MRI		CEA DRE Endoscopy Pelvic MRI Chest and/or abdominal CT
Year 5		CEA DRE Endoscopy Pelvic MRI		CEA DRE Endoscopy Pelvic MRI Chest and/or abdominal CT

NOTE. First follow-up assessments typically occur at 6-8 weeks after the completion of preoperative or definitive treatment.
Abbreviations: CEA, serum carcinoembryonic antigen measurement; CT, computed tomography; DRE, digital rectal examination; MRI, magnetic resonance imaging.
[a]DRE, endoscopy, and MRI for the first 2 years could also be performed every 4 months, instead of every 3 months, as depicted in the table.

6 months of follow-up. However, despite more fecal blood/mucous reported in the boost group, the QoL was similar between the groups after 12 months of follow-up.[96]

Radiotherapy and Immunotherapy

It is hypothesized that the addition of immunotherapy, primarily checkpoint inhibitors, in the neoadjuvant setting may improve tumor response and thereby facilitates organ preservation while reducing the risk of DMs. A small subset of patients with LARC are found to be microsatellite instability-high (MSI-H) defined via polymerase chain reaction sequencing or mismatch repair-deficient (dMMR) on immunohistochemistry testing. In these patients, neoadjuvant immunotherapy has resulted in incredibly high cCR rates, as described below.[97,98] However, most patients with LARC have microsatellite stable (MSS) or mismatch repair-proficient (pMMR) tumors and therefore are more likely to potentially benefit from a multimodal (chemo) radioimmunotherapy approach than immunotherapy monotherapy, a claim supported by ongoing clinical trials demonstrating promising pCR and cCR rates (Table 5).[99,106.]

The effects of radiotherapy on the increase of T cells and PD-L1/PD-1 and CTLA-4 expression provide a rationale for the combination of radiation therapy with immune checkpoint inhibitors.[109] Preclinical studies in various tumor models have shown synergy with this combination.[110-112] However, the heterogeneity of results highlights the complex balance between immune stimulation and suppression induced by radiation, which may be dependent on (1) patient and tumor factors, (2) timing and sequencing of radiotherapy with immunotherapy, (3) radiation dose and fractionation, and (4) radiotherapy technique, planning, dose rate, and target volume. For example, in mouse models that received fractionated radiotherapy, PD-L1 expression was upregulated with concurrent (but not sequential) administration of anti–PD-1/PD-L1 antibodies, leading to enhanced immune response, immune memory, and better OS.[113] Conversely, the administration of anti–CTLA-4 agents several days before the administration of high-fraction radiotherapy seems to facilitate the synergy between the two modalities via T-regulatory cell depletion.[114] Furthermore, hypofractionated schedules, such as 24 Gy in three fractions, may be more immunogenic than conventional schedules or a single high-dose fraction.[115-119] In addition, the implementation of smaller radiation fields, shorter treatment duration, and

TABLE 5. Response Rates to Immunotherapy-Containing Treatment Regimens in MMR Proficient Locally Advanced Rectal Cancer

Study	Patient Population	Treatment Regimen	Sample Size	Tumor Response
Lin et al[99]	cT3-4N0M0 or cT1-4N + M0	SCRT followed by two cycles of CAPOX with camrelizumab followed by surgery after 1 week	N = 30 (28 pMMR, one dMMR, one unknown), 27 for evaluation	pCR rate: 48.1% (13/27, one patient with dMMR)
AVERECTAL trial (meeting abstract ESMO 2021)[100]	cT2 N1-3, cT3 N0-3, evidence of extramural vascular or MRF involvement	SCRT followed by six cycles of mFOLFOX-6 plus avelumab followed by surgery after 3-4 weeks	N = 44, 40 patients for evaluation	pCR rate: 37.5% (15/40); near complete response rate (TRG 1): 30% (12/40)
TORCH (meeting abstract ASCO 2022)[101]	T3-4/N + M0, distance from anus ≤10 cm	Randomly assigned to receive consolidation arm (A) SCRT followed by six cycles of ToriCAPOX or induction arm (B) two cycles of ToriCAPOX followed by SCRT followed by four cycles of ToriCAPOX Both groups receive curative surgery or WW strategy	N = 67, 11 patients for evaluation (all pMMR)	CR rate (pCR + cCR): 81.8% (9/11); pCR rate: 77.8% (7/9)
NRG-GI002, Rahma et al[102]	Stage II/III with distal location (cT3-4 ≤5 cm from anal verge, any N), with bulky disease (any cT4 or tumor within 3 mm of MRF), at high risk for metastatic disease (cN2), and/or who were not candidates for sphincter-sparing surgery	Randomly assigned to receive six cycles of FOLFOX followed by CRT (control arm) or the same dosage of FOLFOX followed by CRT with concurrent pembrolizumab (pembro arm). Surgery was performed 8-12 weeks after the last dose of radiotherapy	N = 185 (95 patients in control arm and 95 in pembro arm), 137 for evaluation	Mean (SD) NAR score: 11.53 (12.43) for the pembro arm *v* 14.08 (13.82) for the control arm ($P = .26$); pCR rate: 31.9% in the pembro arm *v* 29.4% in the control arm ($P = .75$); cCR rate: 13.9% in the pembro arm *v* 13.6% in the control arm ($P = .95$).
NCRT-PD-1-LARC trial, Gao et al[103]	Mid-to-low cT3-4a N0M0 or cT1-4a N1-2M0	CRT with concurrent three 21-day cycles of tislelizumab followed by a radical surgery 6-8 weeks after radiotherapy	N = 26 (all pMMR)	pCR rate: 50% (13/26); TRG 0: 53.8% (14/26); TRG 1: 26.9% (7/26); TRG 2: 19.2% (5/26); NAR score 7.2 ± 10.4
R-IMMUNE trial (meeting abstract ESMO 2021)[104]	cT3-T4 N0 or T any or N1-2, M0	CRT with concurrent atezolizumab (four infusions at weeks 3, 6, 9, and 12). Surgery planned at week 15	N = 26 (interim analysis), 25 patients for evaluation	pCR rate: 24% (6/25)
AVANA trial (meeting abstract ASCO 2021)[105]	At least one of the following features: cN+, cT4, high risk cT3	CRT with concurrent six cycles of avelumab followed by surgery at 8-10 weeks after the end of CRT	N = 101, 96 patients (one patient with dMMR) for evaluation	pCR rate: 23% (22/96); major pathological response: 61.5% (59/96)
VOLTAGE trial, Bando et al[106]	cT3-4 N0-2 M0	CRT followed by five cycles of nivolumab and surgery	N = 39 (pMMR), 37 patients for evaluation	pCR rate: 30% (11/37); TRG: 0-1 38% (14/37); median NAR score: 8.4 (0.0-50.4)
NSABP FR-2 trial (meeting abstract ASCO 2022)[107]	Stage II-IV, pMMR	CRT followed by durvalumab within 3-7 days after CRT completion followed by surgery within 8-12 weeks after CRT	N = 45, 40 patients for evaluation	Mean modified NAR score: 12.03; pCR rate: 22.2%; cCR rate: 31.1%
PANDORA (meeting abstract ASCO 2022)[108]	cT3/4N0/M0 or Tx N1-2/M0	CRT followed by durvalumab and surgery after 10-12 weeks from neoadjuvant therapy	N = 60, 55 patients for evaluation	pCR rate: 32.7% (18/55); near complete regression, moderate and minimal regression in 14 (25.5%), 9 (16.4%) and 11 (20.0%) patients, respectively

Abbreviations: CAPOX, capecitabine plus oxaliplatin; cCR, clinical complete response; CR, complete response; CRT, chemoradiation; dMMR, deficient mismatch repair; LARC, locally advanced rectal cancer; mFOLFOX, modified fluorouracil and oxaliplatin; MMR, mismatch repair; MRF, mesorectal fascia; NAR score, neoadjuvant rectal score; pCR, pathological complete response; pMMR, proficient mismatch repair; SCRT, short-course radiotherapy; SD, standard deviation; ToriCAPOX, toripalimab plus capecitabine and oxaliplatin; TRG, tumor regression grade; WW, watch and wait.

avoidance of low dose baths may save the extremely radiation-sensitive T cells and thereby enhance immune response.[120] Overall, these results suggest that for each tumor type there might be an optimal combination of radiation dose and checkpoint inhibitors for inducing antitumor immunity.

For patients with LARC, ongoing (chemo)radiotherapy-immunotherapy studies evaluating multiple sequencing options, including TNT (using conventional SCRT or CRT schemes) with concurrent or sequential immunotherapy (mainly PD-1 or PD-L1 checkpoint inhibitors) and with or without chemotherapy such as CAPOX and fluorouracil and oxaliplatin (FOLFOX),[121] will provide new insights in how to optimize immunotherapy with radiotherapy. Below, we describe (preliminary) outcomes of the first trials in LARC with pMMR/MSS tumors.

Radiotherapy-Immunotherapy Trials in Locally Advanced Rectal Cancer

Three studies evaluating SCRT and induction or consolidation immunotherapy have presented toxicity outcomes and response rates.[99-101] A single-arm, phase II trial evaluated SCRT followed by CAPOX with camrelizumab (anti-PD-1) followed by surgery after 1 week in patients with $T_{3\text{-}4}N_0M_0$ or $T_{1\text{-}4}N_+M_0$ rectal cancer.[99] Of the 30 patients enrolled (of note, one had MSI-H disease), 27 received at least one dose of CAPOX plus camrelizumab. The pCR rate was 48.1%. Grade 1-2 immune-related adverse events (AEs), which consisted mostly of skin reactions, occurred in 88.9% of the population. Any grade 3 AE occurred in 26.7% and consisted mainly of hematological toxicity. None of the patients demonstrated grade 4/5 AEs. The AVERECTAL study, a single-arm, multicenter, phase II two-stage trial evaluated SCRT, followed by mFOLFOX-6 plus avelumab (anti-PD-L1) and surgery 3-4 weeks after in patients with LARC ($cT_2N_{1\text{-}3}$, $cT_3N_{0\text{-}3}$, evidence of extramural vascular, or MRF involvement), presented the outcomes of 44 patients at ESMO 2021.[100] The pCR rate was 37.5%, and ncCR was 30%. Grade 3, 4, and 5 AEs were 58.1%, 11.6%, and 2.3% (one patient died of cardiopulmonary arrest), respectively, none of which were related to acute effects of avelumab. The TORCH trial, a multicenter phase II trial, randomly assigned patients with LARC ($T_{3\text{-}4}/N_+M_0$, distance from anus $\leq$10 cm) to a consolidation arm including SCRT followed by toripalimab (anti-PD-1) plus capecitabine and oxaliplatin (ToriCAPOX) or an induction arm including ToriCAPOX followed by SCRT followed by ToriCAPOX and presented the first outcomes of 11 patients at ASCO 2022.[101] Both groups receive curative surgery or WW. In this small group of patients, a high complete response rate (pCR + cCRT) was observed (81% of which the pCR rate was 77.8%). Grade 3 AE included thrombocytopenia in 36.4% of the patients. No grade 4-5 AEs were observed (Table 5).

TABLE 6. Clinical Trial Results in Patients With dMMR Localized Colorectal Cancer

Study	Patient Population	Treatment Regimen	Sample Size	Study End Point
Cercek et al[123]	Patients with pMMR and dMMR LARC undergoing neoadjuvant therapy	Neoadjuvant chemotherapy (FOLFOX)	N = 21 (dMMR); N = 63 (pMMR)	6/21 (29%) dMMR with disease progression; 0/63 pMMR with disease progression
De Rosa et al[124]	Patients with dMMR LARC undergoing neoadjuvant therapy	Neoadjuvant chemotherapy and long-course radiation followed by surgical resection	N = 29	8/29 (27.6%) with pCR (one additional patient had cCR and declined surgery)
Cercek et al (ASCO 2022)[125]	Patients with dMMR LARC undergoing neoadjuvant immunotherapy	Dostarlimab × 6 months	N = 14	14/14 (100%) with cCR
NICHE-1; Chalabi et al[97]	Patients with dMMR and pMMR colon cancer undergoing neoadjuvant immunotherapy and surgery	Nivolumab/ipilimumab × 1, then nivolumab × 1, then surgical resection; pMMR patients ± celecoxib	N = 35 patients (20 dMMR, 15 pMMR)	12/20 (60%) dMMR with pCR, 2/15 (13.3%) pMMR with pCR
NICHE-2; Chalabi et al[126]	Patients with dMMR colon cancer undergoing neoadjuvant immunotherapy and surgery	Nivolumab/ipilimumab × 1, then nivolumab × 1, then surgical resection	N = 107	72/107 (67%) dMMR with pCR
Ludford et al[127]	Patients with localized unresectable or high-risk resectable dMMR tumors	Pembrolizumab ± surgical resection	N = 35 (19 colon, 8 rectal, 8 noncolorectal); 33 evaluable; 17 underwent surgery	11/17 (65%) with pCR; 27/33 (82%) ORR

Abbreviations: cCR, clinical complete response; dMMR, deficient mismatch repair; FOLFOX, fluorouracil and oxaliplatin; LARC, locally advanced rectal cancer; ORR, overall response rate; pCR, pathologic complete response; pMMR, proficient mismatch repair.

Four studies evaluated CRT with concurrent immunotherapy.[102-105] The NRG-GI002 trial, a phase II randomized trial, compared FOLFOX followed by CRT (control arm) with FOLFOX followed by CRT with concurrent pembrolizumab in patients with stage II/III rectal cancer.[102] Surgery was performed 8-12 weeks after CRT. The neoadjuvant rectal (NAR) score (on the basis of clinical T stage and pathologic T and N stages), the primary outcome evaluated in 137 patients (95 patients in the control arm and 95 in the intervention arm), was comparable between the groups, as well as the pCR rate and the cCR rate. Grade 3-4 AEs were observed in 48.2% of the patients in the intervention arm and 37.3% in the control arm during CRT. Two patients died during FOLFOX treatment because of sepsis (control arm) and pneumonia (intervention arm). The NCRT-PD-1-LARC trial evaluated CRT with concurrent tislelizumab (anti-PD-1) followed by a radical surgery 6-8 weeks after CRT in a multicenter, single-arm phase II trial.[103] On the basis of the interim analysis of the first 26 patients, the pCR rate was 50%. Immune-related AEs occurred in 19.2%, including one grade 3 event (immune-related colitis) and no grade 4-5. The R-IMMUNE trial, a multicenter phase Ib/II single-arm trial, evaluated CRT with concurrent atezolizumab followed by surgery and presented the interim results of 26 patients at ESMO 2021.[104] The pCR rate was 24% (on the basis of 25 patients). Grade 3-4 AEs were observed in 34.6% (mostly postoperative complications). The AVANA study, presented at ASCO 2021, is a multicenter phase II study in LARC (with at least one of the following features: cN_+, cT_4, and high-risk cT_3) whiche-valuated CRT with concurrent avelumab followed by surgery at 8-10 weeks after CRT.[105] Of the 101 study patients, including one MSI-H tumor, 96 were evaluable for pathological response. The pCR rate was 23%, and major pathological response was observed in 61.5%. Grade 3-4 nonimmune and immune-related AEs were observed in 8% and 4% of the patients, respectively.

Three studies have evaluated CRT with sequential immunotherapy.[106-108] The VOLTAGE study, a phase I-II trial evaluated CRT followed by nivolumab (anti–PD-1) and surgery in patients with MSS and MSI-H LARC, that is, $T_{3-4}N_{0-2}M_0$.[106] Among the 37 MSS patients, pCR was noted in 30%, near-pCR in 8%, and cCR in 3% who adopted the WW approach. Serious AEs related to nivolumab or surgery were reported in eight patients, and immune-related severe AEs were observed in three patients (grade 3 myasthenia, grade 3 interstitial nephritis, and grade 2 peripheral motor neuropathy). During the follow-up period, one patient developed grade 2 colitis. The NSABP FR-2 study is a phase II trial in stage II/III evaluating neoadjuvant CRT followed by durvalumab (anti–PDL-1) within 3-7 days after CRT completion followed by surgery within 8-12 weeks after CRT. Preliminary results demonstrated a mean modified NAR score of 12.03 in 40 patients, pCR in 22.2%, and cCR in 31.1%.[107] Most common grade 3 AEs included diarrhea, lymphopenia, and back pain. There was one grade 4 AE (elevated amylase/lipase) and no grade 5. The PANDORA study is a phase II multicenter trial in patients with LARC evaluating CRT followed by durvalumab and surgery after 10-12 weeks from neoadjuvant therapy and was presented at ASCO 2022. Preliminary results on 55 patients demonstrated a pCR rate of 32.7% and a near complete regression of 25.5%.[108] Grade 1-2 immune-related AE was observed in 36.4%, whereas grade 3 toxicity was seen in 7.3% and included diarrhea, skin toxicity, transaminase and lipase increase, and pancolitis. No grade 4-5 AEs were observed. Although promising, more confirmatory data are needed before immunotherapy can be considered standard of care.

NEOADJUVANT IMMUNOTHERAPY IN MSI-H/dMMR LOCALLY ADVANCED RECTAL CANCER

Although patients with MSI-H/dMMR LARC can have a limited response to FU and oxaliplatin chemotherapy,[123] these dMMR tumors often respond well to chemoradiation. In fact, one retrospective study of patients with dMMR LARC undergoing fluoropyrimidine-based neoadjuvant chemoradiation followed by surgery demonstrated a 27.6% pCR rate with one additional patient achieving cCR and declining surgery.[124] Although not a head-to-head comparison, these results compare favorably with historical pCR rates of approximately 15% in patients with MSS/pMMR disease who undergo neoadjuvant chemoradiation (Table 6).[27]

Concerns regarding inefficacy and toxicities with standard treatment in this population along with high response rates and survival benefit in the metastatic setting for MSI-H/dMMR colorectal cancer (CRC) treated with immunotherapy led to the design of a single-institution study evaluating the use of neoadjuvant immunotherapy for MSI-H/dMMR LARC.[98,128-132] This single-arm phase II study is enrolling patients with stage II and III dMMR/MSI-H rectal adenocarcinoma. Eligible patients are treated with dostarlimab, an anti–PD-1 antibody, every 3 weeks for 6 months. At the completion of therapy, tumor response is assessed by DRE, endoscopy, and MRI. If a cCR is detected (defined as visual disappearance of the rectal primary on endoscopy, a normal DRE, and lack of primary tumor signal and disappearance of pathologically enlarged LNs on pelvic MRI), patients are eligible to pursue a WW approach. Otherwise, patients proceed to standard CRT, followed by surgery. The majority of the first 18 patients treated had T_3/T_4 tumors and node-positive disease (78% and 94%, respectively). Of interest, 59% had evidence of MMR germline mutations in *MSH2*, *MLH1*, *MSH6*, or *PMS2*, with no concomitant *BRAF V600E* mutations noted. With a median follow-up of 6.8 months (0.7-23.8 months), all 14 consecutively treated patients who completed 6 months of dostarlimab therapy achieved a cCR.

Grade 1 and 2 AEs included rash, dermatitis, pruritus, nausea, and thyroid function abnormalities. Thus far, none of the treated patients have required chemotherapy, radiation, or surgery, and no grade 3 or 4 AEs have been observed.[98] In another study of anti–PD-1 therapy in patients with MSI-H/dMMR LARC in China, 17 patients were treated initially with neoadjuvant sintilimab monotherapy.[133] Of 16 evaluable patients, nine achieved a cCR with sintilimab alone and refused surgery, and three of six patients who underwent surgery had a pCR. Although most patients did well with neoadjuvant immunotherapy, unfortunately one patient had a serious AE of grade 3 encephalitis, and one patient had primary progression on neoadjuvant sintilimab therapy.

Although the sample sizes of these two MSI-H/dMMR LARC studies are small and confirmatory studies with larger sample sizes and longer follow-up are needed, these preliminary results of neoadjuvant immunotherapy in rectal cancer are promising. These findings are also supported by other recent studies in colon cancer, which together suggest that neoadjuvant immunotherapy in localized CRC may be more promising than even as definitive therapy in the metastatic setting, in which overall tumor burden and systemic immunosuppression may dampen treatment responses.

For instance, building on intriguing efficacy noted in the NICHE trial which combined nivolumab (anti-PD1 antibody) and ipilimumab (anti-CTLA4 antibody) in the neoadjuvant setting for colon cancer,[97] the NICHE-2 trial examined the efficacy of nivolumab/ipilimumab in patients with MSI-H/dMMR localized colon cancer.[126] Of 112 patients in the intention-to-treat population, 74% were considered to have high-risk stage III disease, with 48% having cT_4 and N_2 on radiologic staging. Overall, 31% of patients were known to have Lynch syndrome. Doublet immunotherapy, albeit with a limited course of c1d1 nivolumab/ipilimumab and c1d15 nivolumab, resulted in any AEs in 61% of the patients. However, only 4% experienced grade 3 or 4 toxicities, such as elevated amylase/lipase, hepatitis, myositis, or rash. Of the 107 patients included in the efficacy analysis, 67% had a pCR, and 95% had a major pathologic response, defined as 10% or less residual viable tumor at surgical resection.

A recent study investigating the use of pembrolizumab in patients with localized unresectable or high-risk MSI-H/dMMR solid tumors demonstrated in the subset of patients with CRC receiving varying amounts of pembrolizumab a pCR rate of 79%.[127] However, with a median follow-up of almost 9.5 months (range, 0-26 months) among 17 patients with GI tumors managed with a nonoperative approach, two patients in this study (one colon and one rectal) demonstrated disease progression events. It should be noted that the eight patients with rectal cancer demonstrated heterogeneous responses with one displaying innate resistance to treatment and disease progression after two cycles of pembrolizumab and one with adaptive resistance and disease progression at 9 months. Although this approach was overall promising in the majority of patients, these results do raise some concern and illustrate the need for additional studies investigating the underlying biological basis for response and resistance to immunotherapy in this specialized cohort of patients and in localized CRC in general.

Currently, the optimal duration and regimen of immunotherapy (anti-PD1 monotherapy *v* anti–PD-1/anti-CTLA4 doublet) remain unclear. The results of ongoing studies including the dostarlimab study and EA2201, a phase II trial of neoadjuvant nivolumab and ipilimumab in MSI-H/dMMR LARC with or without SCRT therapy depending on response to immunotherapy,[134] and ongoing correlative studies exploring the utility of ctDNA are eagerly awaited. Nevertheless, on the basis of published reports, neoadjuvant immunotherapy in the treatment of MSI-H/dMMR LARC holds significant promise to simplify the therapeutic landscape and minimize toxicities for patients who would have previously received trimodality therapy, thereby providing an opportunity for personalized therapy, reduction of toxicity, and improvement in QoL.

CONCLUSION

The development of TNT has resulted in improved oncological outcomes with current evidence favoring consolidation over induction chemotherapy. In addition, TNT has resulted in increased response rates such that with careful patient selection and follow-up, organ preservation may be feasible in approximately half of the patients pursuing a WW approach. Although patients developing a local regrowth may undergo a salvage resection, in some cases, sphincter preservation and/or resection margins may be compromised. On the basis of current nonrandomized, highly heterogeneous data, it appears that rates of DM approximate those in patients undergoing surgery and achieving a pCR suggesting that a WW approach in carefully selected, highly informed patients with long-term follow-up by experienced multidisciplinary teams may be safely pursued.

Advances in radiotherapy techniques have facilitated dose escalation and allow for safe administration of doses over 70 Gy which may result in increased organ preservation rates. The synergism noted, in preclinical studies, between immmunotherapy and chemoradiotherapy on immunogenic cell death may also enhance tumor response and improve organ preservation rates for patients with MSS/pMMR tumors. Although patients with MSI-H/dMMR tumors may respond poorly to neoadjuvant chemotherapy, they often respond well to concurrent chemoradiation. In

addition, neoadjuvant immunotherapy demonstrates great promise in the management of MSI-H/dMMR LARC and may allow for omission of chemotherapy, radiation, and surgery. Therefore, identification of patients with MSI-H/dMMR LARC is critical to optimize treatment decision making.

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Early-Onset GI Cancers: Rising Trends, Genetic Risks, Novel Strategies, and Special Considerations

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Overview

Cancers in young adults (commonly described as early-onset [EO] cancer) represent a group of malignancies that have unique and challenging biology and genetic, treatment, social, and psychological implications. Even more concerning is a rising trend of EO cancers in multiple tumor types. Research and investigation in EO cancers will help elucidate mechanisms of carcinogenesis, differences in biology and response to treatment, and the need for multidisciplinary care to ensure comprehensive treatment and support for young patients.

INTRODUCTION

Historically, cancer has been considered predominantly a disease associated with aging with multifactorial etiology.[1] Early-onset (EO) cancer has conventionally been defined as cancer occurring in adults age between 18 and 49 years. Across a number of global analyses, we are seeing a paradigm shift in the ages at which some of the most common cancers are being diagnosed for reasons that are not entirely clear.[2-5] GLOBOCAN data analyses demonstrate rising incidence of cancers of the colorectum, extrahepatic bile duct, gallbladder, liver, pancreas, stomach, breast, endometrium, bone marrow, thyroid, head and neck, kidney, and prostate.[6] This concerning emerging trend has been listed as a research priority by the US National Cancer Institute, and global research efforts are being made to determine the relative contributions of both known and unknown risk factors to this EO epidemic, particularly with regard to EO colorectal cancer (EO-CRC).[4] Recent evidence also recapitulates this worrying trend across the GI cancer spectrum including gastric, pancreatic, and biliary tract cancers,[7] and for the purposes of this review, we have focused on this spectrum of EO GI malignancies. One prevailing theory is that the significantly altered early life exposome which includes dietary and lifestyle factors, environmental carcinogens, obesity, and antibiotic exposure among others that is characteristic of the 20th century living is playing a central role in this EO cancer epidemic.[3] The influence of the microbiome on immune system development, and indeed carcinogenesis, is being increasingly recognized, and ongoing research may help to further elucidate the relationship between host and exogenous factors and implications for EO cancers (Fig 1).[8,9]

EO-CRC: RISING INCIDENCE AND OPPORTUNITIES FOR PREVENTION AND TREATMENT

CRC is the third most common cancer worldwide, and the second leading cause of cancer-related deaths.[10] EO-CRC refers to CRC diagnosed in individuals younger than 45 years. Incidence rates in individuals younger than 45 years have been increasing since the mid-1990s, driven largely by an increasing incidence in rectal cancer.[11] On the basis of data from the North American Association of Central Cancer Registries, which includes 47 states and the District of Columbia, there has been a 1.1% increase per year (95% CI, 0.3 to 2.0) from 2006 to 2015. This includes an increase of 0.7% per year (95% CI, 0.5 to 0.9) for colon tumors and 1.7% per year (95% CI, 1.4 to 2.0) increase for rectal tumors.[12] By the year 2030, 10% of all colon cancers and 22% of all rectal cancers in the United States are expected to be diagnosed in patients younger than 50 years.[13] Recent evidence reveals a similar rapidly rising incidence of EO-CRC in other developed countries worldwide indicating that this increase is not specific to the United States.[14] This pattern is even more worrisome when placed against the backdrop of a significant decline in the incidence of CRC in patients older than 45 years. This decrease has been attributed to multiple factors, including screening programs and reductions in risk factors such as smoking, diet, and anti-inflammatory medications.[15]

Racial Differences in EO-CRC

Between the year 2000 and 2013, EO-CRC incidence increased 2.5% in American Indian/Alaskan Native patients, 2.3% in non-Hispanic White patients, 1.0% in non-Hispanic Black patients, and 0.2% in Asian/Pacific Islander patients.[16] In an analysis of

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PRACTICAL APPLICATIONS

- Awareness of the early-onset (EO) cancer epidemic should prompt heightened vigilance among health care providers caring for patients who would not be historically considered at high risk for cancer.
- Early detection of symptoms with appropriate diagnostic testing is critical to obtaining a cancer diagnosis in earlier stages which may allow for a greater chance of curative approaches.
- Multidisciplinary management of patients with EO cancers is critical to address unique and challenging issues that younger populations must navigate, including family, social, career, and financial stress.
- Genetic counseling and testing are critical components to multidisciplinary care and may elucidate mechanisms of EO cancer development.

SEER data, from 1992 to 2014, the incidence of EO-CRC increased from 7.5 to 11.0 per 100,000 in White individuals and from 11.7 to 12.7 per 100,000 in African American individuals. The increase in rectal cancer was larger in White (from 2.7 to 4.5 per 100,000) than in African American patients (from 3.4 to 4.0 per 100,000).[17] During this period, in African American patients, mortality declined by 0.4%-1.1% annually, but African American patients still have a higher absolute mortality rate than other populations (6.1/100,000).[18] These racial disparities are likely multifactorial, stemming from a combination of socioeconomic, access to care, dietary, environmental, and biologic factors.[19] In the Hispanic population, CRC incidence rates from 2001 to 2014 have increased among younger (age, 20-49 years) adults.[20] Interestingly, the largest relative increases in incidence occurred in Hispanic patients age 20-29 years (90% *v* 50% relative increase among White patients), suggesting that opposing incidence trends in younger versus older Hispanic patients may reflect generational differences in CRC risk by birth cohort, as well as environmental exposures and lifestyle-related risk factors associated with immigration and acculturation.[20]

Clinical and Pathologic Features

Given that screening is not recommended for adults younger than 45 years, the majority of CRCs in young patients are identified because of signs and symptoms, and diagnosis can be delayed significantly. In a series of more than 1000 EO-CRCs, the most common presenting symptom was rectal bleeding (50.8%), followed by abdominal pain (32.5%) and change in bowel habits (18.0%).[21] When compared with symptomatic older patients with CRC, younger patients are more likely to present with symptoms of hematochezia (28.8% *v* 23.2%) and abdominal pain (41.2% *v* 27.2%).

Patients with EO-CRC experience symptoms for longer (243 *v* 154 days) and have a longer delay to diagnosis (152 *v* 87 days), compared with older patients.[22,23] In addition, younger patients more commonly present with left-sided cancers and are more likely to have rectal cancer (31.2% *v* 22.4%; $P < .001$).[24] EO-CRCs also appear to have more aggressive histopathology than older patients. Overall, mucinous and signet ring histologies were seen in 10.0%-14.5%[25-28] and 2.0%-13.0%[25,26,28] of EO-CRCs, respectively, and up to 27.9% of EO-CRC cancers are poorly differentiated or undifferentiated compared with just 10.8% in average-onset CRC (AO-CRC).[22,29]

EO-CRC tends to present at a more advanced stage with a relative risk of 1.37 (1.33-1.41) and 1.58 (1.53-1.63) for younger patients to present with regional or distant metastasis, respectively, compared with older patients.[24] A retrospective review of EO-CRC revealed a clear association between time from onset of symptoms and stage at diagnosis highlighting the critical need to establish the diagnosis in a timely manner.[22,23]

Molecular Characteristics of EO-CRC

Microsatellite and chromosomally stable (MACS) tumors are near-diploid tumors without the aneuploidy that characterizes chromosomal instability (CIN) and without microsatellite instability (MSI). In a prospectively collected series of 84 microsatellite-stable (MSS) EO-CRCs (younger than 50 years) compared with 90 MSS later-onset CRCs (older than 65 years), EO-CRC had higher frequencies of MACS tumors, and tumors in the EO-CRC were more frequently diploid (46%) than the older-onset group (26%; $P = .006$).[30] The pathological processes that drive MACS may be simply reflective of the distal colorectal location, and it is unclear if this is a characteristic that is unique to EO-CRC. In addition, another large genomic analysis of EO left-sided CRC revealed that younger patients (n = 350), when compared with older patients (n = 776), showed higher mutation rates in genes associated with cancer-predisposing syndromes (eg, Lynch syndrome [LS]), such as MSH6, MSH2, POLE, NF1, SMAD4, and BRCA2.

Somatic Alterations

Evaluation of comprehensive genomic landscapes in EO-CRC has been limited because of relatively small sample sets. Comparisons in the molecular and clinical findings of sporadic CRC of 39 young patients (younger than 45 years) versus 36 older patients (older than 60 years) revealed a

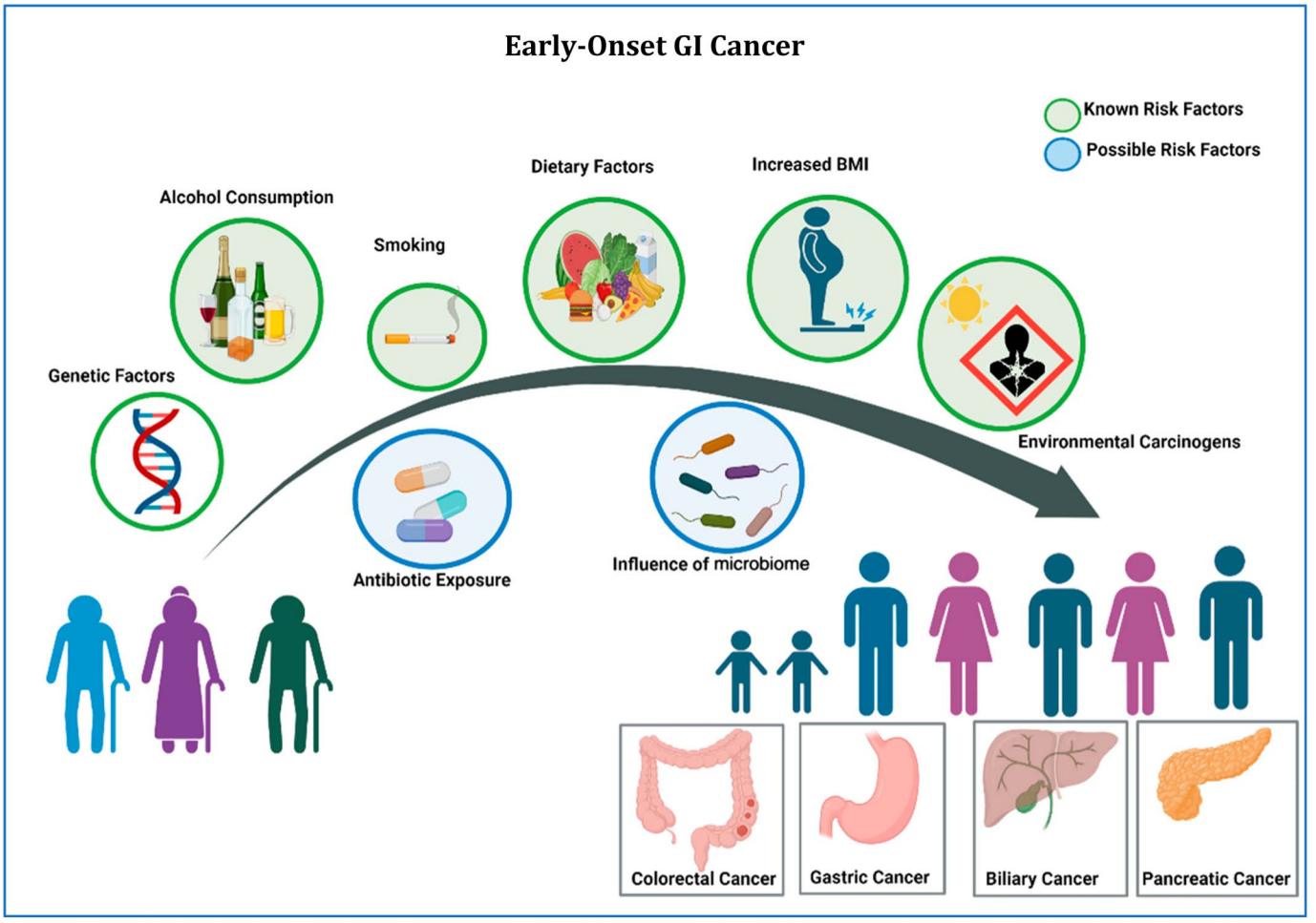

FIG 1. Established and potential risk factors for early-onset GI cancers. Schematic was created with BioRender.com.

higher incidence of distal tumors, synchronous metastases, BRAF V600E wild type, absence of a methylator phenotype, and evidence of CIN in EO-CRC.[31] In 2019, a multicenter study of 18,218 CRC samples with next-generation sequencing was published showing differences in genomic alterations between EO and later-onset CRC. When substratified into EO (younger than 40 years), intermediate group (40-49 years), and older (50 years and older),[32] *TP53* and *CTNNB1* alterations were more common in the EO cohort, whereas *APC*, *KRAS*, *BRAF*, and *FAM123B* variants more frequent in the older cohort.

The observation of genetic heterogeneity across EO-CRC tumors reveals the need to leverage data from next-generation sequencing to define molecular phenotypes. An integrated European multiomics study included tumor transcriptome, plasma proteome, and metabolome-implicated deregulated redox homeostasis, through perturbation of *NRF2*-mediated oxidative stress response, the CXCL12-CXCR4 signaling pathway, and glutathione metabolism, as a molecular hallmark of EO-CRC.[33] Further analysis in diverse populations[34] will be required to better understand and validate these data.

EO-CRC Treatment and Survivorship

Despite seemingly later stage and more aggressive histology at presentation, patients with EO-CRC appear to have similar stage-specific outcomes. In a SEER database analysis, the stage-adjusted, cancer-specific survival was improved in younger patients compared with those diagnosed older than 50 years (local: 95.1% *v* 91.9%; regional: 76% *v* 70.3%; distant: 21.3% *v* 14.1%).[24] However, another analysis in stage IV CRC showed an increased risk of progression and death in younger patients (22% increased risk of progression and 19% increased risk of death), suggesting a reduced benefit of frontline therapy in EO-CRC.[35]

Although there appears to be a different pattern of molecular profile in EO-CRCs and treatment regimens are routinely modified on the basis of the molecular features of CRCs,

these cancers are still a heterogeneous group, and there is currently no specific tailored approach to treatment on the basis of age alone.[32] Secondary to their young age and presumed improved performance status compared with older adults, younger patients tend to be treated more aggressively than older adults without clear survival benefit. Matched for stage and tumor characteristics, younger patients are more likely to be treated with systemic chemotherapy and multiagent regimens compared with older patients.[36,37] This more aggressive approach to therapy has not been associated with survival gain in patients with stage II disease (rate ratio [RR], 0.90; 95% CI, 0.69 to 1.17) but led to a marginal gain for patients with stage III (RR, 0.89; 95% CI, 0.81 to 0.97) and IV (RR, 0.84; 95% CI, 0.79 to 0.90) disease.[37] In addition, an analysis of extended colon resection showed no benefit in younger patients.[38] Another analysis of 6,284 patients from nine phase III studies in stage IV CRC showed that young age was modestly associated with poorer progression-free survival but not overall survival (OS) or RR in treated patients with advanced CRC, and young patients had more nausea but less diarrhea and neutropenia with chemotherapy in general.[39] Given the association of EO-CRC and LS, a higher proportion of young patients will have high MSI which may affect the use of chemotherapy in patients with stage II disease, as well as the use of immunotherapy for patients with stage IV disease which is expected to improve outcomes in this cohort of patients.[40]

Non-CRC EO-GI Cancers: Current Trends

EO gastric cancer. Despite falling overall, gastric cancer incidence conversely appears to be rising in younger generations.[2,41] Using SEER data in a study of 158,599 patients, this rising incidence appears to disproportionately affect Black, Hispanic, and Asian populations.[42] Similar to CRC, EO gastric cancer is more likely to present with multifocal disease, higher grade, and diffuse histology.[43] Additionally, EO gastric cancer is less likely to have MSI compared with later-onset gastric cancer.[44]

EO pancreatic cancer. In considering pancreatic cancer, Sung et al[2] analyzed data sets from 25 US state registries from 1995 to 2014 and identified increasing pancreatic cancer incidence with decreasing age, noting a 2.47% (95% CI, 1.77 to 3.18) annual increase for age 30-34 years and a 4.34% (95% CI, 3.19 to 5.50) increase for age 25-29 years compared with 0.77% (95% CI, 0.57 to 0.98) for patients age 45-49 years. This has been further corroborated by large population-based studies using SEER registry data,[7] and more recently, Jayakrishnan et al[45] demonstrated a relative percentage increase of 33.3% in pancreaticobiliary cancer in patients younger than 50 years from 2004 to 2017. Younger patients are more likely to be diagnosed with stage IV cancer and with a more aggressive phenotype.[46,47] Although the majority of data sets have focused on pancreatic adenocarcinoma, there is also evidence of increased pancreatic neuroendocrine tumors (PNETs); these patients with EO PNETs are more likely to be Black, Hispanic, and female and additionally have improved OS when compared with average-onset PNETs.[48]

EO biliary cancers. Biliary tract cancers also appear to be rising in younger adults across diverse geographical regions, and this again contrasts with the trends in older adults.[49] The unique biological and genomic characteristics of these tumors have been less well elucidated given that this represents a novel phenomenon. However, some of the data that are available specific to this population suggest possibly poorer OS with enrichment of genes associated with poorer differentiation, deubiquination, and WNT signaling pathway.[50] This association with poorer survival was not seen when the US National Cancer database was analyzed from 2004 to 2017 and pancreaticobiliary tumors were analyzed as a group.[61]

EO-GI CANCERS AND GENETIC PREDISPOSITION: KNOWNS AND UNKNOWNS

Classic Model of Genetic Testing

Evaluating the contribution of germline pathogenic variants (gPVs) to the risk of EO-GI cancers is critical not only for the appropriate estimation of lifetime cancer risks but also increasingly for treatment decision making among patients already affected with cancer. Herein, we describe the historical model of genetic testing and its evolution, define the most common high-risk genetic predispositions to GI cancers, and describe how germline genetics has grown to be pivotal in the routine care of oncologic patients and their at-risk relatives.

The classic models of genetic testing for cancer historically hinge on three basic factors: patients' age at diagnosis, rarity of tumor type, and/or family cancer history. The aim of this approach is to identify those with the highest pretest probability of having a gPV while reducing the likelihood of obtaining uncertain results with limited clinical utility (eg, variant of uncertain significance). This is typically conducted by a pretest genetic counseling session in which a certified genetic counselor takes the family history and completes a three-generation pedigree to assess if the patient and/or family meets clinical criteria for genetic testing. Such criteria may be established by national guidelines by cancer type, such as the National Comprehensive Cancer Network (NCCN) for Colorectal Cancer,[51] or syndrome-specific criteria, such as the Amsterdam Criteria and Bethesda Guidelines[52,53] for assessment of and tumor screening for LS.

Although these methods typically capture those at *highest* risk for having a gPV, over the past several years, an

increasing amount of data have demonstrated that a significant portion of patients with gPVs in high penetrance cancer risk genes, such as the mismatch repair (MMR) genes diagnostic of LS, are missed through such stringent criteria. LS is a pan-cancer syndrome with up to an approximate 60% lifetime risk of cancer, with CRC and endometrial cancer (EC) carrying the highest risk. Given that it has been reported that underlying LS is found in approximately 3%-5% of all CRC and ECs, universal screening for LS via assessment for MSI-high and or MMR-deficiency has been recommended for these canonical tumor types for the nearly 2 decades.[52,54,55] One 2019 publication in the *Journal of Clinical Oncology* demonstrated that among 15,000 patients representing a pan-cancer cohort of MSI tumors (>50 cancer types), LS was identified in approximately 16% of cases.[56] Moreover, of patients with LS presenting with cancers other than CRC or EC, only half met clinical testing criteria on the basis of personal and/or family cancer history,[56] highlighting that relying on this classic testing model misses nearly half of LS diagnoses. Importantly, this is not unique to LS as multiple studies have demonstrated a significant incremental pickup rate for gPV in cancer susceptibility genes when classic testing criteria are relaxed.[57-59]

Rising Incidence of EO-GI Cancer and Relative Contribution of Genetic Risk: The Known

Historically, the application of family history has been important in identification of patients for germline testing and potential primary prevention of CRC.[60] Approximately 28% of patients with EO-CRC will have family history of CRC, and the risk conferred by a history of CRC in FDR is greatest in younger individuals.[61] In contrast to studies assessing gPVs among MSI tumors, a large comparison of EO-CRC to AO-CRC MSS cancer found that 17.5% patients with EO-CRC harbored a gPV (3) with the highest mutation prevalence in the cohort with those younger than 35 years (23.2%) compared with 14% in the AO-CRC cohort and that this appeared to be driven by an enrichment of gPVs in high penetrance genes.[62] The majority of gPVs were in known CRC-associated cancer predisposition genes including DNA MMR genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) *EPCAM* terminal deletions, *APC*, and *POLD1*.[62] When assessing all-comers (MSI and MSS EO-CRC), rates of gPVs range from 9% to 26.4%.[63,64] Although LS is the most common genetic syndrome associated with EO-CRC, there is increasing evidence of the association of other high penetrance gPVs with CRC which include TP53, *BRCA1/2*, *ATM*, and *PALB2*, although whether or not these findings are causative of the cancer or incidental findings remain to be fully elucidated.[64-68]

As a result of this increasing appreciation of the potential contribution of gPVs to EO-CRC, the Delphi initiative released the DIRECt recommendations in 2022[69] which have been endorsed by four scientific societies: the Collaborative Group of the Americas on Inherited Gastrointestinal Cancers, the European hereditary Tumor group, the International Society for Gastrointestinal Hereditary Tumors, and the Association Italiana Familirita Ereditarieta Tumori. These recommendations mandate multigene panel testing (MGPT) for all patients younger than 50 years (Fig 2).

NCCN guidelines[70] now recommend germline genetic testing for all patients diagnosed with pancreatic cancer in view of the potential clinical actionability on the basis of the POLO study for maintenance olaparib among g*BRCA* carriers.[71] Importantly, in a cohort of 450 patients with EO pancreatic cancer diagnosed between 2008 and 2018 at a large academic institution,[72] approximately 32% were found to harbor at least one gPV, with 27.5% of gPVs identified in high and moderate penetrance genes.[72] A large study from another large tertiary center demonstrated that patients with EO pancreatic cancer had a significantly higher odds of testing positive than older patients for germline mutations (odds ratio, 1.93; 95% CI, 1.03 to 3.7) although the definition of EO pancreatic cancer for the purposes of this study was defined as age younger than 60 years.[73]

Approximately 1%-3% of gastric cancers are associated with gPVs,[74] and genetically driven tumors are more common among patients with EO disease. The most common syndrome is hereditary diffuse gastric cancer associated with mutations in the *CDH1* gene.[75-77] Beyond *CDH1* gPVs, hereditary diffuse gastric cancer can also be seen in the setting of truncating mutations in the *CTNNA1* (α catenin) gene inferring a genocopy of *CDH1*[76,78] although this represents a minority of diffuse gastric cancer families.[75] Additionally, an autosomal dominant syndrome has been identified characterized by gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) without duodenal or colonic involvement in most individuals reported.[79,80] GAPPS arises in the context of APC promoter 1B mutations (c.-191T>C, c.-192A>G, and c.-195A>C) which reduce the binding activity of the transcription factor Yin Yang 1 and transcriptional activity of the promoter.[81] EO gastric cancer (nondiffuse type) may also occur in the setting of LS (caused by gPVs *in MLH1*, *MSH2*, *MSH6*, *PMS2*, and terminal deletions in *EPCAM*),[82] Li Fraumeni syndrome (caused by gPVs in *TP53*),[83] familial adenomatous polyposis (caused by gPVs in *APC*),[82,84,85] Peutz Jeghers (caused by gPVs in *STK11*),[86,87] and juvenile polyposis syndrome (caused by gPVs in *SMAD4* or *BMPR1A*).[88,89] Importantly, many of the above syndromes have classic, well-described phenotypic presentations, allowing for better estimations of pretest probability of a true positive result in such cases.

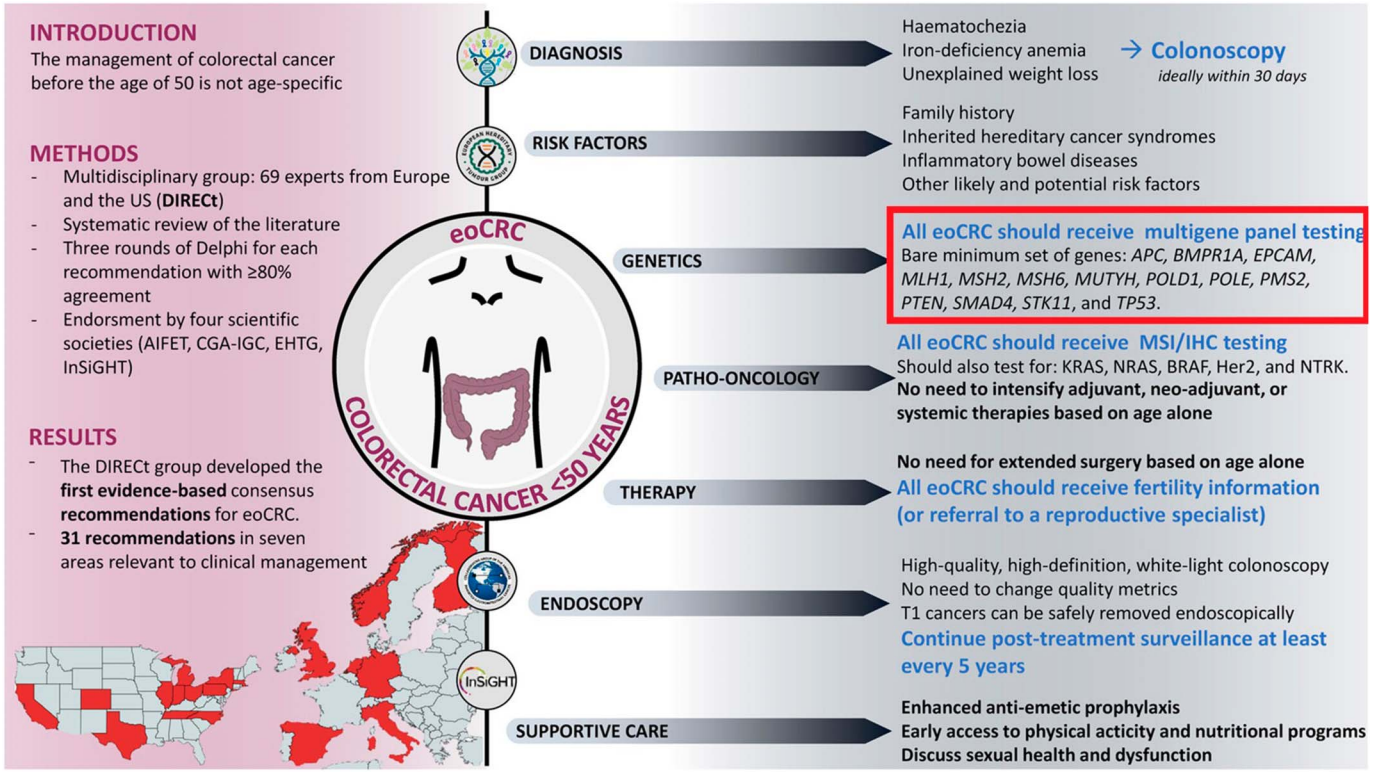

FIG 2. Delphi Initiative for EO-CRC. Red box indicates recommendation that all patients with EO-CRC should receive MGPT. AIFET, Association Italiana Familirita Ereditarieta Tumori; CGA-IGC, Collaborative Group of the Americas on Inherited Gastrointestinal Cancers; DIRECt, Delphi Initiatve for Early Onset Colorectal Cancer; EHTG, European Hereditary Tumor Group; EO-CRC, early-onset colorectal cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; InSiGHT, International Society for Gastrointestinal Hereditary Tumors; MGPT, multigene panel testing; MSI, microsatellite instability.

What is less clearly defined is the association of gastric cancer with pathogenic germline variants in the homologous recombination DNA repair pathway. In a large cohort of more than 5,000 BRCA families, the relative risk of gastric cancer was increased in both *BRCA1* and *BRCA2* carriers, 2.17 (95% CI, 1.25 to 3.77) and 3.69 (95% CI, 2.4 to 5.67), respectively.[90] This association appears to be stronger with *BRCA2* than with *BRCA1*.[91-94] At the present time, these data are not robust enough to recommend routine surveillance gastroscopy in all carriers of gPVs in *BRCA* but could be a consideration in the setting of both gPVs and a family history of gastric cancer.[95]

gPVs on Multipanel Testing and Causality: The Unknown

With the increasing availability of commercial MGPT and expansion of the cancer types in which MGPT is recommended particularly in patients with EO cancer, we will undoubtedly detect more gPVs which are of clinical relevance for the patient as well as at-risk relatives. Although MGPT is recommended for patients with ovarian, pancreatic, and high-risk/or metastatic prostate cancer, the debate about universal germline testing for patients with CRC remains unresolved. In a cohort of nearly 35,000 patients, Coughlin et al[96] reported detection of at least one pathogenic/likely pathogenic germline variant; the majority of which were in genes classically associated with CRC. The rates of gPVs were highest in the youngest age groups, 25.7% in patients younger than 30 years, 17% in patients age 30-39 years, and 14.1% in those age 40-49 years. The rate of clinically actionable variants in individuals younger than 30 years was approximately double than that of patients age between 50-59, 60-69, and 70-79 years, 23.4% versus 13% and 11.7% and 8.9%, respectively. With increased genetic testing, appreciation of novel associations may further evolve and become more clearly defined.

However, what cannot be deduced from germline MGPT alone is the contribution of a particular gPV to causation of the index cancer particularly in the setting of genes not classically associated with that cancer subtype. As such, integration of germline and somatic analysis is critical to elucidate the role of germline variants in GI carcinogenesis by evaluating biallelic loss which when assessed seems to be consistently higher among patients with EO cancer than in average-onset cancer,[62,68] suggesting that these gPVs are driving cancer development at least in proportion of these

cancers. Determination of causality is imperative to identify novel treatment approaches exploiting underlying germline drivers implicated in carcinogenesis. Importantly, although the prevalence of gPVs are consistently higher among patients with EO cancers, decisions regarding germline genetic testing should not be restricted by age alone, particularly as the therapeutic implication of gPVs expands.[71,97]

NOVEL STRATEGIES IN EO GI MALIGNANCIES

Novel Targeted Treatment Strategies

Two potentially paradigm altering trials were presented in 2022 demonstrating a novel targeted approach to MSI colorectal tumors. Building on the total neoadjuvant approach for MSS locally advanced rectal cancers gaining traction globally, Cercek et al[98] demonstrated the potential for the complete omission of both surgery and radiotherapy for locally advanced MSI rectal cancers treated with immunotherapy alone with the interim analysis, demonstrating a 100% response rate. In a similar fashion without the omission of surgery, Chalabi et al[99] demonstrated a 95% major pathological response rate among MSI locally advanced colon cancers treated with combination immunotherapy. The potential to avoid the toxicities of chemotherapy and radiotherapy will have particular relevance among patients with EO-CRC among whom LS is the most commonly seen genetic syndrome and is characterized by near universal MSI status of the associated tumors. In 2023, Andre et al[100] published the interim results of another similar study evaluating the use of neoadjuvant ipilimumab and nivolumab in resectable gastric and gastroesophageal junction tumors demonstrating a high pathological complete response rate and allowing for the omission of surgery in 3 of 32 patients. The OS data from these and other ongoing prospective studies will confirm the utility of this approach.

Novel Research Approaches

To fully elucidate the etiology of EO cancers and evaluate the complex interaction between environmental factors, prospective life-course cohort studies that enable biomarker/omics analyses of specimens obtained during early life in parallel with the collection of epidemiological information will be critical.[2] The pooling of existing data sets is a consideration particularly when evaluating rarer GI malignancies such as biliary tract cancers to develop improved prevention and treatment strategies. Funding research endeavors of this magnitude will require significant cross border and international collaboration.

SPECIAL CONSIDERATIONS

The rise in EO cancers has significant implications on a personal level beyond the physical level for patients whose families are not yet complete and who are often working full time at the time of their diagnosis and more broadly has significant societal impacts both financial and structural with escalating health care costs, reduction of the workforce, and often fragmentation of young families in the event of cancer diagnosis in a parent. Focusing on EO-CRC because of the high rate of diagnosis at later stages of disease, patients with EO-CRC are much more likely to face long-term functional deficits, higher rates of anxiety, poor body image, and difficulties associated with alterations in bowel habits.[101] Recognition of the unique supportive care and developmental and psychosocial needs of patients with EO cancer to inform development of a framework to address the needs of this expanding population in parallel with research into the underlying etiological factors is critical.[102]

Oncofertility

In contrast to average-onset cancers, discussion regarding fertility preservation is critical before the initiation of treatment among patients with EOC. Although recognition of the impact of systemic anticancer therapies on fertility among patients with EO breast cancer has been robustly elucidated, data specific to fluorouracil-based regimens which form the backbone of numerous regimens across the GI caner spectrum are more limited.[14] The effect of fluorouracil on fertility is lower than with agents such as cyclophosphamide; data also suggest that amenorrhea, which may be persistent, is associated with increasing age at the time of chemotherapy receipt, mirroring what has been described in perimenopausal patients with breast cancer receiving chemotherapy.[103,104] The addition of oxaliplatin can induce transient gonadotoxicity in both men and women.[105] The use of gonadotropin-releasing hormone agonists which is commonplace in the treatment of premenopausal patients with breast cancer on chemotherapy is less widespread among patients with EO GI cancers but should be considered to prevent chemotherapy-induced ovarian failure.[41]

A distinct consideration with regard to the management of rectal cancer which appears to be rising in premenopausal patients is the risk of premature menopause induced by pelvic radiation[40]; doses of 45-50 Gy induce premature menopause in >90% of patients.[106] Ovarian transposition may reduce but not eliminate the damaging effect of radiation on the ovaries.[107] It should, however, be considered especially for women age 40 years or younger to avoid premature menopause and associated sequelae. Current clinical guidelines recommend offering cryopreservation of sperm to all patients undergoing gonadotoxic chemotherapy and embryo cryopreservation or preservation of unfertilized oocytes.[108] Referral to fertility preservation specialists should be considered for all patients with EO cancers.

Survivorship and Longer-Term Health Consequences

Patients with EO cancer are particularly susceptible to the financial toxicity associated with cancer care.[109] Patients with EO disease are often early in their careers, and maintaining financial security and employment is often challenging, and additionally they may have minimal savings or assets[8] and may be dependent on the support of family members to cover the costs associated with treatment exacerbated by work absence.

Survivors of EO cancers also have a higher risk of other long-term health problems including secondary cancers and cardiovascular disease.[110,111] Specific to CRC, a large study among older survivors indicated that the 10-year cumulative incidence of new-onset cardiovascular disease and heart failure to be more than double than that of the controls.[112] The magnitude of risk for patients with young-onset CRC has not been clearly elucidated.

CONCLUSION

Despite increasing understanding of genetic contributions to EO cancer, known gPVs only account for a small proportion of these cancers. Emerging data demonstrate the importance of the microbiome in cancer-modulating interactions and indeed response to therapy.[113,114] In addition, the association of obesity with EO cancer is also increasingly being elucidated.[14,115] Dietary factors have also been found to influence the development of colorectal adenomas in patients with LS, highlighting a potentiated, incremental risk in patients who already have up to a 60% lifetime risk of CRC on the basis of their germline status alone.[51,116] Understanding the complex interplay between host factors such as gPVs, gut microbiome, and extrinsic environmental factors will be critical to mitigate the rising incidence of EO cancer globally, particularly across the spectrum of GI cancers.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Next-Generation Approaches to Immuno-Oncology in GI Cancers

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overview

Immunotherapy has only had a modest impact on the treatment of advanced GI malignancies. Microsatellite-stable colorectal cancer and pancreatic adenocarcinoma, the most common GI tumors, have not benefited from treatment with standard immune checkpoint inhibitors. With this huge unmet need, multiple approaches are being tried to overcome barriers to better anticancer outcomes. This article reviews a number of novel approaches to immunotherapy for these tumors. These include the use of novel checkpoint inhibitors such as a modified anti–cytotoxic T lymphocyte–associated antigen-4 antibody and antibodies to lymphocyte-activation gene 3, T cell immunoreceptor with immunoglobulin and ITIM domains, T-cell immunoglobulin-3, CD47, and combinations with signal transduction inhibitors. We will discuss other trials that aim to elicit an antitumor T-cell response using cancer vaccines and oncolytic viruses. Finally, we review attempts to replicate in GI cancers the frequent and durable responses seen in hematologic malignancies with immune cell therapies.

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INTRODUCTION

Although immunotherapy with standard PD(L)-1 or cytotoxic T lymphocyte–associated antigen-4 (CTLA-4) immune checkpoint inhibitors (ICIs) has revolutionized the treatment of melanoma[1] and non–small-cell lung cancer (NSCLC),[2] the benefits in GI cancers have been relatively limited. The most efficacy has been demonstrated in patients with GI tumors with deficient DNA mismatch repair (dMMR)[3] although these are only a small portion of patients with GI cancer particularly in pancreatic adenocarcinoma.[4] Furthermore, not all dMMR cancers respond to therapy with standard ICIs and some that do eventually progress. ICIs have become standard of care in metastatic upper GI malignancies,[5] hepatocellular carcinoma,[6] and bile duct cancers[7] although the benefits are not as great as those seen in more immunosensitive tumors. The most common GI cancers, proficient MMR colorectal cancer (CRC), and pancreatic adenocarcinoma remain resistant to these agents.[3] Therefore, new approaches to immunotherapy are needed. The most mature of these are novel checkpoint inhibitors, tumor vaccines, oncolytic viruses (OVs), and immune cell therapies. The data for their use in GI cancers will be reviewed.

NOVEL ICIs AND COMBINATIONS IN GI TUMORS

ICIs, notably anti–CTLA-4 and PD-1 and PD-L1 inhibitors, have improved treatment for solid tumors, including GI.[3,8-10] Combinations with chemotherapy[5,11] and the anti–human epidermal growth factor receptor 2 antibody trastuzumab are standard of care in cancers of the upper GI tract.[12] Unfortunately, outside of patients with dMMR, these benefits are rarely durable and are nonexistent in colorectal and pancreatic cancers. Therefore, researchers are looking at new versions of standard ICIs, new combinations with other agents to overcome immunosuppression, and finally inhibitors of novel checkpoints (Table 1).

Botensilimab, an Fc-enhanced next-generation anti–CTLA-4 antibody, in combination with balstilimab, a novel anti–PD-1 antibody, showed promising results in patients with microsatellite-stable (MSS), heavily pretreated metastatic CRC (NTC03860272).[16] Data presented by El-Khoueiry et al[17] recently showed that the objective response rate (ORR) was 24% (95% CI, 14 to 39), the disease control rate was 76% (95% CI, 60 to 84), and median duration of response was not reached. The 12-month overall survival (OS) rate was 63% (95% CI, 42 to 75). The patients who did benefit the most from treatment were those without liver metastases. About 12% of the patients had treatment-related adverse events resulting in treatment discontinuation. A phase II trial is currently enrolling (ClinicalTrials.gov identifier: NCT05608044).[18]

The presence of various immunosuppressive cells in GI tumors such as tumor-associated macrophages and regulatory T cells (Tregs) may limit the effectiveness of ICIs. In preclinical models, small-molecule tyrosine kinase inhibitors (TKIs) such as regorafenib can reduce this immunosuppression by inhibiting colony stimulating factor 1 receptor, vascular endothelial growth factor receptor, and other potentially immunosuppressive pathways.[19] The relatively small Japanese REGONIVO

PRACTICAL APPLICATIONS

- Further studies testing antibodies against LAG-3, TIGIT, T-cell immunoglobulin-3, and CD47 should be performed in GI malignancies as they have shown promising results in preclinical studies and phase I/II trials in other cancer types.
- Fc-enhanced cytotoxic T lymphocyte–associated antigen-4 inhibitor botensilimab in combination with an anti–PD-1 has shown remarkable activity in proficient MMR (microsatellite-stable) metastatic colorectal cancer in a phase I study, and results of further trials could have a major impact in standard-of-care treatments.
- Although cancer vaccines and oncolytic viruses have shown limited responses in early phase trials in GI cancers, there are still many unknowns in terms of which cancer types will respond and which combinations of chemotherapy/immunotherapy will improve efficacy.
- T-Cell receptor therapy may prove to be more advantageous than chimeric antigen receptor-T therapy in solid malignancies, but further research in this area is needed.
- Solving the problems of antigen selection and intrinsic tumor immune evasion will allow advances in genetic engineering of T-cell fitness to better promote durable antitumor responses.

trial combining regorafenib with the anti–PD-1 nivolumab showed encouraging results with the response rate (RR) of 44% in gastric cancer and 33% in MSS CRC. Many of these responses appeared to be durable.[13] A phase II North American trial, however, only showed a 7% RR with regorafenib and nivolumab, all in patients without liver metastases. In that small group, interestingly, the RR was 22%. Similar early data have been seen with newer small-molecule TKIs such as lenvatinib and cabozantinib that may inhibit additional immunosuppressive pathways.[20,21] Large-phase trials combining ICIs with lenvatinib (LEAP-017; ClinicalTrials.gov identifier: NCT04776148)[22] and zanzalintinib (XL092; STELLAR-303; ClinicalTrials.gov identifier: NCT05425940)[23] in metastatic CRC are currently underway.

There are multiple other immune checkpoints, and inhibitors of these alone and in combination with anti–PD(L)-1 inhibitors are the subject of active research in GI cancers. Lymphocyte-activation gene 3 (LAG-3) (CD223) is a cell surface molecule expressed on activated CD4 and CD8 T cells, Tregs, natural killer (NK) cells, B cells, and plasmacytoid dendritic cells (DCs).[24] In preclinical studies, the combination of LAG-3/PD-1 blockade resulted in synergistic activity, providing a strong rationale for a combinatorial strategy. In the randomized, phase II/III, RELATIVITY 047 study in patients with untreated or unresectable, advanced melanoma, the combination of relatlimab, a first-in-class, anti–LAG-3 antibody, with the PD-1 inhibitor nivolumab showed improvements in median progression-free survival (mPFS) compared with nivolumab alone (10.1 *v* 4.6 months [hazard ratio, 0.75; 95% CI, 0.62 to 0.92; $P = .006$]).[25] This combination is now approved for treatment by the Food and Drug Administration (FDA). A phase I trial with the anti–LAG-3 antibody favezelimab with pembrolizumab in metastatic CRC had an 11% RR. Combination trials with other LAG-3 antibodies are ongoing in GI cancers.[26]

T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), a member of the Ig superfamily and an immune inhibitory receptor, plays a key role in the suppression of T-cell proliferation and activation.[27] Among its functions, TIGIT inhibits NK cell–mediated tumor killing, suppresses CD8 T-cell priming and differentiation, and prevents CD8 T-cell–mediated killing.[28] Preclinical studies showed that TIGIT is coexpressed and associated with PD-1 expression and dual blockade of TIGIT and PD-1 in the restoration of T-cell[29] and NK cell immunity, providing a good rational for this combination.[30] The CITYSCAPE trial evaluated the efficacy and safety of tiragolumab in combination with atezolizumab as first-line treatment for NSCLC. The primary analysis from this randomized, double-blind, phase II trial showed clinically meaningful improvement in ORR and PFS compared with placebo plus atezolizumab in patients with chemotherapy-naive, PD-L1–positive, recurrent or metastatic NSCLC.[31,32] Unfortunately, these results were not confirmed by the SKYSCRAPER trial, which failed to confirm PFS and OS benefits in the tiragolumab arm.[33] There are ongoing trials of tiragolumab in combination with atezolizumab, chemotherapy, and targeted therapies in upper GI and CRCs (ClinicalTrials.gov identifier: NCT03281369, NCT04929223).[34,35] In the CITRINO study (ClinicalTrials.gov identifier: NCT03250832),[36] encelimab (TSR-033) was combined with dostarlimab and bevacizumab and chemotherapies in patients with CRC, but results are still pending. Vibostolimab (MK-7684), another anti-TIGIT antibody, was evaluated in combination with pembrolizumab in a phase I trial, showing a safe profile and a promising antitumor activity,[37] and is being looked at in MSI-high CRC (ClinicalTrials.gov identifier: NCT04895722).[38]

T-cell immunoglobulin-3 (TIM-3) is an immune checkpoint that promotes immune tolerance.[39] TIM-3 blockade results in decreased myeloid-derived suppressor cells (MDSCs) and increased proliferation and cytokine production by T cells.[40] Given its expression in a variety of T cells and its synergistic effects with other anti–PD-1 agents, several trials are ongoing to evaluate safety and activity of TIM-3 inhibitors in combination with anti–PD-1 antibody. In a

TABLE 1. Novel Immune Checkpoint Inhibitors and Combinations

Target	Mechanism of Action	Ongoing/Completed Trials in GI
Fc-enhanced anti–CTLA-4	Anti–CTLA-4 ab with enhanced FcγR-dependent functionality Promotes superior T-cell priming, memory responses, and depletion of intratumoral Tregs	Phase II of botensilimab with balstilimab in CRC (NCT05608044)
TKIs Regorafenib Zanzalintinib Lenvatinib	TKIs block potentially immunosuppressive pathways	REGONIVO Japanese trial combining regorafenib with nivolumab 11[13] Phase II trial regorafenib/nivolumab in North America (NCT04126733) Phase III zanzalintinib + atezolizumab in mCRC (NCT05425940) Phase III lenvatinib + pembrolizumab in mCRC (NCT04776148)
LAG-3	A cell surface molecule expressed on activated CD4/CD8 T cells, Tregs, NK cells, B cells, and DCs	Phase I trial with favezelimab with pembrolizumab in mCRC (NCT05064059)
TIGIT	Inhibits NK cell–mediated tumor killing Suppresses CD8 T-cell priming/differentiation Prevents CD8 T cell–mediated killing	Phase I trials in combination with ICI (NCT03281369, NCT04929223, NCT03250832, NCT04895722)
TIM-3	Blockade results in decreased MDSCs and increased proliferation and cytokine production by T cells	Phase Ib study of sabatolimab and spartalizumab 11[14]
CD47	Binds to SIRPα that inhibits macrophage phagocytosis	ELEVATE trial in combination with FOLFIRI and bevacizumab (NCT04827576)
ICOS (CD278)	Binds to an ICOS ligand expressed by B cells, macrophages, and DCs Costimulatory for T-cell proliferation and cytokine production Inhibition decreases intratumoral Tregs and increases T effector cells	Phase I/II trial in combination with atezolizumab in advanced malignancies (NCT03829501)
B7-H3 (CD276)	Inhibits CD4/CD8 T-cell activation, proliferation, and cytokine production	Phase I/II trial in advanced solid tumors with enoblituzumab 11[15]

Abbreviations: ab, antibody; CRC, colorectal cancer; CTLA-4, cytotoxic T lymphocyte–associated antigen-4; DCs, dendritic cells; FcγR, Fc gamma receptor; FOLFIRI, folinic acid, fluoruoracil, and irinotecan; ICI, immune checkpoint inhibitor; ICOS, inducible T cell costimulator; LAG-3, lymphocyte-activation gene 3; mCRC, metastatic colorectal cancer; MDSC, myeloid-derived suppressor cell; NK, natural killer; SIRPα, signal receptor protein-α; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domains; TIM-3, T-cell immunoglobulin-3; TKI, tyrosine kinase inhibitor; Treg, regulatory T cell.

phase Ib study, sabatolimab (MBG453), a TIM-3 antibody, and spartalizumab, a PD-1 ICI, generated partial responses in two patients with CRC.[14]

CD47 is a don't-eat-me signal that is a truly novel checkpoint for macrophages and DCs. It binds to signal receptor protein-α that inhibits phagocytosis.[41] Studies with the anti-CD47 antibody magrolimab have shown promising activity in hematologic malignancies.[42] The randomized phase II ELEVATE trial is currently underway in second-line CRC in combination with FOLFIRI and bevacizumab (ClinicalTrials.gov identifier: NCT04827576).[43]

Other novel checkpoints such as V-domain immunoglobulin suppressor of T-cell activation (VISTA), inducible T cell costimulator (ICOS), and B7-H3 have not been closely examined in GI cancer. VISTA is an immunoregulatory molecule involved in maintaining T-cell and myeloid quiescence.[44] It is expressed on resting T cells, indicating its regulatory role in earlier stages, and is more abundant in MDSCs in the tumor microenvironment (TME). The nonoverlapping mechanisms of VISTA and PD-L1 make their combination an ideal treatment strategy to overcome immune suppression. ICOS (CD278) is a member of the CD28 coreceptor family, which includes costimulatory CD28 and coinhibitory receptor CTLA-4.[45] Yap et al[46] evaluated an ICOS agonist, vopratelimab, alone and in combination with nivolumab in patients with advanced solid tumors. The study showed a safe drug profile and efficacy only in a subset of patients, with potential biomarkers to be evaluated in prospective studies. B7-H3 (CD276) is a member of the B7 family, a family of transmembrane proteins that interact with CD28 receptors family and modulate wither stimulatory or inhibitory immune signals.[47] Several agents targeting B7-H3 are currently under investigation in clinical trials. The anti–B7-H3 monoclonal antibody, enoblituzumab (MGA271), was evaluated in combination with pembrolizumab in a phase I/II trial in advanced solid tumors, showing a safe profile and promising antitumor activity in checkpoint inhibitor–naïve patients.[15]

In summary, there are multiple approaches being examined to try to overcome resistance to standard CTLA-4 and PD(L)-1 inhibitors in GI cancers. These promise to improve outcomes in malignancies that have had little improvement over the past two decades. Further development will require more translational research and identification of robust biomarkers of activity.

CANCER VACCINES IN GI MALIGNANCIES

Adaptive immunity is mediated by cytotoxic CD8+ T cells, CD4+ helper T cells, and B cells. In cellular immunity, T cells can recognize and eliminate diseased cells.[48] Vaccines work by inducing an immune response to the antigen(s) encoded by the vaccine. Subsequently, immunologic memory and adaptive immunity elicited against the immunizing antigen can protect an individual against the pathogen from which the antigen was derived.[49] Cancer vaccines are designed with the intent to elicit an immunologic therapeutic response against tumor antigens. Tumor antigens can be divided into tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs). TSAs are expressed only by cancer cells, not normal cells, whereas TAAs are overexpressed in tumor cells compared with normal cells.[50]

Despite numerous attempts over the past century, only two therapeutic vaccines have been approved to date, sipuleucel-T, a DC-based vaccine for the treatment of castrate-resistant prostate cancer,[51] and the Bacillus Calmette-Guerin (BCG) vaccine for early bladder cancer. Despite this track record, vaccines continue to be developed in GI malignancies because of the huge unmet need. There are multiple different vaccine approaches to stimulate anticancer immunity such as autologous or allogenic cancer cells, DCs, and vaccine vectors encoding tumor antigens.[52]

Early studies used whole cancer cells to induce an immune response. OncoVAX combined BCG with autologous cancer cells. In the phase III ECOG 5383 trial of patients with CRC treated with surgery with or without vaccine, there was no significant difference in overall or disease-free survival.[53] GVAX is an allogeneic whole-cell vaccine composed of two human pancreatic adenocarcinoma cell lines modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF).[54] Promising early data with CRS-207, a listeria modified to express the common TAA mesothelin,[55] were not borne out in the larger ECLIPSE trial[56] or in combination with checkpoint inhibitors.[57]

DCs are antigen-presenting cells that can activate naïve T cells against various host insults. A MUC1 peptide–loaded DC vaccine was tested in a phase I/II trial in resected pancreatic cancer with some long-term survivors.[58] Many ongoing trials in CRC involve administrating DCs pulsed with autologous tumor lysates. Immune responses to tumor antigens found in CRC and pancreatic cancer can be generated after DC vaccination, but these have not resulted in improved clinical outcomes.[59]

Another class of vaccines use different vaccine vectors, such as peptides, DNA plasmids, viruses, or RNA, to encode specific tumor. Potential challenges include identifying tumor antigens that will be immunogenic in specific patients. In a phase II trial in advanced CRC, a mixture of five HLA-A*24:04–restricted peptides combined with oxaliplatin-based chemotherapy had no significant effect on clinical outcomes.[60] The RAS G12D/R peptide vaccine ELI-002 is currently being examined in patients with ctDNA-positive only pancreatic and other cancer (ClinicalTrials.gov identifier: NCT04853017).[61] Advances in sequencing and manufacturing of vaccine vectors have enabled the design of personalized and off-the-shelf vaccines that can target neoantigens (tumor antigens derived from mutations). As an example, the mRNA-based phase II trial, KEYNOTE-942 trial, showed encouraging activity and possible proof of concept with this approach, reducing recurrence or death by 44% in patients with stage II/IV melanoma.[62] These data support the concept that treating patients earlier in their course of disease may improve the efficacy of vaccine approaches. A phase I study of a prime boost strategy–personalized vaccine study using chimp adenovirus and self-replicating RNA resulted in robust antitumor immune response[63] and is being examined in the first-line colorectal maintenance setting in the phase II/III GRANITE trial (ClinicalTrials.gov identifier: NCT05141721).[64] New vaccine approaches even have the exciting potential to reduce cancer incidence in patients with high-risk premalignant conditions such as Lynch syndrome.[65]

Although several cancer vaccines have shown induction of vaccine-specific responses, these have not resulted in clinical benefits in GI or most other cancers. The quality and quantity of these immune responses, especially with respect to CD8+ and CD4+ T cells, remain incompletely characterized and are an important consideration in evaluating the effectiveness of cancer vaccines. The antigens targeted by vaccines have important implications in the quality of the immune response as one of the primary issues with overexpressed TAAs is that central and peripheral tolerance mechanisms limit the generation of autoreactive B and T cells that strongly recognize these sequences.[66] Vaccines need to overcome this immune tolerance to mount a response without causing autoimmune reactions. There is still much work to be performed to identify which class of tumor antigens delivered by which vaccine vectors results in an optimal immune response. Additional factors include how to combine vaccines with standard-of-care chemotherapy and other immunotherapy drugs and the treatment setting (ie, adjuvant, early *v* late metastatic disease). A successful vaccine approach aims to overcome tolerance, reverse

immunosuppression, cause tumor death, and generate long-lasting memory responses.

OVs IN GI MALIGNANCIES

The benefits of immune herapies seem to be greatest in immunologically hot TMEs.[67] These tumors have high mutational burdens, high levels of tumor-infiltrating lymphocytes (TILs), and increased PD-L1 expression. The lack of presentation and/or expression of TAAs; infiltration by suppressive neutrophils, regulatory T cells, macrophages, myeloid-derived suppressor cells, or NK cells; low density of TILs; and expression of immunosuppressive factors lead to an immunologically cold tumor.[67] OVs are an exciting class of anticancer immunotherapies that exploit viruses' innate ability to preferentially infect, self-amplify, and lyse tumor cells.[68] They hijack and reprogram the host's cellular machinery, expressing both therapeutic and virus transgenes.[69] OVs were initially designed to just kill tumor cells, but more recent data have shown that at least some of the anticancer effects are by infecting a tumor cell and induce apoptosis, triggering an inflammatory reaction.[70] This activates innate and adaptive immune responses by the release of TAAs, pathogen-associated molecular patterns, and danger-associated molecular patterns from lysed tumor cells to act like a cancer vaccine to achieve an abscopal effect.[69] Talimogene laherparepvec (T-VEC), a herpesvirus designed to produce GM-CSF in the tumor to enhance antigen release, presentation, and antitumor immune response, was the first OV approved for use in the United States and Europe.[67] In a phase III trial, intratumoral injection of T-VEC improved durable RR and other clinical outcomes in advanced, nonresectable melanoma, leading to full FDA approval in 2015.[71] Despite initial encouraging results together with pembrolizumab, in a phase III trial, the combination was not superior to pembrolizumab alone.[72,73]

Multiple classes of OVs have been developed. The nonenveloped double-stranded DNA (dsDNA) adenoviruses were some of the first.[69] ONYX-015 is a first-generation *E1B*-55kD gene-deleted replication-selective adenovirus that preferentially replicates in and kills malignant cells. In a phase I/II trial of endoscopic ultrasound injection of locally advanced or metastatic pancreatic cancer in combination with gemcitabine, two of 21 patients had partial regressions of the injected tumor and eight had stable disease.[74] Although not being developed further in GI cancers, a variant, H101, is approved in China for head and neck cancer.[75] TNFerade, an adenovirus encoding tumor necrosis factor alpha, was examined in combination with chemoradiation in locally advanced pancreatic cancer with encouraging phase I/II results, but a phase III trial was negative.[76,77] Other adenoviruses being examined in GI cancers include enadenotucirev (EnAd, ColoAd1) and telomelysin,[78] which are currently being studied in combination with pembrolizumab in a phase II trial for advanced gastroesophageal adenocarcinoma (ClinicalTrials.gov identifier: NCT03921021).[79]

Herpesviruses are characterized by an icosahedral capsid and a dsDNA genome. Oncolytic herpes simplex viruses (HSVs) have been extensively studied because of a large transgene capacity, lack of insertional mutagenesis, and ability to activate innate and adaptive immune responses against tumors.[69] A phase I study using T-VEC in combination with atezolizumab for triple-negative breast cancer and CRC with liver metastases, however, showed limited evidence of antitumor activity.[80] Other HSV derived agents are in development.[81]

Vaccinia virus has a large dsDNA genome[69] and replicates in the cytoplasm, thereby eliminating the risk of insertional mutagenesis. The best studied vaccinia OV is pexastimogene devacirepvec (Pexa-Vec, JX-594), an engineered thymidine kinase–mutant vaccinia virus armed to express GM-CSF and β-galactosidase as transgenes.[69,82,83] It was found to be trafficked to the tumor as evidenced by the viral genome found in tumor biopsies,[84] and there were early hints of anticancer activity.[85] Unfortunately, a randomized phase IIb trial in hepatocellular cancer was negative[86] and a phase I/II trial with durvalumab and tremelimumab in CRC showed modest benefit.[87]

Pelareorep (Reolysin) is an unmodified oncolytic reovirus, delivered intravenously, that can induce a T-cell inflamed phenotype in pancreatic ductal adenocarcinoma. In a phase Ib study in patients who had progressed after first-line treatment, pelareorep, pembrolizumab, and 5-fluorouracil, irinotecan, or gemcitabine[88] did not add significant toxicity and showed encouraging efficacy. Other phase II trials of pelareorep in pancreatic cancer in combination with carboplatin/paclitaxel have showed similar results of good tolerability but mixed responses in terms of RR, PFS, and OS.[89,90]

This is a nonexhaustive survey of OVs in GI cancers. There are many challenges to overcome in the development of effective OVs. The need for intratumoral injection of some OVs, proper spread and penetration of the therapeutic agent, tumor cell targeting, pre-existing immunity to the viruses, and hypoxia are all factors that can inhibit the effectiveness.[82] The site of injection may also affect efficacy. The liver is particularly immunosuppressive with multiple mechanisms including liver metastases siphoning activated CD8+ T cells from systemic circulation and within the liver, leading to acquired immunotherapy resistance.[91] The optimal degree of infectivity and oncolysis is also unknown. Other unknowns in the study of OVs are which patients and tumor types most benefit from this therapy and in which combinations of chemotherapy and immunotherapy. Potential combinations with cytokines, BiTEs, and even chimeric antigen receptor (CAR)-T cells may improve efficacy.[92,93]

IMMUNE CELL THERAPY FOR GI TUMORS

The ability of infused cultured tumor-reactive immune cells to induce the rejection of human cancers has been well demonstrated. Expanding the resident T cells in melanomas (TIL) and infusing them along with systemic interleukin-2 (after preparative lymphodepletion with chemotherapy) can result in an ORR of over 50%, with half of those responding patients apparently cured of metastatic disease.[94] Genetically modifying peripheral blood lymphocytes (PBLs) with a CAR targeting a B-cell antigen, CD19, can cause objective regressions of large B-cell lymphoma in 82% of patients with refractory disease, again with many of them achieving durable complete remissions after a single administration.[95] A third example is the introduction of a tumor-reactive T-cell receptor (TCR; cloned from a T cell specific for the NY-ESO-1 antigen) into the PBL of patients with synovial sarcoma or melanoma, which resulted in a 58% ORR.[96] The major goal at this time is to expand such results to the common epithelial cancers, and this has proven to be difficult. This review will clarify the differences between these three sources of tumor reactive T cells, review their results, and discuss future directions.

PBLs (or in some cases, NK cells) engineered with CAR-T cells have been quite effective in the treatment of several hematopoietic malignancies. The CAR consists of an antigen-binding domain coupled to the T-cell signaling machinery, often with an interposed costimulatory domain. The antigen-binding domain is typically an antibody single-chain variable fragment (scFv), the T-cell signaling moiety usually uses CD3-zeta, and the costimulator is often CD28 or CD134 although innumerable variations on this framework have been devised. The current obstacle to using CAR T cells against solid malignancies has been the identification of safe TAAs. First, these TAAs need to be outer cell membrane structures and then they must be invariant because of the complexities of creating Ag-binding domains and optimizing the CAR. Most have been normal differentiation antigens on disposable tissues. Targeting cell surface B-cell markers such as CD19 and CD22 to destroy both benign and malignant B cells is tolerable because patients can live without B cells. Unfortunately, the organs giving rise to GI cancers are typically not dispensable. Very limited efforts to target solid tumors with CAR-T cells have been pursued. Early efforts to target carcinoembryonic antigen (CEA) either were ineffective or generated normal bowel toxicity.[97] Targeting the GD2 ganglioside on neuroblastoma and some pediatric gliomas has shown some positive results in small studies, but it is not a target on common epithelial cancers.[98] One very interesting phase I trial targeted the tight junction protein Claudin18.2 with a classic CAR consisting of a scFv-binding domain, CD28 costimulation, and CD3 zeta signaling.[99] Cells were administered after cyclophosphamide and fludarabine preconditioning, but no interleukin-2 was administered. An ORR of 49% was reported in patients with predominantly gastric cancer despite administering a relatively low numbers of cells ($\leq 5 \times 10^8$ cells). All responses were partial, and many of short duration; yet, this represents one of the only CAR-T-cell trials relevant to GI cancers with significant objective responses. Another research initiative has been to apply gating strategies to CARs to allow immune attack on cancer, but block activity when the target is encountered on normal tissues.[100] Logic-gated CAR-T cells have shown activity and specificity in preclinical models, and trials are ongoing in GI cancers expressing CEA.[101-103] Alternatively, one can target two structures with imperfect specificity on cancer that do not coexpress on normal tissues to generate better specificity.[104] These promising ideas are poised to enter early clinical trials, and their effectiveness remains unknown. The idea of CAR-T cells for common solid tumors remains attractive because of the circumvention of the major histocompatibility complex (MHC) restriction of normal T cells, expanding the applicability to more patients. There is also a theoretical advantage to a novel synthetic receptor for cancer. As will be described below, tumors under siege by endogenous T cells rapidly develop diverse immune evasion and escape mechanisms. Using a novel non-native receptor to initiate a T-cell attack has the advantage of not encountering a priori escape mechanisms generated before the adoptive transfer. Yet, the main obstacle remains not having suitable and safe target antigens.

The alternative to using CAR-T cells is to use native T cells and TCRs. Their major disadvantage is that TCRs recognize small processed peptide epitopes presented on MHC molecules. Therefore, a TCR is only pertinent to tumors with both the antigen and the presenting MHC allele and a much larger array of receptors is needed to address a population of patientswith cancer. On the other hand, because the epitope is proteolytically processed and exported to the cell surface on the MHC molecule, the TAA can be any protein made in the cytoplasm, not just outer cell membrane proteins. Humans also have nearly 10^{11} premade T-cell specificities in their repertoire, so there is no manufacturing required. Again, the main problem is finding safe and effective TAA. Here, the critical role of tumor-specific mutations comes into play. It has become clear from laboratory work and checkpoint inhibitor therapies that these mutated proteins are the major driver of the immune response of humans to cancer. Their tumor-specific nature also makes them a safe T-cell target. Unfortunately, the array of tumor-specific mutations is highly specific to each patient and their tumor,[105] with a limited number of common, shared mutations. One method of identifying T-cell reactivities to mutated antigens (neoantigens) has been described and extended to clinical trials.[106] A cancer's mutations are defined by whole exomic sequencing, and those mutations are

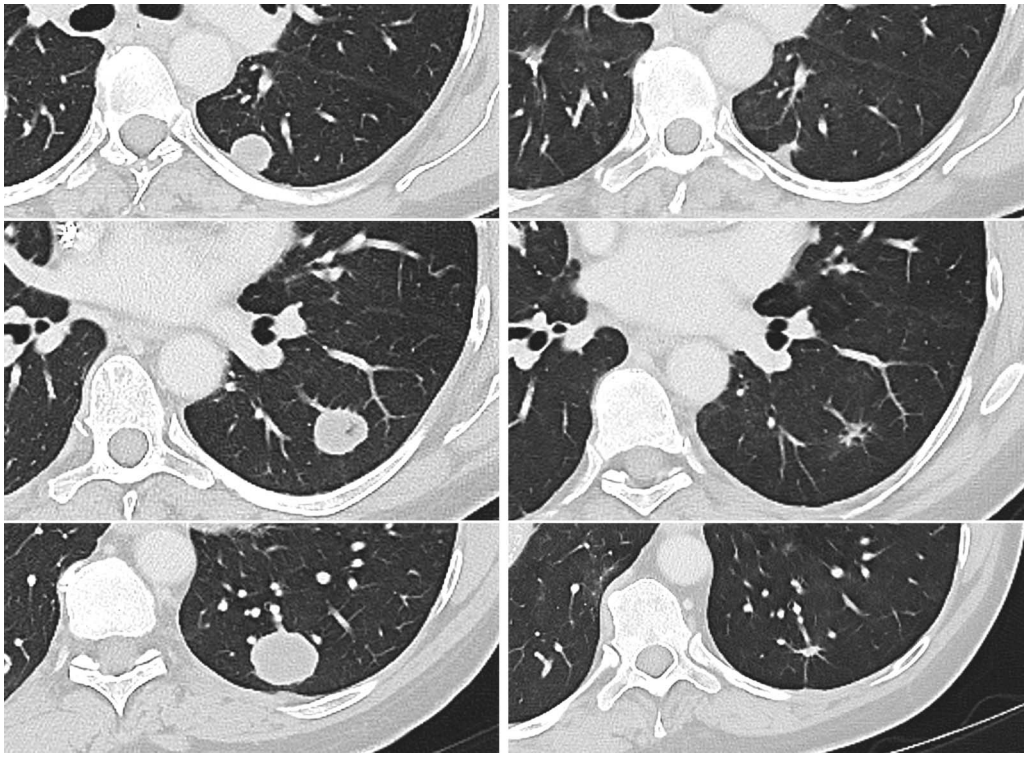

FIG 1. Responses to TIL reactive with neoantigens in colon cancer. Patient with colon cancer metastatic to lungs. Treated with lymphodepletion followed by adoptive transfer of TIL reactive with mutations in *DNMT3A* and *MUC6* and six doses of interleukin-2. The patient had near complete response and had received no other treatment. The left panel is baseline CT scan, and the right is 5-year follow-up showing all residual disease. CT, computed tomography; TIL, tumor-infiltrating lymphocyte.

expressed in autologous DCs by either minigene electroporation or loading synthetic peptides to create an avatar of that cancer's mutanome. This is then cocultured with TILs to identify which TILs are neoantigen-reactive. Patients are infused with subcultures selected for reactivity after undergoing preparative lymphodepletion with chemotherapy, and then systemic IL-2 is coadministered with the cells. The first patient to undergo this had cholangiocarcinoma and had a partial response of liver and lung metastases lasting nearly 3 years. She then relapsed but had persisting TIL from the infusion that expressed PD-1 and reresponded to a short course of pembrolizumab and remains free of disease, now 9 years after cell transfer.[107] Patients with breast cancer,[108] cervical cancer,[109] and colon cancer (Fig 1) have had durable complete responses to TIL reactive with neoantigens. Yet the RR is low despite the proven specificity of the infused TIL. Although this may in part be due to the exhausted phenotype of most TIL,[110] a host of tumor-related evasion mechanisms have been found as well. The simplest is the loss of the neoepitope or the restricting MHC allele. Although the latter was thought to occur from loss of both alleles of β-2 microglobulin (for MHC

TABLE 2. Advantages and Disadvantages of CAR-T Versus Native TCRs

Advantage/Disadvantage	CAR T Cells	T Cells/TCRs
Advantages	No MHC restriction	All proteins can be potential targets
	No previous immune resistance or evasion	Can easily target tumor-specific neoantigens
		Diverse repertoire naturally available
		Thymic tolerance prevents autoimmunity
Disadvantages	Targets essentially limited to shared (self) antigens	MHC restriction requires more TCRs
	Targets must be outer cell membrane structures	Prior selection for resistance occurs
	No thymic protection against autoimmunity	

Abbreviations: CAR, chimeric antigen receptor; MHC, major histocompatibility complex; TCRs, T-cell receptors.

class I), it has become apparent that loss of the single presenting MHC allele (seen as loss of heterozygosity at the MHC locus on chromosome 6) or downregulation[111] is more common and can even occur during the course of treatment.[112] Other evidence from checkpoint inhibitor therapy identified interferon-gamma signaling defects as a cause of tumor resistance to T cells.[113-115] Because the tumor and neoantigen-reactive T cells coexist for years, there is an opportunity for escape mechanisms to evolve; immune pressure leads to immune selection, which can lead to immune escape. Some mechanisms are reversable (such as T-cell inhibition by checkpoint receptors), some are irreversible (tumor MHC loss), some are T-cell–associated, and some are tumor-associated. One drawback of TIL therapy is that there is little control over the T cells that one recovers from a resected tumor. There can be problems with exhausted T cells, a low frequency of reactive cells, and inhibited TIL. One way to address issues with the quality of TIL is to clone the TCRs from neoantigen-reactive TIL and re-express them in fresh autologous PBL for transfer. This can also create an opportunity to target common recurring mutations with off-the-shelf reagents.

Mutations in *KRAS*, TP53, EGFR, BRAF, and PIK3CA, among others, are seen recurrently in many human cancers. Assembling libraries of TCRs specific for these mutations would allow the rapid generation of T cells for transfer by retroviral transduction. This would also allow one to select or genetically engineer optimized T-cell phenotypes to induce tumor rejection. Each mutation would require TCRs with specific MHC restrictions, greatly expanding the TCR libraries required. Yet, less than a 100 TCRs restricted by the most common HLA alleles would apply to the majority of human cancers. Most of the current efforts concentrate on *KRAS* (G12D, G12V mutations)[116,117] and TP53 (high-frequency hot spot mutations),[118] common in GI tumors. These mutations have been shown to be immunogenic, and in some cases, there is evidence that targeting them can be clinically effective.[112,119,120] Preclinical and clinical studies on genetic modifications to improve efficacy have looked at introducing cytokine secretion or orthogonal synthetic cytokine receptors into T cells,[113,121,122] and modifying function instead of just specificity represents the future of T-cell therapy. In summary, the adoptive transfer of tumor reactive T cells can cause curative regressions of some cancers. These T cells can be obtained from the natural repertoire of the patient via TIL or be genetically constructed by introducing either a CAR or a native TCR with tumor specificity. Each of these approaches has their advantages and disadvantages (Table 2). Solving the problems of antigen selection and intrinsic tumor immune evasion will allow advances in the genetic engineering of T-cell fitness to better promote the durable rejection of cancers.

CONCLUSION

Multiple immunotherapeutic approaches are actively being pursued in metastatic GI cancers. Although standard ICIs help some patients for a relatively short time, the immuno-oncology revolution in cancer care has bypassed most of these patients. Novel strategies including new checkpoint inhibitors, cancer vaccines, OVs, and immune cell therapies hold the promise of overcoming barriers to effective treatments. Progress has been slow, but the large number of ongoing studies may lead to improved outcomes.

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Update on Emerging Therapies for Advanced Colorectal Cancer

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overview

Colorectal cancer (CRC) is the third most common malignancy worldwide. It is projected to increase by 3.2 million new cases and account for 1.6 million deaths by 2040. Mortality is largely due to limited treatment options for patients who present with advanced disease. Thus, the development of effective and tolerable therapies is crucial. Chemotherapy has been the backbone of systemic treatment of advanced CRC, but utility has been limited because of invariable resistance to therapy, narrow mechanisms of action, and unfavorable toxicity profile. Tumors that are mismatch repair-deficient have demonstrated remarkable response to immune checkpoint inhibitor therapy. However, most CRC tumors are mismatch repair-proficient and represent an unmet medical need. Although *ERBB2* amplification occurs only in a few cases, it is associated with left-sided tumors and a higher incidence of brain metastasis. Numerous combinations of *HER2* inhibitors have demonstrated efficacy, and antibody-drug conjugates against *HER2* represent innovative strategies in this area. The *KRAS* protein has been classically considered undruggable. Fortunately, new agents targeting *KRAS G12C* mutation represent a paradigm shift in the management of affected patients and could lead the advancement in drug development for the more common *KRAS* mutations. Furthermore, aberrant DNA damage response is present in 15%-20% of CRCs, and emerging innovative combinations with poly (ADP-ribose) polymerase (PARP) inhibitors could improve the current therapeutic landscape. Multiple novel biomarker-driven approaches in the management of patients with advanced CRC tumors are reviewed in this article.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy worldwide and is projected to increase by 3.2 million new incident cases and account for 1.6 million deaths by 2040.[1] Up to 25% of individuals with CRC present with stage IV disease and approximately 25%-50% who initially present with early-stage CRC go on to develop metastases.[2-4] Stage IV CRC has a 5-year survival of 12.5% in the United States, and thus, the development of safe, effective, and tolerable therapy represents an urgent clinical need.[3,5]

Colorectal cancers are classified on the basis of molecular profile. The most studied classification divides tumors into *RAS* (*KRAS*, *NRAS*, *HRAS*) and *BRAF* mutated or wild-type, which guides the use of epidermal growth factor receptor (EGFR) or the serine/threonine-protein kinase B-Raf inhibitors in this disease. More recently identified are the mismatch repair-deficient (dMMR) CRCs that constitute 15% of CRC neoplasms and are characterized by high microsatellite instability (MSI-H) by polymerase chain reaction (PCR) or lack of mismatch repair (MMR) protein expression by immunohistochemistry.[6] These tumors demonstrate an excellent response to immune checkpoint inhibitor (ICI) therapy,[6,7] but 85% of CRCs that are mismatch repair-proficient (pMMR) represent an unmet medical need. Additional targets such as *HER2* have also led to new molecularly based treatment options (Fig 1), and as our knowledge in the tumor genomic landscape deepens, the therapeutic paradigm of CRC is expanding. Herein, we summarize a novel biomarker-based therapy in patients with advanced CRC tumors.

SPECIFIC MOLECULAR TARGETS

Antiangiogenic Therapy

Angiogenesis plays a significant role in CRC metastasis and growth, and therapies targeting the vascular endothelial growth factor (VEGF) pathway have improved patient survival. There are five antiangiogenic drugs that are US Food and Drug Administration (FDA)–approved: bevacizumab, ramucirumab, ziv-aflibercept, regorafenib, and fruquintinib. Bevacizumab, a monoclonal antibody to VEGF-A, is the only drug approved in the first-line setting in combination with chemotherapy.[8,9] Continuation of bevacizumab in the second line with an alternative chemotherapy backbone also improves overall survival (OS) versus chemotherapy alone.[10,11] The phase III RAISE trial studied ramucirumab, a monoclonal antibody that targets VEGF receptor-2, in

PRACTICAL APPLICATIONS

- Novel biomarker-driven approaches in the management of patients with advanced colorectal cancer are leading to improvements in outcomes.
- New therapeutics targeting DNA repair pathways may play an important role for both early- and late-stage diseases.
- Innovative linker technologies, diverse payloads, higher drug-to-antibody ratios, and novel Fc receptor engineering are being investigated in the development of antibody-drug conjugates as cancer therapeutics.

combination with fluorouracil, leucovorin, and irinotecan (FOLFIRI) in the second-line setting for patients with metastatic CRC (mCRC) and demonstrated an OS improvement when compared with FOLFIRI alone. Similarly, ziv-aflibercept, a recombinant fusion protein that binds VEGF-A, VEGF-B, and placental growth factor, was shown in the VELOUR phase III study to improve survival when given in combination with FOLFIRI versus FOLFIRI alone in the second-line setting.[12] Although none of the antiangiogenic agents have been compared with each other prospectively, a recent retrospective analysis compared aflibercept and FOLFIRI (n = 326) with bevacizumab and FOLFIRI (n = 355) in patients with progressive CRC on first-line chemotherapy plus bevacizumab.[13] Bevacizumab was associated with better median progression-free survival (PFS), median OS, and treatment tolerability.

In patients with refractory mCRC, regorafenib, an oral VEGF inhibitor, demonstrated modest yet statistically significant improvement in disease control rate (DCR), median PFS, and median OS compared with best supportive care in two multicenter randomized trials.[14,15] In the phase III FRESCO-2 trial of patients with heavily treated mCRC, fruquintinib,

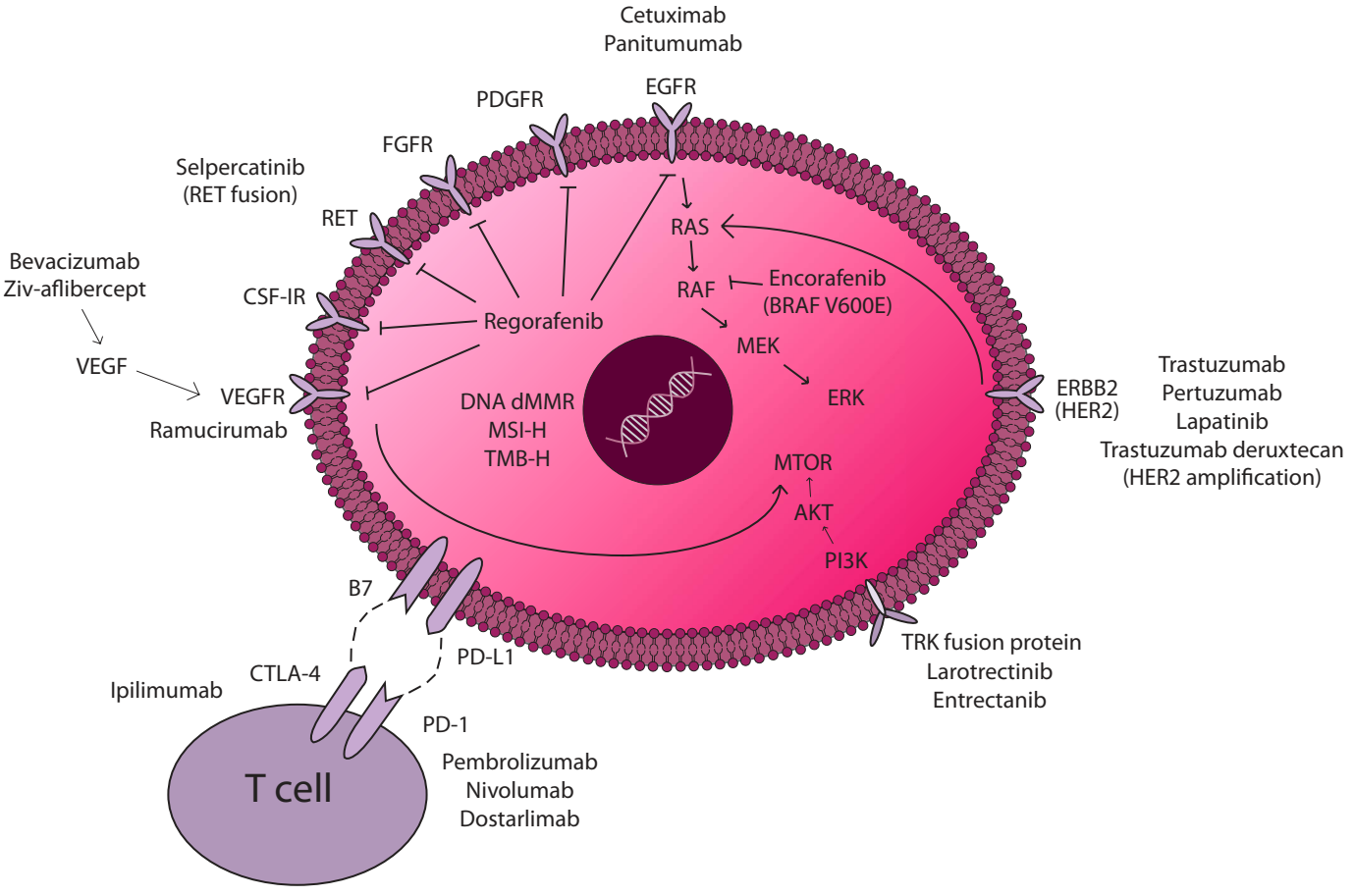

FIG 1. Molecular targets in colorectal cancer. CSF-IR, colony stimulating factor 1 receptor; CTLA-4, cytotoxic T-cell lymphocyte-4; dMMR, mismatch repair deficient; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MSI-H, high microsatellite instability; PDGFR, platelet-derived growth factor receptor; TMB-H, tumor mutational burden-high (≥10 mutations/megabase [mut/Mb]); TRK, tropomyosin receptor kinase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. Artwork for figure graciously provided by Nyah Yao.

another oral VEGFR inhibitor, showed a superior DCR (55.5% *v* 16%) and median OS (7.4 *v* 4.8 months; hazard ratio [HR], 0.66; 95% CI, 0.55 to 0.80; $P < .001$) compared with placebo.[16] The recent phase III SUNLIGHT study randomly assigned patients with mCRC who had one to two previous lines of therapy to either trifluridine/tipiracil alone or bevacizumab, and there was an improvement in median OS with the addition of bevacizumab (10.8 months *v* 7.5 months; HR, 0.61; 95% CI, 0.49 to 0.77; $P < .001$).[17]

Anti–Human Epidermal Growth Factor Receptor 2 Therapy

ERBB2 amplification or human epidermal growth factor receptor 2 (HER2) overexpression occurs in 2%-3% of patients with CRC and is associated with left-sided tumors and a higher incidence of brain metastasis.[18,19] Clinically, retrospective data show that HER2 overexpression is associated with poorer response to anti-EGFR therapies in *RAS* wild-type metastatic CRC.[20] In addition to fam-trastuzumab deruxtecan discussed later in this chapter, dual HER2 blockade has shown benefit in HER2-overexpressing refractory CRC tumors.

The phase II MOUNTAINEER study with trastuzumab, a monoclonal antibody to HER2, plus tucatinib, an oral selective tyrosine kinase inhibitor (TKI) for HER2, reported an overall response rate (ORR) of 38%, a median PFS of 8.2 months, and an OS of 24 months for patients with HER2-amplified and RAS wild-type mCRC and had two or greater previous lines of therapy.[21] The targeted combination is now FDA-approved for patients with refractory HER2-amplified mCRC, and there is an ongoing phase III MOUNTAINEER-03 study that compares tucatinib and trastuzumab in combination with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) versus FOLFOX alone in the first-line mCRC setting (ClinicalTrials.gov identifier: NCT05253651). In the HERACLES trial, patients with HER2-amplified mCRC were treated with trastuzumab and lapatinib, an oral TKI of HER2 and EGFR. ORR was 30%, including one complete response (CR) and seven partial responses (PRs).[22,23] In the MyPathway and TAPUR studies, treatment with trastuzumab and pertuzumab, a monoclonal antibody that inhibits the dimerization of HER2 with HER3, yielded an ORR of 25% in 84 patients and 25% in 28 patients, respectively.[24,25] The challenge ahead will be to see how to best sequence the targeted combinations and if repeated HER2 amplification testing will be necessary after HER2-targeted treatments.

KRAS-Targeting Strategies

Forty percent of CRC tumors harbor *Kirsten rat sarcoma* (*KRAS*) missense mutations in codons 12, 13, or 61, which leads to constitutive activation of the *KRAS* gene, and this drives signaling in the MAPK pathway and carcinogenesis.[26] Anti-EGFR therapy in combination with chemotherapy is effective for patients with *KRAS*, *NRAS*, and *BRAF* wild-type and left-sided primary CRC tumors in the first-line metastatic setting, as demonstrated by multiple clinical trials.[27-29] The KRAS protein has otherwise been classically considered undruggable[30]; however, approximately 3% of CRCs harbor a $KRAS^{G12C}$ mutation that is inhibited by sotorasib and adagrasib, both small oral inhibitory molecules. When used as monotherapy in the phase II CodeBreak 100 study, sotorasib yielded a low ORR of 9.7% (n = 6) in 62 patients with previously treated $KRAS^{G12C}$-mutant advanced CRC.[31] Increased EGFR signaling appeared to be responsible for treatment-related resistance, which provided the rationale for dual $KRAS^{G12C}$ and EGFR blockade.[32] The phase II CodeBreak 101 trial (ClinicalTrials.gov identifier: NCT04185883) is currently exploring the clinical activity of sotorasib plus panitumumab.[33] The phase I/II KRYSTAL-1 trial compared adagrasib alone (n = 43) or with cetuximab (n = 28) in advanced $KRAS^{G12C}$-altered CRC.[34] Adagrasib alone showed an ORR of 19% (95% CI, 8 to 33) and a median PFS of 5.6 months (95% CI, 4.1 to 8.3). Adding cetuximab resulted in a markedly higher ORR of 46% (95% CI, 28 to 66) and a median PFS of 6.9 months (95% CI, 5.4 to 8.1). Interestingly, the doublet was associated with fewer grade 3/4 treatment-related adverse events (16% *v* 34%) which included diarrhea (3%), acneiform dermatitis (3%), and stomatitis (3%). There is an ongoing phase III study in the second-line setting, randomly assigning patients with $KRAS^{G12C}$-mutant mCRC to adagrasib and cetuximab versus chemotherapy (ClinicalTrials.gov identifier: NCT04793958).

BRAF Mutations

BRAF encodes a downstream GTPase of the RAS protein. $BRAF^{V600E}$ mutations occur in 5%-10% of CRC tumors and predict poor prognosis. In contrast, atypical or non-$BRAF^{V600E}$ mutations represent 2%-3% of CRCs and are associated with earlier age of diagnosis, left-sided tumors, and better survival outcomes.[35-37] Biologically, $BRAF^{V600E}$ mutations (designated as class I) produce a mutant kinase that activates as a monomer in a RAS-independent fashion. Atypical *BRAF* mutations lead to a RAS-independent kinase with intermediate/high activity (class II) or a RAS-dependent kinase with absent/low activity (class III). Clinically, the different *BRAF* classes translate into discordant responses to EGFR blockade.[38,39] *BRAF* class I CRCs display resistance to anti-EGFR therapy, which can be overcome by adding BRAF inhibitors.[40-43] In a retrospective analysis, CRCs with a class II $BRAF^{V600E}$ mutation showed a low ORR of 8% (n = 1) in 12 patients treated with cetuximab- or panitumumab-containing regimens while the class III mutation was associated with a significantly higher ORR of 50% (n = 14 of 28; $P = .02$).[39]

Targeted therapy for patients with mCRC with a $BRAF^{V600E}$ mutation is a combination of encorafenib, a BRAF inhibitor

plus an EGFR inhibitor in the second- or third-line settings on the basis of the phase III BEACON study.[30] There is an ongoing randomized phase II study of encorafenib and cetuximab with or without nivolumab, with the rationale that preclinical models have demonstrated a transient MSI-H phenotype with BRAF and EGFR inhibition (ClinicalTrials.gov identifier: NCT05308446). In addition, BREAKWATER is a randomized phase III study investigating encorafenib and cetuximab with or without doublet chemotherapy in the first-line setting for mCRC patients with a *BRAF*^{V600E} mutation (ClinicalTrials.gov identifier: NCT04607421). In contrast, for patients with atypical *BRAF* alterations, therapy selection and sequencing are undefined due to under-representation in trials. Ulixertinib, an orally available inhibitor of extracellular signal-regulated kinase (ERK) 1 and 2, showed an acceptable safety profile in a dose-finding phase I study with 135 patients with MAPK-mutant advanced solid tumors, which included atypical *BRAF* mCRC.[44] A phase II trial examining the clinical activity of ulixertinib is underway (ClinicalTrials.gov identifier: NCT04488003).

PIK3CA Blockade

Approximately 20%-25% of CRCs harbor an activating mutation of the *PIK3CA* oncogene, which encodes the catalytic subunit of phosphoinositide 3-kinase alpha (PI3Kα) as part of the AKT/mTOR pathway.[45] PI3K/AKT inhibition alone has not demonstrated clinical benefit.[46,47] Despite altered PI3Kα being implicated in resistance to anti-EGFR therapy, data on PI3Kα inhibitor-containing regimens remain scarce.[48,49] In a phase Ib study, 26 patients with *BRAF*-mutant metastatic CRC were treated with encorafenib plus cetuximab while 28 also received the PI3K inhibitor, alpelisib. The triplet did not improve ORR compared with the doublet regimen (18% *v* 19%) and was associated with a higher incidence of all-grade hyperglycemia (39% *v* 8%).[50] Early-phase trials are examining the activity of various oral selective PI3K inhibitors in recurrent mCRC, including MEN1611 combined with cetuximab (ClinicalTrials.gov identifier: NCT04495621), alpelisib plus capecitabine (ClinicalTrials.gov identifier: NCT04753203), and inavolisib plus cetuximab or bevacizumab (ClinicalTrials.gov identifier: NCT04929223). As *PIK3CA* mutations result in tumor dependency on glutamine, a trial with a glutaminase inhibitor, telaglenastat (CB-839), plus capecitabine is currently underway (ClinicalTrials.gov identifier: NCT02861300).[51]

NTRK Fusion-Driven CRC

In 0.5%-1% of CRC tumors, structural rearrangements of *neurotrophic tyrosine kinase receptor* (*NTRK*) genes encode a constitutively activated chimeric tropomyosin receptor kinase (TRK), resulting in cancer cell growth and survival. *NTRK* fusion-driven CRC tumors exhibit high tumor mutational burden and MSI-H and are associated with poor prognosis.[52] In a pooled analysis from three phase I/II studies, 159 patients with *NTRK* fusion-positive tumors received the TRK inhibitor larotrectinib.[53] Eight patients with CRC were included, of whom four had an objective response (ORR 50%, 95% CI, 16 to 84) with a median duration of response (DOR) of 3.7 months (95% CI, 3.7 to not estimable). Similarly, the efficacy of entrectinib was recorded by an integrated analysis from three studies (STARTRK-2, STARTRK-1, and ALKA-372-001) comprising 121 patients with 14 different *NTRK* fusion-positive tumor types.[54] In the CRC-specific cohort with 10 participants, two (20%) had an objective response. The median PFS and OS were 2.8 and 16 months, respectively. At present, studies informing the treatment sequence in this tumor subset are lacking. Both of these agents are approved by the FDA for patients whose disease has progressed on standard therapy and for whom there are no remaining treatment options.[55,56]

RET Inhibitors

Fusions in the *rearranged during transfection* (*RET*) gene have been reported in <1% of patients with CRC and are associated with MSI-H and *RAS*/*RAF* wild-type tumors.[57] Selpercatinib received FDA tumor-agnostic approval for refractory advanced solid tumors with a *RET* gene fusion on the basis of the results from the LIBRETTO-001 trial.[58,59] In this phase I/II, open-label, basket study, 45 patients with advanced *RET* fusion-positive tumors received oral selpercatinib twice daily. A PR was observed in 2 of 10 patients with CRC. The median DOR was 9.4 months. The activity of another oral RET TKI, pralsetinib, was examined in the phase I/II ARROW study. In the efficacy-evaluable cohort of 23 participants, two had CRC and both attained stable disease.[60]

TARGETING DNA REPAIR ABNORMALITIES

An aberrant DNA damage response (DDR) is present in 15%-20% of neoplasms.[61,62] New therapeutics targeting DNA repair pathways may play an important role in the management of mCRC. There are four known DNA repair systems that are implicated in the pathogenesis of CRC—nucleotide excision repair (NER), base excision repair (BER), MMR, and double-strand break repair (DSBR).[63] Each DNA repair system is activated in response to distinct DNA insults. The NER pathway responds when DNA damage occurs in the setting of irradiation, chemotherapeutic agents, or mutagens. The BER system uses DNA polymerases to repair damage from oxidation, alkylation, or methylation.[64,65] Ionizing radiation or DNA fork collapse-related insults are typically repaired by DSBR, which involves homologous recombination repair during the S phase and nonhomologous end joining during the S and G2 phases.[63,66] Herein, we discuss current and future therapies for CRC that target proteins involved in DNA damage response pathways.

Poly (ADP-ribose) Polymerase Inhibition

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) are currently used for the management of breast, ovarian, prostate, and pancreatic cancers with *BRCA1/2* alterations.[67-69] PARP inhibition is thought to accelerate replication fork progression or collapse, resulting in cell death.[70,71] Germline or somatic alterations in homologous recombination genes are present in up to 20% of CRCs; thus, PARPi are currently under investigation for both early- and late-stage diseases.[72-74]

DNA-damaging agents have been combined with PARPi with some encouraging results in clinical trials. In a study of 92 patients with advanced solid tumors, 10 patients with CRC were included in a molecularly unselected patient population. PR was achieved in two of nine patients with CRC receiving veliparib (200 mg twice daily) plus FOLFIRI therapy, with an ORR of 22.2%.[75] The treatment was well-tolerated with the most common side effects being nausea, diarrhea, and neutropenia. Other trials have focused primarily on the safety of PARPi in combination with chemotherapy. Investigators concluded that the recommended phase II dose of olaparib when given with irinotecan was 50 mg twice daily on days 1-5 (Table 1).[79] Veliparib combined with capecitabine and radiotherapy also showed an acceptable toxicity profile in a dose-escalation phase Ib study of 32 molecularly unselected stage II and III patients with locally advanced resectable adenocarcinoma of the recturm.[80] Tumor downstaging was noted in 71% of patients, and 29% achieved a pathological CR. The recommended dose of veliparib was 400 mg twice daily.

Studies assessing the efficacy of PARPi in CRC have showed mixed results. In a single-arm, open-label, phase II study, 75 patients with heavily pretreated CRC without selection on the basis of DDR status received veliparib plus temozolomide. The primary end point was met with a 25% DCR. Additionally, 4% of patients experienced a PR, with a median PFS of 1. 8 months and a median OS of 6.6 months.[81] In another phase II study including 33 patients who experienced disease progression on standard treatment regimens, single-agent olaparib did not demonstrate activity as no patient experienced complete response or PR.[82]

Early-stage studies highlight the need to combine PARPi with either other DNA repair agents or DNA-damaging agents to harness the full clinical effect. Other studies have evaluated PARPi and anti-EGFR therapy in breast cancer, lung cancer, and CRC and have shown synthetic lethality.[83-85] The use of the PARPi, niraparib in combination with the EGFR inhibitor panitumumab, is currently being explored in CRC with promising early efficacy data (ClinicalTrials.gov identifier: NCT03983993).[86] Taken together, the use of PARPi in microsatellite stable (MSS), pMMR CRC appears promising and more preclinical and clinical trials are needed to better understand and explore the clinical opportunities this class of drugs may offer.

ATM Kinase Inhibition

Ataxia telangiectasia-mutated (*ATM*) kinase is a member of the PI3K-related kinases and is involved in homologous recombination and nonhomologous end-joining pathways for double-stranded DNA breaks and is involved in G1/S cellular checkpoint activation.[87] This gene is frequently altered in CRC, and inhibition of ATM has been evaluated preclinically. ATM inhibitors M3541 and M4076 have shown suppression of DSBR, with inhibition of cancer cell growth. Additionally, these agents potentiated the antitumor effect of radiation in mice bearing human tumor xenografts.[88] In CRC cell lines and patient-derived xenografts, the ATM kinase inhibitor, AZD0156, was explored as a single agent and in combination with irinotecan (SN38) and fluorouracil (FU).[89] Increased G2/M arrest and improved growth inhibition were observed in the combination treatment compared with single agent.[89]

In the TAPUR phase II basket study, 30 patients with treatment-refractory CRC harboring ATM mutations were treated with olaparib.[78] One of the patients had a PR (ATM P938fs*11 and RAD50 variant of unknown significance), with a duration of response lasting 18.6 weeks. Three patients had stable disease (SD) at 16 weeks or longer (SD16+: ATM R1875*, splice site 4237-11_4241del16, E522*). The duration of SD was 19.7, 25.3, and 27.0 weeks, respectively. The DCR was 23% (95% CI, 6 to 39), with an ORR of 4% (95% CI, 0.1 to 19). Six of the patients had a BRCA2 coalteration, but none of them achieved OR or SD16+. The study concluded that olaparib monotherapy did not show sufficient antitumor activity in patients with advanced CRC with ATM mutations to warrant further study.

ATR Inhibition

Ataxia telangiectasia and Rad3-related 9 (ATR) plays an important role in maintaining genome integrity, and disruption of the ATR pathway leads to replication stress and promotion of cell killing. ATR kinase appears to be a viable target for anticancer treatment.[90] ATR inhibition also leads to sensitization of cells to radiation and chemotherapy.[91,92] Patients with tumors with unstable replication forks but not exhibiting defects in homologous recombination may benefit from ATR inhibitor (ATRi) therapies.[93-95] The combination of chemosensitizing agents with cytotoxic agents to increase synthetic lethality in MSS CRC is an attractive proposition that may prevent chemoresistance.[96] A study using the ATRi, AZD6738, in combination with FU showed markedly decreased cell proliferation when compared with FU alone. The effect of AZD6738 with FU was further evaluated in p53-deficient CRC cells, and it effectively inhibited cell survival in all cell lines.[97] Other studies have shown similar results in TP53-mutant CRC models.[98] ATRi

TABLE 1. Therapies Targeting DNA Repair—Completed Clinical Trials

Study Identifier	Phase	Patient Population	Mutations	Treatment Arm(s)	Results
Chen[27] NCT00535353	I	Locally advanced or mCRC (n = 25)	Not required	Olaparib-PARPi plus irinotecan	Intermittent olaparib dosing tolerable, RP2D 50 mg twice a day, 9 of 25 had stable disease (3-13 months)
Berlin[76] NCT01123876	II	Advanced solid tumors including mCRC (n = 10)	Not required	Veliparib-PARPi plus FOLFIRI	No MTD was established, RP2D-200 mg twice a day veliparib ORR: 11.1%
Leichman[31] NCT00912743	II	mCRC (n = 33; 20 MSS, 13 MSI-H)	Stratified by MSI status	Olaparib-PARPi	No complete or PRs reported. mPFS for all patients at 1.84 months, no difference in mPFS among MSS and MSI patients
Michael[77] NCT01589419	Ib	Locally advanced rectal cancer (n = 32)	Not required	Veliparib-PARPi plus capecitabine plus radiation	MTD not reached, RP2D-veliparib 400 mg twice a day, 72% (of 32) postsurgery tumor downstaging, 28% pathologic CR, 70% of 30 had sphincter sparing surgery
Gorbunova[32] NCT02305758	II	mCRC (n = 130)	Not required	Veliparib-PARPi (*v* placebo) plus FOLFIRI with or without bevacizumab	mPFS: 12 *v* 11 months mOS: 25 *v* 27 months mDOR: 11 *v* 9 months ORR: 57%
Pishvaian[30] NCT01051596	II	mCRC (n = 75)	Not required	ABT-888 (veliparib)-PARPi plus temozolomide	DCR-24% mPFS: 1.8 months mOS: 6.6 months PTEN and MGMT protein expression were not predictive of DCR
Cohen[78] NCT02906059	Ib	mCRC progressed on first line (n = 7)	KRAS, NRAS, or BRAF	AZD1775 (WEE 1 inhibitor) plus irinotecan	No results reported

Abbreviations: CR, complete response; DCR, disease control rate; FOLFIRI, fluorouracil, leucovorin, and irinotecan; mCRC, metastatic colorectal cancer; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; MSI-H, high microsatellite instability; MSS, microsatellite stable; MTD, maximum tolerated dose; ORR, overall response rate; PARP, poly (ADP-ribose) polymerase; PARPi, Poly (ADP-ribose) polymerase inhibitors; PR, partial response; RP2D, recommended phase II dose.

has demonstrated efficacy as monotherapy or in combination. In preclinical models, BAY 1895344, a novel ATRi, showed efficacy in CRC models that have DNA damage repair deficiencies, either as monotherapy or in combination with chemotherapy or external beam radiotherapy, with synergistic antitumor effect.[99]

ATRi has also been studied with other DNA-damaging drugs to explore clinical effects. In a phase I trial, Yap et al[100] used ATRi M6620 (VX-970) as monotherapy and in combination with carboplatin in patients with advanced solid tumors and demonstrated safety and tolerability. Additionally, a patient with mCRC with ATM loss and an ARID1A mutation had complete and maintained response providing rational for future studies with this combination. A preclinical study using pancreatic and colorectal cell lines demonstrated potent synergy between the ATR inhibitor, ceralasertib, and PARPi therapy.[101] ATR inhibition has been studied in cancers other than CRC, including the association of ATM mutations with response. The ATRi elimusertib was evaluated in a phase Ib expansion trial of 143 patients with advanced solid tumors resistant or refractory to standard treatment. The study included patients with CRC, castration-resistant prostate cancer, HER2-negative breast cancer, gynecologic cancers, and advanced cancers with ATM loss by immunohistochemistry (IHC). The elimusertib monotherapy showed clinical effects in patients with DDR defects. Of the five PRs observed, 60% (3 of 5) were in tumors with ATM IHC loss.[102] Other studies have shown good response in pretreated ATM-mutated advanced solid tumors.[103] The results from larger clinical trials are needed to assess the efficacy of ATRi for the treatment of MSS CRC (Table 2).

Checkpoint Kinase Inhibition

Checkpoint kinase 1 (CHK1) is a key mediator of the DNA damage response and regulates the cell cycle.[104] In the presence of replication stress during the S phase of the cell cycle, CHK1 interacts with ATR and promotes replication fork stabilization. CHK1 inhibitors block replication stress signaling in malignant cells that have DNA repair defects[93,105] and induce synthetic lethality.[104] Targeting either MRE11 or RAD51 has shown to increase sensitivity of

TABLE 2. Therapies Targeting DNA Repair—Active Clinical Trials

Study Identifier	Phase	Patient Population	Mutations	Treatment Arm(s)	Primary End Point	Secondary/Exploratory End Point
NCT05201612	II	Refractory mCRC (n = 40)	HRD	Olaparib—PARPi Pembrolizumab	ORR at 10 months	DCR, PFS, OS, DOR at 10 months/HRD score by Myriad MyChoice
NCT05412706	II	mCRC with CR/PR after oxaliplatin induction (n = 46)	Not required	Niraparib-PARPi maintenance	PFS at 36 months	PFS after reintroduction of first-line treatment, OS, ORR, ITEAE
NCT02484404	I/II	Advanced solid tumors including mCRC (n = 386)	Not required (PD-L1 expression)	Olaparib-PARPi Cediranib Durvalumab	Phase I: Recommended phase II dose, safety of doublet therapies Phase II: ORR of durva-O or durva-C in recurrent ovarian cancer	Cohort 4, mCRC: ORR, safety, DOR
NCT03983993	II	Advanced colorectal (n = 40)	RAS wild-type, MSI, MSS	Niraparib-PARPi plus panitumumab	Clinical benefit rate (up to 5 years)	ORR, DOR, PFS, OS (up to 5 years post-treatment)
NCT04644068	I/IIa	Advanced solid tumors including CRC (n = 715)	Not required	AZD5305-PARPi (with or without anticancer agents) Paclitaxel Carboplatin T-Dxd Dato-DXd	Adverse events (approximately 1 year) DLT (up to cycle 1)	Best change in target lesion ORR, DOR, PFS, TTR
NCT03337087	I/II	Metastatic pancreatic, CRC, EGC, or biliary cancer (n = 18)	Not required	Rucaparib-PARPi Fluorouracil liposomal Irinotecan Leucovorin	Phase I: DLT (up to 28 days) Phase Ib: ORR (up to 3 years) Phase II: BRR (at 32 weeks)	DCR, OS, PFS, adverse events
NCT02921256	II	Locally advanced rectal cancer (n = 362)	Not required	Veliparib-PARPi *v* pembrolizumab plus mFOLFOX, radiation and capecitabine	Neoadjuvant rectal score (up to 3 years)	OS, DFS, pCR, sphincter preservation rate (up to 3 years)
NCT04535401	I	Advanced or metastatic gastric, or colorectal cancers (n = 90)	Not required	Elimusertib (BAY 1895344-ATRi Fluorouracil Irinotecan Leucovorin	MTD (up to 28 days)	OvRR, PFS, OS (up to 1 year post-treatment) PBMC gammaH2AX and p-ATM signaling, ATM status
NCT02595931	I	Metastatic solid tumor (n = 66)	Not required	M6620 (VX-970, berzosertib)-ATRi Irinotecan hydrochloride	MTD (up to 28 days) Recommended phase II dose	IAE, OvRR, ISD, PFS (up to 6 months post-treatment) PK/PD parameters

Abbreviations: ATRi, ataxia-telangiectasia mutated and Rad3-related kinase inhibitor; BRR, best response rate; CR, complete response; CRC, colorectal cancer; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; EGC, esophagogastric cancer; HRD, homologous recombination repair deficiency; IAE, incidence of adverse events; ISD, incidence of stable disease; ITEAE, incidence of treatment-emergent adverse events; mCRC, metastatic colorectal cancer; MFOLFOX, modified infusional fluorouracil, leucovorin, and oxaliplatin; MSI, microsatellite instability; MSS, microsatellite stable; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; OvRR, overall response rate; PARPi, poly (ADP-ribose) polymerase inhibitor; PBMC, peripheral blood mononuclear cell; pCR, pathologic complete response; PD, pharmacodynamic studies; PFS, progression-free survival; PK, pharmacokinetic studies; PR, partial response; T-Dxd, trastuzumab deruxtecan; TTR, time to response.

the CHK1 inhibitor prexasertib in CRC stem cells by inducing mitotic catastrophic events, resulting in caspase-dependent cell death.[106] The effect of the CHK1i, LY2606368, was studied in vivo and in vitro in CRC stem cells isolated from 27 patients. It showed that most CRC stem cells which are TP53-deficient entered catastrophic premature mitosis and apoptosis; this was independent of *KRAS* status.[107] This is promising, as *KRAS* alteration is a negative predictive biomarker for many therapies in CRC and is associated with poor prognosis. These cells display intrinsic genotoxic stress and CHK1 and MK2 activity. It has been shown that simultaneous inhibition of CHK1 and MK2

leads to mitotic lethality in *KRAS*-altered cells in xenograft models and murine cancer cells.[108] These findings require exploration in clinical trials for CRC patients with chemotherapy-resistant tumors.[109,110]

Clinical trials examining the effect of CHK1/2 inhibitors are mostly in the early phases. These have included a phase Ib trial of CHK1i, prexasertib, in combination with chemotherapy or anti-EGFR therapy and a phase I/II dose-escalation trial of CHK1i, SRA737, as monotherapy.[111,112] Although another CHK1i, AZD7762, will not undergo further development because of unacceptable cardiac toxicity, this provides insight into potential toxicities of this class of therapy that will need to be monitored in further studies.[113,114]

WEE1 Kinase Inhibition

WEE1 is a tyrosine kinase that regulates the G2 checkpoint through the inhibition of cyclin-dependent kinase 1 (CDK1) by phosphorylation.[115] WEE1 kinase inhibition may also sensitize TP53-deficient tumor cells to DNA damage. FOCUS4-C, a randomized phase II study,[116] enrolled patients who had both *RAS* and *TP53* mutations who had responded to or been stable on chemotherapy. Sixty-nine patients were enrolled and treated with adavosertib (AZD1775), a selective Wee1 inhibitor (n = 44) or active monitoring (n = 25). Adavosertib was associated with significantly improved PFS versus active monitoring (median 3.61 *v* 1.87 months; HR, 0.35; 95% CI, 0.18 to 0.68; $P = .0022$), but there was no difference in OS. There was also a signal of greater adavosertib activity in left- versus right-sided tumors. The drug was well tolerated with grade 3 toxicities including diarrhea, nausea, and neutropenia. WEE1 kinase inhibitors have demonstrated promising activity in the early-phase clinical trials with tolerable toxicity profile and are also being explored in combination with other agents, especially in patients with treatment-refractory CRC harboring *KRAS, NRAS*, or *BRAF* alterations.

IMMUNOTHERAPY IN MSS CRC

One important molecular classification for choosing systemic therapy in patients with advanced CRC is MMR/MSI status. MMR-deficient/MSI high tumors are defined by absence of expression of MMR proteins by IHC or high variability of standardized microsatellites assessed by PCR. In contrast, MMR-proficient/MSS tumors are defined by normal expression of all MMR proteins by IHC and low variability of standardized microsatellites by PCR. These subgroups have different characteristics in terms of tumor immune microenvironment and are characterized by differing sensitivity to ICI therapy. Although dMMR CRCs have higher tumor mutational burden, $CD8^+$ cytotoxic T and Th1 helper cell infiltration and high levels of HLA proteins,[117,118] pMMR or MSS CRC are associated with an immune cold and immune excluded tumor microenvironment (TME) on the basis of T-cell density in tumor core, inner invasive, and outer invasive margins.[118,119] Of the four consensus molecular subtypes (CMS1, CMS2, CMS3, and CMS4), the CMS2-4 subtypes represent less immunogenic phenotypes with a less immunogenic TME and are largely pMMR CRC.[120] Immune cells such as M2 macrophages, regulatory T cells, and myeloid-derived suppressor cells exert immunosuppressive activity.[121] This biology underlies the resistance of pMMR to ICIs. Extensive research has focused on methods for improving the sensitivity of pMMR/MSS tumors to ICI therapy.

Chemotherapy and radiation therapy induce DNA damage including double-strand breaks, leading to genomic instability, which may trigger an antitumor immune response.[122-124] Because of their ability to induce DNA lesions that may encode immune-stimulating neoantigens, chemotherapy and radiation therapy have been explored in combination with ICIs in patients with pMMR/MSS CRC in hopes of improved efficacy in this patient population.

Chemotherapy has been studied in combination with ICI therapy because of its direct cytotoxic activity with the release of neoantigens into the circulation along with reduction in immunosuppressive Treg activity. Additionally, preclinical data in CRC cell lines have demonstrated that chemotherapy increases PD-L1 expression, potentially sensitizing cells to ICIs.[125] Combining chemotherapy with ICIs has been studied in lung and gastric cancers leading to multiple FDA approvals.[126] This approach has been explored in patients with advanced pMMR/MSS colorectal cancer as well—the multicenter, randomized, open-label, phase II AtezoTRIBE study combined FOLFOXIRI (folinic acid, fluorouracil [5FU], oxaliplatin and irinotecan) and bevacizumab (bev), with or without atezolizumab (atezo) in patients with pMMR or dMMR advanced CRC. The combination arm with atezolizumab was associated with significantly improved PFS (HR, 0.69; $P = .012$). Although the magnitude of benefit was higher in dMMR cancer, efficacy signal was noticed in the pMMR group.[127] Further clinical trials will provide more answers as to the role of ICIs in pMMR CRC and hopefully help shape treatment guidelines. One of those trials is the phase II POCHI trial (ClinicalTrials.gov identifier: NCT04262687), a proof-of-concept study combining pembrolizumab with oxaliplatin and bevacizumab in patients with MSS CRC and high immune infiltrates.

Combining radiation therapy with ICIs to improve response has also been explored.[128] Radiation has a cytocidal effect and may synergistically prime and maintain the immune response when combined with ICIs. The combination of radiation therapy with ICIs also leads to cross-priming of tumor-specific cytotoxic T lymphocytes and helps to neutralize immunosuppressive effects of TMEs.[76] Other studies have shown that ICIs potentiate radiosensitivity of cancer cells by repressing PD-L1/PD1.[77,129] Radiation therapy has also been associated with an abscopal effect, where tumor response is observed in lesions outside of the radiation field because of the immune-stimulating effects of radiation

therapy.[130] A nonrandomized phase II study[131] studied pembrolizumab with radiation therapy or ablation. An interim analysis of 26 patients with pMMR/MSS CRC demonstrated an ORR of 9% in the radiation therapy plus pembrolizumab group, but 0% in the ablation plus pembrolizumab group. Interestingly, one patient achieved a PR after radiation therapy in a nonirradiated lesion suggesting an abscopal effect.[131] Furthermore, a phase II single-arm study[132] combined durvalumab, tremelimumab, and radiation therapy in chemotherapy-refractory pMMR CRC to assess ORR (primary end point) in nonirradiated lesions. The ORR was 8.3%, which did not meet the prespecified end point. However, there was regression in nonirradiated lesions suggesting an abscopal effect. Twenty-five percent of patients in the cohort experienced grade 3-4 adverse events.[132] The combination of radiation therapy plus ICIs is feasible with a manageable side effect profile in pMMR CRC.

VEGF signaling exerts immunosuppressive effects in the TME, and anti-VEGF therapies may promote a less immunosuppressive tumor immune microenvironment.[133,134] In the phase II BACCI trial, the addition of atezolizumab (anti–PD-L1) to capecitabine and bevacizumab in refractory pMMR/MSS CRC was associated with improved PFS, meeting the study's prespecified primary end point, although this was considered to be marginal and not clinically signfiicant.[135] The addition of atezolizumab to maintenance therapy with FU and bevacizumab in patients with pMMR CRC in the MODUL trial did not demonstrate a benefit.[136] The NIVACOR trial combining FOLFOXIRI/bevacizumab in association with an anti–PD-1 antibody, nivolumab, in *RAS*- or *BRAF*-altered CRC, regardless of MMR status, preliminarily showed an acceptable toxicity profile.[137] Other options that have been explored in MSS CRC include ICIs in combination with anti-EGFR therapies[138,139] and in combination with MAPK pathway inhibitors with ICIs.[140-143]

In addition to strategies that alter the tumor immune microenvironment, therapies that target multiple immune checkpoints in combination have been explored with preliminary success in CRC. A phase I study of botensilimab, and Fc-enhanced cytotoxic T-cell lymphocyte-4 inhibitor, and balstilimab, and PD-1 inhibitor, in patients with advanced MSS/pMMR CRC was associated with an ORR of 22% in 58 patients, with a DCR of 73%.[144] The most commonly observed grade 3 or 4 adverse event was immune-mediated colitis in 21% of patients. On the basis of these promising results, a phase II randomized trial in MSS CRC is underway (ClinicalTrials.gov identifier: NCT05608044).

Although ICIs have been effective in patients with dMMR/MSI-H CRC, results have been underwhelming in patients with pMMR/MSS CRC.[145,146] Combination therapies of ICIs with chemotherapy and radiation therapy, combination therapies of ICIs with agents that alter the tumor immune microenvironment, and combinations of agents targeting multiple immune checkpoints have demonstrated promise for enhancing the response of ICIs in patients with pMMR/MSS CRC.

ANTIBODY-DRUG CONJUGATES IN COLORECTAL CANCER

There has been increasing interest in antibody-drug conjugates (ADCs) as cancer therapeutics, leading to 12 active FDA approvals across hematologic malignancies and solid tumors.[147,148] ADCs consist of antibodies that target tumor cell surface molecules, a cytotoxic payload (or a payload with a distinct mechanism of action, including immune-stimulating functions), and a linker molecule, all of which can affect the pharmacokinetic, pharmacodynamic, and safety profiles of the agent.[149,150] The rationale behind the design of ADCs is that they have the potential to improve the therapeutic index of potent cytotoxic therapies by delivering them more selectively to tumor tissues with relative sparing of normal tissues. The primary mechanism of action of ADCs involves antibody binding to the target antigen on tumor cells, internalization of the ADC, cleavage of the linker by various mechanisms, and the payload exhibiting its cytotoxic effect in target cells.[150,151] Additional mechanisms contributing to

TABLE 3. Ongoing Trials of Antibody-Drug Conjugates in Colorectal Cancer

Study Identifier	Agent	Target	Payload	Special Features
NCT04744831	Trastuzumab deruxtecan	HER2	Deruxtecan (topoisomerase I inhibitor)	
NCT05464030	M9140	CEACAM5	Exatecan (topoisomerase I inhibitor)	
NCT05493683	Disitamab vedotin	HER2	Monomethyl auristatin E (microtubule inhibitor)	In combination with immune checkpoint inhibitor, tislelizumab
NCT05489211	Datopotamab deruxtecan	Trop2	Exatecan (topoisomerase I inhibitor)	
NCT04410224	ASN004	5T4	Auristatin F hydroxypropylamide (microtubule inhibitor)	Single-chain Fv-Fc antibody
NCT03602079	A166	HER2	Duo-5 (microtubule inhibitor)	
NCT04460456	SBT6050	HER2	TLR8 agonist	Immune stimulatory payload; monotherapy and in combination with PD-1 inhibitor

Abbreviation: Fv-Fc, fragment variable, fragment crystallizable.

efficacy include antibody-dependent cytotoxicity of target cells and the bystander effect by which free cytotoxic payload affects target negative adjacent cells.[152,153]

Numerous ADCs have been evaluated in patients with advanced colorectal cancer (CRC), although only one to date is supported in guidelines for use, and none have yet garnered FDA approval in this patient population.[30] Here, we review the existing data and highlight ongoing studies involving the use of ADCs as a treatment of CRC (Table 3).

Trastuzumab Deruxtecan

The HER2 (ERBB2) receptor is part of the family of receptor tyrosine kinases that include EGFR/ERBB1, ERBB3, and ERBB4. All these receptors have an extracellular ligand-binding region, a membrane-spanning region, and a cytoplasmic receptor tyrosine kinase domain. Binding of ligands to the HER2 receptor promotes dimerization and activation of the intrinsic kinase domain, which activates intracellular signaling pathways that contribute to tumorigenesis and progression.[154] HER2 overexpression is present in up to 20% of breast and gastric cancers but is also overexpressed in 2%-3% of CRCs.[155-157] The HER2-targeting monoclonal antibodies trastuzumab and pertuzumab are approved in combination with chemotherapy for the first-line treatment of metastatic HER2-overexpressing breast cancer, and trastuzumab is approved in combination with chemotherapy (with or without immunotherapy) for the first-line treatment of advanced HER2-overexpressing gastroesophageal cancer.[158-160] In patients with HER2-overexpressing CRC who had previously been treated with standard-of-care therapies, HER2-targeted therapies including trastuzumab plus lapatinib, trastuzumab plus pertuzumab, and trastuzumab plus tucatinib demonstrated ORRs of 30%-38%, supporting continued investigations of HER2-targeted therapies in this patient population.[23,161,162]

Trastuzumab deruxtecan is an ADC with a humanized anti-HER2 antibody, a cleavable, peptide-based linker, and a potent topoisomerase I inhibitor payload.[163,164] Preclinical work demonstrated that the cytotoxic payload is highly membrane permeable and exhibits a strong bystander effect on adjacent HER2-negative cells.[153] Trastuzumab deruxtecan was evaluated in a phase I dose escalation and expansion trial in patients with tumors harboring HER2 overexpression or mutation, including 20 patients with CRC.[163] Among these patients, 45% (9 of 20) had tumors with HER2 IHC 3+, 10% (2 of 20) with HER2 IHC 2+ (one of these tumors was HER2 FISH positive), 10% with HER2 IHC 1+, and 30% (6 of 20) with HER2 mutations. The confirmed ORR was 15% by investigator review, but only 5% by confirmed central review with a DCR of 80%.[163] On the basis of these results, a single-arm phase II trial of trastuzumab deruxtecan was performed in patients with advanced CRC with HER2 expression who had experienced disease progression on at least two previous therapies (DESTINY CRC 01).[165] Notably, patients could enroll if they had previously received treatment with other HER2-directed therapies. Three cohorts were enrolled on the basis of tumor HER2 expression by IHC and FISH: (A) HER2 IHC 3+ or HER2 IHC 2+ with positive FISH, (B) HER2 IHC 2+ with negative FISH, or (C) HER2 IHC 1+. The primary objective was ORR in cohort A which was 45.3% (95% CI, 31.6 to 59.6) among 53 patients with a DCR of 83% (95% CI, 70.2 to 91.9). There were no responses in cohorts B and C suggesting that, in contrast to breast cancer with low HER2 expression, there does not appear to be a signal for efficacy for patients with CRC and low HER2 expression.[165,166]

Regarding toxicity, trastuzumab deruxtecan has been associated with pneumonitis and interstitial lung disease. In DESTINY CRC 01, 6.41% of patients experienced pneumonitis or interstitial lung disease, with 3.8% of patients experiencing grade 3 or higher pneumonitis, including two patients with grade 5 events.[165] Overall, this is consistent with estimates across studies of trastuzumab deruxtecan in advanced solid tumors which demonstrated rates of any grade pneumonitis or interstitial lung disease of 11.40%.[167] On the basis of these findings, trastuzumab deruxtecan is recommended in the second line and beyond for patients with advanced CRC with HER2 amplification or overexpression that are *KRAS*, *NRAS*, and *BRAF* wild-type but does not hold an official FDA approval for this indication. DESTINY-CRC 02 (ClinicalTrials.gov identifier: NCT04744831) is an ongoing study investigating different dose levels of trastuzumab deruxtecan in patients with HER2-overexpressing CRC (Table 3).

ADCs Without Clear Signals for Efficacy and/or Safety in Colorectal Cancer

Although recent success across solid tumors has demonstrated the promise of ADCs, there have been many examples that appeared promising in preclinical development but were found to be too toxic or with insufficient activity in clinical trials. There are many reasons for this discrepancy, including normal tissue target antigen expression in animal models that differs from humans, linker chemistry that leads to free cytotoxic drug and off-target toxicity, and choice of payload to which CRC is not intrinsically sensitive at pharmacokinetically achievable doses.[151] We discuss the following examples to highlight lessons that can be learned from this valuable previous work.

Trastuzumab emtansine (anti-HER2 ADC). Trastuzumab emtansine is a an ADC consisting of trastuzumab linked through a thioether uncleavable linker to a microtubule inhibitor (DM1) with a drug-to-antibody ratio of 3.5:1 that is approved for HER2-positive breast cancer in multiple

disease settings.[168] Before the development of trastuzumab deruxtecan, trastuzumab emtansine was evaluated in patients with advanced CRC with HER2 overexpression. Results were underwhelming as ORR was 0% in 11 patients with CRC treated with trastuzumab emtansine monotherapy and was 9.7% in patients with CRC treated with pertuzumab plus trastuzumab emtansine.[169,170] Despite sharing a common target (HER2) and monoclonal antibody (trastuzumab), trastuzumab deruxtecan demonstrated an ORR of 45% in a similar setting highlighting the importance of the linker technology and the choice of cytotoxic payload in the development of an ADC. Future development of ADCs in CRC should prioritize classes of cytotoxic payloads to which CRC is known to be sensitive.

Labetuzumab govitecan (anti-CEACAM5 ADC). Labetuzumab govitecan is an ADC targeting carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) or CEA that is expressed in >80% of CRCs.[171] The cytotoxic payload is SN-38, an active metabolite of irinotecan.[172] Preclinical models demonstrated enhanced delivery of SN-38 to tumor and less to normal tissues compared with irinotecan.[173] A phase I/II trial evaluated labetuzumab govitecan in patients with advanced CRC with serum CEA levels > 5 ng/mL but <1,000 ng/mL who experienced disease progression on previous therapies, including irinotecan.[174] Eighty-six patients received labetuzumab govitecan two times per week on weeks 1 and 2 of 3-week repeated cycles at 4 mg/kg or 6 mg/kg or once weekly at 8 mg/kg or 10 mg/kg. Of 72 evaluable patients, one experienced a PR and 42 experienced stable disease (ORR of 1.4%). The clinical benefit rate (PR + SD for 4 months or longer) was 29% (25 of 86 patients).[174] Grade 3 or higher neutropenia occurred in 16% of patients while grade 3 or higher diarrhea occurred in 7%, overall favorable compared with irinotecan.[174] Although this study demonstrated modest activity in a heavily pretreated population (with previous treatment including irinotecan) with a favorable toxicity profile, no further studies have evaluated labetuzumab govitecan in a different setting or as part of combination therapy.

Sacituzumab govitecan (anti-Trop2 ADC). Sacituzumab govitecan is an ADC-targeting trophoblast cell surface antigen-2 (Trop2) that is overexpressed in CRC compared with normal colon and has been associated with disease progression but is also highly expressed on normal human tissues including cervix, skin, esophagus, breast, kidney, bile duct epithelium, pancreas, prostate, and uterus.[175,176] The cytotoxic payload for this agent is similarly SN-38. Sacituzumab govitecan was evaluated in patients with advanced solid tumors that had progressed on at least one standard therapeutic regimen.[177] In the overall cohort, notable grade 3 or higher adverse events included diarrhea (7.9%), nausea (3.6%), neutropenia (42.4%), febrile neutropenia (5.3%), and anemia (10.3%). Of 31 patients with CRC treated at doses of 8 or 10 mg/kg on days 1 and 8 of 21-day cycles, one patient experienced a PR. The ORR was 3.2% (95% CI, 0.1 to 16.7), and 51.6% of patients experienced stable disease. Notably, the majority of the patients had received previous irinotecan-containing therapy.[177] Combined with the experience with labetuzumab govitecan, these two studies suggest that SN-38 delivery to the tumor via these ADCs is not sufficient to overcome acquired resistance to irinotecan and its active metabolite, SN-38. Notably, sacituzumab govitecan demonstrated significant activity against relapsed or refractory triple-negative breast cancer and improved OS compared with standard-of-care chemotherapy, resulting in an FDA approval for this indication.[178]

MRG003 (anti-EGFR ADC). MRG003 is an ADC-targeting EGFR and carries a monomethyl auristatin E payload, a potent microtubule inhibitor.[179] A phase Ia/Ib trial evaluated MRG003 in patients with advanced cancers refractory to standard therapies, including a cohort of patients with CRC. In the overall cohort, the most frequently observed adverse events included rash (39% any grade) and AST increase (39% any grade), with the most frequent grade 3 or higher adverse events being hyponatremia (8%), leukopenia (7%), and neutropenia (5%). The ORR for patients with CRC in phase Ib was 0%, with a DCR of 33%. This was compared with ORRs of 50% and 50% for squamous cell carcinoma of the head and neck and nasopharyngeal carcinoma, respectively.[179] Patients were screened for EGFR expression with IHC before phase Ib enrollment, and all but one of the patients with CRC was positive. The lack of efficacy in the CRC cohort is likely due to its lack of intrinsic sensitivity to microtubule inhibitors rather than poor target expression, highlighting the importance of choosing a cytotoxic payload to which the cancer of interest is sensitive.[151]

Additional previously investigated ADCs. Several additional ADCs have failed to demonstrate safety and/or efficacy in CRC. Aprutumab ixadotin (anti-FGFR2 ADC with auristatin W derivative payload) and ABBV-176 (anti-prolactin receptor ADC with pyrrolobenzodiazepine payload) were each studied in phase I trials, but development was stopped on the basis of maximum tolerated dose being below a preclinically determined therapeutic threshold and late and cumulative toxicities, respectively.[180,181] TAK-264 (antiguanylyl cyclase C ADC with monomethyl auristatin E payload) and cantuzumab mertansine (anti-CanAg ADC with maytansinoid payload) were studied in phase I trials with an ORR of 0% among patients with CRC.[182,183] These two studies further highlight that conjugating a cytotoxic agent to a tumor antigen-targeting antibody appears to be insufficient to overcome a lack of sensitivity of colorectal cancer to the cytotoxic agent.[151]

Ongoing Trials of ADCs in Colorectal Cancer

Ongoing trials of ADCs in CRC are primarily targeting previously investigated antigens that are overexpressed in tumors compared with normal tissues (Table 3). Although many of these agents target previously studied antigens, novel linker technologies, diverse payloads, higher drug-to-antibody ratios, and novel Fc receptor engineering are being investigated. In particular, ongoing work should select classes of cytotoxic payloads to which CRC is sensitive, should focus on payloads that optimize the bystander effect while minimizing systemic toxicity, should investigate novel payloads including immune stimulating payloads, and should revisit promising antigen targets for which earlier generation ADCs were unsuccessful.

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Therapy Sequencing in Patients With Advanced Neuroendocrine Neoplasms

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overview

Neuroendocrine neoplasms (NENs) comprise a beautifully complicated, exciting landscape of histologies and clinical behaviors. However, the nuanced complexity of low- and high-grade variants can easily overwhelm both patients and providers. In this chapter, we review the ever-expanding literature on both functioning and nonfunctioning small bowel and pancreatic NENs, touching on somatostatin analogs, hepatic-directed therapies, small molecules, radiopharmaceuticals, immunotherapy, cytotoxic chemotherapy, and new promising agents. Furthermore, we suggest some strategies to address the most challenging scenarios seen in clinical practice, including sequencing of agents, treatment of carcinoid syndrome, and options for well-differentiated high-grade disease.

INTRODUCTION

Neuroendocrine neoplasms (NENs) comprise a rare and heterogeneous group of cancers. Patients with NENs may present variable symptomatology and clinical course, making disease management challenging. Histologically, NENs are epithelial cancers with immunohistochemistry expression of neuroendocrine markers and most commonly originate from the lungs or the gastroenteropancreatic (GEP) tract. Nearly half of patients present synchronous metastatic disease.[1] The therapeutic approach is based on precise diagnosis and staging, and clinical evaluation of NEN-related genetic and/or hormonal syndromes. Such complexity reinforces the need of multidisciplinary discussion teams (MDTs) of NEN specialists to propose the best treatment plans.

Although the number of therapeutic options for advanced NENs is evolving because of their rarity and often more indolent course, randomized clinical trials of NENs may take time to reach their targeted number of events and thus be underpowered to provide precise results. Consequently, there are few randomized trials of NENs, and robust evidence to guide treatment sequencing for NENs is limited. Therefore, clinical decision making should consider patient characteristics, NEN-related features, and treatment toxicities (Table 1). The 2022 WHO classification of GEP NENs (Table 2) provides prognostic information, and Table 3 summarizes trial-level criteria for choosing treatments.[28] In this chapter, we will discuss the scientific evidence along with expert opinions to guide treatment sequencing for patients with advanced sporadic GEP NENs.

INITIAL APPROACH TO GASTROENTEROPANCREATIC NEN

Imaging Tests

Conventional imaging with abdominal and thoracic computed tomography or magnetic resonance are standard methods for clinical staging, response evaluation, and surveillance of GEP NENs.[29] The frequency of monitoring can vary greatly and should be individualized: Slow growing disease on surveillance or treatment can be monitored every 6-12 months while patients with more aggressive tumors could have scans performed every 3-6 months. Additionally, functional imaging with somatostatin receptor imaging (SRI) such as positron emission tomography (PET)/computed tomography or PET/magnetic resonance imaging is recommended in patients with well-differentiated (WD) NENs to improve staging accuracy, to identify the primary NEN site in metastatic disease, and to document expression of somatostatin receptors in the tumor (SSTR).[30] The latter provides prognostic information and utility for treatment planning with radiopharmaceuticals (discussed later). 18-fluorodeoxyglucose-PET (FDG-PET) is usually of little value in patients with slow-growing tumors, such as G1 GEP NENs, but should be considered to clinically stage more aggressive NENs, for instance, G3 tumors.[31,32] Intensity of uptake on FDG-PET is inversely associated with prognosis, with simultaneous higher FDG uptake and low SSTR-PET uptake being linked to inferior survival.[33] Importantly, at this point, SRI is not recommended for response evaluation because fluctuations in NEN uptake do not necessarily reflect tumor progression; conventional imaging is the preferred method to measure tumor response.

Author affiliations and support information (if applicable) appear at the end of this article.

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PRACTICAL APPLICATIONS

- Treatments for patients with gastroenteropancreatic neuroendocrine neoplasms (GEP NENs) have to be individualized with regard to grade, disease burden, origin, and functional status.
- Observation or somatostatin analogs (SSAs) are reasonable options for low-burden, oligoprogressive, nonfunctioning, advanced GEP NENs while SSAs can help most patients with functioning NENs. Patients with high-grade disease derive most benefit from chemotherapy.
- The evidence on treatment sequencing for patients with both low- and high-grade GEP NENs is limited. However, there is evolving, high-quality knowledge on the usefulness of liver-directed therapy, chemotherapy, peptide-receptor radionuclide, and tumor agnostic agents.
- Ongoing clinical trials will help answer that question, and patient participation in those trials is strongly encouraged.

Molecular Testing

Next-generation sequencing (NGS) does not have an established role in the initial evaluation of WD-NENs as they typically present with low mutational burden and rarely demonstrate actionable genomic alterations to guide therapy.[34-36] In contrast, molecular profiling should be performed in neuroendocrine carcinomas (NECs) where genomic alterations such as mismatch repair deficiency, *NTRK* fusions, or *BRAF V600E* mutations can guide the use of successful targeted therapy (see ahead Extrapulmonary Neuroendocrine Carcinoma). The authors believe that patients with advanced NEN progressing through most standard treatments could consider NGS to determine mismatch repair deficiency or eligibility for clinical trials/tumor agnostic treatments.

LOCOREGIONAL THERAPIES FOR ADVANCED G1-2 NONFUNCTIONING GASTROENTEROPANCREATIC NEN

Locoregional (nonsystemic) treatments can be used at any point during a patient's disease course.

Surgery

Surgery has the potential to cure select patients with N0M0 disease regardless of the grade and is often the first option considered on a new diagnosis. However, selected patients with node-positive or oligometastatic low-grade disease and good *performance status*, properly staged with SRI, could be considered for R0 resection.[37,38] Some patients require surgery for symptomatic tumor bulk, hormone hypersecretion, or threatening of critical structures. The timing of surgery and expected outcomes vary between providers and institutions and should be individualized. For example, one study reported a 10-year overall survival (OS) rate of 50.4% after hepatic metastasectomy while in a series of 339 patients who underwent surgical management, disease recurred in 95% of patients at 5 years.[39,40] At this point, metastasectomy for NENs is often a line of therapy, with most patients eventually experiencing tumor recurrence.[41]

As of now, there are no data supporting adjuvant treatment for patients with WD NENs whose tumors have been completely resected. The ongoing (ClinicalTrials.gov identifier: NCT05040360) study is assessing the efficacy of adjuvant capecitabine and temozolomide (CAPTEM) in patients with high-risk pancreatic NEN (PanNEN) after curative-intent surgery.

Liver transplantation remains investigational but can be considered, after MDT deliberation, in selected properly staged cases (age younger than 60 years, unresectable liver metastases, Ki-67 <10%, primary tumor removed, <50% involvement of the liver parenchyma, and a minimum of disease stabilization of 6 months).[42] In this highly selected group, 5-year OS >60% has been described,[43,44] but the data are not mature for further recommendations.

Liver-Directed Therapies

Nonsurgical liver-directed therapies (eg, radiofrequency ablation, thermal ablation, microwave, bland hepatic arterial embolization, chemoembolization, and radiation therapy) for patients with oligoprogressive liver-predominant disease can lead to symptom and tumor control for a median of 16-22 months.[45,46] They can be performed in second or later lines of treatment and repeated in patients who experienced benefit and maintain good hepatic function. They can also be indicated in patients with metastatic disease but focal progression, with retrospective series reporting a median time to new systemic treatments of 32 months.[47]

Radioembolization with yttrium-90 microspheres delivered intrahepatically has been effective in patients with NENs in uncontrolled studies, particularly those at risk of carcinoid crisis and/or with colonized biliary system.[48,49] Optimized tumor radiation dosimetry is important to improve therapeutical response and minimize toxicity to the normal liver parenchyma. Indeed, studies have reported delayed severe hepatic toxicity after liver radioembolization in nearly 30% of patients with NENs.[50] Therefore, the risks of long-term liver injury after radioembolization, especially when used sequentially with peptide receptor radionuclide therapy (PRRT) or after extensive liver resection, should be considered in the treatment sequencing for patients with NENs.[49]

TABLE 1. Checklist of Important Factors for Treatment Strategies in Patients With Advanced NENs

Factor	Aims
Tumor-related factors	
Histopathological diagnosis	Accurate grading by the 2022 WHO classification to inform prognosis and evaluate grade-specific treatments
Radiological staging	Evaluation of tumor burden and surgical resectability
Functioning images[a]	Evaluate SSTR-2 tumor expression and staging 18-FDG-PET: optional for more aggressive tumors
Identify primary tumor	Evaluate clinical behavior and guide site-specific therapies and hormone secretion
Evaluate tumor functional status (clinically and biochemically) and related symptoms	Specific treatments of NEN-related hormone syndromes
Assess criteria for genetic syndrome	Diagnose hereditary syndromes (genetic counseling for patients and relatives) Evaluate impact on treatment strategy
Assess tumor aggressiveness and behavior	Evaluate tumor burden, constitutional symptoms, and, if possible, tumor growth rate on the basis of clinical history and/or previous images to plan treatment strategy according to tumor aggressiveness
Patient-centered evaluation	
Assess clinical condition	Evaluate performance status, comorbid illnesses, and concurrent medications
Assess patient's preferences	Understand patient's perception of therapy-related toxicities, efficacy, convenience, and access

Abbreviations: PET, positron emission tomography; SSTR, somatostatin receptors in the tumor.
[a]18-FDG PET and SSTR-PET.

FIRST-LINE SYSTEMIC TREATMENTS IN ADVANCED G1-2 NONFUNCTIONING GASTROENTEROPANCREATIC NENs

First Line

Observation. Although not a treatment per se, some patients with asymptomatic, low tumor burden, and nonfunctioning (and biochemically inactive) NENs from most organs, including the GEP tract, can be observed with surveillance imaging to determine the rate of clinically significant growth and development of symptoms. Disease stabilization from 6 to 18 months was observed in the placebo arms of randomized trials of patients with WD GEP NENs.[4,5,51,52] Serial imaging can be performed every 3-6 months depending on the disease growth rate and patient preference.

There are no randomized data to guide earlier versus delayed initiation of somatostatin analogs (SSAs; the next usual treatment) for newly diagnosed patients. A cost-benefit analysis on the basis of data from the CLARINET study showed that active surveillance was most cost-effective as initial therapy for newly diagnosed patients at the current lanreotide cost.[53]

Somatostatin analogs. For patients with advanced inoperable G1-2 GEP NENs, disease stability is an acceptable

TABLE 2. WHO Classification and Grading Criteria for Gastroenteropancreatic NENs[2]

Terminology	Differentiation	Grade	Mitotic Count Mitoses/2 mm²[a]	Ki-67 Index[b]
G1 NET	Well differentiated	Low	<2	<3%
G2 NET		Intermediate	2-20	3%-20%
G3 NET		High	>20	>20%
Small-cell NEC	Poorly differentiated	High	>20	>20%
Large cell NEC			>20	>20%
MiNEN	Well or poorly differentiated	Variable	Variable	Variable

Abbreviations: G, grade; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.
[a]Mitotic counts are to be expressed as the number of mitoses/2 mm² (equaling 10 high-power fields) at 40× magnification evaluated in areas of highest mitotic density.
[b]The Ki-67 proliferation index value is determined by counting at least 500 cells in hot spots.

TABLE 3. Selected Randomized Clinical Trials of Approved Systemic Treatments for NENs

Study	Trial Phase Line	N, Population	Previous Progression	NEN Grade	Ki-67 >10%, %	Previous Therapies	Treatment Arms	Response Rate, %	PFS, Months	OS, Months	Main Drug-Related Grades 3-4 Toxicities (%)
G1-2 NEN											
Octreotide											
Rinke et al PROMID (2009)[3,4]	III 1	85, metastatic small bowel NEN[a]	Not reported	G1 (95%)	0	None	Octreotide LAR 30 mg once every 4 weeks Placebo	<1	14.3[c] 6.0	84.7[d] 83.7[d]	Fatigue (8), GI symptoms (14), hematopoietic system (12)
Lanreotide											
Caplin et al CLARINET (2014)[5]	III 1 (mostly)	204, advanced GEP NEN[b] (90, PanNEN)	No	G1 (70%)	0	Any treatment (16%)	Lanreotide 120 mg once every 4 weeks Placebo	— —	38.5[f] 18	NR[f] NR[f]	[e]Diarrhea (26), abdominal pain (10), cholelithiasis (10)
Everolimus											
Yao et al RADIANT-3 (2011)[6,7]	III ≥ 1	410, PanNEN	Within previous 12 months	G1 or G2	—	SSA (50%) Chemotherapy (50%)	Everolimus 10 mg once daily + BSC Placebo + BSC	5.0 2.0	11.0 4.6	44.0[d] 37.7	Stomatitis (7), anemia (6), hyperglycemia (5), infections (2)
Yao et al RADIANT-4 (2016)[8]	III ≥ 1	302, advanced lung and GI NEN[b]	Within previous 6 months	G1 (63%) G2 (37%)	—	SSA (53%) Chemotherapy (26%)	Everolimus 10 mg once daily Placebo	<1	11.0 3.9	— —	Stomatitis (9), diarrhea (7), infections (7), fatigue (3), hyperglycemia (3), rash (1)
Peptide receptor radionuclide therapy											
Strosberg et al NETTER-1 (2017)[9,10]	III 2	229, advanced SSTR+ small bowel NEN	Progressing on octreotide	G1 (66%)	—	SSA (100%)	^{177}Lu-DOTATATE + octreotide LAR 30 mg once every 4 weeks Octreotide LAR 60 mg once every 4 weeks	— —	28 8.5	48[d] 36.3[d]	PRRT: Lymphopenia (9), vomiting (7), nausea (4), abdominal pain (3), diarrhea (3)
Baudin et al OCLURANDOM (2022)[11]	II 2	84, PanNEN	Within previous 12 months	G1 or G2 or G3	37	Chemotherapy (57%)	^{177}Lu-DOTATATE Sunitinib 37.5 mg once daily	—	20.7[g] 11.0	— —	PRRT: Hypertension (12), digestive (12), blood (12) Sunitinib: hematological (23), digestive (21), hypertension (19)
Sunitinib											
Raymond et al (2011)[12,13]	III ≥ 1	171, PanNEN	Within previous 12 months	G1 and G2 (<10%)	8	SSA (36%) Chemotherapy (69%)	Sunitinib 37.5 mg once daily + BSC Placebo + BSC	9.3 0	12.6 5.8	38.6[d] 29.1	Neutropenia (12), hypertension (10), palmar-plantar erythrodysesthesia (6)
Temozolomide + capecitabine											
Kunz et al ECOG-ACRIN 2211 (2022)[14]	II ≥ 1	144, PanNEN	Within previous 12 months	G1 or G2	—	SSA (63%) Everolimus (35%) Sunitinib (10%)	CAPTEM Temozolomide (TEM)	39.7[d] 33.7	22.7 14.4	58.7[d] 53.8	CAPTEM: Neutropenia (13), thrombocytopenia (10), diarrhea (8) TEM: Thrombocytopenia (10), neutropenia (4), lymphopenia (4)
STZ + FU											
Salazar et al SEQTOR (2022)[15]	III ≥ 1	141, PanNEN	Within previous 12 months	G1 or G2	—	SSA (32%) PRRT (6%) Targeted therapy or chemotherapy (<1%)	STZ + FU Everolimus 10 mg once daily	30 11	23.6[d] 21.5	— —	STZ + FU: Fatigue; neutropenia, anorexia, renal toxicity Everolimus: Fatigue, diarrhea, infections, hypertriglyceridemia

Study	Phase Line	N, Population	Previous Progression	NEN Grade	Ki-67 >55%, %	Previous Therapies	Treatment Arms	Response Rate, %	PFS, Months	OS, Months	Main Grades 3-4 Toxicities (%)
G3 NENs											
Platinum-based chemotherapy											
Sorbye et al NORDIC NEC (2013)[16]	Retrospective 1	305, GI or unknown primary	—	G3	53	No	Cisplatin + etoposide Carboplatin + etoposide	31 30	4 4	12 11	
Mitry et al[17]	Retrospective 1	53 (41, poorly differentiated) GI or unknown primary	—	Any		Various	Cisplatin + etoposide	41.5% among poorly differentiated	8.9 among poorly differentiated	15 among poorly differentiated	Leukopenia (21) Neutropenia (30) Thrombocytopenia (6) Anemia (6) Nausea/vomiting (20)

(Continued on following page)

TABLE 3. Selected Randomized Clinical Trials of Approved Systemic Treatments for NENs (Continued)

Study	Trial Phase Line	N, Population	Previous Progression	NEN Grade	Ki-67 >10%, %	Previous Therapies	Treatment Arms	Response Rate, %	PFS, Months	OS, Months	Main Drug-Related Grades 3-4 Toxicities (%)
Mani et al[18]	II 1	19	—	G3		No	Cisplatin + irinotecan	58%	4	NR	Leukopenia (32) Anemia (8) Fatigue (20) Nausea (12) Diarrhea (8) Hyponatremia (8) Hypokalemia (4) Myalgia (4) Dyspnea (4)
Lu et al[19]	Retrospective 1 (mostly)	16 GI NEC	No (15 of 16)	G3		1 patient with previous EP	Cisplatin + irinotecan	57%	5.5	10.6	Leukopenia (5) Neutropenia (9) Anemia (1) Nausea/vomiting (1) Diarrhea (2)
FU-based chemotherapy											
Hadoux et al[20]	Retrospective >1	20 (16, extrapulmonary)	Yes	G3	89%	Various (90% received first-line platinum + etoposide)	mFOLFOX4	29%	4.5	9.9	Anemia (10) Thrombocytopenia (20) Neutropenia (35) AST/ALT elevation (10) Neurotoxicity (5) Asthenia (5) Nausea/vomiting (10) Diarrhea (5)
Walter et al PRODIGE 41-BEVANEC[21]	II 2	133, GI or unknown primary	Yes	G3	80% 80%	Platinum + etoposide	FOLFIRI FOLFIRI + bevacizumab	18% 25%	3.5 3.7	8.9 6.6	FOLFIRI: Neutropenia (10) FOLFIRI + bevacizumab: Neutropenia (14) Diarrhea (10) Asthenia (8)
Butt et al[22]	Retrospective Any	37, GI origin	78% >first line	G3	NR	Various	FOLFIRINOX	46%	5.4	17.8	
Temozolomide plus capecitabine											
Rogowski et al[23]	Retrospective Any	32 (12 with NEC)	69% >first line	G3	22%	Various	Capecitabine + temozolomide	18.3% among NEC	3.3 among NEC	4.6 among NEC	Thrombocytopenia (16) Neutropenia (9) Hand-foot syndrome (6) Diarrhea (6) Fatigue (3)
ECOG-ACRIN EA2142[24]	II 1	67, G3 NEN	No	G3	NR	No	Capecitabine + temozolomide Cisplatin or carboplatin + etoposide	9% 10%	2.4 5.4	12.6 13.6	Capecitabine + temozolomide: Febrile neutropenia (n = 2) Abdominal pain (n = 2) Diarrhea (n = 2) Nausea (n = 2) Neutropenia (n = 2) Dehydration (n = 2) Platinum + etoposide: Anemia (n = 8) Febrile neutropenia (n = 2) Fatigue (n = 2) Lymphopenia (n = 2) Neutropenia (n = 12) Thrombocytopenia (n = 4) Leukopenia (n = 6)
Taxanes											
McNamara et al NET-02 trial[25]	Randomized phase II 2	58, extrapulmonary	Yes	G3	90%	Platinum-based	Irinotecan liposome + FU or docetaxel	10.3% 10.3%	3 2	9 5	Overall 51.7% 55.2%
Immune checkpoint blockade											

(Continued on following page)

TABLE 3. Selected Randomized Clinical Trials of Approved Systemic Treatments for NENs (Continued)

Study	Trial Phase Line	N, Population	Previous Progression	NEN Grade	Ki-67 >10%, %	Previous Therapies	Treatment Arms	Response Rate, %	PFS, Months	OS, Months	Main Drug-Related Grades 3-4 Toxicities (%)
Patel et al DART SWOG 1609[26]	II >1	32 Any NEN (56% with NEC)	Yes	Any	NR	Various	Nivolumab + ipilimumab	25% (44% in G3)	4	11	Alk Phos increased (6.3) Sepsis (6.3) AST increased (6.3) ALT increased (9.4) Lipase increased (6.3) Encephalopathy (6.3)
Chan et al[27]	II >1	22, extrapulmonary poorly differentiated NEC	Yes	G3	NR	NR	Pembrolizumab + irinotecan (77%) or paclitaxel (23%)	9%	2	4	Pain ALT increase Nausea Fatigue Neutropenia Hyponatremia Diarrhea Nausea Acute kidney injury

Abbreviations: —, not available; BSC, best supportive care; CAPTEM, temozolomide + capecitabine; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FU, fluorouracil; G, grade; LAR, long-acting release; N, study population; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasms; NR, not reached; OS, overall survival; PanNEN, pancreatic NEN; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; SD, stable disease; SSA, somatostatin analog; SSTR, somatostatin receptors in the tumor; STZ + FU, streptozocin + fluorouracil; SUN, sunitinib; TEM, temozolomide.

[a]Nonfunctioning (60%) and functioning (40%).

[b]Only nonfunctioning.

[c]Time to tumor progression.

[d]Difference is not statistically significant.

[e]Any grade.

[f]GI cohort only.

[g]No *P*-value (noncomparative study).

TABLE 4. Ongoing Randomized Studies in Advanced G1-3 NEN

Study	Phase	Design	N, Population	Primary End Point	Intervention	Control
NETTER-2 (NCT03972488)	III	Randomized, open-label	222, first-line, SSTR+, G2-G3 (Ki-67 10%-55%) NETs	PFS	^{177}Lu-DOTATATE + LAR SSA	High-dose SSA
COMPETE[75] (NCT03049189)	III	Randomized, open-label	300, progressive SSTR+ G1-G2, GEP-NET	PFS	^{177}Lu-Edotreotide	Everolimus 10 mg daily
COMPOSE[76] (NCT04919226)	III	Randomized, open-label	202, well-differentiated, Ki-67 15%-55%, SSTR+ GEP-NETs. First or second line	PFS	^{177}Lu-Edotreotide	Investigator's choice (CAPTEM, FOLFOX, everolimus)
CABINET (NCT03375320)	III	Randomized, double-blind	395; GEP and bronchial NET; third line (one being SSA)	PFS	Cabozantinib 60 mg once daily	Placebo
RETNET[77] (NCT02724540)	II	Randomized, open-label	120, progressive or symptomatic unresectable NEN liver metastases	Hepatic PFS	Bland embolization	Lipiodol chemoembolization

Abbreviations: CAPTEM, capecitabine and temozolomide; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; G, grade; GEP-NET, gastroenteropancreatic neuroendocrine tumor; LAR, long-acting release; NENs, neuroendocrine neoplasm; NET, neuroendocrine tumor; PFS, progression-free survival; SSA, somatostatin analog; SSTR, somatostatin receptors in the tumor.

disease outcome. In this setting, SSAs are usually the preferred treatment. The randomized PROMID trial showed that long-acting octreotide (30 mg intramuscular injection once monthly) delayed tumor progression by 8.3 months (hazard ratio [HR], 0.34; 95% CI, 0.20 to 0.59; $P = .000072$) in 85 patients with G1-2 progressive small bowel (SB) NEN.[4] The phase III CLARINET trial evaluated an alternative long-acting SSA, lanreotide (120 mg s.c. injection once monthly), in 204 patients with nonfunctioning nonprogressive SRI-positive GEP NEN with Ki-67 index <10%, demonstrating a progression-free survival (PFS) benefit (HR, 0.47; 95% CI, 0.30 to 0.73; $P < .001$).[5] Both SSAs yielded negligible tumor responses (2%) and are usually well tolerated, with most common adverse events being abdominal pain, injection site reaction, diarrhea, hyperglycemia, and cholelithiasis.

SECOND AND FURTHER LINES OF SYSTEMIC TREATMENTS IN ADVANCED G1-2 NONFUNCTIONING GASTROENTEROPANCREATIC NENs

WD Small Bowel NEN

Somatostatin analogs. There are no data on the direct comparative efficacy of SSAs, so we do not suggest switching from one SSA to another in patients whose tumors progress. Because lanreotide is administered subcutaneously, it is preferred over octreotide (which is administered intramuscularly) in obese patients. There are limited data on higher dose or more frequent administration of SSAs. In the phase II trial CLARINET FORTE, 99 patients with G1-2 GEP NENs and disease progression on standard dose SSA received lanreotide 120 mg subcutaneously once every 14 days. The median PFS was 8.6 in the SB cohort. In the NETTER-1 phase III trial (discussed below), the control arm received octreotide long-acting release (LAR) 60 mg once monthly with a median PFS of 8 months for patients with progressive G1-2 SB-NENs.[9]

Peptide receptor radionuclide therapy. PRRT consists of combining a SSA with a radioactive atom, most commonly the beta emitter lutetium^{177}, forming ^{177}-lutetium-DOTATATE. For patients with SSTR-positive G1-2 GEP NENs experiencing unequivocal disease progression on first-line SSA, PRRT is an acceptable second-line option. In the phase III NETTER-1 trial, 229 patients with progressive SRI-positive G1-2 SB-NENs were randomly assigned to second-line treatment with four infusions of lutetium^{177} every 8 weeks along with 30 mg of octreotide LAR once every 28 days or octreotide LAR 60 mg once every 28 days until progression.[9] At a median follow-up of 76 months, the median PFS was 28 months for lutetium^{177} and 8 months for octreotide (HR, 0.18; 95% CI, 0.11 to 0.29; $P < .0001$), with a median OS of 48 and 36 months (HR, 0.84; 95% CI, 0.60 to 1.17; $P = .3$), respectively.[10] Approximately 27% of patients from the control arm were treated with lutetium^{177} on progression, with a median PFS2, that is, the time from random assignment to second investigator-assessed NEN progression, being 45 months for lutetium^{177} and 23.2 months for the control arm (HR, 0.42; $P < .0001$).[54] Serious but rare adverse events included irreversible myelotoxicity, myelodysplastic syndrome (2%), and leukemia (0.5%). Acute common (mostly mild) adverse events are nausea and renal and hepatic toxicity.

A multicenter retrospective study with 508 patients with GEP G1-3 NENs with tumor progression after SSA reported longer PFS with PRRT (HR, 0.37; $P < .001$) when compared with chemotherapy or targeted agents after

adjustment for prognostic factors (tumor functionality, primary site, and tumor grade).[55]

Everolimus. Everolimus, an oral inhibitor of the mammalian target of rapamycin, is an effective therapy in second or further lines for patients with GI NENs, lung NENs, or PanNENs. Everolimus 10 mg once daily led to longer median PFS (11.0 *v* 3.9 months; HR, 0.48; $P < .00001$) in the RADIANT-4 placebo-controlled phase III trial for patients with pretreated progressive, nonfunctional lung or GI G1-2 NENs.[8] Previous systemic therapies included SSAs (53%), chemotherapy (26%), and PRRT (22%). OS numerically favored everolimus (HR, 0.73; $P = .071$).[56] Post hoc subgroup analyses confirmed the efficacy of everolimus regardless of type of previous therapies.[57] Everolimus was also evaluated in another placebo-controlled trial for patients with functioning GI or lung G1-2 NEN pretreated with SSAs (80%) and/or chemotherapy (35%); numerical albeit not statistically significant improvement in median PFS was reported with everolimus.[58] Objective responses with everolimus were seen in <5% of cases. Clinically relevant drug-related adverse events occur in 40%-50% of patients, including stomatitis, rash, fatigue, diarrhea, pneumonitis (severe in <2%), and metabolic abnormalities (eg, hyperglycemia, dyslipidemia).[59] Oral mucositis is often a dose-limiting toxicity, and a randomized study found that the incidence or severity of stomatitis improved with therapeutic dexamethasone mouthwash.[60] A real-world retrospective Latin American study found that 21.6% of patients with NENs treated with everolimus 10 mg once daily had grade 3-4 infections, with 3.6% related deaths.[61] Therefore, everolimus should ideally not be administered in patients with uncontrolled diabetes, moderate/severe preexistent pulmonary disease, or systemic infections and used cautiously in those with uncontrolled dyslipidemia.

Tyrosine kinase inhibitors. NENs are highly vascularized tumors with multiple tyrosine kinase pathways involved in angiogenesis and tumor progression.[62] Currently, only sunitinib has received US Food and Drug Administration (FDA) approval for PanNENs. However, other tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor have been tested after failure on standard treatments, showing encouraging results.

Lenvatinib 24 mg once daily yielded an objective response rate (ORR) of 16% and a median PFS of 15.7 months in a phase II trial of heavily pretreated patients with SB and other GI NENs.[63] In the AXINET phase III placebo-controlled trial, third-line axitinib 5 mg twice daily combined with SSA for patients with G1-G2 extrapancreatic NENs offered response rate in 13.2% of cases, and a blinded independent radiological evaluation observed a median PFS of 16.6 months (*v* 9.9 months for placebo; $P = .01$).[64] An uncontrolled phase II trial with cabozantinib 60 mg once daily demonstrated a median PFS of 31 months in patients with progressive and heavily pretreated G1-2 GI-NENs,[65] and a large placebo-controlled trial (ClinicalTrials.gov identifier: NCT03375320) is currently underway. Sunitinib has shown modest efficacy in G1-2 SB-NENs.[66]

Chemotherapy. Overall, indolent G1-2 SB-NENs are less responsive to chemotherapy. The combinations tried in the past include fluorouracil (FU) with streptozotocin or doxorubicin, dacarbazine monotherapy, capecitabine and oxaliplaitn (CAPOX)/infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX), or CAPTEM, with all providing radiological objective responses in <10% of patients.[67-71]

WD PANCREATIC NENs

SSAs

Similar to G1-2 SB-NENs, oligoprogressive WD PanNENs can be managed by increasing standard SSA dosage. In the phase II trial CLARINET FORTE, the median PFS was 8 months in the PanNEN cohort with Ki67 ≤10%.[72]

PRRT

Retrospective analyses have shown that PRRT is effective in G1-2 PanNENs, with response rates as high as 60%.[73,74] In the phase II OCLURANDOM trial, 84 patients with SRI-positive advanced G1-2 PanNENs treated with at least one previous line of therapy were randomly assigned to receive ^{177}Lu-DOTATATE or sunitinib 37.5 mg once daily.[11] Both 12-month PFS rates (80 *v* 42%) and median PFS (20.7 *v* 11.0 months) favored ^{177}Lu-DOTATATE. Yet, phase III trials are required to determine whether PRRT, targeted therapy (everolimus, sunitinib), or CAPTEM is the preferred second-line option for patients with G1-2 PanNENs (Table 4). Importantly, the sequential use of CAPTEM and PRRT is associated with increased risk of myelodysplastic syndrome and acute myeloid leukemia (8%-10%) in retrospective series.[78]

Everolimus

The placebo-controlled phase III RADIANT-3 trial evaluated everolimus 10 mg once daily in 410 patients with pretreated progressive G1-G2 PanNENs, demonstrating a significant gain in PFS (median, 11.0 *v* 4.6 months; HR, 0.35; $P < .001$).[6] Objective responses were seen in only 2% of patients, and no difference in OS was observed.[7] In subanalyses, antitumor activity was not affected by previous use of chemotherapy (50%) or SSA (49%).[79]

Tyrosine Kinase Inhibitors

Sunitinib. PanNENs are particularly responsive to TKIs. Sunitinib is an FDA-approved oral multitargeted TKI that inhibits PDGFRα/β, VEGFR1-3, fetal liver kinase-3, colony-stimulating factor 1 receptor and RET signaling. Sunitinib at 37.5 mg once daily was tested in 171 patients with

advanced G1-2 PanNENs in a placebo-controlled phase III trial.[12] Prolonged PFS (median, 11.4 *v* 5.5 months; HR, 0.42; $P < .001$) and higher response rate (9.3% *v* 0%; $P = .007$) favored sunitinib. A post hoc analysis adjusted for crossover suggested sunitinib increased OS.[13] The most frequent adverse events of any grade are diarrhea, fatigue, stomatitis, hypertension, and epistaxis; grade 3 or 4 toxicities were neutropenia (12%), hypertension (10%), and palmar-plantar erythrodysesthesia (6%). Given that median PFS times of everolimus and sunitinib seem similar, the choice between these two drugs should be based on their toxicity profiles. Each sequential administration provided similar disease control rates in retrospective series.[80]

Other TKIs. Lenvatinib 24 mg once daily provided a median PFS of 15.6 months and ORR of 44.2% in a phase II trial in patients with PanNENs previously treated with SSA (100%), everolimus (69%), sunitinib (29%), or chemotherapy (32.7%).[63] In the Spanish PAZONET trial, pazopanib 800 mg once daily in patients with progressive G1-G2 lung or GEP NENs provided a median PFS of 10 months for the GI cohort.[81] The ongoing phase III CABINET trial (ClinicalTrials.gov identifier: NCT03375320) compares cabozantinib 60 mg once daily with placebo in patients with GEP NENs previously treated with PRRT or everolimus. Consistent with other indications, TKIs should not be delivered to patients with symptomatic heart failure, uncontrolled hypertension, and high risk of bleeding.

Chemotherapy

For patients requiring tumor shrinkage, chemotherapy with CAPTEM is the preferable therapy. The ACRIN-ECOG 2211 phase II trial randomly assigned 144 patients with G1-2 PanNENs to receive CAPTEM or single-agent temozolomide. About two-thirds had been pretreated with SSA.[14] Despite similar response rate (39.7 *v* 33.7%) and OS (median: 59.7 *v* 53.8 months; $P = .42$), the combination led to improved PFS (median: 22.7 *v* 14.4 months; HR, 0.58; $P = .022$). Forty-five percent of patients experienced grade 3-4 adverse events, with the most frequent ones being myelotoxicity, nausea, and diarrhea.

Nonrandomized trials have also demonstrated that FOLFOX/CAPOX can offer tumor response in approximately 30% of patients with G1-2 PanNENs, with a median PFS in the range of 12 months, including those previously treated with temozolomide-based chemotherapy.[70,82,83] Several studies have also demonstrated the activity of streptozocin-based regimens in advanced PanNENs, with response rates from 10% to 40% and the median PFS of 10-18 months in randomized trials.[84] Yet, the SEQTOR randomized trial failed to show improvement in PFS (median 21.5 *v* 23.8 months; $P = .35$) with streptozocin plus FU when compared with everolimus 10 mg once daily administered in second line; streptozocin led to higher response rate (30% *v* 11%; $P = .014$) and everolimus to more infections (15% *v* 5%).[15]

Immunotherapy

Patients with advanced, mismatch repair deficient NENs should receive immune checkpoint inhibitors at some point in their treatment. Yet, WD GEP NENs are mostly microsatellite stable and harbor low mutational burden, what explains why available immune checkpoint inhibitors targeting programmed cell death receptors have been ineffective in these cases. Rare cases of tumor transformation to hypermutated NENs, with rapidly progressive disease, following treatment with alkylating chemotherapy have been reported. Whether immune checkpoint inhibitors can be used in this setting, similar to de novo high-grade disease, is currently unknown.[85]

TREATMENT SEQUENCING FOR GASTROENTEROPANCREATIC ADVANCED G1-2 NENs

Figure 1 provides overall therapeutic sequencing strategies for patients with advanced nonfunctioning G1-2 GEP NENs. For most patients, either SSA or observation is a good first-line strategy. After tumor progression, decision on second line is based on tumor aggressiveness, disease burden, and expected treatment-related toxicities. Targeted therapies, PRRT, and locoregional therapies can be used in second or later lines. Chemotherapy is mostly reserved for more aggressive disease, particularly for patients with PanNENs. Table 4 depicts the ongoing randomized trials in advanced G1-3 NENs.

TREATMENT SEQUENCING FOR ADVANCED G1-2 FUNCTIONING GEP NENs

NENs which secrete peptide hormones that trigger symptoms are deemed functioning.

Functioning NENs are typically WD, with the most common being carcinoid syndrome (CS). PanNENs are generally nonfunctioning, although approximately 20% present hormone-specific syndromes. It is recommended to have a NEN endocrinologist specialist involved in the care of patients with functioning PanNENs. In Figure 2, we propose a summarized treatment sequencing for patients with functioning NENs.

General Treatments

SSAs. Since the majority of NENs overexpress SSTR, SSAs are the preferred first-line treatment for patients with functioning NENs and should be kept throughout the disease course, even when there is tumor progression. SSAs offer pronounced symptom control in nearly 70% of patients with CS.[86] For patients with functioning PanNENs (except for insulinomas and gastrinomas), SSAs are also the standard first-line therapy.

Liver-directed locoregional therapies. Liver-directed therapies can be performed at any moment of disease course. Tumor debulking with surgical or locoregional treatments

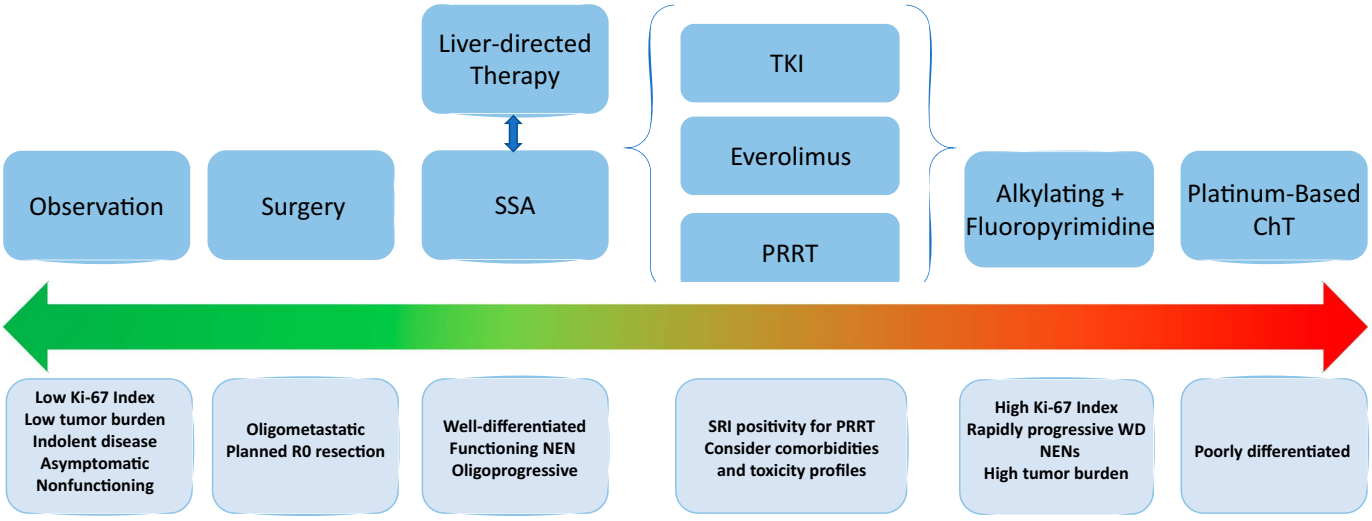

FIG 1. ChT, chemotherapy; NEN, neuroendocrine neoplasm; PPRT, peptide receptor radionuclide therapy; SRI, somatostatin receptor imaging; SSA, somatostatin analogs; TKI, tyrosine kinase inhibitor; WD, well-differentiated.

can offer symptom control, with symptom relief and some degree of biochemical response reported in 80% and 63% of patients with CS, respectively.[86] R2 surgical debulking of large tumors areas can also be performed in selected cases as uncontrolled studies have reported symptom relief in up to 90% of cases, with a median duration of CS control of up to 45 months.[87] Although liver-directed therapies can be repeated if there is good hepatic function, it is not recommended for patients with moderate/severe carcinoid heart disease—for these patients,

Therapy line	Carcinoid syndrome		Functioning Pancreatic NEN	
	Indolent tumors	Aggressive tumors[a]	Indolent tumors	Aggressive tumors[a]
First	SSA[b]	SSA[b]	SSA[c]	SSA[c] + chemotherapy (eg, CAPTEM)
Second	Increase SSA dose and/or shorten injections intervals	Increase SSA dose and/or shorten injections intervals + Hepatic embolization[d] +/- telotristat ethyl[e]	Everolimus, sunitinib or Hepatic embolization[d]	Switch chemotherapy (eg, to oxaliplatin-based)
Later lines	Add telotristat ethyl[e] or Hepatic embolization[d] or Lutetium^{177}	Lutetium^{177d}	Lutetium^{177} or CAPTEM	Palliative surgical debulking or Hepatic embolization[d]
Other options	Everolimus or Alpha-interferon	Chemotherapy	Palliative surgical debulking	Everolimus or Sunitinib

FIG 2. Therapeutic sequencing strategies for patients with advanced functioning GEP NENs. Clinical trials preferred. Surgery can be considered at any therapy line. CAPTEM, capecitabine and temozolomide; NEN, neuroendocrine neoplasm; SSA, somatostatin analog. [a]High tumor and symptom burden, rapidly progressive, complications from hormonal syndrome (eg, carcinoid heart disease, Cushing syndrome). [b]Maintain SSA throughout treatment sequencing. [c]SSA used cautiously in insulinoma. [d]Consider retreatment if prior prolonged benefit. [e]If available.

surgical valve replacement should be performed before these procedures.[88]

Specific Hypersecretion Syndromes

Patients with insulinoma should be treated cautiously with SSAs because these drugs may worsen hypoglycemia by inhibiting the release of counter-regulatory hormones. Therefore, other treatments should be prioritized before resorting to SSA use while actively monitoring glycemia. Everolimus is particularly effective in insulinomas, both for glycemia normalization and tumor control, and should be used in first line.[6]

Gastrinomas should be firstly managed by high dose of proton-pump inhibitors. Patients with VIPomas should receive intravenous fluids and electrolytes. Table 5 summarizes the characteristics and treatment particularities of the most frequent functioning NENs.

Treatments for Patients With Resistant Hormone Hypersecretion Syndromes

Despite the effectiveness of SSAs in recommended doses to control NEN hormonal syndromes, symptomatic and biochemical progression ultimately occurs.

Refractory carcinoid syndrome. Ruling out other causes of diarrhea such as problems with injection administration, infections, or SSA-induced exocrine pancreatic insufficiency is important in patients with CS whose symptoms worsen despite SSA label dosage.

When there is radiologically stable or slow-growing disease and worsening CS, increasing SSA dose and/or shortening the intervals of injections can sometimes alleviate symptomatology.[89] Few trials have been conducted in this setting, with only two randomized trials being conducted to guide treatment sequencing in patients with refractory CS. A double-blind phase III trial compared the symptomatic response of pasireotide LAR, a new SSA with broader affinity to SSTR-5, with octreotide LAR 40 mg. The study was closed prematurely because of futility.[90]

Telotristat ethyl is an oral inhibitor of tryptophane hydroxylase, the enzyme responsible for 5HT synthesis. In a double-blind phase III trial at two different doses (250 mg or 500 mg three times a day), telotristat ethyl significantly reduced diarrhea in patients with refractory CS. With a predefined response of reduction $\geq$30% in the frequency of bowel movements lasting for $\geq$50% during 12 weeks, nearly 40% had a response versus 20% of those on placebo.[91] Another placebo-controlled trial confirmed these results.[92] Telotristat ethyl is approved for CS-associated diarrhea insufficiently controlled by SSAs in few countries, including the United States, at a dose of 250 mg three times a day in combination with SSAs.

In the NETTER-1 trial, diarrhea improved in nearly half of patients with SB-NENs treated with ^{177}-lutetium-DOTATATE combined with octreotide LAR 30 mg once monthly, although similar improvement occurred in patients in the octreotide LAR 60-mg once monthly arm, yet time to deterioration of diarrhea (HR, 0.39), social functioning (HR, 0.63), and pain (HR, 0.62) significantly favored ^{177}-lutetium-DOTATATE.[93] Flushing also improved with ^{177}-lutetium-DOTATATE.[93]

Refractory CS can also be treated with everolimus 10 mg once daily and interferon alpha (IFN-α).[94] Uncontrolled studies have reported CS relief in up to 75% of patients treated with IFN-α (3-5 million UI s.c. three times weekly), although randomized trials failed to prove its clinical benefit in comparison with SSA alone.[87] Given its undesirable toxicity profile, IFN-α can be used in later lines as an add-on to SSAs.

For aggressive CS (high tumor and/or symptom burden, rapidly radiological progressive disease, or presence of carcinoid heart disease), therapies providing higher probability of tumor response are recommended.

Resistant hormone hypersecretion syndromes in PanNEN. Classic systemic treatments for nonfunctioning PanNENs can provide not only growth but also symptom control in functioning counterparts. This includes PRRT, everolimus, and chemotherapy.

PRRT can control hypoglycemia in patients with metastatic insulinomas and ectopic Cushing syndrome in patients with adrenocorticotropic hormone-secreting PanNEN.[6,95,96]

Tyrosine kinase inhibitors are not effective to treat hormonal symptoms but can be used in combination with SSA for tumor control in more indolent functioning PanNENs. Chemotherapy has limited activity in SB-NENs but offers response rate in the range of 30% in PanNENs, consequently improving hormonal symptoms.

TREATMENTS FOR PATIENTS WITH METASTATIC GRADE 3 GASTROENTEROPANCREATIC NEN

Grade 3 (G3) NENs comprise a rare group of WD, high-grade NENs, most commonly of pancreatic origin.[28] G3 NENs are biologically and molecularly distinct from NECs, which reflects in their lower aggressiveness: high-uptake on PET-Ga,[85] low FDG uptake, often with Ki-67 $\leq$30%, and generally slower tumor growth rate compared with NEC, and patients are often oligosymptomatic.[35,97] Although G3 NENs can secrete hormones, NECs are generally nonfunctioning.

More indolent G3 NENs are managed similarly to G2 NENs, for example, with targeted agents, locoregional therapies, and PRRT. There are limited data on the use of either everolimus or sunitinib in G3 GEP NENs, but these are acceptable first-line options in patients with more indolent behaving neoplasms. In highly selected nonfunctioning oligoprogressive cases with SSTR-positive tumors, SSAs can provide a median PFS of 6-7 months.[98] PRRT has demonstrated promising activity in pretreated selected patients with SSTR-positive WD G3 NENs, with an objective response achieved by 42%, a median PFS of 19 months, and a median OS of 44 months.[99]

TABLE 5. Characteristics of Functioning NENs

NEN	Laboratory Marker and Clinical Syndrome	Peptide Hormone Secreted	Site(s) of Origin	Therapy for Hormonal Syndrome
Well-differentiated NENs	24-hour urinary 5-HIAA Carcinoid syndrome: Facial flushing, diarrhea, fibrotic complications (carcinoid heart disease and mesenteric fibrosis)	Serotonin and several vasoactive peptides	Small bowel, lung, thymus, ovary, metastatic unknown primary NEN	Long-acting SSA Add short-acting SSA before, during, and after invasive procedures to prevent carcinoid crises
Glucagonoma	Serum glucagon Diabetes mellitus, necrolytic migratory erythema, dementia/ depression, thromboembolism	Glucagon	Pancreas	Long-acting SSA
Insulinoma	Elevated fasting serum insulin and C-peptide; in doubtful cases, a 72-hour fasting test is performed during hospitalization Symptoms of hypoglycaemia	Insulin	Pancreas	Consider hospitalization for IV glycose, frequent feeding, diazoxide, steroids, calcium-channel blockers, beta-blockers, phenytoin. Everolimus 10 mg once daily SSA: Start with short-acting SSA while monitoring glycose. Unknown benefit of long-acting SSA
Gastrinoma	Fasting serum gastrin >1,000 pg/mL If <1,000 pg/mL, secretin test is indicated Recurrent peptic ulcer, dyspepsia, esophageal reflux, steatorrhea	Gastrin	Pancreas (85%) Duodenum (15%)	High-dose proton-pump inhibitors Long-acting SSA (for steatorrhea and tumor control)
VIPoma	Serum VIP Severe secretory and watery diarrhea, dehydration, hypokalaemia, achlorhydria Hypercalcaemia (if PTH-rp is cosecreted)	VIP with or without concurrent PTH-rP	Pancreas	Long-acting SSA Intravenous electrolytes and fluid administration For hypercalcemia: see PTH-rPoma
ACTHoma	Elevated ACTH and/or CRH, 24-hour urinary free cortisol; Cushing syndrome	ACTH	Pancreas, lung, metastatic unknown primary NEN	Steroidogenesis inhibitors (bilateral adrenalectomy in severe cases) Long-acting SSA Add other NEN-directed therapies only when Cushing syndrome is under control
Somatostatinoma	Serum somatostatin Diabetes mellitus, cholelelithiasis, steatorrhea, hypochloridria	Somatostatin	Pancreas Duodenum (neurofibromatosis I)	Long-acting SSA
PTH-rPoma	Hypercalcemia Elevated serum PTH-rp and low PTH	PTH-rP	Pancreas	Long-acting SSA Therapies for cancer-associated hypercalcemia (intravenous fluids, bisphosphonates/ denosumab, furosemide)

Abbreviations: ACTH, adrenocorticotropin hormone; CRH, corticotrophin-releasing hormone; IM, intramuscularly; IV, intravenously; NEN, neuroendocrine neoplasm; PTH-rP, parathyroid hormone (PTH)–related peptide; SSA, somatostatin analogs (long-acting octreotide 30 mg IM monthly or lanreotide autogel 120 mg SC monthly; short-acting octreotide 100-200 mcg IV); SC, subcutaneously; VIP, vasoactive intestinal peptide.

Importantly, patients with tumors with heterogeneous uptake on SRI and higher ^{18}FDG-PET uptake seem to benefit less from PRRT, although no specific uptake thresholds have been established so far.[100]

In contrast, those with more aggressive features (low uptake on PET-Ga,[85] high FDG uptake, symptomatic patients, Ki-67 >30%, and high metastatic burden) can be treated with CAPTEM or oxaliplatin-doublet chemotherapy.[98] CAPTEM offers objective response in nearly 40%, a median PFS of up to 20 months, and 5-year OS rate ranging from 20% to 68%.[98] FOLFOX is another effective chemotherapy option with objective responses being reported in nearly half of patients and median PFS in the range of 9 months.[101] Differently from NECs, cisplatin and etoposide/irinotecan are not routinely recommended for patients with G3 NENs because they provide inferior disease control when compared with CAPTEM or oxaliplatin-based regimens.[98]

TREATMENTS FOR PATIENTS WITH METASTATIC GASTROENTEROPANCREATIC NECs

Advanced Extrapulmonary NECs

Extrapulmonary NEC is an aggressive disease that, like the more common entity of small-cell lung cancer (SCLC), is characterized by rapid development of chemoresistance and early metastatic spread. Thus, curative-intent resection should be used whenever possible for potentially resectable disease. Specific approaches vary with disease site, but strategies including neoadjuvant or adjuvant chemotherapy with or without radiation have been used, without strong evidence to support one approach over the other.

Platinum-based regimens. First-line systemic therapy for extrapulmonary NEC was initially adopted from regimens used for SCLC. Similar to SCLC, extrapulmonary NEC is associated with high response rate to platinum-based chemotherapy, even compared with WD G3 NENs.[16] Several retrospective studies have evaluated cisplatin or carboplatin in combination with etoposide, with response rates of 31%-67% and a median OS ranging from 11 to 19 months.[16,17,102,103] Cisplatin with irinotecan has shown similar results in the first-line setting.[18,19,104]

FU-based regimens. There is no established second-line regimen for advanced extrapulmonary NEC supported by robust evidence. Particularly for GEP NEC, there is a rationale for using FU-based regimens including FOLFOX, fluorouracil, leucovorin, and irinotecan (FOLFIRI), or fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFIRINOX). A retrospective analysis of 20 patients with G3 NEC (16 extrathoracic or unknown primary site) treated with FOLFOX after failure of platinum and etoposide showed a median OS of 9.9 months.[20] The PRODIGE 41-BEVANEC trial of FOLFIRI with or without bevacizumab after failure of first-line platinum and etoposide showed a 6-month OS of 60% in the FOLFIRI group, with no improvement in outcome from the addition of bevacizumab.[21] A retrospective study of 37 patients with GEP NEC treated with FOLFIRINOX showed an ORR of 46% and a median OS of 17.8 months.[22] Although there is evidence for FU-based regimens in the second line, it is not clear whether, or in which case, these regimens may be appropriate as first-line therapy.

CAPTEM. A Polish retrospective analysis of CAPTEM in 32 patients with G3 NENs, of whom 12 had NEC, yielded a median OS of only 4.6 months, consistent with the aggressive nature of this disease.[23] The ECOG-ACRIN EA2142 trial randomly assigned patients with G3 GEP NENs (including NEC) to CAPTEM or platinum and etoposide in first line.[24] Although this study was terminated early for low accrual, interim analyses suggested similar outcomes between the two regimens. Although this trial suggests that CAPTEM may be used in the first-line setting, indications of more aggressive disease biology (eg, higher Ki-67 or small cell histology) are generally regarded as indicators favoring platinum and etoposide.

Immune checkpoint blockade. Immune checkpoint blockade has been explored alone or in combination with chemotherapy in extrapulmonary NEC. The phase II DART SWOG 1609 trial enrolled 32 patients with nonpancreatic NENs, of whom 26 had extrapulmonary disease and 18 had high-grade disease. These patients received ipilimumab and nivolumab in the second line or later, with an overall response rate of 44% among patients with high-grade disease. Although dual checkpoint blockade was successful in this population, the addition of immunotherapy to chemotherapy showed lackluster results. In a trial of pembrolizumab plus chemotherapy (irinotecan or paclitaxel) in extrapulmonary NEC, the response rate was only 9% with a median PFS of 2 months and a median OS of 4 months.[27] The ongoing SWOG S2012 trial (ClinicalTrials.gov identifier: NCT05058651) evaluates the potential role of atezolizumab in combination with first-line platinum and etoposide, which is standard for SCLC.

Targeted therapy. Given the overall poor outcomes of advanced NEC, these tumors should be evaluated by molecular profiling for genomic indications for targeted therapy. Although no NEC-specific targeted therapies have been identified, therapeutic targets evaluated across multiple tumor types are present in extrapulmonary NEC to varying degrees. Therapeutic targets with evidence of efficacy in extrapulmonary NEC include microsatellite instability or mismatch repair deficiency (pembrolizumab), high tumor mutational burden (TMB; pembrolizumab), *NTRK* fusions (entrectinib or larotrectinib), *RET* alterations (selpercatinib), and *BRAF V600E* mutations (dabrafenib and trametinib).

Microsatellite instability varies in abundance by tissue, with prevalence in pancreatic and ampullary NEC estimated at 5%-8% and up to 12.4% in gastric and enteric NEC.[105-107]

Similar to other MSI-high carcinomas, microsatellite instability is associated with improved prognosis in NEC.[105,107] High TMB is another tissue-agnostic approval for pembrolizumab, and relatively sparse data support its use in TMB-high NEC.[108,109] *NTRK* fusions were identified in 0.3% of all NENs in a study of 2,147 patients with NEN; five of six identified cases were found in NEC (four extrapulmonary).[110] *RET* gene fusions are best known in medullary thyroid cancer and the association with multiple endocrine neoplasia types 2A and 2B. Although *RET* alterations are rare in extrapulmonary NEC, *RET* status should be evaluated as part of panel testing in NEC because of its overall importance in neuroendocrine tumor development and the tumor agnostic approval of selpercatinib for *RET* fusion–positive tumors. Finally, subprotocol H of the NCI-MATCH trial, which evaluated dabrafenib and trametinib in patients with *BRAF V600E* mutations, included two patients with colon NECs and two mixed ductal/NECs of the pancreas. The *BRAF V600E* mutation is relatively common in colorectal NEC, similar to colorectal adenocarcinoma, with one study estimating a prevalence of about 20%.[111]

Sequencing therapy. At this point, there is no optimal sequencing treatment for patients with high-grade NECs. The totality of evidence favors a platinum and etoposide regimen as a first-line option for eligible patients with poorly differentiated or small cell histology and for most patients with a Ki-67 of >55%. Alternative chemotherapies can be considered for patients with poor performance status, less aggressive tumors, and WD histology as mentioned above. Targeted therapy and immunotherapy could be reserved for later lines of treatment. All patients should consider enrolling in a clinical trial whenever possible.

CONCLUSIONS

NENs are a very complex and heterogeneous group of neoplasms. Although several clinical trials have been conducted in patients with advanced NENs of different origins in the past decade, the scientific evidence for treatment sequencing is still limited. In this regard, MDTs are of prime importance to provide the best approach to individual patients. Future ongoing trials (Table 4) will hopefully better define therapeutical sequencing strategies for patients with NEN.

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Advancements in Systemic Therapy for Pancreatic Cancer

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overview

Outcomes for patients with advanced pancreatic cancer have improved in the past 12 years, mainly because of progress made in systemic therapies. New treatment strategies for advanced pancreatic cancer include switch maintenance with cytotoxic therapies, induction maintenance, and the utilization of targeted agents for patients with actionable variants, as well as ongoing development of cytotoxic regimens, such as NALIRIFOX. The activity of immunotherapy has been disappointing to date, but novel combinations and identifying appropriate patient populations may further unlock its potential.

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ADVANCEMENTS IN SYSTEMIC THERAPY FOR PANCREATIC CANCER

Progress with systemic therapy for patients with advanced pancreatic cancer has historically been slow. However, therapeutic advances in the past 12 years have resulted in modest yet tangible improvements for patients. The cornerstone of these improvements has been in the continuous development of cytotoxic chemotherapy combinations, including oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX; 2011)[1]; gemcitabine plus nab-paclitaxel (2013)[2]; fluorouracil (FU)/nanoliposomal irinotecan (2016)[3]; and NALIRIFOX (2023).[4] In addition, for a select population—namely, those with *BRCA* or *PALB2* variants who have stable or improved disease on frontline platinum-based therapy—induction/maintenance has emerged as an option that lengthens time off cytotoxic agents.[5] Although this strategy has not yet been shown to improve survival, it offers patients a less-toxic, chemotherapy-free treatment option. Another major breakthrough has been the progressive expansion of targeted agents for patients with pancreatic cancer. Although the population of patients eligible for targeted treatment remains small, the ongoing development of KRAS inhibitors offers hope that we soon might be able to offer precision therapies to a large number of our patients. Finally, although immunotherapy has historically yielded disappointing results, novel combinations and the use of immunotherapy in novel settings may unlock its potential.

CURRENT STANDARD-OF-CARE APPROACH

Currently, the standard-of-care approach for most patients with metastatic pancreatic adenocarcinoma is perpetual cytotoxic chemotherapy with either FOLFIRINOX or gemcitabine and nanoparticle albumin–bound (nab-) paclitaxel on the basis of the PRODIGE-4/ACCORD-11[1] trial and the MPACT trial, respectively.[2]

Although both these regimens have improved outcomes over the previous generation of gemcitabine monotherapy as first-line therapy, FOLFIRINOX and gemcitabine-nab-paclitaxel have never been compared head-to-head in a prospective clinical trial. However, FOLFIRINOX is generally preferred for first-line treatment of advanced pancreatic cancer in patients who are healthy enough to tolerate it and is endorsed in the ASCO guidelines, with gemcitabine-nab-paclitaxel reserved for the second-line treatment or in the first-line treatment for patients with medical comorbidities.[6] Indirect evidence from the recently reported NAPOLI-3 trial of NALIRIFOX versus gemcitabine-nab-paclitaxel lends further support to this approach and is discussed in more detail later in this review.[4] In clinical practice, FOLFIRINOX is often modified from its original dosing schema with a lower dose of irinotecan (150 mg/m^2 once every two weeks) and elimination of the FU bolus to improve the adverse event profile without reducing the efficacy.[7]

NEW DEVELOPMENTS IN CYTOTOXIC CHEMOTHERAPY FOR ADVANCED PANCREATIC CANCER

NALIRIFOX

Combination of 5-FU, leucovorin, and liposomal irinotecan was previously approved for metastatic pancreatic cancer after progression with a gemcitabine-based regimen on the basis of the global, randomized, phase III NAPOLI-1 trial.[3] In practice, this combination has been historically limited to the second- or third-line setting in patients with progressive disease (PD) who remain candidates for therapy. The combination of NALIRIFOX (liposomal irinotecan 50 mg/m^2, FU 2400 mg/m^2, leucovorin 400 mg/m^2, and oxaliplatin 60 mg/m^2) once daily on days 1 and 15 of a

PRACTICAL APPLICATIONS

- The cornerstone of systemic therapy for advanced or metastatic pancreatic cancer remains cytotoxic chemotherapy.
- NALIRIFOX is a possible option for frontline therapy on the basis of NAPOLI-3 clinical trial.
- All patients with incurable pancreatic cancer should undergo germline and somatic next-generation sequencing to identify possible actionable variants.
- Noncytotoxic maintenance therapy after a period of chemotherapy induction is an option for patients with *BRCA* or *PALB2* variants. Maintenance treatment is actively being explored for a broader population.
- Progress is being made in identifying candidate combinations to enhance the effects of immunotherapy in pancreatic cancer.

28-day cycle was evaluated in a phase I/II study and demonstrated manageable toxicity and a median overall survival (OS) of 12.6 months, generating preliminary data for testing this combination in a phase III trial.[8]

The global, open-label, phase III NAPOLI-3 trial compared NALIRIFOX given on days 1 and 15 of a 28-day cycle with gemcitabine and nab-paclitaxel given on days 1, 8, and 15 of a 28-day cycle in previously untreated patients with metastatic pancreatic cancer.[4] This trial randomly assigned 770 patients (n = 383 NALIRIFOX, n = 387 gemcitabine and nab-paclitaxel) and had a primary end point of OS. After a median follow-up of 16.1 months, the median OS in the NALIRIFOX arm was 11.1 months compared with 9.2 months in the gemcitabine and nab-paclitaxel arm (hazard ratio [HR], 0.84; 95% CI, 0.71 to 0.99; P = .04). Similarly, median progression-free survival (PFS) was significantly improved with NALIRIFOX versus gemcitabine/nab-paclitaxel (7.4 months *v* 5.6 months; HR, 0.70; 95% CI, 0.59 to 0.84; P = .0001). Objective response rates (ORRs) slightly favored NALRIFOX (ORR, 41.8%; 95% CI, 36.8 to 6.9 *v* 36.2%; 95% CI, 31.4 to 41.2). Furthermore, grade ≥3 treatment-related adverse events, serious treatment-related adverse events, and treatment-related adverse events (TRAEs) that led to death were similar between NALIRIFOX and gemcitabine/nab-paclitaxel. Diarrhea, nausea, vomiting, and hypokalemia were the most common grade ≥3 TRAEs in the NALIRIFOX arm.

Although NALIRIFOX has not been directly evaluated against FOLFIRINOX and cross-trial comparisons are challenging and subject to bias across patient populations, the findings from the NALIRIFOX arm in NAPOLI-3 are strikingly similar to the outcomes of the FOLFIRINOX arm of PRODIGE-4/ACCORD-11,[1] whereas gemcitabine and nab-paclitaxel in NAPOLI-3 led to slightly longer OS and higher ORR compared with MPACT.[2] Without direct head-to-head comparisons of FOLFIRINOX and NALIRIFOX and while we await the publication of the NAPOLI-3 trial, it is expected both regimens will be acceptable for frontline standard of care for otherwise healthy patients with advanced pancreatic cancer. Moreover, the results of the gemcitabine and nab-paclitaxel arm lend support to either NALIRIFOX or FOLFIRINOX as the preferred frontline option for patients who are candidates for this intensive therapy.

TARGETED THERAPY IN PANCREATIC CANCER

For patients with metastatic pancreatic cancer, both germline and somatic sequencing should be performed in an expeditious manner as up to a quarter of patients with advanced pancreatic cancer might have a potentially actionable mutation and may be eligible for biomarker-directed therapies or clinical trials.[9-11] The results of such testing can influence the approach to first-line therapy in the case of *BRCA*-mutated pancreatic cancer,[12] inform risk of developing hereditary cancers in family members, identify potentially actionable variants, and facilitate enrollment into clinical trials that may not otherwise be available. Until recently, there were very few druggable targets available, aside from the tissue-agnostic approvals. However, progress is being made in identifying and exploiting potentially targetable mutations.

RET

RET fusions or alterations are uncommon in pancreatic cancer, representing 0.6% of all patients and 1.35% of those with *KRAS* WT disease, but are targetable by selpercatinib.[13,14] LIBRETTO-001 was an open-label phase I/II basket trial designed to assess the ORR of patients with *RET* fusion–containing malignancies treated with selpercatinib.[15] In total, 12 of 45 patients enrolled on this trial had refractory advanced pancreatic adenocarcinoma (27%), of whom 11 were evaluable for a response. The ORR in these patients with pancreatic cancer was 54.5% (95% CI, 23.4 to 83.3).[15] On the basis of these results, the US Food and Drug Administration (FDA) granted selpercatinib an accelerated tissue-agnostic approval for patients with solid tumors harboring a *RET* fusion, offering a potential option for a small population of patients with *RET* fusion–positive advanced pancreatic cancer.[16]

NTRK Fusions

NTRK fusions are extremely rare in pancreatic cancer, reported to be present in up to 0.56% of patients with

pancreatic adenocarcinoma.[17,18] However, there is a tumor-agnostic approval for either larotrectinib or entrectinib in patients with tumors harboring *NTRK* fusions and case reports documenting response to these targeted therapies in patients with refractory pancreatic cancer driven by NTRK fusions.[19,20] It is reasonable to consider evaluation for the presence of *NTRK* fusions in patients with advanced pancreatic cancer to identify patients who are candidates for these targeted therapies.

Targeting KRAS

KRAS is one of the most commonly mutated genes in pancreatic cancer, mutated in over 90% of pancreatic cancers and almost exclusively in the G12 codon, although, up until recently, it has been challenging to target.[14,21,22] Sotorasib is a small molecule that specifically inhibits *KRAS* G12C through an interaction with the P2 pocket of the mutated protein, locking it into an inactive form. Sotorasib was approved for use by the US FDA in late 2022 for non–small-cell lung cancer harboring a *KRAS* G12C mutation.[23-25] In advanced pancreatic cancer, however, G12C is a relatively uncommon mutation, representing only 1%-2% of all patients with pancreatic cancer.[26] The initial report of the phase I CodeBreaK 100 trial testing sotorasib in advanced solid tumors enrolled 12 patients with pancreatic cancer, of whom one experienced a partial response.[27] This led to expansion and investigation specifically into patients with *KRAS* G12C–mutated pancreatic cancer. Thirty-eight patients with pancreatic cancer harboring a pathogenic *KRAS* G12C mutation were enrolled and received sotorasib 960 mg orally once daily. No patient discontinued sotorasib because of toxicity, and the most common treatment-related adverse events were diarrhea and fatigue (5% each). Eight patients (21%) had a confirmed partial response, and 24 (63%) had stable disease as their best response. The median PFS in the trial was 4.0 months (95% CI, 2.8 to 5.6), and the median OS was 6.9 months (95% CI, 5.0 to 9.1). The follow-up CodeBreaK 101 trial investigating sotorasib combinations is currently underway (ClinicalTrials.gov identifier: NCT04185883).

Although the majority of patients will not benefit from *KRAS* G12C inhibition, we have cautious optimism for targeting *KRAS* mutations in pancreatic cancer as a number of novel KRAS inhibitors are just starting to enter the clinic by way of clinical trial. ASP3082 (ClinicalTrials.gov identifier: NCT05382559) and MRTX1133 (ClinicalTrials.gov identifier: NCT05737706) are two drugs with open phase I trials targeting KRAS G12D, a mutation that is found in about 35% of pancreatic cancers, and still many other companies have KRAS G12D inhibitors in various phases of development. In addition, pan-KRAS inhibitors such as RMC-6236 (ClinicalTrials.gov identifier: NCT05379985) are also in development, opening a potential avenue to treat a majority of patients with *KRAS*-mutated pancreatic cancer.[28-31] Furthermore, the conserved mutational profile of *KRAS* in pancreatic cancer and the previous identification of T-cell receptors specific to the mutant KRAS protein in tumor-infiltrating lymphocytes make this a potential avenue for adoptive T-cell therapies in the future,[21,32-34] and this is further discussed later in this review.

CDK

Loss of function of the *CDKN2A* tumor suppressor gene through promoter hypermethylation or deletion is a key event in the tumorigenesis in pancreatic cancer and leads to the loss of the P16 inhibitory signal to CDK4 and CDK6.[35,36] Despite this key interaction, early-phase clinical trials aimed at inhibiting CDK4/6 and its associated pathways have been disappointing, with both a trial of abemaciclib with or without a PI3K inhibitor and a trial of ribociclib with everolimus failing to improve outcomes for these patients.[35]

Ulixertinib is a novel ERK1/2 inhibitor that has shown promising results in preclinical xenograft models.[37] A phase I trial testing the combination of ulixertinib and palbociclib (ClinicalTrials.gov identifier: NCT03454035) reached its maximum tolerated dose of ulixertinib 450 mg PO twice daily and palbociclib 125 mg PO once daily and was reported at the ASCO 2021 Annual Meeting.[38] Three of 16 evaluable patients had stable disease as their best response.[38] An expansion cohort of patients with metastatic pancreatic cancer is currently enrolling. A similar trial of palbociclib and the PI3K inhibitor gedatolisib is also ongoing (ClinicalTrials.gov identifier: NCT03065062).

NRG1

Neuregulin-1 (*NRG1*) fusions are rare but enriched in the *KRAS* wild-type (WT) population of patients with pancreatic cancer, representing only 0.6% of all cases of pancreatic cancer but up to 17% of patients with *KRAS* WT pancreatic cancer.[39,40] These fusions lead to near-constitutive activation of human epidermal growth factor receptor (HER) 3, promoting overactivation of the MAPK and PI3K pathways. Patients with pancreatic cancer driven by these fusions have been successfully treated with agents targeting this pathway, such as afatinib, erlotinib, and pertuzumab.[39]

Seribantumab, a fully human anti-HER3 IgG2 antibody, was also evaluated in the phase II CRESTONE trial, showing promising clinical activity and acceptable toxicity.[41] This study has completed accrual and is expected to report in the summer of 2023. A case report of a patient with *NRG1* fusion who was treated off trial with seribantumab for refractory pancreatic adenocarcinoma informed by preliminary results of this trial exhibited a partial response and disease control for more than 6 months at the time of publication.[40]

In addition, the ongoing phase II study eNRGy is testing whether zenocutuzumab, a bispecific antibody targeting the

HER3 pathway, has clinical activity in patients with treatment-refractory solid tumors (including pancreatic cancer) harboring an *NRG1* fusion (ClinicalTrials.gov identifier: NCT02912949).[42] This study is expected to be completed in late 2024 and may provide another treatment option for these patients.

Trophoblast Cell Surface Antigen-2

Trophoblast cell surface antigen-2 (Trop-2) is a transmembrane calcium signal transducer that is expressed in normal human epithelia and at high levels in many cancers.[43] Its expression has been associated with an increase in cancer growth and the development of metastases although activating mutations have not been described.[44,45] Sacituzumab govitecan is an antibody-drug conjugate that consists of hRS7, an IgG1 anti-Trop2 humanized monoclonal antibody, linked to SN-38, the active camptothecin metabolite of irinotecan.[46] In the first-in-human study, sacituzumab govitecan had an acceptable safety profile and resulted in stable disease in five of five evaluable patients with refractory metastatic pancreatic cancer.[47] In the follow-on basket study IMMU-132-01, 16 patients with refractory metastatic pancreatic cancer were enrolled, of whom seven experienced stable disease as best response, whereas the remainder had PD.[48] The low response rate in pancreatic cancer was partially attributed to previous irinotecan exposure; it is unclear if this compound will be investigated further for pancreatic cancer.[48]

MAINTENANCE THERAPY FOR PANCREATIC CANCER

The standard approach to treatment in pancreatic cancer is continuous cytotoxic combination chemotherapy until either adverse events or progression of disease leads to a change in therapy. Other strategies of evaluating alternative therapies after a period of induction cytotoxic therapy, an approach that has historically albeit admittedly poorly termed maintenance therapy, are being explored. While some of these strategies are truly meant to maintain the response or stable disease achieved by upfront induction chemotherapy in an effort to minimize toxicity, other strategies aim to potentially deepen the response induction chemotherapy achieved.

Maintenance FU

PANOPTIMOX-PRODIGE-35 was a three-arm phase II trial in previously untreated patients with metastatic pancreatic cancer that compared 6 months (12 cycles) of FOLFIRINOX with either the sequence of FOLFIRINOX for eight cycles followed by FU/leucovorin maintenance (an oxaliplatin stop-and-go strategy, LV5FU2) or FIRGEM, a sequential treatment strategy consisting of fluorouracil, leucovorin, and irinotecan (FOLFIRI.3) for four cycles and gemcitabine for two cycles in a previously untreated population of patients with pancreatic cancer.[49] The primary end point of interest was a noncomparative landmark 6-month PFS to select the best regimen to test in a phase III trial. The 6-month PFS for FOLFIRINOX in the study was 41%; for LV5FU2, it was 42.9% (95% CI, 34.3 to 51.4); and for FIRGEM, it was 34.1% (95% CI, 25.7 to 43.3). The median OS, a secondary objective, was 10.1 months (95% CI, 8.5 to 12.2) with FOLFIRINOX, 11.2 months (95% CI, 9.0 to 13.1) with LV5FU2, and 7.3 months (95% CI, 5.7 to 9.5) with FIRGEM. Despite eliminating oxaliplatin after eight cycles of FOLFIRINOX, LV5FU2 had similar rates of grade 3 or 4 neurotoxicity compared with perpetual FOLFIRINOX within the first 6 months of therapy (LV5FU2 11.0%, FOLFIRINOX 10.2%), which, however, were higher overall in the LV5FU2 arm (19.8%) compared with FOLFIRINOX (10.2%) at study completion.[49] This unexpected finding is hypothesized to be due to higher cumulative oxaliplatin dose in the LV5FU2 arm since oxaliplatin was restarted after progression on maintenance therapy in more than a third of patients.[49] Regardless, this study provided support for a maintenance approach for patients with pancreatic cancer that is controlled after induction FOLFIRINOX although this specific strategy does not clearly reduce chemotherapy-induced neurotoxicity.[50]

Cytotoxic Switch Maintenance

The results of the SEQUENCE trial were presented at the ASCO 2022 Annual Meeting, developing an alternative maintenance management concept compared with PANOPTIMOX.[49,51] This was a phase I/II trial exploring a switch maintenance strategy in which untreated patients with metastatic pancreatic cancer were randomly assigned to receive standard gemcitabine plus nab-paclitaxel versus alternating gemcitabine-nab-paclitaxel and modified FOLFOX.[51] The schedule and dosing of the experimental arm were as follows: gemcitabine and nab-paclitaxel on days 1, 8, and 15, followed by modified FOLFOX-6 on day 29 of a 6-week cycle. Safety data from this approach had been previously published, demonstrating acceptable tolerability with few dose delays.[52] This strategy resulted in improved landmark 12-month survival (55.3%; 95% CI, 44.2 to 66.5 *v* 35.4%; 95% CI, 24.9 to 46.0; $P = .016$), 24-month survival (22.4%; 95% CI, 13.0 to 31.8 *v* 7.6%; 95% CI, 1.8 to 13.4; $P = .012$), and median OS (13.2 months; 95% CI, 10.1 to 16.2 *v* 9.7 months; 95% CI, 7.5 to 12.0; HR, 0.676; 95% CI, 0.483 to 0.947; $P = .023$) with the switch maintenance strategy compared with gemcitabine and nab-paclitaxel.[51] Although intriguing, this strategy may complicate further sequencing after progression, particularly with regard to postprogression treatments. Further prospective study is warranted.

Induction/Maintenance Therapy—A New Paradigm for Patients With Unique Biology

Select subgroups of patients with advanced or metastatic pancreatic cancer exhibit durable responses to chemotherapy, correlating with increased OS for some of these

patients.[53] Rather than treating all patients with perpetual chemotherapy, fueling cumulative toxicity, eventual therapeutic resistance, and degradation of quality of life, interest has been growing in identifying patients who may be appropriate for a new paradigm: using chemotherapy as an induction therapy and then switching to noncytotoxic maintenance treatment. Under this paradigm which has been pioneered in other cancer types, select patients with pancreatic cancer who possess unique biology (such as homologous recombination repair deficiency) are treated for a fixed period of time with cytotoxic chemotherapies (induction) to chemically debulk their cancers.[54] After a period of stability on these treatments, the cytotoxic chemotherapies are electively discontinued and the patient is started on the maintenance agent, with a goal of continuing the ongoing response to therapy while avoiding the cumulative effects of cytotoxic chemotherapies.[53] The development of poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) best illustrates this approach in practice in patients with pancreatic cancer.

PARP inhibitors for BRCA- or PALB2-mutated pancreatic cancer. Patients with locally advanced or metastatic pancreatic cancer with a germline or somatic pathogenic variant in *BRCA1*, *BRCA2*, or *PALB2* that has not progressed after at least 16 weeks of platinum-based combination chemotherapy are candidates for PARPi, rucaparib, or olaparib. For these patients, PARPi is an effective, nonchemotherapy maintenance treatment option.[55] For patients with either germline or somatic mutations in *BRCA1/2* or *PALB2*, PARPi maintenance therapy is capable of producing deep and long-lasting responses without chemotherapy.[56,57]

POLO is the only randomized, phase III clinical trial that evaluated maintenance PARPi in pancreatic cancer.[5] This study, which randomly assigned patients with germline *BRCA* variants and at least stable disease after 4 months or more of platinum chemotherapy to either olaparib or placebo, demonstrated a significant improvement in PFS in the experimental arm compared with the control (7.4 months *v* 3.8 months; HR for disease progression or death, 0.53; 95% CI, 0.35 to 0.82; $P = .004$).[5] Although OS was not different between the arms, results from this trial led to the approval of maintenance olaparib for this population by the US FDA in December 2019.

RUCAPANC2 was a single-arm phase II study investigating maintenance rucaparib in patients with platinum-sensitive, advanced pancreatic cancer with germline or somatic pathogenic variants in *BRCA* or *PALB2*.[58] A total of 42 patients without evidence of platinum resistance after at least 16 weeks of platinum-based cytotoxic chemotherapies were enrolled to receive rucaparib 600 mg PO twice daily until unacceptable toxicity or progression. The median PFS on the study was 13.1 months (95% CI, 4.4 to 21.8), and the median OS was 23.5 months (95% CI, 20.0 to 27.0), both of which compare favorably with historical controls. Remarkably, the ORR of 36 evaluable patients on this study was 41.7%, including three complete responses, highlighting the sensitivity of these patients to noncytotoxic treatment and the potential to deepen responses with a maintenance strategy. As a result of this study, rucaparib is now endorsed by the National Comprehensive Cancer Center guidelines as a category 2A recommendation for patients with metastatic pancreatic cancer and germline or somatic *BRCA1/2* or *PALB2* mutations without evidence of progression on previous platinum-based chemotherapy.[59]

Active areas of investigation include developing a better understanding of mechanisms of PARPi resistance, developing clinical models that can more accurately predict homologous recombination deficiency phenotypes, and identifying optimal post-PARPi therapeutic regimens.[60,61] Evaluating patients treated on RUCAPANC2 with rucaparib, we have previously found that reversion mutations that restore *BRCA* or *PALB2* functionality via restoration of the open reading frame were a rare event but were independently associated with short OS and PFS compared with patients whose tumors did not develop reversion mutations.[61] In the post-PARPi progression setting, cytotoxic chemotherapy continues to retain activity for patients who remain fit for intense therapy although the optimal therapy is unknown and should be investigated in the future.[60] Furthermore, expanding the use of PARPi beyond *BRCA* and *PALB2* remains under investigation and will rely on the development of assays that can accurately predict loss of homologous recombination repair phenotype from mutations in noncanonical homologous recombination repair genes.[62] Finally, post-PARPi therapy remains an active area of investigation, with several ongoing trials testing novel agents for patients with HRD and pancreatic cancer who have PD on PARPi (Table 1).

Capitalizing on the success of PARP inhibitors in the advanced pancreatic cancer setting, olaparib is now being tested in the adjuvant setting for patients with early-stage, *BRCA*- or *PALB2*-related pancreatic cancer. The ECOG/ACRIN APOLLO trial (EA2192) is a randomized, phase II, double-blind study of olaparib versus placebo after curative-intent therapy in patients with resected pancreatic cancer harboring a pathogenic *BRCA1*, *BRCA2*, or *PALB2* variant (ClinicalTrials.gov identifier: NCT04858334).[63] Eligible patients are required to have undergone curative-intent surgery and have received at least 3 months and up to 6 months of perioperative chemotherapy (delivered as neoadjuvant, adjuvant, or a combination of both). After this, patients are randomly assigned 2:1 to receive olaparib 300 mg PO twice daily in 28-day cycles for up to 12 cycles (1 year). The study seeks to improve relapse-free survival

TABLE 1. Selection of Trials in Patients With HRD Who Have Progressive Disease

Trial Name	Molecule(s)	Relevant Clinical Setting	Phase/NCT
A trial of AMXI-5001 in advanced malignancies	AMXI-5001 (small molecule; PARPi plus taxane)	Solid tumors with *BRCA* or *PALB2* and PD after PARPi	I/II NCT04503265
A study of ART4215 in advanced or metastatic solid tumors	ART4215 (DNA Polθ inhibitor) Talazoparib	Solid tumors with g/s *BRCA* mutations and PD after PARPi	I/II NCT04991480
NUV-868 as monotherapy and in combination with olaparib or enzalutamide in solid tumors	NUV-868-01 (BETi) Olaparib	Breast, ovarian, pancreatic cancers with *BRCA* mutations and PD after PARPi	I/II NCT05252390
CX-5461 in solid tumors with *BRCA*, *PALB2*, or other HRD	CX-5461 (G4 stabilizer)	Breast, ovarian, pancreatic, prostate cancers with *BRCA* or *PALB2*; platinum-resistant and/or PARPi-resistant	Ib NCT04890613
Lurbinectedin in patients with advanced solid tumors	Lurbinectedin (transcription inhibitor)	Endometrial, biliary, urothelial, breast, pancreatic, or gastric cancer with g/s HRD+, after other tx	II NCT05126433

Abbreviations: BETi, BET inhibitor; g/s, germline/somatic; HRD, homologous recombination deficiency; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, progressive disease; tx, treatment.

from an expected 22 months in the control arm to 44 months with olaparib. This trial is actively recruiting.

PARPVAX (PARP inhibitor plus checkpoint inhibitor). The treatment of pancreatic cancer with PARPi is recognized to increase cytosolic DNA, activate the immune inflammatory stimulator of interferon genes (STING) pathway, and result in an increase in PD-L1 expression in both *BRCA*-mutated and WT tumors.[64] Furthermore, there are preclinical evidence to suggest synergy between PARPi and cytotoxic T-cell lymphocyte-4 (CTLA-4) blockade and evidence that CTLA-4 may be upregulated in HRD tumors.[65,66] The phase Ib/II PARPVAX trial sought to exploit this unique biology.[67] Patients on this trial with advanced pancreatic cancer without evidence of progression after at least 16 weeks of platinum-based chemotherapy (with or without a germline *BRCA1*, *BRCA2*, or *PALB2* mutation) were randomly assigned to receive niraparib 200 mg PO once daily plus either nivolumab (continuous dosing every 2 weeks or every 4 weeks) or ipilimumab (every 3 weeks for four doses) with a primary end point of assessing safety and PFS at 6 months and a null hypothesis of meaningful 6-month PFS of 44%, doubling the PFS observed in the only other published trial of maintenance therapy in pancreatic cancer.[68]

Although the niraparib and ipilimumab arm had a grade 3 or worse treatment-related adverse event rate of 50%, the 6-month PFS was 59.6% (95% CI, 44.3 to 74.9; $P = .045$ compared with the null hypothesis of 44%). While the niraparib and nivolumab arm had fewer grade 3 adverse events (22%), this arm failed to meet the landmark 6-month PFS end point (20.6%; 95% CI, 8.3 to 32.9; $P = .0002$ *v* the null hypothesis of 44%). These results were unchanged when patients with recognized HRD were removed from the analysis. Overall, this study provided important information regarding the feasibility of a noncytotoxic maintenance regimen and data for the potential efficacy of niraparib with ipilimumab in this population. Further study is needed in this area.

Other ongoing maintenance trials of PARPi with immunotherapy include SWOG2001 and POLAR. SWOG2001 randomly assigns patients with metastatic pancreatic cancer and germline *BRCA1* and *BRCA2* mutations without evidence of platinum resistance after 4-6 months of chemotherapy to olaparib with or without pembrolizumab. The primary objective of this study is to improve the median PFS of the experimental arm from 7 months to 11.7 months with a goal of recruiting 78 patients, which is estimated to complete enrollment in mid-2025 (ClinicalTrials.gov identifier: NCT04548752).[69] POLAR is a phase II trial evaluating the safety and efficacy of pembrolizumab and olaparib in patients with metastatic pancreatic adenocarcinoma and either a known gene mutation that results in HRD or response to platinum-based chemotherapy. This trial contains three cohorts of patients—cohort A with core homologous recombination deficiency (recognized pathogenic mutations in *BRCA1/2* or *PALB2*), cohort B with noncore HRD (pathogenic mutations in *ATM*, *BAP1*, *BARD1*, *BLM*, *BRIP1*, *CHEK2*, *FAM175A*, *FANCA*, *FANCC*, *NBN*, *RAD50*, *RAD51*, *RAD51C*, *RTEL1*), and cohort C with platinum-sensitive disease (no HRD mutations qualifying for cohort A or B with either a partial or complete response to platinum-based therapies). This trial is also assessing the primary end point of PFS and is expected to complete accrual in mid-2025 (ClinicalTrials.gov identifier: NCT04666740).[70]

IMMUNOTHERAPY IN PANCREATIC CANCER

Although development of immunotherapy for other cancers has greatly improved prognoses and fundamentally altered the approach to treatment, immunotherapy in pancreatic cancer has been notoriously disappointing. Clinical trials of

single-agent immunotherapy, doublet immunotherapy combinations, and immunotherapy with chemotherapy have all failed to demonstrate clinical efficacy in patients with pancreatic cancer.[71-78] This is, in part, related to the immunosuppressive myeloid infiltration and low T-cell infiltration within the tumor microenvironment, intrinsic low tumor mutational burden, immune privilege.[79] Despite disappointing efficacy with immunotherapy in pancreatic cancer to date, potential novel immunotherapies and novel biomarker selection will be key to future immunologic treatment strategies in this disease.

Immunotherapy Biomarkers in Pancreatic Cancer

Markers that predict response to immunotherapy in other cancers are not effective in pancreatic cancer. For example, PD-L1 expression as assessed combined positive score or tumor proportion score is a biomarker for potential response to PD-1 and PD-L1 inhibitor in malignancies, such as non–small-cell lung cancer, head and neck squamous cell cancer, gastroesophageal cancer, and cervical cancer. PD-L1 expression within pancreatic cancer, however, does not predict response to PD-1 inhibition, noting a 0% response rate to pembrolizumab in PD-L1–expressing pancreatic cancers in KEYNOTE-028.[80] A lack of response to PD-1 inhibition was also noted in the rare population of patients with pancreatic cancer with high tumor mutational burden (TMB $\geq$10 mutations per megabase),[81] despite FDA approval for pembrolizumab for tumors with TMB, regardless of histology. Similarly, although pembrolizumab is approved for use in microsatellite unstable (MSI-high) cancers regardless of histology,[82] the ORR in patients with MSI-high pancreatic cancer treated with pembrolizumab was only 18.2%, at least 50% lower than other MSI-high cancer types.[83] Data are limited on the role of dual checkpoint inhibition in MSI-high pancreatic cancer although it is noteworthy that the isolated response to durvalumab and tremelimumab in metastatic pancreatic adenocarcinoma occurred in an MSI-high patient.[74] Although PD-1 inhibition remains a potential option in the rare population of patients with pancreatic cancer that is MSI-high or has a high TMB, we would recommend consideration of an immunotherapy clinical trial for these patients given limited efficacy to monotherapy PD-1 inhibitors to date.

Ongoing studies in immunotherapy in pancreatic cancer may help to elucidate patient populations who may benefit from therapeutic immune approaches (Table 2). In a retrospective analysis of ipilimumab and nivolumab in patients with chemotherapy-refractory pancreatic adenocarcinoma harboring a pathogenic germline variant in homologous recombination genes, 20% of patients had a complete response, 10% had a partial response, and 20% had stable disease.[84] Pancreatic cancers with homologous recombination deficiencies have increased genomic instability and an associated elevated tumor mutational burden and so may theoretically be more responsive to immunotherapy. As evidenced by the aforementioned studies[81] and the fact that those patients who responded in this retrospective study had a TMB of <10 mutations/MB,[84] tumor mutational burden alone does not explain the responsiveness of this group to immunotherapy. Further analysis is needed, and clinical trials evaluating immunotherapy in homologous recombination-deficient pancreatic cancers are ongoing (ClinicalTrials.gov identifiers: NCT05659914, NCT04548752, NCT04493060).

CD40 agonist has been evaluated in pancreatic cancer in several clinical trials on the basis of preclinical evidence suggesting that treatment with CD40 agonists can change resident tumor immunosuppressive macrophages into tumoricidal macrophages and deplete the tissue stroma, potentially restoring adequate immunosurveillance.[85,86] The PRINCE trial was a phase Ib/II trial evaluating the combination of gemcitabine and nab-paclitaxel with or without the CD40 agonist sotigalimab with or without nivolumab in previously untreated patients with pancreatic adenocarcinoma.[87,88] Although this study was limited by the lack of a chemotherapy-only control arm, the combination of gemcitabine, nab-paclitaxel, and nivolumab was the only arm to meet the primary end point of improved 1-year OS compared with the historical control, which is contrary to previous publications of this combination.[78] Despite the lack of significant efficacy of these chemoimmunotherapy combinations in this unselected population, there did appear to be some patients who benefited in each arm. Moreover, specific tumoral and plasma immune signatures were detected at baseline in patients who benefited from the combination of gemcitabine, nab-paclitaxel, and nivolumab, and this signature was distinct from the signature noted in patients who benefitted from gemcitabine, nab-paclitaxel, and sotigalimab (Padron). These findings are being further evaluated to determine if a novel immune biomarker may be used to select patients for treatment with these chemoimmunotherapy combinations in future clinical trials.

Cell Therapy in Pancreatic Cancer

Although adoptive cell therapy has revolutionized the management of liquid tumors, their role in solid cancers, including pancreatic cancer, has been limited. Chimeric antigen receptor (CAR) T-cell therapy has been ineffective in managing pancreatic cancer to date,[89-92] limited by target selection, CAR manufacturing feasibility, trafficking of CAR T cells to the tumor, and immunosuppressive microenvironment within the pancreatic tumors.[93] Trials evaluating novel targets (ClinicalTrials.gov identifier: NCT04404595) and combination approaches (ClinicalTrials.gov identifier: NCT05057715) are

TABLE 2. Select Ongoing Trials of Immunotherapies in Pancreatic Cancer

Study Title	Setting	Design	Primary End Point	Estimated Completion Date	NCT
Multi-agent Low Dose Chemotherapy GAX-CI Followed by Olaparib and Pembro in Metastatic Pancreatic Ductal Cancer	First-line maintenance olaparib and pembrolizumab after gemcitabine, nab-paclitaxel, capecitabine, and irinotecan	Single-arm, open-label	6-Month PFS	December 2025	NCT04753879
Lenvatinib and Pembrolizumab Maintenance Therapy for the Treatment of Patients of Advanced Unresectable Pancreatic Cancer	Maintenance after at least 16 weeks of first- or second-line chemotherapy without evidence of progression	Single-arm open-label phase 2	4-Month PFS	December 2023	NCT04887805
A Study to Evaluate the Safety and Tolerability of SX-682 in Combination With Nivolumab as a Maintenance Therapy in Patients With Metastatic Pancreatic Ductal Adenocarcinoma	Maintenance therapy after at least 16 weeks of first-line chemotherapy without evidence of PD	Open-label phase 1	Maximum tolerable dose of SX-682 in combination with nivolumab	December 2024	NCT04477343
Niraparib and Dostarlimab for the Treatment of Germline or Somatic BRCA1/2 and PALB2 Mutated Metastatic Pancreatic Cancer	After one or two lines of systemic therapy with at least one line containing platinum chemotherapies	Open-label single-arm phase 2	Disease control rate at 12 weeks	December 2023	NCT04493060
A P1b Study of Odetiglucan With a CD40 (CDX-1140) Agonist	Maintenance after 16-24 weeks of first-line chemotherapy without evidence of PD	Open-label phase 1	Maximum tolerated dose of odetiglucan with CDX-1140	March 2026	NCT05484011
Testing the Addition of Pembrolizumab, an Immunotherapy Cancer Drug to Olaparib Alone as Therapy for Patients With Pancreatic Cancer That Has Spread With Inherited BRCA Mutations	Maintenance therapy after first-line platinum-based chemotherapy without PD	Two-arm randomized phase 2 trial	PFS	March 2025	NCT04548752
A Study of Pembrolizumab and Olaparib for People With Metastatic Pancreatic Ductal Adenocarcinoma and Homologous Recombination Deficiency or Exceptional Treatment Response to Platinum-Based Therapy (POLAR)	Maintenance after first- or second-line platinum-based therapies without evidence of platinum resistance. Three cohorts: (1) core HR mutations, (2) noncore HR mutations, (3) platinum responders without HR mutations	Single-arm, open-label, nonrandomized	6-Month PFS	January 2024	NCT04666740

Abbreviations: HR, homologous recombination; PD, progressive disease; PFS, progression-free survival.

underway to potentially circumvent these barriers to potentially enhance efficacy of this cellular therapeutic approach.

More promising results have been published using T-cell receptor (TCR) therapy in pancreatic cancer. A case report of autologous T-cell therapy expressing HLA-C*08:02–restricted TCRs targeting KRAS G12D showed signs of efficacy.[94] This case report outlines two chemotherapy-refractory patients treated with this therapy in conjunction with tocilizumab and cyclophosphamide preconditioning and high-dose interleukin-2 postinfusion, and although both patients had an initial clinical benefit, only one of these patients had a durable partial response lasting more than 6 months. Although only a single patient response is not a proof of concept and TCR therapy is limited by the specific KRAS mutation and an associated HLA type, the durability of efficacy in this patient is intriguing and is driving ongoing clinical trials evaluating KRAS-directed TCR (ClinicalTrials.gov identifiers: NCT03190941, NCT03745326).

FUTURE DIRECTIONS AND CONCLUSIONS

Progress with systemic therapy for patients with pancreatic cancer has been slow, but the development of novel approaches is improving the prognosis for patients with select biomarkers. Effective cytotoxic chemotherapies with the emerging success of immunotherapies and targeted therapies have proven to be beneficial. Novel approaches to delivering effective therapies such as induction/maintenance and further development of biomarkers may provide additional benefit to selected patients to exploit molecular and immunogenic characteristics of their tumors.

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State of the Art: Multidisciplinary Management of Oligometastatic Renal Cell Carcinoma

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overview

Oligometastatic renal cell carcinoma (OM-RCC) refers to patients who have limited (typically up to 5) metastatic lesions. Although management principles may overlap, OM-RCC is distinguishable from oligoprogressive RCC, which describes progression of disease to a limited number of sites while receiving systemic therapy. Cytoreductive nephrectomy and metastasectomy are common surgical considerations in OM-RCC, and indications are discussed in this review. It is evident that stereotactic ablative radiotherapy is effective in RCC and is being applied increasingly in the oligometastatic setting. Finally, we will review advances in systemic therapy and the role of active surveillance before the initiation of systemic therapy.

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INTRODUCTION

Kidney cancer is one of the 10 most common cancers in the United States with an estimated 81,800 cases and 14,890 attributable deaths in 2023.[1] Most kidney cancers are renal cell carcinomas (RCCs) in which 15% of patients will have metastases at presentation and an additional 20% will develop metastatic disease after the treatment of localized disease.[2]

Metastatic RCC (mRCC) represents a wide spectrum of disease aggressiveness as evident from the risk stratification by International Metastatic Database Consortium (IMDC) where poor-risk patients have survival of less than 1 year, whereas those with favorable-risk disease might have a smoldering progression over many years.[3,4] Patients with oligometastatic RCC (OM-RCC) have a limited number of detectable metastatic lesions at presentation, typically 5 or less.[5] Although commonly encountered, limited direct data are available on the incidence of OM-RCC.

Although some of these patients may be truly oligometastatic where the detectable lesions are the only metastases they have, the assumption is that the majority of these patients likely have sites of undetectable micrometastatic disease. Therefore, depending on the rate of progression of the metastatic sites, many patients may benefit from local therapy alone or a combination of local therapy with systemic therapy. Although not evaluated specifically, IMDC risk stratification should be applied to OM-RCC and divided into subcategories on the basis of the risk of distant micrometastasis and the rate of disease progression. This can help inform the probability of future progression at distant sites, thereby ascertaining the likely duration of disease control and potential benefit from local therapy versus the need for a combination of local and systemic therapies. Those on the slowest end of the progression spectrum may even be candidates for careful surveillance. OM-RCC is distinct from oligoprogressive disease, which describes patients with RCC with any number of metastases but progressing only in a limited number of sites in response to ongoing systemic therapy. Both oligometastatic and oligoprogressive diseases have overlapping multimodality management principles.

There have been significant advances in the surgical, radiation, and medical management of RCC in the past decade. This review summarizes the contemporary multidisciplinary management of OM-RCC.

CYTOREDUCTIVE NEPHRECTOMY

Cytoreductive nephrectomy (CN) refers to surgical removal of the kidney and primary tumor in a patient with synchronous metastatic disease and is often one of the first considerations at initial diagnosis of mRCC.[6,7] In the following sections, we discuss the rationale for CN to delay systemic therapy, as an adjunct to systemic therapy, or for symptom palliation.

Contemporary indications for CN include the following:

1. Limited metastatic disease that would be amenable to active surveillance (AS) after CN[8]
2. Limited metastatic disease that can be controlled completely with metastasis-directed therapy (MDT) after CN
3. One IMDC risk factor with the majority of tumor burden located in the kidney[8]
4. Oligoprogressive disease within the kidney after upfront systemic therapy

PRACTICAL APPLICATIONS

- Patients with oligometastatic renal cell carcinoma (OM-RCC) have a limited number of (typically up to 5) metastatic lesions at presentation.
- Cytoreductive nephrectomy is commonly performed in OM-RCC, and indications should be informed by recent clinical trials.
- Stereotactic ablative radiotherapy is effective in RCC and can be used for both the primary tumor and metastatic lesions.
- Active surveillance or metastasis-directed therapy (metastasectomy or stereotactic ablative radiotherapy) can delay systemic therapy, which may improve quality of life.
- Significant advances in systemic therapy have occurred in the past decade that improved survival in metastatic RCC and has implications for OM-RCC.

5. Significant local symptoms, particularly those that require hospitalization and prevent the receipt of systemic therapy

Relative indications for up-front systemic therapy rather than up-front CN include the following:

1. Significant extrarenal disease
2. Excessive surgical morbidity
3. Poor performance status and/or multiple IMDC risk factors

CN to Delay Systemic Therapy

CN followed by AS. CN may allow for delay of systemic therapy if the extrarenal disease is amenable to AS.[8] AS is a common management strategy, being used in about 32% of patients according to an observational mRCC cohort.[9]

Prospective data for AS originate from a phase II study in which 52 patients with treatment-naïve, asymptomatic, mRCC underwent AS with serial imaging at baseline, every 3 months for year 1, every 4 months for year 2, and every 6 months thereafter.[4] The study allowed previous surgery (nephrectomy or metastasectomy) and radiotherapy (including radiation for CNS metastases). The primary end point was the time to initiation of systemic therapy. Most patients (75%) were in the IMDC intermediate-risk category. Patients had metastases most commonly located in the lung (71%), lymph nodes (25%), and bone (21%) with an overall average tumor burden of 3.2 cm at baseline. With a median follow-up of 38.1 months, the median time on AS was 14.9 months.[4] Patients with IMDC poor-risk disease and a higher number of metastatic sites were associated with a shorter surveillance period. After disease progression on surveillance, patients were usually started on systemic therapy. Subsequent genomic analysis of this cohort has identified TP53 and SMARCA4 mutations as biomarkers for a shorter period of AS.[10]

CN is conventionally performed before AS in mRCC as this is often the site of bulky and or symptomatic disease. Several studies have reported on the feasibility of AS in mRCC to delay the toxicity of systemic therapy and thereby improve quality of life.[4,9,11-13]

CN combined with MDT. Up-front CN and complete MDT may delay systemic therapy for a median time of 1 year, with 20%-30% of patients achieving long-term disease control without systemic therapy.[14-17] Although case series on this approach have been published, CN and complete MDT have not been prospectively compared with either surveillance or systemic therapy. MDT is discussed further in the following sections.

CN as an Adjunct to Systemic Therapy

Complete response in the primary tumor is exceedingly unlikely with systemic therapy alone, and the majority of patients in the landmark systemic therapy trials have received previous nephrectomy.[18-22]

The role of CN in mRCC originated from the cytokine era where SWOG-8949 and EORTC-30947 demonstrated a 5.8-month median survival benefit for those patients randomly assigned to receive CN before interferon alfa-2b compared with interferon alfa-2b alone.[23-26] In the era of targeted therapy, 30%-40% of patients received CN and retrospective data suggested that CN improved survival.[27,28]

Previous enthusiasm for up-front CN has been tempered with the more recent publication of the CARMENA and SURTIME studies.[29-31] Although these studies have a number of limitations, predominantly their use of historic systemic therapy (sunitinib), they have shaped our current CN paradigm.[8]

The CARMENA study randomly assigned 450 patients with mRCC to CN followed by sunitinib versus sunitinib alone.[29,30] Sunitinib alone was noninferior to CN and sunitinib in both the initial study and a subsequent abstract with longer follow-up. In a post hoc analysis, it was noted that patients with one IMDC risk factor had a slight benefit in overall survival (OS) in the CN group (30.5 *v* 25.2 months, nonsignificant), whereas those with two or more IMDC risk factors had a shorter survival in the CN group (16.6 *v* 31.2 months; $P = .015$). This informs current ASCO guideline recommendations that CN be considered in patients with one IMDC risk factor and the majority of their disease in the kidney.[8]

The SURTIME study randomly assigned 99 patients to up-front CN versus deferred CN in patients receiving sunitinib.[31] Although the study was stopped early for poor accrual, findings again demonstrated a lower OS in the group receiving up-front CN (15.0 *v* 32.4 months). A higher proportion of patients in the deferred group were able to receive sunitinib (98% *v* 80%).

These data support the paradigm that patients with a lower number of IMDC risk factors are more likely to benefit from CN and that deferring CN to follow a period of systemic therapy is beneficial. The benefit of this paradigm is likely derived from the increased receipt of systemic therapy in patients with rapidly progressive disease and a poor prognosis. Observational studies with current systemic therapy regimens continue to strongly support the better prognosis of patients who undergo CN but are limited by selection bias.[32,33] Prospective randomized studies are ongoing (Table 1), which will inform us on the role of CN in the current era of systemic therapy.

CN for Symptom Palliation

Large renal masses may result in pain, hematuria, and other local symptoms. Patients with inferior vena cava tumor thrombus might also have specific sequelae from venous obstruction or embolization.[41] Symptomatic disease remains an important indication for CN, particularly for those who are hospitalized for their symptoms and unable to receive systemic therapy.[42] In a patient who is not otherwise a good candidate for CN, there are alternative effective methods for symptom palliation including angioembolization, SBRT, and systemic therapy.

MDT

MDT refers to a treatment focused on control of one or more specific metastatic lesions. MDT was conventionally performed with surgical metastasectomy but is increasingly performed with ablative techniques like SBRT.[8] The oligometastatic patient best considered for up-front MDT is the one who is rendered free of disease by MDT in combination with previous nephrectomy.

The goal of MDT is to improve survival while preserving quality of life by delaying both systemic therapy and the sequelae of metastatic disease. In highly selected cohorts, 20%-30% of patients might have long-term disease control with MDT without systemic therapy.[14-17] MDT also plays an essential role in the palliation of a symptomatic lesion where awaiting systemic therapy response may be detrimental (eg, symptomatic bone or brain disease)—but this indication is not the focus of the following discussion.[42]

The conventional MDT approach outlined above is undergoing a paradigm shift because of (1) increasing utilization of ablative techniques like stereotactic body radiotherapy, (2) recognition of the role of AS in mRCC, and (3) integration with more effective systemic therapy regimens.[43] When integrated with systemic therapy, MDT can be performed up-front followed by adjuvant therapy or used for sites of oligoprogression.[43-45] Oligometastatic patients being considered for MDT benefit from multidisciplinary discussion to see if surveillance or systemic therapy may be more appropriate and whether MDT is best accomplished by surgery or ablative techniques.

Most of the published data for MDT are related to surgical metastasectomy.[46] A recent multi-institutional series of 740 metastasectomies in 522 patients provide contemporary data on surgical outcomes.[47] In this study, 8% of patients experienced a major complication of metastasectomy, with 1% experiencing a perioperative death. Age, multiple sites of resection, and pancreatic resection were associated with major complications.[47]

The oncologic outcomes for metastasectomy originate from retrospective data and have been summarized in recent systematic reviews.[15,17] Complete metastasectomy (to render free from disease) is the goal, and the carefully selected patients who can undergo complete metastasectomy have a favorable prognosis. Two series from the Mayo Clinic illustrate the value of this prognostic factor. For patients treated between 1976 and 2006, 14% of the 887 patients who had undergone nephrectomy had multiple metastases and were able to receive complete metastasectomy.[48] In this population, the 5-year cancer-specific survival was 49.4% with complete metastasectomy as opposed to 13.9% without. An updated Mayo Clinic series including only patients after TKI approval revealed that 27% of patients who had undergone nephrectomy could undergo complete metastasectomy. Those who had a complete metastasectomy had a 2-year OS of 84% compared with 54% in those who had not.[49]

Additional prognostic factors include the number of metastatic sites and disease-free interval since nephrectomy.[15] The prognostic implications of metastatic organ sites are less established—lung metastases are most commonly considered for metastasectomy and appear to have better prognosis.[48] Favorable outcomes have also been described in series of metastasectomy for pancreatic, adrenal, and thyroid locations. Highly selected patients with other organ metastases also had long-term survival (liver, bone, brain, lymph node).

Stereotactic Ablative Radiotherapy

In the wide spectrum of disease aggressiveness for patients with OM-RCC, stereotactic ablative radiation (SAbR) may be applicable to a few subgroups. The first subcategory comprises patients who present with metachronous metastases that develop multiple years after resection of the primary kidney tumor. This suggests that the patient's disease is indolent and portends the best prognosis. A

TABLE 1. Selected Prospective Clinical Trials Relevant to CN

Study	Status	Design	Outcome	Relevance
Reported				
SWOG-8949[34]	Published in 2001	mRCC randomly assigned to CN + ifn alfa-2b *v* ifn alfa-2b alone	Improved survival with CN	Original support for the role of CN in mRCC
EORTC-30947[25]	Published in 2001	mRCC randomly assigned to CN + ifn alfa-2b *v* ifn alfa-2b alone	Improved survival with CN	Original support for the role of CN in mRCC
CARMENA[29]	Published in 2018	Clear cell mRCC randomly assigned to CN + sunitinib *v* sunitinib alone	Noninferiority of sunitinib alone compared with CN + sunitinib. Shorter survival with CN + sunitinib when two or more IMDC risk factors are present (SS). Longer survival with CN + sunitinib when one IMDC risk factor is present (NSS)	Questions dogma supporting CN in mRCC and suggests that patient selection on the basis of IMDC risk is important
SURTIME[31]	Published in 2019	Clear cell mRCC randomly assigned to immediate CN + sunitinib *v* sunitinib for 12 weeks + deferred CN in the absence of progression	Longer OS and higher proportion of patients receiving sunitinib treatment with up-front sunitinib and deferred CN	Supports the concept of deferring CN to follow a period of systemic therapy
NAXIVA[35]	Published in 2022	Resectable ccRCC with venous tumor thrombus treated with 8 weeks of axitinib, single-arm, M0, or mRCC	No patients had an increase in tumor thrombus level	Supports safety of deferring CN in patients with IVC tumor thrombus
Ongoing				
NCT04370509[36]	Recruiting, estimated completion in 2025	ccRCC treated with pembrolizumab with or without axitinib for 9 weeks before nephrectomy or metastasectomy, M0, or mRCC	Primarily the impact of pembrolizumab on composition, phenotype, and function of tumor-infiltrating immune cells Secondarily efficacy, safety, and tolerability of preoperative pembrolizumab	Immunologic impact of pembrolizumab on RCC Efficacy and safety of neoadjuvant pembrolizumab with or without axitinib before CN or metastasectomy
NCT05319015[37]	Recruiting, estimated completion in 2025	RCC with IVC tumor thrombus treated with lenvatinib + pembrolizumab before nephrectomy and IVC thrombectomy, M0, or mRCC	Primarily disease control rate, local and metastatic progression rate, postoperative complications	Efficacy and safety of neoadjuvant lenvatinib + pembrolizumab in patients with RCC with IVC thrombus, many of whom will have mRCC
NORDIC-SUN[38]	Recruiting, estimated completion in 2026	mRCC receiving doublet systemic therapy, randomly assigned to CN *v* no CN if resectable and 3 or less IMDC risk factors are present after 3 months of ST; reassessed for random assignment after 6 months of ST if not eligible at 3 months	Primarily OS	Assess the role for CN in mRCC with contemporary ST regimens
CYTO-KIK[39]	Recruiting, estimated completion in 2027	Clear cell mRCC receives cabozantinib and nivolumab for 12 weeks before nephrectomy	Primarily complete response rate Secondarily median size reduction of primary tumor, PFS, response rate, OS, surgical outcomes	Oncologic and perioperative outcome data after neoadjuvant treatment with cabozantinib + nivolumab
PROBE[40]	Recruiting, estimated completion in 2033	mRCC receiving doublet systemic therapy, randomly assigned to nephrectomy *v* no nephrectomy in the absence of progression at 12 weeks	Primarily OS	Assess the role for CN in mRCC with contemporary ST regimens

Abbreviations: ccRCC, clear cell RCC; CN, cytoreductive nephrectomy; ifn, interferon; IMDC, International mRCC Database Consortium; IVC, inferior vena cava; mRCC, metastatic RCC; M0, nonmetastatic; NSS, not statistically significant; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; SS, statistically significant; ST, systemic therapy.

subgroup of these patients may represent the true oligometastatic state and can potentially be cured with local therapy. For these patients, Although treatment options include AS, metastasectomy, SAbR, or systemic therapy, local therapy with SAbR should be preferred.[4,16,50-53] The second subcategory includes patients with favorable or intermediate IMDC risk. This represents a heterogeneous patient population that will eventually need systemic therapy; however, carefully selected patients can be treated with up-front sequential SAbR that can preserve health-related quality of life and available systemic therapy options. Both retrospective and prospective studies have shown disease control in excess of 15 months for these patients treated with sequential SAbR.[50-53] The benefit of SAbR may be particularly pronounced in delaying the initiation of systemic therapy for patients who have glandular metastasis that is known to be associated with a more indolent RCC biology.[54] The third subcategory involves patients with a high chance of distant micrometastatic disease, including those with IMDC poor risk, grade 4 histology, or sarcomatoid component histology. Despite having oligometastatic disease, this group of patients generally requires up-front systemic therapy. However, there may still be a role for consolidation with SAbR to the bulky therapy-resistant metastatic sites particularly if taking advantage of a potential synergy between SAbR and checkpoint inhibitors as shown in the subgroup analysis of two studies.[43,55] Data are lacking for the application of SAbR for this subgroup of patients with IMDC poor-risk OM-RCC. Nevertheless, these patient scenarios provide a framework in which SAbR may be considered as part of the treatment plan for patients with OM-RCC.

SAbR is a promising treatment option for patients with mRCC with favorable local control and toxicity rates. Reviewing the literature, SAbR's success in treating mRCC is evident, with local control rates ranging from 82% to 98% with minimal acute or late grade 3 or higher toxicities.[50,56-66] Any adverse events that did occur were typically acute and resolved with either no intervention or the use of medication (grade 1 to 2). A recent meta-analysis (SABR ORCA) of pooled data from 28 studies evaluated the use of SAbR for mRCC and reported a 1-year local control rate of 89.1% and a 1-year OS rate of 86.8%, which is comparable with retrospective surgical series.[16,48,67] Overall, the studies support the use of 40 Gy in five fractions, 36 Gy in three fractions, or 25 Gy in a single fraction for optimal local control of treatment-naïve mRCC metastasis. Evidence further supports the need for SAbR dose escalation in the setting of multiple previous systemic therapies that may make RCC metastasis more radioresistant.[68] Although these studies included patients with mRCC, they did not necessarily limit patient inclusion to oligometastatic patients.

Once local control and safety of SAbR for mRCC are established, the next relevant question is whether SAbR can be applied for overall disease control, progression-free survival (PFS), and OS in patients with OM-RCC. Moreover, this strategy can be used sequentially in the setting of additional oligometastatic lesions, thus providing durable disease control. This approach was first described in a retrospective study of 47 patients where 30% of patients received two or more courses of sequential SAbR to sites of metastatic disease, leading to a median PFS of 15.2 months.[50] This strategy was further evaluated in prospective studies, including a multi-institutional registry study that included 143 patients with OM-RCC in the midst of other primary sites and supported the efficacy and safety of this approach with SAbR.[69] A phase II version of this study confirmed that sequential SAbR in patients with systemic therapy–naïve OM-RCC can confer 1 year freedom from systemic therapy in 91.3% of patients.[52,53] This phase II trial also demonstrated a preservation of patient's quality of life using pre- and post-treatment patient-reported quality-of-life questionnaires. In another prospective feasibility study by Tang et al that allowed pretreatment with systemic therapy, SAbR alone showed a median PFS of 22.7 months and a 1-year PFS of 64% with acceptable toxicity.[51] A phase III noninferiority trial (EA 8211, SOAR) randomly assigning patients with OM-RCC to be treated with sequential SAbR followed by systemic therapy at progression versus up-front systemic therapy is currently being designed and expected to open for enrollment in 2023.

The application of SAbR for cytoreduction in the setting of mRCC and OM-RCC has limited prospective data.[70] Given the demonstrated promising local control and safety of SAbR for primary RCC, it would be reasonable to consider SAbR for the treatment of primary RCC for patients with oligometastatic RCC.[71,72]

In summary, SAbR, particularly sequential SAbR, appears to be a promising strategy for the overall disease control that is supported by retrospective and early-phase prospective trials for a subgroup of patients with OM-RCC that includes (1) metachronous metastasis when the metastasis appeared >1 year after addressing the primary, (2) patients with indolent biology, and (3) IMDC favorable- and intermediate-risk patients. Prospective randomized evidence is currently lacking for the application of SAbR for any of the described subgroups of patients with patients OM-RCC.

Systemic Therapy

Patients with oligometastatic disease may be offered systemic therapy in the perioperative setting, frontline metastatic setting, and oligoprogressive setting. The role of systemic therapy in these clinical scenarios is detailed below.

Perioperative systemic therapy. Up until 2021, adjuvant systemic therapy after curative metastasectomy showed no clear benefit in advanced clear cell RCC (ccRCC). In the cytokine therapy era, the efficacy of one course of high-dose bolus interleukin-2 (IL-2) versus observation was tested postoperatively in a high-risk population (T3b-4 or N1-3, or M1 resected to no evidence of disease [NED]). Sixty-nine patients were enrolled in the study and randomly assigned within 12 weeks of surgery, of which 25 were M1 NED. Despite complete accrual, an interim analysis led to early termination of the trial after it failed to meet its primary end point of 30% improvement in 2-year disease-free survival (DFS).[73] Similarly, a pilot study using subcutaneous IL-2 was conducted in the same high-risk patient population with the goal of testing toxicity and tolerability. The study showed that subcutaneous administration of IL-2 improved tolerability, but there was no significant difference in DFS or 3-year survival between the treatment arms.[74] Retrospective data evaluating the role of IL-2 followed by metastasectomy also failed to demonstrate a survival benefit.[75]

After case reports of complete remission of mRCC achieved with targeted kinase inhibition followed by metastasectomy, perioperative strategies using targeted kinase inhibition in combination with metastasectomy were explored.[76] The randomized, phase III ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) E2810 study of pazopanib versus placebo in patients with mRCC after curative metastasectomy demonstrated no difference in DFS between the treatment and placebo group (hazard ratio [HR], 0.85; 95% CI, 0.55 to 1.31; $P = .47$ in favor of pazopanib). In addition, there was a trend toward worse OS for patients who received pazopanib.[77] The phase II RESORT study, which randomly assigned 132 patients with mRCC to sorafenib versus observation after metastasectomy, also showed no difference in relapse-free survival (RFS) between the treatment and observation group (sorafenib: 27 months; 95% CI, 11 to not applicable [NA] *v* observation: 37 months; 95% CI, 20 to NA; $P = .404$).[78]

Over the past decade, the treatment landscape of mRCC has changed dramatically, with immunotherapy-based therapy becoming the standard of care. Concordant with this, the benefit of immunotherapy has been investigated in the adjuvant setting in several clinical trials including IMmotion101, PROSPER, and KEYNOTE-564.[44,79,80] Although most of the patients enrolled to these studies had high-risk nonmetastatic (M0) disease, the aforementioned trials allowed for an M1 population that underwent metastasectomy with NED at study entry. In the phase III IMmotion010 study, the M1 NED category included patients with synchronous metastases to the adrenal gland or lung or metachronous metastatic disease to the lung, lymph node, or soft tissue with recurrence more than 12 months after initial nephrectomy who underwent nephrectomy with metastasectomy within 12 weeks of random assignment. Seven hundred seventy-eight patients were randomly assigned to receive 16 cycles or 1 year of atezolizumab versus placebo, and the median DFS was 57.2 versus 49.5 months, respectively (HR, 0.93; 95% CI, 0.75 to 1.15; $P = .50$), demonstrating no improved clinical outcomes with adjuvant therapy.[79] Similarly, in the randomized phase III PROSPER RCC study evaluating RFS in high-risk patients receiving perioperative nivolumab compared with observation after nephrectomy, RFS was similar between treatment groups (HR, 0.97; 95% CI, 0.74 to 1.28; $P = .43$).[80,81] Patients with $\leq$3 metastases were included if they were planned to undergo local treatment of metastases (metastasectomy, thermal ablation, or stereotactic radiation) within 12 weeks of nephrectomy. Of note, patients with any liver, bone, or brain metastases were excluded because of poor prognosis.

KEYNOTE-564 is currently the only phase III randomized controlled trial demonstrating a benefit of adjuvant immunotherapy in patients who received nephrectomy with metastasectomy.[44] In this double-blind study, 496 patients with ccRCC at high risk for recurrence postnephrectomy were randomly assigned to adjuvant pembrolizumab versus placebo for up to 17 cycles or 1 year. Patients with synchronous M1 disease with metastases completely resected at the time of nephrectomy or within 1 year after nephrectomy were included, except for patients with bone or brain metastases. Pembrolizumab was shown to be associated with significantly longer DFS versus placebo (DFS at 24 months: 77.3% *v* 68.1%; HR, 0.68; 95% CI, 0.53 to 0.87; $P = .002$) in the study population. The subgroup analysis showed that the M1 NED cohort from the trial population derived the greatest benefit from adjuvant pembrolizumab (M1 NED: HR, 0.29; 95% CI, 0.12 to 0.69; M0: HR, 0.74; 95% CI, 0.57 to 0.96). Although the OS data are immature, these results suggest that patients who undergo nephrectomy with metastasectomy and complete resection of disease should be considered for adjuvant pembrolizumab.[44] The RAMPART Trial, a phase III multiarm multistage platform trial evaluating the benefit of perioperative durvalumab and tremelimumab in patients with advanced-stage RCC at intermediate or high risk for relapse, is ongoing (ClinicalTrials.gov identifier: NCT03288532).

Frontline systemic therapy. Frontline systemic therapy may be offered to patients with OM-RCC who are not candidates for AS and have disease that is not amenable to local intervention. This includes patients who are unable to receive local therapy to primary and oligometastatic sites. Patients with mRCC who are likely to benefit from local therapy to primary and oligometastatic sites include IMDC favorable-risk patients with low-volume, asynchronous metastases (particularly limited to the lung), with a prolonged disease-free interval of $\geq$12 months.[15,29,31,82,83] Consequently, up-front systemic therapy is selected for patients with unfavorable IMDC, faster-growing, multiple synchronous metastases, especially when local therapy to all sites is not feasible. These patients are

essentially left with residual, incurable disease, which requires systemic intervention. In this scenario, treatment regimens for oligometastatic and diffuse mRCC are identical.

Preferred first-line systemic therapy for mRCC is dependent on histology, for which the majority encompass ccRCC (Fig 1). For patients with ccRCC across all IMDC risk categories, treatment consists of immune checkpoint blockade (ICB) + vascular endothelial growth factor receptor-tyrosine kinase inhibition (VEGFR-TKI) such as axitinib + pembrolizumab, cabozantinib + nivolumab, and/or lenvatinib + pembrolizumab, on the basis of the phase 3 trials KEYNOTE-426, CheckMate 9ER, and CLEAR, respectively.[19,21,22] For patients with IMDC poor- or intermediate-risk metastatic ccRCC, preferred first-line systemic treatment also includes dual ICB (ipilimumab + nivolumab) or single-agent VEGFR-TKI (cabozantinib), on the basis of the phase 3 CheckMate-214 trial and the phase 2 CABOSUN trial, respectively.[20,84,85] For patients with metastatic non-ccRCC, preferred first-line systemic treatment is nuanced on the basis of individual histology.

Despite several available first-line systemic therapy regimens, 10% of patients treated with ICB-TKI combinations and 15%-25% of patients treated with first-line TKI or combination ICB experience progression.[20,22,86] For patients who develop diffuse recurrence that is no longer considered oligometastatic (>5 metastases), later-line systemic therapies are offered. However, the treatment of oligoprogressive disease is more complex and continues to consider a multimodal approach of local and systemic therapies, as detailed below.

Systemic therapy for oligoprogressive mRCC. As previously defined, oligoprogression represents acquired resistance to systemic therapy in a limited number of sites, whereas the remaining metastasis remains controlled or continues to respond.[87,88] Choosing a particular therapeutic strategy considers several factors including previous treatments or lines of therapy, sites of disease, and patient characteristics.

An important consideration for patients with oligoprogressive disease is whether to continue the current systemic regimen or switch to another later-line treatment. There is some evidence supporting the maintenance of current systemic therapy in progressive disease. In a subgroup analysis of a randomized, phase 2 study of nivolumab in patients previously treated with anti-angiogenic therapy, 36 patients were treated beyond progression and 25 (69%) experienced reduction or stabilization in tumor size.[89] Similarly, in subgroup analysis of the phase 3 CheckMate-025 study of nivolumab in previously treated patients, 153 patients were treated beyond progression, among whom 13% (20 of 153) had ≥30% tumor burden reduction.[90]

Management of oligoprogressive disease in the setting of ongoing systemic therapy has also been investigated in the

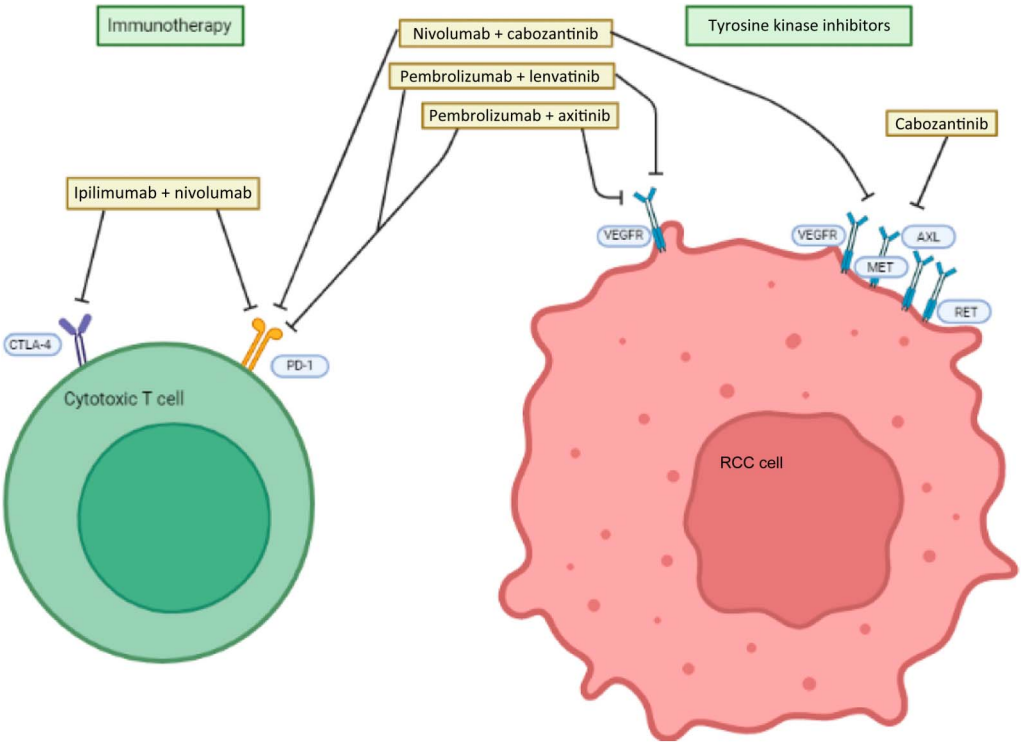

FIG 1. Current frontline systemic therapies for mRCC. AXL, AXL receptor tyrosine kinase; MET, mesenchymal-epithelial transition factor; mRCC, metastatic RCC; RCC, renal cell carcinoma; RET, RET proto-oncogene; VEGFR, vascular endothelial growth factor receptor.

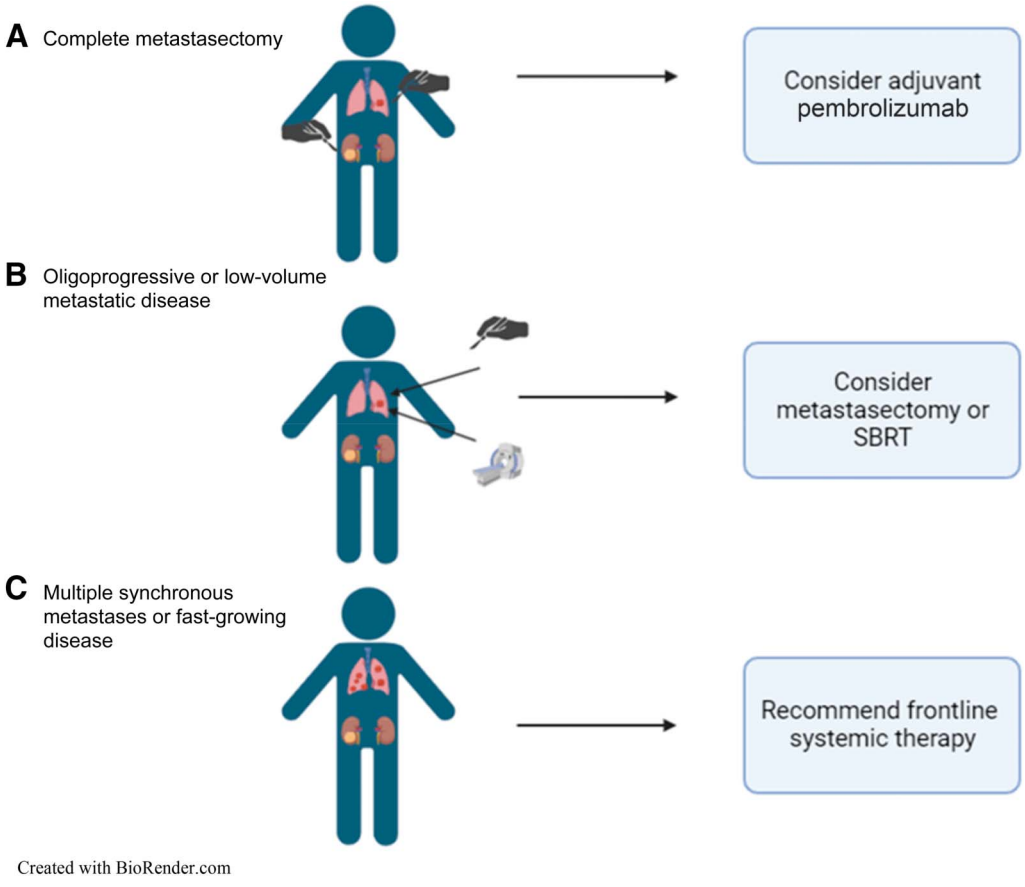

FIG 2. Multimodal treatment strategies for oligometastatic or oligoprogressive RCC. RCC, renal cell carcinoma; SBRT, stereotactic body radiotherapy.

setting of adding local intervention. The rationale is that resistant disease may be amenable to local treatment, whereas other sites remain sensitive to the same systemic therapy.[43,91,92] There are retrospective and prospective data supporting the use of SAbR while maintaining treatment with systemic therapy.[43,55,93-97] Interestingly, when the systemic therapy is checkpoint inhibitor, there appears to be a synergistic effect on the use of SAbR for oligoprogressive RCC.[43,55] We eagerly await the results of the prospective trials of SAbR for oligoprogressive RCC in the setting of checkpoint inhibitors (ClinicalTrials.gov identifier: NCT04974671, NCT04299646), which will provide further insight into whether the addition of SAbR in oligoprogressive disease will support continuation of newer systemic therapies, such as immunotherapy. Further prospective investigation is needed to elucidate the optimal management, especially in the changing treatment landscape of mRCC.

CONCLUSION

OM-RCC represents a heterogenous disease group that requires an individualized treatment approach. Treatment strategies include AS, local interventions (surgery or SAbR), and systemic therapy. There is no definitive treatment algorithm for these patients, and management will often involve a multimodal strategy (Fig 2).

Patient selection is key, and the available data show that patients with oligometastatic disease with IMDC favorable- or intermediate-risk classification, good performance status, metachronous metastases, and no evidence of hepatic, brain, or bone metastases are most likely to benefit from local therapy to the primary tumor and metastatic sites. After complete local control of the disease, patients with clear cell histology are recommended for adjuvant immunotherapy. For patients who are unable to proceed with upfront local therapy, frontline systemic therapy for mRCC is recommended.

In patients with indolent or oligoprogressive mRCC, treatment also involves a multimodal approach. On the basis of the available data, most clinicians proceed with locoregional intervention such as SAbR, while continuing current systemic therapy, allowing for the delay of systemic treatment escalation.

Future management of OM-RCC is contingent on a greater understanding of the tumor biology driving this disease. The

development of prognostic and predictive biomarkers may change the roles for surgery, radiation, and systemic therapy. Furthermore, management of this disease will continue to shift alongside the rapidly changing landscape of systemic therapy. Regardless, treatment of oligometastatic disease will continue to require a multidisciplinary team and ongoing prospective studies are investigating the optimal approach to this disease.

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Triplet Strategies in Metastatic Clear Cell Renal Cell Carcinoma: A Worthy Option in the First-Line Setting?

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Overview

Significant strides have been made in the frontline treatment of patients with advanced clear cell renal cell carcinoma (ccRCC). There are multiple standard-of-care doublet regimens consisting of either the combined dual immune checkpoint inhibitors, ipilimumab and nivolumab, or combinations of a vascular endothelial growth factor receptor tyrosine kinase inhibitor and an immune checkpoint inhibitor. Currently, there is an emergence of clinical trials examining triplet combinations. In COSMIC-313, a randomized phase III trial for patients with untreated advanced ccRCC, the triplet combination of ipilimumab, nivolumab, and cabozantinib was compared with a contemporary control arm of ipilimumab and nivolumab. While patients receiving the triplet regimen demonstrated improved progression-free survival, these patients also experienced greater toxicity and the overall survival data are still maturing. In this article, we discuss the role of doublet therapy as standard of care, the current data available for the promise of triplet therapy, the rationale to continue pursuing trials with triplet combinations, and factors for clinicians and patients to consider when choosing among frontline treatments. We present ongoing trials with an adaptive design that may serve as alternative methods for escalating from doublet to triplet regimens in the frontline setting and explore clinical factors and emerging predictive biomarkers (both baseline and dynamic) that may guide future trial design and frontline treatment for patients with advanced ccRCC.

INTRODUCTION

The advent of immune oncology (IO) and checkpoint inhibitors has dramatically changed the practice of oncology and outcomes for our patients. Clear cell renal cell carcinoma (ccRCC) is a poster child for the success of IO and shows how immunotherapy can be combined with vascular endothelial growth factor receptor tyrosine kinases (VEGFR-TKI) to improve outcomes. With four doublet combinations showing overall survival (OS) advantages, the clinical questions are now how to improve on this new standard of care or make the right decision for an individual patient. In this chapter, we will present current evidence supporting the use of doublet therapy (VEGFR-TKI/IO or dual IO/IO), the rationale for and evidence supporting triplet therapy (VEGFR-TKI plus dual IO/IO), and discuss strategies to select between these therapy plans.

DOUBLET THERAPY AS AN ESTABLISHED STANDARD OF CARE

The combinations of VEGFR-TKI plus IO or dual IO/IO with progressive disease (PD)1 and CTLA4 blockade have become the preferred approach in patients with advanced ccRCC International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate or poor risk groups.[1,2] The IMDC risk groups were initially developed during the VEGFR-TKI monotherapy era; however, they continue to be used to risk stratify patients in combination therapy trials.[1] The move from single agent to combination therapies is largely based on the results of the randomized phase III trials listed in Table 1. All five trials demonstrated statistically significant improvements in progression-free survival (PFS) of the following doublet combinations versus sunitinib: ipilimumab plus nivolumab, axitinib plus pembrolizumab, axitinib plus avelumab, cabozantinib plus nivolumab, and lenvatinib plus pembrolizumab (*v* lenvatinib plus everolimus).[3-7] With the exception of JAVELIN Renal 101 (axitinib plus avelumab *v* sunitinib), each combination has shown an improvement in OS that has proven durable with subsequent follow-ups.[8-10]

The debate continues as to whether dual IO/IO or VEGFR-TKI plus IO combinations are more relevant approaches in subsets of patients. Specific patterns of response observed with dual IO/IO or VEGFR-TKI plus IO may help clinical decision making. The CheckMate 214 trial of nivolumab plus ipilimumab had high rates of complete response (CR) versus sunitinib (9% *v* 1%), and also impressively, more than 80% of patients who

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PRACTICAL APPLICATIONS

- Combination therapy with dual immune checkpoint inhibitors or with a vascular endothelial growth factor receptor tyrosine kinase inhibitor and immune checkpoint inhibitor is the standard of care in the frontline setting for patients with advanced clear cell renal cell carcinoma (ccRCC).
- A triplet regimen consisting of ipilimumab, nivolumab, and cabozantinib demonstrated improved progression-free survival when compared with a doublet of ipilimumab and nivolumab at the cost of excess toxicity with unknown overall survival.
- Strategies to personalize therapy for ccRCC in the frontline setting, including response-adaptive treatment strategies and the use of biomarkers such as gene expression analysis to guide initial therapy, are under study.

achieved a CR did not relapse after 3 years of median follow-up, even in the context of treatment discontinuation.[11] On the other hand, combinations involving VEGFR-TKI with IO allow for swift activity provided by the targeted therapy with more frequent disease control (89%-95% *v* 81% with ipilimumab/nivolumab) and a numerically higher objective response rate (56%-71% *v* 42%). Additional disease features may also affect outcomes on treatment. In the CheckMate 214 trial comparing IO/IO with sunitinib, a subgroup analysis of patients with sarcomatoid features showed a higher overall response rate (ORR) of 61% versus 42% and CR of 19% versus 9% for the entire population.[12] In this trial, an exploratory analysis of favorable risk patients showed a higher ORR for patients in the sunitinib arm at 52%, compared with 29% in the IO/IO arm. As an additional consideration, the VEGF-TKI cabozantinib has shown compelling data in patients with brain metastases.[13-15] In a retrospective study of 88 patients with brain metastases who were treated with cabozantinib, the intracranial response rate among patients who did not receive brain-directed therapy was 55% and the rate among patients who received concomitant brain-directed therapy was 47%.[14,16] Subset analysis of the CLEAR trial while not statistically powered to study these subgroups suggested that despite having difficult-to-treat bone and liver metastasis, these patients still experienced improved trends in PFS hazard ratio (HR) 0.33 and 0.43, respectively, compared with sunitinib. Thus, expert clinical decision takes into consideration IMDC criteria, patient presentation, and requirement for quick response, as well as the aforementioned disease characteristics. There are no approved biomarkers to help with treatment selection in renal cell carcinoma (RCC).

TRIPLET THERAPY AS A NEW FRONTIER

As we continue to make strides in our management of advanced ccRCC, the question of whether less is more remains uncertain. We have several examples across oncology where additional therapies and associated toxicities were accepted due to improved outcomes for patients.[17-20] Within genitourinary oncology, the prostate cancer PEACE-1[19] and ARASENS[20] trials examined both triplet regimens comparing androgen deprivation therapy (ADT) and docetaxel alone versus ADT/docetaxel with abiraterone (PEACE-1) or darolutamide (ARASENS). Both trials had positive outcomes, with improved OS in PEACE-1 and decreased risk of death in ARASENS.

The success of such combination strategies relies on targeting distinct mechanisms of tumor growth and limiting

TABLE 1. Phase 3 Trials of Doublet Therapy

Identifier	Arms of Therapy	Primary Outcome Measure	No. of Patients	OS	PFS	ORR
CheckMate 214[3] NCT02231749	Ipilimumab + nivolumab *v* sunitinib	Coprimary OS, PFS, and ORR in intermediate and poor risk IMDC patients	1,096	HR, 0.63; $P < .001$	HR, 0.82; $P = .03$	42% *v* 27%
KEYNOTE 426[4] NCT02853331	Axitinib + pembrolizumab *v* sunitinib	OS and PFS	861	HR, 0.53; $P < .0001$	HR, 0.69; $P < .001$	59% *v* 36%
Javelin Renal 101[5] NCT02684006	Axitinib + avelumab *v* sunitinib	OS and PFS in patients with PD-L1+ tumors	886	HR, 0.83 (immature)	HR, 0.61; $P < .001$	55% *v* 26%
CheckMate 9ER[6] NCT03141177	Cabozantinib + nivolumab *v* sunitinib	PFS	651	HR, 0.60; $P = .001$	HR, 0.51; $P < .001$	56% *v* 27%
CLEAR[7] NCT02811861	Lenvatinib + pembrolizumab *v* lenvatinib + everolimus *v* sunitinib	PFS	1,069	HR, 0.66; $P = .005$ for lenvatinib + pembrolizumab *v* sunitinib	HR, 0.65; $P < .001$ for lenvatinib + pembrolizumab *v* sunitinib	71% *v* 36%

Abbreviations: HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

primary resistance to therapy. In patients with ccRCC, the VEGF pathway is targeted due to the near ubiquitous loss of von Hippel-Lindau (VHL) function[21] and remains an important biologic mechanism of ccRCC growth. Combining VEGFR-TKI inhibition to dual IO/IO immune checkpoint blockade is a logical step to attempt to increase cure rates and decrease the 20% primary progressive disease rate seen with dual IO/IO therapy alone.[3] As there is no currently validated biomarker to individualize treatment decisions, the field has embarked upon triplet regimens.[22]

A phase I trial conducted across genitourinary malignancies studied different escalating regimens of cabozantinib (40 or 60 mg daily), nivolumab (1 or 3 mg/kg every 3 weeks), and ipilimumab (1 or 3 mg/kg every 3 weeks).[23] The randomized phase 2 dose was determined to be cabozantinib 40 mg oral daily, nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks. Across diverse tumor biology, the ORR was 30.6% and grade 3/4 treatment-related adverse events occurred in 87% of patients treated with the triplet combination. The triplet regimen also showed higher rates of immune-related adverse events requiring treatment with corticosteroids at 29% of patients treated with the randomized phase 2 dose compared with 17% of patients treated with the equivalent dosing doublet regimen.

Additional RCC-specific triplet data next came from the CheckMate 9ER trial. Arm 3 received nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks with cabozantinib 40 mg daily for four cycles, followed by nivolumab 240 mg every 2 weeks with cabozantinib 40 mg daily. Random assignment was stratified by IMDC prognostic risk score, PD-L1 expression, and geographic region. Eligible patients were those with locally advanced or metastatic RCC with a clear cell component, no previous systemic therapy, Karnofsky performance status score $\geq$70, and RECIST measurable disease. All IMDC prognostic risk categories were included. The primary end point was PFS. Shortly after the initiation of this trial in 2017, the CheckMate 214 trial showed improved OS for dual IO/IO combination with nivolumab and ipilimumab compared with sunitinib.[3] Owing to this new evidence for an immediate role for the use of ipilimumab with nivolumab in the management of advanced ccRCC as standard of care, the triplet arm of CheckMate 9ER was discontinued via protocol amendment in late 2017.[24] Given early discontinuation of the study arm, the results were not compared with the other arms of CheckMate 9ER.

An exploratory analysis of the 50 patients randomly assigned to the triplet arm was reported in 2022. In this cohort, 11 patients had IMDC favorable risk, 31 had intermediate risk, and eight had poor risk. With a median follow-up of 39.1 months, ORR was 44% and CR rate was 8%. The median PFS (mPFS) by blinded independent central review was 9.9 months (5.7-16.8), and median overall survival 37.0 months (31.8-not reached). Forty-eight (96%) patients had treatment-related adverse events. The most common adverse events were diarrhea, increased alanine aminotransferase, increased aspartate aminotransferase, and hand-foot syndrome. In total, 84% of patients had a grade 3 or 4 event, and 46% of patients had treatment discontinuation of at least one study drug due to adverse events. Treatment was complicated by toxicity requiring dose delays, with 39 patients delaying at least one nivolumab dose, 19 delaying at least one ipilimumab dose, 43 delaying at least one cabozantinib dose, and 33 of 50 patients requiring dose reduction of cabozantinib. Twenty-four patients discontinued treatment for disease progression, and 11 patients discontinued treatment because of drug toxicity. Overall, these results show that there is clinical efficacy of a triplet regimen, but this is complicated by high rates of toxicity.

The COSMIC-313 study is the first phase 3 trial evaluating triplet therapy with cabozantinib, nivolumab, and ipilimumab compared with a contemporary standard-of-care ipilimumab and nivolumab (ClinicalTrials.gov identifier: NCT03937219).[25] Patients received triple therapy with cabozantinib 40 mg daily, nivolumab 3 mg/kg, and ipilimumab 1 mg/kg every 3 weeks for four cycles, followed by cabozantinib 40 mg daily with nivolumab 480 mg every 4 weeks versus standard dosing of ipilimumab 1 mg/kg and nivolumab 3 mg/kg dosing and nivolumab maintenance 480 mg every 4 weeks with placebo. Random assignment was stratified by region and IMDC risk category. Patients were previously untreated advanced ccRCC, with intermediate or poor risk IMDC. The primary end point was PFS. In the triplet therapy arm, the mPFS was not reached compared with 11.3 months in the dual IO/IO group (HR, 0.73; 95% CI, 0.57 to 0.94). Surprisingly, the mPFS in patients with poor risk disease was lower with triplet therapy at 9.5 months versus 11.2 months in the dual IO/IO group. Triplet therapy had a higher rate of disease control at 86% versus 72% in the dual IO/IO arm, including the ORR of 43% versus 36%. Both arms had low rates of CR at 3%, possibly because of the higher number of patients without previous nephrectomy. OS results are pending ongoing follow-up.

As in the CheckMate 9ER triplet arm, there was a high rate of adverse events with 90% of patients in the COSMIC-313 triplet arm requiring a dose hold of at least one therapy because of adverse events, compared with 70% in the dual IO/IO arm. In the triplet arm, 12% of patients had to discontinue all treatment components because of adverse event versus 5% in the dual IO/IO arm. Fewer patients in the triplet arm were able to complete four doses of ipilimumab (58% *v* 73%). In the triplet arm, 54% of patients had to dose reduce cabozantinib versus 20% of patients reducing placebo dose. As in the CheckMate 214 study,

transaminase elevations were the most commonly observed adverse events in the triplet arm. A higher percentage of patients (58%) in the triplet required treatment with corticosteroids, compared with 35% seen in the dual IO/IO arm.

Maturation of survival data from COSMIC-313 will aid in our ability to understand the broader implication for the use of cabozantinib, ipilimumab, and nivolumab in frontline treatment of advanced ccRCC given the above challenges with toxicity and dosing. Limiting the ability to make cross-comparison studies, it should be noted that COSMIC-313 had higher rates of IMDC poor risk patients (25%) compared with any standard-of-care IO/IO or IO/VEGFR-TKI doublet study (9%-19%), had more patients with primary kidney tumors in place, and did not include any favorable risk patients.

Further studies are needed to find the optimal treatments for patients with advanced ccRCC including the role of triplet therapy. Many ongoing studies will further address this need, evaluating novel agents such as hypoxia-inducible factor (HIF) or AXL inhibitors (Table 2). The rationale of many of these trials is similar to the objective stated above: adding therapies in combination to target a different biologic susceptibility of the tumor as a way to increase cure, decrease resistance, and not worsen toxicity. Several of these trials are taking a similar triplet approach as COSMIC-313 but varying the specific checkpoint inhibitor or VEGFR-TKI. In study 516-008, ipilimumab and nivolumab are combined with sitravatinib a to provide unique targeting and safety profile (ClinicalTrials.gov identifier: NCT04518046). One arm of MK6482-012 combines pembrolizumab (PD1), quavonlimab (CTLA4), and lenvatinib (VEGF-TKI; ClinicalTrials.gov identifier: NCT04736706) using different drugs to combine for IO/IO/VEGFR-TKI triplet. This trial is also looking at pembrolizumab, lenvatinib, and oral HIF inhibition with belzutifan. HIF inhibition is an exciting avenue in ccRCC, as the aforementioned ubiquitous loss of VHL results in upregulation of HIF and downstream cellular proliferation and angiogenesis. The trial adding belzutifan will answer if targeting HIF directly may enhance efficacy. New methods of dual targeting PD1 and CTLA4 with a monovalent bispecific antibody using MEDI5752 are being tested in combination with increasing doses of axitinib or lenvatinib (ClinicalTrials.gov identifier: NCT04522323).

Completely novel mechanisms of action to fight kidney cancer are also being conducted in frontline triplets. In a single-center study of 30 patients, CBM588, a bifidogenic live bacterial product suggested to enhance immune responsiveness, was tested in combination with dual IO/IO ipilimumab and nivolumab with a promising safety profile and an early suggestion of efficacy with ORR of the triplet at 58% versus 20% in the dual IO/IO (ClinicalTrials.gov identifier: NCT03829111).[26] Batiraxcept is a novel decoy protein that binds GAS6 and inhibits activation of AXL being studied in combination with cabozantinib and nivolumab to increase efficacy, decrease resistance mechanisms that may result from upregulation of AXL, and aim for a tolerable and sustainable safety profile (ClinicalTrials.gov identifier: NCT04300140). A number of patients with RCC have dysregulation of the cell cycle, and the APART trial is testing

TABLE 2. Ongoing Clinical Trials to Evaluate Triplet Therapy in the Management of Advanced RCC

Identifier	Arms of Therapy	Primary Outcome Measure	Phase	Status	Estimated Completion Date
MK6482-012 NCT04736706	Pembrolizumab + belzutifan + lenvatinib Pembrolizumab/quavonlimab + lenvatinib Pembrolizumab + lenvatinib	PFS	3	Recruiting	October 2026
APART NCT05176288	Axitinib + avelumab + palbociclib	ORR	2	Not yet recruiting	May 2024
INC NCT05501054	Ciforadenant + ipilimumab + nivolumab	Safety/tolerability Depth of response	1b/2	Recruiting	November 2026
NCT04522323	MEDI5752 + axitinib or lenvatinib	Adverse events Dose limiting toxicity	1b	Recruiting	March 2025
NCT04300140	Batiraxcept + cabozantinib + nivolumab	Adverse events Combination dosing Antitumor activity	1b	Active, not recruiting	December 2024
Study 516-008 NCT04518046	Sitravatinib + nivolumab + ipilimumab	Adverse events	1/1b	Active, not recruiting	March 2023
NCT03829111	CBM588 + ipilimumab + nivolumab	Effect of CBM588 on gut microbiome	1	Active, not recruiting	June 2023

Abbreviations: ORR, overall response rate; PFS, progression-free survival; RCC, renal cell carcinoma.

if the use of palbociclib, which blocks cyclin-dependent kinases 4 and 6 in combination with axitinib (VEGFR-TKI) and avelumab (PD-L1), will enhance efficacy while not having overlapping toxicities (ClinicalTrials.gov identifier: NCT05176288). The INC trial (ClinicalTrials.gov identifier: NCT05501054) is targeting the metabolic vulnerabilities of kidney cancer by combining ipilimumab and nivolumab with ciforadenant, an oral adenosine A2A receptor inhibitor. Adenosine is elevated in the RCC tumor microenvironment, and its inhibition in preclinical models has shown tumor regression and activation of immune effector T and NK cells.[27]

CHOOSING BETWEEN DOUBLET AND TRIPLET REGIMENS

While COSMIC-313 met its primary end point of improved PFS, it remains to be seen whether the addition of up-front cabozantinib to ipilimumab and nivolumab translates to improved OS. It is imperative to consider factors beyond PFS when choosing between therapies for patients with advanced ccRCC. These factors include toxicities of treatment, health-related quality of life (HRQoL), secondary measures of clinical efficacy (including response rates and primary progressive disease rates), and clinicopathologic factors or biomarkers that might enrich response to treatment.

The expected and potential toxicities of IO and VEGFR-TKI are well known and described, and may inform frontline therapy decisions. Toxicities of IO include, but are not limited to, rash, arthralgias and arthritis, colitis, fatigue, endocrinopathies, hepatotoxicity, and pneumonitis.[1] These side effects are more common and severe in patients receiving ipilimumab and nivolumab versus nivolumab alone.[28] There is overlap in toxicities between IO and VEGFR-TKI, the latter of which has adverse effects such as mucositis, diarrhea, rash, palmar-plantar erythrodysesthesia, fatigue, and hepatotoxicity and hypertension.[29] Choosing the appropriate treatment regimen depends on patients and their comorbid conditions. For instance, those with a history of autoimmunity—but still deemed candidates to receive IO—may be better suited for a regimen without ipilimumab, while those with uncontrolled hypertension or heart failure may be better served avoiding a VEGFR-TKI containing regimen. Frailer patients or those with borderline performance status are unlikely to tolerate a triplet regimen. Patients enrolled in the triplet arm of COSMIC-313, all with Karnofsky performance status of 70 or higher, had difficulty tolerating the triplet regimen, as evidenced by the relatively high frequency of dose reductions and treatment delays.[25]

Given the significant toxicity caused by the addition of cabozantinib to ipilimumab and nivolumab in COSMIC-313, justification to use this regimen requires clinically impactful benefits. The addition of cabozantinib to ipilimumab and nivolumab improved PFS and decreased the proportion of patients with primary progressive disease (8% *v* 20%) when compared with ipilimumab and nivolumab alone. However, ORR was not much higher in the triplet arm (43%) than in the dual IO/IO (36%) arm, and CR rates were identical (3% in each; Table 3). One possible reason for the lack of deep responses theoretically expected in the triplet arm is that the excess toxicity seen in the triplet arm prevented adequate treatment exposure, thereby limiting the benefit in the overall population.[30] The overlap in toxicities, especially hepatic toxicity, can make it challenging to determine which agent to dose modify and can force the interruption of both the VEGFR-TKI and the dual IO/IO.

In addition to picking frontline treatments on the basis of efficacy and toxicity, it may also be helpful to make use of clinical predictive markers. This is exemplified by the case of COSMIC-313, in which one unexpected predictive clinical parameter was the IMDC risk criteria.[25] Much of the PFS benefit derived in the intention-to-treat population was reserved for the intermediate risk group (HR, 0.63; 95% CI, 0.47 to 0.85), whereas the addition of cabozantinib did not meaningfully improve PFS in the poor risk group (HR, 1.04; 95% CI, 0.65 to 1.69). Similarly, triplet therapy conferred a 10% improvement in ORR in the intermediate risk group (45% *v* 35%), but the results in the poor risk group were similar between treatment arms (37% *v* 38%). As mechanisms underlying these allegedly distinct outcomes are yet to be explored, bolstering the development of robust predictive biomarkers is a key need.

CLINICAL BIOMARKERS: DEPTH OF RESPONSE AND QUALITY OF LIFE

Clinical parameters may predict long-term benefit from combination strategies and inform adaptative treatment strategies. Among those, depth of response (DepOR) is a clinical marker predictive of long-term outcomes, which can be defined as the percentage of tumor shrinkage and is correlated with clinical outcome in a number of solid tumors.[31-33] In an exploratory analysis of DepOR in the CheckMate 214 trial, the median time to a DepOR of >50% was 4 months for the dual IO/IO arm, compared with 5.6 months in the sunitinib arm.[34] Additionally, 42% of dual IO/IO-treated patients obtained a DepOR of >50%, compared with 26% of sunitinib-treated patients. Powles et al evaluated DepOR in a post hoc analysis of KEYNOTE-426—which randomly assigned patients to receive axitinib plus pembrolizumab versus sunitinib for metastatic ccRCC—and found that increasing DepOR, particularly in the axitinib and pembrolizumab arm, was associated with increased OS.[35] Similarly, in an exploratory 6-month landmark analysis of CheckMate 9ER, Suarez et al analyzed the relationship of DepOR to clinical outcomes of PFS and OS in patients with treatment-naïve metastatic ccRCC treated with either cabozantinib and nivolumab or sunitinib.[36] The DepOR was based on percent tumor reduction measured

TABLE 3. Comparison of Response and Toxicities Between Doublet and Triplet Trials

	Phase 1 Safety Trial[23]		CheckMate 9ER[24,30]			COSMIC-313[25]		CheckMate 214[3,9]
	Nivolumab/ Cabozantinib	Ipilimumab/ Nivolumab/ Cabozantinib	Sunitinib	Nivolumab/ Cabozantinib	Ipilimumab/ Nivolumab/ Cabozantinib	Ipilimumab/ Nivolumab	Ipilimumab/ Nivolumab/ Cabozantinib	Ipilimumab/ Nivolumab
Phase of trial	1		3			3		3
No. of patients	54		651		**50**	855		1,096
No. of randomly assigned renal patients	6		328	323	**50**	428	**427**	550
ORR (%)	39.1	**23.1**	28	56	**44.0**	36	**43**	39.1
CR rate (%)	13	**3.8**	5	12	**8**	3	**3**	10.7
PFS (months)	**5.1**		8.3	16.6	**9.9**	11.3	Not met	12.3
OS (months)	**12.6**		34.3	37.7	**37.0**	Not mature		55.7
PD as best response (%)	17.4	**26.9**	14	6	**8**	20	**8**	17.6
% any grade event	100	**97**	93	97	**96**	91	**99**	94
% grade 3/4 events	75	**87**	54	65	**84**	41	**73**	47.9
Discontinuation rate	17	**23**	10	27	**46**	24	**45**	22.7

NOTE. Bolded text highlights the triplet arm for each study and associated results.
Abbreviations: CR, complete response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

using RECIST and broken into six response levels. Deeper responses were associated with improved mPFS in the nivolumab with cabozantinib arm and in both arms suggested better OS outcomes. There was no clear relationship between DepOR and baseline IMDC risk groups, nor with occurrence of treatment-related adverse events. These analyses by themselves are not practice changing due to their post hoc nature and lack of prospective validation. Nonetheless, these data suggest that DepOR may itself be a mediator of improved OS in ccRCC. If that is the case, an adaptive trial design aimed at improving DepOR may represent an ideal strategy to address the question of whether doublet or triplet therapy is advantageous to select groups of patients.

An important question regarding the development of adaptative strategies relies on the choice of the starting therapy. OMNIVORE was an adaptive study for patients with metastatic ccRCC without previous immunotherapy. Patients received up to 6 months of nivolumab monotherapy, and if they did not achieve at least a partial response (PR), they received two doses of ipilimumab.[37] In total, 16.9% of patients achieved a PR, with no patients achieving a CR. These relatively poor results—in comparison with CheckMate 214—suggest that patients cannot be salvaged with delayed ipilimumab following monotherapy with PD-1 inhibition, and the synergy seen with combined PD-1/CTLA-4 inhibition requires contemporaneous treatment initiation with both agents. Similar results were seen in the HCRN trial evaluating the role of salvage ipilimumab/nivolumab in patients with metastatic ccRCC who achieved PD or stable disease (SD) as best response with nivolumab alone.[38] Therefore, adaptive trials aimed at escalating from doublet to triplet therapy should not focus on escalating from IO/VEGFR-TKI but rather should investigate the use of a dual ICI backbone with possible escalation to a dual IO/IO/VEGFR-TKI triplet, such as the currently enrolling PDIGREE (Alliance A031704) trial (ClinicalTrials.gov identifier: NCT03793166).[39] PDIGREE includes patients with treatment-naïve metastatic ccRCC of intermediate or poor IMDC risk. All patients in PDIGREE start treatment with induction ipilimumab and nivolumab for four cycles. At 3 months, patients undergo repeat imaging and are randomly assigned based on their radiographic response: (1) Patients with CR undergo maintenance nivolumab, (2) patients with SD or PR are randomly assigned to maintenance nivolumab or nivolumab plus cabozantinib, and (3) patients with PD are switched to cabozantinib monotherapy. Among patients with SD or PR, PDIGREE will answer whether DepOR can be augmented using this adaptive approach and if achieving higher DepOR after adaptive change in treatment course will be associated with improved survival outcomes.

There is also evidence in ccRCC that changes in—or maintenance of—HRQoL can serve as an additional predictive clinical marker. CheckMate 214 studied the impact of the change in HRQoL on survival outcomes.[40] HRQoL was measured using the FKSI-19 total scores and disease-related symptom score. FKSI-19 includes the following domains: physical disease-related symptoms, emotional

disease-related symptoms, treatment side effects, and function well-being. Measurements were obtained at baseline, 4 weeks, and longitudinally every 6 weeks for the duration of the study until disease progression. A landmark analysis of the change in HRQoL from baseline to 6 months and association with OS was also performed. Those deemed responders had either no change or an improved score, whereas the nonresponders had worsening score of at least five points from baseline. There was a longer OS (HR, 0.48; 95% CI, 0.39 to 0.59) in those patients who had maintained or improved QoL compared with nonresponders, and it was notable that longitudinal assessment was more predictive of benefit than baseline assessment. Similar to DepOR, a change in HRQOL could be applied in an adaptive design to determine intensification or de-escalation of therapy between doublet and triplet.

EMERGING BIOMARKERS

Current tools provide limited insights at an individual level regarding the biology driving tumorigenesis. Created as a tool to assess outcomes in the era of patients receiving VEGFR-TKI monotherapy, the IMDC criteria as such may be potentially limited in its ability to define patient cohorts for immunotherapy trials. Efforts to validate IMDC in patients on pure immunotherapy are underway, and this biomarker remains the most robust tool available in assessing metastatic renal cell carcinoma. However, several molecular and clinical tools are of interest. The use of simple biomarkers such as PD-L1 remains of limited value in ccRCC.[41] Novel avenues on the basis of molecular tools for patient selection are now undergoing evaluation.

A promising potential biomarker approach is the use of tissue-based transcriptome analysis to characterize tumor cells and the surrounding microenvironment. Such an approach allowed for identification of distinct biological clusters (angiogenesis, immune, cell cycle, metabolism, and stromal programs) in over 800 patients with ccRCC[42] who participated in a randomized phase III trial of sunitinib versus bevacizumab and atezolizumab therapy (IMmotion 151).[43] These cluster panels correlated with potential sensitivity or resistance of metastatic RCC to immune checkpoint inhibitor or antiangiogenic therapy.[42] Transcriptomics in other large trials have identified similar signatures with variable results when applied to other clinical trial samples.[3] These approaches need prospective validation and could be used to assign patients to distinct treatment strategies. The feasibility of such trials has been already demonstrated in the BIONIKK program,[44] and contemporary efforts are now underway with the OPTIC RCC study (ClinicalTrials.gov identifier: NCT05361720). Efforts to bring more easily accessible dynamic biomarkers in metastatic ccRCC may also rely on circulating immune factors, which could accurately reflect the broader immune contexture and individual susceptibility to checkpoint blockade.[45]

Liquid biopsies (including circulating tumor DNA [ctDNA], cell-free DNA [cfDNA], and circulating noncoding RNA) using a variety of commercial assays have been successfully used to define treatment options for patients with solid tumors (GI, lung, breast, and urothelial).[46-48] CtDNA, which detects mutated DNA in the blood (usually plasma to avoid contamination from leukocytes), can be collected longitudinally and sequenced to follow further genomic aberrations. The potential for ctDNA, determining sensitivity to drugs or in detecting the emergence of resistant clones and therefore new directions in therapy, has been demonstrated in other solid tumors, including colorectal, non–small-cell lung, and urothelial cancers. In the SWOG1314 trial of dose dense chemotherapy regimen including methotrexate, vinblastine, Adriamycin, and cisplatin before radical cystectomy for muscle invasive urothelial cancer, response of cfDNA methylation and quantitative bladder cfDNA correlated independently with the pathologic response.[49] A strength of this approach is that concordance of ctDNA mutation to tumor mutation is high.[50] CtDNA can detect longitudinal evolution of genomic aberrations in metastatic RCC.[51]

The yield of ctDNA in metastatic RCC in some analyses is lower than in other solid tumors,[50,51] but exploiting fragment lengths of circulating DNA can improve sensitivity.[52] A more promising approach is the quantification of cfDNA, extracellular DNA shed in plasma, with further sensitivity by the use of methylated DNA immunoprecipitation.[53] Methylated cfDNA is measurable in all stages of ccRCC,[54,55] and ongoing studies are correlating increases or decreases in cfDNA to response to or progression on therapies, as measured using imaging.[55] Future application of cfDNA could be imagined in several ways: First, as both transcriptomic and cfDNA technology evolve, concordance between the two could be used to direct patients to triplet or doublet combinations. Second, and more practically, validating the concordance of cfDNA decrease with imaging response might identify in advance of imaging and toxicity, which patients are benefiting from triplet or doublet therapy or potentially who should continue on current therapy to enhance response, de-escalate, or intensify therapy.

CONCLUSIONS

In summary, standard-of-care frontline treatment remains doublet IO/IO or IO/VEGFR-TKI therapy. There is a growing body of evidence assessing efficacy and safety of treatment with triplet therapy in advanced ccRCC. Triplet therapy has shown improved PFS, but OS outcomes are still maturing. However, a PFS benefit with triplet therapy comes at the expense of significant toxicity. Patient selection will be

crucial in finding those in whom the risk-benefit ratio favors aggressive therapy. Ongoing efforts to develop tools that will allow individualized treatment decisions range from clinical HRQoL and DepOR to biologic transcriptomics and liquid biopsies. Finally, efforts to move the field forward with novel targeting agents and mechanisms to increase cure while not adding to toxicity in triplet therapy are ongoing. We eagerly await the full results of the above trials to better inform therapy selection for our patients with ccRCC.

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Metastatic Hormone-Sensitive Prostate Cancer: Toward an Era of Adaptive and Personalized Treatment

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Overview

The advent of more effective treatment combinations for metastatic hormone-sensitive prostate cancer (mHSPC) has been built on successes in therapy development for metastatic, castration-resistant prostate cancer (mCRPC). Both disease phases hold similar challenges and questions. Is there an optimal therapy sequence to maximize disease control and balance treatment burden? Are there clinical and biologically based subgroups that inform personalized and/or adaptive strategies? How can clinicians interpret data from clinical trials in the context of rapidly evolving technologies? Herein, we review the contemporary landscape of treatment for mHSPC, including disease subgroups informing both intensification and potential deintensification strategies. Furthermore, we provide current insights into the complex biology of mHSPC and discuss the potential clinical application of biomarkers to guide therapy selection and the development of novel personalized approaches.

INTRODUCTION

Prostate cancer is among the most common solid malignancies in men, accounting for a significant proportion of the global burden of cancer morbidity and mortality.[1] The diagnosis and clinical presentation of prostate cancer may be influenced by sociodemographic, geographic, economic, and biological factors. Most men in developed nations are diagnosed when cancer is confined to the prostate gland, and this has stemmed, historically, from the advent and widespread use of prostate-specific antigen (PSA) screening.[2] Despite variation in the mode and stage of diagnosis, the spectrum of disease can be consistently divided by two key clinical factors: (1) the presence or absence of metastasis on conventional imaging modalities and (2) sensitivity or resistance to gonadal testosterone suppression (TS). The former is determined by clinical and radiographic evaluation and remains an area of rapid evolution in recent times with the adoption of novel diagnostic imaging techniques, such as magnetic resonance imaging and positron emission tomography (PET). The latter provides a phenotypic label in relation to response to androgen deprivation therapy (ADT)—the backbone of systemic therapy for metastatic prostate cancer—and has a formalized definition, most notably by the Prostate Cancer Working Group.[3]

The incidence of mHSPC is increasing.[4,5] US-based studies point to shifts in stage of diagnosis, which parallel changes in PSA screening recommendations by the US Preventative Services Task Force.[6] Although not inferring direct causality, the rising incidence of metastatic prostate cancer is considered a high priority because of the incurable nature of advanced disease associated with inevitable therapy resistance and worse survival. Treatment for mHSPC has evolved considerably over the past decade because of successive large, randomized, phase III clinical trials demonstrating improvements in overall survival (OS) and quality of life (QoL) with combination therapy above the historical standard of ADT alone (Table 1). Many of the novel strategies for mHSPC have arisen from therapies proven successful in mCRPC (Fig 1). We have been ushered into a new era of mHSPC, which has led to intense questioning of how we can both balance and improve the benefit, burden, and precision of treatment for patients.

TREATMENT OF mHSPC

Inhibition of the androgen receptor (AR) remains the mainstay of treatment for mHSPC, owing to seminal experiments published in 1941, which proved that prostate cancer is an androgen-driven and androgen-dependent disease that responds to testosterone deprivation.[17] These discoveries led to Charles Huggins receiving the Nobel Prize in Physiology or Medicine in 1966. Indeed, androgen signaling is central in driving growth and survival of prostate cancer even in treatment-resistant states.[18] TS was

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PRACTICAL APPLICATIONS

- The landscape of treatment for metastatic hormone-sensitive prostate cancer (mHSPC) continues to evolve, with a shift to combination systemic therapy being established as the backbone of contemporary treatment.
- Clinical factors, including disease volume and presentation, demonstrate prognostic associations and have been studied in the context of predicting the benefit of combination strategies, including triplet systemic therapy.
- The role of treatment intensity modulation is of high interest, given that modern trials in mHSPC have demonstrated that a subset of patients have favorable long-term outcomes. De-intensification strategies guided by prostate-specific antigen response aim to balance both the benefits and long-term risks and burden of treatment.
- Biomarker development in mHSPC is leveraging the rapid accumulation of knowledge from biological profiling of both localized prostate cancer and metastatic, castration-resistant prostate cancer.
- In the era of precision cancer care, targeted novel therapies are being tested in ongoing clinical trials to further personalize therapy for mHSPC.

originally instituted by surgical castration (bilateral orchiectomy), followed by diethylstilbestrol and subsequent development of luteinizing hormone-releasing hormone (LHRH) agonists and antagonists built on the elucidation of hypothalamic pituitary control of gonadal testosterone production. Labrie et al[19] initially hypothesized that the concomitant administration of an antiandrogen to ADT, or complete androgen blockade, eliminates the activity of testicular and adrenal androgens. Early-generation AR inhibitors, such as flutamide, bicalutamide, nilutamide, and cyproterone acetate, are generally not used as monotherapy and instead are more often combined with TS (termed combined ADT) for prevention of flare responses due to initial agonistic (positive feedback) effects of LHRH agonist therapy. An individual patient data (IPD) meta-analysis of 8,275 men from 27 randomized trials comparing TS alone versus combined ADT[20] showed that 5-year OS was improved with nonsteroidal antiandrogens (absolute benefit 3%; two-sided $P = .005$) and possibly worse with cyproterone acetate (absolute reduction 3%; two-sided $P = .04$), compared with TS alone. These data have laid the basis of combined ADT of TS plus weak, early-generation AR inhibitors as a potential control arm in clinical trials of mHSPC. However, real-world practice remains heterogeneous.

ADT Plus Docetaxel or Novel AR Signaling Inhibitor: Doublet Systemic Therapy

ADT plus docetaxel. From the early 1940s to 2015, TS alone with or without an AR inhibitor was a standard treatment for mHSPC before development of castration resistance. In 2004, the TAX 327 and SWOG9916 trials demonstrated a significant improvement in OS for men with mCRPC treated with ADT plus docetaxel/prednisone (or docetaxel plus estramustine in SWOG9916), compared with ADT plus mitoxantrone/prednisone.[21,22] These findings led to an immediate shift in the treatment paradigm of mCRPC. The combination of hormonal therapy and cytotoxic therapy also reflected a strong scientific rationale as clonal populations in advanced and resistant prostate cancer are diverse (both within and between metastases) and may be differentially driven by AR-dependent and non–AR-dependent mechanisms.[23]

Therapy intensification with ADT plus docetaxel in frontline management of mHSPC was tested in three key phase III trials. GETUG-AFU 15 randomly assigned 385 men to either ADT plus docetaxel once every 3 weeks (up to nine cycles, without prednisone) or ADT alone. At a median follow-up of 50 months, OS was not significantly different between the groups (hazard ratio [HR], 1.01; 95% CI, 0.75 to 1.36).[24] Long-term follow-up, at a median of 83.9 months, again failed to show a significant difference in OS; however, post hoc analysis by volume of metastatic disease demonstrated a trend to benefit in the high-volume subgroup (HR, 0.78; 95% CI, 0.56 to 1.09), which did not meet statistical significance and was notably underpowered.[25] The CHAARTED trial was the first to report a significant OS improvement with ADT plus docetaxel for mHSPC—also the first of any combination strategy.[26] In total, 790 men were randomly assigned to ADT alone or ADT plus docetaxel (for six cycles), with a primary end point of OS. The trial had several prespecified stratification factors including disease volume (high versus low), where high-volume was defined as the presence of any visceral metastases, or four or more bone lesions with at least one beyond the vertebral bodies and pelvis. After a median follow-up of 28.9 months, chemohormonal therapy was associated with significantly prolonged OS (57.6 months *v* 44 months, HR, 0.61; 95% CI, 0.47 to 0.80; $P < .001$), as well as improvements in secondary end points including time to CRPC and the proportion of patients with suppressed PSA (<0.2 ng/mL) at 12 months. The effect of docetaxel was particularly pronounced in the high-volume subgroup (65% of cohort). In long-term follow-up, the median OS for patients with high-volume disease was 51.2 months versus 34.4 months (HR, 0.63; 95% CI, 0.50 to 0.79; $P < .001$) for ADT plus

TABLE 1. Summary Data of Completed Trials in Metastatic Hormone-Sensitive Prostate Cancer

Doublet Systemic Therapy

Trial	Patients Enrolled	Intervention Arm	Control Arm	% Synchronous	% High-Volume	Median Follow-Up (months)	Median OS in Intervention Arm (months)	Median OS in Control Arm (months)	Group: HR (95% CI)
CHAARTED[7]	790	ADT plus docetaxel	ADT	Not allowed	53.7	57.6	47.2	0.72 (0.59 to 0.89)	.0018
STAMPEDE (M1 subgroup)[8]	1,086	ADT plus docetaxel	ADT	Not allowed	78.2	59.1	43.1	0.81 (0.69 to 0.95)	.003
LATITUDE[10]	1,199	ADT plus abiraterone plus prednisone	ADT plus placebo	Not allowed	51.8	53.3	36.5	0.66 (0.56 to 0.78)	<.0001
STAMPEDE[9]	1,917	ADT plus abiraterone plus prednisone	ADT	Not allowed	40	NR	NR	Overall: 0.63 (0.52 to 0.76) M1 subgroup: 0.61 (0.49 to 0.75)	<.001 (overall)
ENZAMET[16]	1,125	ADT plus enzalutamide	ADT plus NSAA	Allowed (concurrent, 45%)	68	NR	NR	Overall: 0.70 (0.58 to 0.84) Early docetaxel: 0.82 (0.63 to 1.06) No early docetaxel: 0.60 (0.47 to 0.78)	<.0001 (overall)
ARCHES[11]	1,150	ADT plus enzalutamide	ADT plus placebo	Allowed (previous, 18%)	44.6	NR	NR	Overall: 0.66 (0.53 to 0.81) Previous docetaxel: 0.74 (0.46 to 1.20) No previous docetaxel: 0.64 (0.51 to 0.81)	<.001 (overall)
TITAN[12]	1,052	ADT plus apalutamide	ADT plus placebo	Allowed (previous, 11%)	44	NR	52.2	Overall: 0.65 (0.53 to 0.79) Previous docetaxel: 1.12 (0.59 to 2.12) No previous docetaxel: 0.61 (0.50 to 0.76)	<.0001 (overall)

Triplet Systemic Therapy

Trial	Patients Enrolled	Intervention Arm	Control Arm	% Synchronous	% High-Volume	Median Follow-Up (months)	Median OS in Intervention Arm (months)	Median OS in Control Arm (months)	Group: HR (95% CI)
ARASENS[13,14]	1,306	ADT plus docetaxel plus darolutamide	ADT plus docetaxel plus placebo	86	77	43.7	NR	48.9	Overall: 0.68 (0.57 to 0.80) Synchronous + HV: 0.69 (0.57 to 0.85) Synchronous + LV: 0.75 (0.45 to 1.27) Metachronous + HV: 0.69 (0.39 to 1.24) Metachronous + LV: NA

(Continued on following page)

TABLE 1. Summary Data of Completed Trials in Metastatic Hormone-Sensitive Prostate Cancer (Continued)

Doublet Systemic Therapy

Trial	Patients Enrolled	Intervention Arm	Control Arm	% Synchronous	% High-Volume	Median Follow-Up (months)	Median OS in Intervention Arm (months)	Median OS in Control Arm (months)	Group: HR (95% CI)
PEACE-1 (docetaxel subgroup)[15]	710	SOC plus abiraterone (with or without RT)	SOC (with or without RT)	100	64	45.6	NR	53.2	Overall (all synchronous): 0.75 (0.59 to 0.95)
ENZAMET (docetaxel subgroup)[16]	503	ADT plus docetaxel plus enzalutamide	ADT plus docetaxel plus NSAA	72	71	68 (overall cohort)	Not reported	Not reported	Synchronous (all): 0.73 (0.55 to 0.99) Synchronous + HV: 0.79 (0.57 to 1.10) Synchronous + LV: 0.57 (0.29 to 1.12) Metachronous (all): 1.10 (0.65 to 1.86)

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; HV, high-volume; LV, low-volume; NA, not applicable; NR, not reached; OS, overall survival; RT, radiotherapy; SOC, standard of care.

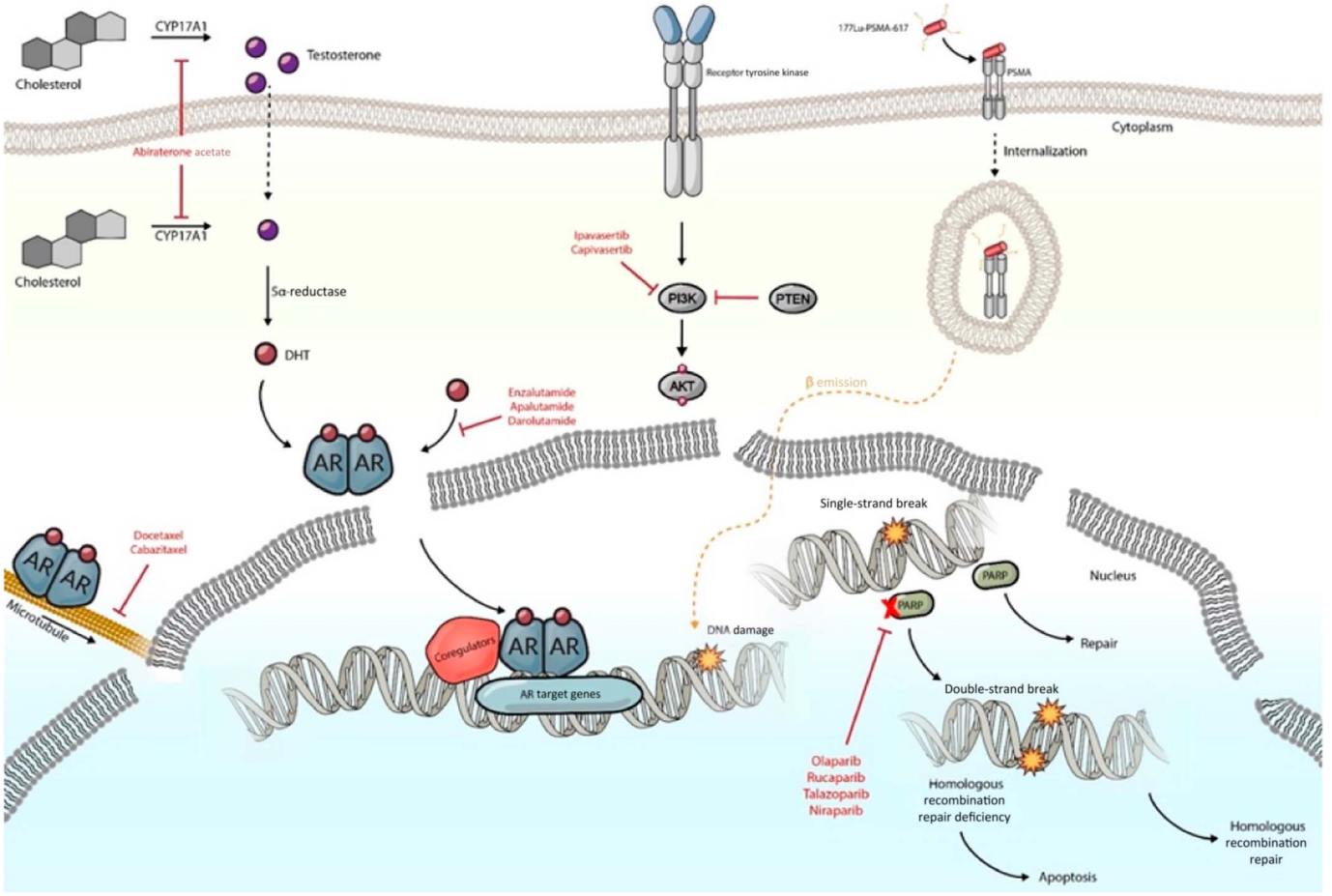

FIG 1. Therapeutic targets of systemic therapies for advanced prostate cancer. AKT, AKR thymoma; AR, androgen receptor; CYP17A1, cytochrome P450 17A1; DHT, dihydrotestosterone; PARP, poly (ADP-ribose) polymerase; PI3K, phosphoinositide 3-kinase; PSMA, prostate-specific membrane antigen; PTEN, phosphatase and tensin homolog.

docetaxel versus ADT alone, respectively.[7] Notably, no significant OS benefit was observed for patients with low-volume disease (HR, 1.04; 95% CI, 0.70 to 1.55; $P = .86$), suggesting marked heterogeneity of effect. Subsequent meta-analysis of aggregate data from GETUG-AFU 15 and CHAARTED with harmonized disease volume definitions confirmed heterogeneity in effect sizes between volume subgroups, with significant OS advantage from docetaxel demonstrated in high-volume disease (synchronous and metachronous), modest OS benefit in synchronous low-volume disease, and no OS benefit in metachronous, low-volume disease.[27] The multiarm, multistage STAMPEDE trial also showed a significant benefit for addition of docetaxel to ADT for mHSPC.[28] In a trial population of 2,962 men, which also included patients with high-risk localized disease (39%), arm C (ADT plus docetaxel) and arm E (ADT plus docetaxel plus zoledronic acid) demonstrated improved OS compared with ADT alone (HR, 0.78; 95% CI, 0.66 to 0.93; $P = .006$ and HR, 0.82; 95% CI, 0.69 to 0.97; $P = .022$, respectively). Subgroup analysis showed this effect clearly in men with metastatic disease. Updated analysis of this subgroup at a median follow-up of 78.2 months failed to show heterogeneity of docetaxel effect on OS by retrospectively evaluated metastatic burden (per CHAARTED definition).[8] Notably, 95% of the patients in the STAMPEDE-M1 cohort had synchronous disease. The latter clearly differed to the patient mix of CHAARTED and GETUG-15, which had 17% of patients with metachronous, low-volume disease. An IPD meta-analysis of 2,261 men from GETUG-AFU 15, CHAARTED, and STAMPEDE by the STOPCAP group demonstrated a gradient effect of OS benefit for the addition of docetaxel to ADT, with the most pronounced effect in the synchronous, high-volume subgroup. A modest effect was noted in the metachronous, high-volume subgroup and synchronous, low-volume subgroup. No effect was seen in metachronous, low-volume disease, which is associated with a more favorable prognosis with TS alone.[29] It should also be noted that not all patients are fit for docetaxel, often because of comorbid conditions. Radiation to the prostate also has an

OS benefit with a more favorable adverse event profile than docetaxel for men with synchronous, low-volume mHSPC.[30]

The role of prostate RT. Treatment of the primary tumor in the face of metastatic disease is an enticing concept with the rationale of eliminating a significant source of lethal metastatic seeding. Between 2013 and 2016, STAMPEDE addressed this strategy in mHSPC, randomly assigning 2,061 men to the standard care arm (ADT, with concurrent docetaxel permitted from late 2015) or standard care plus prostate radiotherapy (RT) delivered over 4-6 weeks.[31] Fifty-four percent of men had high metastatic burden, and 18% received up-front docetaxel. The addition of prostate RT significantly improved failure-free survival, but not OS (HR, 0.92; 95% CI, 0.80 to 1.06; $P = .226$) in the overall cohort. However, there was a pronounced OS benefit in patients with low metastatic burden (HR, 0.68; 95% CI, 0.52 to 0.90; $P = .007$), which was not evident in high-burden disease (interaction $P = .01$). This differential effect was again observed in long-term follow-up, and there was no evidence of deterioration in global QoL and long-term high-grade urinary toxicity.[32] When combined with data from the smaller HORRAD trial, meta-analysis by the number of bone metastases demonstrated significant benefit for patients with <5 bone lesions and not higher burden disease.[30] On the basis of these data, prostate RT is an established standard for synchronous, low-burden/volume mHSPC; however, questions remain regarding its role with combination systemic therapy. The proportion of patients treated with docetaxel in the STAMPEDE radiation cohort does not allow for clear conclusions to be drawn from the subset of patients with low-burden disease treated with chemohormonal therapy. PEACE-1 has similar subgroups that may be pooled for analysis and will also define the role of prostate RT combined with ADT plus abiraterone (with or without docetaxel).

ADT plus AR signaling inhibitor. After the proven OS-prolonging benefit of AR signaling inhibitors (ARSIs) in CRPC, several phase III, randomized trials have cemented the role of intense ADT, with a combination of TS plus ARSI, for mHSPC.

Abiraterone acetate, which decreases androgen synthesis by inhibiting CYP17A1, has been evaluated in the STAMPEDE, LATITUDE, and PEACE-1 trials. STAMPEDE assigned men with HSPC 1:1 to either ADT plus abiraterone plus prednisolone (arm G) or ADT alone.[9] Fifty-two percent of men had metastatic disease. At a median follow-up of 40 months, a significant improvement in the primary end point of OS was noted, with a magnitude of effect in the metastatic subgroup, again 95% with synchronous disease, strikingly similar to the aforementioned docetaxel trials (HR, 0.61; 95% CI, 0.49 to 0.75). The clinically meaningful secondary end point of time to symptomatic skeletal events was also significantly improved with combination therapy. LATITUDE randomly assigned 1,199 men to analogous treatment arms; however, the cohort of patients with mHSPC were selected specifically for poor prognostic features—all patients had synchronous metastatic disease and at least two of Gleason score ≥8, ≥3 bone lesions, and presence of visceral metastasis.[33] ADT plus abiraterone significantly improved OS at a planned interim analysis (HR, 0.62; 95% CI, 0.51 to 0.76; $P < .0001$). Time to pain progression, initiation of chemotherapy, and symptomatic skeletal events were all in favor of the abiraterone arm. At the final analysis after a median follow-up of 51.8 months, survival benefit remained (median 53.5 months *v* 36.5 months, HR, 0.66; 95% CI, 0.56 to 0.78; $P < .0001$).[10]

Three next-generation AR inhibitors (enzalutamide, apalutamide, and darolutamide) have established efficacy in mHSPC. ENZAMET[34] and ARCHES[35] tested the addition of enzalutamide to ADT, with the notable difference that the control arm of ENZAMET required patients to receive ADT plus a nonsteroidal antiandrogen. In ENZAMET, concurrent use of up-front docetaxel (maximum six cycles) was permitted after a protocol amendment early in accrual. A total of 1,125 men were randomly assigned, and after a median follow-up of 34 months, clear OS prolongation with enzalutamide was observed (HR, 0.67; 95% CI, 0.52 to 0.86, $P = .002$). Benefit was observed across stratified subgroups, including disease volume (high/low) and metastatic timing (synchronous/metachronous). The primary end point of ARCHES was radiographic progression-free survival (rPFS), and the study design allowed for previous lead-in docetaxel. The enzalutamide arm had significantly longer rPFS (HR, 0.39; 95% CI, 0.30 to 0.50; $P < .001$). In the final analysis after a median follow-up of 44.6 months, a significant OS benefit for ADT plus enzalutamide (HR, 0.66; 95% CI, 0.53 to 0.81; $P < .001$) was confirmed[11]—similar to effect size in ENZAMET. Apalutamide was evaluated in the TITAN trial, which compared ADT plus apalutamide with ADT alone with coprimary end points of radiographic PFS and OS.[36] High-volume disease comprised 62.7% of the cohort, and a small proportion of patients had received previous docetaxel (10.7%). At the first interim analysis, OS was superior in the apalutamide arm (HR, 0.67; 95% CI, 0.51 to 0.89; $P = .005$), and the frequency of high-grade adverse events was similar between treatment arms. Benefit was observed across subgroups, irrespective of timing or volume of metastatic disease. On the basis of these results, the study cohort was unblinded and crossover permitted. Despite 40% of placebo-treated men crossing over to apalutamide, the effect on OS persisted in long-term follow-up.[12]

ADT Plus Docetaxel Plus ARSI: Triplet Systemic Therapy

Identification of patients who benefit from highly intensified up-front systemic therapy is critical. This group of patients is hypothesized to be at risk of greatest symptom burden,

quicker progression to castration resistance, and early death. Moreover, curtailing potential toxicities (including personal financial and economic burden) of multiple therapies in patients unlikely to benefit from this approach is of high priority. There is ongoing debate regarding the role of so-called triplet systemic therapy (ADT plus docetaxel plus ARSI) for mHSPC, given the expanse of different agents in varying combination across the trials reported to date. There are several informative data sets to highlight (Table 1).

First, the role of darolutamide for mHSPC was tested in the ARASENS trial.[13] This randomized, phase III trial assigned 1,306 patients to darolutamide or placebo, both with a mandated backbone of ADT plus docetaxel for all—unique among reported mHSPC studies. Notably, disease volume was not a stratification factor, and most patients (86%) had synchronous metastatic disease. Addition of darolutamide led to significant improvement in OS (HR, 0.68; 95% CI, 0.57 to 0.80; $P < .001$) and similar benefits in prolonging time to pain progression, symptomatic skeletal events, and initiation of chemotherapy, compared with those receiving ADT plus docetaxel. In a post hoc analysis, adding darolutamide to docetaxel and TS clearly improved OS in patients with the high- but not low-volume disease (as defined by CHAARTED criteria) and clear evidence of benefit was seen in patients with high- and low-risk disease (as defined by LATITUDE criteria).[14]

Second, the European PEACE-1 trial evaluated the efficacy of adding abiraterone plus prednisone to ADT, with or without RT, for synchronous mHSPC using a 2 × 2 factorial design.[15] In a pooled analysis (because of noted noninteraction between abiraterone and RT), men who received abiraterone had significantly longer OS (HR, 0.82; 95.1% CI, 0.69 to 0.98; $P = .03$) compared with ADT control. Across all studies, the rate of high-grade adverse events was higher in abiraterone arms, with common toxicities of hypertension, hypokalemia, and mild transaminase rise.[15] A planned subgroup analysis of PEACE-1 showed significant prolongation of OS with abiraterone among 710 men who received ADT plus docetaxel (HR, 0.75; 95.1% CI, 0.59 to 0.95; $P = .017$). This effect was significant among men with high-volume disease within this subgroup (median OS: 5.14 years *v* 3.47 years, HR, 0.72; 95.1% CI, 0.55 to 0.95; $P = .019$); OS is immature for the low-volume comparison.[15]

Third, ENZAMET allowed for concurrent docetaxel (planned for 45% of patients at investigator discretion), and 85% of patients in the control arm received any subsequent therapy, including 76% who received abiraterone or enzalutamide on progression. A prespecified analysis showed evidence of a difference in OS favoring the enzalutamide arm in the subset of 362 men with synchronous metastatic disease planned for docetaxel (5-year OS: 60% *v* 52%, HR, 0.73; 95% CI, 0.55 to 0.99).[16] This was not evident in patients with metachronous disease planned for docetaxel (HR, 1.10; 95% CI, 0.65 to 186). Within the synchronous population planned for docetaxel, OS point estimates favored enzalutamide in both high- and low-volume subgroups. Curiously, examination of survival curves revealed higher OS rates in the first 30 months for participants receiving enzalutamide plus docetaxel plus TS versus those contemporaneously accrued to enzalutamide plus TS in the highest-risk subgroup (synchronous, high-volume), suggesting the need for early chemotherapy in rapidly lethal disease.

In summary, the collective data support the role of adding an ARSI to those initiating ADT plus docetaxel, particularly for patients with synchronous, high-volume metastatic disease. Further follow-up may more clearly elucidate the role of ADT plus docetaxel therapy in other clinical subgroups. Specifically, the benefit of adding docetaxel to a backbone of ADT plus ARSI is yet unknown; to our knowledge, no randomized trials have reported the outcomes of patients treated with ADT plus ARSI with or without docetaxel. However, exploratory analysis of ENZAMET does highlight the potential of this approach in high-risk subgroups who were chosen for docetaxel and have worse prostate cancer–specific survival.

Baseline Clinical Prognostic Factors

Clinical features at mHSPC diagnosis that associate with survival have largely centered on timing of metastatic disease and volume of disease. In the CHAARTED trial, men with metachronous and low-volume disease had the best prognosis, with a median OS of nearly 70 months with TS and TS plus docetaxel. This contrasted strongly with the synchronous, high-volume subgroup (median OS: 33-48 months) and those with one risk factor falling between those extremes[7]—a stratification also observed in a retrospective registry cohort with aligned definitions.[37] Post hoc analysis of the STAMPEDE-Docetaxel metastatic cohort confirmed the clear prognostic effect of disease volume.[8] IPD meta-analysis of GETUG-AFU 15, STAMPEDE-Docetaxel, and CHAARTED has highlighted, in aggregate, the favorable long-term outcomes of men with metachronous, low-volume disease (5-year OS: 73%) and no evidence of benefit in this group with the best prognosis.[29] The same subgroup has exceptional outcomes on ADT plus ARSIs as observed in the long-term follow-up of ENZAMET (ADT plus enzalutamide, 5-year OS: approximately 85%) versus 65% with TS plus weak NSAA.[16] An update of the STAMPEDE-Abiraterone M1 comparison by disease risk per LATITUDE criteria revealed that the low-risk subgroup (43% of patients) had an estimated 5-year OS of 72% when treated with ADT plus abiraterone.[38] Noting that 95% of participants in STAMPEDE and all patients on LATITUDE have synchronous metastasis, it is reasonable to expect similar outcomes for men with metachronous, low- and high-volume disease treated with abiraterone,[39] as those seen with novel AR inhibitors. This notion was demonstrated one

step earlier in the HSPC continuum in men with high-risk, lymph node–positive M0 prostate cancer treated with RT adjuvant TS plus abiraterone associated with improved OS compared with RT plus TS alone.[40]

DEINTENSIFICATION AND ADAPTIVE APPROACHES

Intermittent and Response-Adjusted Therapy

Many clinicians will have made the observation that there is a subset of patients receiving modern combination therapy, or even ADT alone, that achieve prolonged disease control. Their clinical course is marked by stability of disease symptoms and an undetectable PSA for years. The potential adverse impact of prolonged exposure to these ARSIs remains to be defined, but we do know that abiraterone can exacerbate heart failure and that enzalutamide and apalutamide should not be used with patients at risk for seizure and have been associated with increased falls in the elderly.[41] Indeed, the emergence of treatment-related toxicities may become the dominant clinical priority over time. How do we identify patients suitable for therapy deintensification?

Before the era of combination therapies for mHSPC, deintensification of ADT held a number of proposed benefits. First, progression to castration resistance is adaptive, and replacing androgen levels may therefore prolong the duration of androgen dependence and disease control with AR-directed therapy. Second, intermittent therapy could ameliorate QoL by minimizing adverse symptoms and insidious health effects of continuous castration. SWOG 9346 was a large phase III trial that randomly assigned men with mHSPC to continuous versus intermittent ADT if PSA <4 ng/mL was achieved after 7 months with coprimary end points of difference in QoL at 3 months and OS noninferiority between the arms.[42] After a median follow-up of nearly 10 years, intermittent therapy was not proven to be noninferior for OS, and survival was numerically longer in the continuous arm. Although intermittent therapy resulted in modest improvements in QoL, the lack of definitive OS noninferiority has scuttled widespread adoption of intermittent combined ADT, and clinical practice remains heterogeneous.

Given the apparent stratification of outcomes by baseline clinical factors, there has been increasing interest in identifying response-based end points that may guide not only prognosis but also the development of deintensification strategies for patients with favorable long-term outcomes. PSA is the most thoroughly investigated response end point in this context. SWOG 9346 demonstrated a stratification of outcomes by the level of absolute PSA (PSA ≤0.2 ng/mL, 0.2 ng/mL <PSA ≤4 ng/mL, or PSA >4 ng/mL) after 6-7 months of ADT alone, and a prolonged time to nadir has been associated with even shorter survival in mHSPC.[43-46] Similar stratification of OS by PSA ≤0.2 ng/mL at 7 months was seen in CHAARTED, and this effect remained significant in multivariable analysis adjusting for docetaxel exposure and disease volume.[47] Addition of docetaxel increased the likelihood of PSA suppression (achieved by 37% overall and in a predominately poor prognosis patient population). These data consequently suggest a role for therapy intensification for patients not reaching this PSA milestone on ADT plus docetaxel alone. Similar analyses have been performed in LATITUDE, with 40% of men receiving ADT plus abiraterone who achieved PSA ≤0.1 ng/mL compared with 6.5% on ADT alone.[48] PSA suppression at 6 months correlated with improved rPFS and OS. A preplanned analysis of PEACE-1 showed similar association of rPFS and OS with PSA value measured at 8 months.[49] In ARASENS, addition of darolutamide to ADT plus docetaxel led to a more than doubling of the proportion of patients achieving an undetectable PSA at 24 weeks and 36 weeks, and this correlated with improved OS using either time landmark.[50] In the TITAN trial, achievement of a PSA level of ≤0.2 ng/mL at landmark 3 months of apalutamide therapy was associated with a significantly longer OS (HR, 0.35; 95% CI, 0.25 to 0.48).[51]

Trials combining ADT with ARSIs have a continuous treatment paradigm, which holds several implications. Treatment-related toxicities, effects on health-related QoL, and long-term financial impact need to be considered carefully for all and weighed against efficacy of ARSIs across clinical subgroups—especially in low-volume, metachronous disease where a 90% 5-year prostate cancer–specific survival was noted with TS plus enzalutamide.[16] Moreover, the median OS of control arms across major phase III trials has been consistently improving in the past decade. The SWOG 1216 trial showed a median OS of 70 months in patients treated with ADT plus bicalutamide, twice the value reported in earlier SWOG trials for mHSPC with a similar proportion of patients with extensive disease (visceral metastases and/or presence of at least one bone metastasis beyond the vertebral bodies and pelvis).[52]

Landmark PSA response and other biomarkers may guide treatment de-escalation. The Alliance-sponsored A-DREAM trial (ClinicalTrials.gov identifier: NCT05241860) is a phase II adaptive study where patients receiving ADT plus an ARSI for mHSPC will undergo treatment interruption if PSA <0.2 ng/mL after 18-24 months. Recommencement of therapy will occur on PSA (≥5 ng/mL), radiographic, or clinical progression. The primary end point of the trial is the proportion of men who experience 18-month treatment-free interval (with eugonadal testosterone level) after treatment interruption. EORTC-2238 GUCG (De-Escalate) is a randomized pragmatic trial, sponsored by EORTC, in collaboration with the European Prostate Cancer patient coalition, Europa Uomo, revisiting the concept of intermittent ADT in patients achieving a PSA ≤0.2 ng/mL after 6-12 months of ADT and one of the ARSIs. The study end points include OS, time to next OS-prolonging treatment, health-related QoL,

and resource utilization. In the phase III LIBERTAS trial, men with mHSPC being treated with ADT plus apalutamide and achieving a PSA nadir of ≤0.2 ng/mL within the first 7 months of starting apalutamide will be randomly assigned to continuation of ADT plus apalutamide versus intermittent ADT plus apalutamide. End points include radiographic event-free rate and hot flash severity score and frequency. Novel antiandrogen monotherapy has been tested in an earlier disease setting—for example, enzalutamide without TS in the EMBARK trial (ClinicalTrials.gov identifier: NCT02319837) of biochemically recurrent prostate cancer. Historical data from antiandrogen monotherapy trials suggest lower rates of survival compared with TS.[53] The role of modern noncastrating therapies alone, however, remains undefined.

NOVEL BIOMARKERS AND PRECISION-INFORMED TREATMENT

The answer to guide a new era of therapy modulation and personalization in mHSPC may lie in biology and biomarkers. Much of our knowledge of the biology of mHSPC is derived from deep interrogation of the clinical bookend settings of prostate cancer—localized disease and mCRPC, respectively—over the past 30 years. Large-scale efforts, such as the Cancer Genome Atlas and Stand Up 2 Cancer-Prostate Cancer Foundation program, have provided insights into the genetic, genomic, and transcriptomic landscape of prostate cancer.[54-56]

Although there is a paucity of data to characterize mHSPC specifically, particularly for clinical correlation, recent genomic profiling studies have spurred the need for further investigation. Progression from localized prostate cancer to mCRPC is marked by enrichment of deleterious genomic alterations in the latter disease state. Tumor suppressor genes such *PTEN*, *TP53*, and *RB1* are frequently altered in mCRPC, so too genes that effect DNA damage and repair (*BRCA2*, *BRCA1*, *ATM*, and *FANCA*), PI3K signaling (*PIK3CA* and *AKT1*), chromatin remodeling (*KMT2C* and *KMT2D*), and, most frequently, the *AR*.[57-59] Retrospective data sets reveal that the frequency of such alterations appears to lie between localized prostate cancer and mCRPC, suggesting acquisition of deleterious alterations over time that confers cancer advantage in survival and treatment resistance.[60,61] Interestingly, significant enrichment of such tumor suppressor and *AR* alterations is observed in mCRPC relative to mHSPC (and not mHSPC relative to localized disease). Previous studies have further characterized the mHSPC genomic landscape by clinically relevant groups. High-volume mHSPC has evidence of greater genomic instability measured by global copy number burden and more frequent NOTCH pathway, cell cycle, and Wnt signaling alterations relative to low-volume disease, but no significant differences at an individual gene level.[62,63] Genomic alterations hold prognostic and predictive strength in mHSPC. Tumor sequencing from the STAMPEDE trial has demonstrated a relationship with increasing copy number burden and risk of progression and death in high- and low-volume disease.[64] Time to castration resistance is shorter with alterations in *AR*, *TP53*, *PTEN*, *RB1*, cell cycle, and *MYC* pathways.[61,65] *AR* aberrations detected in circulating tumor DNA (ctDNA) at baseline have been associated with shorter OS.[66] Conversely, *SPOP* mutations are associated with prolonged time to progression and death in patients treated with ARSIs (but not docetaxel) for mHSPC.[67,68]

Prognostic transcriptomic biomarkers are established in localized prostate cancer to the point of clinical implementation.[69,70] The role of such assays in advanced disease is not well-defined; however, recent RNA profiling of mHSPC suggests strong biomarker potential. Profiling of 160 patients from CHAARTED using the Decipher microarray platform was the first to comprehensively map the transcriptomic landscape of mHSPC.[71] Applying discrete signatures, marked differences were noted compared with localized prostate cancer with predominance of luminal B and basal subtypes (and <5% with luminal A), lower AR activity, and enrichment for high Decipher risk. When translated to outcomes, luminal B subtype was associated with poorer prognosis on ADT but significantly benefited from addition of docetaxel (and no significant benefit for docetaxel was seen in the basal subtype). Higher Decipher risk and lower AR activity were associated with shorter OS, and this effect remained significant despite adjusting for disease volume and metastatic timing. These data propose both prognostic and predictive roles for transcriptional subtyping in mHSPC. Comparative data from TITAN demonstrated similar enrichment of adverse-risk subtypes and their association with shorter rPFS. However, there was evidence of benefit for adding apalutamide to ADT across molecular subtypes.[72] Similar findings support the prognostic role of Decipher risk as reported in a STAMPEDE cohort treated with ADT with or without abiraterone.[73] The beneficial effect of abiraterone was noted across subtypes, mirroring the benefit of ARSIs across clinical subgroups (in contrast to docetaxel). Put together, transcriptomic profiling of mHSPC has revealed a molecular landscape skewed toward known aggressive and poor prognosis subtypes. Evidently transcriptomic subtyping can provide prognostic information independent of clinical factors. Its role as a predictive biomarker requires further development, validation, and aggregate analysis across data sets.

We are now getting closer to testing the potential benefits of biomarker-informed clinical trials of precision therapy for mHSPC (Table 2). The expansion of understanding personalized and targeted treatments in mCRPC is ripe for investigation in mHSPC, promising greater balance in the

TABLE 2. Selected Registration Phase III Trials in the Metastatic Hormone-Sensitive Prostate Cancer Setting

Trial	Phase	Target Enrollment	Inclusion Criteria	Previous Docetaxel Therapy in the Metastatic Hormone-Sensitive Setting	Intervention Arm	Control Arm	Primary End Point
PSMAddition (NCT04720157)	III	1,126	PSMA-positive disease on a ^{68}Ga-PSMA-11 PET/CT scan Treatment-naïve or up to 45 days of ADT before inclusion or up to 45 days of ARSI	Not allowed	^{177}Lu-PSMA-617 intravenously once every 6 weeks for six cycles plus standard of care (ADT plus ARSI)	Standard of care (ADT plus ARSI)	rPFS
AMPLITUDE (NCT04497844)	III	788	Positive for deleterious germline or somatic homologous recombination repair gene mutations Ongoing ADT Radiation with curative intent or previous treatment with PARPi not allowed Up to 6 months of ADT or 45 days of abiraterone acetate and prednisone allowed before random assignment	Allowed	Niraparib 200 mg orally once daily plus abiraterone acetate 1,000 mg orally once daily plus prednisone 5 mg orally once daily	Placebo plus abiraterone acetate 1,000 mg once daily plus prednisone 5 mg once daily	rPFS
TALAPRO-3 (NCT04821622)	III	550	Positive for deleterious germline or somatic homologous recombination repair gene mutations Ongoing ADT Previous docetaxel for mHSPC or previous treatment with a PARPi not allowed ≤3 months of ADT with or without ARSI for mHSPC allowed before random assignment	Not allowed	Talazoparib 0.5 mg orally once daily plus open-label enzalutamide 160 mg orally once daily	Placebo plus open-label enzalutamide 160 mg orally once daily	rPFS
CAPItello-281 (NCT04493853)	III	1,000	Synchronous mHSPC PTEN deficiency on tissue immunohistochemistry Ongoing ADT Previous surgery or radiation with curative intent not allowed	Not allowed within 3 weeks of first dose of study treatment	Capivasertib 400 mg orally twice daily (intermittent weekly dosing schedule) plus abiraterone acetate 1,000 mg orally once daily	Placebo plus abiraterone acetate 1,000 mg orally once daily	rPFS
CYCLONE-03 (NCT05288166)	III	900	High-risk mHSPC (≥4 bone metastases and/or ≥1 visceral metastasis) Ongoing ADT Previous systemic treatment for metastatic prostate cancer not allowed except ADT with or without ARSI up to 3 months before random assignment	Allowed	Abemaciclib plus abiraterone acetate plus prednisone	Placebo plus abiraterone acetate plus prednisone	rPFS
KEYNOTE-991 (NCT04191096)	III	1,232	Previous treatment with an ARSI or immune checkpoint inhibitor not allowed Ongoing ADT Up to six previous cycles of docetaxel allowed without evidence of progression Absence of a superscan bone scan	Allowed	Pembrolizumab 200 mg intravenously once every 3 weeks plus enzalutamide 160 mg orally once daily	Placebo plus enzalutamide 160 mg orally once daily	rPFS OS

Abbreviations: ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitor; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PARPi, poly (ADP-ribose) polymerase inhibitor; PET, positron emission tomography; PTEN, phosphatase and tensin homolog; rPFS, radiographic progression-free survival.

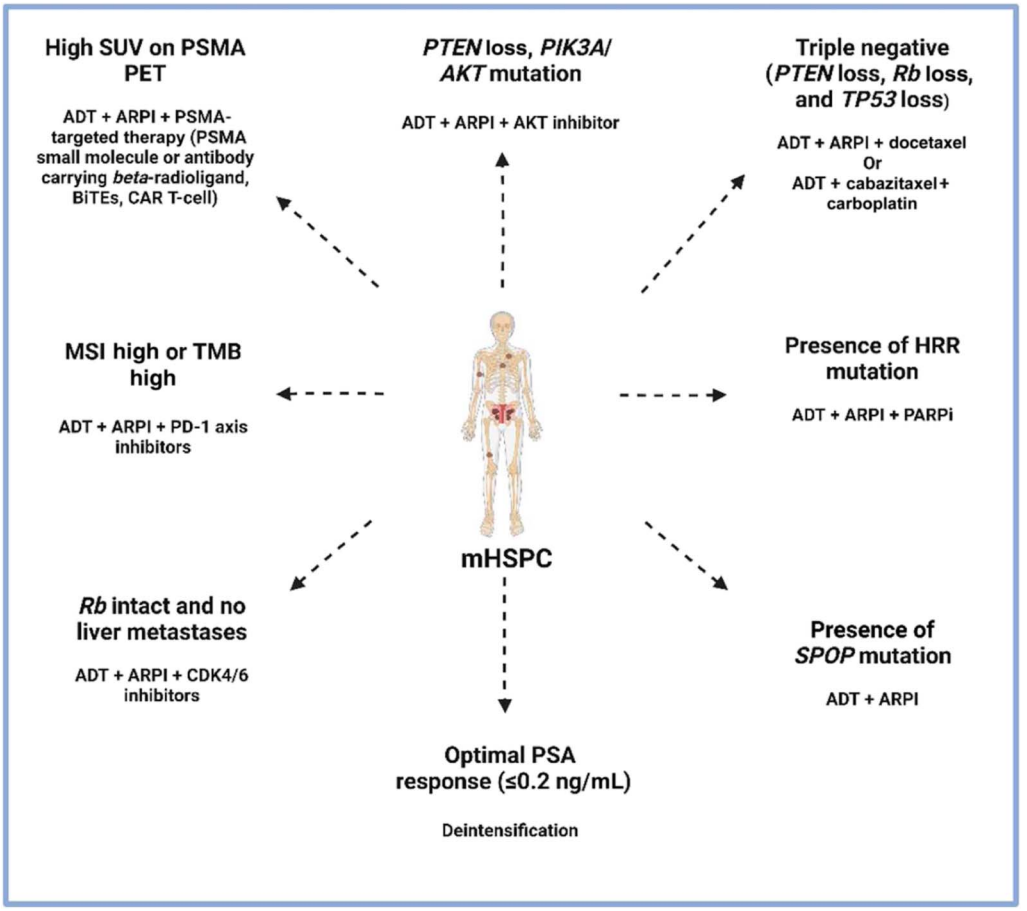

FIG 2. Potential precision therapy approaches in mHSPC. ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BiTEs, bispecific T-cell engager; CAR T cell, chimeric antigen receptor T cell; CDK4/6, cyclin D Kinase 4/6; HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer; MSI, microsatellite instability; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-1, programmed cell death protein 1; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; TMB, tumor mutational burden.

benefit to burden ratio of systemic therapies (Fig 2). The frequency of germline and somatic BRCA1/2 and homologous recombination–associated gene alterations in metastatic prostate cancer and the success of poly (ADP-ribose) polymerase (PARP) inhibitors in this context[74] have led to the development of numerous trials or PARP inhibitor combinations in mHSPC. Targeting frequent PI3K-Akt pathway alterations and cell cycle dysregulation in mCRPC[75,76] has spurred study in the hormone-sensitive setting, combining AKT inhibitors and CDK4/6 inhibitors with hormonal therapy, respectively. ^{177}Lu-PSMA-617 has received FDA approval for the treatment of mCRPC on the basis of significant activity[77] and OS improvement.[78] As a form of molecular-targeted therapy using novel PET imaging, ^{177}Lu-PSMA-617 holds promise in mHSPC because of the widespread expression of PSMA in hormone-sensitive disease. Trials combining ^{177}Lu-PSMA-617 with chemotherapy (eg, UpFrontPSMA, NCT04343885) or ARSI (eg, PSMAddition, NCT04720157) are ongoing. The rapid development of predictive biomarkers is directly influencing the design of future multiarm umbrella trials in mHSPC, guided by baseline and on-treatment molecular, PSA, and imaging characterization and other levels of individual data to define treatment strategies.

CONCLUSIONS

Rapid shifts in the paradigm and complexity of therapy for mHSPC in recent years have led to significant improvement in OS, especially notable for those with synchronous, high-volume disease associated with worse prognosis, converting mHSPC from imminently deadly to a disease with the ultimate goal of durable control. Contemporary data from mHSPC clinical trials highlight notable improvements in the prognosis of patients across the spectrum of risk, and these need to be adopted and realized in the real world. However, many unanswered questions remain. Men are living longer with metastatic prostate cancer, and it remains imperative that new treatment approaches promote personalization to increase patient benefit and decrease the unbalanced burden.

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Management of Prostate Cancer in Older Adults

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Overview

The majority of men with prostate cancer are diagnosed when they are older than 65 years; however, clinical trial participants are disproportionately younger and more fit than the real-world population treated in typical clinical practices. It is, therefore, unknown whether the optimal approach to prostate cancer treatment is the same for older men as it is for younger and/or more fit men. Short screening tools can be used to efficiently assess frailty, functional status, life expectancy, and treatment toxicity risk. These risk assessment tools allow for targeted interventions to increase a patient's reserve and improve treatment tolerance, potentially allowing more men to experience the benefit of the significant recent treatment advances in prostate cancer. Treatment plans should also take into consideration each patient's individual goals and values considered within their overall health and social context to reduce barriers to care. In this review, we will discuss evidence-based risk assessment and decision tools for older men with prostate cancer, highlight intervention strategies to improve treatment tolerance, and contextualize these tools within the current treatment landscape for prostate cancer.

INTRODUCTION

Prostate cancer predominantly affects older men. The median age of diagnosis is 66 years, and 60% of patients are diagnosed in men older than 65 years, with 20% being diagnosed in men older than 75 years.[1,2] Older patients and those with more comorbidities are not proportionally represented in clinical trials.[3-5] Therefore, despite the incidence of prostate cancer peaking in older age, it is not known whether older men derive the same benefit from the treatment strategies used in younger men. Given that older patients tend to have more medical comorbidities and less physical functional reserve (ie, the difference between a person's maximum physical capacity and the minimum necessary to perform daily functioning), they may benefit from tailored approaches to treatment.[6,7]

The first step in developing a tailored approach is to assess a patient's overall health status including a frailty assessment to most appropriately align treatment recommendations with each patient's goals and ability to tolerate treatment. Frailty is a state of vulnerability to external stressors, leading to poor health outcomes. Phenotypically, frail patients experience declines in multiple physiologic systems, resulting in decreased mobility, muscle strength, bone density, balance, motor processing, cognition, endurance, and physical activity. The biology of frailty is complex, with mechanisms spanning inflammation, loss of stem-cell regeneration, DNA damage, metabolic decline, hormone dysregulation, epigenetic changes, and loss of proteostasis.[8] The prevalence of frailty in patients with cancer is high—more than half of older patients with cancer are estimated to have either prefrailty or frailty.[9] One important contributor to frailty is a decrease in testosterone. An estimated 50%-80% of men older than 80 years have hypogonadism, which is associated with decreased muscle mass and bone density, as well as increased falls.[10] This is especially relevant to men with prostate cancer because treatment of advanced and metastatic disease is reliant on androgen deprivation therapy (ADT), which depletes testosterone and can accelerate frailty. In one cohort of prostate cancer survivors, those who had current or previous exposure to ADT were more than twice as likely to be classified as prefrail or frail (40%-43%) compared with those never exposed to ADT (15%).[11] Even short courses of ADT can result in sarcopenia, muscle weakness, declines in bone mineral density (BMD), fatigue, reduced activity levels, and falls.[10]

Identifying frailty or prefrailty in men with prostate cancer can allow the clinician to make decisions around whether to offer prostate cancer–directed therapy and to identify interventions that improve the patient's physical reserve. In the first part of this review, we discuss risk assessment and decision-making tools that can be used in the management of older men with prostate cancer. In conjunction with implementing these assessment tools in the oncology clinic, it is paramount to also have a plan in place for addressing the potential deficits identified. Studies have demonstrated the importance of having an intervention plan and have also shown the significant variation in the rate of interventions after completing a geriatric assessment (GA).[12] The second part of this review will discuss specific interventions that can reduce frailty and improve treatment tolerance in

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PRACTICAL APPLICATIONS

- Geriatric assessments allow for a standardized approach to the evaluation of older adults with the goal of improving informed decision making, acting on intervenable areas, and improving the ability to receive maximally tolerated cancer therapy.
- Clinicians should consider estimating non-cancer–related life expectancy for patients older than 65 years and consider performing geriatric screening with a brief geriatric screening tool, cognitive screening, and an estimate of chemotherapy toxicity with validated tools in patients planned to undergo cytotoxic chemotherapy.
- Before initiation of treatment for older men with prostate cancer, targeted interventions to reduce reversible aspects of frailty should be implemented.
- Universal bone health screening with dual-energy x-ray absorptiometry and selective use of bone antiresorptive therapies is critical in older patients beginning and continuing long-term androgen deprivation therapy.
- Decision making for older patients with prostate cancer should mirror other populations by incorporating patient's goals and values for care and quality of life and may need additional consideration of financial toxicity, social domains, and barriers to care because of the potential vulnerability in older age.

men with prostate cancer, highlighting evidence from prospective studies of interventions that may comprehensively address frailty among men with prostate cancer. The final section will discuss how to synthesize the use of assessment tools and interventions with recent treatment advances in prostate cancer while also considering the social determinants of health at play for each individual (Fig 1).

RISK ASSESSMENT AND DECISION TOOLS FOR OLDER MEN WITH PROSTATE CANCER

Relying on traditional indicators, such as the Eastern Cooperative Oncology Group performance status or Karnofsky performance status (KPS), to predict risk of adverse outcomes with cancer treatment is inadequate in an older adult population. Several studies have shown that these traditional tools are inaccurate assessments of functional status in older adults with cancer.[13-15] GAs provide a standardized approach to the evaluation of older adults to enable informed discussions with patients and caregivers. They also serve to identify reversible areas of frailty that may be intervened upon to improve a patient's ability to tolerate therapy. These assessment tools are not interventions in and of themselves, but rather can point the clinician to appropriate interventions. Understanding non-cancer–based life expectancy, screening for geriatric syndromes, and estimating toxicity associated with specific therapies, including chemotherapy, can improve outcomes for older adults with prostate cancer by ensuring that patients get the optimal balance of disease-directed treatment and support.

Life Expectancy Calculators

Life expectancy calculators are used to estimate non-cancer–based life span. This estimate can inform discussions around the expected risks and benefits of cancer treatment in relation to natural life expectancy. Given the significant heterogeneity in life expectancy among older adults, a validated life expectancy calculator that considers patient-specific factors may mitigate the risk of both over and undertreatment.

The Social Security Administration (SSA) releases actuarial life tables for the US population solely on the basis of age, which can be used to generate a rough life expectancy estimate on the basis of population statistics but does not include specific individual patient characteristics. In a study of 39,191 patients with localized prostate cancer, SSA life tables underestimated survival in patients undergoing brachytherapy, those with D'Amico low-risk disease, and those undergoing radical prostatectomy.[16] In a subset analysis of patients older than 75 years, the difference was even more pronounced.[16]

Other tools may give a more accurate estimate, although they have not been investigated specifically in the prostate cancer setting. Both the Lee Index and the Schonberg Index are well-validated tools for community-dwelling older adults that were created and validated from separate large US-based populations.[15,17-20] The website ePrognosis, produced by the University of California, San Francisco, contains an online calculator that synthesizes the inputs for both indices and produces separate estimates for each (ePrognosis[21]). These calculators account for age, sex, comorbid conditions, functional status, and lifestyle factors. In indices that have a variable for the presence of cancer, answering "no" will allow for an estimate of non-cancer–related life expectancy, which is relevant when trying to understand the overall benefit of cancer therapy. Machine learning–based prognostic calculators are being developed that may provide more accurate prognostic assessments using variables commonly found in the electronic health record.[22]

Geriatric Assessment

GA refers to assessing domains where older patients frequently have needs to characterize overall health status.

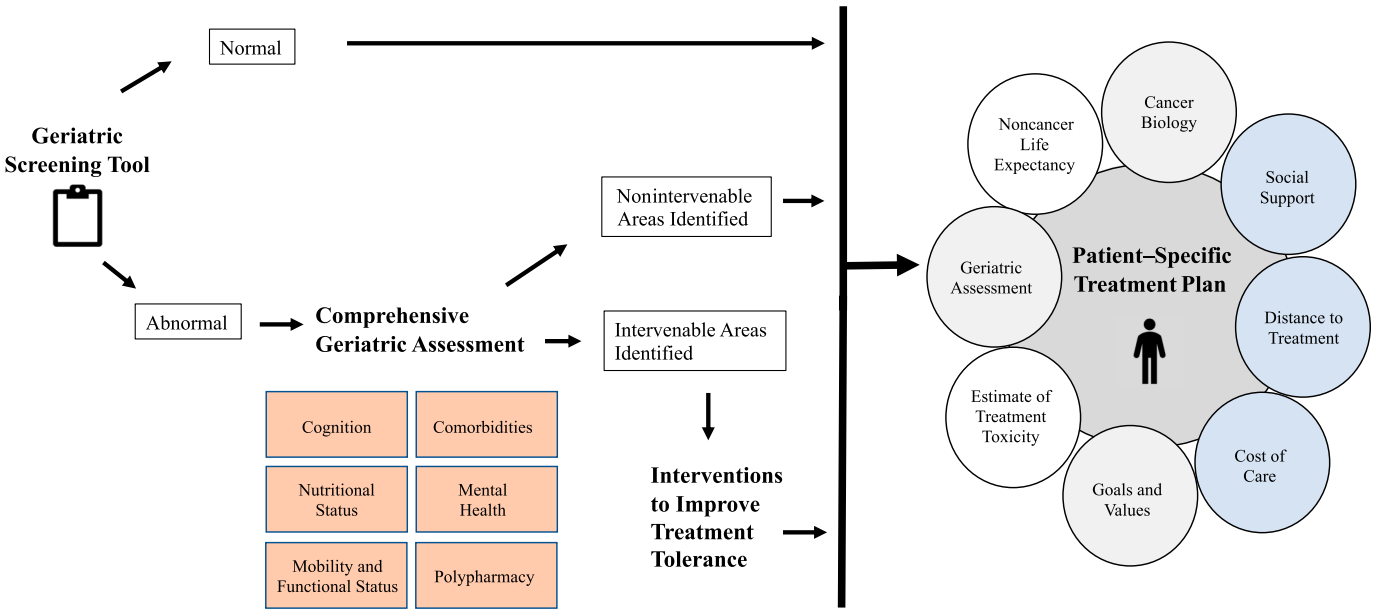

FIG 1. Patient-centered approach to the care of older men with prostate cancer.

The domains of the GA are functional status, mobility, cognition, nutritional status, mental health, comorbidities, polypharmacy, and social support.[23] The use of GA may improve outcomes of patients with prostate cancer by unearthing conditions that may affect cancer treatment tolerance, estimating frailty and resilience, and guiding the clinician by identifying areas in which interventions may be applied to maintain or improve function and quality of life by decreasing cancer treatment toxicity, increasing resilience, and improving communication.[15,23-26]

The areas of the GA can be assessed in several ways, including objective physical performance measures, validated instruments, and detailed history taking. No singular method has been shown to be superior to others, and the choice of how to obtain a GA should be based on the resources and structure of the specific clinical setting that they are being obtained.[23]

Several shorter screening tools are available that can be used to screen patients for those most likely to benefit from a complete GA. The use of a screening tool is more easily implemented than a comprehensive GA and can then focus resources on those in need of further in-depth assessment. The Geriatric 8 (G8) screening tool is validated and highly referenced in geriatric oncology.[27] This screening tool encompasses eight questions that take 4-5 minutes to complete and covers screening for food intake, weight loss, mobility, neuropsychological conditions, body mass index, polypharmacy, self-assessed health status, and age.[28] The G8 ranges from 0 to 17, with lower numbers associated with increasing frailty. In patients with cancer, scoring below 14 has an 85% sensitivity and 64% specificity for detecting frailty.[27] An alternative screening tool, the Vulnerable Elders Survey-13, has a higher specificity (70%-100%) but a lower sensitivity (20%-72%).[29] Either of these tools can be used to screen patients and refer those who are at risk of having an impairment for a complete GA. In one single-center prospective study of the G8 screening tool in 540 patients with localized and metastatic prostate cancer, G8 scores of $\leq$14 were observed in 70% of patients with metastatic disease, 36% of patients with localized disease undergoing radical prostatectomy, 57% of patients with localized disease being treated with radiotherapy, and 91% of patients with localized disease treated with ADT alone. In the metastatic population in that study, OS was significantly different between patients with G8 scores $\leq$13 and >13 (hormone-sensitive disease; P = .049) and between patients with G8 scores $\leq$12 and >12 (castrate-resistant disease; P = .022).[30] This suggests that G8 screening is feasible to administer and may have prognostic value in the prostate cancer population, as it does in other populations.[23]

The Mini-Cog is a validated assessment tool to screen for cognitive impairment. While the G8 contains a question about the presence or absence of dementia, the Mini-Cog provides an objective screen that encompasses three assessments and takes less than 3 minutes to complete. Patients are asked to register three words, then asked to draw a clock, and finally asked to recall the three words in step 1. In a large (nononcologic) population-based sample, the Mini-Cog had a 76% sensitivity and 89% specificity for

dementia.[31] The Mini-Cog is scored out of 5, and a score of 3 or less has been validated for dementia screening. A score of ≤3 suggests the need for a referral for more complete testing. The Mini-Cog is more sensitive and equally as specific for the detection of dementia and mild cognitive impairment as other dementia screening tools, including the Mini-Mental State Examination, which takes longer and is more affected by education level.[32,33] Identifying baseline cognitive impairment in men with prostate cancer allows clinicians to screen for reversible factors of decline (eg, nutritional deficiencies, alcohol use, mood disorders, and medication adverse effects) and enables an informed discussion of treatments risks, many of which have been associated with cognitive decline.[34] Cognitive impairment may also affect a patient's ability to understand treatment options and manage side effects and may prompt the clinician to increase the involvement of caregivers in treatment decisions and use other patient-specific tailored strategies to improve treatment tolerability.

Predicting Chemotherapy Toxicity

Specific tools have been developed to identify older patients at increased risk of chemotherapy toxicity and to quantify the risk of chemotherapy in these patients. This is relevant for older patients with prostate cancer, as docetaxel and cabazitaxel are cytotoxic chemotherapy agents that are frequently used in the treatment of metastatic prostate cancer.[35-37] The Cancer and Aging Research Group (CARG) toxicity tool uses 11 items, of which five are GA items. This tool has been shown to perform better at predicting chemotherapy toxicity than the KPS.[14,38] It is available for free online and takes approximately 5 minutes to complete (Cancer and Aging Research Group[39]).[15] Because it has predominantly been evaluated in terms of chemotherapy toxicity, future work defining the utility of the CARG toxicity tool in terms of predicting risks related to poly(ADP-ribose) polymerase (PARP) inhibitors, radiopharmaceuticals, and other novel approaches to treatment is necessary.

The chemotherapy risk assessment scale for high-age patients (CRASH) tool can also be used to predict chemotherapy toxicity. It has been validated for patients 70 years and older.[40] The CRASH tool takes longer than the CARG tool to complete, but can be considered a GA in and of itself.[15] The CRASH tool estimates the risk of grade 3 or higher hematologic toxicity as well as the risk of grade 3 or higher nonhematologic toxicity. The CRASH score is also available for free online (Senior Adult Oncology Program Tools[41]).

KNOWN AND NOVEL INTERVENTION STRATEGIES FOR OPTIMIZING TREATMENT TOLERANCE

Reducing Frailty in the Perioperative Setting

Radical prostatectomy has an important role in curative-intent treatment for men with localized prostate cancer. Numerous studies have shown that frailty is associated with increased risk of major postoperative complications for patients undergoing a wide range of surgical procedures. This holds true for frail patients treated with radical prostatectomy, who have higher rates of complications, longer length of stay, and higher rates of non-home discharge compared with their less frail counterparts.[42]

Two strategies have been used to mitigate frailty perioperatively: (1) prehabilitation to increase the patient's physiologic reserve preoperatively and (2) coupling formal frailty assessments with multidisciplinary management to tailor intraoperative and postoperative management. Prehabilitation, or enhancing a frail patient's physiologic reserve through physical therapy and nutritional optimization, has been shown to improve outcomes before some surgeries. In a systematic review of eight randomized controlled trials with 856 patients undergoing cardiac surgery, preoperative physical therapy reduced postoperative atelectasis, pneumonia, and length of hospital stay.[43] Unfortunately, to date, prehabilitation studies have not demonstrated similar clinical benefit in patients undergoing cancer surgery generally or urologic oncology surgeries specifically.[44,45] Further investigations are needed to define methods that optimize prehabilitation programs for patients undergoing radical prostatectomy.

Preoperative assessments of frailty predict postoperative outcomes and should be used in addition to surgical risk-assessment tools in risk-stratifying patients before surgery.[46] A growing body of evidence suggests that coupling formal frailty assessments with multidisciplinary management may improve mortality when used to guide intraoperative care. Hall et al evaluated 9,153 patients undergoing elective non-cardiac surgery who participated in a preoperative frailty screening initiative.[47] If a patient was identified as frail by Risk Analysis Index score ≥21 and confirmed on review from the chief of surgery or designee, clinicians from surgery, anesthesia, critical care, and palliative care were notified to potentially modify perioperative plans if indicated. One goal was to use shared decision making to clarify goals and expectations for the surgery and postoperative recovery. For instance, a diagnosis of frailty could change the decision to operate, the surgical approach, or the anesthetic plan. Palliative care consultation, when appropriate, could enhance discussions around ventilator dependence, dialysis, and do-not-resuscitate or do-not-intubate status. After implementation of this frailty screening initiative, among frail patients, 30-day mortality significantly improved (12.2% before implementation to 3.8% after implementation), as did 6-month mortality (24% to 7.7%) and 1-year mortality (34.5% to 11.7%). Further studies are warranted to understand whether a similar approach is beneficial for patients undergoing prostatectomy.

Reducing Frailty in Patients Receiving ADT

The primary definitive alternative to radical prostatectomy is radiotherapy, often administered with a prescribed course of

ADT. In the metastatic disease setting, ADT is generally administered continuously. ADT carries risks regardless of whether it is given for a finite period or indefinitely. In one study, prostate cancer survivors with a history of ADT exposure experienced nearly double the risk of falls.[11] Notably, this elevated fall risk was also seen in patients no longer receiving ADT, suggesting that even after cessation, the effects of ADT on frailty do not completely reverse. This may in part be explained by the link between ADT and sarcopenia—as lean body mass is lost, it may be difficult to rebuild after cessation of ADT.

More work is needed to develop interventions that reduce falls in patients receiving ADT. Nutritional optimization, exercise, and physical therapy are hypothesized to reduce the risk of falls, but as of now, there are no high-quality prospective trials. In a systematic review and meta-analysis of 33 randomized controlled trials of exercise interventions in patients with prostate cancer, exercise had a moderate-to-large effect on cardiovascular fitness and lower body strength; however, these trials did not specifically evaluate patients who were frail.[48] Ongoing trials, such as GET FIT Prostate, are specifically enrolling frail patients with prostate cancer who have either fallen in the past year or are at high risk of falling and assessing the use of supervised programs, such as strength training or Tai Ji Quan training.[49] If second generation androgen signaling inhibitor intensification is being considered in frail patients with high fall risk, abiraterone or daralutamide can be considered in lieu of apalutamide and enzalutamide. The latter two ARSIs cross the blood-brain barrier and are associated with elevated risk of fall and fracture.[50]

ADT can also result in obesity, impaired insulin sensitivity, and cardiovascular complications. Although specific guidelines have not yet been developed, all patients should be counseled on these complications and encouraged to maintain an active lifestyle and heart-healthy diet. In patients at especially high risk of atherosclerotic cardiovascular disease, luteinizing hormone-releasing hormone (LHRH) antagonists can be considered in lieu of LHRH agonists. The LHRH antagonists are hypothesized to have plaque-stabilizing effects, but the precise mechanism of the possible decreased risk of cardiovascular events compared with LHRH agonists has yet to be defined. In the phase 3 HERO trial, patients who received oral relugolix had a lower incidence of major adverse cardiovascular events at 2.9% in comparison with 6.2% in those treated with leuprolide (hazard ratio, 0.46; 95% CI, 0.24 to 0.88).[51]

Optimizing Bone Health in Older Patients Receiving ADT

In a study of 618 men with newly diagnosed prostate cancer, before ADT initiation, 41% met criteria for osteoporosis, 39% for osteopenia, and only 20% had normal BMD.[52] The presence of low BMD is associated with increased fragility fracture risk, which can contribute to decreased mobility, isolation, and loss of independence, particularly in an older adult population. This high prevalence of abnormal bone density at baseline is exacerbated by ADT use. Within the first year of ADT treatment, BMD decreases by approximately 2% at the hip and 3% at the lumbar spine and is associated with a 10%-20% risk of significant fracture at 5 years.[53,54] Pathologic and nonpathologic fractures are a major source of morbidity in men with prostate cancer and are correlated with poor survival outcomes.[55,56]

For men initiating ADT, bone health management with universal dual-energy X-ray absorptiometry (DXA) screening, adequate calcium (1,000-1,200 mg daily from food and supplements) and vitamin D3 (400-1,000 international units daily) intake, and selective administration of antiresorptive therapy should be implemented to reduce future fractures (Table 1).[57] In men with metastatic castrate-sensitive prostate cancer (mCSPC), guidelines recommend that bone antiresorptive therapy (denosumab, zoledronic acid, or alendronate) be reserved for men with either a history of fracture or high risk of future fracture. To define that risk, before receiving ADT, men with mCSPC should be screened with bone DXA scans to evaluate their BMD. Men with osteoporosis (BMD T-score ≤ -2.5) or high-risk osteopenia (BMD T-score between –1.0 and –2.5 and 10-year probability by fracture risk assessment tool of either hip fracture $\geq 3\%$ or major osteoporosis-related fracture $\geq 20\%$) are considered high-risk and should receive bone antiresorptive therapy.

Randomized trials have failed to show reductions in skeletal-related events (ie, pathologic fracture, palliative radiation to the bone, spinal cord compression, or surgery to the bone) when proactively administering antiresorptive therapy (eg, bisphosphonates or denosumab) to all men with mCSPC.[58-60] Even when analyses were restricted to patients who presented with bone metastases, zoledronic acid did not reduce skeletal-related events.[58] Overuse of antiresorptive therapy in mCSPC has been prevalent in recent years. In one real-world study, 18% of Medicare patients with mCSPC but without evidence of increased fracture risk received antiresorptive therapy, which confers a risk of side effects (eg, gastrointestinal irritation, hypocalcemia, or rarely, osteonecrosis of the jaw) and financial burden in a population that is unlikely to experience improved clinical outcomes.[57] Unfortunately, real-world use of DXA screening is also low—only 8% of Medicare patients with mHSPC initiating ADT receive baseline DXA screening.[61] Emerging technologies, such as biomechanical computed tomography (CT), a radiomic technique that measures BMD and bone strength from routine CT scans, may be used in the future to assess fracture risk without the need for DXA.[62] This approach would enable clinicians to define risk of fracture in all older adult patients who were staged by CT scans, allowing improved rates of bone density screening in a high-risk population without the burden of additional testing.

TABLE 1. Summary of Recommendations

Clinical Setting	Tools	Management Recommendations
All patients older than 75 years, consider for patients older than 65 years	Cancer-based assessment of prognosis Non-cancer–related life expectancy Social Security Administration life table Lee Index Schonberg Index ePrognosis GA screening Geriatric-8 screening tool (4-5 minutes) Vulnerable Elders Survey-13 (4-5 minutes)	Referral for comprehensive GA if any deficiencies seen on screening. Identify resources and targeted interventions needed to maintain independence Assess patient goals and values for care and quality of life Communicate options in the context of these factors
	Cognitive impairment assessment Mini-Cog (3 minutes)	Neuropsychiatric testing if possible dementia identified
	Financial toxicity assessment Financial screening question	Involve financial services if support is needed
Surgical resection	Frailty assessment Risk Analysis Index Score	Used to identify whether surgery is appropriate, and if so, what perioperative considerations should be made. Consider prehabilitation (physical therapy and nutritional optimization)
ADT	Bone health management DXA scan on initiation of ADT FRAX calculator	Indications for bone antiresorptive therapy along with vitamin D/calcium mCSPC and previous fracture, osteoporosis (BMD T-score ≤ -2.5), or high-risk osteopenia (BMD T-score between –1.0 and –2.5 and 10-year probability by FRAX of either hip fracture $\geq 3\%$ or major osteoporosis-related fracture $\geq 20\%$) mCRPC and bone metastasis
	Fall risk	Consider physical therapy referral and/or strength training Consider abiraterone or darolutamide in lieu of apalutamide or enzalutamide
	Cardiovascular health	Cardiovascular risk factor optimization Maintain an active lifestyle Heart-healthy diet Consider relugolix in lieu of LHRH agonists
Chemotherapy	Estimate chemotherapy toxicity CARG toxicity CRASH tool	Consider whether to use chemotherapy, adjust doses, and/or monitor more carefully

Abbreviations: ADT, androgen deprivation therapy; BMD, bone mineral density; CARG, Cancer and Aging Research Group; CRASH, chemotherapy risk assessment scale for high-age patients; DXA, dual-energy X-ray absorptiometry; FRAX, fracture risk assessment tool; GA, geriatric assessment; LHRH, luteinizing hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castrate-sensitive prostate cancer.

Improving Tolerance to Chemotherapy

In older patients for whom systemic chemotherapy is being considered, formal GA and multidisciplinary management should be used before initiation of therapy. The GAP70+ cluster randomized controlled trial included patients with cancer who were older than 70 years. Participants who had at least one impaired GA domain who received a tailored GA summary with management recommendations had lower rates of grade 3-5 adverse events (51% *v* 71%; relative risk [RR], 0.74; $P = .0001$) and fewer falls over 3 months compared with those with impairment who did not receive a tailored GA summary (12% *v* 21%; RR, 0.58; $P = .0035$).[63] Similarly, in the GAIN randomized controlled trial, patients who received a GA and multidisciplinary intervention had fewer grade ≥ 3 adverse events compared with participants who received GA alone (51% *v* 61%; $P = .02$).[24] In contrast, the 5C trial was a recent trial that failed to show the benefit of GA and management in patients older than 70 years receiving chemotherapy for cancer.[64] The authors speculated that this could have been because the intervention was conducted after chemotherapy was initiated (and thus was less likely to trigger changes in the plan) and the population was unselected (one-third of patients did not have any impaired frailty domain).

INTEGRATING ASSESSMENTS AND INTERVENTIONS FOR OLDER MEN WITH PROSTATE CANCER IN THE SETTING OF RECENT TREATMENT ADVANCES

Treatment of prostate cancer, particularly advanced prostate cancer, has dramatically changed in the past 10 years,

with more men receiving intensified treatment earlier in their disease course.[65] While these additional treatments significantly improve overall survival, they also have the potential for added toxicity over longer periods of time. Among the most relevant recent developments is the advent of earlier treatment intensification for mCSPC, with agents such as docetaxel chemotherapy with or without secondary hormonal agents as well as secondary hormonal agents alone.[65-71] In trials of secondary hormonal agents, the proportion of men who were 75 years or older ranged from 20% to 25%, and in the CHAARTED trial of early docetaxel chemotherapy, 22% of men were 70 years or older.[66-68,72] In addition, in certain patients with mCSPC, treatment of the primary tumor with definitive radiation can also improve overall survival.[73] In the metastatic castration-resistant prostate cancer (mCRPC) setting, multiple novel treatment strategies with unique side effect profiles are now used. PARP inhibitors are increasingly used alone or potentially in combination with secondary hormonal agents in patients with homologous recombination repair (HRR) mutations.[34,74] In addition, the prostate specific membrane antigen (PSMA)-targeted radionuclide therapy, ^{177}lutetium PSMA-617, has been approved for use in patients with PSMA positron emission tomography–positive disease, with ongoing trials looking at moving it earlier in the disease course.[75,76] Finally, trials continue exploring the role of additional agents in the curative setting, building on the evidence of the benefits of abiraterone/prednisone in addition to radiation therapy and ADT in men with very high-risk localized prostate cancer.[77]

Particularly for older men, clinicians must carefully weigh the benefits of treatment with systemic agents alone or in combination with the trade-offs in terms of side effects, functional status, and quality of life.[65,78,79] Careful attention to the points raised in this article will help clinicians navigate these clinical decisions and conversations with patients. In this section, we will describe specific clinical contexts in which geriatric approaches to evaluation and management can help support optimal clinical care for older men with prostate cancer.

Treatment Decision Making in the Context of Advanced Age

A key concept in the care of older men with prostate cancer is finding the optimal balance between overtreatment and undertreatment, particularly given competing risks of death from cardiovascular and other comorbidities, as well as overall frailty. On the other hand, for older men with prostate cancer in robust health, intensive treatment strategies may be warranted. In this setting, a GA may protect against age-related bias against treatment. Whether the question is that of overtreatment or undertreatment, the main goal for the clinician is to develop a holistic assessment of the patient's clinical and functional status beyond their chronologic age and understand how cancer therapy fits within that context and the patients' goals and values.

On the basis of the information presented in previous sections, we suggest a five-step approach to assessing older men with prostate cancer as they begin treatment.

1. Cancer-based assessment of prognosis (traditional cancer staging and treatment decision making).
2. Aging-based prognosis separate from cancer-based prognosis (ie, life expectancy calculators and geriatric screening tools).
3. Identification of resources needed to maintain independence using GA and targeted interventions.
4. Assessment of patients' goals and values for care and quality of life.
5. Communication about options with the patient and caregivers in the context of the above factors.

To illustrate decision making using this approach, several examples follow.

Metastatic Hormone-Sensitive Prostate Cancer: Early Intensification of Therapy

Case 1. A 72-year-old man with a history of coronary artery disease and coronary artery bypass grafting 2 years before presentation and insulin-dependent diabetes presented to the emergency department with severe back pain. Before his presentation, he was ambulatory and independent in all activities of daily living. Imaging demonstrated diffuse spinal metastatic disease and concern for cord compression. Prostate-specific antigen (PSA) was 1,500, and he was started on a LHRH antagonist in the hospital with significant symptomatic relief. He presented 1 month later for his first outpatient follow-up visit to discuss further treatment recommendations. He is no longer on pain medications and has recovered to his baseline level of functioning, and his PSA is 180 with castrate levels of testosterone.

On considering this patient's cancer-based assessment, he had high-volume metastatic disease, and in addition to being maintained on ADT, treatment intensification was warranted. With the advent of docetaxel chemotherapy and secondary hormonal agents in the mCSPC setting, doublet therapy is now the standard of care.[72,80] Recent data from the ARASENS and PEACE-1 trials suggest that clinicians should consider triplet therapy with ADT as well as both docetaxel and a second-generation androgen signaling inhibitor in patients with de novo and high-volume mCSPC. On the basis of cancer considerations alone, this patient merits consideration of the most aggressive treatment course possible given his dramatic presentation.[70,81]

However, assessment of this patient should consider his other comorbidities and functional status as well as his evolving health in the setting of already-initiated cancer treatment (ie, his dramatic improvement in symptoms and functional status with ADT alone). A post hoc analysis of the PEACE-1 trial demonstrates the importance of this. On

average, older (≥70 years) men derived less benefit from triplet therapy than younger (<70 years) men. However, older men who were fit enough to receive triplet therapy derived similar benefit compared with younger patients.[82]

His history of coronary artery disease and diabetes placed him at higher risk of treatment-related side effects both from chemotherapy and hormonal therapy. If chemotherapy is given, close attention to neuropathy, hyperglycemia (with steroid premedication), cytopenias, and infectious complications will help mitigate complications related to chemotherapy.

Geriatric screening and assessment may also identify other areas of need to help improve tolerance to this intense treatment strategy. Additional supports offered through oncology practices could include physical therapy and nutrition consultation. Social work resources and involvement of caregivers can ensure adequate resources at home, including food and transportation to treatment and follow-up visits. For patients with complex support symptoms or a poor prognosis requiring more intensive management, palliative care consultation is recommended.[83]

Unlike the paradigm for geriatric oncology in other cancer types, the possibility of durable, long-term response and preserved quality of life in older men with mCSPC make the discussion of the risks and benefits of treatment more complex. A focus on supporting patients through optimal treatment rather than avoiding treatments perceived as too toxic for older patients could be an important shift in mindset. In patients with less than 5-year survival for reasons other than their prostate cancer, an approach of ADT alone in the mCSPC setting can be reasonable and appropriate, particularly if patients are asymptomatic from their cancer and have lower volume disease. However, given evidence from multiple trials and real-world data sets of the relative tolerability of novel mCSPC treatment regimens, the population ineligible for intensification beyond ADT is expected to be extremely small.[65,84,85]

Essential to the management of patients is close monitoring for the side effects of ADT and secondary hormonal agents. Studies focused on other cancer types have shown the benefits of proactive symptom monitoring in patients with cancer receiving chemotherapy, and a reasonable degree of monitoring for toxicities of treatment is merited.[86,87] As discussed earlier, attention to bone density, obesity, sarcopenia, metabolic syndrome, and cognitive toxicities because of treatment is essential to ensuring good clinical outcomes for this population.[53,88,89]

Metastatic Castration-Resistant Prostate Cancer: The Promise of Targeted Therapy Balanced With Potential Toxicities

Case 2. An 86-year-old man with a history of chronic obstructive pulmonary disease and Gleason 8 prostate adenocarcinoma was treated 6 years ago with external beam radiotherapy and 2 years of ADT. Two years ago, he experienced a metastatic, asymptomatic recurrence to the pelvis and spine and was placed on continuous ADT intensified with apalutamide. His PSA nadir was nearly undetectable. Recently, he presented with a sharply rising PSA and innumerable new bone lesions throughout the axial and appendicular skeleton. He remains asymptomatic from his metastases, and he requires assistance for some activities of daily living because of arthritis and sarcopenia. He presents for initial treatment planning for mCRPC.

Primary treatment options for first-line mCRPC include docetaxel chemotherapy, sipuleucel-T, radium-223, and targeted treatments, such as PARP inhibitors and pembrolizumab. It is important to recognize that a subset of men with pathogenic mutations in HRR genes may benefit from PARP inhibitors, making germline and somatic genetic testing critical parts of understanding treatment options in mCRPC. Deciding between these options is dependent on the presence/absence of symptoms, likelihood of treatment toxicity, and overall assessment of the patient's ability to tolerate treatment. Men with mCRPC and osseous metastases should also receive bone antiresorptive therapy.

Frailty and performance status in mCRPC are challenging to assess because functional deficits could be related to age and comorbidities but also because of symptoms of cancer itself (eg, bone pain) or previous treatment toxicities (eg, neuropathy from previous docetaxel). In particular, in the mCRPC setting, patients are more likely to be symptomatic from their disease and experience more toxicities from treatment than patients with mCSPC. The conversation with patients about treatment options should balance estimates of life expectancy, expected toxicities, and patient goals and values. For instance, a conversation with this patient about his goals with therapy should focus on the potential trade-offs between length of life, quality of life, and prevention of symptomatic skeletal events, among other toxicities.

Addressing Social Determinants of Health

Health care disparities. There are well-documented health care disparities in men with prostate cancer from underrepresented minority backgrounds, including Black and Latino men. Differences exist in access and use of diagnostic, therapeutic, and supportive cancer care as well as differential cancer outcomes.[90-92] Persistent disparities in prostate cancer incidence and mortality have profound implications for ethnic minorities, with Black men, in particular, having almost a 50% higher incidence of prostate cancer compared with White men.[90-93] Although ADT and other novel therapies are effective treatments of prostate cancer, racial/ethnic minorities are still at increased risk of

prostate cancer-specific mortality.[92] Furthermore, Black and Hispanic/Latino men on ADT reported significantly lower quality of life (QOL) than White men, with about 20% lower uptake of health behaviors such as exercise accounting in part for up to 40% of this QOL difference.[33] However, there are more limited data on the outcomes of older men with minority backgrounds, and further studies on interventions to support this population are urgently needed.

Financial toxicity. Furthermore, discussions of intensification of therapy in older adults with prostate cancer need to incorporate an understanding of the financial costs of this additional therapy. Traditionally, ADT with leuprolide or other injectable medications is covered for most older adults through Medicare's Part A benefit. However, oral drugs are covered under Medicare's Part D prescription drug benefit. Patient financial responsibility for Part D medications is typically much higher than that for Part A medications.[94,95] While many oral medications for mCSPC and mCRPC have or will have patents expired and thus allow the production of cheaper generic versions, many of these drugs are exceedingly costly, to the tune of 10,000 dollars or more per month with patient access programs dwindling and discounted prices less and less available.[96] Asking patients about their cost concerns and involving financial services to support with more specific financial questions can help ensure that patients have access to and stay on optimal treatment.

CONCLUSION

Robust evidence suggests that the use of GA and other assessment tools can improve prognostication and risk stratification, can improve patient-centered and caregiver-centered communication, and can improve tailoring of care to an individual treatment to both avoid undertreatment but also excess toxicity.[23] Although guidelines vary on the age threshold to define an older adult, we suggest that for patients older than 65 years, the following assessments may be considered: (1) estimate of non-cancer–related life expectancy, (2) geriatric screening such as G8 or Vulnerable Elders-13 with referral for complete GA if possible deficits are identified, (3) Mini-Cog with referral for neuropsychiatric testing if possible dementia is identified, and (4) estimate of chemotherapy toxicity with either the CARG or CRASH tools in patients who are planned for cytotoxic chemotherapy. Older adults with prostate cancer have many integrated domains that may require consideration or intervention when treating a cancer. Special attention should be paid to optimizing bone health and reducing frailty to increase tolerance to both ADT and chemotherapy. In addition, this patient population is quite heterogeneous and may require a combination of consideration of their health data and social determinants of health. Many older adults have fixed income, have transportation barriers, require social support for clinic visits, and thus may need a socially conscious approach to their care inclusive of many of the tools we have listed above.

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Genetic and Genomic Testing for Prostate Cancer: Beyond DNA Repair

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overview

Significant progress has been made in genetic and genomic testing for prostate cancer across the disease spectrum. Molecular profiling is increasingly relevant for routine clinical management, fueled in part by advancements in testing technology and integration of biomarkers into clinical trials. In metastatic prostate cancer, defects in DNA damage response genes are now established predictors of benefit to US Food and Drug Administration–approved poly (ADP-ribose) polymerase inhibitors and immune checkpoint inhibitors, and trials are actively investigating these and other targeted treatment strategies in earlier disease states. Excitingly, opportunities for molecularly informed management beyond DNA damage response genes are also maturing. Germline genetic variants (eg, *BRCA2* or *MSH2/6*) and polygenic germline risk scores are being investigated to inform cancer screening and active surveillance in at-risk carriers. RNA expression tests have recently gained traction in localized prostate cancer, enabling patient risk stratification and tailored treatment intensification via radiotherapy and/or androgen deprivation therapy for localized or salvage treatment. Finally, emerging minimally invasive circulating tumor DNA technology promises to enhance biomarker testing in advanced disease pending additional methodological and clinical validation. Collectively, genetic and genomic tests are rapidly becoming indispensable tools for informing the optimal clinical management of prostate cancer.

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INTRODUCTION

Prostate cancer management has undergone substantial transformation within the past decade. Genetic and genomic testing has rapidly matured from a research tool to standard practice across multiple clinical settings, with importance reinforced via inclusion in key practice guidelines. Opportunities for genomic testing in routine practice are continually being refined and expanded, cultivating excitement about precision oncology among patients and prostate cancer health care providers. However, this sea change also emphasizes the importance of having a solid foundational understanding of the data to support clinical practice changes. End users must be aware of testing nuances and potential pitfalls, which transect not only clinical decision making but also patient education and medical resource stewardship. Here, we review key updates in genetic and genomic testing for prostate cancer, including clinical implications of testing for advanced disease, the role of RNA expression tests with emphasis on localized and recurrent disease, and emerging opportunities for minimally invasive plasma circulating tumor DNA (ctDNA) technology to affect the clinical management of advanced prostate cancer.

CLINICAL AND THERAPEUTIC IMPLICATIONS OF GENETIC AND GENOMIC TESTING IN PROSTATE CANCER

Implications of germline genetic testing (ie, testing for inherited alterations) and genomic testing (ie, testing a tumor for somatic and germline alterations) have precipitated major practice changes in the care of patients with prostate cancer, particularly in advanced disease. These changes were heralded by a series of key discoveries beginning in 2015. First, The Cancer Genome Atlas Research Network evaluated 333 primary prostate cancers and found that 19% harbored mutations in DNA repair genes.[1] This was followed up by a Stand Up to Cancer/Prostate Cancer Foundation/American Association for Cancer Research–lead effort sequencing 150 metastatic tissue biopsies collected from patients with castration-resistant disease, revealing that 23% had alterations in DNA repair pathway genes—most commonly within genes *BRCA2*, *ATM*, and *BRCA1*.[2] Shortly thereafter, another pioneering study reported that approximately one in 10 patients with metastatic prostate cancer carried a heritable (ie, germline) mutation in a DNA repair gene.[3] These and subsequent confirmatory studies[4-8] have demonstrated that the DNA damage response pathways—particularly homologous recombination repair (HRR) and mismatch repair—are recurrently altered in a large subset of patients and can drive aggressive prostate cancer biology. Clinically, DNA damage response alterations can confer therapeutic sensitivity to novel targeted agents and potentially constitute life-saving information in the context of navigating familial cancer risk.

DNA Damage Response Defects as Prognostic Biomarkers

Patients with prostate cancer who carry germline *BRCA* mutations are more likely to have poor clinical

PRACTICAL APPLICATIONS

- Defects in DNA damage response genes (eg, *BRCA1/2*, *ATM*, *MSH2/6*) are prevalent in approximately 15%-25% of patients with metastatic prostate cancer and confer treatment candidacy for poly (ADP-ribose) polymerase inhibitors and immune checkpoint inhibitors.
- Germline *BRCA2* pathogenic variants are linked to elevated risk of prostate cancer and have implications for intensified early cancer screening and familial risk management. Polygenic risk scores are poised to improve risk evaluation in future.
- RNA expression tests (using prostate tissue) can help inform treatment options for patients with localized disease, including decisions surrounding definitive local treatment and salvage therapy.
- Minimally invasive circulating tumor DNA (ctDNA) tests are used to identify treatment-predictive and prognostic biomarkers in advanced prostate cancer. Newer generations of tests are rapidly augmenting the biological resolution that can be gleaned from ctDNA but require further clinical validation.

outcomes, intraductal and cribriform morphology, and higher Gleason grades compared with their non-*BRCA* carrying counterparts.[9,10] Moreover, evidence suggests that *BRCA2*-defective localized prostate cancers have singularly aggressive biology resembling treatment-refractory metastatic disease. This is evidenced by greater genomic instability and increased (epi)genomic dysregulation of the WNT-pathway mediator complex (ie, *MED12L*/*MED12*) in *BRCA2*-defective localized disease, which are common molecular hallmarks of castration-resistant prostate cancer.[11]

The link between germline *BRCA1/2*-defective disease and clinical aggression is also supported by studies from Castro et al, who observed that germline *BRCA1/2* mutation carriers were more likely to have Gleason score $\geq$8 (P = .00003), T3/T4 stage (P = .003), nodal involvement (P = .00005), and metastases at initial prostate cancer diagnosis (P = .005). Germline *BRCA1/2* carriers also had shorter prostate cancer–specific survival (CSS)[12] and metastasis-free survival (MFS) after curative intent therapy: *BRCA1/2* carriers (n = 67) had 3-, 5-, and 10-year MFS rates of 90%, 72%, and 50%, compared with 90%, 94%, and 84% for non-*BRCA1/2* patients ($P < .001$), respectively.[13] Multivariable analysis incorporating standard clinical risk metrics for localized disease demonstrated that *BRCA1/2* mutations were independently prognostic for MFS (hazard ratio [HR], 2.36; 95% CI, 1.38 to 4.03; P = .002) and CSS (HR, 2.17; 95% CI, 1.16 to 4.07; P = .016).[13] Finally, a retrospective analysis of the Consortium of Investigators of Modifiers of BRCA1/2 cohort of 6,902 men reported an elevated prostate cancer risk for patients with germline pathogenic variants in *BRCA1/2*, affirming the relevance of germline *BRCA1/2* status for familial risk management.[14]

DNA Damage Response Defects as Biomarkers for Response to Poly (ADP-ribose) Polymerase Inhibitors

Recognition of DNA damage response defects as a core molecular driver of metastatic prostate cancer led to multiple clinical trials therapeutically exploiting these defects. Poly (ADP-ribose) polymerase inhibitors (PARPi) are a key targeted drug class developed initially in the context of breast and ovarian cancer. One of the first trials of PARPi in metastatic prostate cancer was the single-arm, phase II, TOPARP-A study, where patients with alterations in DNA damage response genes *BRCA2*, *ATM*, and *BRCA1* achieved significantly higher response rates to olaparib than biomarker-negative patients.[15] This observation fueled several important PARPi studies culminating in US Food and Drug Administration (FDA) approvals for patients with metastatic castration-resistant prostate cancer (mCRPC). The phase III PROfound study enrolled patients with mCRPC harboring DNA repair alterations who had progressed on at least one AR-pathway inhibitor (ARPI) and randomly assigned them to olaparib versus a second ARPI.[16] Patients in the olaparib arm had improved progression-free survival and overall survival,[16,17] leading to olaparib being the first FDA-approved PARPi for prostate cancer in 2020. The strongest signal was seen in patients with *BRCA1*, *BRCA2*, and *ATM* mutations, although rarer DNA repair gene alterations in *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* are also included within the approval label. In the same year, the phase II TRITON2 study of rucaparib showed a 51% radiographic response rate for docetaxel-refractory patients with *BRCA1/2*-altered mCRPC,[18] leading to FDA-accelerated approval. Recently, multiple phase III studies have investigated the combination of PARPi plus ARPI for mCRPC,[19-21] consistently showing the greatest magnitude of PARPi benefit in patients whose tumors have germline or somatic DNA damage response defects. Several clinical-genomic registries are underway exploring novel biomarkers of PARPi response, including the PROMISE germline-focused registry (NCT04995198)[22] and the PRECISION PARPi-focused registry.[23]

Germline (ie, Inherited) DNA Damage Response Defects as Cancer Risk Genes

Given the relatively high prevalence of germline cancer risk genes and their growing significance in both familial and

therapeutic contexts, the National Comprehensive Cancer Network (NCCN) Prostate Cancer and American Urological Association/American Society for Therapeutic Radiology and Oncology/Society of Urologic Oncology Advanced Prostate Cancer guidelines advise genetic counseling and genetic testing for patients with metastatic or high-risk localized prostate cancer.[24-26] Identification of germline cancer risk genes in patients enables blood relatives to learn if they share the same cancer risk gene and could potentially benefit from cancer screening and/or risk-reducing and prevention options.

There are recognized and established early detection and risk-reducing options to mitigate breast and ovarian cancer risk, but the implications for male carriers of *BRCA1/2* and other prostate cancer risk genes are less widely recognized. On the basis of the associations of increased prostate cancer risk and aggressiveness overviewed above—as well as findings from the ongoing international United Kingdom–led Identification of Men with a Genetic Predisposition to Prostate Cancer study—there is a strong rationale for offering men with germline *BRCA2*, *BRCA1*, *MSH2*, and *MSH6* mutations intensified prostate cancer screening.[27,28] NCCN Prostate Cancer early detection guidelines currently recommend consideration of family history, Black ancestry and familial cancer risk genes (such as *BRCA2*) in prostate cancer screening decisions, and advise initiating screening at age 40 years for *BRCA2* carriers. Additional trials exploring screening and early detection are ongoing at the National Cancer Institute (ClinicalTrials.gov identifier: NCT03805919), Yale (ClinicalTrials.gov identifier: NCT02154672), University of Michigan, Israel (ClinicalTrials.gov identifier: NCT02053805), Sunnybrook (ClinicalTrials.gov identifier: NCT01990521), and University of Washington/Fred Hutch (ClinicalTrials.gov identifier: NCT04472338) and are expected to help clarify screening/interventional strategies for at-risk carriers.

In the foreseeable future, it is likely that further incorporation of genetic risk into screening optimization will occur across at least two domains. The first domain is refining risk prediction beyond the rare variants in genes such as *BRCA2*, *BRCA1*, *MSH2*, *MSH6*, and *HOXB13*. This combined approach involves simultaneously evaluating rare but higher penetrance genes (eg, *BRCA2*) together with more common but lower-risk variants (so-called polygenic risk scores), as recently reported.[29,30] This combined approach is promising due to its potentially broader applicability but will require additional study and validation in larger diverse populations.[31] The second domain is improving cancer early detection methods beyond prostate-specific antigen (PSA) and current imaging modalities. Excitingly, early cancer detection is a highly active research area precipitating advancements in novel DNA, transcription, methylation, and other genomic profiling technologies. These methodological developments will be reviewed (mostly in the context of biomarker profiling for advanced disease) in the section on ctDNA technology below. Overall, enhanced genetic risk prediction together with increasingly sensitive prostate cancer screening tools is positioned to help reduce prostate cancer–related mortality and morbidity.

Implementation of Germline Genetic Testing

Recommendations for germline genetic testing have recently expanded across the prostate cancer continuum. Testing is now standard practice for all patients with metastatic prostate cancer plus a significant fraction of patients with localized disease (eg, those with high-risk features and/or family history). An important challenge in prostate cancer management is determining how to optimally integrate cancer genetics care, which has been reviewed in a previous ASCO Education session.[32-34] However, broader implementation challenges exist, and consensus recommendations have been made to guide further development.[35] Increasing demand for genetic counseling and testing—coupled to existing accessibility barriers (eg, geographic constraints on in-person services)—has led to bottlenecks in testing, treatment decision making, and familial risk planning. Deficiencies in timely and accessible genetic testing have incentivized a number of experimental practical alternatives to traditional testing models. Efforts to broaden access and alleviate overburdened genetic specialists include the use of online patient video education, as well as reallocating responsibilities of consenting, testing, and/or counseling to oncology professionals (ie, "mainstreaming").[36] These and other novel germline genetic testing paradigms are being investigated prospectively (eg, GENTLeMEN,[37] ProGen,[38] and TARGET studies[39]). Nevertheless at present, collaboration with genetic experts remains crucial when a cancer risk gene is discovered, ensuring that patients and their families receive appropriate education[35] and access to relevant cancer prevention and screening services.

WHAT PROVIDERS NEED TO KNOW ABOUT PROSTATE CANCER RNA EXPRESSION AND HOW IT INFLUENCES MANAGEMENT DECISIONS

The D'Amico/NCCN Risk groups remain the dominant strategy to risk-stratify clinically localized prostate cancer. However, over the past several years, information about prostate cancer RNA expression has substantially augmented our ability to predict patient outcomes and has become an important tool in decision making for many patients with prostate cancer.

Most published literature focuses on the Decipher Genomic Classifier (GC). The Decipher GC uses the Affymetrix Human Exome 1.0st array and is based on a locked model of 22 genes, including genes relevant to cell proliferation, cell motility, cell differentiation, androgen receptor signaling, and immune modulation. This model was originally

developed to determine the risk of distant metastasis from radical prostatectomy (RP) specimens, and subsequently, a biopsy version of the test has been demonstrated to be prognostic after surveillance, surgery, or radiation.[40] Two other commonly used tests are the Myriad Prolaris test, based on 31 cell-cycle progression (CCP) genes,[41] and the Oncotype DX Genomic Prostate Score (GPS) that evaluates 17 genes including 12 cancer-related genes (androgen signaling, cellular organization, stromal response, and cellular proliferation) and five housekeeping genes.[42] Here, we review the clinical utility of these RNA expression-based GCs in different prostate cancer disease states.

Selecting Patients for Active Surveillance Versus Treatment

Each of the three GCs has shown some utility in identifying low-risk or favorable intermediate-risk patients at risk of progression while on active surveillance or patients who may harbor occult high-grade or stage disease. Therefore, these classifiers are useful for patients who may be borderline between definitive treatment and active surveillance as candidate management options.

Herlemann et al[43] reviewed 220 patients with favorable intermediate-risk prostate cancer who underwent RP and found that the Decipher GC independently predicted adverse pathology (defined as Gleason Grade Group 3-5, pT3b or higher, or N+ disease) with an odds ratio of 1.34 per 0.1 unit increased GC ($P = .002$). Interestingly, patients with GC low or intermediate (ie, <0.6) did not have an increased odds of adverse pathology compared with a population with exclusively very low- or low-risk prostate cancer, suggesting that patients with GC low/intermediate may be reasonable candidates for active surveillance.

Cuzick et al[44] showed in a cohort of 349 patients diagnosed by needle biopsy and managed conservatively that the Prolaris CCP score was the strongest independent predictor of death from prostate cancer (HR per one unit increase, 1.65 [CI, 1.31 to 2.09]; $P = .00003$). The 17-Gene Oncotype DX GPS score was shown to predict adverse pathology and increased risk of biochemical recurrence after RP among men who were initially on active surveillance.[45] Conversely, Lin et al[46] notably evaluated the performance of the GPS score in the Canary Prostate Cancer Active Surveillance Study cohort and did not find a significant independent association of higher GPS score with adverse pathology. In addition, there was no identified association between higher GPS score and subsequent biopsy upgrading in surveilled patients with low-risk prostate cancer who subsequently underwent prostatectomy.

Use of Androgen Deprivation Therapy with Radiation for Intermediate-Risk Prostate Cancer

All three classifiers can potentially help decide if patients with intermediate-risk prostate cancer should receive definitive radiation alone or with androgen deprivation therapy (ADT). Berlin et al[47] found that among a cohort of both favorable and unfavorable intermediate-risk patients managed with radiation alone, the Decipher GC predicted biochemical recurrence and metastasis, whereas the NCCN risk group was not predictive. This suggested that patients with high GC scores may warrant consideration for the addition of ADT to definitive radiation. This approach is being tested prospectively in the NRG-GU-010 trial (ClinicalTrials.gov identifier: NCT05050084) that aims to either intensify or deintensify therapy based on the Decipher GC score.

Tward et al[48] found among 741 patients treated with radiation that the Cell-Cycle Risk score (comprised by combining the Myriad CCP score with the UCSF CAPRA score) identified patients who benefited from ADT (ie, if they scored above the multimodality threshold of 2.112) versus had no benefit from ADT (ie, if they scored below the threshold of 2.112, where the 10-year risk of metastasis was 3.7%, regardless of ADT use). In a small study of 30 patients with Gleason 3 + 4 prostate cancer, GPS was associated with a higher percentage of Gleason pattern 4 at surgery, leading the authors to conclude that GPS may help inform the addition of ADT to radiation.[49]

Prognostication in High-Risk Disease

The role of GCs in changing treatment decisions for high-risk prostate cancer is less firmly established but can still offer prognostic information. A recent example is the Decipher GC was found to be prognostic for outcomes in three RTOG phase III trials.[50] This finding forms the basis for the NRG-GU-009/PREDICT-RT randomized trial that aims to determine whether the Decipher GC can identify patients whose ADT duration can be reduced from 24 to 12 months versus patients who may benefit from up-front treatment intensification with 24 months of ADT plus apalutamide (ClinicalTrials.gov identifier: NCT04513717).

Postprostatectomy Setting: Salvage Radiotherapy Alone Versus Salvage Radiotherapy + ADT

One of the most commonly used classifiers in the postoperative setting is the Decipher GC, which may inform whether to offer ADT with salvage radiation. While gonadotropin-releasing hormone agonists have been shown to improve metastasis-free survival when added to salvage radiation in both the GETUG-16[51] and RADICALS-HD trials,[52] the RTOG 96-01 trial[53] remains particularly influential because it showed that radiotherapy (RT) plus 2 years of ADT in the form of bicalutamide monotherapy 150 mg daily improved overall survival. A post hoc analysis of the RTOG 96-01 trial found that all the survival benefit of ADT was driven by patients with PSA $\geq$ 0.7, while patients with a PSA $<$ 0.7 did not benefit, causing reluctance among some providers to offer ADT with salvage radiation for patients with PSA $<$ 0.7.[54] However, in a reanalysis of the RTOG 96-01 trial, Feng et al[55] leveraged the

GC score to provide practical guidance on whether to add ADT to RT for patients with PSA < 0.7. This study showed that among patients with PSA < 0.7, those with a low GC score (<0.45) had worse overall survival with bicalutamide. However, patients with intermediate (≥0.45) or high (>0.6) GC score had better outcomes with bicalutamide, including less distant metastasis, reduced prostate cancer mortality, and better overall survival. Consequently, the Decipher GC score may help identify which patients with PSA < 0.7 (for whom salvage radiation is planned) would benefit from concomitant ADT.

Another GC that has shown promise in the post-prostatectomy setting is the PAM-50 classifier, which was adapted from breast cancer and recreated in a cohort of patients with prostate cancer who had the Decipher GC test. Prostate cancer samples can be classified into luminal and basal subtypes using the same Affymetrix Human Exome 1.0st array as the Decipher GC. Zhao et al[56] found that patients with tumors classified as luminal B benefited more from the addition of postoperative ADT than patients with nonluminal B tumor subtypes. The PAM-50 classifier is being tested prospectively in the NRG-GU-006 randomized trial of salvage radiation plus apalutamide or placebo for patients with rising postoperative PSA (ClinicalTrials.gov identifier: NCT03371719).

Androgen Signaling Inhibitor Benefit in Castrate-Resistant Prostate Cancer

The same PAM-50 classifier may also help prioritize choice of systemic treatment for patients with castration-resistant disease. Feng et al[57] observed that patients with non-metastatic castration-resistant disease and luminal tumor subtype are more likely to benefit from ADT plus apalutamide than ADT alone. In the mCRPC setting, Aggarwal et al[58] demonstrated a link between luminal subtype and biological features suggesting heightened androgen signaling, translating clinically to greater ARPI benefit for patients with luminal tumors versus other subtypes. Ultimately, PAM-50 classification may inform on the degree of tumor androgen reliance and facilitate appropriately tailored treatment.

In summary, RNA expression profiling for genomic classification has enhanced prostate cancer risk stratification in early disease, further broadening the repertoire of genomically informed management strategies across the prostate cancer continuum.

HOW CAN TECHNOLOGY HELP US? NEW AND EMERGING USES FOR ctDNA IN PROSTATE CANCER

As aforementioned, genomic biomarkers are increasingly used for clinical decision making in mCRPC, but challenges of tissue analysis impede integration of biomarkers into routine practice. Routine metastatic tissue biopsy is hampered by financial and health toxicity and high failure rates (16%-40%), especially for bone lesions.[59-61] In addition, archival tissues can be difficult to retrieve, exhausted by previous molecular profiling,[59,62] and may ultimately no longer molecularly reflect contemporaneous mCRPC shaped by often years of previous systemic therapy.[2,4]

Plasma ctDNA is an established minimally invasive source of predictive and prognostic biomarkers, overcoming many of the limitations of tissue-only testing.[63] High concordance of genomic alterations between metastatic tissue and ctDNA[64] plus comparative ease of collection has spurred incorporation of ctDNA profiling into mCRPC clinical trials, including recent pivotal trials of PARPi,[16,19,20,65] PI3K inhibitors,[66,67] and umbrella/platform trials that leverage profiling results for treatment arm assignment.[68-71] Finally, ctDNA testing can democratize access to precision oncology since blood samples can be drawn outside specialized cancer centers and mailed for centralized testing.[72]

Applications for ctDNA testing can be broadly categorized into quantification (ie, detection of ctDNA) or characterization (ie, identifying molecular biomarkers in ctDNA). Detection of ctDNA in mCRPC has prognostic implications across clinical scenarios. For example, high pretreatment ctDNA fraction (ie, the proportion of total cell-free DNA [cfDNA] that is tumor-derived rather than from other sources) is linked to poor treatment response, shorter progression-free survival, and abbreviated overall survival across multiple therapeutic contexts and independent of other established clinical prognostic markers.[73-81] The dynamics of the ctDNA fraction during treatment is a potential surrogate for treatment response, with the magnitude of ctDNA decline (relative to pretreatment levels) associating with time to progression on both taxanes and ARPIs.[74,76] Strikingly, changes in ctDNA fraction may be more informative than on-treatment PSA changes as an early metric of tumor response.

Characterization-based applications include using ctDNA to detect clinically relevant biomarkers, such as truncating defects in *BRCA2* that predict vulnerability to PARPi, as well as mutations in *TP53*, *RB1*, *SPOP*, *PTEN*, and *AR* that may inform prognosis and/or androgen dependency.[78,82] *AR* alterations are an acquired resistance mechanism to AR/androgen-axis drugs with prognostic and potentially predictive relevance but can only be detected in treatment-exposed ctDNA or metastatic tissue (ie, are not present in primary tissue).[1,80,83]

Importantly, ctDNA fraction largely determines which classes of alteration are amenable to de novo detection. Copy number variants (CNVs) require severalfold higher ctDNA fraction compared with mutations and in general detection sensitivity (for all alteration classes) scales with ctDNA fraction.[84] Low ctDNA fraction can therefore lead to

false-negative results, especially for deletions such as homozygous *BRCA2* or *PTEN* loss. Importantly, some testing platforms do not analyze matched white blood cell controls, potentially resulting in incomplete filtration of clonal hematopoietic variants which can manifest as false-positive ctDNA mutations.[85] It is therefore ideal to perform synchronous tissue and ctDNA testing to mitigate the limitations of each approach.

Beyond Targeted Panel Sequencing: The Promise of Broader DNA Profiling From Liquid Biopsies

Presently, clinical ctDNA tests typically use targeted panel sequencing: profiling of dozens to hundreds of cancer-related genes in parallel. Most ctDNA tests only capture coding exons, although some tests include introns implicated in recurrent oncogenic fusions. Targeted panel sequencing assays have high sensitivity for single-nucleotide variants (SNVs) and small insertions/deletions (InDels), moderate sensitivity for gene-level copy number changes (eg, *PTEN* deletions), and low sensitivity for complex structural rearrangements and large aneuploidies. Cost feasibility forces a practical tradeoff between sequencing depth (ie, redundant read coverage across target regions) and breadth (ie, number of genes or regions examined). However, diminishing sequencing costs are enabling broader sequencing methods such as whole-exome sequencing (WES) and whole-genome sequencing (WGS) to become cost permissive and clinically feasible at scale.

In contrast to targeted panel sequencing, WES enables detection of SNVs, InDels, and gene-level copy number changes across approximately 20,000 genes, while WGS extends detection to noncoding territory (eg, introns, enhancers, intergenic regions, and other types of regions). Growing data indicate that tumor defects in noncoding areas can drive aggressive cancer biology. Notable examples include *AR* enhancer copy gains[86,87] and genomic rearrangements with intronic breakpoints in *RB1*, *PTEN*, *BRCA2*, and *MSH2/6*.[5,7,88-91] Current clinical assays typically cannot detect these biologically relevant truncating rearrangements (due to not profiling introns), but newer iterations of broader tests will enable their detection in future. Finally, a key advantage of WES/WGS is enhanced resolution for whole-genome doubling (WGD). In prostate cancer, WGD is potentially linked to poorer prognosis and can confound accurate discrimination of homozygous from heterozygous deletions (in key genes such as *PTEN* and *BRCA2*).[92,93]

Tumor cell characteristics and clinical phenotypes are shaped by the totality of somatic and germline defects across the genome. Intriguingly, alterations in genes such as *BRCA2* and *MSH2/6* are associated with genome-wide scars whose quantification may be an alternative biomarker measuring the biological consequences of the gene alteration. WES and WGS enable synthesis of second-order information from all mutations, deletions, and structural rearrangements analyzed in aggregate, overcoming many challenges of detecting alterations within individual genes. These challenges include imperfect detection (eg, poor sensitivity for CNVs in low ctDNA fraction), difficulty of predicting alteration pathogenicity and/or likelihood of sensitization to targeted drugs, and inability to characterize nonsequence mechanisms of gene (in)activation (eg, epigenomic alterations).

Higher-order genomic readouts of emerging clinical relevance in mCRPC include tumor mutation burden, microsatellite instability, and CDK12-associated tandem duplications as predictors of immunotherapy response[91,94,95]; indices of overall genomic instability (eg, large-scale transitions, telomeric imbalance, genomic loss of heterozygosity) suggestive of HRR deficiency and PARPi candidacy[5,96-98]; and mutational signatures that reveal mutation etiologies (eg, tobacco exposure).[99] Sophisticated machine learning techniques (eg, gradient tree boosting) can optimally combine many higher-order genomic features for even more accurate identification of patients likely to benefit from targeted therapy.[100-103] These tools promise to help discover new single-gene and combinatorial genomic mediators of HRR/mismatch-repair deficiency, as well as characterize rare HRR gene defects (eg, *ATM*, *BARD1*, *RAD51* family genes) whose biomarker utility is currently uncertain.

Emerging Techniques for Tumor Phenotyping Using ctDNA

DNA alterations are the blueprint for cell phenotype, but regulation of the epigenome, transcriptome, and proteome also affect tumor behavior. New omic techniques are rapidly expanding the phenotype information that can be measured from ctDNA.

Neuroendocrine prostate cancer (NEPC) is a key clinically relevant phenotype in mCRPC but can be difficult to diagnose. Clinical presentation of NEPC can be heterogeneous, and classical NEPC features are often nonspecific (eg, low PSA),[104] metastatic tissue biopsies for definitive histopathological diagnosis are not always feasible and may not generalize to bulk disease, and known genomic correlates of NEPC (eg, *TP53*/*RB1* loss) are also nonspecific[105,106] and technically challenging to detect.[7,88] Treatment-related NEPC transdifferentiation is an increasingly prevalent clinical trajectory in mCRPC, ostensibly because of the growing cumulative exposure to AR-axis drugs across the spectrum of disease (eg, ARPI for castration-sensitive prostate cancer).[107-114] Therefore, there is mounting urgency to develop more accurate tools to detect treatment-induced NEPC and facilitate timely clinical intervention.

Epigenomic markers (eg, 5-methylcytosine and 5-hydroxymethylcytosine) are promising tools for tumor phenotyping.[115] ctDNA methylation assays can augment

biomarker characterization and classify samples according to global epigenomic features. Methylation assays can distinguish AR-driven mCRPC from NEPC, outperforming traditional DNA-sequencing approaches even in low ctDNA fraction.[116-119] Clinically, ctDNA methylation assays may assess tumor AR dependence, informing timing of treatment change as well as treatment choice (eg, ARPIs versus taxanes or platinum chemotherapy in tumors with low AR signaling). Methylation-based phenotypic subgroups beyond classical NEPC (AR–/neuroendocrine [NE]+)—such as amphicrine (NE+/AR+) and double-negative (NE–/AR–) states[120]—may also be linked to potential therapeutic vulnerabilities (eg, WNT-pathway activation).[106,114,121] Currently, methylation assays are only commercially available for early cancer detection.[122] Standardization and prospective validation are needed to define the role of methylation tests in the management of advanced prostate cancer.

Dying tumor cells release chromatin into the bloodstream as fragmented cfDNA and nucleosomes, which can be analyzed to gain insight into tumor transcriptional activity, gene regulation, and transcription factor binding patterns.[123-129] Fragmentomics is a promising new area that exploits the physical properties of ctDNA to inform tissue of origin and tumor phenotype. In mCRPC, fragmentomic features have been correlated with patient-matched metastatic tissue RNA abundance,[125] as well as AR- and NE-associated transcription factor activity.[123] In a recent article by De Sarkar et al, global fragment features were used to generate a model that classifies prostate cancers along a spectrum of AR- versus NE-driven disease, achieving 90.4% sensitivity (for predicting NEPC) and 97.5% specificity (for predicting AR-driven mCRPC).[128,129] Analogous to methylation-based assays, fragmentomic approaches are being investigated for early cancer detection.[130,131] Chromatin immunoprecipitation and sequencing of cell-free nucleosomes (cfChIP-seq) is another new method that retrieves DNA linked to epigenetically decorated nucleosomes, enabling multiplexed insight into gene regulation and global cell identity.[127] Overall, these experimental techniques are poised to augment the repertoire of ctDNA phenotyping approaches, with methylation techniques most analytically mature for potential clinical use in mCRPC.

Plasma cfDNA includes both DNA from tumor (ctDNA) and from noncancerous normal cells, yet this normal fraction is not currently used for oncology applications. Intriguingly, methylation sequencing and cfChIP-seq can potentially reveal clinically relevant information from normal cfDNA. Normal cfDNA primarily comes from hematopoietic cells, raising the possibility of characterizing immune activity and/or immune-related adverse events.[132] Other cell types can release cfDNA during specific host states, potentially offering measures of organ-specific treatment toxicities (eg, gastrointestinal adverse events) as well as noncancer comorbidities (eg, cardiac dysfunction) that complicate optimal oncological care.[127]

Ultimately, new sequencing and computational techniques that integrate genotype and phenotype are facilitating increasingly multimodal clinical profiling.

CONCLUSIONS

Over the past decade, detailed molecular dissection of thousands of prostate cancer specimens has ushered in a new era of genomics-informed personalized clinical management. DNA biomarkers have become critical tools for informing routine clinical practice, particularly in metastatic disease where FDA-approved PARPi and immune checkpoint inhibitors are available for patients with DNA damage response defects. Genetic and genomic testing is also transforming management for early-stage prostate cancer. Applications include leveraging genetic risk scores for cancer prevention and family risk management and RNA expression tests for navigating options for definitive local therapy and salvage treatment for localized disease. Finally, ctDNA testing has become a recognized minimally invasive tool for biomarker profiling in advanced prostate cancer, and technological advancements for ctDNA tumor phenotyping are continuing to broaden its potential clinical applicability.

A perennial challenge for biomarker-informed care will be balancing clinical pragmatism (eg, dichotomizing patients into easily actionable subgroups) against the risk of oversimplifying complex tumor biology. In the future, multimodal genomic profiling approaches (eg, incorporating DNA, RNA, methylation, and histone markers) will offer increasingly nuanced biological insight, while new machine learning techniques are poised to harmonize this information and streamline clinical decision making. Ongoing education of healthcare practitioners on genomic tools (and their limitations), shifting management practices, and clinical evidence to support decision making will be increasingly critical to ensure caregivers are informed on how to incorporate molecular testing into their daily practice.

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Developing Sustainable Cancer and Aging Programs

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overview

Geriatric assessment (GA) has been shown to decrease toxicity from systemic therapy, improve completion of chemotherapy, and reduce hospitalizations in older adults with cancer. Given the aging of the cancer population, this has the potential to have a positive impact on the care of a large swath of patients seen. Despite endorsement by several international societies, including the American Society of Clinical Oncology, uptake of GA has been low. Lack of knowledge, time, and resources has been cited as reasons for this. Although challenges to developing and implementing a cancer and aging program vary depending on the health care context, GA is adaptable to every health care context from low- to high-resource settings, as well as those in which geriatric oncology is a well-established or just emerging field. We provide an approach for clinicians and administrators to develop, implement, and sustain aging and cancer programs in a doable and sustainable way.

INTRODUCTION

Older adults comprise an ever increasing proportion of those diagnosed with cancer, with aging constituting a driving force for the expected rise in cancer incidence.[1] Demographic shifts because of aging of the American and global populations[2,3] and an increase in the survivorship of older adults with cancer because of more effective therapeutics[4] have led to a dramatic increase in the need for resources and education to meet the needs of this group. The unique challenges that older adults may face when diagnosed with cancer, such as digital literacy and social isolation that were exacerbated by the COVID pandemic, have heightened the health care community's awareness of these special needs.

Management of older adults with cancer is more complex than in their younger counterparts. Older adults become more heterogeneous with aging, with differences in overall health, function, social circumstances, and values and preferences.[5,6] The impact of treatment toxicity for older patients can also be more significant. Although older adults on clinical studies tolerate treatments similarly to their younger counterparts,[7,8] overall older adults are underrepresented in clinical studies, and those included in clinical studies tend to be fitter with less comorbidities than those seen in clinical practice.[9-13] This leads to uncertainty about how best to manage older patients with cancer and results in older adults being less likely to be offered systemic therapy because of concerns about their ability to tolerate treatment.[14,15] Although studies targeting older, and particularly less fit, patients should ideally be conducted to help clinicians and patients make better decisions, geriatric assessment (GA) can help better characterize the health of older adults, predict for treatment toxicity, and improve treatment tolerance.

GA is a multidimensional process including a detailed assessment of an older adult, including physical, functional, and psychosocial aspects of health, to help better determine an older adult's fitness, identify and address impairments, and help improve decision making and management.[16] Domains of a GA include comorbidities, medications, functional status, cognition, nutrition, psychological status, and social supports. A number of randomized clinical studies have shown that GA-directed care can improve outcomes for older adults receiving systemic therapy including decreasing the rates of moderate-to-severe toxicity from chemotherapy and improving completion of chemotherapy.[17-19]

The 2018 American Society of Clinical Oncology (ASCO) Guideline recommends a GA for all adults older than 65 years who are being considered for chemotherapy[20] to assure that shared decision-making conversations are taking place to meet the needs of the individual patient and caregiver. Despite endorsement by multiple international societies, including ASCO, it remains underutilized. Among the respondents to a survey by the ASCO Older Adults Taskforce, who were mostly US academic-based oncologists, only 21% reported using a multidimensional GA as part of the standard care of the older patient with cancer.[21] Similarly, among a group of community-based oncologists, 13% reported using a GA for all their older patients with only 7% using it to inform chemotherapy dose.[22] Most older adults with cancer receiving

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PRACTICAL APPLICATIONS

- Geriatric assessment (GA) can help better characterize a patient's overall health, identify impairments, help decision making, and improve patient tolerance of systemic therapy
- GA is adaptable to a variety of health care contexts. Several different models exist to deliver geriatric oncology care (primary geriatric oncologist, consultative, and embedded with oncologic team), and the ideal model depends on local resources.
- Steps in developing a proposal for a cancer and aging program include engaging and making a case to stakeholders, choosing a model of delivery of geriatric oncology care, and making a business case. Messaging should align with priorities of stakeholders, including clinicians, leadership, and administrators.

systemic therapy and surgery, therefore, do not benefit from the known benefits of GA.

Challenges to implementation of GA include lack of knowledge about the assessment and lack of time and resources.[21] Although initiatives to educate health care providers about GA are ongoing, a key step in translating knowledge gained from research into improvement in clinical care is tackling implementation. This includes understanding both logistics of running a clinic but also developing effective strategies to acquire the resources needed to support the running of a geriatric oncology clinic. Developing a business plan and model to persuade stakeholders, particularly those in charge of monies and resources, is not a skill most health care providers are well trained to do. This article seeks to provide health care providers with the tools to develop a business proposal to support the development and ongoing sustainability of a geriatric oncology service.

BENEFITS OF GERIATRIC ASSESSMENT IN THE ONCOLOGIC SETTING

Although the value of GA has long been accepted by geriatricians, its benefits in the oncologic setting have more recently been demonstrated by multiple randomized clinical trials (Table 1). In patients receiving systemic therapy, GA and management have been shown to decrease moderate-to-severe toxicity,[18,19] increase the likelihood of completing chemotherapy,[17] and decrease hospitalizations[25] compared with usual oncologic care. GA and management may also result in improved quality of life (QOL) for patients.[17,25] In patients undergoing surgery, one study of patients older than 65 years treated for gastrointestinal malignancies suggested a decrease in hospital stay and admission to intensive care in patients who received GA and management.[27] No differences in postoperative mortality, rehospitalization rates, postoperative QOL, or function, however, were seen.[27,28] The rationale for building programs specifically to address the needs of older adults with cancer is thus based on well-established and validated data.

MODELS OF CARE

There are many different methods in which care for older adults with cancer can be delivered. Depending on resources, GA can be adapted to each health care context. There are three main models in which geriatric oncology care can be delivered: primary geriatric oncologist centered, consultative models, and embedded models of care.[29,30]

In the primary geriatric oncologist model of care, older adults with cancer are seen by a physician trained in both oncology and geriatrics. The geriatric oncologist is typically supported by a multidisciplinary team including nurses, pharmacists, dieticians, and physiotherapists. In this model of care, the geriatric oncologist develops a management plan for the older patient, taking into account both oncologic factors and data from the GA. This plan includes both an oncologic plan and management of impairments identified by the GA. Advantages of this model include patient recommendations on the basis of a thorough synthesis of both oncologic and geriatric data. Furthermore, the care is managed by one physician and team so that care delivery is seamless. Unfortunately, the number of dually trained geriatric oncologists is low, particularly relative to the ever-growing population of older adults with cancer, limiting the deployment of this model in most centers.

A consultative model is a common method of delivering care to older adults with cancer. In this model, patients are cared for by the primary oncologic team and referred to the geriatrics or geriatric oncology team for further assessment and management. The consultative team assesses and makes recommendations to the primary oncology team and/or primary care provider. These recommendations can range from management of identified impairments from the GA to suggestions about oncologic management (such as up-front dose reduction, dose escalation, and best supportive care). A consultative model may be more feasible for some centers, particularly if it can use existing geriatric-based services. Compared with a primary geriatric oncology model, a consultative model is also able to see and affect significantly more patients. Disadvantages of a consultative model include potential delays in decision making particularly if there is significant demand for the consultative services. In some cases, the GA may have limited impact on the oncologic decision making, if patients are not seen by the consultative team in a timely manner.[31]

TABLE 1. Randomized Studies on GA in Older Adults With Cancer

Study	Population/Setting	Intervention	Outcomes
Systemic therapy studies			
ESOGIA study[24] N = 494	Age: 70+ years ECOG PS: 0-2 Stage IV NSCLC First-line chemotherapy	All patients had a GA (no specific interventions mandated) Allocation of treatment (doublet, single agent, or BSC) either on the basis of combination of age/PS (standard arm) or results of GA	Standard arm: 35.1% carboplatin doublet 64.9% docetaxel GA arm: 45.7% carboplatin doublet 31.3% docetaxel 23% BSC No difference in treatment failure-free survival (3.2 *v* 3.1 months, $P = .32$) or PFS (3.7 *v* 3.4 months, $P = .59$) More frequent treatment discontinuation because of toxicity in the standard arm (11.8% *v* 4.8%, $P = .007$) No difference in OS (6.4 *v* 6.1 months, $P = .87$) Adverse effects higher in the standard arm (93.4% *v* 85.6%, $P = .015$), but no difference in grade 3+ adverse effects QOL in GA arm was higher but only significant at 36 weeks
GAP-70[19] N = 718	Age: 70+ years At least 1 impairment in GA (excluding polypharmacy) Stage III/IV cancer Starting a new chemotherapy regimen Community oncology practices	GA performed in all patients Randomly assigned to summary of GA-based recommendations *v* no summary	Decreased grade 3+ chemotherapy toxicity (50% *v* 71%, $P < .01$) in the GA-directed arm *v* usual care No difference in 6-month OS (71% *v* 74%, $P = .33$)
GAIN[18] N = 600	Age: 65+ years Solid tumor Starting chemotherapy	GA performed in all patients GA-directed care and implementation of interventions *v* summary provided but no interventions offered	Decreased grade 3+ chemotherapy toxicity in the GA-directed arm *v* usual care (50.5% *v* 60.4%, $P = .02$)
INTEGERATE[25] N = 154	Age: 70+ years Solid tumor or DLBCL New line of therapy (any systemic therapy including targeted or immunotherapy)	GA-directed care and follow-up *v* usual care	Improved QOL at 12, 18, and 24 weeks Decreased hospitalizations (incidence rate ratio 0.59, $P < .001$) and ER visits (incidence rate ratio 0.61, $P = .007$) *v* usual care No difference in 6-month OS
GERICO study[17] N = 142	Age: 70+ years Colorectal cancer Adjuvant chemotherapy or first-line palliative chemotherapy	GA-based intervention *v* usual care	Increased rates of chemotherapy completion (45% *v* 28%, $P = .04$) in the GA arm *v* control No difference in severe chemotherapy toxicities (28% *v* 29%, $P = .16$) No difference in rates of chemotherapy discontinuation because of toxicity (20% *v* 30%, $P = .17$) Improved QOL in domains of mobility and burden of illness No difference in rates of hospitalization (30% *v* 32%, $P = .86$)

(Continued on following page)

TABLE 1. Randomized Studies on GA in Older Adults With Cancer (Continued)

Study	Population/Setting	Intervention	Outcomes
5C study[26] N = 350	Age: 70+ years New line of systemic treatment (first or second line, included targeted and immunotherapy) Estimated life expectancy of at least 6 months, ECOG PS: 0-2	Baseline GA plus monthly phone calls × 6 months *v* usual care	No difference in QOL between arms No difference in function (as measured by IADL dependence)
Surgical studies			
Qian study[27] N = 160	Age: 65+ years Surgery for gastrointestinal malignancy	GA and interventions with preoperative and in-hospital involvement of geriatric team *v* usual care	Per-protocol analysis: Shorter hospital stay (5.9 *v* 8.2 days, $P = .02$) Less ICU admission (13.3% *v* 32.4%, $P = .049$) No difference in readmissions at 90 days (16.7% *v* 25%, $P = .36$) No differences in intention-to-treat analyses seen No differences in patient-reported QOL or depression 60 days postoperative. Slightly less moderate to severe symptoms reported in the GA arm.
Hempenius study[28] N = 260	Age: 65+ years Elective surgery for solid tumor Groningen Frailty Indicator score of 3+ (frail)	Preoperative GA, individualized treatment plan, and daily visits during hospital stay *v* usual care	No difference in mortality No difference in rehospitalization No difference at 3 months posthospital discharge in function (as measured by ADL), return to independent living situation, use of supportive care, cognitive functioning No difference in QOL 3 months postdischarge

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Abbreviations: BSC, best supportive care; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; ER, emergency room; GA, geriatric assessment; ICU, intensive care unit; NSCLC, non–small-cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; QOL, quality of life.

Finally, some models of care use a geriatrician, nurse practitioner, or physician assistant, with expertise in geriatrics or geriatric oncology, who works within the primary oncologic team. This person will often administer and summarize the results of the GA making recommendations to the treating oncologist. An embedded model of care allows the integration of GA directly into the oncology treatment plan. This person has expertise in geriatrics and an understanding of oncology principles facilitating oncology-specific communication.

The composition of the geriatric oncology care team can vary widely depending on local resources. Some teams consist of a single clinician who performs the GA while others include multiple health care providers from several disciplines, such as nursing, physiotherapy, occupational therapy, social work, pharmacy, navigation, and nutrition. In a recent survey of 19 geriatric oncology programs in Canada and the United States, 10 have a primary geriatric oncologist model, seven have both a geriatrician and an oncologist involved, while the remaining were run by either a geriatrician or an oncologist.[32] The majority of clinics have nurses (68.4%) and pharmacists (63.2%), but less than half have physiotherapists and nutritionists involved. Two clinics did not have any support from Allied health. Although the ideal delivery of geriatric oncology may include assessment and input by a multidisciplinary team, the delivery of geriatric oncology models of care is very adaptable to locally available resources and context.

CHALLENGES IN DEVELOPING CANCER AND AGING PROGRAMS

The development of a successful geriatric oncology implementation strategy begins with identifying barriers and understanding which challenge, when overcome, can help achieve the intended goal.

Major barriers to the implementation of GA include (1) lack of knowledge and training, (2) uncertainty about tools to use, (3) lack of resources, and (4) time to carry out the assessments in a busy oncology clinic.[21] Additionally, geriatric expertise is scarce and therefore cannot form the basis of a wide-scale implementation.[33,34] Geriatric education among oncology providers can improve the dissemination of cancer and aging practices in daily cancer care. Multiple efforts are ongoing to address this; however, education on its own is unlikely to propel the implementation of clinical cancer and aging practices without additional tangible resources. The ASCO Older Adults Taskforce survey showed that although those who were aware of the ASCO geriatric oncology guidelines were twice as likely to perform specialized assessment of older patients, they still faced significant challenges.[21] In fact, the implementation of the GA in clinical practice is seen by most providers as a complex procedure that requires time, skills, and a level of resources that are not available in most routine cancer care settings.[21,22,35] Therefore, a comprehensive approach that addresses all these barriers is essential in the design of successful implementation strategies and certainly a critical part in the efforts to take the clinical practice of geriatric oncology beyond select high-resource settings.

Given the time intense nature of GA, a modified form is one strategy to make the assessment more feasible and accessible to the larger community. A modified GA has been developed using a set of multidimensional screening tools.[20,36-38] This GA is mostly based on patient-reported information and requires limited involvement by health care providers, usually only to complete physical performance and cognitive assessments.[39] More importantly, because of its simplified aspect, health care providers of any background can be trained to perform this GA format which allows the dissemination of geriatric evaluations in the oncology practice in a scalable fashion that is not directly dependent on the presence of local geriatric expertise.[39-42] This strategy is most successful when the implementation of the GA is done using an electronic platform and particularly if incorporated into the electronic medical record system, which allows an automated processing of the data that facilitates the identification of the geriatric impairments and proposes targeted interventions.[37,43,44]

The implementation of geriatric oncology into clinical practice can be complex; therefore, direct counseling and advice is often needed. The Association of Community Cancer Centers (ACCC) developed a library of resources to simplify access to the geriatric oncology tools.[45] In addition, the gap assessment tool created by the ACCC on the basis of input from cancer and aging experts allows health care professionals to evaluate and improve their cancer and aging practices by providing an individualized assessment of each of the tools they use and offers recommendations on the basis of best practices.[46] Another resource is the Clinical Implementation Core (CIC) established by the Cancer and Aging Research Group (CARG) to facilitate the dissemination of geriatric oncology evidence-based principles.[47] The primary function of the CARG CIC is to provide health care professionals with guidance regarding the clinical integration of geriatric practices into oncology care and providing support with program development, business model design, and strategic planning.[48]

Additional challenges commonly encountered by health care providers interested in developing a cancer and aging program include identifying and gathering resources to be able to support the implementation of a clinic. A good understanding of the resources available at the local level that could be used to support the clinical operation is a primary component of such a structure. The design of the

geriatric oncology practice should match the available resources otherwise the durability of the program is likely to be at risk. In addition, it should consider the priorities of the geriatric oncology service consumers: patients, caregivers, providers, and the institution. Understanding the health care context in which the proposed program will operate is critical. Specific questions should address (1) the priorities and pressures in the system, (2) the availability of geriatricians and other health care professionals, and (3) physician payment models. In some instances, understanding the political climate and appetite for improving care of older adults can also be helpful when developing strategies to garner resources for an aging and cancer program.

Having a thorough understanding of the opportunities and barriers in one's particular context is an important first step in successfully developing and implementing a cancer and aging program.

DEVELOPING A PROPOSAL FOR A CANCER AND AGING PROGRAM

Making a Case for Stakeholders

The critical first step in the development and deployment of a geriatric oncology model of care is the identification of a physician champion, who is passionate, is committed, and will lead the charge. This individual will need to perform a strategic stepwise stakeholder assessment to best understand the local landscape. Proposals spearheaded by geriatrics should seek to build alliances with oncology and vice versa. Building a coalition of clinicians, health care professionals, and administrators interested and passionate about improving care of older adults with cancer is critical to the development of a cancer and aging program, its successful implementation, and its ongoing success.

Selecting and Developing a Cancer and Aging Program Model

An assessment of locally available resources should be undertaken, including health care personnel with expertise and interest in the care of older adults with cancer. This assessment can then inform the potential model of care delivery (primary geriatric oncology, consultative, or embedded model). An estimate of the number of patients who will be seen and affected by the implementation of a cancer and aging program is important to ascertain and include in the proposal. The capacity of the proposed program will also help guide how patients are identified (age and screening tool) and referral criteria.

Development of a Business Case

The next important step is to develop a business case to present to the local leadership. Key members of the leadership team may include the cancer center director, department/division chairs, administrators from the health system and/or cancer center, and physicians/care team members in the department and/or practice. The business plan will need to address several facets, some of which may be more or less relevant depending on the particular health care context. These include (1) current and future resources needed to develop and grow the program including specific metrics of success, (2) impact of the program on clinical growth/patient care retention, (3) research opportunities, (4) educational and training pipeline opportunities, (5) philanthropy needs and/or opportunities, and (6) additional programmatic development including survivorship and supportive care and specialty specific programs such as cardio-oncology, psycho-oncology, and cancer rehabilitation medicine, all of which can serve to support care of older adults with cancer.

An important part of the discussion with leadership should include the rationale for developing the cancer and aging program and the expected impact of the program. Understanding the priorities of the cancer center and those leading the cancer program and/or geriatrics can be helpful to align messaging about potential benefits of a cancer and aging program. These include outcomes of improving quality, safety, and eliminating disparities in care for the community served by the cancer center, health system, or practice, and the importance the program will have to elevate and differentiate the care provided. Certainly, there are strong data from multiple randomized controlled studies that have shown a decrease in treatment-related toxicity and hospitalizations and an increase in the likelihood of completion of chemotherapy.[17-19,25] From a surgical perspective, one study suggested that GA may lead to decreases in length of stay and intensive care unit (ICU) admissions.[27]

Ensuring the financial feasibility of a new program is extremely important. Showcasing the potential to decrease costs and/or the potential to offset initial investments into the program is important messaging when making a business case for a cancer and aging program. Decreased visits to the hospital and/or hospital admissions because of toxicity can lead to decreased costs to the hospital or health system. Pretreatment GA may also result in change in treatment plans (eg, decision against surgery, change in planned systemic therapy, and decision for best support care). This process can result in considerable cost savings with one study demonstrating a cost saving of almost $7400 Canadian dollar (CAD) per patient assessed, for a net saving of $1.1 million CAD.[49]

Keys to Successful Implementation

Once approved, there are several key factors that can help promote successful implementation of the proposed cancer and aging program. Starting with small-scale changes, creating visible early successes, and building on these can help facilitate and accelerate the implementation process.

A geriatric oncology practice is most likely to succeed if it is not considered intrusive by the consumers and if it does not overwhelm the daily clinical operation. A start low and go slow approach can be extremely beneficial to those building geriatric oncology programs as it allows them to test their resources and modify their approach in a more flexible environment by focusing initially on a smaller implementation scale such as a specific older patient population and/or practice location. In addition, this strategy creates an environment that increases the likelihood of demonstrating success, which is critical at the early stages of implementation, especially when considering the importance of gathering the support at the local level through all disciplines and across all levels of leadership. Building a clinical practice on the basis of this stepwise strategy is likely to require fewer resources at inception and is less dependent of significant initial funding. As the program develops and meets defined metrics, further acquisition of resources should be more easily justified to leadership to facilitate growth.

GERIATRIC ONCOLOGY IN THE HIGH-RESOURCE SETTING: NATIONAL CANCER INSTITUTE–DESIGNATED CANCER CENTERS

Insight from the success of the French Geriatric Oncology National System[50] which aligns clinical and research efforts in a structured model of government-supported geriatric oncology centers would suggest that significant opportunity exists through National Cancer Institute (NCI)–designated cancer centers in the United States to advance the field of geriatric oncology with breakthrough discoveries relevant to older adults with cancer leading to paradigm shifts in the care delivered.

Highly resourced NCI-designated cancer centers have the infrastructure necessary to foster the development of state-of-the-art comprehensive geriatric oncology programs to reduce the cancer burden throughout their respective catchment areas and collectively on a national level. Bridging basic, translational, and population science efforts and linking this to training and education and clinical care delivery will enable unique breakthrough discoveries, that address the specific needs of older adults with cancer, to be moved from the bench to the community and beyond. Emphasis on standardized geriatric patient assessment and care delivery, health professional and caregiver training, and real-world data collection will further augment the ability to move the field forward.

The Sidney Kimmel Cancer Center (SKCC) at Jefferson Health launched the Geriatric Oncology Center of Excellence (GOCE) in November 2022. The GOCE is an important differentiator with the mission of providing the infrastructure necessary to assess the complex and multilevel needs of older adults with cancer, develop tailored care plans that optimize health outcomes, and improve the QOL and survivorship for this unique patient population. It builds on 12 years of consultative experience within the Senior Adult Oncology Center (SAOC), the multidisciplinary outpatient GA clinical consult team, which has now been incorporated structurally into the GOCE. The GOCE will serve as a sought-after training hub to expand a geriatric-sensitive work force, and it will create a research powerhouse designed to improve outcomes, inform best practices, foster paradigm shifting breakthrough discoveries, and enhance representation for a patient population that is rapidly expanding. This center is composed of five cross-functional pillars including (1) Basic Science Research, (2) Translational Research, (3) Clinical Care Delivery and Survivorship (incorporating the SAOC), (4) Population Health Research, and (5) Training and Education (Fig 1).

Research done in the Basic Science pillar will address the aging and cancer interface including senescence, telomere shortening, immune exhaustion, the aging microenvironment, chronic inflammation, and clonal hematopoiesis as drivers of cancer development and growth in the aging population. This work is informed by input from the communities served by the cancer center and will serve as the basis for multi–principal investigator grant development and the development of novel paradigm shifting investigator-initiated trials specifically addressing questions relevant to older adults with cancer. The work in the Translational pillar will be guided by relevant questions developed in the Clinical Care Delivery and Population Health pillars and also informed by the seven-county catchment area served by the

FIG 1. Structure of Sidney Kimmel Cancer Center Geriatric Oncology Center of Excellence.

Sidney Kimmel Cancer Center in Southeastern Pennsylvania and Southern New Jersey. Research areas focused on older adults with cancer for the Population Health pillar include remote monitoring, health informatics, cardiology and aging, disparities, health equity, survivorship, and value-based care.

The Clinical Care Delivery pillar will continue to focus on the highest quality care delivery through the multidisciplinary clinic, using the G8 tool to screen all new older adults with cancer to assess who would benefit from a more in-depth GA. It will deploy novel strategies for expanding access across the larger health system using telehealth and exploring opportunities for nursing and patient-led assessments to ensure compliance with the ASCO guideline. As a certified Age-Friendly health system by the Institute for Healthcare Improvement (IHI), the center will expand Age-Friendly principles across the larger cancer center, bridging inpatient, outpatient, and transitions of care. Using this framework, the clinical pillar will provide geriatric oncology-sensitive survivorship, rehabilitation medicine, and cardio-oncology support and structure to develop relevant research questions.

An essential responsibility of the Center is to train the next-generation geriatric oncology-sensitive health care professionals, including physicians, nurses, pharmacists, navigators, social workers, nutritionists, and rehabilitation medicine providers. Expansion of current infrastructure will enable training of future geriatric oncologists and health care professionals to meet the increasing demand. Using innovative education models such as Project ECHO, the Center will educate an interprofessional and interinstitutional workforce in geriatric oncology principles. Given the advancements in health care and changes in payment structures, most cancer care is provided in the outpatient setting and relies on unpaid caregivers to help manage.[51] In efforts to address this often overlooked care gap, the GOCE intends to provide training and support for caregivers and advocates in the specific issues that older adults face when diagnosed with cancer. As part of these training and education efforts, expansion of the existing programs to focus on older adults with cancer, including cardio-oncology, rehabilitation medicine, survivorship, and transplant/cellular therapy is planned.

CONSIDERATIONS IN THE COMMUNITY SETTING: THE COACH EXPERIENCE

The program for Comprehensive Oncology & Aging Care at Hartford (COACH) was established with the primary aim of integrating geriatric care into the routine daily oncology practice of all older patients at Hartford HealthCare Cancer Institute (HHC CI). An initial pilot project was conducted with the goal of testing the feasibility of integrating a screening tool, the modified G8 (mG8), into the daily clinic flow.[52] The primary aim of the study failed as the completion rate did not reach the predefined threshold for success, but findings from this study emphasized internally the inadequacy of classical performance tools measures: Among 34 patients with a good performance status (Eastern Cooperative Oncology Group 0-1), only 21% (n = 10) were found to be fit by the mG8 score.

The initial phase of the implementation was used as an opportunity to refine the GA operation and identify a process that would be the least demanding on the daily office flow and replicable in other settings. Empirical observation conducted during that period established that a GA visit scheduled immediately before the patient's initial consultation is the most impactful on patient's oncological treatment plan and least burdensome to patients and their caregivers. In addition, it was determined that the GA process would be reproducible in other sites of the cancer institute only if the GA format was improved to be less operator dependent. The Epic Geriatric Oncology Assessment (Epic GOA), an electronic GA tool that is fully integrated into the electronic medical record system (Epic Systems), was developed on the basis of the electronic Rapid Fitness Assessment (eRFA).[37] The Epic GOA performs an automated assessment of a patient's frailty status on the basis of the total number of identified geriatric impairments, estimates chemotherapy toxicity risk using the Cancer and Aging Research group (CARG) tool,[53] and suggests geriatric interventions. On the basis of its user-friendly interface, the Epic GOA became the cornerstone of the geriatric oncology dissemination strategy throughout different sites of the Hartford HealthCare Cancer Institute as it allowed health care professionals of various backgrounds to perform the GA (Fig 2). In the future, the Epic GOA will be implemented at all sites of the HHC CI. As a result of the activity of the COACH team, the HHC CI was designated as age-friendly health care system by the Institute for Healthcare Improvement (IHI) Age-Friendly Healthcare system.

Similar considerations and approaches can be implemented in other community-based practices. Given that community-based practices often have fewer resources, selection of easy-to-use tools that are doable with minimal direct provider involvement is critical to the feasibility and successful implementation of any cancer and aging program. Integration of these data with one's electronic medical system can help facilitate data synthesis and transmission and integrate it into the clinic flow. Seamless integration of data can help alleviate some of the burden that clinicians may perceive with GA.

INTERNATIONAL PERSPECTIVES AND CONSIDERATIONS

Cancer and aging programs have been established in many countries and contexts outside of the United States as well.

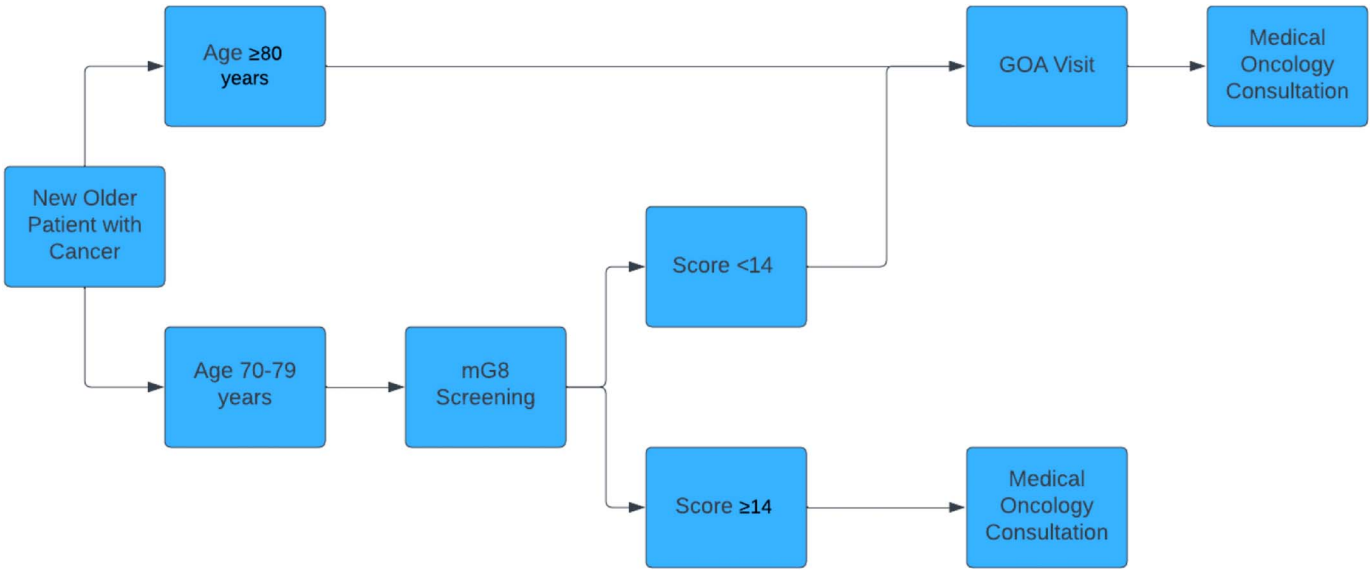

FIG 2. The COACH process. COACH, Comprehensive Oncology & Aging Care at Hartford HealthCare; GOA, Geriatric Oncology Assessment; mG8, modified G8.

Differences in health care systems, including structure and delivery of health care, role and availability of geriatricians, clinician compensation models, and the political and socioeconomic climate may present different opportunities and/or challenges than those faced in the United States.

Recognition and endorsement of geriatric oncology is variable. In some countries, the impact of the aging population on health care and cancer care in particular is well established, while in other countries this is just starting to be recognized. Education and training in geriatric oncology is also quite variable. Although the United States established fellowship training programs in geriatric oncology in the late 1990s,[54] in some countries, geriatric medicine is not even a recognized specialty.[55] Clearly, the challenges faced by countries in the latter category are very different than those with well-established training programs. In countries where geriatric medicine is not established, education about core principles of geriatrics, including the idea of physiological versus biologic age and the concepts of GA and syndromes, will need to be done to establish the foundations of any initiatives to improve care of older adults with cancer. Even in countries with established specialties of geriatrics and oncology, studies suggest that most health care professionals do not receive training in areas outside of their specialty, leading to gaps in knowledge and skills to ideally care for the aging cancer population.[56-59] The International Society of Geriatric Oncology (SIOG) has worked to increase education in geriatric oncology in certain regions such as Asia where exposure to geriatric oncology has thus far been limited.

The specific health care context, particularly the payer and the method in which clinicians are reimbursed, can be important. In countries such as Canada and Mexico, for example, where clinicians are paid a set salary and/or are paid per patient seen (fee for service) but in which the procedures performed (in this case the GA) are not a factor, funding of the clinician may be less of a barrier to the implementation of a cancer and aging program. However, for health care systems in which physicians are not reimbursed for doing a GA, exploration of alternate funding models and/or supplemental funding may be an important consideration.

SUSTAINABILITY

Beyond implementation, considerations on how to sustain a cancer and aging program are important. Sustainability includes strategies for ongoing access to resources and personnel, as well as ensuring longevity of the program as it expands.

Demonstrating the value of the program to clinicians and administrators is important. Value to clinicians includes ensuring a smooth and efficient referral process, timely access, good communication, and improvement in patient care. For some clinicians, this will mean receiving help with decision making or optimizing patients' functional status to enable them to receive treatment, while for others, this may mean managing geriatric syndromes, such as falls and dementia, that oncologists feel they do not have the capacity to manage. Building relationships with referring services and entrenching the program into the oncology culture are important to developing, sustaining, and growing a cancer and aging program. For geriatricians leading the development of a cancer and aging program, attendance at oncology rounds,

including multidisciplinary tumor boards (a staple of oncologic care), may be helpful to establish a presence and provide geriatric-related perspectives to the discussions.

Demonstrating value to administrators may include providing metrics showing improvements in outcomes for older patients (safety, quality, and decreased unnecessary admissions, emergency room visits, and ICU stays), patient retention, and cost savings. Understanding what outcomes administrators and leadership of the cancer center will want evaluated should be determined at the inception of the program to ensure these metrics are collected. For those who work in an academic institution, establishing a program of research with visible outputs, including research projects completed, grant funding, and publications, can bring prestige and recognition to the institution and thus engender ongoing support for the program. Similarly, establishment of the cancer and aging program as a beacon of excellence for care of older adults with cancer may attract philanthropic donations to the cancer center. This may also help to sustain the ongoing sustainability and growth of the program.

Beyond monetary considerations, as the program grows and continues, it is important to plan for growth and possible personnel changes by continuing to engage health care personnel interested in caring for older adults with cancer. Recruiting more physicians, nurse practitioners, physicians assistants, and health care professionals not only increases the capacity of the program but also ensures that the program is able to continue to function during absences or if the primary clinician leaves. One method of engaging new clinicians can be to establish a formal training program. This may be particularly important in regions where geriatric oncology is less well established and where training opportunities in the country are limited. Formal succession plans to ensure stability of the program should be put in place early and frequently updated.

CONCLUSION

There are now robust data supporting the use of GA to improve outcomes in older adults with cancer receiving systemic therapy and/or surgery. This has been endorsed by several international organizations including ASCO. Challenges to developing and implementing a cancer and aging program vary depending on the health care context. Making a case to stakeholders and building coalitions with those interested in and passionate about caring for older adults is a critical first step. Selection of an appropriate model and referral criteria that fits the local health care context is a key next step. Creating a business proposal that considers resources required and addresses the benefits of an aging and cancer program to the institution are important next steps to garner institutional support. Given the enormous potential impact of a cancer and aging program to improve outcomes of older adults with cancer and the adaptability of GA to multiple contexts and resource settings, health care providers and administrators should move beyond dwelling on barriers to implementing GA and work to address these challenges in order for older adults with cancer to have access to the highest-quality cancer care that matches their goals.

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GLOBAL HEALTH

Germline Testing Around the Globe: Challenges in Different Practice Settings

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overview

Cancer is an increasing global public health burden. Lately, more emphasis has emerged on the importance of heredity in cancer, mostly driven by the introduction of germline genetic variants–directed therapeutics. It is true that 40% of cancer risk is attributed to modifiable environmental and lifestyle factors; still, 16% of cancers could be heritable, accounting for 2.9 of the 18.1 million cases diagnosed worldwide. At least two third of those will be diagnosed in countries with limited resources—low- and middle-income countries, especially where high rates of consanguine marriage and early age at diagnosis are already prevalent. Both are hallmarks of hereditary cancer. This creates a new opportunity for prevention, early detection, and recently therapeutic intervention. However, this opportunity is challenged by many obstacles along the path to addressing germline testing in patients with cancer in the clinic worldwide. Global collaboration and expertise exchange are important to bridge the knowledge gap and facilitate practical implementation. Adapting existing guidelines and prioritization according to local resources are essential to address the unique needs and overcome the unique barriers of each society.

INTRODUCTION

Cancer is an increasing global public health burden. Lately, more emphasis has emerged on the importance of heredity in cancer, mostly driven by the introduction of germline genetic variants–directed therapeutics. It is true that 40% of cancer risk is attributed to modifiable environmental and lifestyle factors[1]; still, 16% of cancers could be heritable,[2] accounting for 2.9 of the 18.1 million cases diagnosed worldwide.[3] At least two third of those will be diagnosed in countries with limited resources—low- and middle-income countries (LMICs), especially where high rates of consanguine marriage are already prevalent.[3] Early age at diagnosis is a hallmark of cancer in LMICs, which may reflect a higher rate of hereditary cancer compared with other parts of the world. For example, two third of breast cancer cases in LMICs are diagnosed before age 54 years compared with one third of BC cases in high-income countries (HICs), with a median age at presentation a decade younger than those in HICs.[4,5] Black patients with breast cancer in sub-Saharan Africa (SSA) are twice as likely than White patients in SSA to be the triple-negative subtype.[6] These molecular features are hallmarks of hereditary cancers; indeed, genetic testing for pathogenic sequence variants in the tumor suppressor genes *BRCA1* and *BRCA2* in a series of Nigerian patients with breast cancer suggested a rate of cancers in women with *BRCA1* or *BRCA2* germline-pathogenic sequence variants to be higher than White populations.[7] This creates a new opportunity for prevention, early detection, and recently therapeutic intervention. However, this opportunity is challenged by many obstacles along the path to addressing germline mutations in patients with cancer in the clinic worldwide (Table 1).

THE CHALLENGE OF REFERRAL

The era of clinical cancer genetics was ushered by the discovery of *BRCA1/2* in the mid-1990s. Since then, most HICs have multidisciplinary teams to manage genetic counseling and testing for high-risk and moderate-risk cancer susceptibility genes to guide risk-reduction recommendation and clinical management. However, even in HICs, there is disparity in access to cancer genetics services. For example, Black women were 40% less likely to undergo BRCA1/2 testing than White women in a population-based study in two US states.[8] Another report demonstrated that physician referral rates for women who met criteria for referral to genetic testing from the US National Comprehensive Cancer Network (NCCN) differed significantly by ethnic background; only 75.7% of Black non-Hispanic patients compared with 92.7% White non-Hispanic patients were actually referred.[9] Uptake of genetic counseling, once appropriately referred, was not significantly different by ethnic background. The racial disparity in referral to genetic testing could be explained by a variety of factors, such as inadequate physician education on the prevalence of hereditary risk in patients, physician association of genetic cancer

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PRACTICAL APPLICATIONS

- Awareness campaigns should target society, health workforce, and policymakers alike to raise awareness and education about the importance of germline testing and its implications, particularly in prevention and potentially targeted therapeutics, to facilitate and support widespread implementation.
- A culture-sensitive standardized approach for referral, consent, counseling, and testing needs to be adopted to streamline the process within the oncology service visit.
- Genetic misdiagnoses may occur if genomic tests are developed using only specific populations, and this misdiagnosis extends to both majority and minority populations.
- The universal shortage of genetic counselors mandates educating oncology professionals on the subject of cancer genetics.
- Overcoming the financial barrier, together with collaboration, is key to capacity building, accessibility, and sustainability of germline testing.

TABLE 1. Types of Challenges Related to Germline Testing Around the Globe, in All Resource Settings, With Suggested Possible Solutions

Type of Challenge	Possible Solutions
The challenge of referral	Develop standardized tools for assessing eligibility for testing
	Multidisciplinary team education
The challenge of indication	Focus on those at risk rather than expanding testing to everyone
The challenge of uptake	Culture-sensitive genetic counseling
	Streamline the process within oncology clinic visit
	Public policy to protect against genetic discrimination
	Awareness campaigns
The challenge of interpretation	Focus on those at risk rather than expanding testing to everyone
	Development and improvement of tools such as RNA sequencing and in silico analysis
	Promote collaboration across the world to facilitate sharing information from different populations
The challenge of genetic counseling	Support expanding programs to train more genetic counselors
	Multidisciplinary team education
	Utilization of telemedicine and artificial intelligence
The financial challenge to access	Collaboration between researchers and pharma
	Research to support cost efficacy in cancer care (prevention and treatment)
	Support from insurers and governments

pathogenic genetic variants with certain populations, for example, Ashkenazi Jewish, communication barriers on the basis of cultural norms, differences in patient awareness and assertiveness between different ethnic backgrounds or societies to discuss the issue of heredity, and finally implicit bias. Another ethical challenge for the physician when considering referral, especially in a therapeutic setting, will be the financial implications. For example, if patients with pancreatic cancer do not have access to poly (ADP)-ribose polymerase (PARP) inhibitors, it would be very hard to counsel them about germline testing, still relatively expensive in most LMICs, and discuss potential benefit for relatives, while informing them of a therapeutic choice they cannot afford and, therefore, cannot access.

Besides, the importance of physician education worldwide, developing standardized tools for assessing eligibility for testing, would be more practical to eliminate the effect of physician bias and streamline the referral process. The standard tool would facilitate the accommodation of new indications in this era of rapidly changing indications for genetic testing amid busy clinics.

THE CHALLENGE OF INDICATION

Guidelines detail which patients to refer to genetic testing; however, those are revised frequently and have become more complicated, adding to the burden of the busy physician to keep up and check for each patient. Lately, they have recognized additional genes, besides *BRCA1/2*, for which management guidelines have been proposed or are in development. Testing for multiple genes simultaneously makes panel testing a logical option rather than sequential single-gene testing. Panel testing addresses not only the genetic heterogeneity of hereditary cancer syndromes but also the phenotypic overlap among carriers of different mutated genes. For example, breast cancer is common among women with a germline *BRCA1/2* pathogenic genetic variant and in those with pathogenic genetic variants in *PALB2*, *TP53*, *ATM*, or *CHEK2*, among others.[10,11] Consequently, when requesting a germline genetic test, it is important to understand the different kinds of tools available and individualize the choice during precounseling. Sanger sequencing was the primary method used for DNA sequencing for several decades before being largely replaced by newer technologies, such as massive parallel sequencing. Sanger sequencing could be used when a genetic variant is known to do cascade testing in a family. It can also be used when a specific syndrome with specific variants is suspected, such as MEN1 syndrome or DICER1 syndrome.[12]

Massive parallel sequencing is a high-throughput method used to determine the nucleotide sequence or fragment of

an individual's genome. This approach uses DNA sequencing technologies capable of analyzing numerous DNA sequences simultaneously.[12] This technology is also referred to as next-generation sequencing. It is useful for studying a set of genes, often called a panel, that can range from 2 to 1,000 genes. Access to this technology is limited in LMICs, so testing is performed by sending abroad further complicating the process of testing and subsequently adding to the financial challenge. Massive parallel sequencing can also be used for coding exome sequencing and whole-genome sequencing. However, exome sequencing and genome sequencing are not typically indicated in clinical settings for patients with cancer and are only used in research settings. Multiplex ligation probe assay, polymerase chain reaction, or other method to detect structural variants, including copy number variants and genomic large rearrangements, should always be included.

Several founder mutations (in particular *BRCA1/2* mutations) occurring among defined ethnic groups or individuals from a specific geographic area have been observed. Their identification can facilitate diagnosis and make it cost-effective by focusing testing on those variants initially.[13] For example, deletion 9-12 of *BRCA1* represents 30% of all the cases of BRCA1/2 pathogenic variants in Mexican population.[13]

To complicate the issue of the appropriate indication further, some argue for expanded panel testing for all patients with cancer. Their argument is that many clinically actionable variants are missed by history- or syndrome-focused testing. Indeed, among 2,984 patients with cancer unselected for high-risk, germline testing detected germline variants in 13.3%, ≈50% of which would have been missed by testing guidelines.[14] A couple of studies reported a similar rate of pathogenic/likely pathogenic (P/LP) variants among patients with breast cancer or gynecologic malignancy who met and those who did not meet the NCCN testing criteria.[15,16] This translates to half the patients with a clinically actionable P/LP germline variant not meeting the NCCN testing criteria and missing the therapeutic opportunity. In response to the aforementioned findings, the American Society of Breast Surgeons in 2019 recommended panel testing to be offered to all individuals with a personal history of breast cancer and even recommended updated testing of those who had been previously tested.[16] However, reanalysis of the data reported in one of the studies above,[15] including only variants in genes with definitive evidence for breast cancer susceptibility,[17] determined that of patients who met the NCCN guidelines, 6.47% had a P/LP variant, whereas of those patients who did not meet the guidelines, 3.75% had a P/LP variant, translating to missing four P/LP variants in high-risk genes, three in *BRCA2*, and one in *PALB2*. This represents 0.4% of the tested population, with 54% of patients being found to have variants of unknown significance (VUSs). Most of the variants identified in patients who did not meet the NCCN guidelines were in the moderate-risk genes *ATM*, *BARD1*, and *CHEK2*, which do not affect surgical management. These findings are a testimony for the efficacy of guidelines to guide testing of those at high risk in the current era, while reducing the rate of detection of VUSs. Similarly, germline variants were identified in 15.7% of 515 patients with esophagogastric cancer, with 55.2% of those with high- and moderate-penetrance variants not identified by current testing guidelines; however, most were incidental or unrelated to the patient diagnosis.[18] These results call attention to the implications of expanded germline testing away from guideline indications. Besides the financial implications, the consequences to both the patient and the physician are not trivial. The patient will suffer from unnecessary anxiety because of the VUSs, whereas an incidental and unrelated germline P/LP genetic variant to a patient with advanced tumor will be quite challenging to address. It will be tough to explain that they are unrelated to the patient diagnosis while recommending cascade testing for family members for someone in desperate need for a promising result to improve outcome. The busy physician will be overwhelmed with results enriched for VUSs. Those will take time to interpret and explain to patients and may require follow-up, additional testing, or review in case of reclassification,[19] creating unnecessary burden for the physician. More importantly, it will also increase the chance of misinterpretation with subsequent inappropriate recommendations for the patients. A recent study reported that the confidence of surgeons in discussing testing increased with the volume of patients with breast cancer they treat.[20] Many surgeons (higher volume, 24%; lower volume, 50%) managed patients with *BRCA1/2* VUS the same as patients with *BRCA1/2* pathogenic genetic variant, and one half of average-risk patients with VUSs underwent bilateral mastectomy without discussion with a genetic counselor.[20] There is no short-term solution to the recognized shortage of genetic health counselors,[21] and oncologists will be faced with the need for continuous education to be able discuss germline testing finding and their implications. Therefore, physician awareness of those implications is important while focusing on minimizing the VUS rate by restricting testing to genes that are clinically relevant to the patient's diagnosis.[22]

One might consider polygenic risk scores (PRSs); however, those are subject to the same biases that affect virtually all clinical genomic information, including the limited ethnic diversity of the data used in their development.[23] Most cancer genomic studies have predominantly included populations from Western Europe or North America and, to a lesser extent, East Asia. Other populations, including those from southern Asia, South America, Africa, and Middle East, are remarkably under-represented in these studies, posing

important limitations to the generalizability of findings from one population to another, therefore limiting the interpretation of PRSs, leaving guideline-driven testing the most balanced strategy for now. Currently, NCCN recommends genetic testing for all individuals with ovarian, pancreatic, or advanced-stage prostate cancer, regardless of age at diagnosis, ethnicity, or family history. Indeed, it is estimated that less than a quarter of those eligible for genetic testing in the United States had such testing in 2015, leaving approximately 1 million individuals untested.[15] It seems more reasonable to focus on improving the genetic testing rate among those at risk, as defined by the guidelines, rather than expanding testing to all. A standardized tool to help the busy physicians, especially where genetic counselor is not available, would be a great asset to incorporate in the oncology clinic visit.

THE CHALLENGE OF UPTAKE

The obvious challenge of referral is more complicated by the attitude challenge, driven by social, cultural, and religious barriers to genetic testing. Some patients believe that genetic testing is not important if they do not have children or because of lack of perceived benefits; the latter would preclude discussion with family members as well. One study demonstrated that patients believed genetic testing was not important or beneficial because of insufficient information regarding the rationale for, and benefits of, genetic testing.[24] Patients can be overwhelmed with their diagnosis and miss appointments for genetic counseling. Therefore, the mainstreaming of genetic counseling and molecular testing during oncology outpatient consultations, whether by the oncologist or by the onsite genetic counselor, may lead to a decrease in attrition. When the process of genetic education, consent, and testing was accommodated during scheduled patient appointments (such as during chemotherapy), thus minimizing patients' travel and wait time, the number of patients lost to follow-up was reduced to 4%.[25] This is in contrast to a reported rate of 19.6% when patients were referred for genetic testing by the oncology service (in which genetic counselors were not present in the outpatient clinic).[26] Some patients do understand the importance of genetic testing, but they are worried to know that a genetic variant might be present with subsequent effect/stigma on future generations, such as children and grandchildren. Education about the potential for risk-reduction strategies could reassure them to pursue testing and inform relatives. Even among relatives receiving risk communication support and no-cost testing for familial variants, the rate of cascade testing uptake was only 17.6%,[14] consistent with reported estimates as low as 20%-30%.[27] The latter estimate is also partially driven by restrictions on direct communication between physicians and patients' relatives. The low rate of uptake of cascade testing, even among those diagnosed based on family history, limits the positive impact of germline genetic variants testing on prevention and early detection, challenging its clinical utility to support early detection at a societal level.

There is a real concern about genetic discrimination (GD) across cultures, especially high in the context of insurance, employment, and within social relationships. Some countries do have legislation prohibiting GD, but most do not, especially those with limited resources. A recent study outlined public policy approaches across the globe used to prevent GD. They identified regions featuring extensive policy-making activities (North America and Europe), followed by regions with moderate policy-making activities (Australia, Asia, and South America) and regions with minimal policy-making activities (the Middle East and Africa).[28] Those legislations, however, do not seem to (completely) alleviate fears of GD. Indeed, those legislations have limitations. For example, the Genetic Information Nondiscrimination Act in the United States covers employers in addition to health insurers but does not cover life or disability insurance.[29] In addition, there are ethnic differences in the perception of GD, mostly related to the possible use of genetic information when considering potential spouses for marriage and starting a family in Asia, but not North America and Europe.[30] In a Japanese public survey, the respondents were largely concerned about GD in the context of marriage and pregnancy (41.0%), employment (37.6%), and insurance (43.8%).[31]

Fear also seems to be fueled by previous experiences dealing with the social repercussions of living with an illness in the family. Interaction discrimination concerns seem to be very high, although subtle and implicit, often characterized by more spontaneous forms of stigmatization or disrespect, subsequently playing a pivotal role in the decision to undergo genetic testing.[32]

THE CHALLENGE OF INTERPRETATION

During variant interpretation, variants are classified into five tiers: pathogenic, likely pathogenic, uncertain significance (VUS), likely benign, and benign.[33] Pathogenic and likely pathogenic variants are considered positive results and are often referred to as mutations, although this term is no longer recommended by the American College of Medical Genetics and Genomics. Benign and likely benign variants are considered negative results. VUS are variants in which there is not enough information to classify them. Clinical decisions should not be based on these variants since 80%-90% of them are reclassified as benign or likely benign. VUS pose a challenge, particularly in underrepresented populations where the percentage of VUS is higher because of a lack of representation in large public databases. For example, the proportion of Hispanic people is just 2% of the Cancer Genome Atlas for the glioblastoma cohort.[34]

Adequate clinical interpretability of genetic information mandates characterization and curation of novel variants for pathogenicity and thus clinical actionability. Therefore, it is anticipated that the proportion of VUSs will be higher in understudied populations until careful characterization and curation of these variants can be made.

Data diversity is required for the success of these activities. Studies of genetics and genomics are not optimized if the data used to generate clinically applied tests do not include data from ethnically diverse populations. Optimal discovery and clinical translation of genomic information requires the inclusion of diverse populations. Manrai et al[35] have reported that genetic misdiagnoses may occur if genomic tests are developed using only White populations, and this misdiagnosis extends to both majority and minority populations. Teo et al[36] have demonstrated how multicenter (multiethnic) studies in African populations can yield novel insights about the underlying genetic architecture of human disease because of the unique nature of the African genome. Genomic studies based in African populations are more generalizable to other world populations compared with the same studies performed in non-African populations because of the features of African genomic architecture.[37,38] Population-specific variants, substantial differences in variant frequencies across populations, effect-size heterogeneity, locus heterogeneity (ie, differences in causal variants across populations), and haplotype diversity (linkage disequilibrium differences across populations) all contribute to the potential error in the use of genomics if only single (eg, European descent) populations are studied.[39,40] Friebel et al[41] have recently reported the existence of pathogenic genetic variants seen in African Americans who are of likely African origin. Thus, identification of variants globally can inform genetic medicine in other (eg, non-African) populations. Finally, design and sample size considerations for genomic research studies are highly dependent on accurate knowledge of allele and genotype frequencies.[42] Thus, a lack of diversity in genomic research can limit discovery and translation of genomic information so that all can benefit.

THE CHALLENGE OF COUNSELING

Genetic counselors are professionals with specialized education in genetics (and recently genomics) combined with counseling skills.[43] They assess an individual's risk of a genetic disorder, prepare them for genetic testing, get consent, communicate the results and help in the management of the patients' genetic variant, and provide support to follow with cascade testing for their relatives. The challenge starts when faced by the financial burden of both germline testing and its subsequent implications in terms of prevention and therapy. Despite the significant drop in the prices of panel germline testing, those prices are still unaffordable in most LMICs. A recent study estimated the cost of panel testing to be well above the annual per capita income of LMICs—$1,500 in US dollars (USD) to $6040 USD,[44] let alone the cost of interventions needed for prevention, early detection, or treatment, particularly medications such as PARP inhibitors.

Consenting patients is a complex issue. It should cover the types of results that may come back from the laboratory (ie, pathogenic, uncertain, or benign) and the meaning of each in terms of future risk and disease management, their implications, for both the individual patient and also their relatives, and further plans for genomic data handling. Not only does it address the educational component of counseling but also the psychosocial aspect to support the patient throughout the testing process. However, with mainstreaming of germline testing and universal shortage of genetic counselors, clinicians are taking over the role of genetic counseling and testing. This approach proved effective in a study where patients with prostate cancer were counseled by their urologist or medical oncologist—as part of their routine clinical care and for enrollment in the Germline Genetics in Prostate Cancer Study.[45] Most patients (98%) reported being satisfied with the overall quality of pretest counseling, and 74% of patients elected to undergo genetic testing. Therefore, oncologist training can expand access to germline testing, but post-test counseling is still a challenge best met by professional counselor. Similarly, some researchers started an internet algorithm (chatbot) to guide patients through their testing journey.[46] While those can provide information about tests and their potential results, they cannot replace the psychosocial support that focuses on the needs of patients to understand, adjust, and incorporate this new information into their lives. The psychosocial support is augmented by cultural competence of the genetic counselor. Genetic counselors need to understand the social and cultural influences on patients' health decisions and behaviors, especially those from minority groups. This cultural competence is important to properly support the autonomy of the individual while assisting them in making their own informed choices.[47] Since the individual's decision is not only driven by medical information but also personal, social, and even religious background, cultural competence of genetic counselors is key to increase utilization of genetic testing and counseling.[48] Another challenge for genetic counselors from the majority ethnic group is counseling individuals from the minority group in a multiethnic society.

The quantitative challenge is a universal challenge, with best estimates of only 12 per million population in the United States and 5 per million population in the United Kingdom compared with 20-fold less, with 40 genetic counselors in the Arab region (0.1 per million population).[49] Some countries are now establishing training programs in genetic counseling. However, such programs need to grow significantly to train enough local talent and to meet the significant genetic counseling demand.

THE SURGEON PERSPECTIVE

From the surgeon's point of view, germline molecular testing plays a foremost role in guiding the extent and indication of surgery in patients with known germline genetic variant. For example, even patients with early-stage colon cancers and Lynch syndrome can be offered a total colectomy as opposed to a segmental resection because of the high risk of metachronicity. In many practices, this is guideline-driven, like the NCCN in the United States[50] and National Institute for Health and Care Excellence in the United Kingdom,[51] and these guidelines address the different aspects of the process that are relevant for that health care system. However, in LMICs, many aspects of those guidelines might not be applicable or even affordable.[52] The lack of local guidelines jeopardizes patients' rights and access.[53] In addition, as detailed above, data on the risks for the different genetic variants especially in the cancer setting and the models we use to assess the risks are based mainly on North American and European population. There is not enough knowledge about the genetic risk in LMICs when it comes to the pathogenicity of genetic variants or their level of penetrance. Those uncertainties in assessing the risk, and the lack of expertise in communicating the risk and the benefit of the risk-reducing procedures, make informed consent become an issue.[54]

Decisions regarding the extent of surgery and surveillance are especially complicated—not only are they dependent on the mutational landscape but also on the patient- and system-related factors. The discussion is affected by patient age, education, family, culture, society, and sometimes religious beliefs.[53] For example, risk-reducing mastectomies in many societies are still seen as a taboo.[55] Even when at-risk individuals opt for surgery, availability and cost of breast reconstruction locally is another challenge. The surgical expertise and reconstruction availability are very variable in LMICs, in addition to variations in different parts, and even between the private and public sectors, creating further health care disparities that are multifactorial and complex.[55]

CONCLUSION

The WHO cautions that while genomics can contribute to improving global health equity, equity can only be achieved if the genomic health divide is kept in check and ultimately bridged through equitable economic investment, clinical research, and provision and use of genomic services and technologies globally.[56] Therefore, acknowledging and supporting the importance of collaboration and exchange of information and expertise between HIC and LMIC researchers bridge the knowledge gap and facilitate implementation. Similarly, ASCO—in a policy statement—addressed the importance of optimal deployment of new technologies in cancer genetics in clinical practice.[57] ASCO recommended quality assurance in genetic testing, education of oncology professionals, and access to clinical cancer genetic service. While those facilities are growing in HICs, they are still in their infancy in LMICs. Adaptations of existing guidelines are needed to address the local needs of each society while prioritization is done according to available resources while building sustainable capacity.[58,59] Meanwhile, awareness and education campaigns can help overcome the challenges discussed above. They should focus not only on patients and societies but also on policymakers.

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GLOBAL HEALTH

Colorectal Cancer Screening in the Middle East: What, Why, Who, When, and How?

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overview

The incidence of colorectal cancer (CRC) in the Middle East is increasing, especially among those younger than 50 years. Risk factors including obesity, sedentary lifestyle, and dietary changes are associated with the epidemiologic shift and are a result of socioeconomic changes happening in the region. Worldwide, CRC screening is associated with decreased incidence and mortality of CRC, but screening uptake is still low in the Middle East because of cultural barriers and lack of awareness; in addition, most countries do not have national screening programs. Knowledge of CRC screening and participation rates vary among different countries, but overall they are low. Both primary and secondary prevention approaches are needed in the Middle East, and cost-effectiveness is important in choosing screening modalities. Although colonoscopy is considered the most robust screening method, stool-based testing may be an acceptable screening strategy in resource-limited settings, and focusing on high-risk individuals such as those with hereditary CRC might be the most cost-effective strategy. In addition to financial limitations in many countries in the Middle East, human displacement places an extra toll on cancer control strategies in the region.

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INTRODUCTION

The Middle East extends between the southern and eastern borders of the Mediterranean Sea and includes the Arabian Peninsula, Iran, and Afghanistan. Despite sharing some common cultural characteristics, the population in the Middle East is ethnically heterogeneous, and countries have diverse economies and demographic constitutions. The population in this region is the youngest in the world second to sub-Saharan Africa, with only 5.31% of the population being older than 65 years.[1] The median age distribution varies widely among its countries; for instance, Kuwait and Cyprus have the highest median age of 37 years, whereas Afghanistan has the lowest (18 years).[2] However, life expectancy is increasing in most countries in the Middle East from around 60 years in 1980 to over 70 years. As a consequence, a surge in the geriatric population is anticipated in around 40 years. For instance, the elderly population is expected to double in Lebanon by 2050 and to increase by at least fivefold in Qatar, Kuwait, and the United Arab Emirates (UAE).[3] This increase in life expectancy is associated with a rise in the lifetime cumulative risk of cancer.[3]

Furthermore, countries in the Middle East have different financial capacities, and they vary in terms of the Human Development Index (HDI) classification.[4] This is tightly related to the availability of medical services and public health policies, which are not homogeneous across the region. With several countries undergoing economic transformations that drive lifestyle changes, the burden of noncommunicable diseases has increased in the Middle East, including that of colorectal cancer (CRC).[5,6]

CRC is the third most common cancer in the world, with 1.9 million new cases and 930,000 deaths in 2020. The incidence and mortality of this disease are expected to increase in the future to reach 3.2 million and 1.6 million, respectively, in 2040.[7] This global rise in the CRC burden also affects the Middle East, where limited knowledge about the disease and its prevention makes CRC screening an unmet need. In this article, we will review the epidemiological data of CRC in the Middle East and the available screening strategies while highlighting the challenges in screening adherence and special needs for the region.

WHAT IS THE STATUS OF CRC IN THE MIDDLE EAST?

The Middle East is a relatively lower-risk area for CRC. The age-standardized rates (ASR) for incidence and mortality in the Eastern Mediterranean region (EMR) are 9 and 5.1 per 100,000, respectively, compared with an incidence of 28.8 and mortality of 12 per 100,000 in Europe.[8] A higher incidence is seen in the western region of the Middle East, like countries in the EMR, compared with eastern and southern regions. However, the area has recently witnessed a rise in CRC incidence.[5] In addition, cancer mortality is on the rise in the region, as data from the International Agency for Research on Cancer have shown that between 2020 and 2040, the EMR will have the highest percentage

PRACTICAL APPLICATIONS

- Modulating modifiable risk factors is important for the primary prevention of colorectal cancer (CRC), and further research is needed to investigate the impact of lifestyle interventions on CRC incidence and mortality in the region.
- Addressing the knowledge gap regarding CRC prevention is needed in this region to encourage participation in screening.
- Cost-effectiveness is a main determinant of future CRC screening strategies in the Middle East, and governments should establish screening policies tailored to their resources.
- CRC screening targeting high-risk individuals may be a more suitable approach in low-income settings, as opposed to population-based screening. Stool-based testing is an acceptable screening tool, but measures should be taken to ensure the completion of follow-up colonoscopies for individuals with positive tests.
- Human displacement adds to the complexity of the situation and increases the cancer burden in host countries. Thus, providing screening access to refugees should be factored into national prevention plans.

increase in all cancer deaths, compared with other areas in the world (96.9% *v* 95.7% in Africa, 65.7% in South-East Asia, 64.6% in Western Pacific, 64.2% in the United States, and 34.4% in Europe), and the second highest increase in colon cancer deaths.[9]

The mean age at CRC diagnosis is 10 years younger in the Middle East compared with the United States (median age 60 *v* 71 years).[5,10] In addition, the incidence of early-onset CRC (age at diagnosis younger than 50 years) is increasing worldwide and in the Middle East. Furthermore, around 20% of all early-onset CRC cases worldwide are found in Asia.[11] The ASRs for CRC incidence before age 50 years in countries such as Jordan (6.6 per 100,000), Palestine (6.2 per 100,000), Libya (6.1 per 100,000), Oman (5.9 per 100,000), Turkey (5.9 per 100,000), Saudi Arabia (5.6 per 100,000), Cyprus (5.2 per 100,000), and Syria (5 per 100,000) are among the highest in the world.[8] In Iraq, a registry-based study showed an increased proportion of CRC in patients age 20-50 years from 1.46 per 100,000 in 2000 to 4.36 per 100,000 in 2019.[12]

The incidence of CRC is four times higher in countries with high HDI compared with those with low HDI, and by 2040, almost 80% of new CRC cases are predicted to occur in countries with high or very high HDI.[7,13] A similar pattern is found in the Middle East, where CRC is among the three most frequent cancers in the countries with high and very high HDI, as opposed to those with a medium and low HDI.[4,8]

The rising incidence, especially among the younger age groups, is mainly attributed to dietary and lifestyle changes, which include the Westernization of diet, increased intake of animal-source food, increased intake of red and processed meat, excess body weight, sedentary lifestyle, increased alcohol consumption, and smoking. These changes are related to the ongoing socioeconomic development in several Middle Eastern countries.[14]

The role of modifiable risk factors in predisposing to CRC was emphasized in a recent prospective European study that compared smoking status, alcohol consumption, BMI, and physical activity of a population at two time points 5.7 years apart. A combined score, the healthy lifestyle index (HLI), was calculated based on these factors (the higher the score is, the more the score is favorable). The results show that each 1 unit increase from baseline in the HLI was associated with a 3% decrease in CRC risk. In addition, patients with a favorable baseline score who had a deterioration in their lifestyle at follow-up (drop in HLI) had a higher risk of CRC compared with those who maintained their score (hazard ratio, 1.34; 95% CI, 1.02 to 1.75).[15] Studies from the EMR (including our group) used the population attributable fraction (PAF) to estimate the percentage of cancer that is due to the exposure to risk factors. Among 22 countries in the EMR, smoking, alcohol, and red meat consumption all contributed to the risk of CRC development in variable proportions, but the highest PAF was for high BMI (13.7% in men and 9.8% in women) and insufficient physical activity (6.2% in men and 8.7% in women).[16] Our published data on PAF for the Lebanese population showed that BMI >25 kg/m^2 is expected to result in 41% of CRC cases in male patients and 9% in female patients, low physical activity is expected to cause 17% of cases in male patients and 10% in female patients, and the contribution of low adherence to Mediterranean diet is 2% in both sexes.[17]

Another considerable risk factor is childhood obesity, which is associated with increased risk of cancer in adulthood and increased risk of death from colon cancer.[18,19] The prevalence of overweight children in the Middle East and North Africa (MENA) region is around 22.2%, and that of childhood obesity is 27.9%, which is the highest in countries such as Kuwait, Qatar, and Saudi Arabia.[20,21] Therefore, childhood obesity is a growing concern in the Middle East and can have serious ramifications on future cancer risk in the region.

With respect to genetic factors, it is estimated that the percentage of hereditary or familial CRC is similar to the

West, which is 10%-15%.[22] Studies from the Middle East have shown that 1% of all CRC cases in Saudi Arabia are due to Lynch syndrome,[23] and 7%-14% of cases in Egypt showed evidence for familial or hereditary CRC.[24] However, national registries and larger studies are needed to identify the burden of hereditary CRC and individualize screening in this population.

Inflammatory bowel disease (IBD), which encompasses ulcerative colitis (UC) and Crohn's disease (CD), is also a significant predisposing factor for the development of CRC, especially with UC. The cumulative increased risk of CRC in patients with UC at age 30 years is 18% higher than that in the general population.[25] The incidence of IBD is increasing in the Middle East, and a systematic review estimated that the incidence of UC and CD in the Arab world is 2.33 and 1.46 per 100,000 persons per year, respectively.[26] However, the data on the contribution of IBD to the burden of CRC in the Middle East are insufficient, and further research on the topic is warranted.

WHY IS CRC SCREENING UNDERUTILIZED IN THE MIDDLE EAST?

The benefits of CRC screening are well established in the literature, and studies in high-income countries have demonstrated around 30% decrease in the incidence rate and mortality of CRC because of the widespread uptake of screening.[27,28] For example, the mortality rates from CRC have dropped in the United States by 55% among male patients (since 1980) and 61% among female patients (since 1969).[27] Despite the proved benefits of screening, it is still underutilized in the Middle East. To start with, the knowledge and general awareness of CRC screening remains low. Studies from the UAE, Oman, Lebanon, Turkey, Iran, and Saudi Arabia demonstrated that between 6.5% and 38% of the surveyed individuals were aware of CRC screening, with the exception of one study in Lebanon where the rate was 55%, but this study was conducted at a tertiary care center and is not adequately representative of the whole population.[29-33] In the Middle East, national screening programs are generally lacking. Israel and Qatar have organized population-based fecal immunochemical test (FIT) screening since 1990 and 2016, respectively, with a target population between age 50 and 74 years.[34,35] Some countries, such as Jordan and the UAE, are adopting an opportunistic screening approach.[35]

With respect to screening uptake, the percentages vary across studies and countries, with participation rates as low as 7.5% in one study in Lebanon,[31] 8.3% in a study on high-risk population in Iran,[36] and 4% in another study from the same country.[37] On the other hand, participation rates are higher in Israel, reaching 64.7%, and among first-degree relative of patients with CRC in Turkey and Iran, reaching 48.7% and 49.2%, respectively (Table 1).[38-40] These variable results could be due to the diverse facilitators and barriers affecting access to screening, in addition to selection of participants and their perceived risk of CRC. Studies were conducted in several Middle Eastern countries to identify the barriers to screening. A systematic review from Iran showed that cost, shame, fear of cancer diagnosis, and lack of testing recommendation by the physician were the most common barriers to screening.[41] A national cross-sectional study conducted in Palestine showed that the lack of knowledge regarding screening, distrust in Western medicine, and embarrassments were independently associated with refusing screening on multivariate analysis. Additionally, some factors were identified as barriers to colonoscopy and not stool-based screening, such as education below secondary school, religious objection, and beliefs.[42] In Qatar, the most frequent perceived barriers to screening were the lack of symptoms or family history, low risk due to healthy lifestyle, and lack of reminders by health care workers.[43]

Overcoming these barriers, facilitating access to screening, and addressing misinformation regarding CRC risk and prevention are imperative to improve adherence to screening. Such public health strategies have proven to be effective in the past when applied to breast cancer screening. As an example, yearly awareness campaigns and subsidization of mammography in Lebanon since 2002 have led to almost 50% breast cancer screening rate uptake.[31] This was also demonstrated in a quasiexperimental study in Iran that used a questionnaire on the constructs of the Health Belief Model to measure the rate of participation in fecal occult blood test (FOBT) screening in average-risk men. Participants in the experimental and control arms were asked to answer the questionnaire at baseline, and then, those in the experimental arm received educational sessions on CRC screening. After 3 months, all participants were asked again to fill the questionnaire and were invited for screening. Initially, before intervention, there were no significant differences between the mean scores of both groups with respect to awareness, perceived susceptibility, severity, benefits, barriers, self-efficacy, social support, and cues to action. After intervention, the difference between the two groups was significant, and 74% of the participants in the experimental group underwent screening with FOBT compared with only 6% in the control group.[44]

WHO AND WHEN TO SCREEN?

Both primary and secondary prevention approaches are needed to curb the rising incidence of CRC in the Middle East. Primary prevention should target the modifiable risk factors that are strongly associated with the risk of CRC to promote high fiber diet, weight control, smoking cessation, and physical activity. Secondary prevention poses a more significant challenge because screening strategies derived from high-income countries cannot be blindly adopted in this region because of cultural differences and financial disparities. Even among Middle Eastern countries, not all

TABLE 1. CRC Screening Uptake in the Middle East

Country	Study	Population	Percent Participated in Screening	Screening Modality
UAE	[57]	Average risk	23%	FIT/gFOBT
Iran	[39]	FDR of patients with CRC	49.2%	Colonoscopy
	[67]	Average risk	42%	FIT
	[36]	High risk	8.3%	FOBT
	[37]	Average risk	4%	FIT
	[44]	Average risk	6% in the control arm; 74% in the experimental arm (received education)	FOBT
Saudi Arabia	[68]	Average risk	15.24%	Colonoscopy, stool test
	[69]	Older than 60 years	5.64%	FOBT, colonoscopy
Jordan	[70]	FDR of patients with CRC	62.1%	Colonoscopy
Lebanon	[71]	Average risk	15%	FOBT, colonoscopy,
	[31]	Average risk	7.5%	—
	[72]	Average risk	14.1% in the online survey; 6.1% in the in-person survey	Colonoscopy; FIT
Turkey	[73]	Average risk	12%	FOBT
	[74]	Average risk	7% outside of the study 89% screening part of the study	FOBT
	[38]	FDR of patients with CRC	48.7%	Colonoscopy
	[75]	Average risk	17%	FOBT, colonoscopy, sigmoidoscopy
	[76]	Average risk	30%	FOBT, colonoscopy, sigmoidoscopy
	[77]	FDR of patients with CRC	9% in parents and 20% in siblings	Colonoscopy
Palestine	[42]	Average risk	14%	Stool testing or colonoscopy
Israel	[40]	Average risk	64.7%	FOBT and colonoscopy
Oman	[30]	Average risk	6.1%	FOBT, colonoscopy, sigmoidoscopy

Abbreviations: CRC, colorectal cancer; FDR, first-degree relative; FIT, fecal immunochemical test; FOBT, fecal occult blood test; gFOBT, guaiac fecal occult blood test; UAE, the United Arab Emirates.

governments have adequate financial abilities to build and sustain a cancer control program.

In general, screening can be population-based, meaning that it is planned and implemented for the whole target population. This approach requires a robust public health scheme and health care infrastructure to ensure effective delivery, follow-up, quality assurance, and maximizing the benefits in a cost-effective manner. Screening can be opportunistic when asymptomatic individuals actively seek screening or are offered screening by a health care provider. This is opposed to organized screening when the target population is systematically invited for screening. The second approach consists of targeted screening for high-risk individuals (subpopulation) on the basis of factors related to their genetics or exposures.[45] Given the resource limitations, targeting high-risk populations with a family history of CRC can be a more feasible approach compared with mass screening.[14] The Hereditary CRC Network in the Middle East and Eastern Mediterranean countries suggests screening individuals with hereditary CRC (particularly Lynch syndrome) to be the most cost-effective strategy.[22]

In addition, a prediction model for CRC might be useful to stratify individuals who are otherwise deemed as average risk on the basis of the current guidelines and guide the choice of screening method and frequency accordingly.[46] By offering more intensive screening for high-risk individuals and less intensive testing for those at low risk, the risk-based screening allows a better allocation of resources, especially endoscopy services.[47] This can also facilitate the discussion with the individuals regarding screening and gives them a better understanding of their personal risk, which in turn can empower informed decision making and favor adherence to the screening recommendations.[47,48] For example, most guidelines use an age-stratified approach to identify the target population for screening, and this might inadvertently exclude younger patients who have a higher risk due to other factors such as sex, obesity, and smoking.[47] This is a pertinent issue for the Middle East,

where the early-onset CRC is on the rise. In a retrospective study in Northeastern Iran, the mean age at diagnosis of early-onset CRC was 40 years, and 57% of the early-onset CRC cases occurred between age 40 and 50 years.[11] Although the age to start CRC screening was lowered from 50 to 45 years, considering that the age of onset of CRC is younger in the Middle East compared with the West and that several countries have a high percentage of early-onset CRC cases, further reduction of the age for screening may be necessary. For instance, the Emirate of Abu Dhabi recommends screening with yearly FIT or colonoscopy every 10 years starting at age 40 years for the general population.[49] However, additional epidemiological data from the Middle East are needed in addition to cost-effectiveness studies to decide the age of screening.

HOW TO SCREEN?

CRC screening guidelines have been put in place by several major societies, and ASCO proposes resource-stratified guidelines, which recommend different screening methods depending on their availability. These include FOBT, FIT, colonoscopy, flexible sigmoidoscopy, computed tomography (CT) colonography, and FIT DNA testing.[50] Stool-based screening offers less discomfort to patients, is easier to administer, is less invasive, and is cheaper compared with other modalities. A retrospective study in Lebanon showed that the positive predictive value (PPV) of the FIT test for adenoma and/or carcinoma was 29.3%.[51] A pilot study in Iran on the feasibility of using FIT for screening demonstrated a PPV of 16.7% for any colonic neoplasm.[39] The numbers reported in these studies are on the lower range compared with the literature because of the relative lower prevalence of CRC in Lebanon and the age of younger participants and the lower rate of colonoscopy in the study conducted in Iran. Despite this, stool-based testing may be an acceptable population screening strategy in a resource-limited setting, given data from the literature supporting its diagnostic yield compared with endoscopy. A study from the Netherlands compared FIT testing (once every 2 years for four rounds in total) with once-only sigmoidoscopy or colonoscopy and found similar CRC detection rates in the as-screened analysis between the three modalities (0.8%, 0.5%, and 0.6%, respectively).[52] The NordICC trial evaluated the effect of population-based colonoscopy screening on CRC risk and mortality in individuals who were invited to get screened compared with the usual care group. At 10-year follow-up, there was an 18% risk reduction of CRC in intention-to-treat analysis and 30% in per-protocol analysis. The number of patients needed to invite for screening to prevent one case of CRC within 10 years was 455.[53] However, ensuring access to colonoscopy and an adequate quality of the procedure are necessary to maximize its efficacy for detecting lesions, which is not always attained in limited resource settings.

In a systematic review of 12 randomized controlled studies, Jodal et al showed that compared with no screening, sigmoidoscopy reduces CRC incidence (relative risk [RR], 0.76; 95% CI, 0.70 to 0.83) and mortality (RR, 0.74; 95% CI, 0.69 to 0.80). Sigmoidoscopy compared with biennial FOBT slightly reduced CRC incidence (RR, 0.80; 95% CI, 0.71 to 0.91) and mortality (RR, 0.85; 95% CI, 0.77 to 0.93). Sigmoidoscopy compared with annual guaiac fecal occult blood test (gFOBT) screening had little or no difference on incidence and mortality (RR, 1.07; 95% CI, 0.85 to 1.34). Therefore, sigmoidoscopy and annual and biennial gFOBT can reduce CRC mortality.[54] In another traditional and network meta-analysis, colonoscopy was found to be 50% more effective than gFOBT in reducing CRC mortality. The analysis favored colonoscopy over sigmoidoscopy (RR, 0.71; 95% CI, 0.45 to 1.11) and the latter over gFOBT (RR, 0.74; 95% CI, 0.50 to 1.09) in reducing CRC mortality, but these differences are not statistically significant. The study concluded that all three modalities are effective in reducing CRC mortality.[55] However, limited financial resources may restrict access to colonoscopy, especially that this invasive procedure required a certain level of expertise and availability of health care services. A follow-up colonoscopy for individuals with a positive stool test is important to ensure the success of the stool-based screening strategy. Countries such as Israel (71% follow-up rate)[40] and Iran (60% follow-up rate)[39] have better compliance compared with the United States where a recent study showed the follow-up rate of 56.1% after almost a year from the stool-based test.[56] By contrast, a study from the UAE showed a 30.5% rate of colonoscopy in individuals with a positive gFOBT/FIT.[57] These findings should be interpreted with caution as follow-up rates in clinical studies tend to be higher than real-life scenarios. However, this highlights the necessity of adequate follow-up and awareness to ensure the completion of colonoscopy in the case of a positive stool test.

Cost-effectiveness is another crucial aspect for selecting the appropriate screening tool. A study in Saudi Arabia compared between no screening, annual FIT, biennial FIT, once-only colonoscopy, and colonoscopy every 10 years for effectiveness and used resources. The results showed that the biennial FIT test between age 55 and 65 years is the cheapest efficient screening method. This could prevent three CRC cases and three deaths among– 1,000 individuals age 45 years, with an incremental cost-effectiveness ratio (ICER) of $8,800 per quality-adjusted life year. Once-only colonoscopy starting at age 55 years was similarly cost-effective with slightly higher costs (ICER of $8,900).[58] A study in Iran compared several screening modalities and found that CT colonography was the most effective yet the most expensive technique (2.58 billion Rials, which is around $60,000 as cost per cancer detected in 20 years of screening). Instead, flexible sigmoidoscopy was the most cost-effective method for screening the population

between age 45 and 65 years.[59] In Israel, a cost-effectiveness study found that colonoscopy every 10 years starting at age 50 years resulted in best reduction in mortality rate (93.7%) compared with no screening. On the other hand, the most cost-effective strategies were colonoscopy once or FOBT plus sigmoidoscopy, which yielded a reduction in mortality rate of 59.5% and 83.8%, respectively.[60]

SPECIAL CHALLENGES TO CANCER CARE AND PREVENTION IN THE MIDDLE EAST

Although some Middle Eastern countries are classified as high-income countries, most are low- to middle-income countries, and many face financial and/or political instability. As a result, services that aim at cancer prevention including screening tests face heightened risks of cutbacks, as governments work on reducing financial deficits and prioritize other essentials such as creating jobs.[61] Several studies have reported the impact of financial disparities and economic recession on primary cancer prevention worldwide and in countries such as Switzerland and Korea.[62,63] In Korea, which was affected by the global recession in 2008-2009, individuals were less likely to use costly screening modalities such as sigmoidoscopy or colonoscopy during the recession, regardless of their income. In addition, individuals with a lower income were less likely to participate in opportunistic screening.[62] Therefore, governments should put forth a plan for subsidization of screening, especially for individuals with low income, to boost the participation rate. A second challenge is the deficit in cancer awareness, which is present even in high-income countries, as detailed in Why Is CRC Screening Underutilized in the Middle East? Education level, health literacy, and employment status are all patient-meditated barriers to seeking care for cancer which influence knowledge and awareness of cancer symptoms.[64] A third and substantial challenge in the region is human displacement due to conflicts, violence, disasters, and climate change. The growing number of refugees resulted in increased health burden on host countries, many of which with strained economies, including chronic noncommunicable diseases such as cancer.[64] For example, a study showed that total cancer care for Syrian refugees in Turkey, Lebanon, and Jordan in 2017 is estimated to be around 33.68 million Euros, which is a considerable financial burden on these host countries.[65] This also reinforces the need for implementing cost-effective screening guidelines not only for citizens but also for refugees. Another aspect of military conflict is the prolonged exposure to carcinogens from warfare. For example, oil pollution in Lebanon and Kuwait, chemical contamination in Iraq and Sudan, and depleted uranium in Iran and Afghanistan are all concerning for dumping carcinogens in the environment and promoting the development of cancer, among other diseases.[66]

CONCLUSION AND FUTURE DIRECTIONS

The Middle East is experiencing an increase in the incidence of CRC, especially among young age groups, possibly because of socioeconomic development, dietary changes, and sedentary lifestyle. Despite this, existing CRC screening services are underutilized in the region, knowledge regarding CRC risk and prevention remains suboptimal, and national screening programs are lacking in most countries. Raising awareness, addressing cultural barriers, and providing accessible health care services are essential steps to increase adherence with CRC screening in the Middle East. Given the limited financial resources in many Middle Eastern countries and the added burden of human displacement and refugees, cost-effectiveness is a main determinant of the future CRC screening approaches.

Future directions should focus on identifying the factors driving the rise in CRC in the region to tailor more effective preventive strategies accordingly. In addition, comprehensive studies are needed to investigate the genetic components and environmental exposures influencing CRC occurrence in the region, as well as long-term follow-up studies on the effect of risk factor modulation and screening on CRC mortality. Finally, international collaborations within the Middle East can help in identifying common trends and determining best practices for CRC prevention in the region.

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Managing Adverse Effects Associated With Poly (ADP-ribose) Polymerase Inhibitors in Ovarian Cancer: A Synthesis of Clinical Trial and Real-World Data

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overview

The use of poly (ADP-ribose) polymerase (PARP) inhibitor therapy is standard care in the management of patients with various malignancies including ovarian, breast, prostate, and pancreatic cancers. PARP inhibitors have been approved in different settings for patients with specific hereditary pathogenic variants, most notably homologous recombination repair pathways such as *BRCA1* and *BRCA2* genes. The vast experience with PARP inhibitors (olaparib, niraparib, rucaparib) has been in the management of epithelial ovarian cancer. There have not been any head-to-head comparisons of PARP inhibitors in randomized trials, and we can only perform cross-comparison on the basis of the reported literature. The three approved PARP inhibitors share several common adverse effects because of a class effect including nausea, fatigue, and anemia, but there are notable differences likely because of variations in their poly-pharmacology and off-target effects. Finally, patients included in clinical trials are often younger with a good performance status and less comorbidities than the real-world population, and hence, the potential benefits and adverse effects may not be superimposable. In this review, we describe these differences and discuss strategies to mitigate and manage adverse side effects effectively.

POLY (ADP-RIBOSE) POLYMERASE INHIBITORS: OVERVIEW

The use of poly (ADP-ribose) polymerase (PARP) inhibitor therapy is standard care in the management of patients with various malignancies including ovarian, breast, prostate, and pancreatic cancers. PARP inhibitors have been approved in different settings for patients with specific hereditary pathogenic variants, most notably homologous recombination repair pathways such as *BRCA1* and *BRCA2* genes.

The vast experience with PARP inhibitors (olaparib, niraparib, rucaparib) has been in the management of epithelial ovarian cancer (EOC). Studies first focused on the treatment of recurrent EOC and then their use as a maintenance strategy after platinum-based therapy. In 2020, ASCO published a comprehensive guideline on PARP inhibitor therapy in the management of EOC after ground-breaking studies in the first-line maintenance setting.[1] In 2022, a rapid update to the guidelines was issued to provide context to emerging survival data and revisions to the US Food and Drug Administration (FDA) indications, which occurred in the treatment setting and the maintenance therapy setting for the *BRCA1/2* wild-type population.[2] These are summarized in Table 1 and Figure 1.

The goal of this article is to highlight side effects of PARP inhibitors and focus on strategies to improve tolerance.

ADVERSE SIDE EFFECTS OF PARP INHIBITORS

It is challenging to obtain reliable real-world estimates of PARP inhibitor adverse events (AEs; frequency, grade) and dose modifications. It is likely that real-world events are similar to those reported in randomized clinical trials; however, given that strict eligibility criteria often lead to trial participants who are younger and fitter compared with community practice, it is possible that side effects are under-reported in clinical trials.[3]

The largest study of real-world experience was a longitudinal retrospective cohort analysis of the US MarketScan Commercial and Medicare Supplemental Databases.[4,5] The adverse effects were generally consistent with the safety reports from the randomized trials, which are, however, somewhat lower than those reported in clinical trials, as common toxicities (nausea, fatigue) may not be recorded in health care claims data unless severe enough for medical intervention. There are inherent limitations of such studies because of potential biases with using health care data, which are recorded for billing as opposed to research purposes. Dose reductions were required in 23%, 35%,

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PRACTICAL APPLICATIONS

- It is important to be proactive and take care to prevent and/or reduce the likelihood and impact of adverse effects associated with poly (ADP-ribose) polymerase (PARP) inhibitors. This could allow patients to continue treatment and potentially derive clinical benefit while enjoying good quality of life.
- The three approved PARP inhibitors (olaparib, niraparib, rucaparib) share several common adverse effects because of a class effect including nausea, fatigue, and anemia, but there are notable differences likely because of variations in their poly-pharmacology and off-target effects.
- Baseline doses may need to be modified on the basis of the PARP inhibitor being prescribed depending on renal and hepatic function and concomitant medications.
- Baseline dose reduction with niraparib is recommended for patients with platelet counts of <150,000/μL and/ a body weight of <77 kg.
- In patients with moderate renal impairment, olaparib should be started at a reduced dose of 200 mg twice a day, but dose reduction is not required for niraparib or rucaparib.

and 29% of patients on olaparib (n = 637), niraparib (n = 538), and rucaparib (n = 227), respectively, which are lower than those reported in clinical trials (Fig 2).[5] For example, in the PRIMA trial of maintenance niraparib after response to first-line chemotherapy, 71% of participants required a dose reduction, which was similar to the 66% requiring a dose reduction in the NOVA trial of maintenance therapy in participants with platinum-sensitive recurrent ovarian cancer after response to chemotherapy.[6,7]

An alternative source of real-world data is national databases of adverse drug reactions (ADRs) that are reported to regulatory authorities by clinicians even if they are uncertain whether there is a causal link with the drug.[8,9] However, only a minority of ADRs are reported and may underestimate important AEs.[9-11] Nonetheless, data repositories such as the FDA adverse event reporting system (FAERS) designed to support postmarketing surveillance provide important insights into ADRs including rare events that may not be observed in clinical trials.[8] Our discussion and commentary are based on the key adverse effects reported in the pivotal ovarian cancer clinical trials that led to the regulatory approvals for olaparib, niraparib, and rucaparib, but we also highlight relevant safety data including postmarketing reporting of ADRs that have emerged from real-world experience and provide guidance on management.

There have not been any head-to-head comparisons of PARP inhibitors in randomized trials, and we can only perform cross-comparison on the basis of the reported literature. They appear to be equally effective at least on the basis of comparison of hazard ratios across trials for similar indications in ovarian cancer.[12] The three approved PARP inhibitors for ovarian cancer share several common adverse effects because of a class effect including nausea, fatigue, and anemia, but there are also some notable differences likely because of variations in their polypharmacology and off-target effects.[11,13,14] They exhibit different binding affinities to PARP isoforms and may also inhibit transporters, kinases, and ion channels to a greater or lesser extent.[11,14,15] Rucaparib appears to be associated with higher incidence of adverse drug reactions reported probably because of many off-target effects.[11] There is high interindividual variability in pharmacokinetic exposure levels observed with olaparib, rucaparib, and niraparib, which could also account for some of the variability in adverse effects observed between patients as higher levels of exposure appear to be associated with greater toxicity, particularly hematologic.[13,14,16]

TABLE 1. PARP Inhibitors: FDA Indications (March of 2023) for Epithelial Ovarian Cancer[a]

Maintenance Therapy	PARP Inhibitor
First-line maintenance after response to platinum-based chemotherapy for newly diagnosed, advanced-stage, high-grade ovarian cancer	Olaparib (germline or somatic deleterious *BRCA* alteration) Olaparib with bevacizumab (germline or somatic deleterious *BRCA* alteration and/or HRD score positive) Niraparib (all—any *BRCA* or HRD status)
Second- or greater-line maintenance after response to platinum-based chemotherapy for recurrent platinum-sensitive ovarian cancer	Olaparib (all—any *BRCA* or HRD status) Rucaparib (all—any *BRCA* or HRD status) Niraparib (germline or suspected germline *BRCA* deleterious alteration)

Abbreviations: FDA, US Food and Drug Administration; HRD, homologous recombination–deficient; PARP, poly (ADP-ribose) polymerase.
[a]Of note, change in FDA approvals (as of March of 2023): (1) withdrawn indications for maintenance: second- or greater-line maintenance after response to platinum-based chemotherapy for recurrent platinum-sensitive ovarian cancer—niraparib in nongermline *BRCA* is no longer FDA-approved in this setting and (2) withdrawn indications for treatment—olaparib, rucaparib, and niraparib are no longer FDA-approved in this setting.

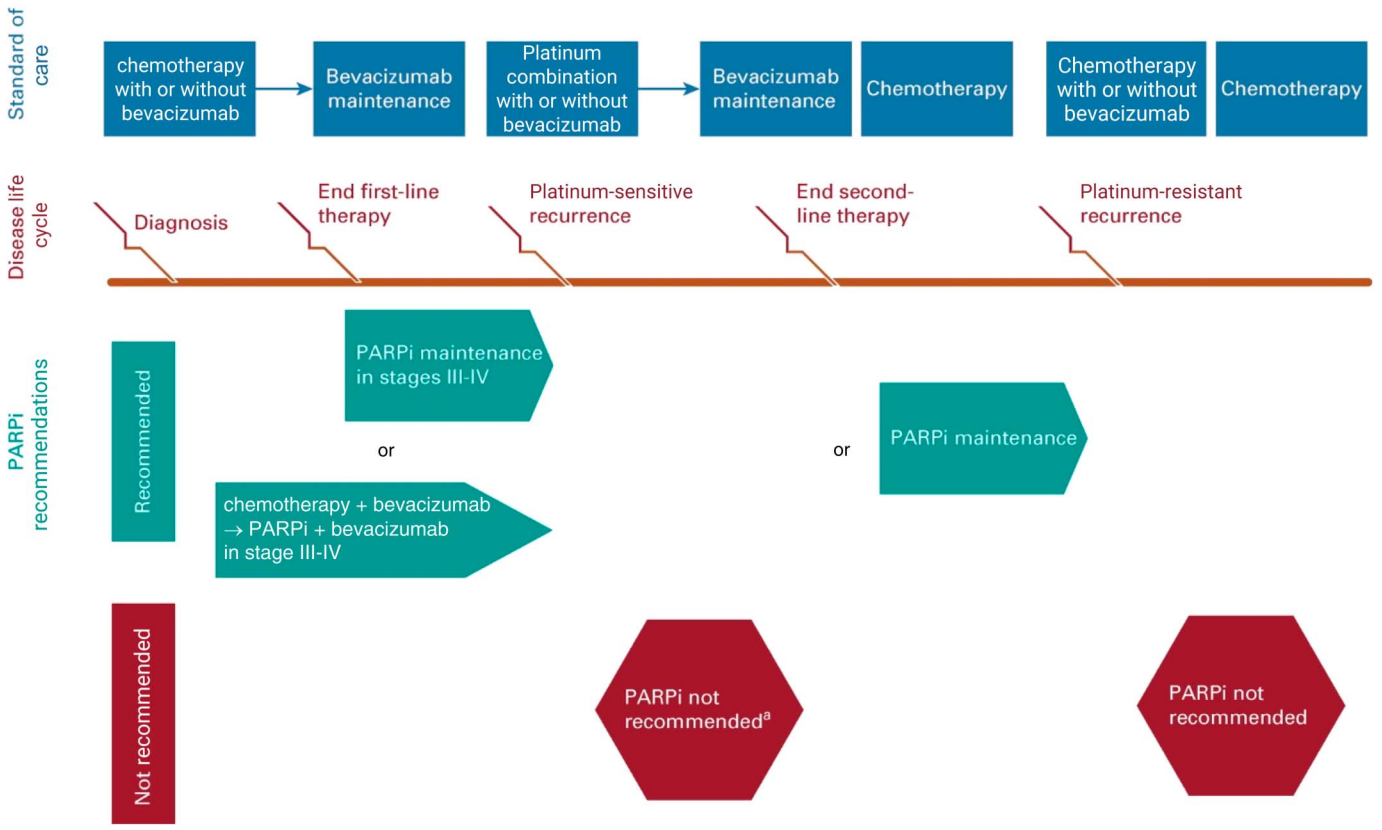


FIG 1. PARPi treatment indications: summary from ASCO rapid update guideline PARPi (Tew et al[2]). PARPi, poly (ADP-ribose) polymerase inhibitor. [a]Evidence on PARPi use as treatment in platinum-sensitive recurrence is evolving and data are continuing to emerge. Any decision to proceed with PARPi treatment in select populations should be based on individualized patient and provider assessment of risks, benefits, and preferences.

The defining characteristics of the three PARP inhibitors are summarized in Table 2 and 3 lists the frequency of AEs reported in the registration clinical trials, whereas Figure 2 lists the frequency of dose interruptions, reductions, and discontinuations in different disease settings.[4,6,7,17-23] Table 4 lists the recommended management for common AEs associated with PARP inhibitors. It is challenging to interpret the adverse effects reported in all clinical trials as they are typically presented in dense tables and include a long list of adverse effects including grading documented by clinicians over the long duration of the clinical trial. It is not possible to ascertain the timing, duration, and trajectory over time of the adverse effects from these tables or determine how they individually affect adherence and tolerability. Furthermore, it is important to acknowledge that there may be significant discordance in the frequency and grading of adverse effects reported by patients and clinicians.[24]

This article is not intended to be a definitive source for detailed prescribing information, or all the possible adverse effects associated with PARP inhibitors, but rather a summary of the more common and important adverse effects and approaches to their management. There are several excellent papers published on this topic, which are referenced for interested readers.[25-30] In addition, comprehensive prescribing information is provided by the pharmacologic companies for each of the approved PARP inhibitors. It is beyond the scope of this review to include adverse effects associated with PARP inhibitors combined with other agents.

SAFE PRESCRIBING AND STRATEGIES TO REDUCE THE LIKELIHOOD OF ADVERSE EFFECTS

First and foremost, it is important to be proactive and take care to prevent and/or reduce the likelihood and impact of adverse effects associated with PARP inhibitors. This could allow patients to continue treatment and potentially derive clinical benefit while enjoying good quality of life. It is essential to ensure that the patient is fully educated and well informed before commencing a PARP inhibitor and understands the potential benefits, as well as the possible adverse effects, and what is recommended to mitigate adverse effects. In addition, the patient should be made aware of the importance of close surveillance particularly in the first 12 weeks when many of the adverse effects occur such as nausea, vomiting, and hematologic toxicities including anemia and thrombocytopenia and require prompt intervention and management (Table 4).

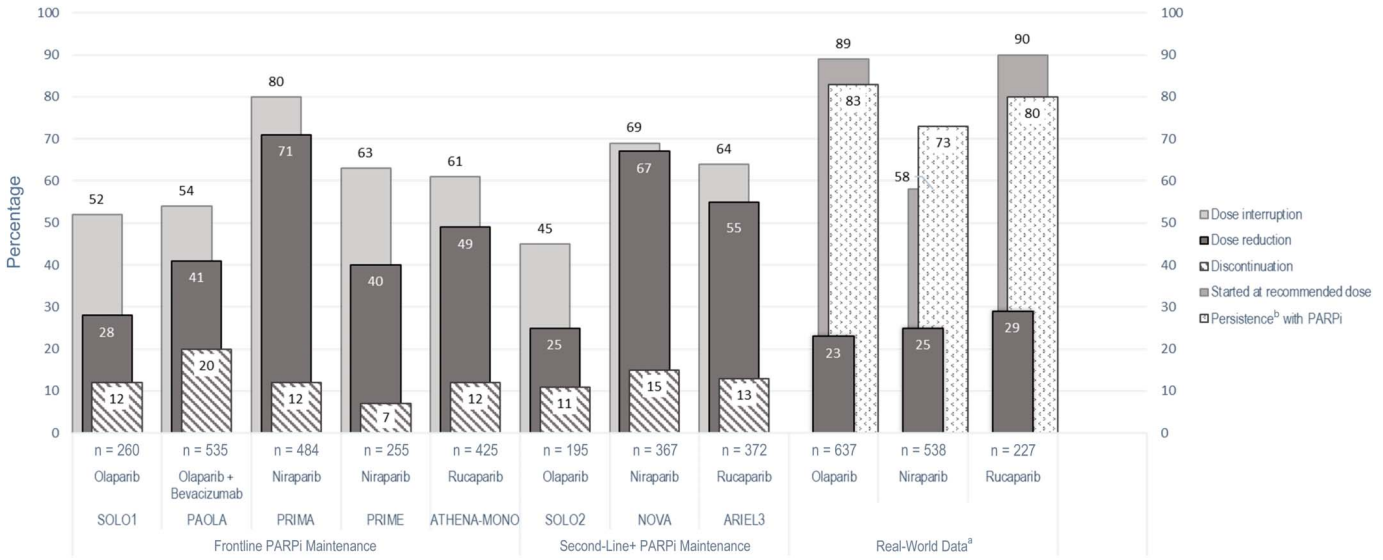
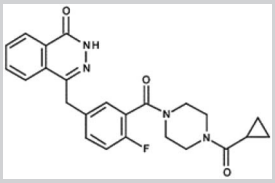
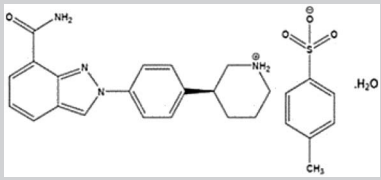
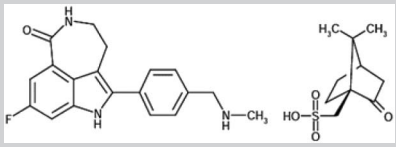


FIG 2. Dose interruptions, reduction, and discontinuation in studies of PARPi in frontline and second-line onward maintenance settings and real-world data. PARPi, poly (ADP-ribose) polymerase inhibitor. [a]Real-word data reported by O'Malley et al.[5] [b]Persistence was defined as the percentage of patients with no index PARPi regimen treatment gaps of >90 days of those with at least 6 months of continuous enrollment.

There are several factors to take into consideration before commencing a patient on maintenance treatment with a PARP inhibitor including the choice of PARP inhibitor, the starting dose, and when to commence maintenance therapy. Ideally, the patient should have recovered as much as possible from chemotherapy and should not start treatment <28 days after a last cycle chemotherapy to allow bone marrow recovery. The clinical trials allowed patients to commence maintenance therapy within 8-12 weeks depending on the trial.[6,7,17,19,22,23] In SOLO2, the predictors for reduced dose intensity included nausea at baseline and a performance status of 1 and delaying the start of treatment until symptoms are controlled would be prudent in such patients.[31] In NOVA, a weight of <77 kg and platelet counts of <150,000 μL were associated with greater hematologic adverse effects with 300 mg, once daily of niraparib, and this has led to recommendations to commence niraparib at 200 mg, once daily in patients who fit these criteria.[32,33] In the maintenance trials of PARP inhibitors in ovarian cancer, patients typically had to meet eligibility criteria including a hemoglobin of ≥10.0 g/dose level with no blood transfusion in the past 28 days, an absolute neutrophil count of ≥1.5 × 10^9/L, a platelet count of ≥100 × 10^9/L, a total bilirubin level of ≤1.5 × upper limit of normal (ULN), and a serum creatinine level of ≤1.5 × ULN. These eligibility criteria should be kept in mind when prescribing a PARP inhibitor. Although there is more flexibility in clinical practice than in clinical trials, it would be prudent to adhere as closely as possible to these criteria in practice.

Doses may also need to be modified on the basis of the PARP inhibitor being prescribed depending on renal and hepatic function and concomitant medications (Table 2). For example, in patients with moderate renal impairment, olaparib should be started at a reduced dose of 200 mg twice a day, but dose reduction is not required for niraparib or rucaparib.[13,14] Olaparib and rucaparib appear to be safe in patients with moderate hepatic impairment, but it is recommended that niraparib is reduced to 200 mg, once daily.[13,34] There are no data in patients with severe hepatic impairment, and it is advisable to avoid PARP inhibitors if this is the case. It is particularly important to take note of all concomitant medications as there may be important drug-drug interactions particularly in patients on olaparib.[35] Olaparib is primarily metabolized by CYP3A, and rucaparib is primarily metabolized by CYP2D6 and, to a lesser extent, by CYP1A2 and CYP3A4, whereas niraparib is metabolized by carboxylesterases.[35] Inhibitors or inducers of CYP3A4 may interact with olaparib, and the dose of olaparib should be reduced if being coadministered with a strong or moderate CYP3A4 inhibitor.[36] If a strong CYP3A inhibitor must be coadministered, the recommended olaparib dose reduction is to 100 mg, twice daily; if a moderate CYP3A inhibitor must be coadministered, the recommended olaparib dose reduction is to 150 mg, twice daily. The patient should be carefully monitored for AEs. Strong or moderate inducers of CYP3A4 should be avoided in patients on olaparib. There are good sources that can provide guidance on which drugs could interact with olaparib.[35,36] Dietary recommendations are also required for, in particular, advising patients on olaparib to avoid Seville oranges, starfruit, and grapefruit as they inhibit CYP3A4J5.[13,14] In addition, over-the-counter medications such as St John's

TABLE 2. Specific Characteristics of PARP Inhibitors

PARP Inhibitors	Olaparib	Niraparib	Rucaparib
Chemical structure			
Target	PARP-1, PARP-2, and PARP-3	PARP-1 and PARP-2	PARP-1, PARP-2, PARP-3
Formulation	Tablet[a]	Capsule	Tablet
Dose forms	150 mg, 100 mg	300 mg, 200 mg, 100 mg	300 mg, 250 mg, 200 mg
Storage	2°C-30°C	Up to 25°C	20°C-25°C
Method of administration	Swallowed whole, with or without food	Swallowed whole, with or without food	Swallowed whole, with or without food
Starting dose	300 mg BD	200 mg daily; or 300 mg daily if the weight is ≥77 kg or the platelet is ≥150,000/μL	600 mg BD
Dose adjustment because of AEs	DL-1: 250 mg BD DL-2: 200 mg BD DL-3: discontinue	If starting dose at 200 mg daily, DL-1: 100 mg daily DL-2: discontinue If starting dose at 300 mg daily, DL-1: 200 mg daily DL-2: 100 mg daily DL-3: discontinue	DL-1: 500 mg BD DL-2: 400 mg BD DL-3: 300 mg BD DL-4: discontinue
Mean terminal half-life	15 hours	36 hours	25.9 hours
Metabolism	CYP3A4	Carboxylesterase and conjugation (UDP-glucuronosyltransferases)	CYP2D6, CYP1A2, CYP3A, CYP2C9, and CYP2C19 substrates
Drug-drug interactions	CYP inhibitors,[b] CYP inducers[c]	NA	CYP inhibitors,[d] CYP inducers[d] Multidrug and toxin extrusion transporters (MATE-1, MATE-2K) Organic ion transporters (OCT1, OCT2)
Drug-food interactions	Grapefruit, star fruit, pomegranate, and seville oranges[e]	NA	NA
Elderly (older than 65 years)	No adjustments in starting dose, limited clinical data in patients older than 75 years	No adjustments in starting dose, but greater sensitivity of some older individuals cannot be ruled out	Safety data unknown
Renal adjustment	CrCl 51-80 mL/min: no adjustment CrCl 31-50 mL/min: 200 mg BD CrCl < 30 mL/min: not recommended	CrCl 30-89 mL/min: no adjustment Severe impairment/on dialysis: safety data unknown	CrCl 30-89 mL/min: no adjustment Severe impairment/on dialysis: safety data unknown
Hepatic adjustment	Child-Pugh grade A or B: no adjustment Child-Pugh grade C: not recommended	Mild impairment[f]: no dose adjustment Moderate impairment[f]: 200 mg daily Severe impairment[f]: safety data unknown	Mild impairment[f]: no dose adjustment Moderate—severe impairment[e]: safety data unknown

Abbreviations: AE, adverse event; BD, twice daily; DL, dose level; NA, not available; PARP, poly (ADP-ribose) polymerase; ULN, upper limit of normal.

[a]Olaparib is also available as 50 mg capsule formulation; however, this is not to be substituted with olaparib tablets on a milligram-to-milligram basis because of differences in the dosing and bioavailability of each formulation.

[b]Coadministration with strong or moderate CYP3A inhibitors is not recommended. If a strong CYP3A inhibitor must be coadministered, the recommended olaparib dose reduction is to 100 mg, twice daily; if a moderate CYP3A inhibitor must be coadministered, the recommended olaparib dose reduction is to 150 mg, twice daily. The patient should be carefully monitored for AEs.

[c]Coadministration with a strong or moderate CYP3A inducer is not recommended. The efficacy of olaparib may be substantially reduced if coadministered with strong or moderate CYP3A inducer.

[d]Strong CYP3A4 inhibitors and inducers are not recommended. Dose adjustment should be considered for CYP1A2, CYP2C9, and CYP3A4 substrates with a narrow therapeutic window. CYP1A2 or CYP2D6 inhibitors did not affect rucaparib exposure.

[e]These fruits are known to inhibit CYP3A4 and may increase olaparib plasma concentration.

[f]Mild hepatic impairment was defined as total bilirubin ≤1.5× ULN and any AST level, or bilirubin ≤ULN and AST > ULN; moderate hepatic impairment was defined as total bilirubin >1.5 to 3.0 × ULN and any AST; severe hepatic impairment was defined as total bilirubin >3.0 × ULN and any AST.

TABLE 3. AEs of Poly (ADP-ribose) Polymerase Inhibitors Reported in Front-Line Maintenance Trials and Real-World Data

	SOLO1[17,18]				PAOLA1[20]				PRIMA[6] (overall)				PRIMA[6] (individualized dosing subgroup)				ATHENA-MONO[19]				Real-World Data[4]		
	Olaparib (n = 260)		Placebo (n = 130)		Olaparib + Bevacizumab (n = 535)		Placebo + Bevacizumab (n = 267)		Niraparib (n = 484)		Placebo (n = 244)		Niraparib (n = 169)		Placebo (n = 86)		Rucaparib (n = 425)		Placebo (n = 110)		Olaparib	Niraparib	Rucaparib
Adverse Events	**All**	**≥G3**	**All**	**≥G3**	**All**	**≥G3**	**All**	**≥G3**	**All**	**≥G3**	**All**	**≥G3**	**All**	**≥G3**	**All**	**≥G3**	**All**	**≥G3**	**All**	**≥G3**	**CEI**	**CEI**	**CEI**
Hematologic, %																							
Anemia	**39**	*22*	10	2	**41**	*17*	10	<1	**63**	*31*	18	2	**50**	*23*	**28**	1	**47**	*29*	9	0	**39**	**48**	**42**
Neutropenia	23	9	12	5	18	6	16	3	**26**	*13*	7	1	**24**	*10*	7	1	**28**	*15*	7	1	17	24	23
Thrombocytopenia	11	1	4	2	8	2	3	<1	**46**	*29*	4	<1	**34**	*15*	5	1	24	7	1	0	19	**42**	**31**
Leukopenia	13	3	8	0	18	2	10	1	**28**	5	9	<1	**28**	5	11	0	NR	NR	NR	NR	17	24	23
General, %																							
Fatigue	**64**	4	**42**	2	**53**	5	**32**	1	**35**	2	**30**	<1	**48**	3	**36**	0	**56**	5	**37**	1	**26**	**28**	**30**
Musculoskeletal pain[a]	10	0	10	0	22	1	24	1	18	<1	19	0	**37**	1	**41**	0	**33**	<1	**32**	0	**28**	**26**	22
Hypertension	3	<1	8	2	**46**	*19*	**60**	*30*	17	6	7	1	17	5	9	2	NR	NR	NR	NR	**32**	**46**	**40**
Rash	10	0	11	0	3	0	4	<1	NR	NR	NR	NR	NR	NR	NR	NR	14	<1	7	0	5	3	7
Respiratory, %																							
Cough	18	0	22	0	NR	NR	NR	NR	15	0	14	<1	15	0	21	0	12	0	10	0	NR	NR	NR
Dyspnea	15	0	6	0	8	1	3	<1	18	<1	12	1	19	0	12	1	11	1	11	0	NR	NR	NR
GI, %																							
Nausea	**77**	1	38	0	**53**	2	22	1	**57**	1	**28**	1	**53**	1	21	0	**56**	2	**30**	0	**26**	**33**	43
Vomiting	**40**	<1	15	1	22	1	11	2	22	1	12	1	17	0	9	1	24	1	12	0	3	5	8
Diarrhea	**34**	3	**25**	0	18	2	17	2	19	1	23	<1	14	1	23	0	24	1	21	2	13	19	19
Constipation	**28**	0	19	0	10	0	10	<1	**39**	<1	19	0	**33**	1	16	1	19	0	16	0	7	6	11
Dysgeusia	**26**	0	4	0	8	<1	1	0	NR	NR	NR	NR	NR	NR	NR	NR	21	<1	6	0	NR	NR	NR
Abdominal pain	24	2	18	1	19	1	20	2	22	1	31	<1	**28**	2	**37**	2	**25**	1	**28**	2	NR	NR	NR
Decreased appetite	20	0	10	0	8	<1	4	<1	19	1	8	0	19	1	5	0	18	1	15	0	NR	NR	NR
AST/ALT elevation	NR	NR	NR	NR	NR	NR	NR	NR	11	2	7	0.4	8	2	7	1	**43**	11	8	1	0	1	2
Acute kidney injury[b]	8	0	2	0	6	0	1	0	12	<1	4	0	12	1	5	0	11	<1	6	0	9	14	18
Nervous system disorders, %																							
Headache	23	<1	24	2	14	<1	13	1	**26**	<1	15	0	22	1	17	0	20	1	15	0	NR	NR	NR
Dizziness	20	0	15	1	5	<1	4	<1	15	0	11	<1	11	0	11	0	13	0	8	0	NR	NR	NR
Insomnia	10	0	12	0	4	<1	4	0	**25**	1	14	<1	21	0	14	0	14	<1	7	0	5	10	10

NOTE. AEs with ≥10% G3 reported are given in italics, and AEs with ≥25% all grade reported are given in bold.

Abbreviations: AE, adverse event; CEI, clinical events of interest; G3, grade 3; NR, no response.

[a]Musculoskeletal pain includes arthralgia, backpain, pain in extremity, myalgia, and other related terms.

[b]Acute kidney injury includes blood creatinine increased, blood urea increased, and renal failure.

TABLE 4. Recommended Management for Common AEs Because of PARP Inhibitors[a]

General approach	Ensure that the patient has adequately recovered from chemotherapy; aim to start maintenance PARP inhibitor within 8-12 weeks of last cycle of chemotherapy Consider potential drug interactions with PARP inhibitors, which may affect the starting dose or choice of PARP inhibitor Proactively educate patients about the range of possible AEs, action plans, and frequency of investigations Implement close surveillance particularly in the first 12 weeks of treatment when AEs commonly occur	
AE	**Low-Grade Symptoms (or initial management)**	**High-Grade Symptoms (or follow-up management)**
Nausea with or without vomiting	Do not replace vomited dose; take next dose at scheduled time Consider prophylactic metoclopramide 30-60 minutes before PARP inhibitor and taking with a light meal Treat gastroparesis and dyspepsia when indicated Consider antiemetics such as metoclopramide or 5-HT3 antagonist for symptom management Consider taking PARP inhibitor later in the day (10 AM instead of 8 AM) at twice daily dose schedule or at night before bed for daily dose schedule (niraparib)	Dose interruption until AE resolves to grade 1 or less Exclude other causes (partial or complete bowel obstruction) Resume the same dose with prophylactic antiemetic therapy Dose reduction if AE recurs despite prophylactic therapy
Fatigue	Encourage a balance of physical activity and energy conservation. Tailor realistic expectations with structured daily routine Consider nonpharmacologic intervention: massage therapy and psychosocial interventions Optimize treatment for depression, sleep dysfunction, and nutritional deficit	Dose interruption until AE resolves to grade 1 or less Exclude anemia, electrolyte imbalance, or endocrine dysfunction as the contributing cause Exclude depression as a contributor Resume the same dose or consider dose reduction if AE recurs despite supportive management
Anemia	Workup investigations to exclude other causes of anemia including iron, vitamin B12, folate deficiencies, or hypothyroidism Consider a short period of dose interruptions without dose reduction	Dose interruption when Hb $<$ 8 g/dL, and bloods should be monitored weekly until Hb returns to $\geq$9 g/dL Blood transfusion is recommended when Hb $<$ 7 g/dL or higher levels if symptomatic or significant comorbidities are present Once recovered, resume PARP inhibitor at the same or reduced dose level (if dose interruption took place because of symptomatic anemia) If AE not recovered after 4 weeks or repeated occurrence, the patient should be referred to a hematologist to exclude MDS/AML
Neutropenia	Observe asymptomatic cases	Dose interruption when the neutrophil count is $<1.0 \times 10^9$/L, and bloods should be monitored weekly until recovery Once recovered, resume PARP inhibitor at a reduced dose level If AE is not recovered after 4 weeks or repeated occurrence, the patient should be referred to a hematologist to exclude MDS/AML
Thrombocytopenia	Review concomitant medications to exclude other causes of thrombocytopenia For niraparib Ensure that weight-based dosing was used for those $<$77 kg Dose interruption when the platelet count is $<100 \times 10^9$/L, and bloods should be monitored weekly until the platelet count is $\geq 100 \times 10^9$/L For olaparib and rucaparib, Dose interruption when the platelet count is $<50 \times 10^9$/L, and bloods should be monitored weekly until the platelet count is $\geq 100 \times 10^9$/L	Platelet transfusion recommended when the platelet count is $<10 \times 10^9$/L or higher if bleeding or on anticoagulants For niraparib: dose reduction if the platelet count falls to $<75 \times 10^9$/L or higher if bleeding For olaparib/rucaparib: dose reduction if the platelet count falls to $<50 \times 10^9$/L or higher if bleeding If AE is not recovered after 4 weeks or repeated occurrence, the patient should be referred to a hematologist to exclude MDS/AML

Abbreviations: 5-HT3, 5-hydroxytryptamine-3; AE, adverse event; MDS, myelodysplastic syndrome; PARP, poly (ADP-ribose) polymerase.
[a]It is important to refer to prescribing information for guidance on dosing, dose interruptions, and dose reductions for each PARP inhibitor.

Wort, which is among the most commonly used herbal medications in the United States, should be avoided as it is an inducer of CYP3A4. It is important to take care in the choice of antibiotics if required later in patients on olaparib because of potential drug-drug interactions (eg, ciprofloxacin, erythromycin) and a pharmacist should be consulted if in doubt. There is also a risk for drug-drug interactions when rucaparib is coadministered with substrates of multidrug and toxin extrusion transporters MATE-1 and MATE-2K and the organic ion transporters OCT1 and OCT2 such as metformin.[13,35] It is suggested that dose adjustments and close monitoring of patients on rucaparib should be considered for CYP 1A2, CYP2C9, and CYP3A4 substrates particularly for drugs with a narrow therapeutic index such as theophylline.[37]

MANAGING ADVERSE EFFECTS OF PARP INHIBITORS

GI Adverse Effects

A recent meta-analysis of phase II and III randomized trials with PARP inhibitors across all cancer types found that PARP inhibitors significantly increased the risk of all-grade nausea, vomiting, diarrhea, and decreased appetite although not constipation.[38] Patients with ovarian cancer have a higher risk of all-grade nausea and vomiting compared with other cancers for reasons that are unclear.[39] There is a paucity of real-world data on the incidence of GI side effects with PARP inhibitors apart from relatively small single-institution reports, which mirror the experience in clinical trials. There is a tendency to report only severe adverse effects in the FAERS or similar reporting systems in other countries, and it is likely that GI side effects would be underreported in them.[40]

Nausea and vomiting. Nausea and, to a lesser extent, vomiting are among the most common adverse effects associated with all the three FDA-approved PARP inhibitors (olaparib, niraparib, and rucaparib) in patients with ovarian cancer and thought to be mediated through off-target kinase inhibition.[41] They are a class effect and reported in over 75% of patients although grade 3 or 4 nausea and vomiting are uncommon at 1%-2% (Table 3). According to National Comprehensive Cancer Network (NCCN) guideline criteria, they would all be considered moderately high emetogenic agents although they are quite different from chemotherapy on which the guidelines are based.

Nausea typically occurs within the first few days to weeks of starting treatment, is usually low grade in most patients, and lessens and/or resolves over time although it may persist in a subset.[25] In patients who only develop these symptoms of nausea and vomiting after the first 3 months of starting treatment, alternative causes such as tumor progression should be excluded. The median time to first onset of nausea with olaparib tablets in the SOLO1 trial was 4 days (range, 0.03-21.49 months), and the median duration was 1.4 months.[42] The median time to first onset of vomiting was 1.46 months (range, 0.03-20.60 months), and the median duration was 2 days.[42] Relatively few patients discontinue PARP inhibitors because of nausea or vomiting, and proactive efforts should be taken to prevent and treat nausea and vomiting given the high incidence across all studies. In SOLO1, 3% of patients discontinued olaparib because of nausea, which was similar in the placebo arm (2%), and 1.9% ceased because of vomiting.[17] Nonetheless, even low-grade nausea and vomiting can affect quality of life particularly if persistent, and it is therefore important to educate and inform the patient of these adverse effects including the time course and trajectory over time, the approaches to mitigate them, and strategies to prevent or lessen their impact.

There have not been any controlled trials of antiemetics in patients treated with PARP inhibitors, and guidance is based on expert opinion and experience (Table 4). First and foremost, supportive treatment including antiemetics for prophylaxis and treatment are usually effective and dose interruption and dose reduction were only required in 5% of patients in SOLO1 for nausea and in none for vomiting.[17,42] Antiemetics such metoclopramide or domperidone or olanzapine are usually sufficient in most patients, whereas serotonin 5-hydroxytryptamine-3 receptor antagonists may be of value in selected patients for a short duration but are commonly associated with constipation. There are anecdotal reports that pyridoxine (vitamin B6), which is commonly used for pregnancy-associated nausea and vomiting, may be effective in some patients and is cheap and safe.[43] Dexamethasone is rarely used if ever needed and ideally avoided. The neurokinin-1 receptor antagonist aprepitant should be avoided with olaparib as it is a CYP3A4 inhibitor and can interact with it.[13,25] Anecdotally, advising patients to take the PARP inhibitor with food or shortly after eating and administering a prokinetic agent such as metoclopramide 30-60 minutes before the PARP inhibitor can help prevent or reduce nausea, which is prevalent in the first few weeks of starting treatment.[25,27-29] In patients on niraparib, which is administered once a day, taking the capsules at night before bed may be associated with less nausea and may be complemented by taking metoclopramide 30 minutes before if needed. In some patients with troublesome nausea, dose interruptions can be helpful and if ongoing despite antiemetics, dose reductions are usually effective. Patients who had dose reductions for any reasons in clinical trials could not re-escalate to the starting dose, whereas this may be considered in clinical practice for adverse effects such as nausea or vomiting although it would be ill advised if the dose reduction was for grade 3 or 4 anemia or thrombocytopenia.[44] It should be noted that recent analyses showed no adverse outcomes with respect to progression-free survival in patients with protocol-mandated dose reductions or interruptions for adverse effects.[31]

Other GI AEs. There are several other GI adverse effects including reduced appetite, dysgeusia constipation, diarrhea, abdominal pain, and symptoms of reflux. These can differ between the three PARP inhibitors (Table 3). For example, there was more constipation with niraparib on the basis of ADR reports in the United Kingdom.[11] These adverse effects can be managed effectively on the basis of standard practice, for example, proton pump inhibitors or prokinetic agents such as metoclopramide for reflux symptoms, laxatives for constipation, and loperamide for diarrhea. GI symptoms may also herald recurrence of ovarian cancer and include cramping abdominal pain, bloating, nausea, and vomiting.

Fatigue

Fatigue is a very common adverse effect associated with all PARP inhibitors and has been reported to occur in up to 60%-70% of patients with most having low-grade fatigue.[45] For example, in SOLO1, 64% of patients reported any-grade fatigue compared with 42% on placebo, with 4% of patients having grade 3 or 4 fatigue on olaparib and 2% on placebo.[42,46] Perhaps more important than the percentage of patients reported to have fatigue over the duration of the trial are the timing, duration, and trajectory over time. This was analyzed by Colombo et al[42] who reported that about 40% of patients experienced fatigue at 1 month after starting olaparib, which was mostly low grade, but importantly persisted over 2 years and was about twice as high as a placebo.

Interestingly, the findings are somewhat different from the responses of patients in SOLO1 to the question (GP1) in functional assessment of cancer therapy - ovarian, "I have a lack of energy," which could be considered as a surrogate for fatigue. Almost 80% of patients on olaparib reported lack of energy compared with 70% on placebo, which was mostly mild-moderate in both groups with a similar number of patients reporting more severe symptoms in the olaparib and placebo arms over 2 years.[47] These data underscore the high prevalence and impact of fatigue/lack of energy in ovarian cancer survivors including those not on a PARP inhibitor and the need to address this symptom. It is beyond the scope of this review to cover management in detail, but approaches include exercise programs and cognitive behavioral therapy as well as excluding reversible and treatable causes such as anemia, hypothyroidism, and depression. Insomnia is also very common in ovarian cancer survivors and could exacerbate symptoms of fatigue (see Table 4 and NCCN guidelines).[48]

Hematologic Adverse Effects

Hematologic adverse effects including anemia, neutropenia, and thrombocytopenia are common with all the PARP inhibitors, but there are some notable differences between them.[49] A recent meta-analysis that included over 9,000 patients enrolled in 29 randomized controlled trials reported that PARP inhibitors significantly increased the risk of all-grade anemia (risk ratio (RR), 2.32; 95% CI, 1.78 to 3.01; $P < .00001$), neutropenia (RR, 1.69; 95% CI, 1.38 to 2.07; $P < .00001$), and thrombocytopenia (RR, 2.54; 95% CI, 1.87 to 3.45; $P < .00001$).[49] Inhibition of PARP-2, in particular, as well as PARP trapping, is believed to be responsible at least in part for the hematologic toxicities.[30,50] In addition, thrombocytopenia may also be related to the volume of distribution (Vd) and bone marrow exposure, which could explain the higher risk of thrombocytopenia with niraparib as it has a Vd value of 1,074/L compared with 420/L for rucaparib and 158/L for olaparib.[14]

Close monitoring of patients particularly in the first 12 weeks after commencing a PARP inhibitor is required as hematologic adverse effects usually occur early but not invariably, and regular blood counts should continue while patients are on treatment. Anemia is the most common hematologic toxicity observed with PARP inhibitors and typically is macrocytic, and although it is not due to folate or B12 deficiency, grade 3/4 anemia was observed in 22% of patients on olaparib, 27% of patients on rucaparib, and 31% of patients on niraparib in the first-line maintenance therapy ovarian cancer trials.[6,17-19] Anemia should be managed with dose interruptions and dose reductions if dose interruption for symptomatic anemia is required. Transfusions should be used if the hemoglobin level falls to <7 g/dL accompanied by a dose reduction (Table 4).

Thrombocytopenia is also an important adverse effect. All-grade thrombocytopenia was observed in 11% of patients in SOLO1, 24% in ATHENA, and 46% in PRIMA.[6,17,19] More importantly, grade 3 or 4 thrombocytopenia was reported in 29% of patients in the PRIMA trial, 7% in ATHENA, and 1% in SOLO1.[6,17,41] Given the high incidence of thrombocytopenia with niraparib, it is recommended that patients with baseline platelet counts of <150,000/μL and/ a body weight of <77 kg should be treated with a reduced dose of 200 mg, once daily instead of 300 mg, once daily as they appear to have a higher risk of thrombocytopenia.[32] In the PRIME trial, which is a first-line maintenance trial of niraparib vs placebo that was performed in China, the incidence of grade 3 or 4 thrombocytopenia was 14% using the reduced dose of niraparib according to the above criteria.[21] It is worth noting that in the PRIME trial, which used individualized starting doses of niraparib, 40% of patients commenced on 200 mg, once daily still required further dose reductions. The median time to first dose reduction or interruption was 29 days. Dose reductions did not compromise patient outcomes.[51]

The niraparib prescribing information advises that patients should have weekly full blood counts in the first month of starting niraparib as thrombocytopenia typically occurs early, then monthly for the next 11 months, and periodically

thereafter.[52] If the platelet count falls to $<100 \times 10^9$/L, niraparib should be discontinued until the platelet count increases to above 100,000/μL, and if it falls to $<75 \times 10^9$/L, it should be restarted with a dose reduction once the level rises to >100,000/μL, provided that the count has recovered within 28 days (Table 4). The prescribing information also recommends platelet transfusions if the platelet count drops to $<10 \times 10^9$/L. If patients are on anticoagulants or antiplatelet agents, then consider interrupting these agents and have a lower threshold for platelet transfusions. Thrombopoietin receptor agonists such as avatrombopag have been reported to rapidly mitigate niraparib-associated thrombocytopenia and, in a small case series, enabled patients to continue therapy.[53] The dose interruption criteria are somewhat different with olaparib and rucaparib, and prescribing recommendations are that treatment should be temporarily discontinued only if the platelet count falls $<50 \times 10^9$/L and recommenced once it has recovered at either the same dose or a dose reduction depending on how low and how long the thrombocytopenia persists, with guidance provided in prescribing information for each agent. Close monitoring is recommended for platelet count between 50-75 $\times 10^9$/L, and dose interruption can be considered at the clinician's discretion.

Grade 3/4 neutropenia is common (20% with niraparib in PRIMA; 9% with olaparib in SOLO1, and 15% with rucaparib in ATHENA), and febrile neutropenia is rare.[6,17-19] Grade 3 or 4 neutropenia is managed with dose interruption until the platelet count recovered to $>1.5 \times 10^9$/L and dose reduction as well. Growth factors are not required.

Cardiovascular Adverse Effects

The most important cardiovascular adverse effect is hypertension. Niraparib is the only PARP inhibitor reported to cause hypertension, which may be due to an off-target inhibition of the kinase DYRK1A, which may increase levels of neurotransmitters in the dopaminergic system.[54] Hypertension was reported in 17% of patients in the PRIMA trial, with only 6% being grade 3 or greater.[6] The median time to first onset was 43 days in PRIMA, and there were no discontinuations because of hypertension. Hypertension can be managed with antihypertensive agents, but care should be taken to ensure that blood pressure is well controlled before commencing niraparib in patients with a history of hypertension. On commencing niraparib, blood pressure should be monitored regularly, at least weekly for the first 2 months, then monthly for the first year, and periodically thereafter. It should be noted that rare cases of hypertensive crises were reported postmarketing and could develop as early as within the first month of niraparib. In cases of hypertensive crisis or medically significant hypertension that cannot be adequately controlled with antihypertensive therapy, niraparib should be discontinued.[55]

Arrhythmias including tachycardia and palpitations have also been reported with niraparib. Postmarketing ADR reports include rare cases of hypotension with olaparib and rucaparib and arrhythmias with rucaparib.[8,11]

Neurologic Adverse Effects

Headaches have been reported in between 20% and 25% of patients treated with olaparib, niraparib, and rucaparib (Table 3). However, the incidence is similar to that reported in the placebo arms of all the trials. For example, in SOLO1, headache was reported in 23% of patients on olaparib and 24% on placebo and was in the majority low-grade and likely incidental rather than related.[17] Rarely, psychiatric adverse effects have been reported in postmarketing reports including mania, anxiety, and depression.[36,37,52] They have been reported with all PARP inhibitors although there was a trend suggesting that they may be higher with niraparib, which may be due to its higher blood brain barrier penetration. Posterior reversible encephalopathy syndrome has been reported with niraparib in 0.1% of patients treated and can occur in association with hypertension or with normal blood pressure during the first month of niraparib.[52] The diagnosis should be suspected in patients who present with seizures, headaches, cortical blindness, or visual disturbance and should be confirmed with an magnetic resonance imaging. This is potentially life-threatening, and niraparib should be ceased and not restarted.[55]

Laboratory Abnormalities That May Occur on PARP Inhibitors

There are a number of abnormal nonhematologic laboratory results that may occur in patients on PARP inhibitors and can vary depending on the PARP inhibitor. An elevated creatinine (grade 1 or 2) is observed in 10%-15% of patients on olaparib and rucaparib although not niraparib. This is due to inhibition of renal transporter proteins such as MATE 1 and MATE 2 and does not necessarily imply a decline in glomerular filtration rate or require dose modification, but alternative causes should be excluded.[56,57] Rucaparib is commonly associated with elevated levels in ALT/AST, with elevated levels occurring in just over 40% of patients in ATHENA-MONO.[19,57] These mostly grade 1 or 2 and transient but grade 3 or 4 elevations occur in 10%, which requires dose interruptions until levels are grade 2 or lower and dose reduction. Elevated ALT/AST is also observed in about 11% of patients treated with niraparib but almost always low grade. Dose interruption/reductions are not required for grade 1 or 2 elevations in ALT/AST. Elevated cholesterol levels are common with rucaparib, but grade 3 or 4 is reported in only 2%-4% of patients.[57] Statins may be required depending on the level and other risk factors.

Myelodysplastic Syndrome and AML

Treatment-related myeloid neoplasms (t-MNs), myelodysplastic syndrome (MDS), and AML are the most significant and clinically important adverse effects that have been

associated with PARP inhibitors. A recent meta-analysis that included 5,693 patients treated with a PARP inhibitor and 3,406 with placebo reported that PARP inhibitors increased the risk of MDS and AML with an overall risk of 2.63 (CI, 1.13 to 6.14; $P = .026$).[58] The incidence of MDS/AML was 0.73% across all PARP inhibitors compared with 0.47% in controls. The risk is related in part to the number of previous lines of chemotherapy, with a lower incidence of MDS/AML observed in the first-line maintenance trials compared with the recurrent setting. In SOLO1, which has the longest follow-up of all the first trials, one additional case was reported in the 7-year follow-up since the primary analysis in 2018 in the olaparib arm and 1 case in the placebo arm.[59] The overall incidence of MDS/AML was 1.5% in the olaparib arm (n = 260) and 0.8% in the placebo arm (n = 130) in SOLO1.[59] Similar findings have been reported in PAOLA, PRIMA, and ATHENA-MONO.[6,19,20] By contrast, the 5-year follow-up of SOLO2 reported that 8% of 195 patients were diagnosed with MDS (5%) or AML (3%) compared with 4% treated with placebo (n = 99).[22] Some of the patients in the placebo arm were diagnosed with AML/MDS after receiving subsequent chemotherapy and a PARP inhibitor.

The authors of the meta-analysis referred to above also interrogated the WHO pharmacovigilance database, which included 178 cases of MDS/AML, and looked at median treatment duration, latency, presenting features, and outcomes. There was clinical information available for only about 30% of cases; the median treatment duration was 9.8 months, the median latency period since first exposure and diagnosis of MDS/AML was 17.8 months, and the mortality was 45% in the 104 cases.[58]

Delayed cytopenia after the first 3 months of commencing a PARP inhibitor with pancytopenia, bicytopenia, or thrombocytopenia may be an early safety signal and identify patients at potential risk of t-MNs.[60] There is evidence to suggest that pre-existing TP53 clonal hematopoiesis of indeterminate potential variants before commencing a PARP inhibitor may be associated with t-MN and that in patients with cytopenias, the risk of t-MN is increased in the presence of these variants.[61] Clinicians should be alert to this possibility, treatment should be interrupted, and a hematologic consultation and bone marrow biopsy are advised. Conventional cytogenetics is recommended as about 30% of cases of t-MN may not meet morphologic dysplasia criteria as reported in a comprehensive study from France.[60] Complex karyotypes, frequent TP53 mutations, and a high rate of mutations in DNMT3A and TET2 are commonly observed.[62] The mortality of MDS and AML is high and a devastating consequence of treatment. It is beyond the scope of this review to discuss the management of patients with t-MNs.

Pneumonitis

PARP inhibitors have been linked to a risk of pneumonitis, most notably with olaparib and niraparib. According to a recent meta-analysis involving 5,771 patients treated with a PARP inhibitor (or control), PARP inhibitors increased the risk of pneumonitis with the Peto odds ratio of 2.68 (95% CI, 1.31 to 5.47; $P = .007$).[63] In patients treated with a PARP inhibitor, the incidence of all-grade pneumonitis was 0.79% (28 of 3,551), whereas it was 0.24% (5 of 2,060) in those treated with control.[63] The median time to event onset for pneumonitis associated with PARP inhibitors was 81 days, with most cases occurring during the first 6 months of treatment (IQR, 27-131).[63] The diagnosis should be suspected in patients with unexplained shortness of breath and confirmed on radiologic investigations where the features are consistent with interstitial lung disease.[64] Treatment includes cessation of the PARP inhibitor and commencement of corticosteroids.

Cutaneous Toxicities

All three of the licensed PARP inhibitors have been associated with cutaneous toxicities, but only the ARIEL3 trial specifically reported incidence of rash (12%, n = 46 of 372), pruritus (13%, n = 47 of 372), any-grade photosensitivity reactions (17%, n = 64 of 372), and peripheral edema (10%, n = 39 of 372).[23,25] There were only a few grade 3 AEs (1% or less), and the toxicities were mainly low grade.[23] When starting PARP inhibitor therapy, it is important to alert patients to the possibility of photosensitivity and to consider sun protection using sunscreen and hats and liberal use of skin moisturizers when appropriate.

SPECIAL POPULATIONS

Older Age

Women older than 65 years are under-represented in clinical trials, and there is a paucity of data on the efficacy and safety of PARP inhibitors in older patients. Only 20% of patients in SOLO2 were older than 65 years and met eligibility criteria to be enrolled in the trial limiting interpretation of analyses of safety and efficacy.[65] However, there did not appear to be any differences in dose interruptions and dose reductions in older patients or any safety signals. By contrast, very different findings were reported in ARIEL 3, which reported higher incidence of grade 3 toxicities in patients older than 65 years (70% *v* 54%) and higher percentage of dose reductions (71% *v* 47%) and dose discontinuations (21% *v* 12%) in older patients versus younger.[66] In PAOLA, patients older than 70 years had higher rates of grade 3 or 4 anemia and grade 3 or 4 neutropenia and higher incidence of severe hypertension than patients younger than 70 years.[67] A recent meta-analysis that included 4,364 patients enrolled in eight phase III trials of PARP inhibitors demonstrated that they were as effective in patients older than 65 years as in younger patients.[68] Safety information was limited to hematologic toxicities that were available in only a subset of patients and suggested that there may be a higher risk of thrombocytopenia in older patients. It

has been suggested that geriatric assessment should be considered in older patients before commencing a PARP inhibitor, which we agree with.[69] Real-world studies of PARP inhibitors in older populations are required as participants in clinical trials may not be representative.

Ethnicity

White patients dominate the patient populations enrolled into most trials of PARP inhibitors, and it is possible that there might be differences in safety and efficacy in different ethnic and racial groups. However, on the basis of limited information, it appears that safety and tolerability of PARP inhibitors are similar in Asian populations to White populations although there is a trend toward higher incidence of hematologic adverse effects, but this is an area that requires more research.[70]

CONCLUSIONS

PARP inhibitors are playing an increasingly important role in the treatment of EOC and breast, prostate, and pancreatic cancers, particularly in patients with pathogenic variants in *BRCA1* and *BRCA2* but also among those with other mechanisms of homologous recombination deficiency. The benefits and the adverse effects associated with PARP inhibitors have been very well documented in clinical trials, but less well so in real-world settings. Patients included in clinical trials are often younger with a good performance status and less comorbidities than the real-world population, and hence, the potential benefits and adverse effects of treatment with PARP inhibitors may not be superimposable in older patients or those with medical comorbidities or those who are on medications that might have precluded them from entry onto clinical trials. It is incumbent on us as clinicians to be aware of the long list of potential adverse effects associated with PARP inhibitors and to ensure that where possible they are prevented or mitigated and managed effectively. It is also imperative to educate and inform patients and their families about what to expect including the potential adverse effects including their timing, trajectory, and treatment and stress the importance of close monitoring in the first few months of starting treatment with appropriate management of adverse effects as outlined above. Awareness of the potential for drug-drug interactions as well as identifying those patients at greater risk of adverse effects is important and affects the choice of PARP inhibitor, the starting dose, and intensity of follow-up. Meticulous attention to all these factors is likely to improve tolerability and permit patients to continue treatment. It appears that the adverse effect profile will be less with the next generation of selective PARP1 inhibitors[71] but for the foreseeable future, we need to focus on the PARP inhibitors that we have access to in clinical practice and take the effort to understand how best to use them and how to avoid and manage the adverse effects.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Antibody-Drug Conjugates in Gynecologic Cancer

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Overview

The present article reviews the current evidence for antibody-drug conjugates (ADCs) in gynecologic cancer. ADCs consist of a highly selective monoclonal antibody for a tumor-associated antigen and a potent cytotoxic payload conjugated through a linker. Overall, the toxicity profiles of ADCs are manageable. Ocular toxicity is a known class effect of some ADCs and is managed with prophylactic corticosteroid and vasoconstrictor eye drops as well as dose interruptions/holds and dose modifications. In ovarian cancer, mirvetuximab soravtansine, an ADC targeting alpha-folate receptor (FRα), received US Food and Drug Administration (FDA) accelerated approval in November 2022 after data from the single-arm phase III SORAYA trial. A second ADC targeting FRα, STRO-002, received FDA fast track designation in August 2021. Multiple studies with upifitamab rilsodotin, an ADC comprising a NaPi2B-binding antibody, are underway. In cervical cancer, tisotumab vedotin, an ADC-targeting tissue factor, received FDA accelerated approval in September 2021 after the phase II innovaTV 204 trial. Tisotumab vedotin in combination with chemotherapy and other targeted agents is currently being evaluated. Although there are no currently approved ADCs for endometrial cancer, there are many under active evaluation, including mirvetuximab soravtansine. Trastuzumab-deruxtecan (T-DXd), an ADC targeting human epidermal growth factor receptor 2 (HER2), is currently approved for HER2-positive and HER2-low breast cancer and shows promise in endometrial cancer. Like all anticancer treatments, the decision for a patient to undergo therapy with an ADC is a personal choice that balances the potential benefits with the side effects and requires thorough and compassionate support of their physician and care team and shared decision making.

INTRODUCTION AND ANTIBODY-DRUG CONJUGATE STRUCTURE

Treatment of gynecologic cancers is becoming more targeted with biomarker-directed therapy. For example, in ovarian cancer, three poly (ADP-ribose) polymerase (PARP) inhibitors are approved for patients with *BRCA* mutations or homologous recombination deficiency after progression on multiple lines of therapy or in the maintenance setting for newly diagnosed cases.[1] In cervical cancer, the US Food and Drug Administration (FDA) approved the immune checkpoint inhibitor (ICI) pembrolizumab in 2021 for use in combination with chemotherapy, with or without bevacizumab (monoclonal antibody against vascular endothelial growth factor), for recurrent or metastatic tumors expressing PD-L1.[2] In endometrial cancer, pembrolizumab was FDA approved in 2022 for advanced tumors that are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).[3] Recent updates in 2023 for the RUBY trial and GY-018 trial offer promise to move checkpoint inhibition into the first-line treatment of endometrial cancer.[4,5] Despite these advancements, additional strategies are needed to more specifically target tumor antigens and enhance drug delivery directly to the tumor.

A promising new treatment modality for cancer is the use of antibody-drug conjugates (ADCs), which have been FDA approved for breast cancer, lymphoma, multiple myeloma, gastric, and ovarian cancer.[6,7] ADCs combine the tumor-targeting capabilities of monoclonal antibodies with cytotoxic agents. There are three components to ADCs: (1) a highly selective monoclonal antibody for a tumor-associated antigen, (2) a potent cytotoxic agent designed to induce cell death when internalized in the tumor cell, and (3) a linker that is stable in circulation and releases the cytotoxic agent in target cells.[8,9] In this review, we will focus on the most promising ADCs for the treatment of ovarian, cervical, and endometrial cancer while staying mindful of the decisions the patient faces.

Overview of ADC Components: Antigen and Antibody

The target antigens should be present on the cell surface so that the ADC can find them and have high expression on tumor cell but not on normal tissue. For example, the protein human epidermal growth factor receptor 2 (HER2) is expressed up to 100 times more in tumor than in normal cells.[10] Additionally, the target antigens should be internalized so that the ADC can be transported into the cell. Once in the cell, proteases digest the antibody to

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PRACTICAL APPLICATIONS

- Enhanced understanding of carcinogenesis and underlying molecular biology has accelerated drug development, and antibody-drug conjugates (ADCs) represent recent improvements in targeted therapies for gynecologic cancer.
- ADCs are currently Food and Drug Administration approved in ovarian and cervical cancer, with ongoing research to improve outcomes in various settings and in combination with other agents.
- Several ADCs show promise in endometrial cancer and continued subtype-specific research is necessary to determine the best therapeutic approaches.
- Careful monitoring of treatment-related adverse events, including class-specific eye toxicity, is necessary to mitigate serious side effects of ADCs.

release the cytotoxic agent, which causes apoptosis of the cancer cells.

Overview of ADC Components: Cytotoxic Payloads

The cytotoxic molecules used in ADCs tend to be microtubule-targeting and DNA-damaging agents. Microtubule-targeting agents are functional only in proliferating cells and induce cell death by inhibiting tubulin, disrupting microtubules, and arresting the cell cycle in the G2/M phase.[11] DNA-damaging agents function independent of cell cycle and are cytotoxic in both proliferating and nonproliferating cells. Next-generation ADCs are now using RNA polymerase inhibitors and other agents for the cytotoxic payloads.[12]

Overview of ADC Components: Linkers

To ensure that the cytotoxic payload is delivered once it enters the tumor, linker stability is essential.[13] Linkers are generally classified as noncleavable and cleavable. Noncleavable linkers are mainly covalently bonded and must be internalized into cells and broken down by lysosomes to release toxins. Cleavable linkers are those that are cleaved depending on intracellular circumstances, including acid pH levels, glutathione levels, or the action of lysosomal proteases.[14] Some cleavable linkers can also deliver the drug extracellularly, inducing a bystander effect in which nearby tumor cells without expression of the targeted antigen are killed. The bystander effect can be desired in heterogeneous tumors in which not all tumor cells express the selected antigen.[15]

TOXICITY PROFILE OF ADCs

General Safety

As ADCs become more common, understanding their toxicity profiles is important. Premature release of cytotoxic payloads into the bloodstream is associated with hematologic toxicity, hepatotoxicity, and gastrointestinal reactions.[16] Secondary damages due to immune responses partially induced by antibodies to ADCs are also reported.[17] Ocular toxicity, discussed in more depth below, is a known side effect of certain ADCs and a dose-limiting toxicity in some trials. A recent meta-analysis published in *Cancer* characterized treatment-related adverse events (TRAEs) reported in clinical trials of ADCs. Covering multiple types of ADCs in several cancer types, the analysis included reports from 169 clinical trials encompassing 22,492 patients. The overall incidence of TRAEs was 91.2%, with the most common being lymphopenia (53.0%), nausea (44.1%), neutropenia (43.7%), blurred vision (40.5%), and peripheral neuropathy (39.6%). The incidence of grade 3 or higher TRAEs was 46.1%, with the most common being neutropenia (31.2%), hypesthesia (23.3%), thrombocytopenia (22.6%), febrile neutropenia (21.2%), and lymphopenia (21.0%). The incidence of treatment discontinuation because of TRAEs was 13.2%, and the rate of fatal TRAEs was 1.3%.[18]

It is important to note the variability of TRAEs associated with different ADCs. Variability is driven by differences in payloads, antibody targets, and to a certain extent, the linkers. For example, neuropathy is most associated with ADCs that have MMAE payloads, such as tisotumab vedotin, likely due to the disruption of the interphase microtubule function.[16] However, not all ADCs that share the same payloads have the same common TRAEs. Target type also plays a role. ADCs that target HER2, such as trastuzumab-deruxtecan (T-DXd), are associated with pulmonary toxicities and cardiotoxicity.[17,18] Interstitial lung disease (ILD) and pneumonitis are the most common cause of treatment-related death in patients treated with ADCs.[18] Finally, as mentioned above, linker stability is important for the timely release of the payload from the antibody, and premature release can cause a broader toxicity profile. The toxicity profiles of the various ADCs used in gynecologic cancer are listed below.

Ocular Toxicity

Ocular toxicities are known effects specific to certain ADCs. Ocular toxicities are off-target effects as most antigens that are targeted by ADCs are not significantly overexpressed in the eye. However, with tisotumab vedotin, these are on-target ocular adverse events as tissue factor (TF) is expressed on the eye. Most commonly, patients experience reversible blurry vision and keratopathy, which can be managed with dose adjustments and/or treatment delays.[19] Prophylactic corticosteroid and vasoconstrictor eye drops

are useful to reduce frequency and severity of these adverse events. Ophthalmic examinations and appropriate referral to ophthalmology are necessary to mitigate new or worsening ocular signs.[20]

ADCs IN OVARIAN CANCER

Management of ovarian cancer is challenging because of its late diagnosis and high recurrence, with 5-year survival rates of around 45%.[21] First-line treatment consists of surgery and platinum-based chemotherapy, followed by maintenance therapies. Targeted therapies, including PARP inhibitors and bevacizumab, have improved ovarian cancer management in the past decade, but many patients will still recur and succumb to the disease.[22] ADCs are a promising approach in recurrent ovarian cancer to improve outcomes in this malignancy.

ADCs Targeting Alpha Folate Receptor

Alpha-folate receptor (FRα) is expressed in more than 80% of epithelial ovarian cancers and is associated with poor prognosis.[23-25] Mirvetuximab soravtansine is the first ADC to receive FDA accelerated approval in platinum-resistant ovarian cancer. Mirvetuximab soravtansine is an ADC comprising a FRα-binding antibody, a cleavable disulfide linker, and a tubulin-disrupting maytansinoid DM4 payload.[26] The FDA also granted approval of the FOLR1 RxDx assay to identify patients eligible for mirvetuzimab soravtansine with high levels of FRα expression, defined as ≥75% tumor cells staining with 2+ intensity.[27]

The FDA approval decision in November 2022 was supported by findings from the phase III global single-arm SORAYA trial, which enrolled 106 patients with platinum-resistant ovarian cancer whose tumors expressed high levels of FRα and who had been treated with one to three previous systemic therapies, one of which had to have included bevacizumab. The primary end point was confirmed objective response rate (ORR) as assessed by investigator, and the key secondary end point was duration of response (DOR). Participants received intravenous mirvetuximab soravtansine at 6 mg/kg once every 3 weeks until disease progression or unacceptable toxicity. Mirvetuximab soravtansine produced an ORR of 31.7% (95% CI, 22.9 to 41.6), including a 4.8% complete response rate and a 26.9% partial response rate. The DOR was 6.9 months (95% CI, 5.6 to 9.7). The most common TRAEs (all grade, grade 3+) included blurred vision (41%, 6%), keratopathy (36%, 9%), and nausea (29%, 0%). TRAEs led to dose delays in 32%, dose reductions in 19%, and discontinuations in 7% of patients.[28]

MIRASOL (ClinicalTrials.gov identifier: NCT04209855), the confirmatory phase III registration trial for mirvetuximab soravtansine to convert the accelerated approval to full approval, has completed accrual, and data are expected in 2023. Progression-free survival (PFS) of mirvetuximab soravtansine versus investigator's choice chemotherapy will be compared in patients with advanced platinum-resistant high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers that are FRα-high by immunohistochemistry percent staining 2+.[29] Additionally, the phase III randomized GLORIOSA trial (ClinicalTrials.gov identifier: NCT05445778) is ongoing and will evaluate mirvetuximab soravtansine in combination with bevacizumab maintenance versus bevacizumab alone as maintenance therapy after platinum-based chemotherapy for patients with FRα-high platinum-sensitive disease (Table 1).

STRO-002 also targets FRα and received FDA fast designation for ovarian cancer in 2021.[30] STRO-002 comprises the FRα-binding antibody SP8166 (H01), a cleavable protease linker, and a hemiasterlin-derivative payload. The hemiasterlin-derivative payload has a potentially dual mechanism of effect by both inhibiting tubulin and inducing an immunogenic response on cell death. Interim safety data of a phase I dose-expansion study of 15 patients with advanced ovarian cancer treated with a higher dose level of STRO-002 (5.4 mg/kg once every 3 weeks) along with prophylactic pegfilgrastim were recently reported. The higher starting dose led to greater patient benefit than the lower dose (4.3 mg/kg once every 3 weeks), with an ORR of 43.8% compared with an ORR of 31.3%. Safety data were consistent with previous findings with 85.5% of TRAEs grades 1 or 2 and no ocular toxicity. At the higher dose, prophylactic pegfilgrastim led to reductions in grade 3 or higher neutropenia compared with the patients not given prophylactic pegfilgrastim.[31] From these data, the registration-directed phase II/III REFRaME study will be initiated later this year. Additionally, STRO-002-GM2 (ClinicalTrials.gov identifier: NCT05200364) is a phase I multicenter dose-escalation study to assess STRO-002 in combination with bevacizumab in patients with advanced ovarian cancer that is refractory or has relapsed after standard therapy.

Finally, MORAb-202 (farletuzumab ecteribulin) is an ADC comprising the FRα-binding antibody farletuzumab conjugated to the cytotoxic inhibitor eribulin mesylate through a cleavable linker. A phase I dose-escalation trial in FRα-positive solid tumors had a 75% disease control rate, including one complete response and two partial responses in the nine patients with ovarian cancer.[32] From these initial data, MORAb-202 0.9 mg/kg (cohort 1) and 1.2 mg/kg (cohort 2) once every 3 weeks were chosen as doses for the expansion part of Study 101 in patients with FRα-positive tumors (defined as >5% of cells stained at 1+ to 3+ intensity level). In patients with platinum-resistant ovarian cancer, the ORR was 25.0% (95% CI, 9.8 to 46.7) in cohort 1 and 52.4% (95% CI, 29.8 to 74.3) in cohort 2. ILD/pneumonitis was the most common TRAE and was of low-grade severity in most patients. Antitumor activity was observed across

TABLE 1. ADCs in Gynecologic Cancer

ADC	Target	Linker	Payload	Status	Ongoing Trials
Ovarian					
Mirvetuximab soravtansine	FRα	Sulfo-SPDB (disulfide linker)	DM4	FDA accelerated approval	MIRASOL
					GLORIOSA
STRO-002	FRα	Protease-labile Val-Cit-PABA	Hemiasterlin	FDA fast track	REFRaME
MORAb-202	FRα	Cathepsin-B cleavable linker	Eribulin	Under investigation	MORAb-202 G000-201
Upifitamab rilsodotin	NaPi2B	Protease-labile linker	AF-HPA	Under investigation	UPLIFT
					UPNEXT
					UPGRADE-A
Cervical					
Tisotumab vedotin	Tissue factor	Protease-labile mc-val-cit-PABC linker	MMAE	FDA accelerated approval	InnovaTV 205 ENGOT-cx8 GOG-3024
					innovaTV 301 ENGOT-cx12 GOG-3057
Endometrial					
Mirvetuximab soravtansine	FRα	Sulfo-SPDB (disulfide linker)	DM4	Under investigation	IMGN853
Trastuzumab deruxtecan	HER2	Lysosomal cathepsins-cleavable tetrapeptide linker	Deruxtecan	Under investigation	STATICE
					DESTINY PANTumor02
					NCI 2020-07841
DB-1303	HER2	Enzymatically cleavable peptide linker	P1003	FDA fast track	DB-1303-O-1001
Sacituzumab govitecan	Trop2	Acid-labile linker, CL2A linker	SN-38	Under investigation	IMMU-132

Abbreviations: ADC, antibody-drug conjugate; AF-HPA, auristatin F-hydroxypropylamide; DM4, N2′-deacetyl-N2′-(4-mer-capto-4-methyl-1-oxopentyl)-maytansin; FDA, US Food and Drug Administration; FRα, alpha-folate receptor; HER2, human epidermal growth factor receptor 2; mc-val-cit-PABC, maleimidocaproyl-L-valine-L-citrulline-p-aminobenzyl alcohol; MMAE, monomethyl auristatin E; NaPi2B, sodium-dependent phosphate transport protein 2B; SN-38, 7-ethyl-10-hydroxy-camptothecin; Trop2, trophoblast cell surface antigen-2; Val-Cit-PABA, L-valine-L-citrulline-p-aminobenzoic acid.

varying FRα expression levels, and dose optimization is ongoing[33] (ClinicalTrials.gov identifier: NCT04300556).

ADCs Targeting NaPi2B

NaPi2B (sodium-dependent phosphate transport protein 2B) is expressed in two thirds of patients with high-grade serous ovarian cancer.[34] Upifitamab rilsodotin (UpRi) is an ADC comprising a NaPi2B-binding antibody, a cleavable ester linker, and an AF-HPA payload. The UPLIFT trial is a phase II, single-arm, registrational study of NaPi2B in platinum-resistant ovarian, fallopian tube, and primary peritoneal cancer with up to four previous lines of therapy. In promising preliminary results presented at the Society of Gynecologic Oncology (SGO) Annual Meeting 2022, the ORR for the 75 evaluable patients was 23%, and in those who were NaPi2B-high (n = 38), the ORR was 34%. In the NAPi2B-high cohort, the ORR was 44% in dose group 36 mg/m^2 versus 27% in dose group 43 mg/m^2. The most common TRAEs were fatigue, nausea, vomiting, pyrexia, and transient aspartate transaminase elevations. Lower frequencies and lower-grade pneumonitis occurred in dose group 36 versus dose group 43. Grade 3 or greater neutropenia, ocular toxicity, and peripheral neuropathy have not been observed.[35]

Two ongoing studies will shed light on UpRi in different settings. UPNEXT is a phase III study of UpRi versus placebo as maintenance therapy in recurrent platinum-sensitive high-grade serous ovarian cancer expressing high levels of NaPi2B (ClinicalTrials.gov identifier: NCT05329545). This trial is important not only because it focuses on platinum-sensitive cases but also because as maintenance therapy with bevacizumab or PARP inhibitors is moved to the frontline for ovarian cancer; there is no standard of care for patients treated with these agents who subsequently relapse. For example, if a patient receives a PARP inhibitor in the frontline setting, it is not clear if they could be rechallenged with another PARP inhibitor. Additionally, some comorbidities preclude current maintenance therapies. The UPNEXT trial will hopefully provide an additional maintenance option.[36] UPGRADE-A is a phase I dose-escalation and dose-expansion study to evaluate UpRi and carboplatin in recurrent platinum-sensitive high-grade serous ovarian cancer, followed by UpRi maintenance (ClinicalTrials.gov identifier: NCT04907968). This trial is

currently recruiting, and if positive and findings are confirmed, it could potentially provide another platinum doublet in the treatment of patients with platinum-sensitive recurrent ovarian cancer.

ADCs IN CERVICAL CANCER

Cervical cancer is the fourth most common cancer in women and has a 5-year survival rate of 67%.[37] Doublet chemotherapy (paclitaxel plus either platinum or topotecan) with bevacizumab (if eligible) is recommended for first-line treatment of recurrent or metastatic cervical cancer. Cervical cancer incidence and mortality has markedly decreased over the past few decades because of increased screening and vaccination practices against HPV. New treatments include targeted therapies, such as bevacizumab and pembrolizumab, as well as ADCs.[38]

ADCs Targeting TF

TF is the main initiator of the extrinsic coagulation pathway, and in cancer, it contributes to cell proliferation, survival, angiogenesis, and the epithelial to mesenchymal transition that promotes tumor development.[39,40] TF is highly expressed in cervical cancer (up to 90%-95%) and other solid tumors.[41-43] Tisotumab vedotin is an ADC comprising an anti-TF monoclonal antibody covalently linked to the microtubule-disrupting agent MMAE through a protease-cleavable linker.[44] This ADC was granted FDA accelerated approval in September 2021 for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.[45]

The decision for accelerated approval was supported by data from the single-arm, multicenter, phase II innovaTV 204 trial, which enrolled a total of 101 patients with recurrent and/or metastatic cervical cancer who experienced disease progression during or after doublet chemotherapy with bevacizumab (if eligible), had received two or fewer prior systemic therapies, and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were administered tisotumab vedotin at a dose of 2.0 mg/kg once every 3 weeks until disease progression or unacceptable toxicity. The primary end point was ORR per RECIST v1.1 criteria and independent imaging review committee assessment. Secondary end points included ORR per investigator assessment and RECIST criteria, overall survival (OS), and safety. Tisotumab vedotin resulted in a confirmed ORR of 24% (95% CI, 15.9 to 33.3) with 7% of responders experiencing a complete response and 17% a partial response. The median DOR was 8.3 months (95% CI, 4.2 to not reached). The median time to response was 1.4 months (range, 1.1-5.1), and activity was noted within the first two treatment cycles. Tisotumab vedotin had a manageable safety profile, with mostly mild-to-moderate adverse events. Grade 3 or higher TRAEs were reported in 28% and included peripheral neuropathies (7%), neutropenia (3%), fatigue (2%), ulcerative keratitis (2%), and bleeding (2%).[46]

InnovaTV 205/ENGOT-cx8/GOG-3024 is a global, randomized, multicohort phase Ib/II trial to evaluate tisotumab vedotin in combination with bevacizumab, pembrolizumab, or carboplatin. Interim safety and efficacy data from two dose-expansion cohorts were presented at European Society for Medical Oncology 2021. Of 33 patients treated with first-line tisotumab vedotin plus carboplatin (median five cycles), the confirmed ORR was 55% (95% CI, 36 to 72), and prespecified grade 3 or higher TRAEs included peripheral neuropathy (12%), ocular toxicity (3%), and bleeding (6%). Of 35 patients treated with second-line/third-line tisotumab vedotin plus pembrolizumab (median six cycles), the confirmed ORR was 35% (95% CI, 20 to 54), and prespecified grade 3 or higher TRAEs included peripheral neuropathy (3%), ocular toxicity (3%), and bleeding (9%).[47] At ASCO 2022, interim safety and efficacy results from a third dose-expansion cohort evaluating first-line tisotumab vedotin and pembrolizumab were reported. Of 33 patients treated as of the cutoff, the confirmed ORR was 41% (95% CI, 24 to 59), with 3 (9%) complete responses and 10 (31%) partial responses. The median PFS was 5.3 months (95% CI, 4.0 to 12.2), and the median OS was not reached. Prespecified grade 3 or higher TRAEs included peripheral neuropathy (3%), ocular toxicity (9%), and bleeding (6%).[48] This trial is ongoing (ClinicalTrials.gov identifier: NCT03786081). Finally, innovaTV 301/ENGOT-cx12/GOG-3057 is a global, randomized, open-label, phase III trial evaluating tisotumab vedotin versus investigator's choice of chemotherapy in patients with recurrent and/or metastatic cervical cancer who have progressed on one to two previous lines of therapy. The primary end point is OS, and the trial has completed accrual (ClinicalTrials.gov identifier: NCT04697628).

ADCs IN ENDOMETRIAL CANCER

Endometrial cancer is the most common and second deadliest gynecologic cancer in the United States, with rising incidence and mortality rates.[49] After the discovery of four molecular subtypes by The Cancer Genome Atlas and their influence on prognosis, treatment consideration by subtype is now recommended.[50] FDA-approved ICIs include pembrolizumab and dostarlimab for previously treated dMMR/MSI-H cases and pembrolizumab/lenvatinib for mismatch repair-proficient/microsatellite-stable cases.[51] ADCs are an active area of research within this molecularly focused landscape.

ADCs Targeting FRα

Although no ADCs are currently FDA approved in endometrial cancer, there are several promising agents. Like in ovarian cancer, FRα is overexpressed in endometrial tumors with approximately 64% of endometrial tumors positive for

FRα receptors.[52] However, despite promising preclinical data, clinical efficacy of the anti-FRα ADC, mirvetuximab soravtansine, has been less clear.[53] In a study of multiple solid tumors, there was a positive response in 2 of 11 (18.2%) endometrial tumors at a dose of 5 mg/kg once every 3 weeks.[54] A phase II trial is ongoing to evaluate mirvetuximab soravtansine in microsatellite-stable endometrial cancer (ClinicalTrials.gov identifier: NCT03835819). STRO-002 is also being evaluated in endometrial cancer in a phase I trial (ClinicalTrials.gov identifier: NCT03748186).

ADCs Targeting HER2

HER2, a receptor tyrosine-protein kinase encoded by *ERBB2*, is another potential therapeutic target for endometrial cancer therapy.

Immunohistochemistry studies show high HER2/neu expression in approximately 35% of patients with uterine serous carcinoma.[55,56] T-DXd is an ADC consisting of the anti-HER2 antibody trastuzumab and a topoisomerase I inhibitor payload combined by a cleavable tetrapeptide linker. This drug received accelerated FDA approval in 2019 for HER2-positive breast cancer, and following recent data from DESTINY-Breast04 which showed a 50% risk reduction in disease progression or death in cases with low expression of HER2 (PFS, 9.9 *v* 5.1 months; hazard ratio, 0.50; 95% CI, 0.40 to 0.63), it received accelerated approval for HER2-low breast cancer in August 2022.[57,58] ILD/pneumonitis occurred in 12.1% of patients who received T-DXd, and the most common TRAEs of grade 3 or higher were neutropenia (13.7%), anemia (8.1%), and fatigue (7.5%). The incidence of TRAEs associated with discontinuation of treatment and death, respectively, were 16.2% and 3.8% in the T-DXd group compared with 8.1% and 2.9% in the physician's choice chemotherapy group.[57]

As there is no standardized scoring system for HER2 expression in endometrial cancer, the use of ADCs such as T-DXd could be widely beneficial. Results from the STATICE trial evaluating efficacy of T-DXd in HER2-positive uterine carcinosarcoma showed a response rate of 55% and a PFS of 6.2 (95% CI, 4.0 to 8.8) months in HER2 2+/3+ patients. Grade 1-2 ILD occurred in 23.5% and Grade 3 ILD in 2.9% of patients.[59] Endometrial cancer is also being evaluated in the DESTINY-PanTumor02 trial using T-DXD in HER2-positive tumors (ClinicalTrials.gov identifier: NCT04482309). In HER2-positive serous endometrial cancer, combined T-DXd and olaparib (PARPi) is being evaluated (ClinicalTrials.gov identifier: NCT04585958). Finally, the FDA has granted fast track designation to DB-1303, an ADC comprising an anti-HER2 monoclonal antibody, a cleavable peptide-linker, and a topoisomerase I inhibitor. DB-1303 displayed favorable antitumor activity and safety in both HER2-positive and HER2-low tumor models and is under evaluation in an ongoing phase I/IIa trial (ClinicalTrials.gov identifier: NCT05150691) in patients with advanced/unresectable, recurrent, or metastatic endometrial cancer.[60]

ADCs Targeting Trophoblast Cell Surface Antigen-2

Trophoblast cell surface antigen-2 (Trop2) is a tumor-associated calcium signal transducer. ADCs targeting Trop2 have primarily been researched in breast cancer. However, preliminary findings suggest that it may be effective in gynecologic oncology as overexpression has been observed in ovarian (over 80%), cervical (over 80%), and endometrial (over 90%) cancers.[61-65]

Sacituzumab govitecan is an ADC comprising an anti-Trop2 monoclonal antibody conjugated to SN-38, the active metabolite of the topoisomerase I inhibitor irinotecan, through a cleavable linker.[66,67] Sacituzumab govitecan has a high drug-to-antibody ratio (7.6:1), and SN-38 is released extracellularly in the tumor microenvironment on hydrolysis of the linker, providing a bystander effect.[67,68] In a phase I/II basket trial, the ORR was 22.2% (95% CI, 6.4 to 47.6) in the endometrial cancer cohort (n = 18) at a dose of 10 mg/kg once daily on days 1 and 8 of a 21-day cycle. The median PFS was 3.2 months (95% CI, 1.9 to 9.4), and the median OS was 11.9 months (95% CI, 4.7 to not calculable). The safety profile was consistent with the overall basket study, and the most common TRAEs were nausea (83%), diarrhea (67%), fatigue (61%), vomiting (56%), decreased appetite (56%), and neutropenia (56%).[69]

THE PATIENT EXPERIENCE: WHAT MAKES TREATMENT WORTH IT?

> *"Cancer begins and ends with people. In the midst of scientific abstraction, it is sometimes possible to forget this one basic fact… Doctors treat diseases, but they also treat people, and this precondition of their professional existence sometimes pulls them in two directions at once."*
>
> June Goodfield, The Siege of Cancer

What makes treatment with an ADC, or any treatment, worth it to a patient? It depends on the patient. And, it may depend on the physician and care team.

Sachia Stonefeld Powell, an ovarian cancer survivor, knows because she's been there. "I was diagnosed with high grade serous ovarian cancer in early 2017 at the age of 50, with a recurrence in mid-2020, and I've had to make difficult decisions for which there was no clear *right* choice. Deciding what made a treatment option *worth it* required a thoughtful analysis; how many extra days of life the treatment will likely give me weighed against what the treatment will likely take away. And I relied on my oncologist to help find the right balance for me."

Whether a given treatment is worth pursuing may depend on the patient's understanding of the possible benefits. Will the

treatment cure them or at least buy enough additional time that other options may become available? Once complete, will the patient likely enjoy a lengthy break before the next treatment is required? A patient may also consider whether the therapy could provide enough time to reach a personal milestone, such as a family wedding or a significant birthday, or simply provide more time to watch children or grandchildren grow. Ultimately, how much hope does the treatment provide?

Whether a treatment is worth it also may depend on the cost to the patient, including time, money, and missed moments. Obstacles such as transportation, childcare, or financial hardship may discourage a patient from pursuing treatment. For those with the resources to address these hurdles, the impact on their quality of life may influence the decision. For example, the potential risk of ocular toxicities, common in ADCs, will likely affect a professional photographer far differently than a patient who relies less on their vision in daily activities. Similarly, the possibility of long-term or permanent side effects, such as neuropathy, and the time necessary to manage those side effects may discourage some patients from pursuing a treatment. A patient also may consider how much of the treatment will be covered by insurance and how much time will be spent fighting to obtain that coverage.

Whether a treatment is worth it may also depend on where the patient is in their cancer journey, including whether the patient and their support system can handle the additional burden—both physical and psychological. A patient who feels physically well may be more willing to take on the rigors of additional toxicities. A patient who is psychologically worn down may not be ready for the proverbial fight. And whether treatment is worth it may depend on the extent to which the patient and their support system have accepted the patient's own mortality.

A patient's internal values or external influences may also factor into the decision. Someone with a strong spiritual conviction may put their future into the hands of a higher power. Certain families or cultures may downplay illness, and patients from those backgrounds may be less willing to embark on a treatment that will bring attention to their disease. A treatment may seem worth it to a patient if it could help others—for example, if their clinical trial participation could help ensure better options for future survivors. In addition, some may be influenced by the experiences of other patients or by what they have read on the Internet.

In considering this myriad of factors, the patient naturally relies on their physician and care team; the choice may well depend on the physician counseling of the treatment, how well it is explained, and how enthusiastically it is endorsed. How well the physician explains the efficacy of the treatment and in what terms (ie, PFS, OS, etc) affect what the patient takes away from the conversation. Several studies have shown that shared decision making improves health-related quality of life.[70-72] However, in a web-based survey of more than 14,000 ovarian cancer survivors conducted by the SGO Ovarian Cancer National Alliance, there was a disconnect between patients and physicians regarding expectations for PFS, OS, and acceptable treatment-related toxicities.[73] Continued efforts by the oncology community to personalize the balance between efficacy and toxicity for individual patients are needed. Choice of treatment also likely depends on what the patient actually hears, which may be limited by their emotional state, their reluctance to ask questions, cultural or linguistic barriers, or overall health literacy. Ultimately, the decision may be influenced by how much the patient trusts the physician and care team to be honest and forthcoming with them and to view them as a whole person and not just a disease.

For some patients, maintaining the best possible quality of life will guide their decision while for others longevity prevails. For some, the choice to pursue a particular treatment may be crystal clear; for others, it may be a heart-wrenching decision. For us all, it is a balance of many factors that are deeply personal. As patients, we look to the physician and care team to help balance what the treatment will give against what it will likely take and to help us formulate our plan.

What makes treatment worth it? It depends.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Current Treatment Strategies and Risk Stratification for Oral Carcinoma

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overview

Management of oral cavity squamous cell carcinoma (OSCC) involves a multidisciplinary team approach. Surgery is ideally the primary treatment option for nonmetastatic OSCC, and less invasive curative surgical approaches are preferred in early-stage disease to minimize surgical-related morbidity. For patients at high risk of recurrence, adjuvant treatment using radiation therapy or chemoradiation is often used. Systemic therapy may also be used in the neoadjuvant setting (for advanced-stage disease with the intent of mandibular preservation) or in the palliative setting (for nonsalvageable locoregional recurrence and/or distant metastases). Patient involvement in treatment decision is the key for patient-driven management, particularly in clinical situation with poor prognosis, for example, early postoperative recurrence before planned adjuvant therapy.

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INTRODUCTION

Oral cavity cancer (OCC) accounts globally for an estimated 377,000 new cases yearly (2% of all cancers) and over 177,000 deaths (1.8% of all cancers).[1] Almost 90% of these cancers are squamous cell carcinomas.[2] There are noticeable geographic disparities in the incidence of oral cavity squamous cell carcinoma (OSCC) with approximately two thirds of the cases occurring in the developing countries.[2] Tobacco use in all its forms, betel quid, and alcohol consumption are well-established risk factors of OSCC.[2,3] In recent years, there has been an increase in the prevalence of the disease among nonsmokers, suggesting that other factors may be implicated; however, further studies are required to identify these risk factors.[4] The majority of the patients with OSCC are presented with advanced disease, with relatively poor overall survival (OS).[5]

In principle, management of OSCC is decided by a multidisciplinary team after comprehensive, clinical, and radiographic review.[2] Surgery remains the primary treatment approach for OSCC.[6] However, morbid effects on cosmetic and functional outcomes related to the extent of disease and the required surgical resection emphasize the importance of using less invasive curative surgical approaches (eg, use of sentinel lymph node [SLN] biopsy) in early-stage disease to minimize surgical-related morbidity.[7] In addition, radiation therapy (RT) or chemoradiation (CRT) is usually added as an adjuvant treatment for patients with high risk for recurrence.[8] In some instances, RT/CRT can be the primary treatment modality, especially for patients who are unfit for surgery.[9] Early locoregional recurrence (LRR) and/or distant metastases (DM) are associated with worst prognosis in OSCC.[10,11] Systemic therapy is usually indicated in such cases; however, it can potentially be used in the neoadjuvant setting for patients with advanced-stage disease aiming for tumor reduction that may permit better functional and cosmetic outcomes (eg, mandibular preservation), while maintaining similar oncologic outcomes.[12,13]

SLN BIOPSY FOR EARLY-STAGE ORAL CAVITY CANCER

The use of SLN biopsy provides clinicians with a diagnostic procedure, which may be followed by an escalation of treatment (ie, completion neck dissection [CND]) when necessary. After multiple randomized control trials (RCTs), this diagnostic tool is now established as the standard of care for melanoma, breast cancer, and endometrial cancer.[14-20] Utilization of SLN biopsy for head and neck cancer (HNC) is under active investigation with appealing applications, particularly for stage I to II (cT1-2N0M0) OSCC.

Staging of OSCC requires imaging of the neck, with small nodes (under 1.1-1.5 cm) without adverse features considered to be clinically node-negative (cN0).[21,22] All larger nodes or those demonstrating adverse features should undergo ultrasound-guided fine needle aspiration biopsy to enable appropriate clinical staging before consideration of surgical management of OSCC in the neck.[23]

Patients with early-stage OSCC and clinically and radiographically negative neck have been found to have up to 20%-30% occult neck disease.[24,25] NCCN guidelines recommend proceeding with an elective neck dissection (END) for tumors with a depth of invasion (DOI) over 3 mm. Within this setting, up to 80%

PRACTICAL APPLICATIONS

- Sentinel lymph node biopsy–based clinical trials provide evidence for personalized neck management for oral cavity cancer (OCC).
- High-dose radiation (with concurrent chemotherapy) for OCC could be a reasonable alternative management strategy to primary surgery when it is not feasible and also for patients with early recurrence before the planned postoperative radiation.
- Identifying patients with OCC at high-risk distant metastases (DM) could allow (1) the risk-adaptive DM screening protocol with possible local ablative treatment of early-detected oligometastases and (2) future evaluation of novel systemic multiagent regimens in the setting of a clinical trial in the group of patients with high-risk DM.
- Induction chemotherapy can potentially be used with an aim of mandibular preservation for OCC after careful multidisciplinary discussion and patients' involvement in treatment decision.
- In the adjuvant setting for patients with OCC and high-risk features (positive margin and/or extranodal extension), the standard of care is cisplatin concurrently with radiotherapy. In cisplatin-ineligible patients, docetaxel with postoperative radiation is supported by the best evidence. Other possible options include concurrent cetuximab, carboplatin/5FU, carboplatin/paclitaxel, or the use of accelerated radiation.

of patients undergoing END for early-stage OSCC are ultimately found to be pN0.[26] SLN biopsy, if proven efficacious and sensitive for OSCC, may aid in reducing the morbidity and cost associated with END.

SLN Biopsy: Novel Diagnostic Framework

END has been the standard of care for OSCC. When comparing END to active surveillance with therapeutic neck dissection (TND) as needed, a landmark RCT of 500 patients concluded that disease-free survival (DFS) and OS had statistically significant improvements for the END cohort.[27] That said, this study did provide higher rates of adjuvant radiation to the END cohort given the availability of surgical pathology data, and the TND group may not have had rigorous active surveillance. Further study of management of OSCC with END compared with active surveillance with as-needed TND continues with JCOG1601 in Japan for patients with OSCC with a DOI of 3-10 mm.[28]

Although END is comprehensive and aggressive, regional recurrence continues for patients with pN0 OSCC with rates ranging from 9% to 18%.[29-32] Patients found to be pN1 using END have a similar regional recurrence rate of 20%.[32] Lending to the discussion of SLN biopsy utility, regional recurrence is often seen in the contralateral neck (30%-39%).[32,33]

Comparisons of SLN biopsy with END have been conducted, and investigations continue. In 2010, a multi-institutional phase II trial identified a 96% negative predictive value (NPV) for SLN biopsy in OSCC.[34] Similarly, in 2015, the Sentinel European Node Trial (SENT) identified SLN biopsy used for OSCC to have an 86% sensitivity for negative sentinel nodes.[35] This study confirmed that 70% of patients with early OSCC staged using SLN biopsy were able to avoid CND with a 3-year DFS of 92%. In addition, a National Cancer Database retrospective study revealed equal OS for SLN biopsy compared with END with a reduced hospital length of stay for patients undergoing SLN biopsy.[36] A multicenter RCT reported in 2020 performed by Garrel et al[37] with 307 patients with oral cavity and oropharyngeal cancer receiving either SLN biopsy or END revealed similar recurrence-free survival and OS with noninferiority margin at 10%. Similarly, an RCT published in 2021 by Hasegawa et al[7] of 275 patients revealed noninferiority, margin at 12%, in survival and postoperative complications. Multiple trials have subsequently shown SLN biopsy to be safe with patients deemed cN0 preserving a high NPV, disease-specific survival, and OS.[7,34,35,38-44] In addition, cost is reduced with SLN biopsy compared with END by an estimate of 23%.[41]

Identification of aberrant nodal distribution is a major potential advantage of SLN biopsy. One study identified up to 40% of patients revealing aberrant nodal drainage on preoperative lymphoscintigraphy.[39] Furthermore, contralateral drainage has been seen in 2%-17% of patients, most commonly with floor of mouth lesions.[29,39,45]

The NRG-HN006 is a phase II/III RCT currently comparing SLN biopsy and END in early-stage OSCC (ClinicalTrials.gov identifier: NCT04333537).[46] The coprimary end points are to determine whether patient-reported neck and shoulder function and related quality of life 6 months postoperatively is superior with SLN biopsy compared with END and to determine whether DFS is noninferior with SLN biopsy compared with END. Unlike previous studies with larger noninferiority margins (10%-12%), NRG-HN006 is based on a noninferiority hazard ratio (HR) for DFS (time to event) for an absolute difference of 5% in 2-year DFS rates.[46]

As definitive evidence is developing to address standard-of-care approaches to management of early-stage OSCC in the neck, certain considerations regarding patient selection, surgical technique, and postoperative surveillance must be considered.

Patient Selection

SLN biopsy remains a valuable diagnostic procedure. As such, performing SLN biopsy in patients with multiple comorbidities should not be performed as a means of reducing surgical burden given that an additional anesthetic event may become necessary in the event of a positive SLN for CND.

Proceeding with SLN biopsy in patients with previously treated HNC or lymphatic disease may be considered given the potential for mapping of aberrant nodal distribution patterns. This patient population has commonly been excluded from current investigative studies but definitely merit careful trial-based examination.

Patients' ability to engage in follow-up should be taken into consideration as well since negative SLN biopsy will require active surveillance with clinical and imaging examination every 3 months.[35] Patients unable to adhere to this follow-up pattern may not be ideal for SLN biopsy.

Tumor Selection

Given the anatomic variation within the oral cavity, tumor selection is critical for appropriate utilization of SLN biopsy for OSCC. Primary T1-2 tumors that can be reliably resected with appropriate margins without requiring neck access have been deemed appropriate for SLN biopsy.[35] Free flap reconstruction is often required for defects of the floor of mouth, retromolar trigone, palate, buccal mucosa, and gingiva, thus necessitating entry to the neck. Such lesions may be more appropriate for END given the need for neck vessel access for free flap reanastamosis.

The eighth edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Cancer Staging Manual includes DOI for OSCC as this increases the risk of metastasis. The current literature varies on DOI cutoff for SLN biopsy utilization with 10 mm, which is the highest limit. In 2015, Schilling et al[35] suggested the utility of SLN biopsy for tumors with DOI up to 10 mm. In 2021, Hasegawa studied SLN biopsy for tumors with DOI up to 4 mm.[7] Each millimeter of DOI increase has been associated with a potential increased risk of nodal metastasis, although there is clear variability depending on tumor thickness.[47]

Patients with a distinct lesion with biopsy revealing carcinoma in situ may have regions of invasive carcinoma on final pathology. As such, these patients may be considered for SLN biopsy.[48] Patient comorbidities and oral cavity status should be taken into consideration when selecting patients for SLN biopsy. Patients with a T1-2 lesion also presenting with immunologic deficit, pervasive dysplasia, and concern for field cancerization are less appropriate for SLN biopsy selection.[48] Future studies may elucidate whether the utilization of biomarkers in addition to DOI, such as CD44, may be helpful in predicting nodal metastasis.[49]

Surgical Considerations

Across specialties, SLN biopsy has proven to be operator-dependent with an expected learning curve.[42,50,51] Specific to OSCC, surgeons more experienced with SLN biopsy have been found to have an improved NPV.[34] Thus, surgeon credentialing and case review are critical components for prospective clinical trials.

The preoperative imaging and injection of OSCC lesions require multidisciplinary training and cohesion. The preferred radioisotope is technetium-99m (^{99m}Tc). The SLN is identified by a gamma count at least 10 times higher than background and with a count at least 10% of the hottest SLN. For oral cavity lesions, utilization of radiotracer and an optical tracer (eg, indocyanine green) may be helpful. Oral cavity subsites such as the floor of mouth may especially benefit from optical tracer use given the likelihood of shine through from radiotracer signal to the upper neck basin intraoperatively.

Appropriate pathologic analysis is critical for any SLN biopsy program. Step-sectioning at 150 μm is recommended.[52,53] This methodology increases the number of pathologic sections over 10 times compared with conventional lymph node assessment and has been shown to significantly upstage nodal involvement.[53] Given the increased pathology needs, the number of SLNs removed has been studied with recommendation for removal of 2-3 SLNs from the neck with over five SLNs rarely seen.[35,44,45,54]

Frozen section is not recommended in the SLN practice for breast cancer given its destructive nature. Of note, both Hasegawa et al and Garrel et al used frozen section and were able to identify 64%-68% positive SLNs with continuation to CND.[7,37] Most centers are not able to perform thin step-sectioning for frozen evaluation, and so a two-stage procedure is the most common practice.

Postoperative Surveillance

Patients with early OSCC and positive SLN biopsy results merit a CND. This includes proceeding with CND for micrometastases (<2 mm) and isolated tumor cells found on SLN biopsy. Patients with a negative SLN biopsy and those who have a CND merit active surveillance with the current recommendation for imaging (eg, ultrasound) and clinical examination every 3 months for the first 12-18 months.[48] This ensures that false-negative SLN biopsy cases are identified early to enable salvage surgery. Median time to recurrence has been reported at 9 months with no isolated neck recurrence seen after 24 months.[35]

Recommendation

Support for SLN biopsy is increasing through improved multicenter RCTs that provide evidence for personalized oncologic care. With appropriate techniques used, the addition of SLN biopsy for early-stage OSCC may provide comparable outcomes with END with potentially reduced morbidity and cost.

DEFINITIVE RADIATION THERAPY (ie, NONOPERATIVE MANAGEMENT) FOR ORAL CAVITY CANCER

In a substantial proportion of patients with OSCC, up-front curative-intent surgery may not be possible for one or more of the following reasons: (1) cancer-related factors (eg, unresectable tumor), (2) patient-related factors (eg, patient refusal to undergo surgery or those with old age, poor performance status [PS], or medical comorbidities with high operative risk), (3) treatment-related factors (eg, extent of curative-intent surgery will result in unacceptable local morbidity and unsatisfactory functional outcomes), and (4) health care system–related factors (eg, limited health care insurance or unavailable access to proper operative facilities and resources).[9] In these clinical scenarios, primary RT/CRT may be considered a potential alternative treatment choice for OSCC.[9]

In a subgroup analysis of 129 patients with advanced resectable OSCC/oropharyngeal carcinoma who were randomly assigned to either preoperative RT versus postoperative radiotherapy (PORT) versus definitive RT at an RTOG-7303 phase III RCT, there were no statistically significant differences in locoregional control (LRC; 43% *v* 52% *v* 38%, respectively, $P = .4$) or in OS (30% *v* 36% *v* 33%, respectively, $P = .8$).[55] Another RCT compared primary surgery with PORT versus definitive CRT (with cisplatin/fluorouracil [FU]) for stage III/IV HNC (n = 119; 27% were OSCC). There were no statistically significant difference in 3-year DFS (54% *v* 43%, $P = .4$) and 3-year OS (50% *v* 40%, $P = .6$).[56] However, these RCTs included a relatively small number of patients with OSCC, and the findings should be interpreted in the context of potential value of definitive RT/CRT as an alternative treatment approach for OSCC in settings when up-front primary surgery may not be possible.

Several retrospective studies assessed the effectiveness of primary RT or CRT for OSCC. Among published studies, the 5-year OS ranged from 0% to 78%.[9,57-62] A review and meta-analysis of patients with resectable OCC revealed that primary RT/CRT was linked to a significantly higher risk of death in early-stage disease (HR, 2.39; 95% CI, 1.56 to 3.67; I^2, 63%) and was not associated with a statistically increased risk of death (HR, 1.98; 95% CI, 0.85 to 4.64; I^2, 84%) in patients with advanced OSCC treated with CRT.[63] The reported 5-year local and regional control ranged between 53%-92% and 24%-92%, respectively, for patients with OSCC who underwent nonoperative management.[9,64-68] However, these studies included a wide range of variations in tumor characteristics, tumor site, stage, delivered RT techniques, and types of chemotherapy regimens administered.[9,57-62,69]

Recommendation

Definitive RT/CRT for OSCC could be a reasonable alternative management strategy to primary surgery when it is not feasible in view of patient, tumor, treatment, or health care system–related factors.

EARLY LOCOREGIONAL RECURRENCE BEFORE PLANNED PORT IN OSCC: RISK FACTORS AND SALVAGE TREATMENT

In the adjuvant setting, patients with OSCC are traditionally classified according to the risk of LRR into three main categories: (1) low-risk group (no adverse histopathologic features and no need for adjuvant therapy), (2) intermediate-risk group (presence of one or more adverse pathologic features [eg, pT3-4 category, pN2-3 category, close resection margin(s), etc] that indicate the need of PORT), and (3) high-risk group (patients with involved resection margin(s) and/or pathologic extranodal extension [pENE] that require postoperative CRT).[8] Moreover, previous studies showed that patients with OSCC and early recurrence had worse outcomes than those with late relapse, indicating that the timing of recurrence does really matter.[70] In a subgroup of patients with OSCC, LRR after curative-intent surgery could happen too early, even before the planned PORT, reflecting the aggressive behavior of the disease and alarming for complex postoperative treatment course and poor outcomes.[71] In a retrospective review of 601 patients with OSCC treated with PORT after curative-intent surgery, it was reported that 15% of patients with advanced OSCC developed early recurrence before the planned PORT. Oral tongue subsite, pT3-4 category, pN2-3 category, and microscopic positive resection margin were the risk factors for developing early recurrence.[71]

The diagnostic confirmation of early recurrence is challenging and adds to the complexity of such cases for two main reasons: (1) difficulty of clinical detection of early recurrence after surgery even with comprehensive head and neck physical examination and (2) possibility of delaying the planned PORT after performing nonroutine diagnostic procedures postoperatively with subsequent prolongation of the overall treatment package time (ie, from surgery to end of PORT), which can affect the oncologic outcomes.[70,72-74] Therefore, arranging postoperative imaging before RT planning is crucial for patients with higher risk of early recurrence. The ideal time of conducting such imaging is controversial; however, 4 weeks after surgery, it is acceptable to allow for postoperative changes to resolve and to avoid delay in the start of PORT.[72,75] The pathologic confirmation of early LRR is recommended to avoid unnecessary aggressive treatment.[76] However, performing such diagnostic tests would require patient engagement

and collaborative efforts between head and neck surgical and radiation oncologists along with imaging and pathology specialists to avoid delay in PORT.

Once the early recurrence is confirmed, intensified postoperative treatment strategies should be discussed with the patient by the multidisciplinary team members. Salvage treatment options include (1) additional revision surgery (if feasible); (2) use of intensified radiation by planning higher total radiation dose (≥66 Gy), higher radiation dose per fraction (hypofractionation), or accelerated PORT schedules[77-79]; and/or (3) addition of adjuvant systemic therapy concurrently with PORT.[8] The use of high-dose accelerated hypofractionated PORT (70 Gy/33 fractions, 66 Gy/30 fractions, or equivalent) with concurrent cisplatin (for patients who were fit [and agreed] to receive chemotherapy) in patients with OSCC and early recurrence has resulted in a successful salvage rate of 36% at 5 years after PORT; however, this rate was potentially lower for patients with large volume of early recurrent disease.[71]

Recommendation

Postoperative head and neck imaging before RT planning is recommended for patients with OSCC and higher risk of early recurrence (eg, oral tongue subsite, pT3-4 category, pN2-3 category, and microscopic positive resection margins). Treatment intensification with high-dose accelerated hypofractionated RT and concurrent cisplatin (for fit patients) could provide a successful salvage option for early recurrence in approximately one third of patients.

DISTANT METASTASIS IN ORAL CAVITY CANCER: PREDICTION AND POTENTIAL PREVENTION

As advances in treatment of OSCC have resulted in improved LRC,[68,80] more patients with OSCC are exposed to the risk of developing DM with a cumulative incidence ranging between 5% and 15%.[81-83] Several studies showed that predictors of DM in patients with OSCC included patient age, pT category, pN category, histological grade, lymphovascular invasion, and pENE.[56,70,71,73,81,84-86] These risk factors can be used to develop and validate a risk group classification of DM.

Identifying a higher-risk group for DM may have the potential to improve the outcomes of patients with OSCC. This could happen by evaluating imaging surveillance strategies to detect oligometastases in the defined high-risk group of DM at an earlier stage and subsequently assessing the oncologic outcomes after local ablative therapy for oligometastases. Meta-analysis of lung oligometastases in 403 patients with HNC (30% with primary OSCC) showed that lung SBRT or metastectomy was associated with better OS compared with systemic therapy or best supportive care only.[87]

Evaluation of intensified treatment for patients at high risk of DM at the time of initial surgery could also contribute to improve the outcome for OSCC. In a phase III RCT, patients with OSCC who were treated with preoperative chemotherapy (cisplatin and FU) followed by surgery with or without PORT had a lower (but not statistically significant) rate of 5-year DM as compared with patients who were treated with up-front surgery with or without PORT (4.1% *v* 9.3%).[88] In another phase III RCT, the use of chemotherapy (docetaxel, cisplatin, and FU) in the neoadjuvant setting showed a trend of improving the rate of DM (5.5% *v* 8.7%) compared with patients with OSCC who did not receive neoadjuvant chemotherapy; moreover, in subgroup analysis, only patients with cN2 disease had lower rates of distant metastasis-free survival (P = .043) with subsequent improvement in OS (P = .043) when received neoadjuvant docetaxel, cisplatin, and FU.[89]

Recommendation

Identifying patients with OSCC at high-risk DM could allow (1) risk-adaptive DM screening protocol with possible local ablative treatment of early-detected oligometastases and (2) future evaluation of novel systemic multiagent regimens in the setting of a clinical trial in the group of patients with high risk of DM, rather than the entire population with locally advanced OSCC.

INDUCTION CHEMOTHERAPY FOR MANDIBLE SPARING

The role of induction chemotherapy for organ preservation in advanced laryngeal and hypopharyngeal carcinomas is well-established.[90,91] Somewhat more controversial is the role of induction chemotherapy for organ preservation in advanced OSCC.[92,93] In OSCC that invades or abuts the mandible, surgical management has traditionally involved a mandibulectomy. However, mandibular resection is associated with long-term morbidities even after sophisticated reconstruction techniques, including impairment in speech and swallowing, cosmesis, body image, and QOL.[94-96] Preservation of the native mandible thus represents a worthwhile endeavor. Induction chemotherapy is one of the strategies used to shrink the tumor preoperatively and facilitate mandibular preservation.

Studies on Induction Chemotherapy for Mandibular Preservation

The potential purpose of induction chemotherapy in advanced OSCC is not to replace surgery with CRT but rather to decrease the extent of surgery permitting mandible preservation. Several studies have evaluated the role of induction chemotherapy in resectable locally advanced HNC. Ma et al performed a meta-analysis that included the data of 2,099 patients from 14 randomized studies that assessed induction chemotherapy in resectable HNSCC. They found that induction chemotherapy led to an 8% (95% confidence interval [CI], 1 to 16; P = .02) decrease in the rate of DM without significantly affecting the LRR rate, DFS, or OS.[97]

However, most of the studies on resectable HNSCC, including the study by Zhong et al[89] (which evaluated induction chemotherapy exclusively in patients with resectable OSCC), have not studied or reported the mandibular preservation rates. Table 1 provides the details of the studies that evaluated the utility of induction chemotherapy specifically for mandibular preservation in resectable OSCC. The primary end point in the study by Licitra et al was not organ preservation, and hence, this should be considered indirect supporting evidence for mandibular preservation. The study by Chaukar et al[13] is the best available evidence in this setting, although this was a phase II study. Definitive evidence of the efficacy of induction chemotherapy for mandibular preservation is currently under evaluation in a phase III RCT with mandibular preservation as the primary end point.[99]

Induction Chemotherapy Regimen

The study by Lictra et al was an older study, with recruitment between 1989 and 1999. The induction chemotherapy regimen was CF (cisplatin + FU). We now know that the addition of docetaxel to CF (DCF) induction chemotherapy potentially improves oncologic outcomes.[100,101] Accordingly, in the study by Chaukar et al, the more efficacious DCF induction chemotherapy regimen was chosen. The reported objective response rate from DCF in the study by Chaukar et al was surprisingly low (38%) compared with the response rate of 82% reported in the study by Licitra et al; however, the limitation of using radiologic response criteria to predict pathologic response was previously noted for advanced HNC postinduction chemotherapy.[102] Nevertheless, the mandibular preservation rate achieved in the study by Chaukar et al was reassuring and supports the choice of DCF as the induction chemotherapy regimen of choice.

Surgical Margins Postinduction Chemotherapy and Adjuvant Therapy

An important issue to consider when using induction chemotherapy, particularly in patients with borderline resectable or unresectable cancers, and for organ preservation, is whether to consider the preinduction chemotherapy margin status for surgical resection or to resect only the residual tumor volume postinduction chemotherapy. In the study by Licitra et al, the resection was planned according to the original tumor volume; however, the final surgical resection plan was left to the discretion of the operating surgeon, so long as a macroscopic 1.5 cm margin was obtained. Positive surgical margins were noted in 4 patients (4%) in the induction chemotherapy arm and 12 (12.4%) in the up-front surgery arm. Complete pathological remission or only microscopic residual tumor was noted in 27 patients (33%) who received induction chemotherapy. In a matched-pair analysis of patients with T4 buccal mucosa tumors who had received induction chemotherapy for technically unresectable disease (wide margins taken around the postinduction chemotherapy tumor volume) and those with T4 buccal mucosa tumors that were technically resectable and underwent up-front surgery (gross margin of 1 cm was taken around the tumor), the margin positivity rate reassuringly did not differ between the two groups.[103] Accordingly, in the study by Chaukar et al, the surgical resection margins were based on the postinduction chemotherapy tumor volume. To address the possibility of persistent residual microscopic tumor islands in case the tumor had shrunk nonconcentrically from induction chemotherapy, all patients in the induction chemotherapy arm received adjuvant cisplatin-based concurrent CRT, regardless of pathologic risk features. None of the patients in the study of Chaukar et al had positive margins, and the pathologic complete remission rate was 11.8% (n = 4). In both studies, there were no differences in LRR between the patients treated with up-front surgery with or without adjuvant therapy and those who received induction chemotherapy, suggesting that the approach taken by Chaukar et al may be appropriate for properly selected cases, that is, resection on the basis of the postinduction chemotherapy tumor volume, followed by adjuvant concurrent radiation with or without chemotherapy. Caution should be exercised at the time of planning the concurrent chemotherapy regimen, and the cumulative dose of cisplatin that the patient has received as part of the induction chemotherapy regimen should be calculated.

Complications of Induction Chemotherapy, Postsurgical Complications, and QOL

In the study by Licitra et al in which the induction chemotherapy regimen was three cycles of CF, 25 patients (25.5%) developed grade 3, 11 (11.2%) had grade 4, and 3 (3%) had grade 5 (fatal) toxicities. Common grade 3/4 toxicities included neutropenia in 18 patients (18.4%), mucositis in 8 (8.1%), nausea/vomiting in 7 (7.1%), and cardiac in 6 (6.2%). There was no difference in the surgical morbidities and the hospitalization times between the patients who received induction chemotherapy and those who had up-front surgery. In the study of Chaukar et al that used three cycles of DCF induction, 14 patients (41.2%) had grade 3 toxicities and 11 (32.4%) had grade 4 toxicities. Surgical morbidities occurred in 2 (5.9%) in the induction chemotherapy arm while no patients in the up-front surgery arm experienced surgical complications. Thus, with all the caveats of cross-trial comparison, it seems that DCF induction chemotherapy does lead to relatively more toxicities.

It has been well-established that with increasing bony resection, the QOL of patients gets increasingly compromised.[95] However, with the addition of induction chemotherapy and associated toxicities, it would be important to objectively assess whether the strategy of induction

TABLE 1. Studies Evaluating the Role of Induction Chemotherapy for Mandibular Preservation in Patients With Locally Advanced Oral Cavity Carcinomas

Study	Trial Design	Patients Enrolled	Sample Size	Induction Chemotherapy Regimen	Response Rate to Induction Chemotherapy	Mandible Preservation Rate	Adjuvant Therapy	Oncological Outcomes
Licitra et al[98]	Phase III RCT comparing induction chemotherapy followed by surgery versus surgery alone	Untreated locally advanced resectable oral cavity squamous cell carcinoma; T2-T4 (>3 cm), N0-2	195	CF x 3 cycles: cisplatin 100 mg/m^2 + 5FU 1000 mg/m^2 as a 120-hour infusion once every 21 days	82% -CR: 28 (33%) -PR: 42 (49%)	21%; 95% CI, 7-34 (segmental mandibulectomy performed in 31% in the induction chemotherapy arm *v* 52% in the up-front surgery arm)	Adjuvant RT administered for high-risk patients. Criteria for high risk: -Positive surgical margins -Invasion of soft tissues of the face (cheek, chin) -Involvement of > 3 lymph nodes -Extracapsular tumor spread 32 (33%) in induction chemotherapy arm *v* 45 (46%) in the up-front surgery arm 13% difference; 95% CI, 0-27	5-yr EFS: induction chemotherapy arm 57% (95% CI, 46 to 67) *v* up-front surgery arm: 46% (95% CI, 36-57); *P* = .499 5-yr OS: Induction chemotherapy: 55% (95% CI, 45 to- 66), and up-front surgery: 55% (95% CI, 44 to 65); *P* = .767
Chaukar et al[13]	Phase II RCT comparing induction chemotherapy, followed by mandibular preservation surgery versus up-front surgery followed by adjuvant therapy	Untreated cT2-T4 and N0/N1, M0 oral squamous cell carcinoma, which required mandibular resection for paramandibular disease, with no clinicoradiologic bone erosion	68	DCF × three cycles: Docetaxel 75 mg/m^2 on day 1+ cisplatin 75 mg/m^2 on day 1 + 5FU 750 mg/m^2 on days 1-5; once every 21 days	38.2% CR: 1 (2.9%) PR: 12 (35.2%) SD: 16 (47.3%) PD: 2 (5.8%)	47% (95% CI, 31.49 to 63.24) Induction chemotherapy arm (n = 34): 14 (41.1%) underwent segmental mandibulectomy, 15 (44.1%) underwent marginal mandibulectomy, and 5 (14.8%) no surgery In up-front surgery arm, all 34 (100%) patients underwent segmental mandibulectomy	All patients in both arms received adjuvant RT with or without chemotherapy In induction chemotherapy arm: 26 (76.4%) received adjuvant CRT (weekly cisplatin 30 mg/m^2) and 3 (8.8%) received RT alone In up-front surgery arm, 16 (47%) received adjuvant CRT (weekly cisplatin 30 mg/m^2), 16 (47%) received adjuvant RT alone, and 2 (5.8%) were observed	Median DFS: Induction chemotherapy arm: 3.8 years (range, 0.04-9.38) and up-front surgery arm: 3.4 years (range, 0.13-8.74); HR 0.911 (95% CI, 0.516 to 1.607); *P* = .715 Median OS: Induction chemotherapy arm: 4.1 years (0.12-9.38) and up-front surgery arm: 3.4 years (range, 0.29-8.74); HR, 0.899 (95% CI, 0.510 to 1.587); *P* = .747

Abbreviations: CF, cisplatin + fluorouracil; CR, complete remission; CRT, chemoradiation; DCF, docetaxel + cisplatin + fluorouracil; DFS, disease-free survival; EFS, event-free survival; FU, fluorouracil; HR, hazard ratio; OS, overall survival; PD, progressive disease; PR, partial remission; RCT, randomized controlled trial; RT, radiation; SD, stable disease.

chemotherapy leads to an improvement in the QOL. Unfortunately, neither of the two studies reported the QOL of patients; hence, this remains an unanswered question.

Recommendation

In patients with locally advanced OSCC that would necessitate mandibulectomy, but no clinical and radiographic evidence of mandibular erosion, induction chemotherapy with three cycles of docetaxel + cisplatin + FU followed by an attempt at mandibular preservation surgery (possibly on the basis of the postinduction chemotherapy tumor volume) and adjuvant concurrent chemoradiotherapy may be a potential strategy for organ preservation, without compromising oncologic survival outcomes in carefully selected cases. Multidisciplinary discussion and patient-centered approach are the keys for selecting these potential cases.

ALTERNATIVE STRATEGIES TO CISPLATIN COMBINED WITH RADIOTHERAPY AS ADJUVANT TREATMENT

The established standard of care for patients with high-risk features (pENE and/or positive margins) is postoperative concurrent CRT with high-dose cisplatin at 100 mg/m^2 once every 3 weeks.[104] This strategy improves LRC, DFS, and OS. However, this comes with acute and long-term toxicities (eg, ototoxicity and nephrotoxicity). Besides, a substantial proportion of patients are platinum-ineligible or unfit. Hence, there have been multiple attempts to discover alternatives to high-dose cisplatin. Changing the schedule (ie, lowering the dose and administering cisplatin once a week) was the first strategy that was widely used in practice[105] and subsequently tested by several groups.[103,105-107] Noronha et al[108] found that once-weekly cisplatin at 30 mg/m^2 administered concurrently with adjuvant radiation was not noninferior to high-dose cisplatin once every 3 weeks and significantly lowered the LRC. Kiyota et al[107] increased the dose of once-weekly cisplatin to 40 mg/m^2 and found that this dose led to a noninferior OS as compared with high-dose cisplatin once every 3 weeks. However, the weekly cisplatin regimen also led to significant adverse events: 71.6% acute grade 3 and higher toxicities in the once-weekly cisplatin arm, which, although lower than the 84.6% grade 3 and higher toxicities in the once-every-3-weeks cisplatin arm, was certainly not insignificant. Thus, the search continued for alternatives to cisplatin.

Alternatives to Cisplatin in Platinum-Fit Patients

Reasons to seek out alternatives to cisplatin in patients who are fit include possible increased efficacy or decreased toxicity. A phase III RCT evaluating whether carboplatin added to radiation improved outcomes was stopped prematurely because of poor accrual; it showed no benefit in DFS from the addition of carboplatin to radiation. Although there are no studies that directly compared cetuximab with cisplatin as adjuvant CRT for OSCC, by extrapolating the data from the definitive setting, cetuximab does not seem to be an appropriate option for platinum-eligible patients. There have been attempts to escalate therapy with the addition of immune checkpoint inhibitors to standard definitive cisplatin-based CRT: avelumab in JAVELIN Head and Neck 100[109] and pembrolizumab in KEYNOTE-412,[110] both of which failed to improve outcomes. The GORTEC 2017-01 (REACH) study that evaluated the combination of immunotherapy with cetuximab as compared with cisplatin CRT (nonoperated) in locally advanced HNC (cisplatin-fit cohort) was recently stopped for futility.[111] In the adjuvant setting, the most promising data are for docetaxel + cetuximab.[112,113] Table 2 provides the details of studies that evaluated various alternatives to cisplatin CRT in the postoperative adjuvant setting. A noninferiority trial is currently assessing docetaxel to high-dose cisplatin concurrently with radiotherapy in both the adjuvant and definitive CRT settings.[116] Finally, the recently published OCAT study conducted on 900 patients with resected stage III/IV OSCC, and at least one poor prognostic feature on the histopathology (pENE, $\geq$2 involved regional lymph nodes, positive margin(s), extensive soft tissue and/or skin infiltration requiring major reconstruction, or perineural or lymphovascular invasion) reported that for the entire cohort, there was no difference in oncological outcomes (LRC, DFS, or OS) between the three arms: arm A—standard adjuvant radiotherapy alone (60 Gy/30 fractions, 5 days a week over 6 weeks); arm B—concurrent CRT with once-weekly cisplatin 30 mg/m^2 for six cycles with standard radiation (60 Gy/30 fractions, 5 days a week over 6 weeks); or arm C—accelerated radiation (60 Gy/30 fractions, 6 days a week over 5 weeks). The group of patients at the highest risk (ie, T3-4 N2-3 disease and pENE) was shown to have a significantly longer DFS and OS from both the addition of chemotherapy to standard radiation and the acceleration of radiation.[117]

Defining Cisplatin Ineligibility

Contraindications to cisplatin and to platinum in general may be absolute or relative. Based on the criteria established by Ahn et al,[118] absolute contraindications to cisplatin include an Eastern Cooperative Oncology Group (ECOG) PS score of 3 or 4, renal dysfunction (<50 mL/min), and grade 2 or higher organ dysfunction, including deafness, tinnitus, and neurologic dysfunction, hypersensitivity to platinum, pregnancy and lactation, and patients with HIV/AIDS with a CD4 count <200/μL. Relative contraindications to cisplatin, that is, conditions that skew the risk-benefit ratio of cisplatin, include an ECOG PS score of 2, age > 70 years, borderline organ dysfunction, calculated creatinine clearance of 50-60 mL/min, various comorbidities, lack of social support, previous cumulative platinum dose >200 mg/m^2, unintentional weight loss >20%, and the concurrent use of nephrotoxic drugs. In 2019, Szturz et al modified the criteria for cisplatin ineligibility and removed the age > 70 years criterion. In older persons, rather than using the chronological age and/or merely the PS of the patient to determine

TABLE 2. Randomized Studies in Patients With Locally Advanced Head and Neck Squamous Cell Carcinomas Evaluating Various Alternative Regimens to the Standard Cisplatin-Based Chemoradiotherapy

Study	Trial Design	Patients Included	Chemotherapy Regimens	Sample Size/No. of Patients With Oral Cavity Cancers (%)	Toxicities	Oncological Outcomes	Interpretation and Comments
Studies performed in cisplatin-eligible patients							
RTOG-0234 (Harari et al[113])	Phase II randomized study comparing the addition of cetuximab with cisplatin 30 mg/m^2 once per week or docetaxel 15 mg/m^2 once per week both concurrently with RT	Stage III-IV HNSCC postoperatively with high-risk pathologic features including positive margins, extracapsular extension, or >two positive lymph nodes	Cetuximab 400 mg IV loading dose, started 5-9 days pre-RT, then 250 mg/m^2 once weekly infusions × 6 (both arms) Cisplatin arm: cisplatin 30 mg/m^2 IV once weekly × 6 Docetaxel arm: 15 mg/m^2 IV once weekly × 6	N = 203; Oral cancers: 95 (46.8%)	Common grade 3 and higher toxicities (cisplatin + cetuximab *v* docetaxel + cetuximab): Mucositis: 55.7% *v* 53.8%, dysphagia: 38.1% *v* 36.8%, skin rash: 36.1% *v* 38.7%, hematologic toxicities: 27.8% *v* 14.2%	DFS in each arm was compared with the historic control of high-dose 3-weekly cisplatin in the RTOG 9501 study: Cisplatin + cetuximab arm: 2-year DFS: 57%; HR, 0.76; 95% CI, 0.54 to 1.06; *P* = .05 Docetaxel + cetuximab: 66%; HR, 0.69; 95% CI, 0.50 to 0.96; *P* = .01; 2-year OS: Cisplatin arm: 69% Docetaxel arm: 79%	Docetaxel + cetuximab as postoperative CRT led to an absolute improvement in 2-year DFS of 11.1% as compared with the historical control (RTOG 9501) and seems to be a promising regimen
Argiris et al[114]	Phase III randomized study comparing carboplatin + RT with RT alone in the postoperative setting for high-risk HNSCC	Stage III/IV HNSCC with macroscopic resection, with at least one high-risk pathologic feature: ≥three lymph nodes, extracapsular extension, perineural or angiolymphatic invasion, or positive margins (0.5 mm or less)	Carboplatin 100 mg/m^2 IV once weekly × 6	N = 72; Oral cancers: 25 (34.7%)	Carboplatin did not lead to a significant increase in toxicities; No grade 4 toxicities Grade 3 toxicities: 18% in RT alone arm, *v* 36% in carboplatin + RT arm; *P* = .17	2-year DFS (primary end point): RT alone, 58% (95% CI, 39 to 76) *v* carboplatin + RT-71% (95% CI, 56 to 88); HR, 0.82, *P* = .6 2-year OS: RT alone, 51% *v* carboplatin + RT-74%; *P* = .04	Carboplatin when added to postoperative RT did not prolong 2-year DFS (13% absolute improvement in 2-year DFS from the addition of carboplatin but statistically negative); study was terminated early because of poor accrual

(Continued on following page)

TABLE 2. Randomized Studies in Patients With Locally Advanced Head and Neck Squamous Cell Carcinomas Evaluating Various Alternative Regimens to the Standard Cisplatin-Based Chemoradiotherapy (Continued)

Study	Trial Design	Patients Included	Chemotherapy Regimens	Sample Size/No. of Patients With Oral Cavity Cancers (%)	Toxicities	Oncological Outcomes	Interpretation and Comments
Studies performed in cisplatin-ineligible patients							
DHANUSH (Patil et al[115])	Phase II/III randomized trial comparing docetaxel with cisplatin concurrently with RT in cisplatin-unfit patients	HNSCC, arising in oral cavity, oropharynx, hypopharynx, larynx, planned for radical RT (both definitive and adjuvant) who were deemed platinum-ineligible	Docetaxel 15 mg/m^2 IV once weekly × maximum seven cycles	N = 356; Oral cavity cancers: 133 (37.4%) Postoperative setting: 139 (39%)	Grade 3 and higher toxicities: RT alone, 102 (58%) *v* docetaxel + RT-146 (81.6%), $P = .001$; Common grade 3 or higher toxicities (RT *v* docetaxel + RT): Mucositis, 22% *v* 49.7%; $P < .001$; Odynophagia, 33.5% *v* 52.5%, $P < .001$; Dysphagia, 33% *v* 49.7%; $P = .002$; Dermatitis, 8.5% *v* 15.1%; $P = .07$; Hyponatremia, 19.3% *v* 30.2%; $P = .02$	2-year DFS (primary end point for the phase II): RT alone, 30.3% (95% CI, 23.6 to 37.4) *v* docetaxel: 42% (95% CI, 34.6 to 49.2); HR, 0.673 (95% CI, 0.521 to 0.868; $P = .002$); Median locoregional failure-free survival: RT alone, 5.9 months (95% CI, 4.9 to 7.5) *v* docetaxel + RT-12.4 months (95% CI, 8.6 to 23.5); HR, 0.661 (95% CI, 0.512 to 0.854; $P = .002$); 2-year OS: RT alone, 41.7% (95% CI, 34.1 to 49.1) *v* docetaxel + RT-50.8% (95% CI, 43.1 to 58.1); HR, 0.747 (95% CI, 0.569 to 0.980; $P = .035$)	Docetaxel when added to RT (both definitive and adjuvant) in cisplatin-ineligible patients significantly prolonged DFS and OS

Abbreviations: CRT, chemoradiation; DFS, disease-free survival; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; IV, intravenous; OS, overall survival; RT, radiation.

cisplatin suitability, a geriatric assessment is appropriate to evaluate for frailty and various vulnerabilities.[119,120] Szturz et al also recommended that grade 2 hearing impairment should be a relative rather than an absolute contraindication.

Alternatives to Cisplatin in Platinum-Unfit Patients

Extrapolating the data from the cisplatin-eligible setting, carboplatin is likely to be ineffective and should not be used, although it has been a relatively popular choice in the past for cisplatin-ineligible patients. Various alternative chemotherapeutic options such as paclitaxel + carboplatin have been described in case series/retrospective cohorts.[121] Although there is no convincing evidence that cetuximab is used in the postoperative setting on patients who are cisplatin-ineligible, by extrapolation, on the basis of the trial of Bonner et al[122] (definitive CRT, nonoral cavity subsites).

The results of the DHANUSH study proved that docetaxel when added to radiation in patients who were cisplatin-ineligible (defined as per Ahn's criteria) significantly prolonged both DFS and OS.[115,118] The enrollment criteria were broad: locally advanced HNSCC arising in the oral cavity, oropharynx, hypopharynx, and larynx and carcinoma of unknown primary, warranting radiation in the definitive or adjuvant settings. There was no significant interaction between the addition of docetaxel and the treatment settings, that is, docetaxel was effective in both the definitive and adjuvant settings. There was a significant increase in toxicities from the addition of docetaxel; however, the QOL was maintained. There were 160 patients (44.9%) with ECOG PS 2 and 58 (16.3%) who were older than 70 years; thus, the regimen is suitable for a relatively frail population.

Finally, this is an area of active research, with a slew of newer molecules undergoing testing. One such promising drug is xevinapant, an antagonist of inhibitor of apoptosis proteins.[123] The XRAY VISION study will evaluate the efficacy of xevinapant in the postoperative setting in cisplatin-ineligible patients.[124]

Recommendation

In cisplatin-eligible patients, the standard of care for OSCC with high-risk features is high-dose cisplatin 100 mg/m^2 once every 3 weeks or lower-dose cisplatin 40 mg/m^2 once weekly, which should be added concurrently to radiotherapy. In cisplatin-ineligible patients, docetaxel 15 mg/m^2 once weekly with PORT is supported by the best evidence. Other possible options include concurrent cetuximab, carboplatin/5FU, carboplatin/paclitaxel, or the use of accelerated radiation.

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Management of Advanced Thyroid Cancer: Overview, Advances, and Opportunities

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overview

Thyroid cancer is the most common endocrine malignancy with almost one million people living with thyroid cancer in the United States. Although early-stage well-differentiated thyroid cancers account for the majority of thyroid cancers on diagnosis and have excellent survival rates, the incidence of advanced-stage disease has increased over the past few years and confers poorer prognosis. Until recently, patients with advanced thyroid cancer had limited therapeutic options. However, the landscape of thyroid cancer treatment has dramatically changed in the past decade with the current availability of several novel effective therapeutic options, leading to significant advances and improved patient outcomes in the management of advanced disease. In this review, we summarize the current status of advanced thyroid cancer treatment options and discuss recent advances made in targeted therapies that have proven promising to clinically benefit patients with advanced thyroid cancer.

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INTRODUCTION

Thyroid cancer is the most common endocrine malignancy with the prevalence in the United States currently exceeding 900,000 cases.[1] Overall, the majority of thyroid cancers detected are early-stage well-differentiated thyroid cancers (DTCs) that have an excellent prognosis[1]; however, some evidence shows that the incidence of advanced thyroid cancers has increased in recent years.[2] In 2022, 2,230 patients died of thyroid cancer in the United States.[1]

Follicular-derived thyroid cancers include papillary thyroid cancer, follicular thyroid cancer, Hürthle cell cancer, poorly DTC, and undifferentiated (anaplastic) thyroid cancer (ATC). Although surgery and radioactive iodine (RAI) are the standard of care for DTCs often leading to cure, patients with radioactive-iodine refractory (RAIR) disease, DTCs, and ATCs confer poorer prognosis and pose significant challenges for treating clinicians. Medullary thyroid cancer (MTC) arises from parafollicular or C cells and accounts for fewer than 5% of thyroid cancer diagnoses but approximately 13% of thyroid cancer deaths.[3] Overall, approximately 20% of cases are familial secondary to a germline rearranged during transfection (*RET*) mutation while the remaining cases are sporadic.[4] Patients with MTC who present with regional lymph node metastases and/or distant metastases are less likely to be cured of their disease.[5]

This review focuses on the current status of advanced thyroid cancer treatment options, summarizing the role of surgery in advanced thyroid cancer management, challenges in the management of RAIR thyroid cancer, and advances in systemic therapies, particularly progress pertaining to targeted therapies.

DEFINITION OF ADVANCED THYROID CANCER

Advanced thyroid cancer is a term used to describe aggressive tumors; however, there is significant variability among specialties. Surgeons refer to unresectable tumors as advanced thyroid cancers, endocrinologists to describe RAIR tumors, and oncologists when there are distant metastases.[6] A recent consensus statement by the American Head and Neck Society (AHNS) Endocrine Surgery Section and International Thyroid Oncology Group defined advanced thyroid cancer according to four categories. The *structural/surgical* category encompasses the following: (1) bulky, invasive, or inoperative locoregional disease; (2) recurrence; (3) distant metastases; (4) gross residual neck disease without option for reoperation; (5) rapid progression on imaging; and (6) imminent threat posed by tumor burden. Tumors refractory to RAI, unresponsive to thyroid-stimulating hormone (TSH) suppression, and rapid calcitonin, carcinoembryonic antigen, or thyroglobulin doubling times constitute the *biochemical* category. The *histologic/molecular* category includes findings such as poorly differentiated or other aggressive histology components, high Ki67 index, high mitotic count or tumor necrosis, and all anaplastic thyroid carcinoma. Finally, tumors can be categorized as advanced thyroid cancer at the discretion of the treating physician if there are features that portend aggressive tumor behavior (*clinician prero*gative).

PRACTICAL APPLICATIONS

- Surgical management of advanced thyroid cancer is challenging and should evolve from multidisciplinary discussion integrating individual disease characteristics, expected surgical morbidity, and patient preferences.
- Common clinical scenarios suggestive of radioactive iodine (RAI) refractory thyroid cancer include a negative diagnostic RAI uptake whole-body scan, loss of RAI uptake on post-therapy RAI scan, presence of RAI in some tissues but not others, and metastatic disease progression despite ability to concentrate RAI, including a cumulative activity of >600 mCi.
- An improved understanding of thyroid cancer pathogenesis has led to a remarkable change in the landscape of available systemic targeted therapies for patients with advanced and refractory disease in the past several years.
- Treatment decisions regarding use of targeted therapies for advanced thyroid cancer should be made judiciously by a multidisciplinary team while weighing risks versus benefits and undertaking close surveillance for disease progression and adverse events.

ROLE OF SURGERY IN ADVANCED THYROID CANCER

DTC

The 2015 American Thyroid Association (ATA) guidelines established protocols for surgically managing tumors on the basis of size, stage, and aggressive features.[7] The guidelines provide guidance regarding surgical indications and extent of surgery (lobectomy *v* total thyroidectomy). There has been a shift toward lobectomy in certain cases, as detailed below.

Preoperative workup in patients with thyroid cancer includes imaging and thyroid function tests. Ultrasound is the recommended initial imaging modality and should include the thyroid, central compartment, and bilateral lateral neck nodes.[7] Additional imaging, that is, computed tomography (CT) and magnetic resonance imaging (MRI) with intravenous contrast, is recommended in patients with advanced thyroid cancer, suspicion for local invasion, and multiple or bulky lymphadenopathy. Chest CT should be considered if there is concern for low mediastinal nodes or pulmonary metastasis. Positron emission tomography (PET) may be used in recurrent cases or for surveillance.[8] In cases of advanced disease when invasion is suspected, additional preoperative workup including larynx evaluation, swallow function, and dedicated imaging with CT of the chest (trachea) and MRI (esophagus) is recommended.[9]

According to the ATA guidelines, patients with DTC are subdivided into three categories with treatment implications[7]:

1. Thyroid cancer >4 cm, gross extrathyroidal extension (ETE; clinical T4), nodal disease (clinical N1), or distant metastasis
2. Thyroid cancer >1 cm and <4 cm without ETE and without nodal disease or metastasis
3. Thyroid cancer <1 cm without ETE and without nodal disease

For group 1, total thyroidectomy is the recommended treatment. For patients in group 2, either option of lobectomy or total thyroidectomy is acceptable. The decision-making process regarding the extent of surgical resection in these patients involves a cohesive discussion between the treatment team and the patient. If RAI is planned or likely to be recommended, total thyroidectomy would be indicated. Finally, for patients in group 3, watchful waiting with surveillance may be an option in cases of low-risk differentiated tumors; if surgery is preferred, thyroid lobectomy is recommended unless there is an indication to remove the contralateral lobe or a history of previous head and neck radiation or familial thyroid carcinoma.[7,10]

The ATA guidelines also incorporate indications for nodal dissection. With clinically evident central compartment and/or lateral neck disease, dissection is recommended at the time of initial surgery. Central compartment lymph node dissection, or level VI, includes pretracheal and paratracheal nodes. Lateral neck dissection typically incorporates level II-IV nodal levels, extending from the skull base superiorly to the clavicle inferiorly and from the strap muscles medially to the posterior border of the sternocleidomastoid muscle laterally. Nodal dissection of an additional level may be incorporated if there is clinically evident nodal disease. Prophylactic central compartment dissection can be considered in patients with advanced papillary carcinoma (T3 or T4), clinically involved lateral nodes, or if the nodal tissue may guide adjuvant treatment.[7]

In regard to management of invasive DTC, which occurs in up to 15% of patients, the AHNS published a series of consensus statements in 2014.[9] These consensus statements can be used to guide preoperative workup and intraoperative management. The recurrent laryngeal nerve (RLN) is involved in 33%-61% of patients with invasive cancer. Fiberoptic laryngoscopy is the preferred method of laryngeal evaluation, particularly when voice is abnormal, if history of thyroid surgery, or if ETE is suspected. Management of the RLN during surgery varies according to preoperative function, degree of invasion, and status of the contralateral nerve and has important functional

implications for voice, breathing, and swallow. Although intraoperative RLN monitoring is commonly used for evaluation of nerve status, the nerve should still be identified intraoperatively.[7,11,12] Postoperative unilateral dysfunction is often evident if voice changes occur and may lead to aspiration, whereas bilateral dysfunction typically presents with shortness of breath and stridor. Preservation of the parathyroid glands should be attempted with dissection along the thyroid capsule to avoid inadvertent injury to their vascular supply. Intraoperatively, the thyroid specimen should be carefully examined after removal for any parathyroid tissue. If identified, the parathyroid should be reimplanted into nearby muscle, and postoperative calcium and parathyroid hormone levels should be monitored.[7]

Additional structures including the trachea and larynx may be abutted or directly invaded in patients with advanced DTC. If invasion is suspected, direct laryngoscopy and bronchoscopy are performed. The extent of invasion helps to guide the recommended intraoperative decision making, for example, whether to perform a tracheal shave versus a circumferential tracheal resection or partial versus total laryngectomy.[9] Because esophageal invasion usually involves only the muscularis layer, extent of invasion may not be seen on esophagoscopy. Similar to the larynx and trachea, esophageal resection may be limited to the outer layers or involve composite resection if intraluminal tumor is present.[9] Although rare, in cases of suspected major vascular invasion by tumor, CT or magnetic resonance angiogram is performed preoperatively. If the carotid artery is involved, balloon occlusion testing and potential carotid sacrifice may be considered in select cases of differentiated, locally advanced cancers.[9]

It is important to note that nearly one-quarter of patients with invasive cancer die from airway obstruction secondary to tracheal invasion and 28% from respiratory failure secondary to lung involvement.[13] Patients with locally invasive cancer who are candidates for surgical resection and achieve gross total resection have good outcomes, with one study reporting >90% 5-year disease-free survival.[14] Tumors invading the prevertebral fascia or encasing the carotid artery are classified as unresectable; however, there are instances when near total gross resection may be indicated for palliation in well-differentiated tumors with overall good outcome.[15] In addition, palliation with tracheostomy may be recommended in patients where airway obstruction from tumor is imminent or when planned for nonsurgical therapy.[16] Finally, as more targeted therapies are being selectively used, some patients who would not have been good candidates for surgery may now be considered for surgical treatment either for local disease control or for palliation. The nuances stemming from having received neoadjuvant treatment and the implications on surgery remain to be studied.

Finally, in 2016, the AHNS published a consensus statement recommending revision surgery for tumor and nodal recurrence, if feasible. In revision surgery, the primary goal is to remove recurrent cancer in the thyroid or nodal tissue, remove remaining thyroid tissue, and perform nodal dissection in regions suspected to have microscopic disease.[17]

Medullary Thyroid Carcinoma

Total thyroidectomy and central neck dissection (level VI), with dissection of lymph nodes in the lateral compartments (levels II-V) depending on calcitonin levels and ultrasound findings, is a standard treatment for patients with sporadic or hereditary MTC.[18,19] When preoperative imaging is positive in the ipsilateral lateral neck compartment but negative in the contralateral neck compartment, contralateral neck dissection should be considered if the basal serum calcitonin level is >200 pg/mL.[18]

Anaplastic Thyroid Carcinoma

Surgical options must be carefully evaluated in patients with ATC while balancing risks and benefits with goals of care. The primary goal for resectable tumors (stages IVA and IVB) is an aggressive approach with complete resection, followed by definitive chemoradiation. In stage IVC ATC, the limited benefit from surgery must be carefully weighed against other palliative approaches, such as radiation and systemic therapy.[20]

RAIR-DTC

After thyroidectomy, RAI remains the most frequently used adjuvant therapy for follicular-derived thyroid cancers, with the main goals to improve disease-specific survival, reduce recurrence rates, and improve progression-free survival (PFS).[7] However, several patients with advanced DTC are radioactive-iodine resistant/refractory. According to the 2015 ATA guidelines, DTCs are considered refractory to RAI when (1) they do not concentrate RAI at the time of initial treatment, such as in patients with structurally evident disease and a negative RAI uptake whole-body scan, suggesting that RAI treatment would provide no clinical benefit; (2) they lose their ability to concentrate RAI in the setting of previous RAI uptake, often occurring in patients with multiple large metastases; (3) concentrate RAI in some tissues but not others, evident by comparing findings from a RAI whole-body scan with those from a ^{18}FDG-PET scan; or (4) there is metastatic disease progression despite ability to concentrate RAI.[7] However, the exact definition of RAIR-DTC is still controversial, and different definitions have been proposed by different societies. A recent consortium of experts from the ATA, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association noted that no current definition, classification, criterion, or clinical scenario is an absolute indicator that a patient has RAIR-

DTC.[21] The common clinical scenarios suggesting that a patient may have RAIR-DTC derived from this consortium are outlined in Table 1 and provide a framework addressing important management issues in patients with RAIR-DTC. Importantly, factors such as the amount of RAI uptake on post-therapy whole-body scans compared with the total RAI dose the patient received, tolerability of side effects, and tumor response to previous RAI treatments should be considered to optimize therapy in these patients.

Patients with inoperable and/or metastatic RAIR-DTC have a worse overall prognosis than those who have RAI-sensitive follicular-derived thyroid cancers.[21-23] Before the routine availability of targeted therapies, studies showed that patients with RAIR-DTC had median 5-year disease-specific survival rates of 60%-70%, and those with metastatic RAIR-DTC had the worse outcomes with a median 10-year survival rate of 10%.[23,24] The significance of identifying patients who may harbor RAIR disease lies with the need for early intervention in these patients to improve disease-free progression and survival, with molecular testing and mutational mapping having emerged as adjuncts to imaging and pathology of identification of more aggressive disease.

Many patients with RAIR-DTC have slow-growing, low-volume disease. For patients with asymptomatic RAIR-DTC which may persist for years, low tumor burden or minimal progression over time, watchful waiting with TSH suppression, and periodic imaging can be used.[25-27] In patients with locoregional recurrence, surgical intervention is usually used as the therapeutic approach of choice, with external-beam radiation therapy used in combination with surgery in select cases.[25] Typically, symptomatic patients with distant metastases to the lungs and/or bone are often offered local therapies before consideration of systemic treatments.[28]

SYSTEMIC THERAPY IN ADVANCED THYROID CANCER

The decision to initiate systemic therapy in thyroid cancer is an area in endocrine oncology where significant clinical practice variability exists. The specific histopathological variables play a role in the timing of antineoplastic treatment. In general, the sole increase of tumor markers is not decisive in starting systemic therapy for thyroid cancer. Patients with metastatic RAIR-DTC and MTC with asymptomatic disease and small tumors with slow indolent progression are amenable to close active surveillance with serial imaging.[29] Specifically, for RAIR-DTC and MTC, targeted therapy is recommended for (1) rapidly progressive tumors not amenable or failure to alternative localized therapies, (2) symptomatic disease, or (3) tumors in a threatening location.[7,30]

The evolving availability of different molecular testing modalities has allowed the incorporation of precision oncology for prognostic and therapeutic purposes in advanced thyroid cancer and is consistent with current National Comprehensive Cancer Network guidelines.[31] Given the potential for druggable targets, the preferred somatic testing approach is next-generation sequencing (NGS) in contrast to single-gene tests.[6] All ATC tumors should undergo molecular testing. However, immunohistochemistry (IHC) evaluation for BRAF V600E should also be incorporated into the initial assessment of ATC while awaiting NGS results; rapid BRAF V600E IHC–positive results can lead to early therapeutic interventions with dabrafenib and trametinib.

TABLE 1. Common Clinical Scenarios Suggestive of RAIR-DTC

Clinical Scenario	Considerations
No RAI uptake on diagnostic ^{131}I scan	Adequate low-iodine diet and TSH stimulation before scan High-resolution imaging with SPECT/CT scan provides more functional detail than planar imaging
No RAI uptake on a post-therapy ^{131}I scan (performed several days after therapy)	Post-therapy ^{131}I scans may miss up to 12% of DTC metastases that have RAI uptake
RAI uptake is only present in some but not other tumor tissues	Can treat RAI-avid tumor tissues with ^{131}I and use local treatment modalities for non–RAI-avid tissues
Progression of DTC metastases despite ^{131}I uptake	Metric used for successful response to previous ^{131}I therapy, duration of response, metric used to determine progression of disease post-^{131}I therapy, amount of ^{131}I activity previously administered, potential for administering higher ^{131}I activity, side effects, and patient preferences should be considered when deciding to pursue additional ^{131}I administrations
Progression of DTC metastases despite cumulative ^{131}I activity of >600 mCi	Increased likelihood of DTC becoming RAIR with increased cumulative ^{131}I activity and number of doses Response to previous treatments, duration of response, individual ^{131}I activity administered in each previous treatment, side effects, and patient preferences should be considered when deciding to pursue additional ^{131}I administrations

Abbreviations: DTC, differentiated thyroid cancer; mCi, millicuries; RAI, radioactive iodine; RAIR, radioactive-iodine refractory; SPECT/CT, single-photon emission computed tomography with computed tomography; TSH, thyroid-stimulating hormone.

For the remaining thyroid cancer variants, molecular testing should be considered in the setting of RAIR-DTC, locally invasive or unresectable tumors, distant metastatic disease, and aggressive histological features and on the basis of the clinician's judgment.[6] Available systemic targeted therapies for advanced thyroid cancers and their mechanism of action are outlined in Table 2 and Figure 1.

DTC

Initial oral antineoplastic regimens for advanced thyroid cancers consisted of multikinase inhibitors (MKIs). The DECISION study, a phase III multicenter randomized, double-blind clinical trial, evaluated the utilization of sorafenib 400 mg twice daily versus placebo. Study treatment in this trial continued until radiographically documented disease progression, unacceptable toxicity, noncompliance or withdrawal of consent. Sorafenib resulted in a meaningful improvement in PFS of 10.8 versus 5.8 months in the placebo cohort (hazard ratio [HR], 0.59; 95% CI, 0.45 to 0.76; $P < .0001$). The overall response rate (ORR) was 12.2% versus 0.5% in favor of sorafenib.[32] Adverse events occurred in most patients (98.6%) treated with this MKI, classified predominantly as grade 1-2. Common noted side effects included hand-foot skin reaction (76.3%), diarrhea (68.6%), alopecia (67.1%), rash (50.2%), fatigue (49.8%), weight loss (46.9%), hypertension (40.6%), anorexia (31.9%), and mucositis (23.2%), among others.[32]

Furthermore, lenvatinib, an MKI aiming at vascular epithelial growth factor receptor (VEGFR), fibroblast growth factor receptors, RET, KIT, and platelet-derived growth factor receptor α, has shown substantial responses in advanced thyroid cancer. In the SELECT trial, the lenvatinib-treated cohort attained a PFS of 18.3 months compared with 3.6 months in the placebo group (HR, 0.21; 99% CI, 0.14 to 0.31; $P < .001$).[33] In patients pretreated with another MKI, lenvatinib, the PFS was 15.1 months. The ORR is 64.8% in the oral antineoplastic cohort; the majority were partial responses (63.2%) by RECIST 1.1. In addition, lenvatinib has demonstrated a benefit in the overall survival of patients older than 65 years. Frequently noted adverse events included hypertension (67.8%), diarrhea (59.4%), fatigue (59%), decreased appetite (50.2%), weight loss (46.4%), nausea (41%), stomatitis (35.6%), palmar-plantar erythrodysesthesia syndrome (31.8%), proteinuria (31%),

TABLE 2. Summary of Systemic Targeted Therapies in Advanced Thyroid Cancer

Targeted Therapy	Tumor Target	Response	Common Side Effects
Multikinase inhibitors-DTC			
Sorafenib	VEGFR, PDGFR, RET	PFS, 10.8 months ORR, 12%	Hand-foot, diarrhea, alopecia, rash, fatigue, weight loss, HTN
Lenvatinib	VEGFR, PDGFR, RET, FGFR	PFS, 18.3 months ORR, 64.8%	HTN, diarrhea, fatigue, decreased appetite, weight loss, nausea
Multikinase inhibitors-MTC			
Vandetanib	RET, VEGFR, EGFR	ORR, 45%	Diarrhea, rash, HTN, nausea, headache
Cabozantinib	RET, VEGFR, c-MET		Diarrhea, HTN, hand-foot syndrome
BRAF/MEK inhibitors			
Dabrafenib and trametinib	BRAF V600E	DTC: dabrafenib alone ORR, 42% *v* dabrafenib plus trametinib ORR, 48% ATC: ORR, 61%	Fever, fatigue, nausea, chills, skin toxicities (rash, skin cancers)
RET inhibitors			
Selpercatinib	RET	*RET* fusion-TC (previously treated) ORR, 79% *RET*-mutant MTC (no previous treatment) ORR, 73% *RET*-mutant MTC (previously treated) ORR, 69%	Dry mouth, gastrointestinal side effects, elevated liver enzymes, QT prolongation
Pralsetinib	RET	*RET* fusion-TC ORR, 85.7% *RET*-mutant MTC (no previous treatment) ORR, 71% *RET*-mutant MTC (previously treated) ORR, 60%	Dry mouth, gastrointestinal side effects, elevated liver enzymes, QT prolongation
NTRK inhibitors			
Larotrectinib	NTRK	*NTRK* fusion-TC ORR, 71%	Myalgia, fatigue, elevated liver enzymes, edema, gastrointestinal side effects

Abbreviations: ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor; HTN, hypertension; MTC, medullary thyroid cancer; ORR, overall response rate; PDGFR, platelet-derived growth factor α; PFS, progression-free survival; RET, rearranged during transfection; TC, thyroid cancer; VEGFR, vascular epithelial growth factor receptor.

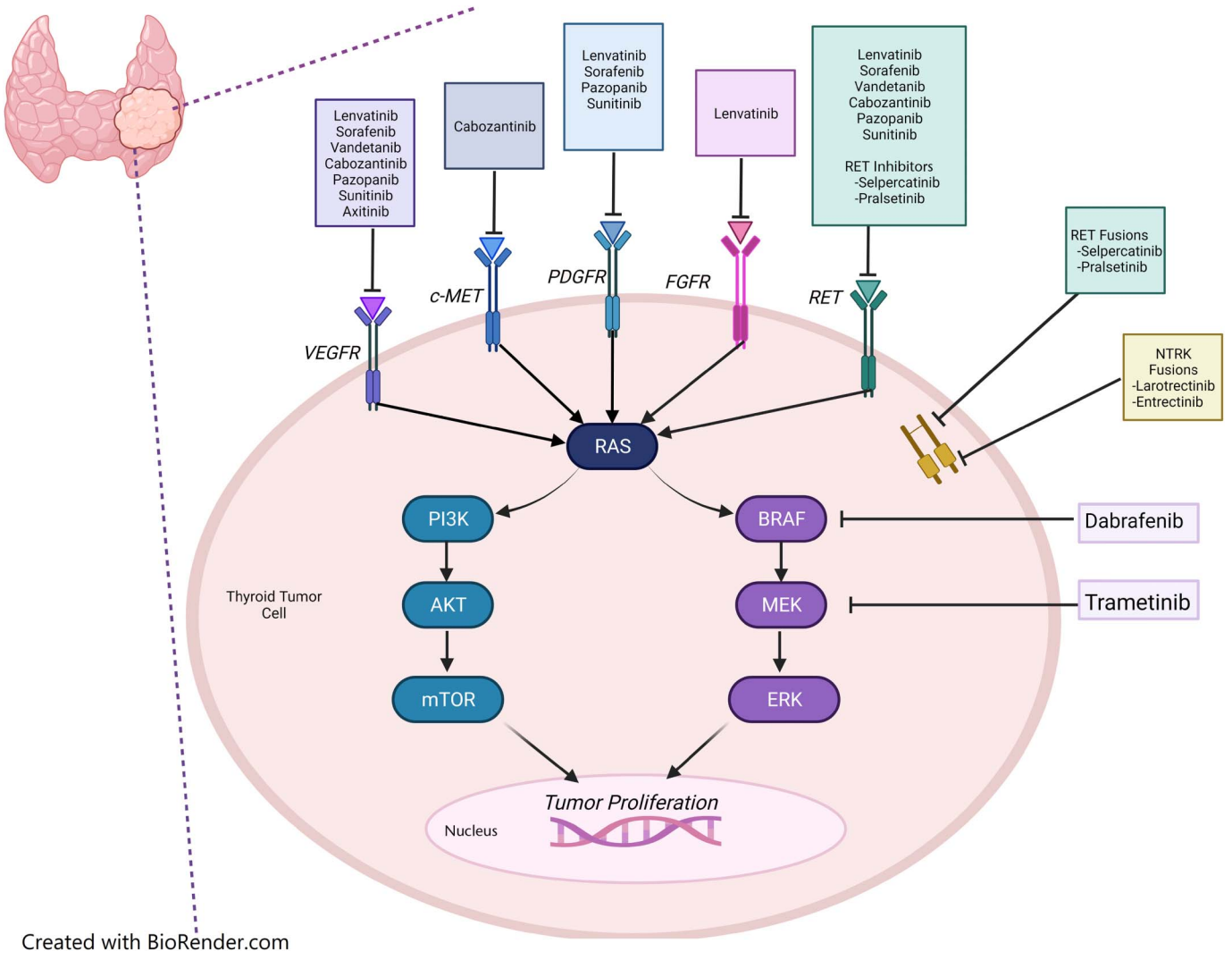

FIG 1. Available systemic targeted therapies for advanced thyroid cancer and mechanisms of action. ERK, extracellular-regulated kinase; FGFR, fibroblast growth factor; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor α; PI3K, phosphatidylinositol 3-kinase; RET, rearranged during transfection; VEGFR, vascular epithelial growth factor receptor.

vomiting (28.4%), headache (27.6%), and dysphonia (24.1%), among others.[33]

Both sorafenib and lenvatinib are Food and Drug Administration (FDA)–approved therapies in the United States for advanced RAIR-DTC. Given the development of resistance mechanisms resulting in progression, many patients with advanced thyroid cancer require an eventual change in treatment. Recently, cabozantinib has received FDA approval as second-line therapy for RAIR-DTC on the basis of COSMIC-311 study results. In this trial, which enrolled patients after progression on anti-VEGFR therapy, cabozantinib resulted in a PFS of 11 months over 1.9 months in placebo with an ORR of 11%.[34] The best overall responses included 11% partial responses, 69% stable disease, and a confirmed complete response (1%).[34] Adverse event profile was similar to previous discussed antiangiogenic MKIs, including any-grade diarrhea (62%), palmar-plantar erythrodysesthesia (47%), and hypertension (32%).[34] Smaller studies have explored the utilization of additional MKIs in RAIR-DTC, including pazopanib, sunitinib, vandetanib, and axitinib.[35-38]

Although MKIs described above are used without any biomarker selection, there are several inhibitors that are approved only in presence of specific gene alterations. For *BRAF V600E*–altered RAIR-DTC, the utilization of BRAF and MEK inhibitors has been studied, given the success of these therapies in other solid tumors. Recently, a phase II open-label multicenter clinical study explored the implementation of BRAF inhibitor dabrafenib alone or in combination with a MEK inhibitor.[39] Using a modified

RECIST including minor responses (decreased tumor by 20%-29%), partial and complete responses, the ORR-modified RECIST was 42% for dabrafenib monotherapy versus 48% dabrafenib with trametinib ($P = .67$). Periodic dermatological assessments are recommended as skin toxicities can occur, especially if treated with dabrafenib monotherapy (65%). Pyrexia was present in both cohorts in more than 50% of patients. In addition, BRAF inhibitor alone was commonly associated with hyperglycemia, whereas the BRAF/MEK inhibitor had a frequency of 52% for fatigue, nausea, and chills.[39]

Highly selective RET inhibitors, including selpercatinib and pralsetinib, have been approved for metastatic *RET*-mutant MTC and *RET* fusion–positive progressive RAIR-DTC. In previously treated *RET* fusion–positive thyroid cancer, the objective response was 79% with a PFS of 20.1 months. Best response distribution by RECIST 1.1 was 5% complete responses, 74% partial responses, and 21% stable disease.[40] In this group of patients with thyroid cancer, who were on pralsetinib, the ORR was 85.7% with a PFS of 19.4 months.[41] Both antineoplastic agents had dose reduction requirements in <45% of patients, which is a reflection that the majority of adverse events were minor in severity (grade 1-2). Common adverse events of RET inhibitors include dry mouth, gastrointestinal side effects, elevated transaminases, and QT prolongation. With selpercatinib, grade 3 events occurred in a minority of patients including hypertension (12%) and high liver enzymes (17%), and in <5% headache, diarrhea, QT prolongation, and weight gain.[40] Cytopenias are more frequently developed with pralsetinib; grade 3 side effects noted (>10%) included hypertension, neutropenia, lymphopenia, and anemia. Severe rare side effects may happen, including pneumonitis in a minority of patients (4%) or hypersensitivity reactions.[41,42] *NTRK* gene rearrangements have been reported in up to 6.7% of papillary thyroid cancers; in pediatric patients, the frequency of *NTRK* fusions is higher.[43] Grouped data from several phase I/II trials revealed a 71% ORR for larotrectinib, a NTRK inhibitor.[44] Common side effects included myalgia, fatigue, nausea, transaminitis, edema, and gastrointestinal symptoms; nevertheless, toxicities were low grade and <10% dose reductions.[44]

The profound responses and toxicity profile of the gene alteration–specific antineoplastic agents such as the RET, NTRK, and ALK inhibitors highlight the importance of ensuring that patients with advanced thyroid cancer undergo comprehensive molecular testing, including comprehensive evaluation of mutations and gene rearrangements. In addition, several clinical trials and case reports demonstrate restoration of iodine uptake in tumors, an approach known as redifferentiation, after a course of the gene alteration–specific inhibitors targeting BRAF, MEK, RET, or NTRK. The advantages include the possibility of discontinuation of targeted therapy after an additional RAI treatment, resulting in tumor control. Nevertheless, further studies are warranted to identify the best responders to ensure the appropriate selection of candidates and ideal implementation time on the disease course.[45-48]

Medullary Thyroid Carcinoma

Vandetanib, an MKI-targeting RET, VEGFR, and epidermal growth factor receptor, was, to our knowlege, the first FDA-approved targeted therapy for MTC.[49-51] After safety and tolerability data from phase II trials, the phase III ZETA trial demonstrated improvement in the PFS compared with placebo; however, this trial did not require progression at the time of enrollment. Cabozantinib-treated patients had an improvement in PFS of 11 months versus 4 months in placebo.[52]

Both RET inhibitors, selpercatinib and pralsetinib, induced sustained responses in *RET*-mutant MTC. *RET*-mutant MTC cases without previous targeted therapies treated with selpercatinib had an objective response of 73% and 69% for pretreated patients.[40] Pralsetinib resulted in an ORR of 71% for *RET*-mutant, treatment-naïve MTC versus 60% in the cohort previously treated by vandetanib, cabozantinib, or both TKIs.[41] As expected with targeted therapies, the predominant responses were partial responses, 67% and 58% in the previously mentioned cohorts, respectively.[41] Neoadjuvant RET inhibitor treatment has shown promise to facilitate successful resection of thyroid cancers; this novel utilization of targeted therapy is currently studied in clinical trials.[53,54]

Anaplastic Thyroid Carcinoma

ATC, as a stage IV highly lethal malignancy, benefits from expedited comprehensive evaluation, airway assessment, and molecular testing (BRAF V600E and NGS). For resectable tumors (stage IVA-IVB), surgical resection is followed by definitive chemoradiation. Between 20% and 50% of ATC tumors are driven by *BRAF V600E* mutation, allowing for combination dabrafenib and trametinib therapy in a neoadjuvant approach for stage IVB unresectable tumors or as up-front long-term therapy for stage IVC disease.[20] Combination BRAF/MEK inhibitor in *BRAF*-altered ATC has demonstrated an ORR of 61%, including complete responses.[55] Targeted therapies have improved overall survival in ATC.[56] RET or NTRK inhibitors may be used in the management of ATC tumors with the respective identified fusion drivers. In addition, immunotherapy, particularly in combination therapies, whether along BRAF/MEK inhibitor or antiangiogenics, has provided further therapeutic pathways for patients with ATC.[57-59] Consideration for enrollment in ongoing clinical trials is recommended given the rarity and aggressiveness of this tumor.

CONCLUSION

Management of advanced thyroid cancer requires a multidisciplinary approach to optimize patient outcomes and provide access to the latest cutting-edge therapies. There has been significant progress in understanding the genetic landscape and molecular basis of thyroid cancer, leading to the development of novel targeted therapies for advanced disease. These advances have revolutionized the management of patients with advanced thyroid cancer leading to improved PFS; however, questions still remain in regard to optimal timing of systemic treatment initiation for advanced thyroid cancer and relevant variables that inform decision making. Future studies on redifferentiation and neoadjuvant therapy in the presence of bulky neck disease, immunotherapy, and development of other gene alteration–specific therapies will hopefully further advance the field leading to thyroid cancer cure.

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Personalizing Surveillance in Head and Neck Cancer

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overview

Head and neck squamous cell carcinoma (HNSCC) encompasses a spectrum of heterogeneous diseases originating in the oral cavity, pharynx, and larynx. Within the United States, head and neck cancer (HNC) accounts for 66,470 new cases, or 3% of all malignancies, annually.[1] The incidence of HNC is rising, largely driven by increases in oropharyngeal cancer.[2-4] Recent molecular and clinical advancements, particularly with regard to molecular and tumor biology, reflect the heterogeneity of the subsites contained within the head and neck. Despite this, existing guidelines for post-treatment surveillance remain broad without much consideration given to different anatomic subsites and etiologic factors (such as human papillomavirus [HPV] status or tobacco exposure).[5] Surveillance incorporating the physical examination, imaging, and emerging molecular biomarkers is an essential part of care for patients treated for HNC and allows for the detection of locoregional recurrence, distant metastases, and second primary malignancies aiming for better functional and survival outcomes. Additionally, it allows for evaluation and management of post-treatment complications.

INTRODUCTION

HNC surveillance should incorporate a multidisciplinary approach centered on cancer monitoring for both index case and second primary, evaluation and management of function, optimization of quality of life, and management of cancer and treatment-related side effects and toxicity. A comprehensive head and neck physical examination should be performed at every follow-up. Cranial nerves should be evaluated for deficits. Each subsite should be systematically evaluated. Inspection of the oral cavity and oropharynx should include visualization and palpation of the mucous, buccal and gingival membranes, floor of the mouth, anterior two thirds of the tongue, hard palate, base of the tongue, tonsillar fossae, and posterior pharyngeal wall. Special attention should be given to evaluating tongue mobility and trismus. Although nasal speculum can readily allow for evaluation of the anterior nasal cavity, thorough evaluation of the posterior nasal cavity and nasopharynx should be performed with rigid or fiberoptic endoscopy. Otoscopy can be useful in evaluating for otitis media that can be seen in postradiotherapy eustachian tube dysfunction or nasopharyngeal mass. Although indirect mirror examination can be appropriate in certain cases, fiberoptic endoscopy is an otherwise indispensable component of the clinical examination.

FREQUENCY OF SURVEILLANCE

Current recommendations in the National Comprehensive Cancer Network (NCCN) guidelines favor detailed follow-up every 1-3 months for the first year, every 2-6 months for the second year, and every 4-8 months for years 3 through 5.[5] Approximately 80%-90% of all recurrences occur within the first 2 years after completion of treatment, so close surveillance during this period should be emphasized.[6,7] Compared with no follow-up, current surveillance guidelines have shown a gain-of-life expectancy of 0.3-1.5 years for patients with laryngeal cancer.[8] Another study found that mean survival after detection of locoregional recurrence, distant metastases, or second primary tumor was significantly higher in those with routine follow-up compared with those with self-referral (58 *v* 32 months, respectively, $P < .05$).[9] However, other studies did not show significant differences in overall survival with regard to surveillance frequency.[10,11] Despite a lack of clear evidence that prolonged follow-up after 5 years is beneficial, it is generally recommended because of late recurrences and heightened risk of secondary malignancy within the first 10 years, with an overall 10%-20% lifetime risk of developing a second primary tumor.[12-14] Furthermore, recognition and management of late post-treatment complications is important. Those who continue to consume tobacco and alcohol are especially at risk. Adherence to surveillance has been shown to be an independent predictor of survival in the 5-10 years after treatment, again underlining the importance of close observation.[15]

Even so, a more nuanced approach to surveillance could better address the needs of patients. A more recent retrospective study analyzed a novel approach to

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PRACTICAL APPLICATIONS

- Surveillance incorporating the physical examination, imaging, and emerging molecular biomarkers is an essential part of care for head and neck cancer (HNC) survivors and allows for the detection of locoregional recurrence, distant metastases, and second primary malignancies aiming for better functional and survival outcomes.
- Current recommendations in the National Comprehensive Cancer Network (NCCN) guidelines favor detailed follow-up every 1-3 months for the first year, every 2-6 months for the second year, and every 4-8 months for years 3 through 5.
- We advocate for a risk-stratified approach to personalize HNC surveillance that accounts for important clinical features, such as initial staging, tobacco use history, and human papillomavirus status.
- Given the absence of a dominant framework for post-treatment surveillance among HNC survivors, the adoption of Neck Imaging Reporting and Data Systems has the potential to add value for patients and providers and personalize imaging algorithms by tumor site, stage, and patient risk factors.
- Molecular biomarkers could prove useful in surveillance as adjuncts to complement physical examination and imaging.

calculating optimal follow-up schedules for various HNC subtypes. Lee et al analyzed a group of 673 patients diagnosed with nasopharyngeal, hypopharyngeal, and HPV-positive and HPV-negative oropharyngeal and laryngeal cancers across two tertiary centers to calculate event-free survival curves and resultant surveillance intervals. Their study identified significantly different follow-up intervals for each subsite, with shortest intervals recommended for hypopharyngeal cancer and longest intervals for HPV-positive oropharyngeal cancer.[16] Furthermore, post-treatment surveillance may be most beneficial for patients with earlier stages of disease. One study found that 87% of patients who survived after recurrence initially had T1 or T2 index tumors and only 30% had nodal disease at the time of primary diagnosis.[17] Despite high adherence to surveillance guidelines, those with more advanced-stage disease unfortunately had poor survival rates overall.[18]

Subsite-driven surveillance schedules should be balanced with a consideration for the patients' overall well-being. The foremost concern for patients after treatment is risk of recurrence.[19] Follow-up can help address therapy-related complications (xerostomia, osteoradionecrosis, hypothyroidism, dental disease, or dysgeusia), voice and swallowing rehabilitation, nutritional support, depression, anxiety, and other comorbid conditions. A systematic review on patient perspectives by McLaren et al found that surveillance was viewed generally positively and brought significant reassurance. However, patients did indicate preferences for higher levels of access to dental professionals and psychological support regarding recurrence.[20] In fact, there are a wide range of cancer and treatment-related complications that affect the oral cavity, regardless of tumor location, associated with impaired quality of life that should be closely managed by dental professionals.[21-23] Furthermore, it is also critical to acknowledge the racial disparities between African American and White patients with HNC; African American patients are more likely to present with advanced disease and have worse outcomes,[24] and subsequent follow-up should focus on addressing these differences.

There is mixed evidence to support routine surveillance compared with symptom-directed surveillance. Nevertheless, it is not always possible to delineate symptoms related to side effects from treatment from tumor recurrence without comprehensive examination and/or imaging. As an example, routine surveillance with clinical follow-up and imaging identified more recurrences and second primaries than symptom-driven monitoring.[9] However, other studies have demonstrated that surveillance driven by patient symptoms is more sensitive at detecting locoregional recurrence than imaging.[10] Beyond its utility in detecting recurrence or secondary malignancy, addressing patient symptomology can improve comprehensive care in this patient population.

IMPACT OF SMOKING STATUS

In addition to its role as a major risk factor for the development of HNC, tobacco use is associated with increased all-cause mortality, cancer-specific mortality, and elevated risk of secondary primary cancers. Furthermore, tobacco smoking during and after therapy has been linked to poorer local disease control, increased risk of cancer progression, and death.[25-27] Despite this, a population-based study found that only 51.7% of individuals with a cancer diagnosis and active tobacco use were counseled on cessation by health care providers.[28] Given that cigarette smoking is a significant risk factor for HNC development, recurrence, and second primary cancers, all health care providers should actively promote cessation of use of all tobacco products (along with avoidance of alcohol consumption). The NCCN recommendations for patients who are smokers highlight the following three principles: (1) evidence-based motivation strategies and behavior therapy, (2) evidence-based pharmacotherapy, and (3) close follow-up with retreatment as needed.[29] Furthermore, the NCCN recommends annual

screening with computed tomography (CT) of the chest for patients with HNC and a history of 20 pack-years of smoking on the basis of their high-risk categorization.

IMAGING AS PART OF SURVEILLANCE

The head and neck is one of the most anatomically complex regions, with unique challenges in interpreting imaging related to complicated postsurgical and postradiation changes and lack of standardization of imaging reporting. This is compounded by an ever-expanding arsenal of treatment options with advances in minimally invasive surgery, therapeutic de-escalation protocols, intensity-modulated radiation therapy, and proton therapy.[30-33] The combination of structural intricacies of the head and neck, need for careful monitoring after treatment, and large growing population of HNC survivors[34] underscore the need for optimal surveillance regimens and standardized reporting. Standardized reporting will, in turn, facilitate data gathering to further refine the best surveillance algorithms by tumor subsite, stage, biology, and risk factors.

IMAGING MODALITIES AND TECHNIQUES

Imaging modalities, such as CT, positron emission tomography (PET)/CT, and magnetic resonance imaging (MRI), play a critical role in diagnosis, staging, treatment, and surveillance of cancers involving the head and neck.[35] There are also emerging techniques, such as PET/MR[35] and dual-energy contrast-enhanced CT (CECT) for surveillance imaging, which have shown promising results.[36] Ultrasound has been widely used in the detection, risk stratification, and surveillance of uncomplicated thyroid malignancy[37] and image-guided biopsies. Most HNC imaging for staging and treatment planning includes a neck CECT for less advanced tumors with the addition of chest CT and/or PET/CT for more advanced tumors.

MRI with contrast has superior soft-tissue resolution, particularly when malignancy involves the intracranial structures, skull base, orbit, perineural disease, or deep fascial planes.[38,39]

Therefore, MRI surveillance is best for tumors in the nasopharynx, sinonasal cavities, skull base, orbits, face, salivary glands, and cutaneous tumors with perineural spread.[35] Alternatively, CECT with or without PET/CT is more commonly used for cancers involving the oropharynx, oral cavity, larynx, and hypopharynx because intracranial, orbital, and perineural extensions from these subsites are less common.[40]

Although the current NCCN guidelines recommend imaging after treatment within the first 6 months, there is no official recommendation for surveillance imaging in an asymptomatic patient beyond 6 months, leading to extreme variation in clinical practice on the basis of institution and oncologist and surgeon preference.[41,42] Among the challenges in post-treatment imaging surveillance are variation from normal anatomy and the lack of standard lexicon to describe findings on post-treatment imaging.

NECK IMAGING REPORTING AND DATA SYSTEMS LEXICON AND RISK CATEGORIES

The American College of Radiology (ACR)-Neck Imaging Reporting and Data Systems (NI-RADS) committee attempted to address these limitations with (1) standardized lexicon and reporting template with risk categories and (2) guidelines for the timing and modality for imaging surveillance.[43] NI-RADS[44] and other lexicon and categorization systems for cancer surveillance[45-48] have streamlined communication between radiologists, clinicians, and patients, which have proven invaluable in guiding management.

An ACR committee developed the NI-RADS for surveillance CECT imaging with or without PET in patients with treated HNC in 2018[48] and subsequently developed a template for contrast-enhanced MRI in 2022. NI-RADS offers a comprehensive imaging-based risk stratification system and framework for HNC surveillance to create a shared language that links easily to actionable management steps.[48-50] Furthermore, NI-RADS serves to simplify communication, standardize nomenclature and reporting across institutions, and facilitate ongoing data collection.[48] Standardized scores are assigned based on the interpreting radiologist's perceived risk for recurrent or residual disease or inability to adequately assess. The primary site (local recurrence; Fig 1) and the neck (regional recurrence; Fig 2) are each assigned an ordinal score from 0 to 4, which in turn corresponds to management guidelines by modality (Figs 3 and 4) that may or may not be appended to the radiology report.

Unlike other tumor-reporting systems that record only a single data point, such as size, in the RECIST criteria or fluorodeoxyglucose (FDG) uptake, NI-RADS incorporates many data points, including morphology, contrast enhancement, superficial versus deep location, FDG avidity, and MRI signal characteristics (diffusion and even timing after treatment). Consideration of these collective data points adds value for each patient. Size alone is not even considered in NI-RADS as it is a flawed measurement alone to determine the presence or absence of disease in HNC. Furthermore, irregularly shaped mucosal primaries and complex post-treatment appearances create unique challenges for target measurements. The Hopkins criteria[51] is a reporting tool to quantify FDG uptake and can easily be applied to NI-RADS.

NI-RADS SURVEILLANCE MODALITY AND TIMING

The ACR NI-RADS recommendation for surveillance reflects a combination of the current and past literature, various multidisciplinary institutional approaches, and consensus of the ACR committee members, which are detailed below.[48]

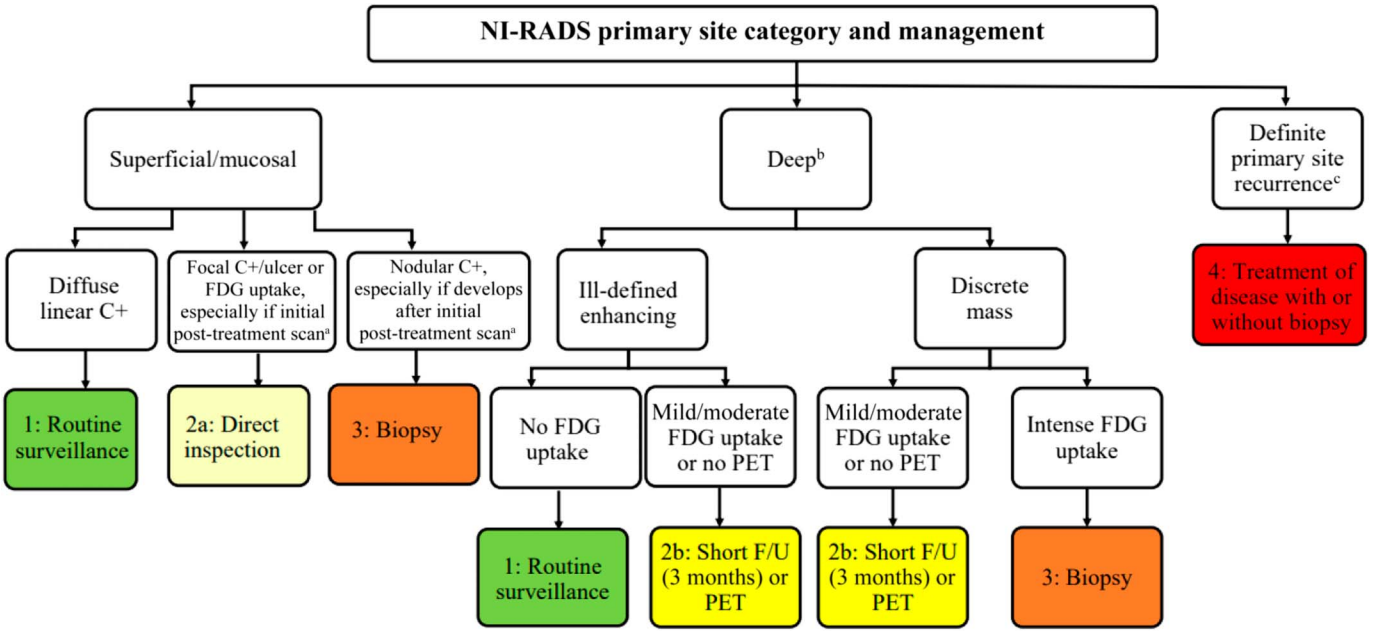

FIG 1. NI-RADS primary site category and management. [a]Most mucosal abnormalities are assigned NI-RADS category 2a as the surgeons or oncologists can best assess the mucosal surfaces, and focal mucosal abnormalities have a high likelihood of being treatment related on the initial post-treatment scan. However, more mass-like mucosal or very superficial submucosal abnormalities can be upgraded to NI-RADS category 3, especially if they develop after the post-treatment baseline study. [b]Outside of the post-treatment baseline study, surveillance may be done with a CECT or MRI without a PET. Recommendation for PET may be NI-RADS category 2 management. [c]On the basis of pathologic confirmation or definitive radiologic progression, biopsies may be needed so that patients can enroll in a trial or otherwise continue with treatment. CECT, contrast-enhanced computed tomography; FDG, fluorodeoxyglucose; F/U, follow-up; MRI, magnetic resonance imaging; NI-RADS, Neck Imaging Reporting and Data Systems; PET, positron emission tomography.

- PET/CECT (with diagnostic neck CT) at 8-12 weeks after completion of definitive therapy as a baseline;
- if this is negative, a CECT 6 months later;
- if CECT is negative, a CECT of the neck alone 6 months later (if two consecutive PET/CECTs are negative, consider stopping surveillance imaging); and
- if second CECT is negative, CECT of the neck and chest at 12-month intervals.

MRI is often woven into and may replace CECT in this same general algorithm for tumors in and around the skull base, and emerging PET/MRI protocols may offer the advantage of streamlining surveillance in many cases, such as nasopharyngeal cancer. Early studies suggest that PET/MRI may improve the evaluation of tumor extension compared with PET/CT in certain HNC.[35] For example, instead of using MRI to follow the primary site and then using PET/CECT for regional and distant disease, it may be advantageous to use PET/MR to accomplish all three.

The inclusion of PET with CECT for the initial restaging baseline, especially in patients treated with up-front chemoradiation, is recommended to have the best combination of sensitivity and negative predictive value (NPV). Much of the current literature is based on noncontrast PET/CT interpreted by nuclear medicine specialists alone, rather than PET with CECT interpreted with a neuroradiologist. CECT with PET appears superior to CECT alone as initial post-treatment surveillance imaging.[52,53] A lack of FDG avidity in soft tissues located in the area of regressed lymphadenopathy on initial post-treatment PET/CT demonstrates an NPV of 90%-100%.[54] On the other hand, noncontrast PET/CT without a diagnostic CECT of the neck has increased the likelihood of false positives without the superior anatomic detail of a CECT and without the expertise of a diagnostic radiologist. Obtaining surveillance imaging immediately after the completion of therapy can lead to false positives.[55]

NI-RADS has shown good discrimination and risk stratification, with positive recurrence rates ranging from 1% to 3.8% for NI-RADS category 1, 5.6% to 17% for NI-RADS category 2, 59.4% to 66.7% for NI-RADS category 3, and 100% for NI-RADS category 4, with recent studies further refining on the basis of primary versus regional recurrence.[44,56] NI-RADS categories 1 and 2 have shown good NPV (85%-91%) on first post-treatment surveillance imaging.[57,58] Another study found a positive predictive value (PPV) of 56% for NI-RADS category 3 at the primary, 65% in the neck, and 79% at distant sites, with a PPV of 100% for NI-RADS category 4.[59] In the absence of a dominant framework for post-treatment surveillance in HNC survivors, the adoption of NI-RADS has the potential to

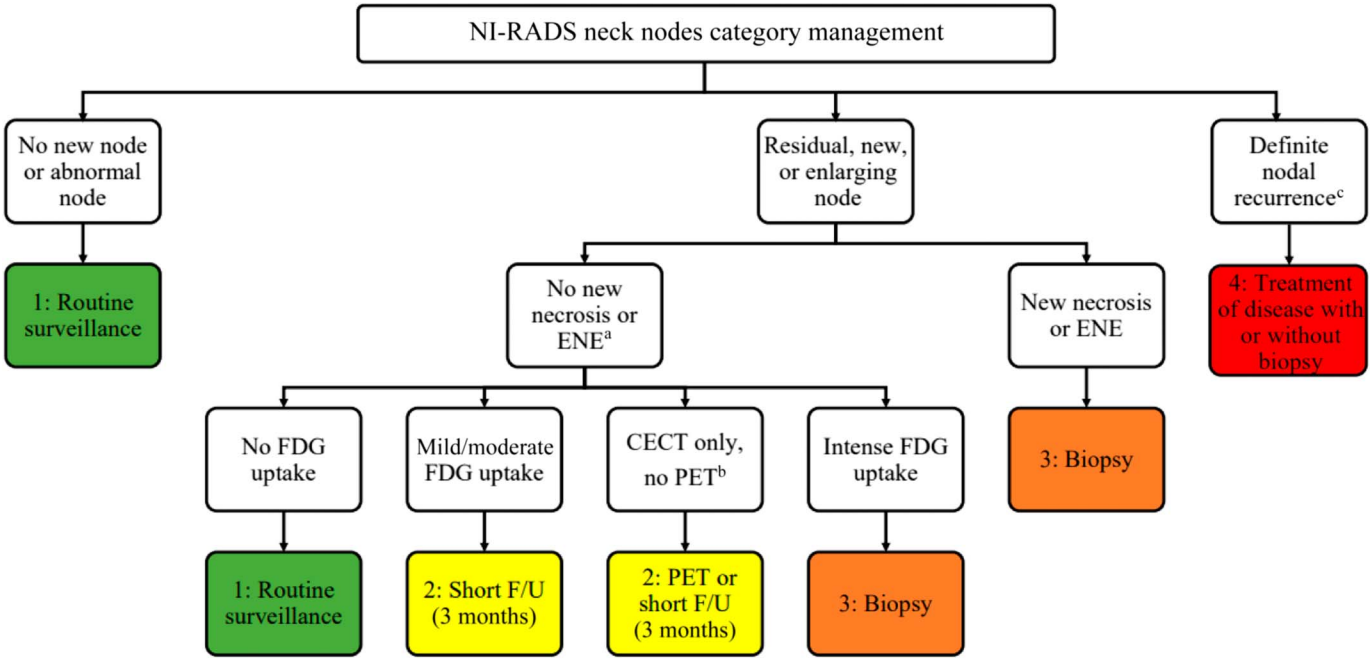

FIG 2. NI-RADS neck nodes category and management. [a]Treated pathologic nodes can have central low density/rim enhancement/necrosis and are scored NI-RADS category 1 if there is no FDG uptake. [b]Newly enlarging node on a CECT alone, without definite morphologically abnormal features, could be given NI-RADS category 2 with recommendation for PET. FDG activity can be used to downgrade to NI-RADS category 1 or upgrade to NI-RADS category 3. [c]On the basis of pathologic confirmation or definitive radiologic progression, biopsies may be needed so that patients can enroll in a trial or otherwise continue with treatment. CECT, contrast-enhanced computed tomography; ENE, extra nodal extension; FDG, fluorodeoxyglucose; F/U, follow-up; NI-RADS, Neck Imaging Reporting and Data Systems; PET, positron emission tomography.

add value for patients and providers and personalize imaging algorithms by tumor site, stage, and patient risk factors.

MOLECULAR BIOMARKERS IN SURVEILLANCE

Circulating or liquid biomarkers are of interest in HNSCC. These cancers can release heterogeneous circulating tumor cells that have been associated with later disease stage and recurrence risk, but detection sensitivity may be limiting.[60] Circulating tumor DNA (ctDNA) arises from apoptotic or necrotic tumor cells and offers a chance to capture unique somatic mutations found in the cancer.[61] Furthermore, tumor cell–secreted vesicles (exosomes) can carry molecular elements or which can also be detected in circulation.[62]

HPV ctDNA

HPV-positive oropharyngeal carcinoma (HPV+ OPC) is characterized by favorable survival characteristics, but up to 20% of patients relapse with locoregional or distant metastatic spread.[63] Relapses can occur late in the disease natural history, and patients presenting with oligometastatic disease can sometimes be treated with curative intent, underscoring the value of early recurrence detection.[64] ctDNA has emerged as a diagnostic tool to detect the presence of cancer or quantify tumor burden.[65] Given that OPC is often causally linked to high-risk HPV subtypes with viral DNA integrated into the host cell genome, this represents an ideal model with which to apply ctDNA.[66] Droplet digital PCR is a newer method that facilitates ultrasensitive detection of even single copies of DNA permitting monitoring and quantification of low-level targets. Recent tests for circulating, cell-free tumor tissue–modified viral (TTMV)-HPV DNA have been developed to distinguish tumor-associated HPV DNA,[67,68] yielding a unique biomarker produced during the fragmentation or shed of integrated or episomal HPV DNA.

A series of observational cohort studies have shown that HPV DNA in both oral rinses and plasma (Table 1) precedes clinical detection of disease recurrence.[74] When considering these data in aggregate, accuracy characteristics seem to depend on the sample tested (favoring plasma over oral rinses), the assay detection methods, and the site of recurrent disease (locoregional *v* distant). Notably, high NPV seems consistent across these cohorts at 89%-100% such that patients with recurrent or active disease would be unlikely to have an undetectable result—findings that appear comparable with PET/CT imaging.[75,76] To our knowledge, the largest data set to date was published in 2022 by Berger et al[73] demonstrating a 95% NPV among 1,076 patients across hundreds of participating centers using the commercially available, plasma-based NavDx (TTMV)-HPV DNA assay (Naveris, Waltham, MA). Although prospective data are needed, these collective findings suggest that

NI-RADS™ PET/CT Category Descriptors, Imaging Findings, and Management

Category	Primary Site	Neck	Imaging Findings		Management
			Primary Site	Neck	
Incomplete	**0**	**0**	New baseline study without any prior imaging available ***AND*** knowledge that prior imaging exists and will become available as comparison		Assign score in addendum after prior imaging examinations become available
No evidence of recurrence	**1**	**1**	Expected post-treatment changes Non-mass-like distortion of soft tissues Low-density post-treatment mucosal edema Diffuse linear mucosal enhancement or FDG If residual nodal tissue, no FDG uptake or enhancement		Routine surveillance
Low suspicion	**2a**	**2**	Focal mucosal enhancement or FDG uptake on initial post treatment scan[a]	Mild/ mod FDG in residual nodal tissue or persistent areas of heterogenous enhancement Enlarging or new lymph node without definitive abnormal morphologic features[a] Any discordance between PET and CECT: enlarging lymph node but little to no FDG uptake[b]	2a: Direct visual inspection
	2b		Deep, ill-defined soft tissue, with only mild/ moderate FDG if PET available Any discordance between PET and CECT: discrete CECT abnormality but little to no FDG uptake or focal FDG uptake but no CT correlate[b]		2b or neck 2: Short interval follow-up (3 months) or PET if scoring on CECT alone
High suspicion	**3**	**3**	Discrete nodule or mass at the primary site with intense focal FDG uptake if PET available Residual nodal tissue with intense FDG New enlarged lymph node or enlarging lymph node with abnormal morphologic features[c] on CECT only or focal intense FDG uptake if PET available		Image-guided or clinical biopsy if clinically indicated
Definitive recurrence	**4**	**4**	Pathologically proven or definite radiologic and clinical progression		Clinical management

FIG 3. NI-RADS PET/CT surveillance key. [a]Focal mucosal abnormalities have a high likelihood of being treatment related, especially on the initial post-treatment PET/CECT, so that in most cases, it is prudent to assign a 2a and let surgeons or oncologists directly inspect. If a more mass-like or nodular mucosal abnormality develops later in the time course of surveillance, it may warrant a 3. [b]This guideline for PET and CECT discordance only applies if the original tumor was FDG avid. [c]Morphologically abnormal features that are definitive = new necrosis or gross ENE as evidenced by invasion of adjacent structures. (1) Residual nodal tissue = node that was abnormal and identified on pretreatment scan. In these cases, hypoenhancement and irregular borders are not unexpected and are likely a sign of treatment response, especially if there is no FDG uptake. (2) New or enlarging node = node that develops during surveillance (not on pretreatment scan). In these nodes, irregular borders or necrosis are definitively abnormal features. If primary tumor is unknown, the authors suggest designating P-unknown primary; if the primary cannot be assessed (dental artifact, motion, or other technical reasons or outside FOV), the authors suggest P-x. NI-RADS categories are designed for use after definitive/curative treatment for HNC and are therefore not designed to be used during treatment. CECT, contrast-enhanced computed tomography; CT, computed tomography; ENE, extra nodal extension; FDG, fluorodeoxyglucose; FOV, field of view; HNC, head and neck cancer; NI-RADS, Neck Imaging Reporting and Data Systems; PET, positron emission tomography.

NI-RADS™ MRI Category Descriptors, Imaging Findings, and Management

Category	Primary Site	Neck	MR Imaging Findings: Primary Site	MR Imaging Findings: Neck	Management
Incomplete	0	0	New baseline study without any prior imaging available ***AND*** knowledge that prior imaging exists and will become available as comparison		Assign score in addendum after prior imaging examinations become available
No Evidence of Recurrence	1	1	Expected posttreatment changes Diffuse thin linear mucosal enhancement or submucosal edema Low T1 and T2 signal intensity suggesting scar/fibrosis Non-mass-like distortion of soft tissues with T2-hyperintense (not T2-intermediate) signal, suggesting edema / inflammation *Note: Be familiar with appearance of flaps (which often have different enhancement and signal characteristics than the original tumor)*		Routine surveillance
			Comparison with prior post-treatment studies available: No new focal nodular or mass-like soft tissue Unchanged or decreased effacement of fat planes on pre-contrast T1WI and/or unchanged or decreased enhancement at skull base foramina and in perineural locations	Residual nodal tissue[b] that is hypoenhancing in the region of original node, and no FDG uptake if PET is available	
	1f		***First post-treatment baseline study***[a]: Resolution of tumor seen on pre-treatment study; no focal nodular or mass-like soft tissue Decreased soft tissue and/or enhancement in skull base foramina and perineural regions, decreased effacement of fat planes on pre-contrast T1WI		
Low Suspicion	2a	2	Focal non-mass-like mucosal enhancement[c] or focal reduced diffusion	Residual nodal tissue with persistent areas of heterogeneous enhancement or mild/moderate FDG uptake if PET is available New or enlarging lymph node[f] without definitive abnormal morphologic features Any discordance between PET and MRI if PET or PET/MRI is available: enlarging lymph node or discrete neck mass but little to no FDG uptake, or focal uptake with no MRI correlate[g]	Primary 2a: Direct visual inspection
	2b		Deep, ill-defined non-nodular soft tissue Soft tissue in which MRI features are different from the original tumor: different DWI, enhancement, or T1 and T2 signal characteristics (and therefore considered 2b rather than 3)[d] Soft tissue with intermediate rather than hyperintense T2 signal and intermediate rather than intense enhancement (and therefore considered 2b rather than 1)[e]		Primary 2b or 2f, or Neck 2: Short interval follow-up MRI or PET to assess deep submucosal abnormality or questionable nodes. *Note: PET is not as helpful for evaluation of perineural disease at the skull base. As such, for a Primary 2b or 2f related to perineural soft tissue, short interval follow-up MRI would be preferable over PET.*
	2f		***First post-treatment baseline study***: Partial resolution of tumor when compared to pre-treatment study No change in soft tissue in skull base foramina and perineural regions which is of same signal and enhancement characteristics when compared to pre-treatment study New thin smooth enhancement in skull base foramina and perineural regions within radiation field		
High Suspicion	3	3	Discrete nodule or mass at the primary site especially if new/enlarging ***AND*** signal characteristics and enhancement match original tumor Intense focal FDG uptake if PET is available Increased soft tissue and/or enhancement in skull base foramina and perineural regions, increased effacement of fat planes and skull base foramina on pre-contrast T1WI, and/or increased enhancement and nodular soft tissue along major nerves supplying the site of primary disease	Residual nodal tissue with intense FDG uptake ***OR*** definite enlargement/ increased enhancement New or enlarging lymph node[f,f] with necrosis or irregular borders, or focal intense FDG uptake if PET is available	Image-guided or clinical biopsy if clinically indicated
Definitive Recurrence	4	4	Pathologically proven or definite radiologic and clinical progression		Clinical management

FIG 4. NI-RADS MRI surveillance key. [a]The first post-treatment MRI serves as a new baseline study for the future comparison. On the first post-treatment MRI, skull base foramina and perineural findings are indeterminate (in the absence of features suspicious for residual or progressive tumor (continued on the following page)

FIG 4. (Continued). described under NI-RADS categories 2 and 3) and can be presumed to be post-treatment related and assigned NI-RADS category 1, until further assessment on the next MRI. [b]Residual nodal tissue = tissue as a site where an abnormal node was present and identified on pretreatment scan. In these cases, hypoenhancement and irregular borders are not unexpected and are likely a sign of treatment response, especially if there is no FDG uptake. [c]Focal mucosal abnormalities have a reasonable likelihood of being treatment-related, especially on the initial post-treatment study, such that, in most cases, it is prudent to assign NI-RADS category 2a and recommend correlation with direct visual inspection. If a more mass-like or nodular mucosal abnormality develops later in the time course of surveillance, the assignment of NI-RADS category 3 may be warranted. [d]If there is persistent enlargement or growth of discrete mass-like soft tissue that differs in signal characteristics from the original tumor, this should be designated NI-RADS category 3 despite the mismatch in signal characteristics. [e]Tumor tends to exhibit intermediate T2 signal and enhancement, white hyperintense T2 signal and intense enhancement are more often seen with reactive/inflammatory changes. [f]New or enlarging node = node that newly develops or grows during the course of surveillance (node not present or smaller on pretreatment scan). In these nodes, irregular borders or new necrosis are definitively abnormal features. Irregular borders with new gross ENE as evidenced by invasion of adjacent structures is another abnormal feature. This is in contradistinction to irregular border or necrosis in nodes unchanged or decreasing in size after radiation treatment, which are considered expected post-treatment findings in radiated nodes. [g]This guideline for PET and MRI discordance only applies if the original tumor was FDG avid. If the primary tumor is unknown, the authors suggest designating P-unknown primary; if the primary cannot be assessed (dental artifact, motion, or other technical reasons or outside FOV), the authors suggest P-x. Head and neck surveillance MRI examinations are often tailored to a specific area of concern (eg, skull base for perineural tumor spread), in which case the entire neck may not be imaged. If the neck cannot be assessed, the authors suggest N-x. NI-RADS categories are designed for use after definitive/curative treatment for HNC and are therefore not designed to be used during treatment. DWI, diffusion weight imaging; ENE, extra nodal extension; FDG, fluorodeoxyglucose; FOV, field of view; HNC, head and neck cancer; MRI, magnetic resonance imaging; NI-RADS, Neck Imaging Reporting and Data Systems; PET, positron emission tomography; T1WI, T1 weighted image.

guideline recommended clinical surveillance intervals might be modified or reduced in the future among those with undetectable HPV ctDNA during surveillance. This notion is likely to have a broader long-term economic impact, where cost modeling predicts a potential for future health care cost-savings with HPV ctDNA incorporation.[77]

HPV ctDNA assay performance in detecting disease recurrence has been somewhat variable, with PPVs ranging from 63% to 100%.[78] Again, the largest data series to date initially reported a PPV of 95% (updated to 97.5%),[73] and in many independent cohorts, there is a notable median lead time between a positive test result and a confirmation of recurrence (on imaging or biopsy) ranging from 2 weeks to 10 months.[68] Prospective studies, such as NCT04965792, will help clarify how often HPV ctDNA testing should occur during surveillance to complement clinical examination and imaging time points. A newly detectable HPV ctDNA result during surveillance should raise concern, and some argue should prompt short-interval retesting, an updated examination, and reflex PET/CT imaging. In the setting of locoregional disease, baseline HPV ctDNA values do associate with cervical lymph node involvement,[78] but absolute values or cutoffs do not currently inform disease burden or site. Furthermore, providing HPV ctDNA testing may affect patient-reported fear of recurrence.

On the basis of these data and the commercial availability of the NavDx platform, some have adopted the use of plasma (TTMV)-HPV DNA into routine surveillance practice for patients with HPV+ OPC while others await prospective data and national guideline recognition.

Epstein-Barr Virus ctDNA

Epstein-Barr virus (EBV) is endemically linked to nasopharyngeal carcinoma (NPC) particularly in Northern Africa and Southeast Asia.[79] Previous studies have collectively demonstrated that elevated plasma EBV ctDNA may be useful for screening and early disease detection.[80] Large prospective trials have reported high sensitivity and specificity in screening endemic patients for NPC with EBV ctDNA.[81] Furthermore, clearance of EBV ctDNA after chemoradiation has been shown to inform treatment response,[81] and recrudescence of detectable values after curative-intent therapy predicts recurrence. Moreover, post-treatment detectable EBV ctDNA predicts worse survival outcomes.[82] Although variability in assay performance and meaningful cutoffs for detection have

TABLE 1. Studies Investigating Human Papillomavirus ctDNA for Recurrent Disease Detection

Study	Treatment	Median Lead Time, months (range)	No. of Patients	PPV, %	NPV, %
Ahn et al[69]	S, R, or both	4.4	52	83.3	93.5
Chera et al[68]	R	3.9 (0.4-12.9)	115	94.0	100.0
Reder et al[70]	S, R, or both	—	23	62.5	100.0
Rutkowski et al[71]	R	—	216	83.0	100.0
Tanaka et al[72]	R	10	35	100.0	89.7
Berger et al[73]	Any	—	1,076	95.0	95.0

Abbreviations: ctDNA, circulating tumor DNA; NPV, negative predictive value; PPV, positive predictive value; R, radiation; S, surgery.

been cited as concerns, many clinicians use EBV ctDNA monitoring as part of NPC surveillance.

ctDNA

Beyond viral ctDNA as a liquid biomarker for surveillance, more than half of advanced HNC patients may yield detectable plasma (nonviral) ctDNA.[82,83] Several commercial assays are now available (Signatera, Seraseq, Invitae PCM, Guardant360, Sysmex Inostics HNSCC-SEQ, etc) with data emerging in various solid tumor types. Recent studies show that even among early-stage HNCs, plasma and/or oral salivary detection of somatic mutations, such as *TP53*, *PIK3CA*, *NOTCH1*, *FAT1*, *CDKN2A*, *CASP8*, *FBXW7*, and/or *HRAS*, is feasible.[84,85] The high frequency of *TP53* loss-of-function mutations and *CDKN2A* inactivation in carcinogen-related HNSCC and *PIK3CA* mutations in HPV+ HNSCC make these obvious candidate biomarkers,[86] with *TP53* most commonly detected overall.[87,88] However, even when both oral and plasma samples are tested together, ctDNA detection rates can be variable.[82,89,90] Furthermore, clearance studies suggest that ctDNA half-life is limited to hours to days.[91] One recent study demonstrated ctDNA detection among five of seven patients with HNSCC who later developed recurrence, but not among 13 recurrence-free cases, and observed that ctDNA detection was more sensitive than imaging.[92] To date, most ctDNA studies in HNSCC present an aggregate of total somatic mutations rather than specific mutational distributions and are limited by small, single institutional bias.

ctDNA Gene Methylation

Expanding on plasma-based ctDNA, tumor-derived fragmented DNA may undergo epigenetic changes or methylation, which typically leads to gene silencing. Since tumor heterogeneity is inherent and somatic mutations may occur at low frequency, detecting methylated ctDNA may have added value.[93] For the present, early studies in HNSCC suggest that ctDNA genetic methylation may occur more frequently compared with cancer-free controls.[94] Diagnostic test characteristics vary widely among hypermethylation assays, and future investigations are needed.

Exosomes

Virus-sized extracellular vesicles can contain a number of proteins or micro(mi)-RNA released from tumor cells and are found in various bodily fluids. Recent data suggest that plasma exosomes may be more prevalent in patients with HNSCC and differential shed may exist based on HPV status.[95] Furthermore, isolated exosomes from patients with HNSCC have yielded differential PD-L1 and miRNA levels that appear associated with disease stage[96,97]—an active area of investigation that also interplays with the tumor immune microenvironment.

CONCLUSIONS

Surveillance for the HNC survivor should incorporate physical examination, imaging, and emerging molecular biomarkers to promote early recurrence detection and identification of second primary malignancies to optimize functional and survival outcomes. NI-RADS should be adopted to guide imaging interpretation, timing, and modality choice during HNC surveillance. Molecular biomarkers, such as HPV ctDNA, could prove useful in clarifying minimal residual disease status beyond what examination findings and imaging can detect. The authors advocate for a risk-stratified approach to personalize surveillance that accounts for important clinical features, such as initial staging, tobacco use history, and HPV status.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Shared Decision Making in the Care of Patients With Cancer

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overview

Shared decision making (SDM) is a method of care that is suitable for the care of patients with cancer. It involves a collaborative conversation seeking to respond sensibly to the problematic situation of the patient, cocreating a plan of care that makes sense intellectually, practically, and emotionally. Genetic testing to identify whether a patient has a hereditary cancer syndrome represents a prime example of the importance for SDM in oncology. SDM is important for genetic testing because not only results affect current cancer treatment, cancer surveillance, and care of relatives but also these tests generate both complex results and psychological concerns. SDM conversations should take place without interruptions, disruptions, or hurry and be supported, where available, by tools that assist in conveying the relevant evidence and in supporting plan development. Examples of these tools include treatment SDM encounter aids and the Genetics Adviser. Patients are expected to play a key role in making decisions and implementing plans of care, but several evolving challenges related to the unfettered access to information and expertise of varying trustworthiness and complexity in between interactions with clinicians can both support and complicate this role. SDM should result in a plan of care that is maximally responsive to the biology and biography of each patient, maximally supportive of each patient's goals and priorities, and minimally disruptive of their lives and loves.

SHARED DECISION MAKING IN THE CARE OF PATIENTS WITH CANCER

Shared Decision Making as a Method of Care

In recent years, the field of cancer treatment has seen a significant increase in the availability of treatment options, including immunotherapy, targeted therapies, and multidisciplinary care, which are being offered to almost every patient with cancer. Simultaneously, individuals living with cancer are exposed to a multitude of informational channels, including social media, which provide them with information about their disease and possible treatments.[1] The complexity of cancer care and the abundance of cancer-related information complicate the development of care plans that make sense for each person. Cocreation of such plans may lead to plans that maximally support patient priorities, respond well to the patient's situation, and minimally disrupt their lives and loves.[2] Doing so may also increase patient satisfaction with treatment, boost confidence in the plan of care, and improve trust in the medical team.[3]

Shared decision making (SDM) is a collaborative approach to care by which patients and their clinicians work in partnership to address the problematic situation of the patient and respond by cocreating sensible plans of care.[4,5] SDM begins with determining the nature of the patient's situation, which often involves insights that only the patient and their family can provide, including aspects of the patient's biology (the nature of the cancer itself and of the health state and comorbidities of the patient) and biography (the personal history of the patient, social and economic contexts including forms of discrimination, exclusion, and injustice; their relationships and responsibilities; and their expectations and dreams) and their mutual interactions.

In the case of cancer care, clinicians must work with patients, with competence and compassion, to develop a practical cancer care plan that is informed by relevant evidence, addresses emotional aspects of the problem, and is both feasible and sustainable for the patient.[6,7] Seen in this way, SDM is not an additional task for clinicians but a fundamental method of care that is central to the clinician's art, similar to history taking, physical examination, selection and interpretation of diagnostic tests, and patient education and counseling.[8]

How Can SDM Contribute to the Care of Patients With Cancer?

We have previously described how to implement SDM in practice[8]; these steps can easily be translated in everyday cancer care practice.

Foster a productive conversation. The initial step involves promoting productive dialogues that encourage

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PRACTICAL APPLICATIONS

- Shared decision making (SDM) is a method of care on the basis of conversations conducted to arrive at a cocreated plan of care that addresses the problematic situation of each patient.
- Unhurried conversations, SDM tools, and collaborative deliberation methods are essential to coproduce care plans.
- Health care systems that favor the processing of people rather than the care of patients are hostile to methods of patient-centered care, such as SDM, and must be radically reformed.
- The experience of patients contributing to care that fits requires access to trustworthy information and expertise within and between clinical encounters.

active patient-clinician collaboration, facilitate the process of care plan development, and support the cocreation of a comprehensive care plan.[9] Throughout the patient's journey, from screening to cancer diagnosis, treatment, and end-of-life discussions, the clinician is tasked with exploring with curiosity the patient's problematic situation, identifying any changes in their health status, concerns, or shifts in their life circumstances. This crucial phase involves the clinician's ability to understand the patient's condition and assess the effectiveness, feasibility, and desirability of the current care plan. It is particularly critical in cancer care, where biologic parameters such as laboratory tests and imaging, alongside other factors such as treatment burden,[10,11] financial toxicity,[12,13] and insurance coverage,[14] contribute significantly to the patient's problematic situation.

The SDM team—patients and clinicians—engages in a continuous and collaborative process of noticing and responding, striving to arrive at an approach that makes sense intellectually (ie, reflects the situation as understood and the response is based on the best available evidence),[5,15] practically (ie, given our understanding of what capacity can be mobilized, what may prove to be feasible to implement in the life routines of the patient, and within what is available in the health care system), and emotionally (ie, addresses, responds, and supports the emotional experiences and feelings of those involved).

Through a thorough examination of the available actions (including those that the parties can identify, uncover, or invent) to address the situation, the team may need to reframe the issue and reformulate the problem at hand.[9] For instance, a patient facing a cancer diagnosis with poor prospects for a cure may initially seek aggressive treatment but may ultimately reframe the situation as one of the seeking ways to achieve a peaceful and dignified death. In such cases, alternative options must be identified, evaluated, and implemented as needed. Throughout this process, the patient plays a critical role in determining the extent to which the plan of care is likely to be effective, feasible, and compatible with other treatments and daily routines, that is, to what extent care fits at the point of life.

Purposefully select and adapt the SDM process. There are four distinct ways in which patients and clinicians can work together to address the patient's problematic situation: (1) focusing on matching preferences, (2) reconciling conflicts, (3) problem-solving, or (4) meaning making.[9] Each of these forms of SDM and representative applications in cancer care are given in Table 1.

In our experience, clinicians and patients who do SDM well work within a form of SDM until a better one becomes apparent and they flexibly, gracefully, and perhaps intuitively switch according to the challenges uncovered during the conversation.[16]

Protect the space (and quality time) for SDM. For SDM to be effectively conducted, it is essential for both patients and clinicians to engage in the process. The conversation itself serves as the primary workspace within which this collaborative work takes place. As such, it is crucial that the conversation space are deliberately designed to promote and facilitate the SDM process.[17] In today's world, this conversation space may take the form of remote consultations[18] and virtual platforms because of the widespread adoption of telehealth in oncology care.[19,20] To ensure a conducive environment, clinicians vigilantly eliminate any visual or auditory distractions that may impede the decision making process. This involves protecting the conversation space and the allocated time for these consultations. Policies must be implemented to safeguard the sacred time of consultation with patients and minimize electronic medical record burdens to eliminate any potential disruptions or interruptions. It is paramount that clinicians (and those whose job is to support care) take these measures to optimize the SDM process and ultimately improve patient outcomes.

Make the most of participation. Having set the stage for an unhurried conversation,[17] it is necessary to determine who should participate in that conversation, including patient caregivers and other significant people in the patient's life as well as clinicians from other specialties with a stake in the decision, a common situation given the high prevalence of multidisciplinary care. Multidisciplinary clinics and multidisciplinary cancer care patient navigators can help to avoid confusion and secure better coordination of care. These stakeholders can take part or assist the established patient–clinician dyad in cocreating a plan of care.

TABLE 1. Forms of SDM (adapted from the study by Montori et al[8])

SDM Form Method Description	Situations in Which This Form May Be Preferred
Matching preferences	
Patients and clinicians compare features (ie, efficacy, burdens, side effects) of the available options and match them with the patient's values, preferences, goals, and priorities. They may use an SDM tool to share information about the options. Patients and clinicians deliberate until the best match is identified	Patients and clinicians discuss options for adjuvant treatment in early-stage resected lung cancer
Reconciling conflicts	
Using a collaborative process, the clinician helps the patient articulate the reasons for their position while reconciling those reasons with the varying possibilities ahead	Patients and clinicians discuss options for clinical trial participation when the patient is afraid of being treated with placebo—while there is no placebo in this trial
Problem-solving	
Potential solutions are tested—in conversation or therapeutic trials—and become justified on the basis of the extent to which these can demonstrably and successfully address the problem and improve the patient's situation	Patients and clinicians discuss different ways in which the toxicity of a systemic therapy can be managed and mitigated given the comorbidities of the patient
Meaning making	
Using conversations, patients and clinicians develop insight into what the patient's situation means, at a deep level, to the patient and their community and to find the reasons within that process for pursuing a particular approach	Patients and clinicians seek to make sense of the lack of cancer response to therapy and develop a way to frame the situation and bring patient, family, and others into a joint understanding that the patient care has new goals and approaches

Abbreviation: SDM, shared decision making.

Deploy useful tools. To facilitate effective SDM, it is important for both clinicians and patients to carefully consider the tools that are introduced into the conversation. This includes specialized tools that have been specifically designed to support forms of SDM that have demonstrated effectiveness, usability, and desirability. Depending on the circumstances, various tools can be used to aid in the decision making process, such as self-management logs, patient-reported outcome trends, and results from ancillary laboratory and imaging tests, all of which can support the problem-solving mode of SDM. One notable tool is the My Healthcare, My Life conversation tool.[21,22] This tool is specifically designed to foster a mutual understanding between patients and clinicians regarding the social and economic challenges that patients may encounter on a regular basis and how these factors may affect their health and the implementation of treatments.

The Making of an SDM Tool

The team at the Knowledge and Evaluation Research (KER) Unit is one of the several groups worldwide which has been developing and evaluating SDM tools.[23] The KER Unit has been working on this for more than a decade, pioneering user-centered design and participatory action research in clinical practice.[24]

Our process follows the steps described in Figure 1:

1. Assemble a multidisciplinary team comprising designers, patients, oncologists and other clinicians, decision making scientists, and a stakeholder group comprising oncologists, primary care clinicians, patients, a designer, and other stakeholders.
2. Consult with a Patient Advisory Group—a group of 8-10 volunteer patients living with the condition of interest who engage with developers to ensure that the work is pertinent and responsive to patient priorities. This group helps identify relevant outcomes that must be considered in both the evidence synthesis and the SDM tool.
3. Synthesize the evidence about the benefits and potential harms and inconveniences of potential cancer treatments including existing practice guidelines. If pertinent, after reviewing the results with the stakeholder group, we produce an evidence table that outlines the efficacy, harms, and practical implications for each management option (ie, adjuvant treatment or surveillance).
4. Conduct observations of current treatment conversations between patients and their oncologists. Over 95% of clinicians and patients routinely consent for video recording. We use institutional review board–approved procedures for obtaining and securely storing the recordings and accessing them with rigorous protection of patient and clinician privacy.
5. Design a first prototype—using information from the evidence synthesis, insights about outcomes and practical considerations from our patient advisory group and on the basis of what is hard or difficult in existing, directly observed, conversations, an experienced interaction designer produces a first prototype of the SDM tool. This

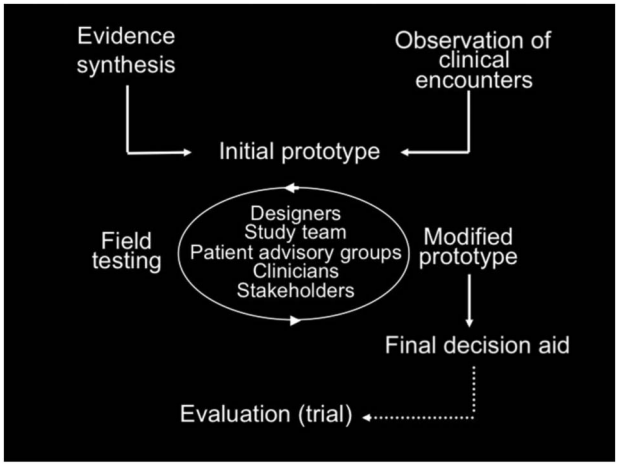

FIG 1. Design process for encounter decisions conducted by the Knowledge and Evaluation Research Unit at Mayo Clinic.

prototype pays attention to the needs in practice primarily, while seeking adherence to the International Patient Decision Aid Standards.[25]

6. Field testing: the prototype is used in consultations by oncologists and patients. Each clinician will use it in about three to four real-life clinical encounters either directly observed or video recorded. After each use of the prototype, we ask patients and clinicians about their experience and whether they recommend any changes. On the basis of observations and participant input, the developer team modifies the tool and field tests it again. Arriving at a final prototype that patients and clinicians find useful, usable, and desirable usually requires three to five iterations and about 20 or so encounters.

Two Examples of SDM Tools for Cancer Risk

The Thyroid Cancer Treatment Choice is a tool grounded in evidence that facilitates the discussion of treatment options for papillary microcarcinomas. Pilot testing has indicated that using this tool enhances the acceptance of active surveillance, suggesting that it is a viable and desirable alternative for patients who are well-informed. Following its initial implementation as a paper-based instrument, Thyroid Cancer Treatment Choice has been adapted as an electronic tool. This new version (Fig 2) permits risk stratification on the basis of age and cancer progression and can be integrated into electronic health records for individualized care. Furthermore, this updated version includes the option of ultrasound-guided percutaneous ethanol ablation for institutions that provide this form of treatment.[26]

Non–small-cell lung cancer (NSCLC) Adjuvant Choice is a tool for patients and clinicians to engage in SDM for the adjuvant treatment of resected NSCLC. Given the advances in the adjuvant treatment of NSCLC and the incorporation of immunotherapy and targeted treatments in selected patients, this tool supports the discussion for personalized options of the patients on the basis of their disease's biomarkers. The prototype was developed to include a personalized calculator of the patient's risk of dying within 5 years depicted in a 100-person pictograph on the basis of available treatments, stage, PD-L1 expression, and EGFR mutation status. It supports the discussion of the different options by depicting each treatment option's special considerations and side effects (Fig 3). The tool is undergoing field testing.

Making (CANCER) Care Fit Manifesto

In March 2021, a group of 25 individuals led by Dr Marleen Kunneman and hailing from seven countries convened to identify and deliberate on the indispensable prerequisites for establishing care that is tailored to the unique needs of each patient.[2] Their official statement states the necessity for clinicians, patient advocates, policymakers, researchers, and editors to collaborate toward promoting and facilitating initiatives that streamline the process of personalized care, in conjunction with patients and their caregivers.[27]

We contend that the principles described in the manifesto are very relevant to cancer care. In line with the Making Care Fit Manifesto, care optimized for patients with cancer must adhere to the following criteria:

1. Maximally responsive to patients' unique situation.
2. Maximally supportive of patient priorities.
3. Minimally disruptive of patient lives.
4. Minimally disruptive of patients' loved ones and social networks.

One could argue that an additional requisite is now essential—that care processes and systems be maximally disruptive of structural inequities.

A PATIENT REVOLUTION IN CANCER CARE?

Efforts to implement patient-centered care, such as SDM, however, face seemingly adverse conditions that drive toward efficiency, making it difficult to implement these practices routinely.[28]

For patient-centered care to thrive, health care organizations must foster conditions that favor care.[29] In addition to ensuring the provision of evidence-based treatments, clinicians and patients should be able to cocreate plans of care that maximally respond to the goals and priorities of each person and to their biologic and biographical situations and that are desirable, useful, and feasible in their lives. Every clinician and patient would want this, and health care organizations must ensure that they enable patient-centered care within relationships of trust not simply transactional encounters.[30] Achieving careful and kind care for all will facilitate formation, practice, and innovations in patient-centered care, including SDM as a method for cancer care.

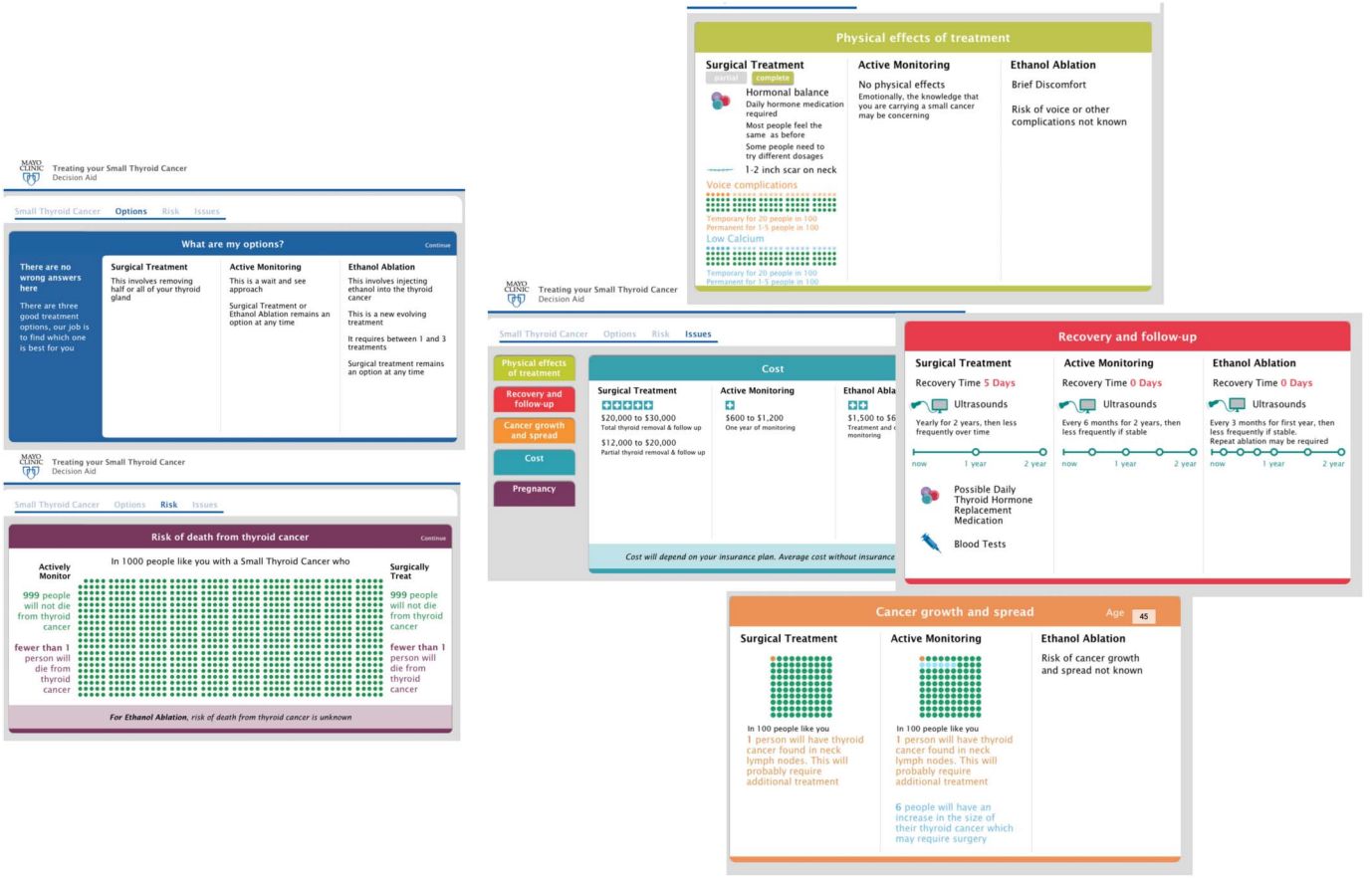

FIG 2. Screen captures of the online shared decision making tool about the treatment of patients with small thyroid cancer. Reproduced with permission. 2023 Mayo Foundation for Research and Education.

Yet, innovations to facilitate patient-centered care and SDM cannot wait for more supportive care conditions. Such innovations are in fact emerging in many cancer settings, especially within cancer genetics. Here, patients routinely undergo genetic testing, a test that can have a broad range of implications for the patient and their family, underscoring the need for SDM.

DIGITAL TOOLS TO ADVANCE SDM FOR CANCER GENETIC TESTING

Genetic testing to identify whether a patient has a hereditary cancer syndrome (HCS) represents a prime example of the importance for SDM in oncology. Nearly one in 10 patients diagnosed with cancer have an underlying HCS.[31-33] Patients with HCS have a germline gene mutation that predisposes them to develop multiple, early-onset cancers over their lifetime. Common types of HCS include hereditary breast and ovarian cancer (HBOC) syndrome because of *BRCA1/2* gene mutations and Lynch syndrome because of mutations in mismatch repair genes.[32,34,35] Females with HBOC have increased risks for multiple cancers, including 60%-80% chance of developing breast cancer and 11%-44% chance of developing ovarian cancer, whereas males have a 1%-8% risk for breast cancer and 20%-60% risk for prostate cancer.[31,34-40] Males and females with Lynch syndrome are at up to a 70% risk for colorectal cancer, 18% risk for stomach cancer, and 20% risk for small bowel, hepatobiliary tract, urinary tract, brain, and skin cancers (sebaceous neoplasms),[31,41-45] with males also having a 20% risk of prostate cancer[41-44] and females also at risk for endometrial cancer (12%-46%), breast cancer (13%), and ovarian cancer (20%).[41-44] Given these high risks, the National Comprehensive Cancer Network, ASCO, and the American Society of Breast Surgeons recommend that patients with a personal and family history of cancer undergo genetic testing to identify whether they have an underlying HCS and advocate for the importance of SDM in counseling patients for genetic testing.[46-49]

SDM is important for genetic testing because results have broad implications, including influencing current cancer treatment, changing future cancer surveillance, triggering management changes for relatives, generating complex

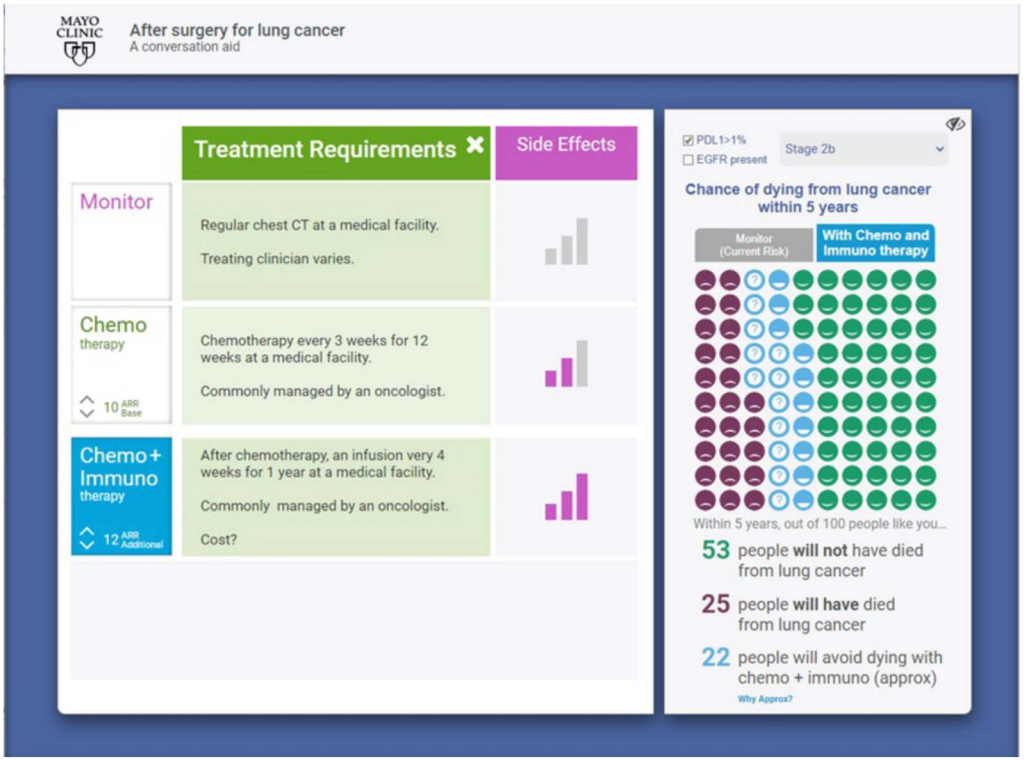

FIG 3. Screen capture of the online shared decision making tool about the treatment of patients with non–small-cell lung cancer after initial surgery. Reproduced with permission. 2023 Mayo Foundation for Research and Education.

results, and causing psychological concerns. Oncologists offering genetic testing can address these issues during counseling, akin to counseling that they routinely undertake for diagnoses and treatments. This counseling should include an in-depth review of important educational concepts and psychosocial issues. For example, patients need to understand that identification of an HCS can lead to tailored treatment for a current cancer and targeted surveillance for future cancers. For example, a woman recently diagnosed with ovarian cancer with an underlying *BRCA1* mutation can be treated with PARP inhibitors, which can improve her survival compared with conventional treatments.[50] Patients identified to have Lynch syndrome become eligible for annual/biennial colonoscopies, beginning at age 20-25 years, in addition to consideration of prophylactic surgeries for women (eg, hysterectomy). These risk-reducing measures lead to earlier detection and prevention, reducing morbidity and mortality in this high-risk population.[51-53] For the patient's relatives, a new diagnosis of an HCS means that they become eligible for genetic testing, with potential ramifications for their own cancer treatments and surveillance.

Another point of concern is the recent transition to larger, more comprehensive genetic tests (eg, large gene panels, genome sequencing); these have increased the likelihood that uncertain results and secondary findings will be revealed, both of which can contribute to challenges in the patients' cancer management and surveillance. Patients should also be informed about the possibility of psychological harms triggered by the genetic testing process or results (eg, distress associated with new cancers, uncertain findings, anxiety and burden around sharing results, guilt of passing on an HCS to children, etc). Adding on to these challenges is the fact that there is often no clear right or wrong decision about whether to pursue genetic testing; the decision is often informed by the patients' values and preferences. As such, it is imperative that patients and their clinicians undertake in SDM, a process that ensures that patients understand all their options and that they incorporate their values into their decision making, to choose the option that is most consistent with their preferences and goals.[54-56]

Despite the increasing importance of SDM, the ability to achieve it has become more challenging as the quality and extent of patient-clinician consultations have decreased over time. Within oncology, this decline can be attributed to multiple factors including the shortage of health care professionals, increased demand for cancer services because of an aging population, and the increasing *industrialization of health care*.[28,57,58] The latter describes the application of management and improvement approaches used in the manufacturing industry and applied to health care delivery.[28] Although designed to enhance standardization, reliability, and efficiency, the industrialization of health care has also exacerbated burnout among clinicians and exhaustion in patients.[28] Moreover, the emergence of the COVID-19

pandemic in early 2020 further exacerbated resource constraints in oncology. The pandemic also transitioned most medical appointments to virtual settings, reducing face-to-face encounters between providers and their patients. Engaging in SDM has become even more challenging with these constraints.[28] As such, new and innovative models of SDM are needed within oncology.

Digital tools are one strategy that can facilitate SDM in patient-clinician consultations and move away from industrialization of health care in oncology.[28] There is evidence from the literature to support this; a recent systematic review found that digital tools can support the many facets of SDM, including increasing patient knowledge, improving psychosocial well-being and engagement, and facilitating decision making.[59] For clinicians, the review found that digital tools provide efficiencies by reducing the time needed with patients and enhancing workflow (eg, less time needed to prep charts).

One example of a digital platform that can support patients and oncologists in delivering genetic testing and SDM is the Genetics Adviser.[60,61] The Adviser is an interactive, patient-facing, digital platform that supports the fundamentals of SDM—by providing both education and psychosocial support at all points in the patients' cancer journey. The Adviser includes interactive educational module that provides in-depth, patient-targeted information. The platform also encompasses values clarification exercises that can help patients explore their values and preferences. Even after patients finish the education modules and values exercises, they have the option to return to the platform at any time, review any materials they completed, and access additional support resources. They can also generate a printable summary that can be easily shared with their circle of care and support (Fig 4). All these steps can be completed at the patients' pace—allowing them to involve their relatives and larger support system in the decision making process. The Adviser's modules and exercises can easily be customized to the oncologists' and patients' needs. They can be used to support patients undergoing genetic testing in mainstreaming practices, patients undergoing rapid genetic testing for treatment purposes, and patients having their tumor profiled, which could reveal germline findings. Moreover, for patients undergoing genetic testing during cancer treatment, the platform provides a flexible resource that can be accessed at any time using multiple modalities (eg, smartphone, desktop, etc) and within any setting (eg, home, work, clinic).

There is considerable evidence that supports the effectiveness of the Genetics Adviser platform in advancing SDM in the oncology setting. For example, one qualitative study found that the Adviser promoted informed dialogue, facilitated preference-sensitive deliberation, and deepened personalization of decisions of patients with cancer.[62] These three functions represent fundamental elements of patient-centered care[63,64] and provide evidence that the platform can facilitate SDM.[65] In addition to facilitating SDM, digital tools like the Genetics Adviser are in line with principles of the *Open Notes Movement*.[66] The real-time sharing of genetic test results through a secure portal reduces uncertainty and promotes transparency. Furthermore, the inclusion of communication through the portal enables asynchronous interaction between the clinician and the patient, reducing the risk of anxiety as the patient awaits their scheduled appointments.[66]

Digital tools such as the Genetics Adviser can educate and empower patients with cancer, giving them agency in their cancer journey. Patients can use the platform to prepare themselves before the initial consultation and then come to a subsequent clinic appointment with their oncologist better prepared and empowered to engage in SDM. As evidence from a recent trial revealed,[67] this will reduce the consultation time that patients need with the health care providers. Therefore, the platform provides an opportunity to have an efficient appointment, reserving the precious and limited clinic time to focus on each patient's unique concerns. Instead of receiving information for the first time at the appointment, patients are coming to the first consultation empowered, having already had a chance to digest the medical information, consult with their circle of care and family, and come prepared with questions. Since the patient has already reviewed the technical and background information, clinicians can focus the time on the patients' specific questions and explore preferences and values to help patients make informed decisions. This indeed was observed in a recent qualitative study, which found that the Genetics Advisor platform increased the degree of deliberation and verbal engagement between patients with cancer and the clinician.[62] This provided the clinician with opportunities to respond to the unique perspectives and experiences of each patient, including clarifying misunderstandings and highlighting personal values, consistent with patient-centered care. Therefore, digital tools can make it easy for oncologists to achieve true SDM with their patients.

Digital tools and other SDM innovations are also facilitating a paradigm shift toward the cocreation of plans of care as a collaborative method to uncover, discover, or invent a response to each patient's problematic situation. This joint work must address the situation as understood by the patient and the clinician, must draw from the best research evidence and from the experience and expertise of the patient and the clinician, and must consider health care resources and the resources that the patient and their caregivers can mobilize to implement the care plan effectively and safely. This places the patient not as a party who must be engaged, involved, or

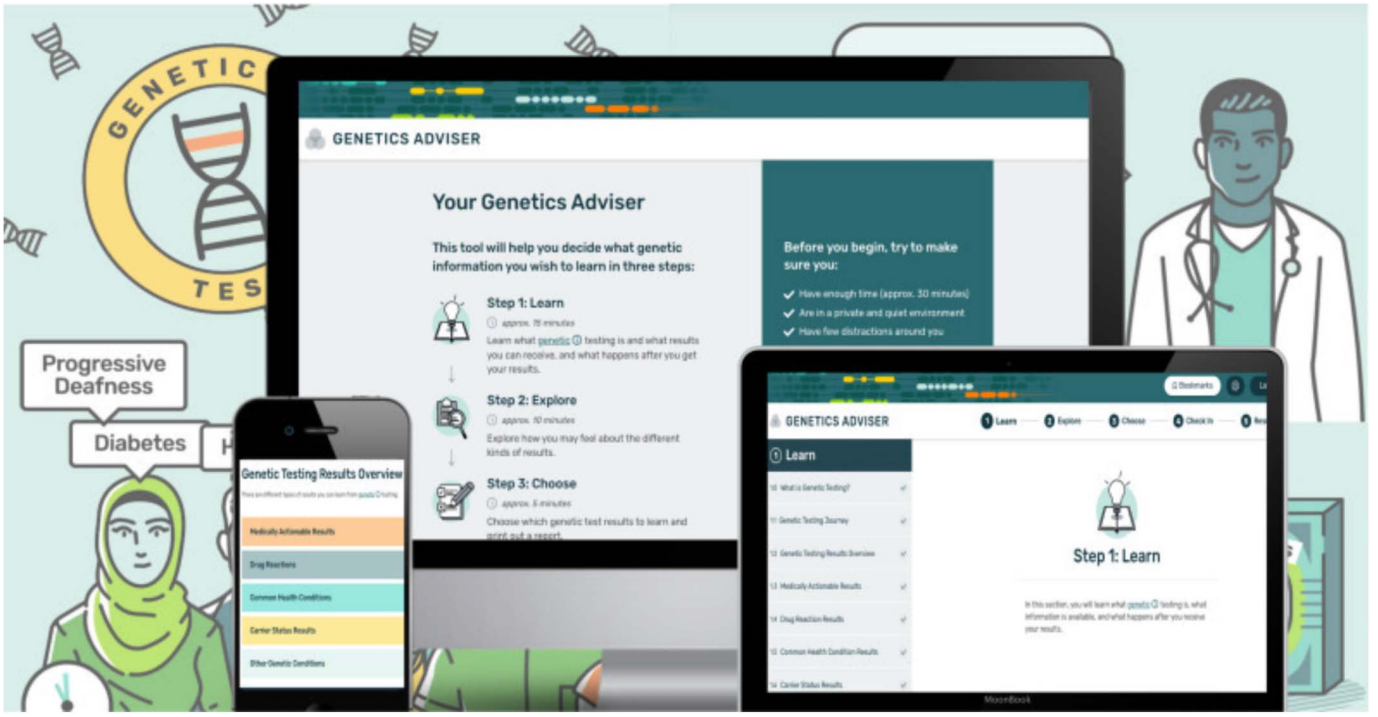

FIG 4. The Genetics Adviser, delivering pretest counseling, waiting period support, and result disclosure via all mobile applications such as smartphones and tablets or computer/desktop applications. Source: PMID: 35487723 with permission.

empowered, but who takes a practical role as an integral codeveloper of plans of care.

SDM FROM A PATIENT PERSPECTIVE

The paradigm guiding interactions between the clinician and the patient is undergoing a sea change. Under the long-prevalent model of paternalism, the doctor was the predominant—if not exclusive!—source of judgment as to the proper course of medical action. But, increasingly, the patient's embodied perspective is being considered when making clinical choices, a shift that respects both an ethical emphasis on autonomy and a pragmatic need to individualize care. Sometimes, SDM is contingent on factors that are known only to the patient and beyond the discernment of quantitative tools at the diagnostician's disposal, obligating an information transfer back and forth for authentic shared governance[68] (M.A.L. is an oncologist living with a hereditary cancer. He has shared his perspective as a patient here: The ASCO Post[69]).

However, it must be acknowledged that even SDM is a term encompassing multiple approaches in need of careful differentiation. In the *informative model*, the clinician provides the patient with all relevant information without recommending a course of action. In the *interpretive model*, the clinician aims to elucidate the patient's values and desires and to help the patient select the available medical intervention that is most congruent with their principles and goals. Although both models require an explanation beyond the dictums of paternalism, the second is a more open exchange of ideas, a bidirectional discourse that does not presuppose an outcome and calls on both sides to adapt to what they are hearing.[70,71] This model is particularly well-suited to decisions in which there is more than one medically reasonable option, and the best plan hinges on patient goals, priorities, values, and preferences.

Implicitly or explicitly, the interpretive model acknowledges the patient as the ultimate stakeholder in their medical outcome. Although fiduciary responsibility is a noble lodestar for minimizing any interference from the physician's own self-interest, even the most empathetic of clinicians does not experience cancer in the same way as those entrusted to their care. Whether the relative abstractions of quality of life or the most clear-cut end point of mortality, it is the patients' own fitness and longevity that are threatened by disease (and, in some cases of iatrogenic harm, its treatment!). As such, they are appropriately positioned as the arbiters *par excellence* as to which metrics matter and which risk/benefit ratios are acceptable, including the ever-present choice of forgoing cancer-directed therapy altogether.

Adding to this modernization of the doctor-patient relationship is the surfeit of digital resources made available to

the public in the information age. Unsurprisingly, among patients with online access, 97% will use the Internet on diagnosis to find information about cancer, with 94% searching on Google. However, the ready yield of results from such a massive search engine carries important caveats; although Google can provide relatively accurate information about etiology and symptoms, it is far less reliable in its descriptions of treatment and prognosis. Efforts to use wording commensurate with average scientific literacy, for example, plain language summaries, are admirable in their inclusivity but carry tradeoffs between reliability and readability. Patients with rarer cancer are particularly vulnerable to the surfacing of misinformation, and even more common diagnoses still require shrewdness about the algorithmic ordering of recommendations for treatment; for instance, searches about specific medications will lead to pharmaceutical websites approximately 20% of the time introducing at least the specter of commercial bias.[72-76]

All told, such patient-initiated digital engagement is both entirely understandable and vulnerable to exploitation or at least misinterpretation. Medical professionals can provide critical assessment of what patients discover during their own online inquiries, vetting search results and separating fact from fiction, meritorious studies from pseudoscience. The once-fallow time between visits now becomes a fertile opportunity for the patient's own preparation asynchronous from their doctor's; they can arrive at their appointments with questions shaped by their independent reading and learn which resources are validated for further self-directed research.[66]

Another potential opportunity for misunderstanding arises through the direct access of laypeople to their *own* test results through patient-facing portals. With the commendable intent of empowering patients, the Open Notes movement embraces transparency and timeliness in the sharing of medical documentation.[77-79] The near-instantaneous delivery of results through secure channels ideally reduces uncertainty and decouples the reporting of a diagnostic test from an in-person visit. Surveys have revealed that many patients taking advantage of this technology feel as if they are more active participants in their treatment when granted this access. They are also more likely to retain the content of in-visit discussions with their doctor, as opposed to purely verbal recall.[80,81] However, if a patient receives the results of a test when an ordering physician is unavailable to help them interpret it, the temporal mismatch may engender more apprehension than if the doctor was explaining the clinical meaning in proper context.[82]

This is especially true of genetic results, which can have life- and family-altering consequences while also being freighted with diagnostic uncertainty, for example, variants of unknown significance. Even the fundamental bifurcation of mutations into somatic and germline defects may be overlooked, with the concern that the former could be extrapolated to a presumption of a hereditary risk. As Martin *et al* frame it, "despite the well-understood benefits of biomarker and genetic testing in precision medicine, uptake remains low… Patients report having limited familiarity with testing terminology and may not be able to accurately explain testing's role in treatment decisions. Patient confusion and lack of understanding is exacerbated by a multiplicity of overlapping terms used in communicating about testing."[83] As a corrective, they propose "democratizing comprehension about precision oncology testing through intentional use of plain language and common umbrella terminology by oncology health care providers and others in the oncology ecosystem may help improve understanding and communication and facilitate shared decision-making about the role of appropriate testing in treatment decisions and other aspects of oncology care."

Outside of cancer medicine, Huntington's disease is often cited as an incisive exemplar of genomic foreknowledge's double-edged sword. The subject's awareness of being the gene carrier of an inexorably progressive and uniformly fatal neurodegenerative disorder can induce intrusive emotions, denial-avoidance behavior, and pessimistic expectancies of the future and adjustment problems.[84] Within oncology, several germline mutations require relatively major surgical interventions early in life to mitigate the risk of oncogenesis. Patients with the CDH1 mutation might have to undergo prophylactic total gastrectomy by the fourth decade, whereas patients with familial adenomatous polyposis have often been considered for colectomy by around the same age. Parents of children with multiple endocrine neoplasia type 2 can even face the wrenching prospect of prophylactic thyroidectomy by their infant's first birthday to avoid medullary thyroid carcinoma arising from proto-oncogenic RET codons 883, 918, or 922.[85,86]

But even the advanced awareness of less lethal predispositions before they become phenotypically evident can pose threats that are harder to quantify. Some medical ethicists posit that contemporary predictive biomedicine has created a *sui generis* diagnostic category: the prepatient. Such persons risk being perceived as ill before they are diseased. As a transitive responsibility, the moral burden of conveying a bad prognosis shifts to the kin, who are then obliged to make decisions about when and how to share or withhold genetic information with other potentially presymptomatic relatives.[87,88]

CONCLUSION

SDM is a method of care on the basis of conversations conducted to arrive at a cocreated plan of care that addresses the problematic situation of each patient. Unhurried

conversations, SDM tools, and collaborative deliberation methods are essential to coproduce care plans with active participation of patients and clinicians. The experience of patients in contributing to care that fits requires access to trustworthy information, experience, and expertise, both within and between clinical encounters. Health care systems that favor the processing of people rather than the care of patients are hostile to methods of patient-centered care, such as SDM, and must be radically reformed if SDM is to become routinized in care.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Patient-Reported Outcomes, Digital Health, and the Quest to Improve Health Equity

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Overview

The theme of the 2023 American Society of Clinical Oncology Annual Meeting is Partnering With Patients: The Cornerstone of Cancer Care and Research. As we aim to partner with patients to improve their health care, digital tools have the potential to enhance patient-centered cancer care and make clinical research more accessible and generalizable. Using electronic patient-reported outcomes (ePROs) to collect patients' reports of symptoms, functioning, and well-being facilitates patient-clinician communication and improves care and outcomes. Early studies suggest that racial and ethnic minority populations, older patients, and patients with less education may benefit even more from ePRO implementation. Clinical practices looking to implement ePROs can refer to the resources of the PROTEUS Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders). Beyond ePROs, in response to the COVID-19 pandemic, cancer practices have rapidly adopted other digital tools (eg, telemedicine, remote patient monitoring). As implementation grows, we must be aware of the limitations of these tools and implement them in ways to promote optimal function, access, and ease of use. Infrastructure, patient, provider, and system-level barriers need to be addressed. Partnerships across all levels can inform development and implementation of digital tools to meet the needs of diverse groups. In this article, we describe how we use ePROs and other digital health tools in cancer care, how digital tools can expand access to and generalizability of oncology care and research, and prospects for broader implementation and use.

INTRODUCTION

The theme of the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting is Partnering With Patients: The Cornerstone of Cancer Care and Research. This theme serves as a call to deepen our commitment to connect with the communities we serve. As we aim to partner with patients to improve their health care, patient-reported outcomes (PROs) offer a systematic approach to incorporate the patient's perspective in oncology care and innovation. PROs are patients' own reports of how they feel, function, live their lives, and survive.[1,2] They include outcomes such as symptoms, functional status, and health-related quality of life and are assessed with standardized validated questionnaires reported directly by the patient without interpretation from a clinician or anyone else. To our knowledge, one of the most well-established and increasingly prevalent examples of digital implementation in cancer care to date is electronic patient-reported outcomes (ePROs). Beyond ePROs, digital tools are a growing part of care delivery, contributing to collaboration between patients and their clinicians by supporting communication, health literacy, measurement, timely symptom management, and research needs.

In response to the COVID-19 pandemic, cancer practices have rapidly adopted and expanded ePROs, telemedicine approaches, remote patient monitoring, and other digital strategies to meet the unprecedented needs of the moment for their patients. As implementation grows, we must be aware of the limitations of these tools and implement them in ways to promote optimal function, access, and ease of use. In this article, we describe how we use ePROs and other digital health tools in cancer care, how digital tools can expand access to and generalizability of oncology care and research in the US, and prospects for broader implementation and use.

HOW DO WE USE DIGITAL HEALTH TO IMPLEMENT PROs IN CANCER CARE?

A key aspect of partnering with patients is ensuring that their perspectives are directly incorporated in their care journey. Having patients complete questionnaires about their symptoms, functioning, and well-being—and using that data to inform that patient's own care—promotes patient-centeredness. Benefits include improved communication between patients, physicians, and other members of the care team,[3-6] which can help them monitor treatment response and detect problems.[6-8] Integrating PROs with

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PRACTICAL APPLICATIONS

- Digital tools have the potential to enhance patient-centered cancer care and make clinical research more accessible and generalizable.
- Electronic patient-reported outcomes (ePROs) have the potential to improve care and outcomes, with some evidence suggesting particular benefits among racial and ethnic minority populations, older patients, and patients with less education. Resources to aid practices in implementing ePROs are available from the PROTEUS Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders).
- Beyond ePROs, digital tools such as patient portals, telemedicine, remote patient monitoring, and hospital at home can enhance patient care; electronic consent can facilitate enhanced enrollment and participation in research.
- Barriers to digital implementation at the infrastructure, patient, provider, and system-level need to be addressed. Partnerships across levels can inform development and implementation of digital tools to meet the needs of diverse groups.
- When implemented effectively, digital tools can narrow, rather than widen, health disparities.

care pathways reduces the time to symptom management and improves patient outcomes.[9,10] As our understanding of how best to incorporate PROs in clinical practice has improved, we have increasingly seen beneficial impacts on patients' functional status, quality of life, overall care management, and satisfaction with care.[3,5,10-16] Recent studies have even demonstrated improved survival.[10,12] In the United States, ePRO inclusion in the Centers for Medicare and Medicaid Innovation's alternative payment model pilot, the Enhancing Oncology Model, is a sign that ePRO implementation should be a mainstay of high-quality and transformational cancer care and will likely foster broader adoption.[9]

Some early indications suggest that using PROs in clinical practice benefits vulnerable populations even more. Basch et al randomly assigned 766 patients receiving routine outpatient chemotherapy for advanced solid tumors at Memorial Sloan Kettering Cancer Center to symptom reporting or to usual care (symptom monitoring at the discretion of clinicians).[11,17] Patients in the intervention group had better health-related quality of life, remained on chemotherapy longer, had fewer emergency department visits, and lived longer. Preplanned subgroup analyses on the basis of patients' level of computer experience showed that these benefits were even greater in the computer-inexperienced subgroup, including for emergency department visits, hospitalizations, and overall and quality-adjusted survival. Notably, computer-inexperienced patients were more likely to be older, Black, and have less education. In another example, planned exploratory analyses of a randomized controlled trial conducted at Johns Hopkins examining different PRO questionnaires for use in clinical practice found a trend toward patients from minority racial groups, with less education, or less computer usage reporting greater benefit from completing PRO questionnaires as part of their routine care.[18]

Opportunities and Challenges of ePRO Systems

Advances in technology have increased the feasibility of incorporating PROs in routine care.[19] PRO measures have to be completed by the patient, scored, and then, for maximal benefit, reported to the clinical team—ideally graphically and incorporating other clinical information (eg, previous scores on the measure along with dates of various clinical interventions). Historically, manual (paper) questionnaire completion, scoring, and reporting limited the incorporation of real-time PRO data during clinical encounters. The increased availability of ePRO systems that enable electronic questionnaire completion (in-clinic, remotely via the Internet, or both) as well as automatic scoring and reporting, has substantially expanded the scalability and use of PROs in routine clinical care.

For example, a 2014 review identified 33 unique ePRO systems for use in cancer care[20]; in a 2019 review, also cancer-focused, the number of systems identified had increased to 41.[21] More recently, several electronic health record (EHR) systems have added built-in functionality for PRO collection and reporting. A 2020 review found that ePRO systems were associated with the following advantages: lower costs, better data quality, equal or faster time to complete, lower administrative burden, and being generally preferred over paper forms.[22] However, increased use of electronic reporting systems runs the risk of inadvertently excluding vulnerable populations with less ability to use or access technology.[22] Although a recent review article found that PRO implementation is generally feasible and acceptable in the care of diverse and underrepresented patient populations (US only and not specific to electronic reporting or to cancer), it also documented disparities in PRO completion among racial and ethnic minority groups; patients who speak Spanish; patients with low income, employment status, education, and health literacy; and older populations.[23]

One of the challenges in effective patient-centered implementation of PROs relates to the mode of administration. In

a randomized clinical trial across 52 US-based community oncology practices, over a third (35%) of participants chose to complete their PRO questionnaires via an automated telephone system (*v* via computer); the investigators had anticipated only 10%-15% would choose the telephone option.[24] Similarly, Griffin et al found key demographic differences in 15,181 unique patients with cancer asked to complete PROs via the EHR patient portal, an automated telephone system, or in-clinic tablet: Patients who responded only using the telephone system were more likely to be older than 70 years or disabled.[25] The nearly 18% of patients who did not respond using any mode were more likely to be of non-White race and have a high school education or less. The data from these studies demonstrate the importance and difficulty of designing electronic PRO interventions that are widely inclusive and readily accessible to all patients.[26]

Key Tools to Support the Use of PROs in Clinical Practice

There are many topics that require consideration when implementing PROs as part of routine care, including for diverse populations. A number of tools and resources have been developed to support these efforts (Table 1).

The User's Guide to Implementing PROs in Clinical Practice was developed by the International Society for Quality of Life Research (ISOQOL).[27,28] This User's Guide walks step-by-step through the process of implementing PROs in clinical practice, starting with delineating the goals for the intervention, then determining which questionnaires are going to be completed by which patients at what frequency using which mode of administration, and finally defining approaches for reporting the results, aiding interpretation of the scores, and facilitating actions to address issues that require clinical attention. For each step in the process, the User's Guide does not recommend one right approach but rather offers a range of options with their relative advantages, disadvantages, and resource requirements. In this way, users can determine which approach fits best within their context. A companion to the User's Guide, published in 2018, uses real-world case studies to describe operational issues involved in using PROs in clinical care.[29]

An increasingly necessary consideration when implementing PROs into clinical practice relates to the integration of PRO data with EHRs. To support integration, a Users' Guide specifically focused on the considerations of PRO-EHR integration was published in 2017.[30,31] Similar to the ISOQOL tool, the PRO-EHR Users' Guide walks step-by-step through the process of PRO-EHR integration and offers a range of options along with relative advantages and disadvantages. It complements the ISOQOL User's Guide by focusing specifically on EHR integration considerations.

Another issue related to the use of PROs in clinical practice is the best way to graphically display the PRO scores so that patients and clinicians can easily and accurately interpret their meaning. A multiphase international research study explored approaches for displaying patients' PRO scores graphically to identify the formats that are interpreted most accurately and rated clearest.[32-34] The research study results then informed the development of stakeholder-engaged, evidence-driven recommendations for how to display PRO data to promote understanding and use.[35]

Two other important aspects of using PROs in clinical practice are aiding interpretation of the PRO scores and facilitating clinical responses to issues identified through the PRO assessments. To address these issues, the journal *Medical Care* published a supplement series of papers that provide a methodological toolkit for interpreting and acting on PRO scores.[36] The first six papers in the series describe different approaches for aiding interpretation of PRO scores, including quantitative, qualitative, and psychometric approaches.[37-42] The following eight papers describe different ePRO systems from multiple countries and the approaches they use to aid PRO score interpretation and/or to facilitate action in response to the PRO results.[43-50] As such, the *Medical Care* supplement offers a range of methods that users can apply in their own PRO implementations.

Finally, the ePROs in Clinical Care Toolkit was developed to help health care systems implement ePRO data in clinical care delivery.[51] It builds on several of the resources described above, including the ISOQOL and PRO-EHR Users' Guides, but is unique in that it focuses primarily on the health system perspective, specifically governance, integration, and reporting. Similar to the other resources, it does not provide a prescription for addressing these issues but rather presents a range of strategies that have been used in other health systems. The website also includes interactive tools to support translation of the guidelines into practice.

The above tools are being implemented and disseminated through the international PROTEUS (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders) Consortium.[52] PROTEUS helps navigate the use of PROs in clinical trials and clinical practice by engaging with key stakeholder groups to disseminate and implement relevant tools and resources. On the basis of input from the 53 patient, clinician, research, health system, industry, policy, government, and regulatory groups in the Consortium, a new tool is currently under development to synthesize and consolidate the information from the five separate tools to create a single, unified resource. This new tool is expected to be available on the PROTEUS website in Spring 2023.

Ensuring Inclusion of Vulnerable and Underserved Populations in PRO Systems

As noted above, the use of PROs to inform the monitoring and management of patients with cancer might have particular value for vulnerable and underserved populations,

TABLE 1. Summary of Key Tools to Support the Use of PROs in Clinical Practice

Tool	Purpose	Content Covered
User's Guide to Implementing Patient-Reported Outcomes Assessment in Clinical Practice	To outline the steps in implementing PRO assessment as part of routine care and, for each step, provide a range of options and their relative advantages and disadvantages	Identifying the goals for collecting PROs in clinical practice Selecting the patients, setting, and timing of assessments Determining which questionnaire(s) to use Choosing a mode for administering and scoring the questionnaire Designing processes for reporting results Identifying aids to facilitate score interpretation Developing strategies for responding to issues identified by the questionnaires Evaluating the impact of the PRO intervention on the practice
Users' Guide to Integrating Patient-Reported Outcomes in Electronic Health Records	To outline the steps in integrating PRO assessment and reporting in electronic health records and, for each step, provide a range of options and their relative advantages and disadvantages	Strategy for linkage Governance Training and engaging Patients/populations Outcomes Measure evaluation Questionnaire administration Score display Acting on results Data pooling Ethical/legal issues
Recommendations for graphically displaying patient-reported outcomes data	To report stakeholder-driven, evidence-based recommendations for graphically displaying PRO data to promote understanding and use	Recommends the consistent use of line graphs of scores over time Addresses confusion associated with differing directionality in scoring (ie, whether higher scores are better or worse) Suggests approaches to convey score meaning (eg, what is mild, moderate, severe) Describes how to identify possibly concerning results
A PRO-cision Medicine Toolkit to Address the Challenges of Personalizing Cancer Care Using Patient-Reported Outcomes	To describe a range of methods to address the issues of (1) aiding interpretation of PRO scores and (2) acting on PRO results	Quantitative, qualitative, and modern measurement theory-based approaches for identifying cutpoints (eg, mild, moderate, severe) How reference values, aggregated data, and group-level PRO metrics may aid interpretation Descriptions of how eight PRO systems aid interpretation of, and promote action based on, PRO results

(Continued on following page)

TABLE 1. Summary of Key Tools to Support the Use of PROs in Clinical Practice (Continued)

Tool	Purpose	Content Covered
ePROs in Clinical Care Toolkit	To help health care systems implement ePRO data in clinical care delivery	Governance to align ePROs with health system goals Align goals for ePRO use with information technology infrastructure Establish an ePRO governance structure Identify governance activities that guide practice Disseminate best practices for use and management Integration to clarify how data will be accessed and support care Design workflows for easy data capture Leverage health information technology to encourage maximum ePRO use Engage users in ePRO adoption and use Encourage continuous learning during implementation Reporting to display most useful statistical presentation Provide longitudinal PRO information Provide comparative PRO information Augment PRO data with contextual information Automate to improve ePRO workflow Customize to enhance usability Include drill down and up capacity Provide means to filter PRO data Integrate PRO and clinical data platforms Accommodate multiple platforms Visually enhance key information Provide simple and familiar graphs Organize display of multiple visualizations Model clinical use of ePRO reports

Abbreviations: ePRO, electronic PRO; PRO, patient-reported outcome.

but these populations might also require special attention to ensure that PRO systems are designed to meet their needs. To address these issues, the PROTEUS Consortium is forming an Advisory Group for Patient-Reported Outcome Implementation in Vulnerable and Underserved Populations, focused on oncology care in the United States. The aims of this Advisory Group are to (1) improve our understanding of the facilitators of and barriers to implementing routine PRO assessments in institutions caring for vulnerable and underserved populations and (2) build capacity for PRO implementation to improve care for patients with cancer who are vulnerable or underserved. The Advisory Group will include a range of perspectives, reflecting expertise both in PRO implementation and in care for vulnerable and underserved populations. On the basis of the discussions, a strategy document will be prepared to outline action steps that PROTEUS and other organizations can take to promote the inclusion of vulnerable and underserved populations in PRO interventions.

EXPANDING ACCESS TO AND GENERALIZABILITY OF ONCOLOGY RESEARCH AND CARE WITH DIGITAL HEALTH TOOLS IN THE UNITED STATES

Although ePRO implementation in routine oncologic care offers a clear opportunity to partner with patients using technology, additional digital tools can further facilitate remote care monitoring and decentralization of both research and care (Fig 1). This section will focus on implementation in the United Sates, though it should be noted that expanding access to and generalizability of oncology research and care, particularly in low- and middle-income countries, is a global priority and challenge, warranting dedicated efforts and international collaboration. At present, clinical trials in the United Sates are not available or accessible to many patients with cancer and thus the real-world applicability of trial results is limited.[53] Digital health tools provide an opportunity to facilitate health equity in cancer care by expanding the reach of high-quality oncologic care and research to patients and by facilitating generation of data that better represents the population. However, as described earlier with ePROs, these technologies have the potential to both narrow and widen a digital divide in cancer care and must be adopted thoughtfully to achieve key goals in health equity, access to care, and representation of a real-world population (Fig 2).

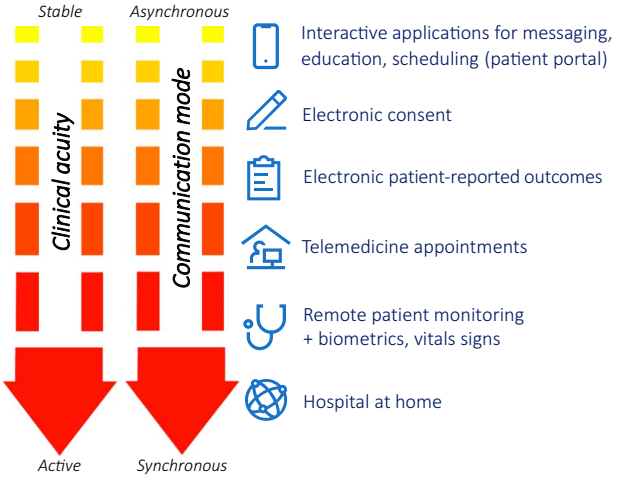

FIG 1. Examples of digital tools being implemented across the continuum of cancer care and research.

Opportunities Provided by Digital Health Tools in Oncology Research and Care

The historical underrepresentation of many Americans in cancer clinical trials is reflective of deep structural barriers to high-quality cancer care. Despite representing 13.4% and 18.5% of all patients with cancer, <6% of cancer clinical trial participants are Black or Hispanic, respectively.[54-57] Although populations older than 70 years comprise more than 42% of the US population with cancer, only 25% of participants in cancer clinical trials are older than 70 years.[53,58-60] Although 20% of the US population lives and works in rural areas, only 3% of oncology practices provide local care and clinical trial opportunities in these areas, and it is well known that clinical trial involvement and travel burden have a direct impact on clinical outcomes for rural patients with cancer.[55,61-64]

While efforts to improve these disparities are ongoing, the unprecedented growth of digital health tools as a result of the COVID-19 pandemic has provided a unique opportunity for accelerated progress. In the research setting, digital health technologies have the potential to facilitate clinical trials with broader reach, generating data more representative of the population.

For example, the deployment of remote consent and follow-up is a strategy adopted by many trials to sustain access and accrual during the height of the COVID-19 pandemic.[65,66] This remains a viable approach, enabling ongoing decentralization of therapeutic trials for patients who may not otherwise be able to participate. Furthermore, remote consent and decentralization can facilitate pragmatic outcome studies with a focus on enrolling real-world cohorts. In the ongoing study Integrating 4 Measures to Assess Physical Function in Cancer Patients (In4M),[67] the US Food and Drug Administration and academic collaborators from Mayo Clinic and Yale University aim to capture multimodal data on physical function in patients with cancer undergoing chemotherapy using patient reports, wearable sensor data, clinician-reported Eastern Cooperative Oncology Group performance status, and a 6-minute walk test. Data on symptomatic and laboratory adverse events, hospitalizations, acute care visits, dose modifications, and quality of life

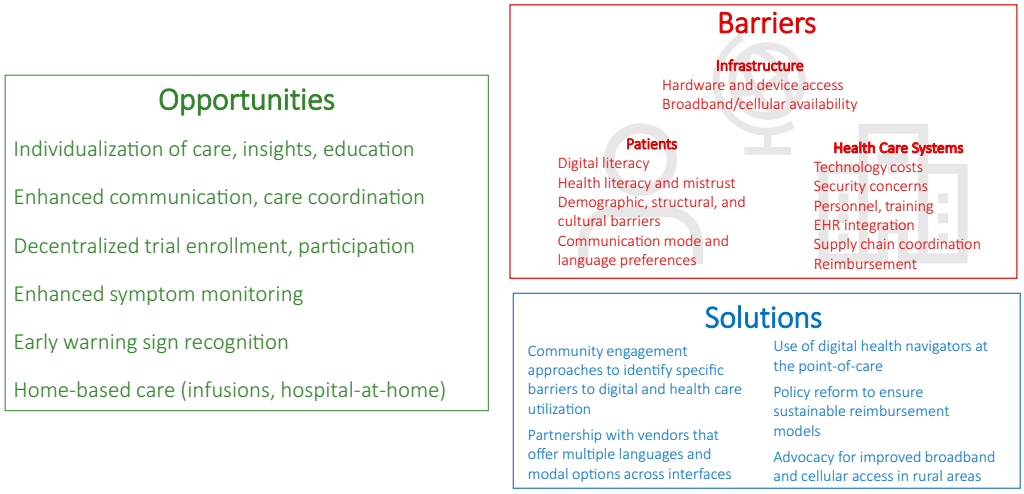

FIG 2. Implementation of digital tools across cancer care and research: opportunities, barriers, and solutions. EHR, electronic health record.

are also collected. The study is available to patients treated at their home sites, who are followed remotely by the study team and a data-aggregating digital platform. Efforts like this—which integrate digitally captured ePROs and biometrics in a decentralized fashion—represent a new model to help researchers and clinicians better assess cancer treatment tolerability in real-world populations in real time.

In the practice setting, use of digital health technologies has expanded access as well. Given the significant patient-related costs required for rural patients to receive in-person cancer care (greater travel distances, additional lodging, etc), telehealth services had long been considered a potential solution.[68,69] However, this approach had minimal adoption until 2020, when the national public health emergency (PHE) declaration and executive shelter-in-place orders propelled cancer practices to rapidly implement nontraditional models of care delivery.[69-73] Since 2020, with improved reimbursement and loosened restrictions provided through the PHE declaration, US cancer practices have been able to sustain rapid adoption of telemedicine services.[69,72,73] Beyond the initial pandemic response, a study presented at ASCO 2022 demonstrated ongoing growth and integration of telemedicine across a major multiregional cancer practice.[72,73] Furthermore, this study demonstrated that increased telehealth visit utilization did not result in duplicative care or compromise patient satisfaction with care.[73] In another study presented at ASCO 2022, the experience of implementing digital tools across a large community oncology practice was reported. In more than 600,000 episodes of digital tool use, engagement was high across various demographic parameters—age, sex, ethnicity, and rural versus urban.[74]

Beyond telemedicine, ePROs are being used in conjunction with prespecified nurse-driven clinical management algorithms to further streamline and individualize care. In the CAPRI trial, ePRO-driven nurse navigator support was shown to increase adherence to oral anticancer agents while also decreasing treatment-related toxicities and total hospital days.[75] The incorporation of devices capable of uploading vital signs and biometric data for real-time review by care teams has further enabled the use of remote patient monitoring (RPM) programs in acute and subacute care settings. The Mayo Clinic DEFeNDR program provides patients with a kit of preconnected, cellular-enabled devices to upload vital signs and symptoms directly integrated with the EHR, facilitating real-time ambulatory monitoring and management of febrile neutropenia as an alternative to hospital-based care (Pritchett et al, ASCO 2023). Similar RPM programs are being used to facilitate outpatient monitoring and management of patients receiving CAR T-cell therapy[76] and have been shown to reduce hospitalizations and acute care utilization in cancer patients with COVID-19.[77] Further still, digital advancements across multidisciplinary care ecosystems have enabled institutions to shift administration of some chemotherapy infusions to the home environment, as well as provide complex, inpatient-level care in the ambulatory setting. Penn Medicine's Cancer Care at Home (CC@H) program has demonstrated the safety, feasibility, and scalability of this approach,[78] and Huntsman Cancer Institute's Huntsman at Home model has shown the feasibility of this model to overcome geographic disparities among rural populations with cancer.[79]

Challenges of Digital Health Tools in Oncology Research and Care

Although digital tools have the potential to make research more accessible, generate research findings that are more representative of real-world populations, and enhance individual patient care, they also have the potential to exacerbate disparities among the very populations they are intended to serve.[80] Ensuring that digital tools resolve disparities in care requires attention to multilevel factors that influence whether patients can access and use them.

These factors span infrastructural issues, patient-specific considerations, and provider and health care system limitations (Fig 2).

In terms of infrastructure, access to adequate hardware and Internet connectivity represent two important barriers. In a 2020 study, 41.4% of Medicare beneficiaries did not have a computer with high-speed Internet connection at home, 40.9% lacked a smartphone with wireless capability, and 26.3% had neither (this was even higher for Black or Latinx individuals, those with lower income, high school education or less, patients on Medicaid, and those who reported having a disability).[81] Differences in digital care utilization such as patient portal use have been shown to be significantly affected by Internet access,[82] and the availability of high speed broadband and/or cellular-based Internet access in many rural areas represents a major barrier.[83,84] Among rural populations with cancer, video visit utilization rates have been shown to be significantly lower and phone visit rates significantly higher than patients from nonrural residences.[73] Although the comparatively high rate of phone visit utilization indicates a willingness of rural patients to participate in telehealth overall, the disparity in video visit utilization compels a need for further studies to examine barriers to video visit use among rural populations. Ultimately, telehealth solutions can only enhance access to care for rural populations if the necessary equipment and connectivity are available to serve them. With the potential removal of reimbursement for telephone visits associated with the end of the PHE declaration in 2023, such disparities may become compounded as cancer practices may be less inclined to offer telephone-based services without adequate reimbursement.[73]

In terms of patient-level factors, demographics such as age are relevant. Many older adults are technologically savvy, although virtual care utilization among older adults has historically been lower than in younger patients.[85,86] As the delivery of cancer care becomes increasingly technology-enabled, strategies aimed at improving digital health literacy and accessibility among older adults—such as the deployment of digital navigators and digital education resources[87]—should be considered to ensure equitable access to these services. Additionally, as discussed above, offering multiple modes of engagement (eg, computer, telephone) facilitates participation by older adults.[23,24] Encouragingly, higher adherence with PRO-based remote symptom monitoring has recently been shown to be a direct result of increased telemedicine utilization during the pandemic, with the greatest gains being observed in older adults with cancer.[88]

Beyond a patient's age, race and ethnicity warrant specific consideration. Lower digital health utilization has been reported among racial and ethnic minority populations in multiple studies.[89-91] Utilization of digital health technology by seniors, for example, is known to be significantly lower in Black and Hispanic/Latinx seniors than in White seniors, even when adjusting for educational attainment.[85] The reasons for these disparities are complex and multifaceted. Health literacy, health care mistrust, digital access, structural barriers, and language gaps have all been demonstrated to be contributing factors that can affect these and other populations.[89,91] There have been clear examples of exacerbating disparities in digital care during the COVID-19 pandemic as well. In a study conducted during the peak pandemic period in New York City, Black and Hispanic/Latinx patients, regardless of age, were significantly more likely to bypass virtual care options and seek in-person care than their peers despite the clear hazards and limitations of seeking in-person care under such circumstances.[89] A more recent analysis of telehealth utilization conducted by the United States' Office of Health Policy found that Latinx, Black, and multiracial respondents had higher odds of using telehealth services overall in 2021,[92] suggesting a promising trend. Direct community engagement and participatory approaches to assess specific digital barriers are essential to ensure equitable implementation.[93]

Health care systems and providers also face barriers to effective implementation of digital tools across an increasingly complex digital health landscape. As clinical enterprises increase their investments in digital tools, patient communication and collaboration has transitioned from phone calls and voicemails to omnichannel communication, whereby patients can use a single interface with multimodal communication options to enable synchronous and/or asynchronous connection with their clinical team. Additionally, the background architecture can be designed to manage appointment scheduling or billing with additional administrative capabilities, and clinical questions in the form of portal messages or phone calls can be delivered to clinical staff directly or triaged for added efficiency via embedded artificial intelligence–based tools such as voice recognition or bot technology. Given the increasing complexity of digital health integration, it is crucial for health systems to remain focused on a goal of enabling patients to effectively navigate the health care landscape analogous to how we use our smartphone to navigate the world. However, such care transformations can produce substantial disruptions to the clinical workflow, creating critical implementation barriers.

TENETS AND SOLUTIONS FOR BROADER USE OF DIGITAL HEALTH APPROACHES IN ONCOLOGY

Most digital tools have the potential to bridge gaps in health care inequity because they are typically more flexible, more convenient, and less dependent on patient-related resources. For example, patients can communicate asynchronously with their clinical team from their home or

TABLE 2. Tenets for Successful ePRO Implementation

Partner with ePRO vendors offering software designed for seamless EHR integration
Develop simple patient interface that is available on a wide variety of platforms
Prioritize functional ease, promote efficient workflow, and minimize alert fatigue for clinic interface
Consider frequency and duration for patient interfaces with the system
Institute time tracking of clinical alerts and alert resolution to measure system effect
Base survey instrument selection on clinical setting and application
Ensure free-text response option remains available to patients
Consider specific populations and timing for initiation, ie, at onset of new therapy
Conduct staffing capacity and needs assessment prior to implementation
Ensure process for systematic onboarding and re-enforcement for staff and patients
Establish administrative and clinical champions to oversee implementation
Refer to PROTEUS tools as a valuable resource

Abbreviations: EHR, electronic health record; ePRO, electronic patient-reported outcomes.

workplace through their patient portal, engage with ePROs, enroll and participate in clinical trials through electronic consent, conduct appointments through telemedicine, and even receive higher levels of care through continuous real-time technological solutions such as RPM and hospital-at-home programs (Fig 1). This patient-centered approach offers a degree of flexibility across the continuum of cancer care that is not possible without digital tools. Patients can continue with their daily routine, transportation is not a barrier, and they do not have to arrange care for dependents to access health care services. Additionally, digital tools provide just in time solutions with rapid turnaround. Clinics and health systems can also benefit from the use of digital tools, including the use of virtual-based teams to address staffing shortages and other challenges. However, the required infrastructure and staffing to support implementing these tools may not be feasible for some groups.

When planning to implement ePROs, it is important to consider several tenets to optimize the function of the delivery platform (Table 2).[16] First, PRO software design should integrate patient responses, notifications, and clinic actions in the EHR. Many established vendors offer this functionality. Second, the patient interface should be simple to use and available on a wide variety of platforms. Third, attention should be given to the clinic interface to ensure functional ease, prioritize efficient workflow, and minimize alert fatigue for clinical personnel. Before implementation, it is also important to choose the frequency with which a patient interfaces with the system—at routine intervals, on demand, or both—as well as duration of tool use to ensure sustainable use without generating fatigue, which decreases usefulness. Time tracking of clinical alerts and alert resolution is a useful feature that will help measure the effect of the system. Additionally, attention to survey instrument choice should be given before implementation; although many cancer-specific ePROs are already broadly implemented across systems, there may be some instances where a narrower instrument may be more useful. Patients should have the ability to document in free text in addition to reporting using close-ended, prespecified response options. Consideration should be given to which patient populations may benefit from ePRO use and when to initiate implementation—frequently with the onset of new therapy. Staffing capacity and needs assessment should be conducted before implementation to consider how patient symptom information will be managed. Finally, patients and clinic staff need systematic onboarding and re-enforcement to ensure successful implementation and championship, with administrative and clinical leaders being key to success. As clinical entities seek to incorporate ePROs in clinical practice, the PROTEUS tools can serve as a valuable resource. Practices can also partner with established vendors who have considered integration and optimal use.

The availability of tools in multiple languages would assist individuals who primarily speak a language not spoken in clinic. Use of digital health navigators, foreign language options of educational materials, and translation services could improve function for non-native English speakers. System-wide issues also require attention. Advocacy for improved broadband access in rural areas will make digital health care and other resources more available to rural areas. Internationally, implementation of mobile health technology faces unique challenges in low- and middle-income countries where access, at least initially, may be limited to middle- and high-income individuals. Investments in infrastructure and technology can democratize the availability of digital health resources for people living in these areas.[94]

CONCLUSION

The theme of this year's ASCO meeting highlights the importance of partnering with patients. Connecting with patients using ePROs and other digital health tools offers opportunities to improve care for all. They also offer the opportunity to improve health equity. However, infrastructure, patient, provider, and system-level barriers need to be addressed. Partnerships across all those levels can inform development and implementation of digital tools to meet the needs of diverse groups, both within the United Sates, as addressed here, and globally. When implemented effectively, digital tools can narrow, rather than widen, health disparities.

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Partnering With Patients and Caregivers in Cancer Care: Lessons From Experiences With Transgender, Hispanic, and Pediatric Populations

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overview

A cancer diagnosis thrusts patients and caregivers into a foreign world of health care with systems, protocols, and norms that can leave little room for individual needs and circumstances. Quality and efficacious oncology care requires clinicians to partner with patients and caregivers to understand and incorporate their needs, values, and priorities into information sharing, decision making, and care provision. This partnership is necessary for effective patient- and family-centered care and access to individualized and equitable information, treatment, and research participation. Partnering with patients and families also requires oncology clinicians to see that our personal values, preconceived ideas, and established systems exclude certain populations and potentially lead to poorer care for all patients. Furthermore, inequitable access to participation in research and clinical trials can contribute to an unequal burden of cancer morbidity and mortality. Leveraging the expertise of the authorship team with transgender, Hispanic, and pediatric populations, this chapter provides insights and suggestions for oncology care that are applicable across patient populations to mitigate stigma and discrimination and improve the quality of care for all patients.

"No Man Is an Island"

John Donne

> No man is an island entire of itself; every man is a piece of the continent, a part of the main; if a clod be washed away by the sea, Europe is the less, as well as if a promontory were, as well as any manner of thy friends or of thine own were; any man's death diminishes me, because I am involved in mankind.
> And therefore never send to know for whom the bell tolls; it tolls for thee.[1]

INTRODUCTION

Human connection and partnerships are vital in life and in death. Patients are people who love and are loved, with lives outside of their illnesses and who often identify with or belong to a family or community outside of the health care system. These are people with a past, a present, and a future, albeit a sometimes uncertain and fraught future.

Yet in health care, when people become patients, too often they are expected to function as an island entire of itself. This is despite health care in the United States (and plausibly in other Western health care systems) having grown increasingly complex, fragmented, and difficult to navigate.[2] Patients are, therefore, heavily reliant on their physicians at their most vulnerable times. The patient-physician relationship is the backbone of patient care and translates to positive outcomes, including for patients with cancer. In a study of 283 patients with breast or lung cancer, health-related quality of life was associated with the doctor's level of respect, patient involvement in decision making, and patient satisfaction with the quality of their care.[3] Conversely, in another study, poorer experiences of the patient-physician relationship were related to greater fears of cancer recurrence.[4] For women with breast cancer, psychosocial interventions improved quality-of-life measures and 12-month cancer survival.[5]

Patient-centered care includes (1) patient involvement in decisions and respect for patients' values, (2) clear information and communication, (3) access to reliable care, (4) emotional support and empathy, (5) involvement and support for family and caregivers, (6) continuity of care and smooth transition between health care settings, (7) physical comfort, and (8) effective treatment by trusted professionals.[6] Patient-centered care allows oncology clinicians and oncology systems to adjust to or account for the contradictions and limitations of our algorithms to create better care for all patients. Davis et al[7] suggested that quality of patient-centered care might be defined by the achievement of providing the care that the patient

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PRACTICAL APPLICATIONS

- The patient-physician relationship is the backbone of patient care and affects outcomes for patients with cancer.
- Health care systems' protocols, regulations, and norms often do not fit neatly with patients' and caregivers' unique needs or lives.
- Oncology clinicians must recognize that personal values, preconceived ideas, and established systems may exclude certain populations and potentially lead to poorer care for patients.
- Partnering with patients and caregivers allows clinicians to understand and incorporate patient and caregiver needs, values, and priorities into information sharing, decision making, and care provision.
- Learnings from transgender, Hispanic, and pediatric patients can be applied at a direct patient and systems level across oncology care more broadly to enhance equitable and efficacious care for all oncology patients and caregivers.

needs in the manner that the patient desires at the time that the patient desires.

This chapter will focus on three patient populations, transgender, Hispanic, and pediatric populations, with whom the authors have experience and will be the focus of invited presentations at the ASCO 2023 Annual Meeting. We highlight the importance of partnering with patients and caregivers to promote inclusive and equitable oncology care, provide oncology clinicians with skills to care for these populations, and apply lessons learned to provide more efficacious care for all patients.

PART 1: MITIGATING BARRIERS TO ONCOLOGY CARE EXPERIENCED BY TRANSGENDER PEOPLE

Ontological Contradictions Leading to Stigma

Medical concepts, or ontologies, of the body include the notion that sex is an immutable fact of the body and that this encompasses both biological constructs—including karyotype, hormonal milieu, anatomy, and body size—as well as gender, that is, one's sense of themselves as a man, woman, nonbinary, genderqueer, butch, femme, or something else.[8] The motivations for these ontologies are inseparable from gender-based oppression and served to distinguish so-called men and women to establish social hierarchy between them.[9] The repercussions of these ontologies are various and include the impacts on transgender and intersex people.

Ontological oppression[10] is structural harm that occurs when one's body or experience does not fit into pre-established categorical understandings. For example, medical ontologies include the notion that someone whose sex is female will have the chromosomes XX, a vagina, uterus, fallopian tubes, ovaries, and an estrogen- and progesterone-predominant hormonal milieu and be a woman. Thus, transgender or intersex people whose bodies, experiences, and/or genders do not fit these pre-established ontologies experience stigma, discrimination, exclusion, and poor care.[11-13]

Ontological oppression is also salient in oncology care, in which transgender people experience stigma, paternalism, discrimination, denial of care, and lack of safety.[14-16] Qualitative research has suggested that one reason clinicians stigmatize transgender people is to manage their lack of knowledge or familiarity with transgender bodies and experiences.[17] When transgender people's bodies do not fit within medical ontologies, clinicians can feel confused or uncertain, in contrast to transgender people who often know more about their bodies and health needs than their physicians.[13] This upsets the usual balance of power on the basis of clinical expertise. Clinicians may use stigma and discrimination to reset the balance of power.[17]

Instead, partnering with transgender people allows for the possibility that transgender people are not just an exception to an algorithm but an opportunity to rethink its validity and utility.[18] Instead of stigmatizing transgender people, oncology systems could re-envision sex, hormonal milieu, karyotype, anatomy, and size as distinct categories, which are separate from gender. Such new ways of seeing bodies and disease would end exclusions of transgender and intersex people. Shifting these categorical assumptions could also be a first step toward building algorithms and categories that are more precise. If sex were no longer used as a proxy for other biological constructs—for example, if data regarding anatomy, hormonal milieu, body size, and karyotype were collected on trials instead—the role of each of these in cancer pathology could be assessed independently and understood more deeply, setting the stage for more efficacious care for all people with cancer.

In the section that follows, we describe manifestations of conflated concepts of gender, sex, and biological factors in disease discourse, laboratory values, and chemotherapy dosing that set the stage for structural oppression and poor care. We also make suggestions to shift these ontologies to decrease the impetus for oppression of transgender people, intersex people, and additional people who may not conform to expectations on the basis of these conflated concepts. Shifting these categorical assumptions about bodies and disease could also be a first step toward more precise data and care for all people with cancer.

Disease Discourse, Misgendering, and Stigma

In oncology, one extension of the ideology that gender is an immutable fact of the body is that certain cancers are attributed only to people of specific genders. For example, prostate cancer is associated with men. This is manifested in care settings that are gendered with language, symbols, and iconography to reinforce these concepts. For example, cancer centers in which people are treated for ovarian, endometrial, fallopian tube, cervical, and other cancers may be named Center for Women's Cancers. The walls of such centers may be pink, and the walls may include photographs of women. In contrast, educational materials for people with prostate cancer may be blue and may contain images of ties or mustaches. Such spaces may implicitly exclude intersex people, men, or nonbinary people. Such settings may also create circumstances in which clinicians and staff may be more likely to use pronouns, an honorific, or gender marker that imply the wrong gender for patients, a phenomenon referred to as *misgendering*.[19] Similarly, curricula, educational materials, and guidelines for clinicians may also associate certain cancers (eg, testicular) with specific genders (eg, men), creating circumstances in which clinicians will be unprepared to see intersex or transgender patients and may respond by misgendering or stigmatizing them. Clinical trial documents and eligibility criteria may also contain these concepts, which can exclude transgender people from clinical trials and signal to transgender people that trials were not developed with them in mind.[20]

Laboratory Values and Drug Dosing

Laboratory value reference ranges have been derived on the basis of cohort or population studies of large groups of people who are categorized as women or men. Such laboratory values also reflect the idea that sex is indistinguishable from a variety of biological factors, including organ size, muscle mass, menses, hormone levels, and bone health, that influence laboratory values such as hemoglobin, iron studies, calcium, liver function tests, and creatinine clearance. Transgender and intersex people have bodies that do not match such categorical assumptions and thus often have laboratory values that are persistently flagged as abnormal when they may not be.[21,22] Other people may also be harmed by laboratory value reference ranges that have been determined on the basis of mean values and confidence intervals for so-called men and women. For example, many nontransgender women may have their iron deficiency anemia go undiscovered because of gendered laboratory reference ranges that have lower values for hemoglobin, hematocrit, ferritin, and transferrin saturation than for men. An extension of this concern is that dosing for some chemotherapeutics are calculated by creatinine clearance, which is based on a sex/gender marker. To our knowledge, no data exist about how these ranges apply to transgender and intersex people, but some data suggest that these algorithms may lead to drug toxicity in people with certain body composition.[23]

Partnering With Patients and Caregivers

Qualitative data suggest that gendered assumptions exclude transgender people from oncology care and that these exclusions are reinforced using misgendering, stigma, and paternalism. Individual oncology clinicians can take immediate steps to ensure that their care is accessible and efficacious. First, oncology clinicians can ask for and use the terms that patients tell us to use about them and their bodies, including their name, pronouns, honorific, and words to describe their anatomy and consistently use these with colleagues and in the electronic health record. One participant in a qualitative study suggested, "Use the pronouns that the patient told you to use. It's not enough to use it when you're talking to the patient and they're in the room, you need to use it in your notes. You need to use it when you're talking to other providers about the patient. You need to use it all the time. The same goes for the gender identity…It's very frustrating to see notes [with phrases] like, 'She wants to be called he.'"[24]

Second, oncology clinicians can creatively prioritize patients' desired interventions for their oncology care. Guidelines and educational norms suggest that we prioritize anatomy-sparing interventions in the setting of cancer (eg, lumpectomy over mastectomy). When several treatment options offer equivalent outcomes, however, the principles of shared decision making stipulate that patients have agency over their decisions. In some cases, patients may prefer more surgery rather than less for a myriad of reasons, including the relationships individual patients have to these parts of their bodies.[14,25] For example, a patient may desire orchiectomy rather than androgen deprivation in the setting of prostate cancer.[14]

Third, we must emphasize patient priorities when making decisions about gender-related hormone therapy or surgeries in the setting of cancer treatment in the absence of clear data. Hormone therapies and surgeries decrease suicidality and improve quality of life for transgender people.[26] Symptoms and illness are often misattributed to these interventions likely because they are a surrogate target for transphobia.[27] Little is known about the outcomes of transgender people with hormonally driven cancers who take hormone therapy (eg, testosterone in the setting of androgen receptor–positive breast cancer). Oncology clinicians thus navigate difficult waters with little concrete guiding data. More research is needed to support such conversations. In the interim, if patients or clinicians have questions about the safety of hormone therapy in the context of cancer treatment, we suggest clinicians (1) specifically

ask about patients' priorities in regard to hormone therapy, (2) investigate whether any evidence exists to suggest hormone therapy may worsen oncology outcomes, and if so, present these data to the patient, and (3) follow the patient's lead in regard to decision making, balancing the knowledge that hormone therapies are lifesaving interventions for transgender people who desire them, the largely unknown risks of hormone therapy in the setting of cancer treatment, and ethical considerations including respect for persons, beneficence, and justice.

On a broader structural level, oncology clinicians, administrators, and educators must update potentially oppressive habits by distinguishing sex from other biological constructs as well as from gender and accordingly revising oncology discourse in guidelines, curriculum, clinical documentation, and elsewhere as has been done by ASCO, which recently changed their guideline template to emphasize the importance of gender-neutral guidelines.[28] Laboratory values and chemotherapy dosing must also be reimagined and recalculated not on the basis of a sex/gender marker but more precise data such as hormone levels, body surface area, or body composition as is being done in the setting of race-based calculations of creatinine clearance.[29] In summary, transgender and intersex people with cancer face ontological oppression because their bodies, experiences, and preferences may not fit prevailing assumptions. Clinicians can mitigate the oppression transgender people face by following patients' leads in terms of describing and caring for their bodies and by making structural changes that can improve care for all patients.

PART 2: SHIFTING THE POWER DIFFERENTIAL IN THE PATIENT-PROVIDER RELATIONSHIP BY EMPOWERING HISPANIC PATIENTS AND THEIR CAREGIVERS

Eliminating long-standing disparities and inequities in the delivery of oncology care, including research and clinical trial participation, requires a transformative vision that involves health system leaders, diverse research teams, patients and their families, and affected communities. As proposed by Harold Freeman over a decade ago,[30] there is a disconnect between the research discoveries that largely occur in academic institutions and the delivery of these to underserved communities, which represents a key determinant of the unequal burden of cancer morbidity and mortality in the United States (Fig 1). With the rapid emergence of precision oncology and immunotherapy, we urgently need solutions to overcome the limited access of underrepresented racial and ethnic groups to cancer therapies so that every person with cancer benefits.[31] In the case of Hispanic patients, community-engaged and culturally and linguistically appropriate strategies targeting patient-, provider-, and institutional-level factors are essential to address the disconnect between what we discover and what we deliver. Health systems must play a role in bridging this gap by meeting the needs of individual patients and their caregivers to mitigate language, cultural, and other barriers to quality oncology care.

Barriers to Clinical Research Participation in Adult Patients

The University of California Moores Cancer Center (MCC) is located in San Diego County, one of two US-Mexico border counties in California. MCC's Community Outreach and Engagement (COE) team works diligently to engage patients, families, providers, and the MCC catchment area community, 35% of whom are Hispanic, to assess and address barriers related to oncology care delivery, including research participation and clinical trial enrollment. This work is guided by a formal framework (Fig 2) that was adopted from previous work[32] and largely focuses on Hispanic patients and their families.

Patient-Provider Language Concordance

Delivering linguistically competent care is critical to serving patients who have limited English proficiency (LEP) and represents a key strategy to help reduce health disparities and inequities. Current acceptable standards of communication with patients who have LEP include providers communicating through professional interpretive services or bilingual providers communicating in the patients' preferred language. Our research examined the effect of patient-provider language concordance on patient satisfaction in adult Spanish-speaking patients with cancer.[33] We found that, compared with patients who receive care leveraging interpreter services, patients cared for by a Spanish-speaking oncologist reported significantly improved general satisfaction (P = .001). Spanish-speaking patients served by a Spanish-speaking oncologist also reported improved satisfaction with quality of care (P = .005), care team interpersonal skills (P = .004), communication (P = .018), and time spent with patients (P = .028). Patients also rated direct Spanish language care higher in perceived opportunity to disclose concerns (P = .001), physician empathy ($P < .001$), confidence in physician abilities (P = .001), and general satisfaction with their physician ($P < .001$). Analyzing the content of consultation encounters revealed further differences between the two

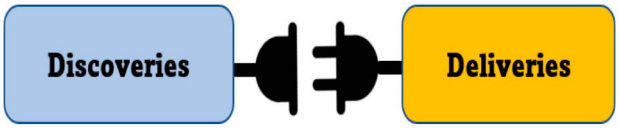

FIG 1. The disconnect between lifesaving discoveries and their delivery to underserved communities.

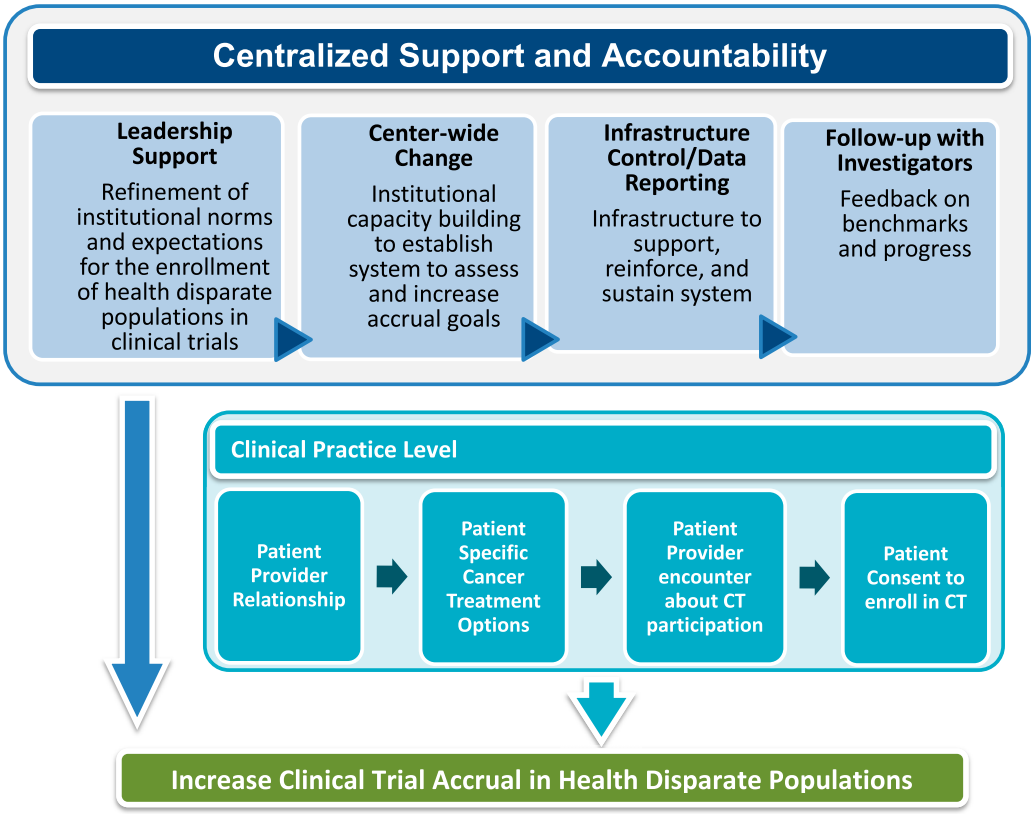

FIG 2. Moores Cancer Center approach and framework for clinical trial accrual. There is a need to centralize recruitment of health disparate populations to clinical trials, have organizational accountability, and have continued monitoring. Structural changes are needed on four levels: (1) leadership support, (2) center-wide policy change, (3) infrastructural process and control, and (4) follow-up with clinical investigators. CT, XXX.

groups, with the direct Spanish language arm having more physician dialog related to patient history verification ($P = .01$) and partnering activities ($P < .0001$). Additionally, patients in the direct Spanish language arm were more likely to initiate unprompted speech ($P < .001$) and asked their providers more questions ($P = .007$). These results underscore the importance patient-provider language concordance plays in providing quality care to Hispanic patients with cancer.

Provider and Patient Surveys and Interviews

Using the established framework presented in Figure 2, the MCC Clinical Trials Office (CTO) and COE teams conducted qualitative and quantitative assessments among patients, caregivers, and oncology providers (physicians, patient navigators, and social workers) to assess barriers and facilitators to recruiting and enrolling patients from underrepresented groups into clinical research and clinical trials.

Provider feedback. The most common barriers noted by providers were patient-clinical team language and cultural barriers (92%), logistics/transportation barriers (89%), patients' lack of knowledge about clinical trials (69%), negative attitudes and beliefs about clinical trials (61%), and lack of payment/insurance coverage for clinical trials (58%). One recurring theme was limited availability of translated consents to overcome language barriers. Interviewed providers who reported success in recruiting Hispanic patients underscored the importance of understanding patient needs, fears, and challenges. For example, one common challenge relates to geographic constraints. Although public transportation options near clinical trials sites is viewed as a solution, in actuality, transit time and transfers prohibit true access by patients with cancer who reside far away from the clinical site.

Patient feedback. We conducted qualitative interviews to understand factors that influence and impede participation in cancer research and clinical trials among English- and Spanish-speaking Hispanic patients with breast cancer and their caregivers (Table 1). The findings show that Hispanic patients with breast cancer have a high interest in participating in clinical trials, particularly when clinical teams practiced respect, built trust, and considered study participant needs. There were clear gaps between patient and provider understanding, exacerbated by language and

cultural barriers accentuating the power differential in the patient-provider relationship and limiting the ability of patients to self-advocate and identify areas of misunderstanding. A strong theme that emerged from the interviews with patients was a general unfamiliarity with research that was compounded by patients feeling overwhelmed with and confused about diagnosis and treatment information. Patients also often described an inability to establish trust and comfort with the many providers they encountered, particularly when there was language discordance or fears about immigration status for themselves or loved ones. These unsettled feelings prevented patients from engaging in dialog around added complexity, such as considering a clinical trial or research study, even it was offered to them. The importance of care team members dedicating time to establish trust and clear communication (with professional interpreters for patients with LEP and clinicians without Spanish proficiency) was a crucial theme woven throughout patient interviews.

After these assessments, systematic solutions were implemented at the MCC to address some of the barriers, which centered on culturally and linguistically concordant care and clinical trial navigation. These include (1) monthly COE/CTO reporting and monitoring of racial/ethnic trial accrual; (2) Spanish language (and other languages) consents available alongside English language consents in multiple short-form formats to streamline consenting for patients who require urgent access to studies; (3) annual/biennial cultural competency trainings for CTO staff; (4) hiring racially and ethnically diverse (approximately 75% non-White) and bilingual (approximately 33%) clinical trial coordinators and staff; and (5) hiring bilingual navigators representing eight languages other than English, centered on culturally and linguistically concordant care and patient navigation to address barriers. On the basis of these findings, recommendations are offered to increase the accrual of Hispanic patients to clinical research and trials (Fig 3).

Caregiver-Provider Communication in Hispanic Families of Children With Cancer

Although childhood cancer survival has significantly improved to more than 80%, driven in large part by participation in multicenter clinical trials, racial/ethnic disparities persist. Compared with non-Hispanic White children, Hispanic patients have significantly higher mortality, relapse rates, and poorer survival.[34-36]

The MCC team's research related to equity in pediatric oncology care delivery has largely focused on patient/caregiver-provider communication during informed consent for clinical trials by assessing social determinants of health, with a particular focus on health literacy (HL) and LEP. Delivering informed consent in the pediatric oncology setting poses significant challenges because of the urgency to begin treatment, the lengthy informed consent, and lack of formal informed consent training for providers,[37] which influence patient-provider communication during informed consent.[38,39] Our published work[37] on the role of HL and acculturation on informed consent outcomes showed that limited HL was significantly associated with lower perception of voluntariness ($P = .001$). Moreover, limited HL was significantly associated with Hispanic ethnicity ($P < .001$) and Spanish language spoken at home ($P < .001$). In addition, limited HL and Spanish language were significantly associated with lower informed comprehension ($P < .001$).[40] These findings suggest that caregivers with limited HL or LEP may not fully comprehend the informed consent for cancer clinical trials and thereby not truly make informed decisions. To improve patient-provider communication during informed consent, it is imperative that discussions be tailored to the language, HL, and cultural needs of parent/caregiver. Using in-person interpreters facilitates comprehension of informed consent content in different languages.[41,42] For caregivers who hesitate to ask questions, engaging them in decision making and checking their comprehension using techniques such as the teach back method can improve patient-provider

TABLE 1. Perceptions of Barriers and Facilitators to Clinical Research and Trial Participation Among Hispanic Patients With Cancer

Barriers	Facilitators
Patient-provider language and cultural discordance	Study information is delivered in-person
Lack of information about cancer clinical trials or research	Study location is geographically close to their home
Clinical trial not being offered	Provide appointment reminders by phone or text
Fear of potential risks in participation	Keep appointment duration short
Competing focus and confusion between patient's cancer treatment and clinical trial/research project activity	Study uses less invasive procedures and treatments
Patients' lack of time	Study personnel deliver a supportive experience (ie, respectful and professional) during enrollment and throughout the study
Inability to establish trust and comfort with care team providers	

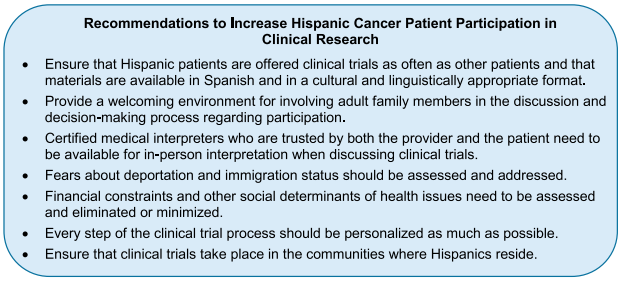

FIG 3. Recommendations to increase the participation of Hispanic patients with cancer in clinical research.

communication.[39] This method requires that patients/caregivers are asked to recount what they have been told in the informed consent discussion.[43] Moreover, staged informed consent delivery,[44] decision aids, patient navigation, and interventions at the provider and health care system levels[31,37] could potentially improve patient-provider communication during informed consent.[45,46]

In summary, addressing the disconnect between lifesaving research discoveries and delivery of these to underserved communities represents an unprecedented opportunity for achieving equity in oncology care delivery so that all patients have an opportunity to benefit from lifesaving cancer interventions. Instead of patients and their caregivers assuming the responsibility to adapt to the health system's environment when receiving care, health care organizations serving Hispanic patients with cancer need to proactively meet the unique needs of these patients. Effective patient-provider communication is one essential component of high-quality oncology care delivery. For Hispanic patients and their providers, communication should be tailored to the individual's language, culture, background, and HL and education levels.

PART 3: BALANCING THE NEEDS OF CHILDREN AND CAREGIVERS IN PEDIATRIC ONCOLOGY CARE

In pediatrics, it is vital to partner with both patient and caregiver as the unit of care is frequently, if not always, the family unit and not the patient in isolation.[47] Children exist within their family context, and family members' influence is central, pervasive, and enduring.[48] Parents and family members are fundamental in pediatric care[48] and serve as a conduit between children and health professionals during assessment and treatment interactions. The child's experience and wishes, articulated independently of the family unit, are equally important. Incorporating the voice of both child and caregiver and balancing the needs of both parties are vital. Although some of the detail outlined below relates to incurable cancer and life-limiting pediatric illness, the learnings are relevant to pediatric oncology care (and arguably across the age spectrum), regardless of treatment intent.

Balance of power in a therapeutic relationship is an important consideration. Children can be at risk of not being heard or listened to, and so too can parents or caregivers. This may be due to tensions about whose needs to prioritize, particularly when there appear to be competing interests between the child and the caregiver. Health professionals may appear to bear the ultimate power in the relationship, and with this comes a responsibility to hear and balance the needs of both child and caregiver. For example, children may wish to be involved in diagnostic and prognostic conversations while their parents may prefer to exclude them from such conversations.

Oncology clinicians and oncology systems may make assumptions regarding children's presumed lack of understanding about their illness, with implications about the degree to which they are involved in their own health care. Children understand more about illness than what has previously been thought.[49] Age is not the only factor that determines a child's understanding and engagement with illness. In her ground-breaking book, *The Private Worlds of Dying Children*, Bluebond-Langner illustrated the impact of experience, culture, and society on children's understanding of health and illness.[50] Even when not included in discussions about their leukemia diagnosis and prognosis, children on the oncology ward came to understand what was happening to them and to the children around them. It became clear to Bluebond-Langner that terminally ill children were aware that they were dying, before death was imminent, yet they tended to keep this knowledge secret from their parents and caregivers.

The 2009 European Standards of Care for Children with Cancer articulate that hospitalized children and young adults should have access to appropriate information.[51] However, the guidelines also recognize the role of parents as partners in the care of their sick child and their crucial role in supporting their sick child through illness. Therefore, although developmental age and stage are important when approaching conversations with a young person about their cancer diagnosis and treatment options, this must be done within their family construct and dynamics.

Family and Loved Ones—The Caregiver Role

Roles are tied into an individual's identity and sense of self.[52] A parent's role is to sustain, care, advocate for, and protect their child. This role is challenged when a parent's sense of control is stolen away by their child's cancer diagnosis, leaving them at the mercy of strangers (health professionals) and institutions (hospitals). Parents of children with cancer typically think about the features that make them a good parent to their sick child, but these attributes vary between parents and may change over time.[53-55] Priorities may include making informed medical care decisions, making

sure the child feels loved, and advocating for the child.[53] Of course, these attributes are not mutually exclusive.

In the pediatric cancer world, partnering with caregivers can involve exploring what helps parents to feel like they are meeting their role as caregiver to their child. Understanding drivers for parents' behaviors can promote a therapeutic relationship between parents and clinicians. For example, when parents face the devastating news that their child's cancer has progressed despite treatment, they may be confronted with seemingly impossible decisions such as the pursuit of experimental treatments versus a symptom-based palliative approach to care. Naming and normalizing these difficult dilemma that parents face can open a space for parents to share their hopes, fears, and priorities.[56] This in turn can help guide discussions about prognosis and treatment decisions. Regret and unfinished business may be associated with distress for parents of children with cancer, both while caring for their child and in bereavement.[57] Health professionals can play a role in mitigating regret and unfinished business by supporting their decision making and validating their choices.[57]

A cancer diagnosis throws a child and family's world into turmoil; roles, priorities, and day-to-day life need to be adjusted to accommodate the child's new care needs.[52] Understanding the structure and dynamics of a family is key for health professionals to provide tailored delivery of health information and emotional and decision-making support. An important dynamic for health professionals to uncover relates to the communication style and information needs of a family.

Glaser and Strauss described awareness contexts to illustrate what patients might know about their illness trajectory; for example, in an environment of closed awareness, families and care providers protect patients from the secret of the seriousness of their illness, whereas in an open awareness context, all parties share honest and open communication.[58] Mutual pretense refers to the collusion between patients, families, and even care providers to avoid or deny the seriousness of an illness and the possibility (or certainty) of death.[58] Both parties are aware of what is happening, but neither acknowledges this openly. Mutual pretense may be used to allow the maintenance of a narrative that the right treatment will restore health and a normal life, and health providers may perpetuate this narrative because of a fear of causing additional harm by taking away hope.[59] Bluebond-Langner expanded on the phenomenon of mutual pretense in the pediatric context, illustrating how parents and children may avoid talking about illness and death to protect each other. In the pediatric context, mutual pretense protects and maintains the social norm and expectation that children in Western society have a future.[50,52] It is important to remember that children equally engage in mutual pretense and seek to protect their parents from pain and suffering. This may occur, for example, by minimizing symptoms, physical or emotional, and avoiding talking about their cancer or their worries.

Child Role—The Patient Role

In pediatric oncology care, the child should be at the center of care and decisions, and their voice should be sought, listened to, and respected. However, as mentioned earlier, it must be recognized that the child exists within the tapestry of their family. Balancing the needs of children and caregivers can be challenging.

Studies now illustrate that children as young as 7 years can complete patient-reported outcomes and provide a voice in their symptom assessment. An important symptom assessment tool is the multidimensional Memorial Symptom Assessment Scale (MSAS) that inquires not just about the presence of a symptom but also its impact. If a symptom has occurred, the MSAS tool asks about its frequency, severity, and related distress, providing rich information to health professionals about where to focus time and management. Children with advanced cancer report high physical and psychological distress, for example, from pain, fatigue, drowsiness, and irritability.[60-62]

From a prognostic and information perspective, young people with cancer often want honest information, in the form of human contact as opposed to the internet. They generally want truthful information, even if the information is confronting, but conveyed in a way that leaves room for hope.[63] Importantly though, no one size fits all; some young people do not want information while for others, withholding information can exacerbate loneliness and fear.[64]

Shuttle Diplomacy—A Model for Bridging Gaps in Communication

Power (im)balances should not preclude access to the right amount and type of information for children and their caregivers. Parents may ask health professionals to hide information about their child's diagnosis or prognosis for fear of causing them distress and harm. As discussed earlier, this may be despite the child's awareness of their condition and desire for information while simultaneously perhaps wanting to protect their parents.

To truly partner with children and their caregivers and meet them where they are, health professionals are tasked with gently challenging rather than perpetuating a narrative of mutual pretense. This requires a sensitive approach to bridge gaps in communication and an awareness of the broader family context and culture of communication: How does this child-parent dyad usually communicate difficult matters? What are their preferences for receiving information, and who would the child like to deliver and interpret their health information? What are the parents' views and preferences in guiding their child through

TABLE 2. Summary of Clinical Practice Level Recommendations

Mitigating barriers to oncology care experienced by transgender people
Enquire about and use the terms that patients tell clinicians to use about them and their bodies, both in consultations and in health record documentation
Ask and partner with patients about their preferences and priorities and avoid assumptions, especially regarding cancer gender-related hormonal therapy and surgery
Provide patients with as much information as possible and work with them to weigh the risks and benefits in the absence of data
Considering cultural differences to improve quality cancer care
Include language and cultural concordant staff on study teams (eg, bilingual/bicultural investigators and study personnel)
Provide a welcoming environment for involving family members in discussions related to care delivery and research study recruitment
Encourage cultural competency training opportunities for study team that are specific to communities of focus
Establish partnerships with community providers and health organizations to assist with education, recruitment, retention, and dissemination
Form sustained partnerships between clinical trials office and community outreach and engagement teams
Balancing the needs of children and caregivers in pediatric cancer care
Consider information provision in the context of a child's developmental and chronological age, as well as their family dynamics and communication style
Utilize validated patient-reported symptom scales and outcome measures for children with cancer
Be sensitive to awareness contexts, for example, closed awareness or mutual pretense where the child and their caregivers may be aware of, but choose not to speak of, the seriousness of the child's illness
Where possible, engage in shuttle diplomacy to bridge gaps between the child and caregivers' experiences and worries

difficult conversation? Shuttle diplomacy, or diplomatic negotiation, is a process whereby health professionals aim to help parents feel heard and respected and at the same, help them to see their child's experience. For example, taking the time to understand why a parent does not want their child to know something allows an opportunity for exploration and discussion about parental fears and worries. In addition, sharing with parents that their child may already be aware and worried may open a space for parents to consider having difficult conversations with them. The goal of shuttle diplomacy is for parents and children to have their voices heard and respected and to enhance the relationship between them, not to achieve truth telling at all costs. When considering children in decision making, Bluebond-Langner described the importance of avoiding deceit and coercion and respecting the right to information, providing this is what the child desires. However, "the challenge in creating a role for children in decision making is to balance these values with the social fabric of family life and the rights that are accorded to parents in light of their responsibilities for their children" (p 337).[65] Ultimately, an understanding that unraveling the fabric of a family may be more harmful than information provision itself is an important underpinning of illness conversations with families and children in pediatric oncology care.

SUMMARY

Oncology clinicians are in a unique and privileged position of caring for people at some of the most vulnerable times of their lives. This vulnerability is multilayered; for example, structural and individual vulnerability may relate to the patient's age, gender, or cultural context, and from the patient's point of view from the cancer diagnosis itself, the shattered world of normalcy, the uninvited contemplation of mortality, and the grueling nature of cancer treatment. Focusing on the three specific populations, transgender, Hispanic, and pediatric patients, this chapter has described three common themes: (1) the risks that prevailing assumptions may exert on preference-sensitive decision making (hormonal treatment in transgender patients; differences in language concordance, even in the presence of translators to enter clinical trials; and how children understand their disease); (2) the imposition of institutional and societal norms, including normal laboratory values; and therefore, (3) the importance and value of truly partnering with patients and caregivers in the delivery of oncology care on interpersonal and systemic levels. A summary of clinical practice recommendations from the three patient groups is shown in Table 2.

When people become patients, they are thrust into health care systems whose protocols, regulations, and norms often do not fit neatly with patients' and caregivers' unique needs or lives. Clinicians well-steeped in the culture of health care can make unbidden assumptions about their patients' circumstances, priorities, and fears, which in turn can lead to missed opportunities for appropriate

information provision, shared decision making, and equitable care. Caregivers play a vital role in supporting patients with their practical and emotional needs and may influence patients' treatment decisions. Importantly, caregivers have their own experience of their loved one's illness with individual support needs that may affect patient care. Learnings from the three patient groups described in this chapter can be applied at a direct patient and systems level across oncology care more broadly to enhance equitable and efficacious care for all oncology patients and caregivers.

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Using Measurable Residual Disease to Optimize Management of AML, ALL, and Chronic Myeloid Leukemia

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Overview

In this review, we discuss the use of measurable residual disease (MRD) in AML, ALL, and chronic myeloid leukemia (CML). Our aims were to review the different methodologies for MRD assessment; describe the clinical relevance and medical decision making on the basis of MRD; compare and contrast the usage of MRD across AML, ALL, and CML; and discuss what patients need to know about MRD as it relates to their disease status and treatment. Finally, we discuss ongoing challenges and future directions with the goal of optimizing MRD usage in leukemia management.

INTRODUCTION

AML, ALL, and chronic myeloid leukemia (CML) are heterogeneous diseases which exhibit widely variable prognoses that are a function of both disease and patient characteristics. Both treatment decisions and prognosis are dependent on patient disease status, which requires accurate assessment of measurable residual disease (MRD). MRD is defined as the persistence of leukemic cells after treatment at levels below morphologic detection.[1,2] MRD below certain thresholds is associated with longer progression-free survival (PFS) and overall survival (OS) in patients with leukemia, and MRD is increasingly used as a secondary end point in clinical trials.[3-6] In this article, we review the usage of MRD and its clinical implications in patients with AML, ALL, and CML.

MRD MEASUREMENT TECHNIQUES

MRD assessment may be performed via three different modalities: multiparameter flow-cytometry (MFC), quantitative polymerase chain reaction (qPCR), or next-generation sequencing (NGS). Specimens for MRD assessment can be obtained via peripheral blood or from a small volume of first pull bone marrow to avoid hemodilution. For each leukemia type, MRD is usually assessed after initial treatment, serial testing during therapy, and also during follow-up once therapy has been completed. Yet, there are significant differences between MRD assessment methodologies, and sensitivities vary across each leukemia subtype. The sensitivities, advantages, and disadvantages of each MRD assessment method across leukemia types are briefly discussed below and summarized in Table 1. Detailed reviews on these techniques are available in the literature.[1,10] MRD negativity or undetectable MRD refers to an MRD result that is below the recommended prognostic threshold. This threshold is discussed below for various diseases (see also Figs 1–3 and Table 1). MRD may be detectable below the prognostic threshold but above the assay's limit of detection. Different approaches may be used for this so-called MRD at low level, as discussed below.

The molecular and immunological heterogeneity of AML requires tailoring the MRD assessment method(s) for specific patient populations (Fig 1). Per the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN), the first step in MRD assessment for AML should focus on molecular mutations such as *NPM1* and fusion oncogenes using qPCR. Although molecular qPCR-based techniques are sensitive, their disadvantage is that they can only be applied in a subset of patients harboring these genetic mutations.[7] If these mutations are absent, MFC can be used if specific immunophenotypes are present. Although NGS can assess and quantify mutations with prognostic value in patients with AML,[11-14] it is not yet recommended as a stand-alone technique in routine clinical practice because of lack of standardization and incomplete validation of its target mutations.[7] To use MRD prospectively as a predictive biomarker, it is important to standardize MRD across all laboratories. The ELN-DAVID MRD network and the Foundation of the National Institutes of Health (FNIH) Biomarkers Consortium very actively promote standardization of all MRD assays.[15] This has resulted in a program for external quality assessments (EQA), which are offered quarterly by United Kingdom National External Quality Assessment Service (UK-NEQAS) and should be followed by all laboratories.

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PRACTICAL APPLICATIONS

- Measurable residual disease (MRD) is a critical diagnostic tool that predicts disease progression and is increasingly used as an important end point to monitor disease status and evaluate novel treatments for leukemia.
- In AML, MRD is evolving toward a clinical decision support tool, but standardization of the technology across laboratories and among technologies need international efforts.
- MRD has a major impact on clinical decision making in patients with ALL. For example, MRD status influences treatment regimens and the decision to proceed with allogeneic hematopoietic cell transplantation. Emerging data suggest that more sensitive modalities that use next-generation sequencing are superior in predicting outcomes in patients with ALL.
- MRD is well standardized in chronic myeloid leukemia and is fully established to guide treatment decision during treatment and before and after stopping tyrosine kinase inhibitors.
- MRD technologies rapidly evolve toward sequencing-based assays, but machine learning and new flow cytometers also innovate cell-based assays.

MRD in ALL is typically assessed via MFC (sensitivity of 10^{-4}), qPCR for patients with Philadelphia chromosome–positive ALL (Ph+ ALL; sensitivity of 10^{-4} to 10^{-5}), or NGS (sensitivity of 10^{-6}; Table 1).[8] NCCN guidelines state that MRD testing for ALL must have a sensitivity of at least 10^{-4}; however, emerging data suggest that more sensitive modalities are superior in predicting outcomes in patients with ALL.[16,17] In light of these findings, the majority of academic centers in the United States are now incorporating NGS-based platforms for MRD monitoring. One US Food and Drug Administration (FDA)–approved NGS-based test is currently available in the United States (ClonoSeq, Adaptive Biotechnologies, Seattle, WA). This test follows immunoglobulin H (IgH) rearrangements in B-ALL and T-cell receptor gene rearrangements in T-ALL, and approximately 90% of patients will have a trackable clone.[18] This assay is not clone-biased, meaning that it can detect new clones as they arise over time.[19] In addition, there is evidence to suggest that NGS-MRD monitoring in the blood has a similar sensitivity to that of the bone marrow, allowing for more frequent monitoring without the need for invasive procedures.[20] The main shortcomings of NGS include requiring a large number of cells, cost, and long turnaround time which may delay clinical decision making. By contrast, MFC is widely available, relatively inexpensive, and results are available quickly. However, there is no standardized MFC testing available in the United States, and sensitivities vary across centers.

Detection of residual disease in CML is relatively straightforward as all leukemic cells carry the BCR::ABL1 fusion oncogene, the product of the t(9;22) (q34;q11) reciprocal translocation. Once patients obtain a complete hematologic response, residual leukemic cells can be evaluated by reliable techniques in routine practice including conventional cytogenetics and molecular biology. Both cytogenetic and molecular MRD monitoring provide key prognostic information at the individual level and play a crucial role in patient management and decision making; however, regular assessment of MRD with karyotyping until a complete cytogenetic response (CCyR) is obtained tends to disappear in favor of molecular biology techniques. Molecular-based quantification of MRD is performed using the gold standard quantitative qPCR technique by amplifying peripheral blood *BCR::ABL1* transcripts and *ABL1* or *GUS* as control genes, with a $10^{-4.5}$ to 10^{-5} sensitivity.[21] To do so, it is of utmost importance to characterize the *BCR::ABL1* transcript type at diagnosis. Indeed, for most patients harboring major-type e14a2 or e13a2 BCR::ABL1 transcripts, standardized assays with results expressed on an international scale (IS) are used, but these assays are not designed for the rare patients with atypical transcripts.[22] BCR::ABL1 point mutations are a well-known mechanism of acquired resistance to tyrosine kinase inhibitors (TKIs) and can be detected and characterized using Sanger sequencing with a limit in sensitivity of 10%-20%.[23] NGS techniques tend to replace Sanger sequencing in routine practice because of the greater sensitivity, ability to detect low-level mutations (although with a risk of error), and to differentiate polyclonal mutations and compound mutants.[23]

In the next sections, we discuss the clinical relevance and medical decision making related to MRD testing in AML, ALL, and CML.

CLINICAL ROLE OF MRD IN AML

Monitoring of MRD in AML: Clinical Recommendations

In patients with AML with complete remission (CR) or CR with incomplete hematologic recovery prognosis can be further refined by MRD, with a median OS at 5 years of 68% in MRD-negative and 34% in MRD-positive patients.[5] The prognostic effect is well established for all MRD techniques in AML and different time points, for example, after two cycles of chemotherapy, at the end of treatment, before allogeneic hematopoietic cell transplantation (alloHCT), and during follow-up.[24] However, age and disease characteristics, such as genetic aberrations and treatment characteristics, influence the likelihood to achieve MRD negativity.[25] It is,

TABLE 1. Comparison of Measurable Residual Disease Techniques

Technique	Method	Sensitivity	Advantages	Limitations
Morphology	Identify and distinguish the presence of leukemic cells from nonmalignant cells in bone marrow using microscopy	5×10^{-2} (5%)	High availability	Low sensitivity
Cytogenetics (karyotyping)	Assessment of changes in the size, shape, structure, or no. of chromosomes (karyotype) in leukemia cells	1-5 $\times 10^{-2}$	High availability Needs a bone marrow aspiration and at least 20 metaphases Allows to detect ACAs (CML)	Low sensitivity
FISH	Cytogenetic method used to detect targeted abnormalities in leukemia genes or chromosomes	1×10^{-2}	Fast turnaround	Low sensitivity Not used to quantify MRD
Multicolor flow cytometry	Identify leukemic cells with a specific aberrant leukemia-associated phenotype using a panel of fluorochrome-conjugated antibodies	ALL: 10^{-4} to 10^{-5} (0.01%-0.001%) AML: 10^{-3} to 10^{-4} (0.1%-0.01%) CML: NA	Fast turnaround (<4 hours) Relatively low cost Provides information on antigen expression High availability	Variable sensitivity Technical laboratory expertise required No quality assurance and less standardized Requires fresh cells (<48 hours) Immunophenotypic shifts can lead to false-negative results Reduced sensitivity to detect MRD in blood samples Not established for monitoring during follow-up
qPCR for fusion genes	Quantification of *BCR-ABL* fusion gene RNA expression (p190 or p210 subtype)	ALL: 10^{-4} to 10^{-5} (0.01%-0.001%) AML: 10^{-5} (0.001%) CML: 10^{-5} (0.001%)	Standard primers used for specific fusion genes Fresh sample not needed High sensitivity Rapid turnaround Low cost	Absence of targets in >50% of patients Limited to *BCR-ABL1* in the United States Risk of contamination Not scalable for high volume Not standardized for minor transcripts
High-throughput NGS	Identify, quantify, and track unique disease-associated Ig mutations by sequencing IgH, IgK, and IgL rearrangements as well as TCR translocations, or somatic mutations in AML	ALL: 10^{-6} (0.0001%) AML: 10^{-4} (0.01%) CML: NA	Applicable to majority of patients Can identify, quantify, and track multiple unique clones and their evolution Only FDA-approved assay (for ALL) May be used in peripheral blood Fresh sample not needed Can scale up for high volume	High cost Requires diagnostic pretreatment sample Longer turnaround time than MFC (10-21 days) The analysis of NGS MRD data requires a bioinformatic pipeline Reliable markers not fully defined (AML) CHIP-associated variants not useful before alloHCT (AML) Limited throughput if targeted approach is chosen (AML)

NOTE. Sensitivity, advantages, and disadvantages are identical across the leukemia subtypes, unless otherwise indicated.

Abbreviations: ACA, additional cytogenetic abnormalities; alloHCT, allogeneic hematopoietic cell transplantation; CHIP, clonal hematopoiesis of indeterminate potential; CML, chronic myeloid leukemia; FDA, US Food and Drug Administration; FISH, fluorescence in situ hybridization; Ig, immunoglobulin; MFC, multiparameter flow cytometry; NA, not applicable for this leukemia type; NGS, next-generation sequencing; qPCR, quantitative polymerase chain reaction; TCR, T-cell receptor (adapted from [1,7-9]).

therefore, important to evaluate the prognostic value of MRD in the context of the current ELN risk classification, which specifies the MRD technology, time point, tissue, and cutoff for the use of MRD as a prognostic biomarker in patients with AML (Fig 1).[26] Importantly, a large retrospective study confirmed the prognostic importance of MFC-MRD in each of the three ELN risk groups.[27]

MRD results are frequently requested by clinicians as a prognostic marker; however, the predictive role of MRD in selecting treatment options for patients with AML is just evolving. The most important clinical question currently is whether MRD can help assigning patients to chemotherapy consolidation or alloHCT. This question was first addressed in an Italian study, where MFC-MRD guided the transplant

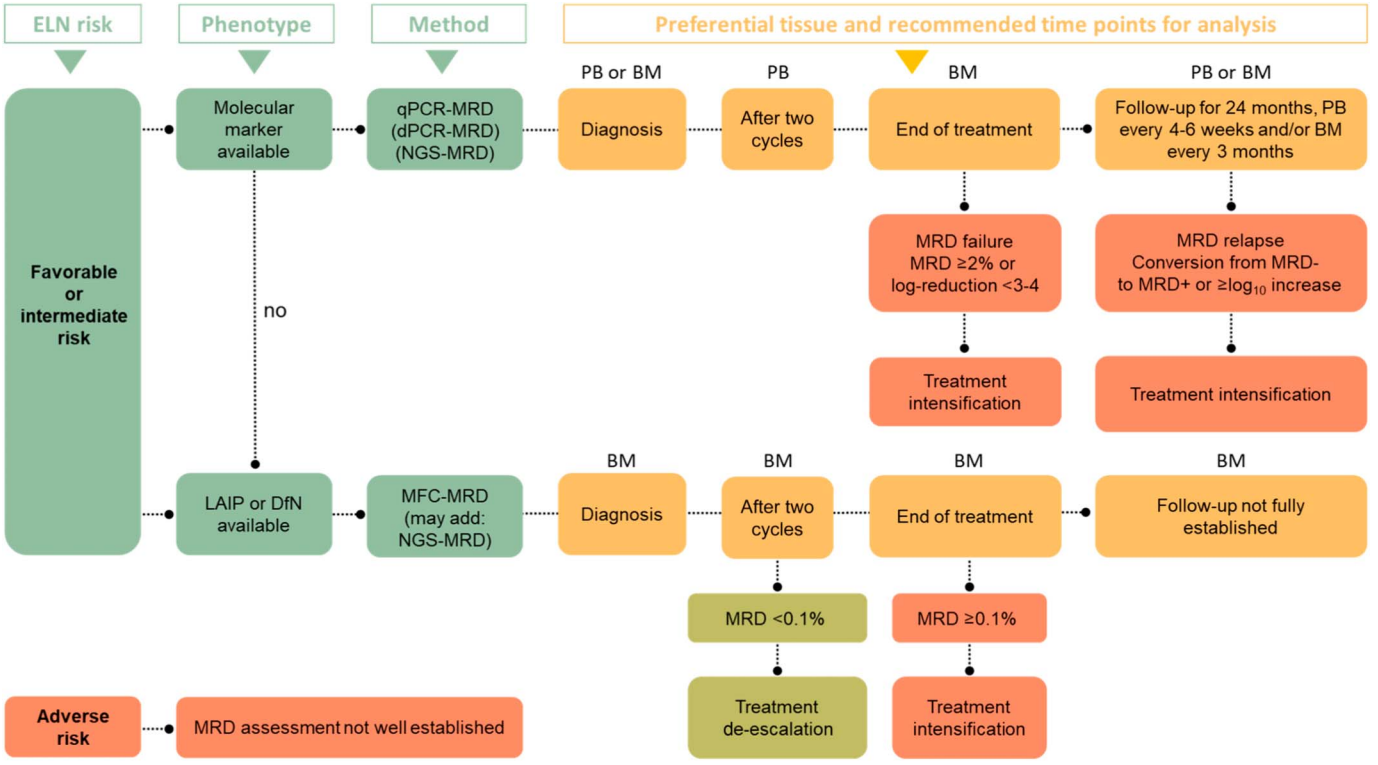

FIG 1. Incorporation of MRD quantification in standard care for AML. BM, bone marrow; DfN, different-from-normal phenotype; dPCR, digital polymerase chain reaction; ELN, European LeukemiaNet; LAIP, leukemia-associated immunophenotype; MFC, multiparametric flow cytometry; MRD, measurable residual disease; NGS, next-generation sequencing; PB, peripheral blood; qPCR, quantitative polymerase chain reaction.

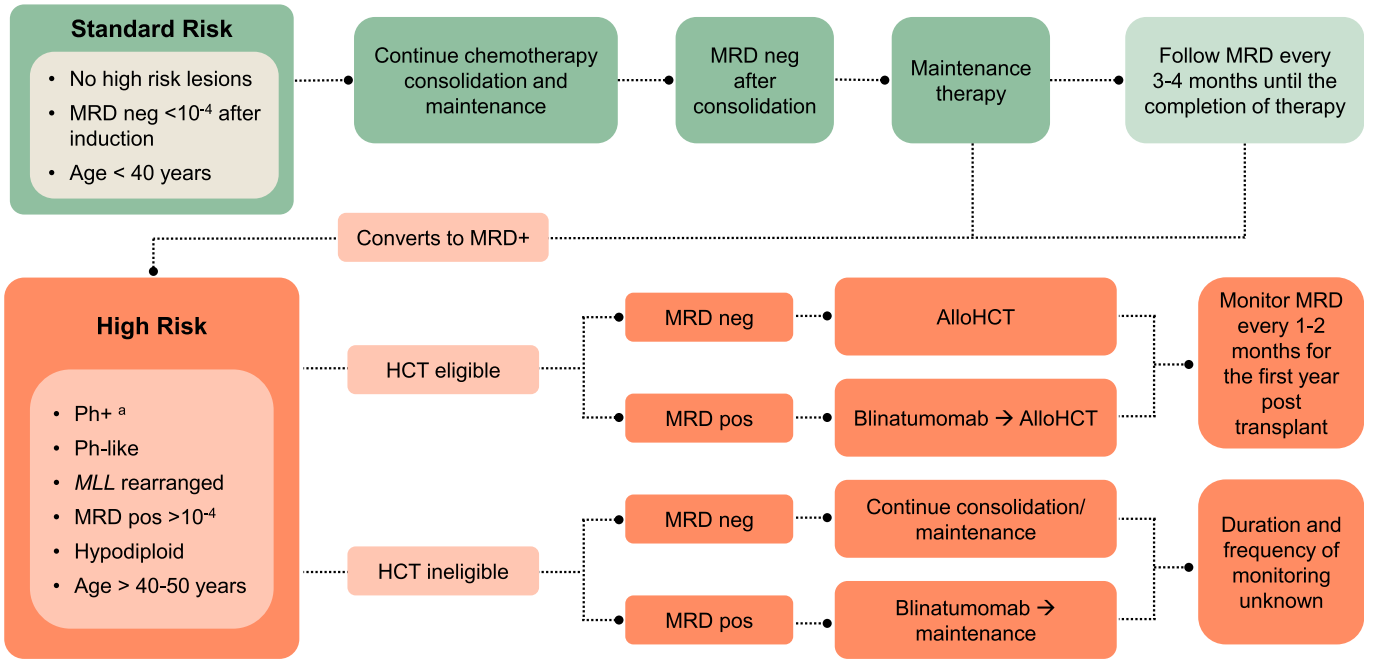

FIG 2. Incorporation of MRD quantification in standard care for ALL. alloHCT, allogeneic HCT; HCT, hematopoietic cell transplantation; MRD, measurable residual disease; neg, negative; pos, positive. [a]Possibly no longer high risk with emerging clinical data.

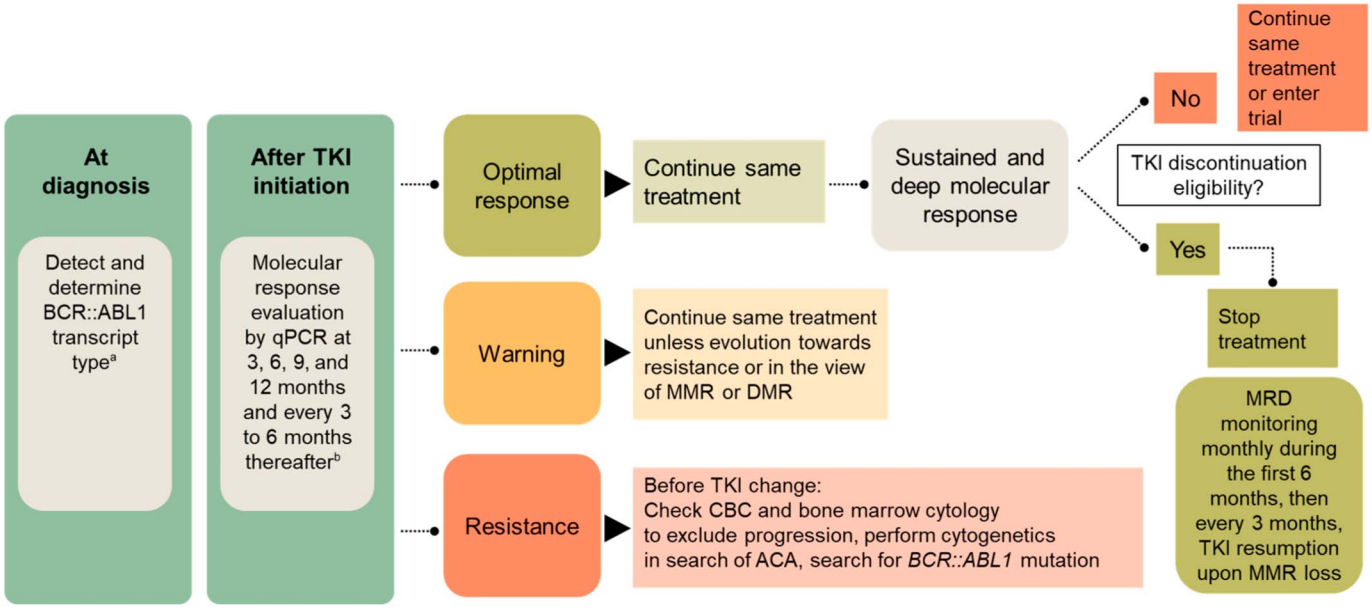

FIG 3. Incorporation of MRD quantification in standard care for CML. ACA, additional chromosomal abnormality; DMR, deep molecular response, defined as normalized *BCR-ABL/ABL1* ratio <0.01%; MMR, major molecular response, defined as normalized *BCR-ABL/ABL1* ratio <0.1%; qPCR, quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor. [a]Precise quantification by qPCR not mandatory except if halving times planned to be measured in the setting of a research approach. In this situation, use *GUS* or *BCR* as a control gene until MMR is reached, then *ABL1*. [b]Measured in peripheral blood.

decision in NCCN-defined intermediate risk patients with AML.[28] MRD-negative patients were recommended to undergo consolidation with chemotherapy or autologous transplantation while MRD-positive patients were recommended to undergo alloHCT. Disease-free and OS were identical among MRD-negative and MRD-positive patients, suggesting that the risk-adapted consolidation approach overcame the negative prognostic effect of MRD on the one hand and could spare alloHCT-associated toxicity for a significant number of patients on the other hand. A similar risk adapted consolidation approach was also applied in the HOVON 132 study.[29] The study showed that MRD no longer had a prognostic effect in the ELN intermediate-risk group and that alloHCT could be spared in a significant number of MRD-negative patients.[30] Outcome in MRD-negative patients, who were consolidated with high-dose chemotherapy and autologous transplantation, was similar to outcome of MRD-positive patients, who underwent alloHCT.

A recent study by Zhang et al[27] investigated the role of alloHCT in 769 patients who achieved CR within two cycles of chemotherapy in the context of ELN risk groups. In the ELN-favorable and intermediate-risk groups, MRD-negative patients did not benefit from transplantation. However, MRD-positive patients had a highly significant survival benefit with alloHCT. MFC-MRD in the adverse risk group was not prognostic when assessed after two cycles of chemotherapy, and OS was improved in patients undergoing alloHCT independent of MRD status. These data led to the ELN MRD recommendation that MFC-MRD measured after two cycles of standard induction chemotherapy in CR patients is a predictive biomarker that can guide the consolidation strategy (Fig 1). However, a prospective study proving this approach is lacking, and to our knowledge, no data comparing an MRD-guided with an MRD-unguided approach are currently available.

What is the Best MRD Conversion Strategy in Patients With AML?

MRD-positive patients who undergo alloHCT have a high relapse rate and shorter OS than MRD-negative patients. The question has been raised whether MRD-positive patients should be converted to MRD-negative with additional treatment before undergoing alloHCT. Emerging data are helping to clarify this issue. Paras et al[31] published a large retrospective study including 810 patients undergoing alloHCT in CR1 or CR2. MRD was assessed with MFC-MRD before and after alloHCT. Sequential MRD assessment revealed that of the 161 MRD-positive patients before alloHCT, 118 became MRD-negative after HCT, corresponding to a 73% MRD conversion rate by alloHCT. Patients who were MRD-negative before and after alloHCT had the lowest relapse incidence and highest OS. Importantly, MRD-positive patients who converted to MRD-negative had a significantly lower relapse incidence than patients who were MRD-positive before and after alloHCT and also had a

significantly longer OS. Thus, alloHCT currently is the only MRD conversion treatment for which a survival benefit has been shown. A MRD conversion rate of 60%-74% by alloHCT, including an improved OS, was also found when MRD was assessed with NGS.[32,33]

MRD conversion has also been investigated outside the setting of alloHCT. A prospective phase II study treated primarily *NPM1*-mutated patients with rising MRD with venetoclax and low-dose cytarabine. MRD response was achieved in 69% with 54% becoming CR MRD-negative. After a median follow-up of 18 months, the 2-year OS was 72.6%, and the EFS was 55.4%.[34] A retrospective study by Othman et al[35] evaluated the conversion efficacy of FLT3 inhibitors in patients with molecular failure. Of 49 evaluable patients treated with one of the available FLT3 inhibitors, 63% responded, of whom 45% achieved complete response. The molecular response (MR) rate was 93% in patients who had received previous alloHCT compared with 50% in patients who did not. After a median follow-up of 24.2 months, 2-year OS was 79%. In summary, the MRD conversion rate appears similar within the respective target populations with direct alloHCT in MRD-positive patients and patients with MRD relapse who receive either venetoclax/azacitidine or FLT3 inhibitors. Currently, it seems reasonable to proceed with alloHCT directly in MRD-positive patients and treat with FLT3 inhibitors after transplantation (in *FLT3*-mutated patients) while the results of the ongoing venetoclax/azacitidine maintenance study after alloHCT should be awaited, before such an approach can be routinely used after alloHCT for MRD-positive patients with AML. Few patients may be MRD negative after induction chemotherapy and turn MRD positive directly before alloHCT. These patients very likely have aggressive disease, and alternative treatments before alloHCT may be considered.

MRD in Patients With AML Not Eligible for Intensive Chemotherapy

Several studies have recently evaluated the prognostic effect of MRD in patients with nonintensively treated AML. Randomized studies evaluating venetoclax and cladribine in combination with azacitidine or low-dose cytarabine evaluated MRD most often with MFC-MRD. Sixty percent to seventy-one percent of patients were MRD positive when evaluated with MFC-MRD while 71%-100% of patients were MRD-positive using molecular methods.[36-46] MRD proved to be highly prognostic for relapse-free survival (RFS) and OS. The median RFS was 16.2 months in MRD-negative patients compared with 7.05 months in MRD-positive patients. The median OS was 26.2 months in MRD-negative patients compared with 13.8 months in MRD-positive patients. Appropriate time points for MRD assessment and potential impact for treatment guidance are currently being evaluated. In the Viale-A trial, 25% of all MRD-negative patients were identified after the first cycle, 27% after the fourth cycle, 27% after the seventh cycle, and 21% thereafter.[36] However, patients treated with 10 days of decitabine and venetoclax who were MRD positive 2 months after the start of treatment had a median EFS of only 5.8 months and a median OS of 7.1 months.[37] Thus, patients who are MRD positive after four to seven cycles of a hypomethylating agent combined with venetoclax seem to comprise a patient population in which additional treatment strategies should be developed to decrease the relapse risk.

CLINICAL ROLE OF MRD IN ALL

Predictive Value of MRD in Patients With ALL

MRD is a strong predictor of outcome and relapse risk in pediatric and adult ALL.[4,47] In a recent meta-analysis including 39 studies with more than 13,000 patients with ALL from both the adult and pediatric populations, MRD was uniformly associated with improved EFS and OS in both groups.[48] A cross-sectional physician survey on the use of MRD testing in adult and pediatric ALL showed that the use of MRD is standard protocol for 93% of pediatric physicians versus 53% of adult physicians.[49] Short et al evaluated the clinical impact of highly sensitive NGS in a medium-sized single-center study (74 patients). They demonstrated that many patients who are MRD negative by MFC still have clinically significant MRD that is detectable with ultrasensitive NGS assays.[50] In this cohort, all patients who were MRD positive by MFC were also MRD positive by NGS. However, 46% of MRD-negative samples by MFC were MRD positive by NGS. None of the MRD-negative patients by NGS relapsed after induction.[50] The importance of ultrasensitive NGS MRD monitoring was confirmed in a larger multicenter cohort of adult patients with ALL who underwent HCT at Stanford University or Oregon Health & Science University (n = 157).[17] Liang et al demonstrated that detectable pre-HCT MRD, even at a low level of 10^{-6} and any detectable post-HCT MRD, increased the risk of post-HCT relapse. Patients with undetectable pre-HCT MRD who continued to have undetectable MRD post-HCT through the first 2 years after transplant have excellent outcomes (<10% likelihood of relapse).[17] These findings are consistent with previous work in pediatric populations. Sekiya et al[51] previously found that NGS-based monitoring of MRD in pediatric B-ALL predicts leukemia-free survival. Another study by Wood et al[52] showed that MRD detection by NGS improves risk stratification for pediatric B-ALL. Gokbuget et al[53] used MRD-directed treatment with blinatumomab administered for $>10^{-3}$ MRD after three blocks of intensive chemotherapy and demonstrated that 80% of patients achieved MRD $<10^{-4}$ after one cycle, and median OS was not reached in the subset of patients who attained MRD negativity.

MRD measurements are also predictive of relapse in patients with B-ALL undergoing chimeric antigen receptor T-cell therapy. In pediatric and young adult patients treated with tisagenlecleucel, failure to achieve MRD negativity by day 28 or 3 months was associated with poor outcomes, with patients relapsing before 3 months. Sensitivity of MRD assessment was also predictive of outcomes. The risk of relapse was 50%, 31%, and 0% for MRD negativity at the level of 10^{-4}, 10^{-6}, and below 10^{-6}, respectively.[4] Ongoing studies are evaluating the prognostic significance of MRD positivity after treatment of adult patients with brexucabtagene (eg, NCT02614066).

Monitoring of MRD in ALL: Clinical Recommendations

Figure 2 illustrates how MRD quantification can be incorporated in standard care for patients with ALL. We recommend identification of patient-specific immunophenotypes or clonotypes for MRD tracking at baseline, then following MRD after induction, consolidation and delayed intensification, and then every 3-6 months throughout the course of maintenance therapy.[8] For patients undergoing alloHCT, we recommend obtaining a pretransplant MRD assessmen, and then serial monitoring via the blood or bone marrow within the first 45 days after transplant and then every 1-2 months for 1 year post-transplant.[17] The high sensitivity of NGS allows for MRD quantification in peripheral blood, and this appears to be an adequate alternative and allows for more frequent monitoring than frequent bone marrow assessments in the post-transplant setting.[20] Patients with standard-risk ALL who are eligible for treatment with a pediatric-inspired regimen and MRD negative at the level of $<10^{--4}$ should continue chemotherapy, consolidation, and maintenance. If these patients convert to MRD positivity, they should be treated similarly to patients with high-risk ALL. Patients with high-risk ALL (Ph+, Ph-like, MLL rearranged, hypodiploid, early T-cell precursor (ETP)-ALL, MRD positivity $>10^{-4}$) in CR should be assessed for HCT eligibility. HCT-eligible patients who are MRD positive should receive blinatumomab before transplant while blinatumomab is not required for MRD-negative patients. Of note, the use of blinatumomab to clear pretransplant MRD has not been studied in a randomized clinical trial, and it is unlikely that such a trial will ever be undertaken. High-risk MRD-negative patients who are HCT ineligible should continue consolidation and maintenance. High-risk MRD-positive patients who are ineligible for HCT should receive blinatumomab and then continue with maintenance. At this time, there are no agents approved to treat MRD in patients with T-cell ALL, and this remains an unmet clinical need. In adults with Ph+ ALL, it remains unclear whether MRD detected by BCR-ABL qPCR or NGS should be used to monitor disease. Measuring MRD via both NGS and BCR-ABL qPCR may help identify patients who are at very low risk for relapse or identify those at higher risk for progressive disease. There is a subset of patients who are MRD negative by NGS but have ongoing BCR-ABL positivity, but the clinical significance of this group is unclear.[54,55] Studies are underway to determine the relative specificity of NGS versus BCR-ABL qPCR in adults with Ph+ ALL and the prognostic implications of discrepant MRD results.[56]

It is important to note that MRD should be evaluated within the context of specific genotypes and clonotypes. For example, Jeha et al[57] examined the prognostic implications of leukemic subtypes in pediatric ALL by using genomic analysis and MRD assessments during remission induction. Their results suggest that both genomic analyses and MRD measurements are required to accurately stratify children with ALL into risk groups. Liang et al[58] recently examined the prognostic significance of various clonotypes (eg, IgH *v* Ig/Ig) detected by NGS MRD in adult B-cell ALL. They demonstrated that detection of IgH clonotypes after HCT, but not Ig/Ig clonotypes, is associated with increased risk for relapse.

CLINICAL ROLE OF MRD IN CML

Clinical and Prognostic Significance of MRD in CML

In the early 2000s, imatinib, the first TKI to specifically target activity of the BCR::ABL1 oncoprotein through direct competitive inhibition of ATP binding, was introduced into the clinic to treat patients with CML. During imatinib development, the drug was able to transform this fatal leukemia into a disease compatible with a near-to-normal lifespan providing early and durable Philadelphia chromosome (Ph1) negativity on bone marrow cell metaphases, highlighting the key prognostic value of cytogenetic responses on PFS in the TKI era.[59] Using more sensitive MRD detection techniques such as quantification of peripheral blood *BCR::ABL1* transcripts by qPCR assays, it was also discovered that most patients in CCyR retained detectable leukemic cells but over a wide range with varying clinical significance. Patients with highest long-term PFS rates were those in CCyR together with a 3-log reduction in *BCR::ABL1* transcript levels. Landmark analyses demonstrated a robust association between the degree of *BCR::ABL1* transcript decline on-therapy and long-term clinical outcome, supporting the use of time-dependent molecular measures to determine response to therapy.[60] Since then, qPCR assays have improved in sensitivity, reliability, and reproducibility, and international efforts have been made toward standardization of techniques.[21] Deep molecular responses (DMRs) at or below the 10^{-4} and down to the 10^{-5} level have been accurately defined given their importance for TKI discontinuation decision making in the view of treatment-free remission (TFR).[61] MRD levels after TKI discontinuation is used to predict and define molecular relapse which

triggers TKI resumption.[62] The therapeutic arsenal against CML now comprises the first-generation TKI imatinib, three second-generation ATP-competitive TKIs (bosutinib, dasatinib, and nilotinib), one third-generation TKI ponatinib, and one selective allosteric inhibitor asciminib. This arsenal of orally targeted agents is essential to meet ambitious treatment goals for patients diagnosed with chronic phase (CP)-CML.[63]

Monitoring of MRD in CML: Clinical Recommendations

Both the ELN and the NCCN recommend assessing MRs every 3 months (Fig 3).[63,64] *BCR::ABL1* ≤10% (MR1) corresponds to a 1-log reduction of a standardized leukemic load baseline. *BCR::ABL1* ≤1% (MR2) is a molecular equivalent of a CCyR and corresponds to a 2-log reduction in leukemic load. *BCR::ABL1* ≤0.1% (MMR or MR3) corresponds to a 3-log reduction in leukemic burden. DMR includes MR4 (*BCR::ABL1* ≤0.01%), MR4.5 (*BCR::ABL1* ≤0.0032%), and MR5 (*BCR::ABL1* ≤0.0001%). MR is defined at specific time points and divided into three categories: optimal, warning, and resistance, with a specific focus on the first 3 to 12 months after initiation of TKI treatment.[63,64] Optimal responders do not require treatment modification unless they qualify for TKI discontinuation. Resistance mandates a change in therapy guided by results from *BCR::ABL1* kinase domain (KD) mutation analysis. Warning corresponds to a situation where *BCR::ABL1* transcripts decrease at or below the 1% IS level after 1 year of treatment, but MMR is not achieved. Overtime, the warning category may remain as such or evolve toward either resistance or an optimal response with a longer treatment duration. However, the likelihood of reaching DMR levels in the absence of any TKI treatment modification is low.[65]

Long-term TFR with continued optimal MR off-therapy is currently the most optimal benefit of CML TKI treatment, and a sustained DMR is one of the prerequisites for TKI discontinuation.[66] ELN minimal criteria for safely stopping TKIs include (1) CML in first chronic phase (CP); (2) TKI taken first or second line providing that treatment change was driven by intolerance; (3) at least 5 years of treatment with the first-generation TKI imatinib or 4 years with second-generation TKIs dasatinib, nilotinib or bosutinib; and (4) at least 2 years of sustained MR4 or better.[63] NCCN selection criteria for TKI discontinuation are less stringent: At least 3 years of treatment are requested, including at least 2 years of sustained MR4 or better.[64] Patients qualifying for TKI discontinuation have a long-term TFR chance of 50%, but prolonged DMR is associated with better TFR probabilities.[67] On TKI discontinuation, MRD monitoring is key as relapse is defined as a loss of MMR, which triggers TKI resumption. Once TKIs are discontinued, it is recommended to monitor MRs monthly during the first 6-12 months as the majority of molecular relapses (about 85%) occur within this time frame and to continue subsequent monitoring every 3 months.[66]

WHAT PATIENTS NEED TO KNOW ABOUT MRD

MRD testing is common, but not universal. Provider education on appropriate testing and MRD quantification is needed as well as improved access to MRD testing. The main barriers to MRD assessment for patients are cost, insurance approval, and the proximity to tertiary care. Consensus is lacking on the timing of testing during treatment, and serial measurements can help with ambiguity in MRD test results. The turnaround time for the three major MRD technologies is quite different. MFC-MRD is usually assessed on the same day the bone marrow sample is collected. qPCR can be done from frozen tissue material and therefore typically is stored for some days until sufficient samples are collected to run an MRD assay. NGS also usually uses frozen tissue samples, and current methods require time for sample and library preparation, high coverage sequencing, bioinformatic medical analysis, and reporting. Thus, results are available most quickly with MFC, after a few days with qPCR, and after 2-3 weeks with NGS.

Patients should be informed that MRD is one of the several prognostic markers and contributes to decision making in concert with other prognostic information. Patients with AML should understand that an appropriate MRD marker may not be available for all patients, that the MRD technology varies depending on the type of AML, and that the MRD markers may change over time. After two cycles of treatment, MRD may be used to decrease treatment intensity, whereas at the end of treatment and during follow-up, MRD results may be used to increase treatment intensity. Patients with ALL should be aware of the major impact of MRD measurements on clinical decision making. Changes in treatment regimens, the decision to proceed with allogeneic stem-cell transplant, and how much therapy to give before stem-cell transplant are all based on the presence or absence of MRD. Patients with CML should understand that MRD reflects the sensitivity of the leukemic cells to TKIs and influences treatment decisions and thus the importance of a high-quality MRD monitoring on a regular basis. However, patients should be informed that intrinsic variations of the qPCR assay may be devoid of biological and clinical relevance as a minor increase in *BCR::ABL1* transcripts because of technical aspects may be a source of anxiety.

PERSPECTIVES IN MRD MONITORING

MRD monitoring in ALL, particularly in pediatric patients, has long been established as part of standard of care. It is well understood that residual MRD is a poor prognostic marker, and blinatumomab has become the first FDA-

approved agent to treat MRD. Clinical trials are underway investigating the usage of other agents for the treatment of MRD, with the end point being MRD negativity. Positive results could lead to more approvals for agents to target MRD, including inotuzumab for B-ALL, daratumumab for T-ALL, and ponatinib for Ph+ ALL. As we gain additional evidence that MRD negativity correlates with improved outcomes, MRD is more frequently being adapted as a surrogate end point for clinical trials, which could speed the approval process for novel agents. One area of unmet need in MRD monitoring for ALL is the detection of isolated extramedullary or CNS disease. Isolated extramedullary relapse has been found to be a major mechanism of blinatumomab failure,[68] and isolated CNS relapse is a well-known phenomenon in ALL. It remains unknown whether blood-based MRD assessments, which rely on circulating leukemia cells, can detect isolated extramedullary or isolated CNS disease. New techniques for MRD monitoring include measuring cell-free DNA and DNA methylation profiling. These methods may overcome the limitations of using cell-based assays to follow extramedullary-only disease, and preliminary evidence suggests that these assays are able to detect CNS disease through blood measurements.[69]

Although standardization of *BCR::ABL1* monitoring and ALL-MRD is well established, standardization of MRD assessment in AML is one of the major tasks for the next few years. New methods of MRD quantification are currently emerging for all leukemias.[70] Transcript monitoring by digital PCR offers a greater precision than qPCR and can also be used to detect mutations in the target genes such as the *BCR::ABL1* KD. DNA PCR can be standardized; it offers a greater sensitivity than RNA PCR (up to 10^{-6}) and enables leukemic cell detection, in which the target transcript is transcriptionally silent. However, it requires the sequencing of breakpoints and primer design on an individual basis. There are several attempts to identify residual leukemic stem cells (LSCs) by flow cytometry, but there may be variations in surface markers among individuals, and to our knowledge, none of current candidate markers have a 100% specificity. Spectral flow cytometry allows evaluation of many more antigens than conventional flow cytometry, possibly leading to robust, reproducible panels that require fewer cells for analysis. Automation of flow cytometry analysis is another critical goal for the future to improve reproducibility of AML MRD. Single-cell analyses may help better understand resistance and LSC persistence and heterogeneity. To what extent these new methods will help better predict outcomes is under evaluation.

CONCLUSION

In summary, MRD has evolved to become a critical diagnostic method that predicts disease progression and is increasingly used as an important end point in evaluating novel treatments for patients with leukemia. The science behind MRD monitoring continues to evolve, with new and more sensitive assays actively being investigated.

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The Times, They Are A-Changing: The Impact of Next-Generation Sequencing on Diagnosis, Classification, and Prognostication of Myeloid Malignancies With Focus on Myelodysplastic Syndrome, AML, and Germline Predisposition

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overview

Myeloid malignancies are a manifestation of clonal expansion of hematopoietic cells driven by somatic genetic alterations that may arise in a potential background of deleterious germline variants. As next-generation sequencing technology has become more accessible, real-world experience has allowed integration of molecular genomic data with morphology, immunophenotype, and conventional cytogenetics to refine our understanding of myeloid malignancies. This has prompted revisions in the classification and the prognostication schema of myeloid malignancies and germline predisposition to hematologic malignancies. This review provides an overview of significant changes in the recently published classifications of AML and myelodysplastic syndrome, emerging prognostic scoring, and the role of germline deleterious variants in predisposing to MDS and AML.

INTRODUCTION

Dr Janet Rowley first described a series of chromosomal abnormalities associated with specific hematologic malignancies in the 1970s laying the groundwork for establishing myeloid malignancies as a genetic disease.[1] However, it was not until 2001 when the third edition of the WHO classification incorporated karyotype as defining criteria for subtype of AML,[2] moving away for the first time from the morphologically defined diagnoses laid out in the French American and British (FAB) classification. In contrast to this slow pace of incorporating genomic data into clinical diagnosis, driven by easy access to next-generation sequencing (NGS) technology, the past two decades have seen almost revolutionary progress in incorporating genomics into disease diagnosis, classification, and risk stratification.[3-5] Furthermore, as our understanding of the pathogenesis of myelodysplastic syndrome (MDS) and other myeloid malignancies continues to improve, we now know that there are germline variants that determine not just predisposition to hematologic malignancies but also our choice of initial therapy and decision to transplant. The review provides an overview of how the ever-expanding array of genomic data affect classification of myeloid malignancies, risk stratification of MDS, and evaluation for germline predisposition to hematologic malignancies.

UNDERSTANDING THE 2022 WHO AND INTERNATIONAL CONSENSUS CLASSIFICATION OF MYELOID NEOPLASMS

For reasons outside the scope of discussion within this manuscript, two different updates were published on the classification of hematopoietic tumors. The International Consensus Classification (ICC) retained the process of seeking input from the Clinical Advisory Committee (CAC) and published the outline of its classification in the journal *Blood* in 2022.[6] A significant proportion of the ICC authors have contributed to the previous WHO classifications. Since the publication of the outline in *Blood*, additional and more detailed manuscripts on specific categories of myeloid malignancies and leukemias have been published by the ICC authors. In contrast, the WHO identified editorial board members who in turn formed a multidisciplinary team of authors to generate the fifth edition of the WHO classification (WHO-5). An outline of WHO-5 was published in 2022 in the journal *Leukemia*.[7] A beta version of the blue book with additional details is available online; publication of the hard copy of the monograph is imminent. There is minimal overlap between the authors who contributed to the previous editions of WHO and WHO-5.

Simultaneous publication of two different classifications has understandably created much confusion and

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PRACTICAL APPLICATIONS

- Genomic characterization determines diagnosis, classification, and prognostication of the myeloid malignancies myelodysplastic syndrome (MDS) and AML.
- Recognizing genetic lesions as invariable determinants of disease biology allows for a diagnosis of specific types of myeloid malignancies independent of traditional morphologic criteria such as presence of ring sideroblasts (*SF3B1* mutation), dysplasia (chronic myelomonocytic leukemia), or specific blast counts (AML with defining cytogenetic abnormalities). More commonly evaluated genetic lesions are listed in Table 1.
- Multiple models have shown that incorporation of molecular data generates prognostic scores that outperform older models such as International Prognostic Scoring System and revised IPSS in predicting disease progression in MDS. It is, therefore, recommended that molecular data should be integrated into decision making for MDS clinical care including eligibility for clinical trials.
- It is now recognized that germline predisposition to myeloid malignancies may exist independent of any syndromic presentation. Testing for germline variants should be performed on nonhematopoietic tissue using specifically designed panels on the basis of clinical findings (including a thorough family history).
- Identifying germline variants has a significant impact on decisions regarding therapy including donor selection for potential hematopoietic stem-cell transplant.

consternation among hematologists, pathologists, and oncologists alike. Fortunately, despite the many differences between the two classifications, there are common themes that provide the rationale for the most significant differences between WHO 2016 and both the recent ICC and WHO-5 classifications. Table 2 provides the overarching classification of myeloid malignancies. We focus specifically on changes in the classification of chronic myelomonocytic leukemia (CMML), MDS, and AML. Additional changes were also seen in myeloproliferative diseases and lymphoid disease which are beyond the scope of this article.

CMML

Tremendous progress has been made in teasing out the biology of CMML in the past decade. Whole-genome sequencing coupled with single-cell analysis demonstrates linear accumulation of somatic variants in different classes of genes starting with epigenetic (*TET2*, *DNMT3A*, *ASXL1*, and *EZH2*), followed by RNA splicing (*SRSF2*, *SF3B1*, *U2AF1*, and *ZRSR2*) and finally cell signaling (*NRAS*, *KRAS*, *CBL or JAK2*). A smaller proportion of patients will also have mutation in transcription factors (*RUNX1*) and nucleosome assembly (*SETBP1*).[8,9] Two themes emerge from this treasure trove of molecular data in CMML—(1) more than 90% of the patients will have a demonstrable clonal mutation in their hematopoietic stem cells and (2) the complement of mutation will determine the dysplastic versus proliferative phenotype of CMML in any given patient. Thus, both the ICC and WHO-5 integrate genetic mutations into the diagnostic criteria for CMML. Furthermore, when a mutation is present, a diagnosis of CMML can now be made with a lower monocyte count (0.5 to $<1 \times 10^9$/L, oligomonocytic), provided the relative monocyte count is >10%. The ICC requires the variant allele frequency (VAF) of the somatic mutations to be >10%. In as much as somatic mutations are part of the diagnostic criteria for CMML, WHO-5 provides recommendations on minimal genes to be included in the workup for possible CMML without specifying a VAF threshold to establish clonality. Finally, both ICC and WHO-5 recognize that the more myeloproliferative CMML presenting with WBC $>13 \times 10^9$/L are enriched for mutations in the signaling pathways (*NRAS*, *KRAS*, *CBL*, *or JAK2*).[9] WHO-5 specifically incorporates CMML-MD and CMML-MP subtypes into the classification. Although CMML-MP is discussed in the ICC monograph, there is no recommendation on how to include this in the diagnosis topline. In contrast, and not related to the presence of genetic mutations, both classifications recognize the lack of reproducibility and clinical significance for the category of CMML-0 defined by <2% blasts in peripheral blood and <5% blasts in the bone marrow. Both classifications now eliminate this category, subsuming this category into CMML-1 (<5% blasts in the peripheral blood and <10% in the bone marrow). Finally, both classifications acknowledge challenges associated with presence of *NPM1* mutations in cases that previously met the criteria for a diagnosis of CMML.[10] However, it is likely that most of these patients will get an up-front diagnosis of AML on the basis of the lowered blast threshold in both classifications.

Clonal Cytopenias of Undetermined Significance

Clonal hematopoiesis (CH) is defined by the acquisition of somatic mutations in hematopoietic stem and progenitor cells in healthy individuals.[11] ICC and WHO-5 identify two precursor conditions, clonal hematopoiesis of indeterminate potential (CHIP) and clonal cytopenias of unknown significance (CCUS), that have been formally defined. CHIP is defined as CH mutations that occur in leukemia driver genes with VAF ≥2% in patients without cytopenias and who

TABLE 1. Genetic Variants Associated With Cytopenias, MDS, MDS/MPN, and AML

Indication	Single-Gene Mutations (NGS)	Structural Variants (karyotype, FISH, RNA-Seq)
MDS, MDS/MPN, cytopenia	*ASXL1*, *BCOR*, *BCORL1*, *CBL*, *CEBPA*, *CSF3R*, *DDX41*, *DMNT3A*, *ETV6*, *ETNK1*, *EZH2*, *FLT3-ITD*, *FLT3-TKD*, *GATA2*, *GNB1*, *IDH1*, *IDH2*, *JAK2*, *KIT*, *KRAS*, *KMT2A-PTD*, *NF1*, *NPM1*, *NRAS*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *RAD21*, *RUNX1*, *SETBP1*, *SF3B1*, *SRSF2*, *STAG2*, *TET*, *TP53*, *U2AF1*, *UBA1*, *WT1*, *ZRSR2*	
AML	Genes required for diagnosis and risk stratification: *ASXL1*, *BCOR*, *CEBPA*,[a] *DDX41*, *EZH2*, *FLT3-ITD*, *FLT3-TKD*, *IDH1*, *IDH2*, *NPM1*,[a] *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *TP53*, *U2AF1*, *ZRSR2* Other genes: *ANKRD26*, *BCORL1*, *BRAF*, *CBL*, *CSF3R*, *DNMT3A*, *ETV6*, *GATA2*, *JAK2*, *KIT*, *KRAS*, *NRAS*, *NF*, *PHF6*, *PPM1D*, *PTPN11*, *RAD21*, *SETBP1*, *TET*, *WT1*	Common fusions: *BCR::ABL1* *CBFB::MYH11* *DEK::NUP214* *MECOM::R* *KMT2A::R* *RUNX1::RUNX1T1* *PML::RARA* Rare fusions: *PRDM16::RPN1* *NPM1::MLF1 KAT6A::CREBBP RBM15::MRTF1* *ETV6::MNX1 PICALM::MLLT10 FUS::ERG RUNX1::CBFA2T3 CBFA2T3::GLIS2* *NUP98::NSD1* *NUP98::KMD5A*

Abbreviations: FISH, fluorescent in situ hybridization; ICC, International Consensus Classification; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NGS, next-generation sequencing.

[a]Mutations in *CEBPA* and *NPM1* define specific entities in ICC and WHO classifications. Additional details on the techniques and specific timing for performing the NGS assays can be found in the study of Duncavage et al.[47]

do not otherwise meet diagnostic criteria for a myeloid neoplasm (MN); when CHIP is accompanied by unexplained cytopenias, it is termed CCUS.[6,7,12]

Myelodysplastic Syndrome

Both ICC and WHO-5[6,7] have made significant changes to the classification of MDS (Table 3). The ICC retains the historical nomenclature of MDS and excess blasts (EBs). In contrast, WHO-5 transitions to the term myelodysplastic neoplasms (abbreviation MDS is retained) and increased blasts instead of EBs used in the previous classifications. Both classifications recognize CH as the foundation for MDS contributing to a spectrum of hematopoietic abnormalities ranging from CCUS to MDS. It should be pointed out that both classifications define CCUS to include not just cytopenias associated with somatic mutations with VAF >2% but also several karyotype abnormalities that would have resulted in the diagnosis of MDS, unclassifiable in WHO-4 R in the absence of morphologic dysplasia. Both classifications recognize MDS-SF3B1 mutation as a genetically defined entity with comparable diagnostic criteria. However, there is divergence in how ICC and WHO-5 approach the diagnosis of MDS in the presence of >15% ring sideroblasts without *SF3B1* mutation. In ICC, such cases would be diagnosed as MDS, NOS, provided additional criteria for diagnosis of MDS are met. In contrast, WHO-5 retains the category of MDS with low blasts and ring sideroblasts to allow inclusion of MDS cases harboring driver mutations in other RNA splicing components.[13] The impact that this might have on a small subset of patients who would potentially receive specific therapy with compounds such as luspatercept-aamt remains to be seen. Both classifications also recognize the significance of multihit TP53 alterations to identify a specific category of high-risk MDS[14] albeit with comparable but not identical definitions for identifying biallelic *TP53* mutations. A morphologic diagnosis and subclassification of MDS can be made on the basis of the blast count and the number of lineages affected by dysplasia (Table 3). Of note, although both ICC and WHO-5 have philosophical agreement on MDS and AML representing a continuum when bone marrow blast count is ≥10% (or peripheral blood blast count ≥5%), there is a difference in how MDS would be formally classified by ICC and WHO-5. In ICC, such disease in adults would be classified as MDS/AML to allow eligibility for both MDS and AML trials[15] and in WHO-5 as MDS-IB2 in the absence of fibrosis or MDS-F if there is increased bone marrow fibrosis. Of note, as written in the current beta version of WHO-5, MDS-IB1 and MDS-IB2 are subsumed into a single diagnosis of MDS-F irrespective of the peripheral blood and bone marrow blast count. Although this difference in nomenclature is likely to cause much anguish, it should be noted that a diagnosis of AML can be made if an AML defining genetic abnormality is present without reaching a threshold of 20% blasts in either classification.

TABLE 2. ICC and WHO-5 Classification of Myeloid Neoplasms

ICC	WHO
Myeloproliferative neoplasms	Myeloproliferative neoplasms includes JMML
Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions	Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangement
Mastocytosis	Mastocytosis
Myelodysplastic/myeloproliferative neoplasm	Myelodysplastic/myeloproliferative neoplasms
Premalignant clonal cytopenias and myelodysplastic syndrome	Myeloid precursor lesions, clonal hematopoiesis
	Myelodysplastic neoplasms (retained abbr MDS)
Pediatric and/or germline mutation–associated disorders	Myelodysplastic neoplasms of childhood (specific category in MDS)
	Myeloid neoplasms associated with germline predisposition (specific category in myeloid neoplasms and proliferations associated with antecedent or predisposing conditions)
AMLs	AML
Myeloid proliferations associated with Down syndrome	Myeloid proliferations associated with Down syndrome (specific category in myeloid neoplasms and proliferations associated with antecedent or predisposing conditions)
Blastic plasmacytoid dendritic cell neoplasms	Blastic plasmacytoid dendritic cell neoplasms (discussed in histiocytic dendritic cell neoplasms)
Acute leukemia of ambiguous lineage	Acute leukemias of mixed or ambiguous lineage (discussed in myeloid proliferations and neoplasms)
B-lymphoblastic leukemia/lymphoma	B-lymphoblastic leukemia/lymphoma (discussed in B-cell lymphoid proliferations and lymphomas)
T-lymphoblastic leukemia/lymphoma	T-lymphoblastic leukemia/lymphoma (discussed in T-cell and NK-cell lymphoid proliferations and lymphomas)

Abbreviations: ICC, International Consensus Classification; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndrome; NK, natural killer.

AML

Both ICC and WHO-5 have made significant changes to the classification with the intent to prioritize genetics in defining specific subtypes. Both classifications expand the category of genetically defined entities to include uncommon but AML defining cytogenetic abnormalities such as AML with t(7;12) (q36.3;p13.2)/*MNX1::ETV6* rearrangements. In the presence of these abnormalities, a diagnosis of AML can be made with a blast count of <20%. Similarly, both classifications emphasize the use of genetics rather than morphology in defining myelodysplasia-related AML. In addition to chromosomal abnormalities, both classifications have expanded to include gene mutations *in ASXL1*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2* to allow for a diagnosis of AML-MR. The ICC, but not WHO-5, also includes *RUNX1* in the group of genes that can be used to define AML with myelodysplasia-related gene mutations. In addition, the ICC mirrors the ELN2022 recommendations to generate a hierarchical classification of AML.[4] In this scheme, the presence of mutated TP53 at a VAF ≥10% would result in a diagnosis of MDS/AML (blasts ≥10%) or AML (blasts ≥20%) with mutated *TP53*. In WHO-5, such disease could be variably classified as MD-IB2, erythroleukemia, MN, secondary, etc depending on the morphology and antecedent history. The two schemes also diverge in their approach to classification of AML without defining genetic abnormalities. WHO-5 formally retains a category of AML, defined by differentiation. In contrast, the ICC uses the broad category of AML not otherwise specified (AML, NOS) with the caveat that the pathologist may continue to subclassify such cases on the basis of morphology and cytochemistry if desired. Finally, although WHO-5 retains the category of MNs, secondary to include MNs after cytotoxic therapy and MNs associated with germline predisposition, the ICC recommends the use of diagnostic qualifiers therapy-related, progressing from MDS, progressing from MDS/MPN and germline predisposition to acknowledge antecedent history and genetic background. Therefore, although much has been made for the elimination of the category of therapy-related MNs by ICC, the use of appropriate classifiers will result in comparable diagnoses if the recommendations of the two classifications are carefully followed.

UPDATING MDS PROGNOSIS IN THE MOLECULAR ERA

Early Prognostic Tools

Initially recognized as a distinct malignant disease by the 1982 French-American-British group,[16] MDSs now comprise the most common clonal myeloid disorder in the

TABLE 3. ICC and WHO-5 Classification of MDS

ICC	WHO-5
Precursor lesions Clonal cytopenia of undetermined significance	Myeloid precursor lesions Clonal cytopenia of undetermined significance
MDS with mutated SF3B1 (MDS-SF3B1) MDS with del(5q) MDS with mutated TP53	MDS with defining genetic abnormalities MDS with low blasts and SF3B1 mutation (MDS-SF3B1) MDS with low blasts and 5q deletion (MDS-5q) MDS with biallelic TP53 inactivation (MDS-biTP53)
MDS, NOS with single lineage dysplasia MDS, NOS with multilineage dysplasia	MDS, morphologically defined MDS with low blasts (MDS-LB) Subtype MDS-LB-SLD Subtype MDS-LB-MLD MDS, hypoplastic
MDS with excess blasts (MDS-EB) MDS/AML or MDS/AML with mutated *TP53*	MDS with increased blasts (MDS-IB) MDS with increased blasts-1 (MDS-IB1) MDS with increased blasts-2 (MDS-IB2) MDS with fibrosis (MDS-F)

Abbreviations: ICC, International Consensus Classification; MDS, myelodysplastic syndrome; MLD, multilineage dysplasia; NOS, not otherwise specified; SLD, single-lineage dysplasia.

world. MDS varies in natural history from mild isolated cytopenia to bone marrow failure and high risk of evolution to AML.[17] Given this range of clinical outcomes, management also varies widely: some patients may be able to undergo surveillance with peripheral blood tests for years without any therapeutic intervention while others may need aggressive monitoring, dense transfusion support, chemotherapy, and hematopoietic stem-cell transplantation (HSCT) for curative intent.

Efforts to assess disease risk and predict outcomes have evolved over time. The initial prognostication tool published in 1997 was the International Prognostic Scoring System (IPSS),[18] which incorporated bone marrow blast percentage, cytogenetic risk category, and number of cytopenias. Patients were grouped into low, intermediate-1, intermediate-2, and high-risk groups by IPSS. In 2007, the WHO classification-based Prognostic Scoring System (WPSS)[19] was published using WHO subgroups, karyotype, and transfusion requirement to stratify patients among five risk categories. Subsequently the revised IPSS (IPSS-R)[20] was published in 2012; it refined multiple features including the degree of bone marrow blast percentage, additional cytogenetic risk groupings, and increased granularity for degree of cytopenias. The number of risk categories was further divided from 4 to 5 (very low, low, intermediate, high, and very high risks). These tools, and others,[19,21-23] have been incredibly useful over time to prognosticate for patients with MDS. However, an often-cited limitation was their inability to capture all relevant disease biology in a patient, as cytogenetics is the only genetic parameter included through the early 2020s. Furthermore, their applicability in treatment-related disease is also less clear.[21]

Integration of Molecular Genetics Into MDS Diagnosis and Classification

As NGS technologies have evolved, our understanding of molecular alterations has allowed us to better appreciate their impact on disease phenotype and natural history. For example, MDS with ring sideroblasts per the 2016 WHO MN classification was defined by at least 15% ring sideroblasts of nucleated erythroid cells or at least 5% in the presence of an *SF3B1* mutation.[24] On the basis of the fact that *SF3B1* mutation is highly associated with this clinicopathologic entity,[25] classification schemas reclassified this entity in 2022 on the basis of the presence of this mutation as opposed to morphologic features.[6,7] Further complexity underlies the pathologic effect of gene mutations as different amino acid substitutions can have varying prognostic effects[26] as can variant allele frequencies. The *TP53* mutations are an excellent example of the latter[27] and have long been a harbinger of inferior outcomes. Multihit *TP53* mutations identifies aggressive disease regardless of blast count, therapy relatedness,[28,29] or IPSS-R.[14] Per the 2022 ICC, MDS/AML with *TP53* mutation is recognized as a composite disease group with 10%-19% blasts[6] given that outcomes do not appear to be affected by blast count or therapy relatedness in the presence of this dismal prognostic feature.[28]

Integration of Molecular Data Into Prognostic Schemas

Given the increasing availability and implications of molecular data in MDS, multiple molecular genetic prognostic tools have been recently published. First, the EuroMDS consortium studied a population of more than 2,000 patients with MDS to first develop a prognostic tool that

incorporated 63 clinical and genomic variables, including mutations affecting 47 genes.[30] Eight groups were identified: patients with *SF3B1* mutations, *TP53* mutations and/or complex karyotype, *SRSF2* mutations, *U2AF1* mutations associated with the deletion of chromosome 20q and/or abnormalities of chromosome 7, AML-like mutation patterns, and finally, those without specific genomic profiles. The SF3B1 and SRSF2 groups were further divided into additional groups based on comutation patterns. This model was independently validated in a cohort of 318 patients and was shown to improve prognostic assessment beyond conventional age-adjusted IPSS-R.

Next, a multicenter group built the personalized prediction model for myelodysplastic syndromes using artificial intelligence software and a cohort of nearly 1,500 patients with MDS from Europe and the United States.[31] Aside from the clinical variables included in the IPSS-R, this model included the absolute lymphocyte and monocyte counts, peripheral white blood cell count, peripheral blast percentage, patient age, and WHO 2016 subtype. Relevant molecular data included the number of mutations and presence of mutations in seven genes: *SF3B1*, *STAG2*, *RUNX1*, *RAD21*, *SRSF2*, *ASXL1*, and *TP53*. This model groups patients in the same risk strata as the IPSS-R. Again, this model was found to outperform prognostication from IPSS and IPSS-R.

The next iteration of a molecularly based prognostic schema published was the IPSS-Molecular (IPSS-M)[32] which was developed using a cohort of almost 3,000 patients with MDS. Multihit *TP53* state, *FLT3* mutations, and partial tandem deletion of the MLL gene were adverse predictors, whereas SF3B1 associated with favorable outcomes. The model, available online (https://mds-risk-model.com/), uses clinical factors, cytogenetics, and molecular features to categorize MDS across six groups (very low, low, moderate low, moderate high, high, and very high). Sixteen genes with significant prognostic value were included, as were the presence of up to 2 of 15 residual genes. Like the above models, IPSS-M improves risk stratification as compared with IPSS-R, but uniquely it offers flexibility (given the ability to note input values are missing) and a high degree of personalization (as the output value is on a continuous scale essentially unique to that person).

Finally, the GenoMed4All consortium published two stratification tools incorporating sex, one of which also incorporates molecular features.[33] This group used four different MDS cohorts with a total of more than 13,000 patients to evaluate for a prognostic effect of sex on outcomes in MDS. Specific genes and mutation pathways were more specific to women (*TP53*, *DNMT3A*) and others to men (*ASXL1*, *SRSF2*, *ZRSR2*, *DDX41*, *IDH2*, *TET2*, and *U2AF1*). In all cohorts studied, men had worse median overall survival than women. Both tools are available online (https://mds.itb.cnr.it/#/mds/home): The sex-informed prognostic scoring system uses the same variables as the IPSS-R plus age and sex, whereas the sex-informed genomic scoring system also incorporates 12 cytogenetic and 22 molecular aberrations. Both systems have the same five risk categories as IPSS-R, and about half of patients were restratified by this sex- and genomic-informed approach depending on the cohort.

The Future of MN Risk Assessment

Although currently there is no formal consensus around which of the above risk schemas to use routinely, the guidelines[34] all favor universal incorporation of molecular data for clinical care and ongoing assessment for clinical trial eligibility and risk stratification. The different schemas vary in the data they require, risk categories, and availability of online platforms, but ongoing interest and consensus are building. One further complicating issue remains the notion that there is less clear value in using a blast percentage cutoff to distinguish MDS and AML, given the increasing evidence that disease genetics drives phenotype,[15,35] including blast count. If MDS and AML are to be considered the same disease in certain blast percent ranges[6] and disease genetics are the ultimate harbinger of outcome, the future may require a unifying tool to stratify risk among the spectrum of MNs. As MDS and AML continue to be studied, we will increasingly appreciate the relationship between disease genetics, phenotype, and risk. Finally, now that CCUS is a pathologic/genetic disease entity, there is the need to prognosticate for these patients as to who is more likely to evolve to overt myeloid disease requiring therapeutic intervention. Future scoring systems to delineate this risk will be welcome in the clinic.[36]

INHERITED PREDISPOSITION TO HEMATOLOGIC MALIGNANCY SYNDROMES: RECOGNITION AND IMPLICATIONS FOR THE PRACTICING CLINICIAN

A growing subset of patients with cancer are now recognized to carry a germline genetic predisposition to malignancy. Before the availability of clinical genetic testing, recognition of genetic predisposition to malignancy relied on syndromic clinical features or concerning family history. The clinical phenotypes of these genetic conditions are highly variable, and patients with genetic predisposition to malignancy often lack apparent syndromic features.[37] Some genetic predisposition conditions, such as *CEBPA* or *DDX41* or *TP53*/Li Fraumeni, only manifest with cancer without associated syndromic features. The diagnosis of genetic predisposition to malignancy informs treatment decisions and clinical monitoring. Because of limitations of space, we will focus on germline genetic predisposition to myeloid malignancy, but many of these concepts are broadly relevant for genetic predisposition to malignancies more broadly.

Classification of Germline Genetic Predisposition to Myeloid Malignancy

Genetic predisposition to myeloid malignancy was recognized as a distinct category in both the 5th edition of the World Health Organization Classification of Hematolymphoid Tumors[7] and the 2022 International Consensus Classification of Lymphoid and Myeloid Neoplasms.[6] Both classifications include categories for hematologic neoplasms with germline predisposition: (1) without other organ dysfunction, (2) with a constitutional/preexisting platelet disorder, and (3) with potential organ dysfunction or affecting multiple organ systems, which includes bone marrow failure syndromes, RASopathies, and Down syndrome. Additional or provisional conditions are also discussed. Appending a qualifier to the diagnosis of MDS or AML (MN with germline pathogenic variants in [gene]) allows a scalable diagnostic approach that can adjust as new genes are identified in this rapidly growing field.

Clinical Implications of Germline Genetic Predisposition to Myeloid Malignancy

Diagnosis of genetic predisposition to myeloid malignancy informs clinical care. Many genetic predisposition conditions require tailored therapy to avoid excessive treatment-related toxicities. For example, patients with Fanconi anemia, a condition caused by mutations in genes functioning in DNA repair, are sensitive to genotoxic agents and required individualized therapy for their malignancies.[38] Some genetic predisposition conditions are associated with comorbidities that increase risks of treatment-related morbidities. Patients with telomere biology disorders (TBDs), also known as dyskeratosis congenita, are prone to develop pulmonary fibrosis, liver disease, and arteriovenous malformations.[39] Patients with TBD benefit from evaluation for such complications to guide treatment choice, and clinical trials for specific transplant regimens for these patients are underway. Patients with germline *GATA2* mutations are at risk for severe infectious complications because of immune dysfunction, so some patients may benefit from early HSCT.[40] Some genetic predisposition conditions are associated with both hematologic and solid tumors, so diagnosis allows initiation of appropriate surveillance, particularly since the risk of secondary malignancies may be elevated after chemotherapy or radiation. For some of these genetic predisposition conditions, such as inherited bone marrow failure syndromes, HSCT is the curative treatment of choice for myeloid malignancies. Patients with genetic predisposition conditions may also be prone to emergence of additional leukemic clones unless treated with a HSCT. Diagnosis of a genetic predisposition condition allows testing of potential HLA-matched family donors to avoid choosing an affected, but clinically unrecognized, donor. For young families, early diagnosis provides opportunities for family planning.

Recognition of genetic predisposition to myeloid malignancy also guides diagnosis of hematologic malignancies. Many of these conditions are characterized by a high level of baseline dysplasias that may be mistaken for malignancy.[41] For example, patients with germline variants in *RUNX1* or *GATA2* may have megakaryocyte dysplasia without malignancy. Early diagnosis before the development of malignancy allows a baseline marrow examination for comparative evaluation of increasing dysplasia. For patients with genetic bone marrow failure syndromes, the observation of progressive cytopenias with increasing marrow cellularity warrants further evaluation for potential clonal evolution. Many of these genetic predisposition conditions are associated with bone marrow failure, which further complicates the diagnosis of myeloid malignancy. The clinical evaluation of clonal abnormalities may also be affected by an underlying germline predisposition condition. For example, clonal deletions of 20q are frequently observed in patients with Shwachman Diamond syndrome but are not associated with increased risk of clonal evolution.[42] Indeed, such clones result in adaptive somatic reversion of the germline genetic abnormality.[43,44]

Caution is needed in clinical decision making on the basis of germline variants. The identification of a heterozygous mutation in a gene associated with a recessive cancer predisposition syndrome often elicits consternation. An example is the frequent observation of heterozygous mutations in genes causing Fanconi anemia, a DNA repair disorder, in patients with myeloid malignancy. No increased cancer risk was identified in a study including older relatives of patients with Fanconi anemia, with the exception of the known dominant solid tumor predisposition genes *BRCA1*, *BRCA2*, *PALB2*, *BRIP1*, and *RAD51C*.[45] However, orthogonal testing for chromosomal breakage may be helpful to assess for potential pathogenic variants on the second allele. For HSCT using related donors, potential clinical implications of donor mutations in genes predisposing to nonhematologic malignancies remain to be clarified.

Whom to Screen for Germline Genetic Predisposition to Myeloid Malignancy

In the past, recognition of a germline genetic predisposition condition relied primarily on clinical findings and family history; however, multiple studies have consistently demonstrated that a significant subset of patients are diagnosed by genetic testing without any other clinical suspicion for a predisposition condition. Although presentation with a myeloid malignancy in childhood or early adulthood is a flag for a potential germline genetic condition, patients with germline genetic predisposition may present with malignancy at any age.[46] Indeed,

patients with germline mutations in *DDX41* present with malignancies at older ages.[44] Patients with telomere biology disorders also often first present at older ages.[45]

A detailed clinical history and examination may identify clues to an underlying genetic predisposition condition. A preceding history of unexplained cytopenias or bone marrow failure raises suspicion for a genetic predisposition condition. Many, but not all, genetic predisposition conditions may have associated clinical findings such as congenital anomalies, short stature/poor growth, recurrent infections, or a history of excessive sensitivity to genotoxic treatments. Patients with telomere biology disorders may develop liver disease or pulmonary fibrosis. Some findings are nonspecific such as a history of eczema (germline *RUNX1*, Shwachman Diamond syndrome), warts or lymphedema (*GATA2* syndrome), easy bleeding (*RUNX1*, *ANKRD26*, *ETV6*), or skin hyper/hypopigmention (Fanconi anemia, TBD) but warrant attention in patients presenting with myeloid malignancy. A personal or family history of malignancy is also a red flag, especially a history of more than one malignancy in a given individual, an unusually young age at malignancy diagnosis, multiple family members with malignancy, or excessive sensitivity to genotoxic therapies. A related donor with a cytopenia(s), abnormal marrow examination, or poor stem-cell mobilization also warrants further evaluation for a germline genetic predisposition.

Laboratory testing is guided by clinical findings. A preceding history of unexplained macrocytosis may flag a genetic predisposition to myeloid malignancy. Chromosomal breakage testing for Fanconi anemia is recommended for pediatric and young adult patients with bone marrow failure or MDS or adults with a concerning history/physical examination or myeloid malignancy and a history of squamous cell carcinoma of the head, neck, GI tract, or vulva. Telomere length testing is also helpful to diagnose patients with TBD. Caution is needed to interpret telomere length in adults and should be integrated with genetic testing. Of note, chromosomal breakage or telomere length testing are difficult to assess in patients with peripheral blasts or recent genotoxic therapy. Screening for immunologic abnormalities, including immunoglobulin levels and lymphocyte subsets (T cells, B cells, and natural killer cells), can be helpful to flag germline conditions associated with immune deficiencies and is best sent before initiation of therapy.

Some gene mutations may be of either somatic or germline origin, so identification of a variant in such a gene in a somatic cancer genetic panel needs further assessment. Persistence of a mutation at a high VAF in remission may flag a germline origin. The gold standard to establish a germline variant is to test a nonhematopoietic tissue such as fibroblasts from a skin biopsy. DNA from saliva, hair follicles, and nails may contain blood cells and are not currently recommended to differentiate somatic versus germline mutations for hematologic malignancies. Somatic genetic panels are not interchangeable with germline genetic panels because of differences in genes included, regions sequenced within a given gene, differences in analytic pipelines for somatic versus germline variant curation, limitations in analysis of copy number variants/gene deletions, and confounding effects of somatic reversions.

Since the risk of a genetic predisposition condition is high in pediatric and young adult patients with myeloid malignancy, genetic evaluation is increasingly integrated into the diagnostic workup. Clinical practice is evolving for adults with myeloid malignancy as studies continue to emerge demonstrating genetic predisposition in increasing numbers of older patients. The field is rapidly advancing, so consultation is recommended with centers experienced in the diagnosis and clinical care of patients with genetic predisposition to myeloid malignancy.

In conclusion, genetic mutational profiling is increasing our understanding of the biology of myeloid malignancies—both through somatic and germline genetics. This added knowledge is now used for possibly earlier diagnosis, more precise disease classification and risk stratification, and in some instances, to guide therapeutic decision making in a biologically rational way. The next frontiers include unification of classification schema, access to a broader array of therapeutics, and personalized treatment options for all lower- and higher-risk myeloid malignancies.

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Embracing Myeloma Chimeric Antigen Receptor-T: From Scientific Design to Clinical Impact

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Overview

Despite recent advancement of treatment strategies in multiple myeloma (MM), patients with relapsed/refractory MM disease, particularly after triple-class refractoriness, continue to have poor prognosis. Chimeric antigen receptor (CAR-T) cells were developed and applied to improve outcomes in this setting, and two products, idecabtagene vicleucel and ciltacabtagene autoleucel, both targeting B-cell maturation antigen, have been approved by the Food and Drug Administration in the United States and European Medicines Agency in Europe. Both have shown unprecedented clinical outcomes with high response rate and prolonged progression-free survival and overall survival in this patient population with grim prognosis. Currently, further investigations are ongoing for CAR-T targeting different tumor antigens such as G protein–coupled receptor, class C, group 5, member D or with different combinations of intracellular signaling domains, as well as fourth-generation CAR-T with antigen-unrestricted inducible cytokines. Although CAR-T therapies hold hopes and enthusiasm from the myeloma community, several hurdles remain before these treatments become available for all patients in need. These barriers include CAR-T-cell manufacturing availability, access to administering centers, financial cost, caregivers' availability, and socioeconomic and racial disparities. Expanding clinical trial eligibility criteria and real-world data collection and analysis is crucial to understand the efficacy and safety of CAR-T in the patient cohort who tends to be excluded from current trials.

INTRODUCTION

The treatment landscape of patients with multiple myeloma (MM) has significantly evolved in recent years, leading to unprecedented survival rates.[1] Nevertheless, MM remains an incurable disease and patients continue to relapse requiring further therapy. Importantly, patients who have been previously exposed to the three main classes of agents, namely, proteasome inhibitors, immunomodulatory derivatives (IMIDs), and anti-CD38 monoclonal antibodies, have limited treatment options and poor survival.[2] In this setting of unmet medical need, novel T-cell–redirecting agents, with high clinical efficacy, have been developed, including chimeric antigen receptor (CAR-T) cell therapies and bispecific antibodies targeting not only the B-cell maturation antigen (BCMA) but also G protein-coupled receptor, class C, group 5, member D (GPRC5D) or Fc receptor homolog 5, among others.[3-7]

Here, we discuss the design and biologic principles of CAR-T therapy for MM, clinical data, and barriers to access to CAR-T therapy.

THE DESIGN AND BIOLOGIC PRINCIPLES OF CAR-T CELLS FOR MM

First proposed by Eshhar et al,[8] CARs enable T cells to recognize and kill their targets expressing the cognate antigen through engagement of an antibody-derived single-chain variable fragment independent of major histocompatibility complex (MHC) restriction. CARs have evolved over the years: first-generation CARs only provided a T-cell receptor activating signals through expression of CD3ζ. Second-generation CARs added the intracellular domain of the costimulatory molecule, CD28, to deliver both activating signals and costimulatory signals as to enhance T-cell efficacy and persistence,[9] whereas the third generation modified the intracellular signaling domains with various costimulatory molecules from 4-1BB, CD28, or OX-40 to enhance performance.[10-12] These modifications in each generation of CAR-T cells have significantly improved the overall efficacy, and two products have obtained a Food and Drug Administration (FDA) approval to treat relapsed/refractory MM. However, despite the initial success, several challenges remain to enhance the therapeutic efficacy of this approach (Fig 1).

Identification of Suitable Myeloma Targets

BCMA is a receptor protein expressed on all healthy and malignant plasma cells and is a receptor for APRIL ligands, which regulate the development of B-cell immunity by supporting antibody production, immunoglobulin class switching, and plasma cell

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PRACTICAL APPLICATIONS

- Patients with triple-class exposed (TCE) relapsed/refractory multiple myeloma have an unmet medical need with poor outcomes when treated with standard-of-care regimens. In this setting, B-cell maturation antigen (BCMA)–directed agents and, in particular, BCMA-directed chimeric antigen receptor (CAR-T) cells have demonstrated encouraging clinical efficacy, leading to the approval of two CAR-T-cell constructs (idecabtagene-vicleucel [ide-cel] and ciltacabtagene-autoleucel [cilta-cel]).
- ide-cel and cilta-cel have also been evaluated in early disease settings in the population of unmet clinical need. Indeed, evidence from two different phase 3 randomized trials has demonstrated that treatment with BCMA-CAR-T-cell therapies is superior to standard-of-care regimens in the setting of patients with TCE early relapse disease (KarMMa-3 trial—ide-cel) and in patients with early relapse and lenalidomide-refractory disease.

homeostasis and proliferation.[13,14] It has a favorable therapeutic index as its selective expression is limited to late-stage B cells, short-lived proliferating plasmablasts, and long-lived plasma cells. Importantly, expression is increased on malignant compared with healthy plasma cells.[15] Interestingly, expression of BCMA wanes over time because of enzymatic cleavage of the protein via gamma-secretase cleavage of the extracellular domain. Lower antigen expression caused by either shedding or downregulation has been reported as one mechanism of relapse in BCMA and other CAR-T-cell therapies.[16,17] To this effect, gamma secretase inhibitors[18] alone or in combination with all trans-retinoic acid[19] are being used to increase BCMA surface antigen expression and improve therapeutic efficacy of CAR-T-cell therapy.[20] In fact, KarMMa-7 is currently exploring several adjunctive agents to enhance the overall efficacy of BCMA CAR-T including a novel gamma-secretase inhibitor. An alternative approach to maximize efficacy has been to generate CARs to additional targets.

GPRC5D is another intriguing target; its expression is limited to malignant plasma cells as well as keratinocyte-derived tissues such as nail, skin, and hair follicles. One study observed that its expression levels correlated with a shorter progression-free survival (PFS).[21] Early clinical trials show evidence of promising clinical activity even in patients previously treated with BCMA therapies.[3,22]

CD38 has proven to be an excellent target of monoclonal antibodies and is also being examined in CAR-T cells.[23] Its targeting with monoclonal antibodies has dramatically changed the treatment paradigms in myeloma. However, in contrast to the abovementioned targets, CD38 expression is not only limited to plasma cells but also found on B cells, activated T cells, and erythrocytes.

There are also other targets being explored. CD229 is a SLAM receptor present on the surface of MM plasma cells in chemoresistant myeloma and is relatively absent on normal plasma cells.[24] In contrast to BCMA whose expression is mostly limited to the terminally differentiated plasma cells, CD229 is also found on transitional and memory B cells.[25,26] CD19 is also being explored on the basis of data, suggesting that the postgerminal memory B cell is, in fact, the clonogenic malignant precursor. As such, targeting this stem cell could potentially more effectively eradicate the disease, and this is being investigated in the clinical setting.[27-30]

Intracellular Signaling Domains

The intracellular signaling domains ultimately determine the efficacy and persistence of CAR-T cells. Although several costimulatory molecules exist such as CD28, 4-1BB, ICOS, and OX40, CD28 and 4-1BB are the two that have primarily been used. CD28-CD3ζ generates tonic signaling and increased

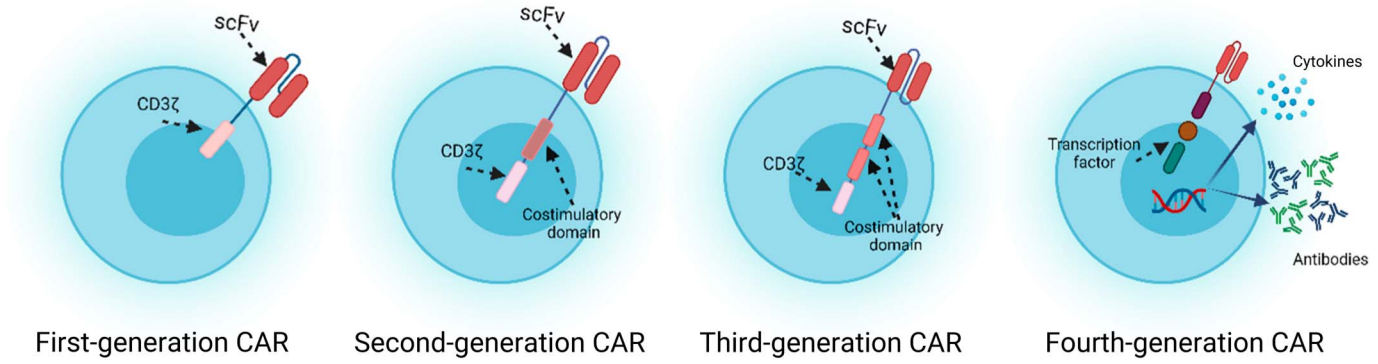

FIG 1. Main characteristics of different CAR-T generations (made with BioRender.com). CAR, chimeric antigen receptor; scFv, single-chain variable fragment.

NFkB activation, resulting in high cytotoxic efficacy and significant T-cell expansion but limited persistence, and likely generates a more severe cytokine release syndrome (CRS).[31,32] By contrast, 4-1BB skews toward greater effector memory (T_{EM}) and stem-cell memory (T_{SCM}) T cells, which translate into enhanced persistence and less exhaustion. Mechanistically, 4-1BB activates mammalian target of rapamycin and upregulates the antiapoptotic genes, Bcl-xL and BFL-1,[33] with a metabolic profile favoring fatty acid oxidation and mitochondrial biogenesis.[34] By contrast, CD28 leads to greater glycolysis and a more exhausted phenotype.[35] In summary, CD28 CAR-T cells show greater cytotoxicity but less persistence, whereas 4-1BB results in less cytotoxicity but greater persistence.

Third-generation CARs attempted to titrate the activation of CD28 with persistence of 4-1BB. Preclinical data demonstrated that combined stimulation with both CD28 and 4-1BB generated more efficient CAR-T cells. It increased cytotoxicity and the production of interferon-gamma, tumor necrosis factor-alpha, and granulocyte-macrophage colony stimulating factor, upregulated the antiapoptotic protein, Bcl-X_L, and prolonged the activation of the phosphoinositide 3-kinase/serine/threonine specific protein kinases pathway.[11] Additional preclinical studies showed that combining 4-1BB with a modified CD28 domain resulted in better killing, antigen recognition at lower densities, greater polyfunctional cytokine production, and greater persistence.[36]

A more recent advance has been the development of: T cells redirected for antigen-unrestricted cytokine-initiated killing (TRUCKs) also considered the fourth generation of CAR-T cells. This concept was initially developed as a strategy to overcome the profound immunosuppressive environment of solid tumors but has potential applicability even for hematologic malignancies.[37] The TRUCKs are equipped with tumor-specific CARs and a nuclear factor of activated T cells-inducible expression cassette coding for a transgenic protein, typically a cytokine. After TRUCKs bind to the antigen, CAR signaling induces NFAT phosphorylation, which eventually drives transgene expression. The inducible cytokines that have been coengineered into CAR-T cells include IL-12, IL-15, and IL-18.[38] In preclinical models, TRUCKs have shown superior antitumor efficacy compared with early-generation CARs coadministered with the exogenous cytokine. This approach allows for high local expression of the cytokine to maximize antitumor efficacy and minimize toxicity.

T-Cell Activation and Exhaustion

As the limitations of CAR-T cells become more apparent, increasing interest exists in understanding the determinants of long-term disease control. In addition to biologic attributes that can be conferred by the CAR construct itself, the overall health of T cells plays a critical role in mediating both cytotoxicity and persistence. Chronic antigen exposure that defines a cancer-bearing host has been shown to induce a state of T-cell exhaustion characterized by reduced effector function, limited cytokine secretion, and increased expression of inhibitory receptors to generate exhausted T cells known as Tex.[39] However, Tex contain subsets of proliferation-competent precursors and also a less proliferative, terminally differentiated effector T cell. Wherry et al recently mapped out a hierarchical model using acute and chronic infection of lymphocytic choriomeningitis virus as a model and identified four subsets: (1) Tex^{prog1}—hypoproliferative, stem-cell–like progenitors located primarily in lymphoid tissues (Tcf-1^{+++}, PD-1^{low}, Ki67^{low}); (2) Tex^{prog2}—proliferative progenitors that transition from lymphoid tissue to blood (Tcf-1^{++}, PD-1^{low}, Ki67^{int}); (3) Tex^{int}—an intermediate effector subset found in blood (Tcf-1^{low}, PD-1^{int}, Ki67^{high}); and (4) Tex^{term}—a hypoproliferative, terminal effector population with low persistence absent in the blood and only found in blood accessible organs (Tcf-1^{-}, PD-1^{high}, Ki67^{low}).[40] These subsets are increasingly being recognized as critical to understand the quality and efficacy of the CAR-T-cell response (Fig 2).

A major barrier to clinical responses following CAR-T cells has been T-cell persistence. On infusion, CAR-T cells undergo rapid proliferation with associated methylation changes, resulting in repression of genes responsible for the memory phenotype and activation of a gene pattern consistent with a more exhausted phenotype.[41] Prevention of the transition to an exhausted phenotype is a major target of potential intervention to enhance persistence and possibly clinical outcomes. Evidence that the T-cell health dictates clinical outcomes has also been elegantly shown in patients with chronic lymphatic leukemia treated with CD19 CAR-T cells.[42-44] In analyzing the CAR-T products from responders and nonresponders, they reported that responders possessed a stem-cell memory, nonexhausted phenotype and exhibited decreased glycolytic metabolism. Interestingly, the responders also had higher expression of STAT3 and signaling mediators and targets including IL-6 and IL-17, suggesting a critical role of STAT3 activation in generating more potent, less differentiated T cells.

In summary, as CAR-T-cell therapies continue to demonstrate remarkable clinical efficacy, there is an increasing awareness of their limitations. To enhance the therapeutic benefit, research is focusing on new surface targets and cell persistence. Persistence is being addressed by modifications of the intracellular signaling domains beyond CD28 or 4-1BB and increasing our understanding of the importance of the overall biology of T-cell exhaustion and its metabolic state. A summary of the main mechanism of resistance and potential avenues for improvement is included in Table 1.

CLINICAL IMPACT AND SEQUENCING OF CAR-T THERAPY FOR MM

Currently, two different BCMA-directed CAR-T-cell products have been approved for the treatment of patients with

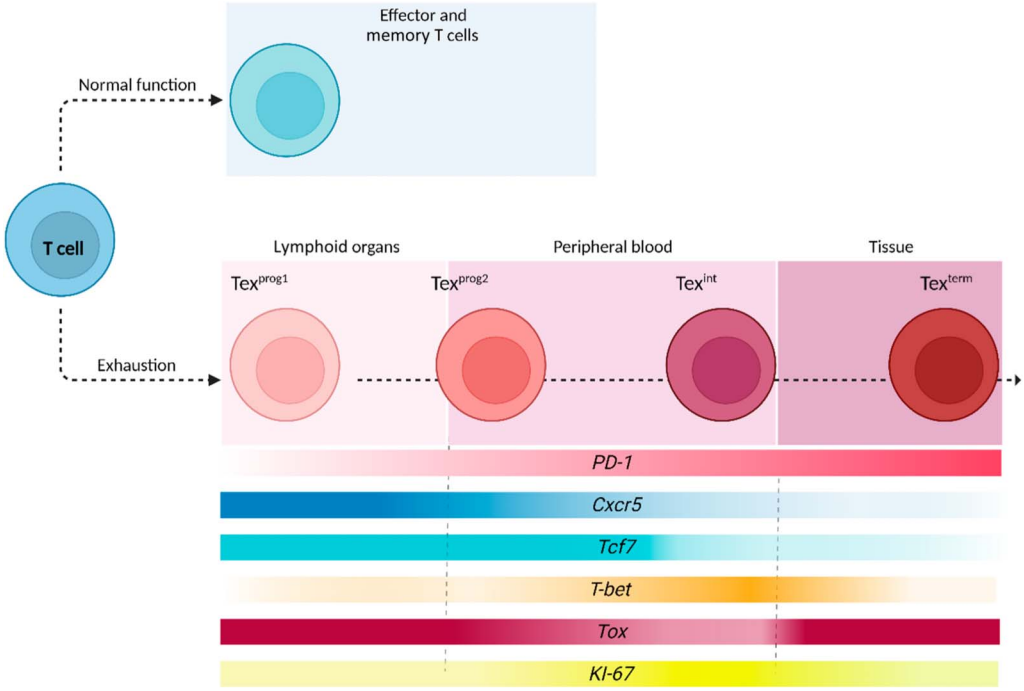

FIG 2. Schematic representation of progressive T-cell exhaustion characterized by reduced effector function, limited cytokine secretion, and increased expression of inhibitory signals in the setting of chronic antigen exposure.

triple-class exposed (TCE) relapsed/refractory MM (RRMM), a population with a high unmet clinical need.

Idecabtagene-vicleucel (ide-cel, bb2121, ABECMA) was the first cellular therapy approved for the treatment of TCE RRMM on the basis of the results of the phase 2 pivotal KarMMa trial.[45] Overall, 128 patients received a single ide-cel infusion. The population of patients was heavily pretreated, with a median number of six previous lines (range, 3-18), and 84% of them were triple-class refractory. The overall response rate (ORR) was 73% among all treated patients and 81% in those receiving a single infusion at the target dose level of 450 $\times$ 10^6 CAR-T+ cells with 33% and

TABLE 1. Potential Mechanism of Resistance to CAR-T-Cell Therapy and Potential Avenues for Improvement

Mechanism of Resistance	Potential Solution	Rationale
Heterogeneity in target expression in the tumor	Dual targeting (ie, BCMA-CD38, BCMA-CD19)	Will target tumor cells with low expression of BCMA
	Combinations with gamma-secretase inhibitors	Increase target density in the tumor cell
Loss of expression of BCMA because of antigen loss or mutations	Development of CAR-T targeting different antigens such as GPRC5d, among others	
Lack of expansion	Increase memory T-cell phenotypes in the product	Incubation with PI3K inhibitors
	Higher CD4/CD8 ratio	
Loss of persistence	Reduce immunogenicity of CAR constructs	Humanized constructs
	Increase proportion of memory T-cell subsets	
Impaired functional persistence because of T-cell exhaustion	Combinations with immunomodulatory drugs such as IMIDs, checkpoint inhibitors, and anti-CD38 monoclonal antibodies, among others	
Impaired T-cell fitness in the apheresis product	Avoid previous therapies that may alter T-cell composition or decrease proportion of T cells	Avoid high-dose alkylators
		Possibility to prime T cells before apheresis to increase functionality
Immunosuppressive microenvironment	Third-generation CAR-T cells or TRUCKs	

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; GPRC5d, G protein–coupled receptor, class C, group 5, member D; IMIDs, immunomodulatory derivatives; PI3K, phosphoinositide 3-kinase; TRUCKs, T cells redirected for antigen-unrestricted cytokine-initiated killing.

39% of complete responses (CR), respectively. The median PFS was 8.8 months in the overall population and was longer in patients receiving the target dose (median PFS, 12.1 months). The median overall survival (OS) was 24.8 months (95% CI, 19.9 to 31.2). Safety was manageable with CRS reported in 84% of patients, with the majority of events being grade 1 or 2. Neurologic complications were less common, reported in 18% of patients and mostly grade 1-2. Cytopenias were frequent, not dose-related, with the median time to recovery from grade ≥3 neutropenia and thrombocytopenia of 2 and 3 months, respectively.[45] These data supported the approval of ide-cel use after the receipt of at least four previous lines of therapy in patients in the United States and after at least three previous therapies in patients in the European Union.[46]

Ciltacabtagene-autoleucel (former LCAR-B38M, cilta-cel, CARVIKTY) is another second-generation CAR-T cell containing two BCMA binding domains, which was approved on the basis of the results of the phase 2 CARTITUDE-1 study. Overall, 97 patients were infused with a median number of six previous lines and 87.6% were triple-class refractory. The ORR was 97.9%, with 82.5% of patients achieving a stringent CR (sCR). With a median follow-up of 27.7 months in the most recent update, median PFS has not yet been reached, with the 27-month PFS of 54.9% (95% CI, 44 to 64.6) and 64.2% (95% CI, 51.9 to 74.1) for patients in sCR. The 27 month OS was 70.4% (95% CI, 60.1 to 78.6). Regarding safety, cytopenias and CRS were the most frequent treatment-related adverse events reported. Any grade neutropenia was present in 96%, which is grade ≥3 in 95% of patients. The incidence of CRS was 95%, mostly grade 1-2 with a median time to onset of 7 days (range, 1-12). Neurologic events were reported in 20 patients. Among these, 16 of 20 presented immune effector cell–associated neurotoxicity syndrome (ICANS) and 12 patients presented with other neurotoxicities, of whom 5 showed a movement and neurocognitive disorder occurring with a median time to onset of 27.0 (IQR, 16.0-73.0) days.[47]

Albeit impressive clinical results are obtained thus far, no plateau is seen in the survival curves and relapses continue to occur. The current and subsequent evolution is focused on the development of new constructs and the early use in populations of unmet clinical need.

In this context, patients with early relapse disease that is TCE continue to have poor outcomes with no standard of care available. ide-cel has been evaluated in this setting in the phase 3 randomized KarMMa-3 trial. Patients with RRMM who had received two to four previous lines of therapy and were TCE were included. Enrolled patients were randomly assigned 2:1 to receive ide-cel or standard regimens.[48] Patients allocated in the ide-cel arm received a single infusion of ide-cel with a target dose range of 150 to 450 $\times 10^6$ CAR-T+ cells. Patients assigned to the standard regimen arm were treated with one of five regimens chosen by the investigator at the time of random assignment on the basis of exposure and refractoriness to previous therapies. Treatment in the standard arm continued until disease progression, unacceptable toxicity, or study withdrawal. The primary end point was PFS assessed by the independent review committee in the intention-to-treat (ITT) population, with ORR and OS as key secondary end points. Of the 386 patients randomly assigned, 254 were assigned to the ide-cel group (ITT) and 132 to the standard regimen arm (ITT); 225 patients received a single infusion of ide-cel (median dose of 445 $\times 10^6$ CAR+ T cells), whereas 126 received the standard treatment, with daratumumab-pomalidomide-dexamethasone being the regimen most frequently used. Baseline characteristics were balanced between the two treatment arms. The median number of previous regimens was 3, and overall, 65% of the patients were triple-class refractory with a median time of 4 years from diagnosis to study entry and a median time to progression on last previous antimyeloma therapy of only 7 months in the two arms. At a median follow-up of 18.6 months, PFS was significantly longer with ide-cel, with a median PFS of 13.3 months (95% CI, 11.8 to 16.1) versus 4.4 months (95% CI, 3.4 to 5.9) with standard regimens (hazard ratio, 0.49 [95% CI, 0.38 to 0.65]; P value $< .0001$). Notably, PFS benefit of ide-cel was observed across multiple patient subgroups including older age, high-risk cytogenetic abnormalities, high tumor burden, or extramedullary disease. The PFS benefit was also seen in patients regardless of the number of previous lines and in patients with triple-class refractory disease. Treatment with ide-cel also resulted in a higher ORR (71% *v* 42%; odds ratio, 3.47 [95% CI, 2.24 to 5.39]; P value $< .0001$). OS data were immature and remain blinded. Regarding safety, the most common adverse events were hematologic. Grade 5 adverse events occurred in 36 patients in the ide-cel arm and eight in the standard regimen arm. Importantly, 18 of 36 and three of eight had grade 5 events consistent with disease progression. Overall, the safety profile of ide-cel was consistent with previous studies with no new safety signals.[48]

In the same direction, patients with early relapse disease and disease refractory to lenalidomide also represent a population with poor outcomes with current approved therapies. Previous preliminary data with cilta-cel in cohort A of the phase 2 CARTITUDE-2 trial demonstrated encouraging efficacy with an ORR of 95%, a CR rate of 85%, and a 12-month PFS rate of 84% (95% CI, 59.1 to 94.7).[49] The randomized phase 3 CARTITUDE-4 trial compares cilta-cel with standard-of-care (SOC) therapy in lenalidomide-refractory patients with 1-3 previous lines of therapy. The two control SOC regimens used were pomalidomide, bortezomib, and dexamethasone or daratumumab, pomalidomide,

and dexamethasone. cilta-cel has demonstrated a significant improvement in PFS in the first prespecified interim analysis. The full disclosure of the data is still pending.[50]

Furthermore, both cilta-cel and ide-cel have been evaluated in other settings of unmet clinical need and functional high risk such as patients with early relapse after frontline therapy. In cohort B of the CARTITUDE-2 trial, 19 patients with early relapse (within first 12 months) after frontline therapy were treated. The ORR was 100%, and 89% of patients achieved at least CR, with an 18-month PFS rate of 83% (95% CI, 55.9 to 94.3).[51] Safety profile was comparable with previous publications without any new safety signals.[49,51] Similarly, ide-cel was evaluated 37 patients with early relapse, here defined as progressive disease within 18 months after diagnosis. 86% were refractory to any IMID. At a median follow-up of 21.5 months, the ORR was 83.8% and the CR rate was 45.9%. The median PFS was 11.4 months (95% CI, 5.6 to 19.6), and the 24-month OS rate was 84.7%. Safety was consistent with previous reports.[52] ide-cel was also tested in patients with suboptimal response after frontline autologous stem-cell transplantation, a patient population with short PFS and poor prognosis. A total of 31 patients received a single CAR-T infusion with a median dose of 440 $\times$ 10^6 CAR T+ cells (range, 244.9-514.5). The ORR was 87.1%, and the CR rate was 74.2%. Median PFS has not yet been reached with a PFS rate at 24 months of 83.1%. Interestingly, the safety profile was comparable with previous reports with the exception of one grade 3 Parkinsonism event reported in one patient at day 22 post–ide-cel infusion.[53] Other studies are ongoing evaluating these two constructs in other populations including the frontline setting (BMTCTN1902—ClinicalTrials.gov identifier: NCT05032820, CARTITUDE-5—ClinicalTrials.gov identifier: NCT04923893, and CARTITUDE-6—ClinicalTrials.gov identifier: NCT04181827; Table 2).

Altogether these results have established BCMA-CAR-T-cell therapy as a new standard of care for the treatment of TCE RRMM in either late or early RRMM. In addition, other BCMA-targeted therapies (Table 3) are approved and available, such as bispecific antibodies (ie, teclistamab) or antibody drug conjugates (ADCs; ie, belantamab mafodotin—only in Europe). Therefore, understanding the correct sequence between the different BCMA-directed therapies is of utmost importance although the evidence is still rather scanty. In the real-world experience from the US Myeloma CAR-T consortium with ide-cel, the use of a previous BCMA-therapy negatively affected PFS with a median PFS of only 3.2 months (95% CI, 2.8 to not reported [NR]) versus 9.0 months (95% CI, 7.6 to NR) in BCMA-naïve patients.[60] Similarly, with cilta-cel, both ORR (60%) and PFS (median, 9 months [95% CI, 1.5 to 13.2]) were shorter in patients previously exposed to BCMA-ADC or bispecific as compared with BCMA-naïve patients treated in the CARTITUDE-1.[61] On the contrary, salvage therapy with bispecific antibodies in patients progressing after BCMA-CAR-T seems to be rather efficacious with an ORR of 52.2% with teclistamab[62] or 62.7% with talquetamab,[63] which is comparable with that of the BCMA-naïve cohorts, suggesting that whenever possible, CAR-T-cell therapy should be prioritized to prevent continuous T-cell exhaustion or BCMA downmodulation after continuous exposure to BCMA ADC or bispecific antibodies.

Future development is ongoing, with novel constructs and different targets[3,22] being explored aiming to overcome some of the limitations of current CAR-T-cell therapies, and the possibilities are endless. A summary of some of these novel products that have clinical data is included in Table 4.

BROADENING ACCESS TO NOVEL MM THERAPEUTICS

Novel immunotherapies, including the two FDA-approved CAR-T-cell products, ide-cel and cilta-cel, have shown remarkable efficacy in patients with relapsed/refractory MM who have received multiple lines of therapy.[6,47] Although the unprecedented response rates have been met with enthusiasm and hope from patients and the myeloma community, several hurdles remain before these treatments are routinely and widely available for all patients.

Hurdles to CAR-T access in myeloma include the limited availability of CAR-T products because of manufacturing constraints[72,73] and the limited number of centers that offer CAR-T therapy, creating a challenge for patients who do not live in close proximity to such centers or may not otherwise have access. Additional barriers to CAR-T therapy include overcoming socioeconomic and racial disparities that have been shown to affect access to novel therapies, including significant financial and caregiver burden during the treatment.[74] In this section, we will discuss these barriers and potential solutions to broadening CAR-T access for patients with RRMM.

CAR-T-Cell Availability

Since becoming commercially available, both ide-cel and cilta-cel have limited manufacturing availability. This is due in part to the shortage of commercial-grade good manufacturing process viral vectors needed to make CAR-T cells. Most designated centers are provided one to two slots per month for each product, resulting in a long waiting list of patients who are in desperate need of these products. The treating physicians at these centers must decide which patients receive these slots, which can pose an ethical challenge.[75,76] Some centers select patients on the basis of availability of alternate treatment options, disease burden, and aggressiveness of relapse. At some centers, likelihood of favorable response may factor into this decision making, with CAR-T being offered to patients whose disease is refractory but with less aggressive biology and lower disease

TABLE 2. Summary of Ongoing Studies Evaluating CAR-T-Cell Therapy in Earlier Lines of Therapy or in Combinations With Standard-of-Care Treatment

Trial	Study Population	Study Design	CAR Name	scFv Origin	Phase	No.	Antigen	Cell Source	End Point	Dose	Status
FUMANBA-2 (NCT05181501)	NDMM High-risk	VRD/PAD/PCD × 3—ASCT (if eligible) >> CT103A	CT103A	Human	1	20	BCMA	Autologous	MRD negativity 2-Year PFS	1×10^6/kg	Not yet enrolled
NCT04287660	NDMM	BiRD + BCMA CAR-T cell	NA	NA	3	20	BCMA	Autologous	ORR at 4 weeks	$2\text{-}3 \times 10^7$/kg	Recruiting
CARTITUDE-5 (NCT04923893)	NDMM not intended for ASCT	A: VRD × 8+ Rd B: VRD (6 + 2) + cilta-cel	cilta-cel	Llama	3	650	BCMA	Autologous	PFS	0.75×10^6/kg	Recruiting
NCT04935580	NDMM-TE High-risk	Two cycles of induction + CAR-T + Len maintenance	GC012F	Human	1/2	20	BCMA-CD19	Autologous	Safety ORR, PFS, MRD	3×10^5/kg	Recruiting
CARTITUDE-6 (NCT05257083)	NDMM-TE	A: DVRd × 4 + ASCT + 2× DVRd + Len B: DVRd× 6 + cilta-cel + Len (2 y)	cilta-cel	Llama	3	750	BCMA	Autologous	PFS	0.75×10^6/kg	Not yet enrolled
KarMMa-4 (NCT04196491)	NDMM High-risk (R-ISS 3)	Standard induction × three cycles + ide-cel	ide-cel	Murine	1	13	BCMA	Autologous	Safety	450×10^6	Active Not recruiting
CARTITUDE-2 (NCT04133636)	Multicohort	Cohort A: 1-3 previous lines of Len-Ref Cohort B: early relapse after frontline treatment Cohort C: relapse after BCMA Cohort F: NDMM after frontline Cohort E: NDMM Tx not planned (high-risk)	cilta-cel	Llama	2	157	BCMA	Autologous	MRD negativity at 1 year	0.75×10^6/kg	Recruiting
KarMMa-2 (NCT03601078)	Multicohort	2a + b: R-ISS 3 + early relapse 2c: suboptimal response to ASCT	ide-cel	Murine	2	181	BCMA	Autologous	ORR	$150\text{-}450 \times 10^6$	Recruiting
KarMMa-7 (NCT04855136)	1-3 PL + Len R ≥3 PL RRMM	(A): ide-cel + iberdomide maintenance (B): ide-cel + gamma secretase Inh	ide-cel	Murine	2	181	BCMA	Autologous	ORR	$150\text{-}450 \times 10^6$	Recruiting
BMTCTN1902 (NCT05032820)	NDMM post-ASCT	ide-cel + Len maintenance	ide-cel	Murine	2	40	BCMA	Autologous	ORR	450×10^6	Recruiting

Abbreviations: ASCT, autologous stem-cell transplantation; BCMA, B-cell maturation antigen; BiRD, bortezomib, clarithromycin, lenalidomide, and dexamethasone; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene-autoleucel; DPd, daratumumab, pomalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; EloPd, Elotuzumab, pomalidomide, and dexamethasone; ide-cel, idecabtagene-vicleucel; Inh, inhibitor; IxaRd, ixazomib, lenalidomide, and dexamethasone; Kd, carfilzomib and dexamethasone; Len, lenalidomide; Len-Ref, lenalidomide-refractory; MRD, minimal residual disease; NA, not available; NDMM, newly diagnosed multiple myeloma; NDMM-TE, newly diagnosed transplant-eligible; ORR, overall response rate; PAD, bortezomib, doxorubicin, and dexamethasone; PCD, bortezomib, cyclophosphamide, and dexamethasone; PFS, progression-free survival; PL, prior lines of therapy; PVd, pomalidomide, bortezomib, and dexamethasone; Rd, lenalidomide-dexamethasone; R-ISS, revised international staging system; RRMM, relapsed and refractory multiple myeloma; scFv, single-chain variable fragment; Tx, treatment; VRD, bortezomib, lenalidomide, and dexamethasone.

TABLE 3. Summary of Main Efficacy and Safety for the Different Off-the-Shelf BCMA-Targeted Therapies That Are Currently Being Developed

	Belantamab-Mafodotin (n = 97)	**Teclistamab (n = 165)**	**Linvoseltamab (n = 73)**	**ABBV-383 (n = 118)**	**Elranatamab (n = 123)**	**Alnuctamab (n = 68)**
MoA	ADC	Bispecific antibody	Bispecific antibody	Bispecific antibody	Bispecific antibody	Bispecific antibody
Target	BCMA	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA (2 + 1)-CD3
Route	IV	SC	IV	IV	SC	SC
Dose and schedule	2.5 mg/kg every 3 weeks	1.5 mg/kg/weekly	Weekly × 16w; W ≥ 16: every 2 weeks	Every 3 weeks	76 mg/weekly C ≥ 7: every 2 weeks if PR	Weekly × 8w every 2 weeks C3-C7 C ≥ 7 every 7 weeks
Median previous LoT	7 (3-21)	5 (2-14)	5 (2-17)	5 (1-15)	5 (2-12)	4 (3-11)
Triple refractory	97 (100%)	77.6%	89%	61%	96%	63%
CRS, G ≥ 3	NA	72.1%, 0.6%	38%, 0%	54%, 3%	57.7%, 0%	53%, 0%
Neurotoxicity, G ≥ 3	NA	3%, 0%	4%, 0%	NR, 6 patients	4%, 3.4%	2 patients, 3%
ORR (%)	32	63	75 at 200-800 mg	60/81[a] at ≥40 mg	61	53
≥CR (%)	7.2	39.4	16	20/30[a]	27.6	23
Median PFS, months (95% CI)	2.8 (1.6 to 3.6)	11.3 (8.8 to 17.1)	NR	NR	NE (10.4 to NE)	NR
Median DoR, months (95% CI)	11 (4.2 to NE)	18.4 (14.9 to NE)	NR	NR	NE (12.0 to NE)	NR
MRD (10^{-5})	NR	26.7%	4/10	NR	90.9% (n = 22)	16/20
Reference	54	55	56	57	58	59

NOTE. All CAR-T cells are single infusion.

Abbreviations: ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; C, cycle; CR, complete response; CRS, cytokine release syndrome; DoR, duration of response; G, grade; IV, intravenous; LoT, lines of treatment; MoA, mechanism of action; MRD, minimal residual disease; NA, not applicable; NE, not evaluable; NR, not reported; NT, neurotoxicity; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase 2 dose; SC, subcutaneous; VGPR, very good partial response.

[a]Dose-escalation and dose-expansion phase, n = 60.

TABLE 4. Main Reported Clinical Trials of CAR-T Cells in RRMM

	BB21217 CRB-402 (n = 72)	CT053 LUMMICAR (n = 18)	CT103A FUMANBA-1 (n = 79)	C-CAR088 (n = 23)	P-BCMA-101 PRIME (n = 53)	ALLO-715 Universal (n = 43)	ARI-002h (n = 30)	BMS-986354 (n = 65)	MCARH109 (n = 19)	BMS-95266 (n = 33)
Phase	1	1b/2	1/2	1	1/2	1	1	1	1	1
Follow-up (months), median (range)	23 (9-46)	6 (2-11)	25.3 (4.1-36.7)	6.2 (0.7-16.1)	NA	10.2	17.5 (5-23)	9 (1-16)	10.1	3.1
Target/ costimulation	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	GPRC5d/ 4-1BB	GPRC5d/ 4-1BB
scFv	Mouse	Human	Human	Human	Mouse	Human	Human	Human	Human	Human
Specificity	Autologous	Autologous	Autologous	Autologous	Autologous	Allogeneic	Autologous	Autologous	Autologous	Autologous
CAR-T-cell dose	150-450 $\times 10^6$	1.5-3.0 $\times 10^8$	1.0 $\times 10^6$/kg	1.0-6.0 $\times 10^6$/kg	51-1,178 $\times 10^6$	40-480 $\times 10^6$	3 $\times 10^6$/kg	10-80 $\times 10^6$	25-450 $\times 10^6$	25-450 $\times 10^6$
Population										
Age, years, median (range)	62 (33-76)	62 (36-78)	56 (39 - 70)	60 (45-74)	60 (42-74)	64 (46-77)	61 (53-65)	63 (43-75)	60 (38-76)	63 (48-80)
Previous lines, median (range)	6 (3-17)	5 (3-11)	5 (3 - 13)	4 (2-12)	8 (2-18)	5 (3-11)	4 (3-5)	5 (3-13)	6 (4-14)	4 (3-13)
Triple-class refractory, No. (%)	50 (69)	85	13 (16.5)	NR	60	90.7	67	90.8	16 (94)	NR
Penta-refractory, No. (%)	NR	50	NR	NR	NR	42	23	47.7	NR	NR
Efficacy										
ORR, No. (%)	69	94	75 (94.9)	22 (95.7)	50-75	55.8	100	95.1	71	89.5
CR, No. (%)	36	27.8	58.2	43.5	NR	≥VGPR: 34.9	67	39.3	6 (35)	47.4
PFS (months), median (95% CI)	12.8 (7.3 to 18.6)	NR	25.3 (3.0 to NE)	6 PFS: 65.1%	NR	NR	NR (53% at 18)	NR	NR	NR
CRS										
All grade, No. (%)	54 (75)	15/18 (83.3)	72 (92.4)	21 (91.3)	17%	24 (55.8)	80%	53 (81.5)	15 (88)	21 (63.6)
Grade 3-4, No. (%)	3 (2 grade 5)	0 (0)	2 (2.5)	1 (4.3)	0%	1 (2.3)	0 (0)	1 (1.5)	1 (6)	2 (6.1)
Onset (days), median (range)	2 (1-20)	2 (DL0) and 1 (DL1)	6 (1-12)	6 (1-11)	NR	7	7 (4.5-8)	4 (1-8)	NR	3 (1-9)
Duration (days), median (range)	4	4 (DL0) and 3 (DL1)	5 (1-30)	5 (2-9)	NR	4	2 (1-14)	2 (2-9)	NR	4 (1-11)
Tocilizumab/steroids %/%	53/17	≈30/20	20/34.7	26/9	7/6	23.3/14	63/15	≈70/30-57	53/24	45.5/24.2
ICANS										
All grade, No. (%)	11 (15)	2 (DL0) and 1 (DL1)	1 (1.3)	1 (4.3)	4	6 (14)	0	6 (9.2)	1 (6)[a]	2 (6.1)
Grade 3-4, No. (%)	3 (4)	1 patient	0	0 (0)	4	0 (0)	0	1 (1.5)	1 (6)	0

(Continued on following page)

TABLE 4. Main Reported Clinical Trials of CAR-T Cells in RRMM (Continued)

	BB21217 CRB-402 (n = 72)	**CT053 LUMMICAR (n = 18)**	**CT103A FUMANBA-1 (n = 79)**	**C-CAR088 (n = 23)**	**P-BCMA-101 PRIME (n = 53)**	**ALLO-715 Universal (n = 43)**	**ARI-002h (n = 30)**	**BMS-986354 (n = 65)**	**MCARH109 (n = 19)**	**BMS-95266 (n = 33)**
Onset (days), median (range)	7 (2-24)	NR	10	8	NR	NR	—	5 (5-9)	NR	NR
Duration (days), median (range)	2	NR	1	1	NR	NR		2-4		NR
Status	Not further developed	Ongoing	Ongoing	Ongoing	Not further developed	Ongoing	Ongoing	Not further developed	Not further developed	Ongoing
Reference	44	64	65	66	67	68	69,70	71	3	22
Identification	NCT03274219	NCT03915184	NCT05066646	NCT05066646	NCT03288493	NCT04093596	NCT04309981	NCT03446040	NCT04555551	NCT04674813

NOTE. Data of safety and efficacy are shown. All CAR-T cells are single infusion.

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DL, dose limiting; ICANS, immune effector cell–associated neurotoxicity syndrome; Tox, toxicity; NE, not evaluable; NR, not reported; ORR, overall response rate; PFS, progression-free survival; RRMM, relapsed and refractory multiple myeloma; scFv, single-chain variable fragment; VGPR, very good partial response.

[a]Cerebellar toxicity in two patients.

burden. Other centers select patients simply by the order they were listed in the list. One study showed that only 15% of patients with RRMM who were listed for commercial CAR-T received the therapy by 6 months and 29% by 12 months. About a third of patients died while waiting for the CAR-T therapy.[77] Enhancing manufacturing capacity will require significant commitment and investment from pharmaceutical partners who manufacture these products. Some pharmaceutical companies that make standard-of-care CAR-T products for lymphoma indications have moved to in-house manufacturing of viral vectors to have secure and constant availability of viral vector for manufacturing. Such effort is sought in manufacturers of ide-cel and cilta-cel. Another potential consideration would be to restrict CAR-T clinical trials to areas of urgent clinical need only, while awaiting the ramp-up of the CAR-T supply for standard-of-care manufacturing. The supply will also improve as other CAR-T-cell products become available commercially.

Access to CAR-T Centers

CAR-T therapy can only be given at select specialized centers and requires centers in the United States to meet accreditation requirements from Foundation for the Accreditation of Cellular Therapy (FACT). This creates geographic barriers to access as CAR-T therapy is mostly limited to large academic medical centers with hematopoietic transplant experience. Currently, there are fewer than 250 FACT-accredited centers that can provide cellular therapies across the United States.[78] These facilities are unevenly located across the country, resulting in a challenge in access to most patients. Even in clinical trials of CAR-T treatment, it was shown that about a quarter of patients lived over 2 hours away.[79] To undergo CAR-T therapy, patients are required to stay close to the treating centers for up to 30 days after CAR-T-cell infusion, resulting in significant direct and indirect financial costs of relocating and time away from paid work for patients and their caregivers. Many centers require patients to have a caregiver for 30 days post–CAR-T, and this can be a hurdle for some patients. These issues cannot be solved without thinking at a national and international level. Geographically uneven distribution of medical resources affects not only access to cellular therapy but also oncologic care in general. Having a better distribution of FACT-accredited facilities would improve access to CAR-T-cell therapy. In addition, assistance with medical leave for patients and caregivers, transportation centers, and local lodging would broaden access to CAR-T therapy.

Financial Cost

CAR-T products currently approved for RRMM carry a list price of $419,500 in US dollars for ide-cel and $465,000 USD for cilta-cel in the United States, which does not include the cost of hospitalization or outpatient specialized care. In 2019, the Center for Medicare and Medicaid Services finalized the decision for Medicare to cover CAR-T-cell therapies under FDA-approved indications. However, patients who are uninsured or underinsured have significant hurdles in accessing CAR-T therapy. In addition, out-of-pocket expenses including the cost of transportation and local lodging, co-pay for visits and medications, and short-term loss of income for the patient and their caregiver can pose a significant challenge for patients. In a study of patients with non-Hodgkin's lymphoma undergoing CAR-T therapy, the mean financial burden during CAR-T-cell therapy per patient was estimated to be $5,368, with the greatest financial burden coming from the lodging and meals for the patient and their caregivers.[80] Many programs use grants and other funding to support local housing cost during the treatment; however, this is not always available. Lowering the out-of-pocket expenses and securing appropriate financial assistance is crucial to improve access.

Socioeconomic and Racial Disparities

Access to CAR-T-cell therapy is limited especially for minorities and those in a lower socioeconomic stratum. A study performed with Vizient Clinical Database showed that the African American (AA) population, despite representing nearly 20% of newly diagnosed myeloma cases, made up only 1% of patients who received CAR-T-cell treatment in clinical trials.[79] Hispanic patients were under-represented at 5.4%. CAR-T therapy is not the only entity where we see disparities in access to care. It was demonstrated that utilization of bortezomib was 37% lower among AA patients compared with White patients,[81] and they were 37% less likely than White patients to undergo stem-cell transplantation even after adjusting for income and insurance.[81] This suggests that structural barriers may exist in the health care system, such as referral bias and cultural barriers, as well as difference in social support and comorbidities. This study also showed that only 6% of CAR-T cell therapy–related hospitalizations (including indications for lymphoma, MM, and ALL) were for patients from neighborhoods with a mean income under $40,000, likely because of the lack of adequate insurance coverage, high out-of-pocket expenses, and requirement of having a caregiver,[75] underscoring the disparities in access to CAR-T cell therapy. In addition to overcoming financial barriers, a systematic approach that includes streamlining referral to CAR-T centers and significant nursing and navigation support is needed to expand access to CAR-T for racial and ethnic minorities. A recent study observed that Black patients receiving standard-of-care ide-cel were more likely to develop any-grade CRS and had a longer hospital stay and prolonged cytopenias. Although the findings may be related to underlying disease burden, it potentially suggests that different strategies in monitoring and follow-up may be needed on the basis of patients' race and ethnicity.[82]

TABLE 5. Summary of Main Advantages or Disadvantages Between Allogeneic CAR-T Cells and Autologous CAR-T Cells

Autologous CAR-T Cell		Allogeneic CAR-T Cells	
Advantage	**Disadvantage**	**Advantage**	**Disadvantage**
Better expansion	Longer turnaround time	Off-the-shelf product	Complex genetic manipulation using gene-editing techniques
Longer persistence	Higher cost	Healthy donors	Lower expansion
Easier genetic modification	Higher variability between products	Higher homogeneity between products	Lower persistence
Potential lower immunogenicity	Impact of previous therapies in T-cell fitness	Lower cost (same donor = multiple products)	Inferior efficacy in the products developed so far
Absence of GVHd	Out of specification products	Multiple cell sources	Need for a more intense lymphodepleting regimen
Need for less intense lymphodepletion	Manufacturing failure	Absence of manufacturing failure or out of specification products	Delayed immune reconstitution leading to a potential higher risk of infections
Better immune reconstitution (because of the above)	Variable cell quantity	Cell quantity is controlled	Risk of immune rejection
Regulatory approval of several constructs and longer follow-up	Toxicity (CRS, ICANS, cytopenias)	Better toxicity profiles. No GVHd so far reported but short follow-up in the trials	Absence of regulatory approval so far

Abbreviations: CAR, chimeric antigen receptor; CRS, cytokine release syndrome; GVHd, graft versus host disease; ICANS, presented immune effector cell–associated neurotoxicity syndrome.

Manufacturing Time

Even after securing insurance approval, financial resources, and a spot for apheresis, long manufacturing times of 4-8 weeks for current approved BCMA CAR-T products pose a huge hurdle for CAR-T therapy. Most patients have disease that is refractory to available treatments, and waiting 4-8 weeks for manufacturing is often not feasible, even while on bridging therapy. Of all enrolled patients in the two pivotal trials that led to FDA approval of BCMA CAR-T, 9% and 14% of patients in KarMMa trial (ide-cel) and CARTITUDE-1 trial (cilta-cel), respectively, did not receive the products. Several patients have died waiting for CAR-T manufacturing, in both clinical trial and the standard-of-care setting. Potential solutions include shortening manufacturing times for currently available products through optimization of manufacturing processes and developing products with rapid manufacturing[83] or off-the-shelf allogeneic CAR-T products[68] (Table 5).

Expanding Clinical Trial Eligibility Criteria

Clinical trials of myeloma CAR-T-cell therapy have excluded patients with renal impairment, which affects a significant proportion of patients with myeloma and patients with cytopenias, central nervous system involvement, and plasma cell leukemia, with the latter two being harbingers of aggressive disease and arguably populations that might benefit significantly from CAR-T therapy. This is an area of huge unmet need. Expanding clinical trial eligibility criteria or creating special nested cohorts with CAR-T trials to allow for safety and efficacy data generation in such cohorts is critical. In addition, analysis of real-world data with standard-of-care CAR-T can also help generate preliminary data, which can then be used to advocate for access to standard-of-care therapy for these patients and inclusion of these patients in future clinical trials. As an example, in a real-world analysis of patients with renal impairment receiving intended standard-of-care ide-cel, ide-cel could be given safely to patients with renal insufficiency including one patient on dialysis, with dose adjustment of lymphodepletion chemotherapy. The incidence of CRS (89% *v* 84%) and neurotoxicity (21% *v* 19%) was comparable between patients with or without renal insufficiency. PFS was comparable (6.5 *v* 8.1 months), suggesting that patients with renal insufficiency also benefit from ide-cel.[84] As such data accumulate in above special populations, CAR-T can be given more widely and safely.

Other Immunotherapies

Many other CAR-T-cell constructs are in clinical trials for MM and may become commercially available in the future. Other types of immunotherapies, including various bispecific antibodies, are also being studied.[85] Teclistamab, which is a bispecific antibody[86] approved by FDA in October 2022, is an excellent option for patients with relapsed/refractory myeloma. Centers that are not set up for CAR-T therapy can potentially administer this regimen although they need to have expertise in the management of toxicities such as CRS and neurotoxicity. Such treatments will likely be more widely available geographically although they are still limited to tertiary care centers and patients generally require hospitalization during the step-up dosing. In the future, increasing access to bispecific antibodies through community-based practices can increase access to novel immunotherapies.

SUMMARY

In summary, CAR-T therapy has resulted in unprecedented response rates in myeloma, with two BCMA-targeted constructs approved for treatment of late relapse and several other constructs in development, including for earlier-line treatment. However, patients face several barriers to accessing CAR-T therapy and researchers, and clinicians and CAR-T manufacturers need to come together to implement solutions to broaden access to CAR-T therapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Frontline Management of Nodal Peripheral T-Cell Lymphomas

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overview

Peripheral T-cell lymphomas (PTCLs) represent only 10%-15% of all non-Hodgkin lymphoma but encompass a diverse group of diseases with over 30 different subtypes. As a result of both disease heterogeneity and rarity, therapeutic progress of PTCLs has lagged behind B-cell lymphomas with very few randomized controlled studies to guide management. The most common subtypes are the so-called nodal PTCLs: PTCL-not otherwise specified (NOS), anaplastic large cell lymphoma (ALCL), and nodal T follicular helper cell lymphoma (TFHL) lymphoma, the latter of which includes angioimmunoblastic T-cell lymphoma. Anthracycline-based primary chemotherapy is still the mainstay of treatment for these common PTCL subtypes, but in recent years, we have moved into an era where more personalized therapy can be applied in some settings. Cyclophosphamide, doxorubicin, prednisone, and brentuximab vedotin CHP-BV is the first therapy in PTCL to show an overall survival benefit and represents a new standard for ALCL; however, there is less therapeutic certainty in other CD30-positive PTCLs. Recurrent mutations of epigenetic modifier genes typify TFHLs lymphomas, and collective studies demonstrate a heightened sensitivity to epigenetic therapies, leading to trials integrating these agents in the frontline setting. Molecular studies of PTCL-NOS have defined at least two subtypes, GATA3 and TBX21, the former having a poorer prognosis, but how this guides therapeutics remains unknown. Outside of ALCL, there is a growing debate as to whether trials should focus on adding a novel agent to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or whether combination novel therapies should be explored in the frontline therapy setting. Finally, the role of consolidative autologous stem-cell transplant in first remission remains an area of active debate.

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INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) represent a diverse and complex collection of lymphomas with more than 30 different entities that share a common derivation from either a mature T or NK-cell precursor. In 2022, both the WHO fifth edition lymphoma classification update and the International Consensus Classification (ICC) published additional refinements which are largely concordant with few exceptions, including nomenclature differences[1,2] (Table 1). The so-called nodal PTCLs include peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), systemic anaplastic large cell lymphoma (ALCL), and nodal T-follicular helper cell lymphomas (TFHL), representing ≈60% of all PTCLs encountered in Western populations (Table 1). With the exception of ALK-positive ALCL, the prognosis is typically poor (Table 2). Historically, treatment has been modeled after B-cell lymphomas, leading to the use of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as standard therapy in PTCLs. However, it is clear that a one-size-fits-all approach is not optimal across PTCLs. In many of the rare extranodal PTCL subtypes, such as extranodal NK/T-cell lymphoma, CHOP has been abandoned.

This past decade has been a period of great advancement in PTCLs, both in understanding disease pathogenesis and in the development of new therapies tailored specifically for PTCLs. The anti-CD30 antibody drug conjugate, brentuximab vedotin (BV), demonstrated unparalleled response rates in relapsed/refractory (R/R) ALCL, and in 2018, cyclophosphamide, doxorubicin, and prednisone (CHP)-BV was approved for use in the frontline treatment of CD30-positive PTCLs. Outside of CHP-BV, CHOP remains the standard and is typically the backbone to investigate the addition of novel agents. However, with high complete remission (CR) rates seen with combination therapies, this paradigm has been recently challenged, particularly in TFHLs where a heightened sensitivity to epigenetic therapies is observed. This review will focus on these common PTCL subtypes and the current status of personalized therapy.

UPDATE ON CLASSIFICATION AND GENETICS OF NODAL PTCLs

Despite modern diagnostics, 30%-50% of patients are designated as PTCL-not otherwise specified (NOS). It has long been recognized that this is a heterogeneous group defined more by diagnostic exclusion as one of the specified subtypes. Cases of

PRACTICAL APPLICATIONS

- Nodal peripheral T-cell lymphomas (PTCLs)—peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), systemic anaplastic large cell lymphoma (ALCL), and T-follicular helper lymphoma (TFHL)—are the most common subtypes in Western populations.
- Although progress in PTCLs has lagged behind B-cell lymphomas, the past decade has been a period of advancement both in understanding disease biology and therapy progress.
- Cyclophosphamide, doxorubicin, prednisone, and brentuximab vedotin (CHP-BV) is a new treatment paradigm in ALCL, but its role in other CD30-positive PTCLs remains unclear.
- TFHLs are characterized by recurrent mutations in epigenetic modifiers with heightened sensitivity to this class of agents, and recent clinical trials have integrated these agents in the treatment-naïve setting.

PTCL-NOS that are cytotoxic marker-positive (ie, TIA1, granzyme B, perforin)/EBV-positive are now called primary nodal EBV-positive T/NK-cell lymphoma (International Consensus Classification [ICC]—provisional entity) or nodal EBV-positive T and NK-cell lymphoma (WHO—HAEM5 distinct entity) (Table 1). Previous molecular profiling studies identified two main groups in PTCL-NOS by unsupervised hierarchical clustering: GATA3 with high expression of GATA3 and target genes (CCR4, IL18RA, CXCR7, and IK), resembling TH2 cells, and TBX21 (TBet) with higher expression of TBX21, EOMES, and known targets (CXCR3, IL2RB, CCL3, and IFNγ), resembling TH1 cells.[6] Although patient numbers were low, patients with a GATA3 profile had an inferior prognosis to TBX21, and subsequent genetic studies demonstrate a greater genomic complexity.[6] This dichotomization is largely captured by an immunohistochemical (IHC)-based algorithm using GATA3, CCR4, TBX21, and CXCR3(4). The IHC panel reproduced the gold standard gene expression profiling results in 85% of patients, with only 11% unclassified, and retained prognostic significance (5-year overall survival [OS] GATA3 10%-20% *v* TBX21 45%-50%).[7] Cytotoxic marker expression also delineates more aggressive disease, and almost all are of TBX21-subtype and harbor DNMT3A mutations.[8] A nanostring assay can molecularly classify the main PTCL subtypes, which may ultimately be the better tool in clinical practice.[9] As of 2023, the designation of PTCL-NOS according to these subgroups, either by molecular profiling or IHC, is not part of routine

TABLE 1. WHO and ICC of Lymphomas 2022 Updates for Nodal PTCLs[1,2]

2017 WHO Fourth Edition	2022 ICC	2022 WHO Fifth Edition	Informative Molecular and Genomic Information if Available
PTCL-NOS			
PTCL-NOS	PTCL-NOS	PTCL-NOS	Research setting: GATA3 and TBX21 subtypes (by GEP or IHC)
Not listed as entity, included with PTCL-NOS	*Primary nodal EBV+ T/NK-cell lymphoma*[a]	EBV+ nodal T-and NK-cell lymphoma	
ALCL			
ALK-positive, ALCL	ALK-positive, ALCL	ALK-positive, ALCL	
ALK-negative, ALCL	ALK-negative ALCL[b]	ALK-negative ALCL	Ideal in clinical practice: *DUSP22R* and *TP63R* by FISH (if available)
Nodal lymphomas of T follicular helper origin	Follicular helper T-cell lymphoma	Nodal T-follicular helper (TFH) cell lymphoma	Ideal in clinical practice: *TET2*, *DNMT3A*, *IDH2*^{R172}, and *RHOA*^{G17V} targeted mutation panel (if available)
Angioimmunoblastic T-cell lymphoma	Follicular helper T-cell lymphoma, angioimmunoblastic-type	Nodal TFH cell lymphoma, angioimmunoblastic-type	
Nodal PTCL with TFH phenotype	Follicular helper T-cell lymphoma, NOS	Nodal TFH cell lymphoma, NOS	
Follicular T-cell lymphoma	Follicular helper T-cell lymphoma, follicular-type	Nodal TFH cell lymphoma, follicular type	

NOTE. TFH = any two of BCL6, CD10, CXCL13, PD1, and ICOS (if available) positive by immunohistochemistry.
Abbreviations: ALCL, anaplastic large cell lymphoma; FISH, fluorescent in-situ hybridization; GEP, gene expression profiling; ICC, International Consensus Classification; IHC, immunohistochemical; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; TFH, T-follicular helper.
[a]provisional entity in the ICC; distinct entity in WHO-HAEM5 and called EBV+ nodal T-and NK-cell lymphoma.
[b]*DUSP22* rearranged ALK negative ALCL is a genetic entity in the ICC.

TABLE 2. Selected Large-Scale Retrospective Outcome Studies including Nodal PTCLs Treated With Primarily Anthracycline-Based Chemotherapy[3-5]

Retrospective Study	International Peripheral T-Cell Lymphoma Project All Ages	Swedish Registry All Ages	Netherland Cancer Registry <65 Years
Patients, No. Years of PTCL diagnosis	1,153 (overall) 1990-2002	755 (overall) 2000-2009	1,427 (nodal only) 1989-2018
Central pathology review	Yes	No	No
Patients, No.			
ALK-positive ALCL	87	68	145
ALK-negative ALCL	72	115	90
PTCL-NOS	340	256	629
AITL	243	104	294
5-year PFS, %			
ALK-positive ALCL	60	63	NR
ALK-negative ALCL	36	31	NR
PTCL-NOS	20	21	NR
AITL	18	20	NR
5-year OS, %			
ALK-positive ALCL	70	79	72
ALK-negative ALCL	49	38	52
PTCL-NOS	32	28	32
AITL	33	32	44

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; NOS, not otherwise specified; NR, not reported; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma.

practice and how this translates therapeutically requires additional study.

Few recurrent genetic abnormalities have been reported in PTCLs with the exception of the *t*(2; 5) (p23; q35) translocation in ALK-positive ALCL. More recently, next-generation sequencing (NGS) identified two recurrent rearrangements in ALK-negative ALCL: *P63* on 3q28 and *DUSP22-IRF4* locus on 6p25.3. Cases with *DUSP22R* have pathopneumonic doughnut cells and, by IHC, are negative for cytotoxic markers, PDL and pSTAT3. More recently, recurrent mutations in MSC^{E116K} have been identified and overexpression of the common testicular antigen (CTA) has been reported by molecular profiling.[10,11] In an initial study, approximately one third of patients with ALK-negative ALCL harbored a *DUSP22R* and had a 5-year OS indistinguishable from ALK-positive ALCL (5-year OS 90% for *DUSP22R*-positive ALK-negative ALCL *v* 85% for ALK-positive ALCL).[12] Conversely, patients with rearranged *TP63* (8%) had a 5-year OS of only 17%. Subsequent studies have demonstrated a more variable outcome for patients with *DUSP22R* ALK-negative ALCL,[13,14] which may also be affected by clinical factors as shown by a large series from the LYSA group TENOMIC database, where those with a performance status of ≥2 have a 4-year OS of only 29%.[15] Taken together, the 5-year OS ranges from 40% to 100%, and there is more limited reporting of progression-free survival (PFS; 5-year 40%-57%).[16] Patients with a relapsing remitting course and rare CNS relapse have been described.[13] The unique pathobiologic features established *DUSP22R* ALK-negative ALCL as a genetic subtype of ALK-negative ALCL in the ICC but not in the WHO fifth edition because of uncertainties around clinical behavior.[1,2] If available, FISH testing for both *DUSP22R* and *P63R* in ALK-negative ALCL should be performed (Table 1).

In the 2017 fourth edition WHO update, an expanded disease category called "angioimmunoblastic T-cell lymphoma (AITL) and other nodal lymphomas of T-follicular helper cell origin" was created to include cases with PTCL-NOS with a TFH phenotype (as identified by ≥2 of BCL6, CD10, PD1 CXCL13, and ICOS by IHC) but not having the morphologic criteria to be defined as AITL and also to include the morphologically distinct follicular type (Table 1). Nomenclature updates to these lymphomas were outlined in the ICC and WHO with minor differences (Table 1). In this review, they will be referred to as TFH lymphomas (TFHLs) and specific subtypes will be referenced as appropriate. Importantly, NGS and targeted sequencing–identified recurrent mutations in $RHOA^{G17V}$ as well as the epigenetic regulators *TET2*, *IDH2*, and *DNMT3A* occur frequently in TFHLs, and this TFH mutational profile, especially TET2 mutations, have been associated with response to epigenetic modifier therapies (see below).[17-20]

FRONTLINE COMBINATION CHEMOTHERAPY: WHAT IS THE EVIDENCE FOR CHOP IN PTCL?

Thirty years ago, the landmark SWOG phase III study established CHOP as the standard combination chemotherapy in aggressive lymphomas, including PTCLs.[21] However, it was performed in an era where diagnoses were based on the Working Formulation, and thus, the immunophenotype was not known. A few prospective and several large retrospective series have reported outcomes with primarily anthracycline-based chemotherapy in PTCL, including subtype-specific outcomes (Tables 2 and 3). Patients with ALK-positive ALCL have a more favorable outcome; however, this is in part driven by a younger age at diagnosis, and importantly, those with a high International Prognostic Index (IPI) score have a poor outcome, not unlike the other PTCL subtypes (IPI ≥3 5-year PFS range; 5-year OS 23%-33%).[27] Outcomes also tend to be better in ALK-negative ALCL, which is more evident in the clinical trial

TABLE 3. Phase III Randomized Studies in Treatment-Naïve PTCLs

Phase III Trial	AATT[22]	ACT1[23]	ACT2[24]	LYSA[25]	ECHELON-2[26]
Novel agent or approach	Allogeneic transplant	Alemtuzumab (A)	alemtuzumab (A)	Romidepsin (Ro)	Brentuximab vedotin (BV)
	Graft *v* lymphoma	Anti-CD52 antibody	Anti-CD52 antibody	HDAC inhibitor	Anti-CD30 antibody drug conjugate
Study size	103	131	116	421	452
Treatment arms	CHOEP ×4, DHAP ×1 + ASCT	CHOP14-A ×6	CHOP14-A ×6	Ro-CHOP ×6	CHP-BV ×6-8
	CHOEP ×4, DHAP ×1 + allo-SCT	CHOP-14 ×6	CHOP14 ×6	CHOP ×6	CHOP ×6-8
Inclusion criteria	18-60 years, stage II-IV/aa IPI >0	18-65 years	61-80 years	18-80 years	≥18 years, IPI ≥2 (for ALK-pos only)
Eligible PTCL	All (no ALK-pos)	All (no ALCL)	All (ALCL 6%)[c]	All	CD30+ PTCL[d]
Consolidative transplant	Yes by design (auto *v* allo)	Yes by design (auto)	No	No	Investigator discretion
Outcome	Negative study	Negative study[b]	Negative study	Negative study	Positive study
	Stopped early[a]	Accrual 42%			
PFS	3 years 43% (allo)	3 years 37% (CHOP14-A)	3 years 28% (CHOP14-A)	2 years 43% (Ro-CHOP)	3 years 51% (CHP-BV)[e]
	3 years 39% (auto)	3 years 26% (CHOEP)	3 years 29% (CHOP14)	2 years 36% (CHOP)	3 years 43% (CHOP)
OS	3 years 57% (allo)	3 years 52% (CHOEP14-A)	3 years 37% (CHOP14-A)	2 years 64% (Ro-CHOP)	3 years 70% (CHP-BV)[e]
	3 years 70% (auto)	3 years 50% (CHOEP)	3 years 56% (CHOP14)	2 years 63% (CHOP)	3 years 61% (CHOP)

Abbreviations: AATT, autologous or allogeneic transplantation in T-cell lymphoma; ALCL, anaplastic large cell lymphoma; allo, allogeneic; ASCT, autologous stem-cell transplant; CHOEP, CHOP + etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP-BV, cyclophosphamide, doxorubicin, prednisone, and brentuximab vedotin; DHAP, dexamethasone, cytarabine, cisplatin; HDAC, histone deacetylase; IPI, International Prognostic Index OS, overall survival; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma.

[a]Recruitment stopped after interim analysis showed that the study was highly unlikely to meet its primary input. Transplant-related mortality contributed to decision—103 of planned 104 patients were enrolled.

[b]Recruitment stopped because of slow accrual and a negative ACT2 study. Accrued 116 of planned 274 patients.

[c]Discovery that ALCL is universally negative for CD52 led to an amendment for exclusion.

[d]CD30-positive ≥10% of neoplastic cells (total lymphocytes may be used if enumeration of neoplastic cells not possible); by design, the study was powered to enroll approximately three-fourth of patients with ALCL.

[e]Comparison statistically significant.

setting and with the introduction of CHP-BV (see Table 3). In addition to the IPI, prognosis is also affected by recently discovered genetic heterogeneity in ALK-negative ALCL as previously described. Historically, AITL has had a similar outcome to PTCL-NOS[3,4]; however, more consistent use of autologous stem-cell transplant (ASCT) in recent years may have improved outcomes[5] (Table 2). Of note, there have been no large studies evaluating outcomes in nodal TFH NOS, and most reported studies will have included this subtype in the broader PTCL-NOS group.

There has been some debate whether anthracyclines are an essential component for cure of non-ALCL subtypes. An exploratory analysis of the International Peripheral T-cell Lymphoma Project in both PTCL-NOS and AITL evaluating the impact of anthracyclines demonstrated no significant OS difference, although power was limited, and a trend favoring the use of anthracyclines was observed for PTCL-NOS (P = .11) but not AITL (P = .48).[3] Almost all patients received anthracyclines for systemic ALCL precluding a similar analysis.[27] Although bias cannot be completely remedied, a separate retrospective study from the Mayo group did support that anthracycline use was associated with improved PFS and OS in all nodal PTCLs and the subgroup with AITL/PTCL-NOS, adjusting for the IPI in multivariate analysis.[28] With uncertainty around the importance of anthracyclines, as well as concern of pGP-mediated resistance, a number of studies emerged evaluating gemcitabine-based alternative frontline chemotherapy. The UK group compared CHOP with gemcitabine, solumedrol, and cisplatin (GEM-P) in a randomized phase II study with a 2-year PFS of 38% and 37% (P = .82) and a 2-year OS of 64% versus 51%, respectively (P = .31). Although highly exploratory, patients with PTCL-NOS (and EATL) had a significantly better outcome with CHOP (odds ratio [OR], 0.036; P = .012); in contrast, outcomes by treatment arm were similar in AITL (OR, 0.69; P = .578). The SWOG group evaluated the cisplatin, etoposide, gemcitabine, and solumedrol (PEGS) regimen in newly

diagnosed patients (and also included 21% of patients with relapsed/refractory PTCL because of poor accrual) with a 2-year PFS of only 12% and a 2-year OS of 30%.[29] These novel gemcitabine-based combinations also exclude cyclophosphamide, a highly active drug in aggressive lymphomas, and it is likely an important component. Taken together, CHOP and, in particular, cyclophosphamide and doxorubicin may be most important in ALCL and possibly PTCL-NOS, although the latter is challenged by disease heterogeneity, with less certainty in AITL.

SHOULD CHOEP BE CONSIDERED IN SOME PATIENTS WITH PTCL?

The addition of etoposide to CHOP (CHOEP) was first explored in a retrospective analysis of published German high-grade lymphoma (DSHNHL) studies (now German Lymphoma Alliance [GLA]) that suggested that it improved event-free survival (EFS) in young, good-risk (normal lactate dehydrogenase) patients; however, the benefit was most evident in ALK-positive ALCL (3-year EFS 91% *v* 57%, $P = .01$), with a trend observed in other nodal PTCL subtypes (3-year EFS 61% *v* 48.3%, $P = .057$).[30] This was an unadjusted analysis, and the findings did not translate into an OS benefit.[30] Other retrospective series have also suggested improved outcomes with CHOEP over CHOP in ALK-positive ALCL[5,31] with more inconsistent results in other subtypes. The Netherlands Cancer Registry noted improved OS in nodal PTCLs <65 years in a later era where CHOEP and ASCT were used more routinely (2009-2018 *v* 1989-2008).[5] In multivariate analysis of patients diagnosed between 2014 and 2018, a period when the regimen type was entered, a high IPI and absence of up-front ASCT were associated with an inferior OS, but the use of CHOEP did not affect outcomes. Collectively, the evidence for CHOEP is strongest in ALK-positive ALCL, but CHP-BV has largely replaced its use as outlined below. For the other subtypes, use should be restricted to younger robust patients given additional myelotoxicity.

RANDOMIZED FRONTLINE STUDIES OF CHOP-BASED REGIMENS IN PTCLs

The landmark ECHELON-2 double-blind/double-dummy phase III pivotal study evaluated CHP-BV in treatment-naïve CD30-positive PTCL.[26] Brentuximab vedotin is an anti-CD30 antibody drug conjugate linked to the antitubulin agent monomethyl auristatin E and was initially developed in both classical Hodgkin lymphoma and systemic ALCL in the relapsed setting. In R/R ALCL, the efficacy was striking with an overall response rate (ORR) of 86% and CRs observed in >50% of patients.[32] With a 5-year follow-up, 14% remained in remission in the absence of transplant, suggesting that cure was possible.[33] In the phase I study, BV was combined with CHP with omission of vincristine to avoid overlapping peripheral neuropathy.[34] ECHELON-2 compared BV plus CHP with CHOP in newly diagnosed CD30-positive PTCLs (non-ALCL PTCLs CD30 ≥10%; ALK-positive ALCL IPI ≥2; Table 3). As this was intended to be a confirmatory trial for the regulatory approval of BV in R/R ALCL in Europe and Canada, the study was designed to enroll approximately three-fourth of the patients with a diagnosis of systemic ALCL. Ultimately, 70% of patients had ALCL (ALK-negative, n = 218, 48%; ALK-positive n = 98, 22%), and consequently, the other CD30-positive PTCL subtypes are under-represented (PTCL-NOS n = 72, 16%; AITL n = 54, 12%). In the intention-to-treat group, CHP-BV was associated with improved PFS (3-year PFS 51% *v* 43%, $P < .01$) and OS (5-year OS 70% *v* 61%, $P = .04$; Table 3). PFS and OS benefits were maintained in the 5-year update (5-year PFS 51.4% *v* 43%, $P = .0.007$; 5-year OS 70% *v* 61%, $P = .042$) and driven by ALCL (5-year PFS 60.6% *v* 48.5%, $P = .0009$; 5-year OS 75.8% *v* 68.7%, $P = .053$). There was a higher incidence of acute diarrhea (38% *v* 20%) and persistent neuropathy (38% *v* 24%) with CHP-BV compared with CHOP.[26,35] The benefit of CHP-BV is not certain in PTCL-NOS and AITL subgroups, with all CIs for hazard ratios crossing 1 for PFS and OS. Of note, the study mandated that PTCLs have 10% or more CD30 staining; however, regulatory approvals were not restrictive on the basis of CD30 expression. A trial is ongoing evaluating the efficacy of CHP-BV in those with PTCL with CD30 <10% (ClinicalTrials.gov identifier: NCT04569032). With the benefit unclear for the non-ALCL subtypes, regulatory approval differs globally with FDA approval of CHP-BV in the eligible CD30-positive PTCL population, Health Canada approval in ALCL and CD30-positive PTCL-NOS/AITL, but in Europe, it is only approved in ALCL.

Despite the excellent results of CHP-BV, there is still room for improvement. Approximately 50% of patients with ALCL fail frontline therapy, mostly the ALK-negative subtype.[35] Rare CNS relapse in ALCL would not expect to be affected by BV as it has not been shown to cross the blood-brain barrier. As CHOEP is frequently used in clinical practice, a phase II study explored the safety and efficacy of CHEP-BV in 46 patients positive for CD30 (≥1%), which demonstrated an ORR of 91% and CR 80% by investigator assessment at the completion of CHEP-BV.[36] This regimen may have a role in young, high-risk patients.

Romidepsin and alemtuzumab have also been evaluated in combination with CHOP(-like) therapies in phase III trials (Table 3). Romidepsin is a selective histone deacetylase (HDAC) inhibitor and was originally approved on the basis of modest efficacy in a phase II study in R/R PTCL (ORR 25%, CR 15%).[37] A phase III study was conducted by the LYSA group investigating romidepsin plus CHOP (Ro-CHOP) versus CHOP in previously untreated PTCL, excluding ALK-positive ALCL[25] (Table 3). The addition of romidepsin

did not translate into an improved PFS in the intention-to-treat population ($P = .096$; Table 3) and was associated with increased toxicity. Unfortunately, as it was intended to be a confirmatory study, this also led to delisting of romidepsin for R/R PTCL setting in the United States and Canada, which is particularly relevant for the management of TFHLs (see below).

CD52 antigen is a GPI-linked glycoprotein that is present on normal and pathologic B and T cells and is variably expressed in PTCLs. Alemtuzumab is an anti-CD52 humanized monoclonal antibody and was combined with CHOP-14 or CHOEP-14 in phase III trials conducted by the Nordic and DSHNHL/GLA groups in younger (CHOEP-14 18-65 years ACT 1)[23] and older (CHOP14 >65 years ACT 2)[24] patients with newly diagnosed PTCLs, the former incorporating ASCT into both treatment arms (Table 3). In ACT 2, the 3-year PFS was 28% versus 29% in CHOP-A versus CHOP, respectively ($P = .248$) and the experimental arm was associated with significant toxicity. Similarly, there was no observed benefit in the ACT 1 trial (3-year EFS: A-CHOP 35% *v* 26%; Table 3).

ROLE OF CONSOLIDATIVE AUTOLOGOUS TRANSPLANT IN THE PRIMARY THERAPY OF NODAL PTCLs

In the absence of a randomized controlled study, there is a lack of uniform consensus regarding the role of high dose chemotherapy/ASCT in first remission in PTCL. Comparisons between studies are challenging because of inclusion of diverse subtypes as well as variable response to induction chemotherapy at the time of transplant. The largest prospective study was by the Nordic Lymphoma Group (NLG-T-01), which enrolled 115 patients with nodal PTCL, excluding patients with ALK-positive ALCL.[38] Depending on age, patients received CHOEP (<60 years) or CHOP-14 (>60 years), followed by high dose chemotherapy/ASCT. With a transplant rate of 70% and median follow-up of 5 years, the 5-year PFS and OS were 44% and 51%, respectively, which although unsatisfactory, appears to be better than historical expectations. In multivariate analysis, age (as a continuous variable), ALK-negative ALCL, good performance status, and absence of bone marrow involvement were associated with a more favorable outcome.

Multiple retrospective studies have also explored the utility of ASCT. A comprehensive discussion is beyond the scope of this review, but several recent studies most of which have evaluated patients in a CR are summarized in Table 4. The LYSA group performed an analysis by intent to transplant in nodal PTCLs (n = 269) where ASCT and non-ASCT groups were determined on the basis of the physician's management plan before starting induction therapy. With the analysis confined to those in a CR or PR, in multivariate analysis and with propensity score-matching, there was no PFS or OS benefit of ASCT (Table 4).[41] In contrast, in the Norwegian Cancer Registry study, omission of ASCT was associated with inferior OS in multivariate analysis. In this study, a separate 9-month landmark analysis and a sensitivity analysis evaluating only those in a CR also showed a benefit of ASCT (landmark 5-year OS 78% *v* 45% [$P < .01$]; CR-only 5-year OS 82% *v* 47% [$0 < 0.01$]). Other studies focused on patients in a CR have been mixed with some showing a benefit of ASCT,[43] but others have not.[39,40,42] Complicating interpretation, most studies have combined diverse subtypes obscuring potential subtype-specific benefit.

With uncertain benefits of ASCT, GLA and LYSA study group evaluated consolidative allogeneic SCT (allo-SCT) versus ASCT in newly diagnosed PTCL but was stopped early because of futility and similar PFS rates (3 years 43% [allo] *v* 39% [auto]).[22] Although no relapses were observed in the allo-SCT group, toxicity was high and offset any benefit[22] (Table 3).

The impact of consolidative ASCT after CHP-BV was evaluated in a subgroup analysis of the ECHELON-2 trial in patients who had achieved CR at the end of treatment with the hypothesis that a better upfront therapy may offset any benefit of ASCT[44] (Table 4). However, the PFS was better with ASCT (5-year PFS was 65.3% *v* 46.4%, hazard ratio [HR] 0.36 [95% CI, 0.17 to 0.77]; Table 4). This benefit was not evident in the CHOP arm (HR, 0.63; 95% CI, 0.32 to 1.24), although power was limited for all comparisons.[44]

Taken together, despite data limitations, consolidative ASCT is still a treatment consideration in the up-front setting; however, larger studies are needed overall to identify low-risk patients who can be managed with chemotherapy alone, and decisions should be individualized in the absence of a randomized trial. Importantly, the recently activated randomized controlled TRANSCRIPT trial in France will formally address the role of ASCT in nodal PTCLs (excluding ALK-positive) patients who are in a CR after CHOP(-like) induction therapy (CHOP, CHOEP, CHP-BV in ALCL; ClinicalTrials.gov identifier: NCT05444712).

BREAST IMPLANT–ASSOCIATED ALCL

Breast implant–associated ALCL (BIA-ALCL) was defined as a provisional entity in the 4th WHO edition and was upgraded to a distinct entity by both the ICC and WHO fifth edition update because of unique features. Although not a nodal PTCL given primary breast involvement, it is described here to highlight prognosis and management differences with classic nodal ALCL. It is elicited by a chronic inflammatory/immune reaction by the implant with secondary genetic change resulting in JAK-STAT pathway activation as well as epigenetic and cell cycle deregulation.[45] The risk of BIA-ALCL is exclusively associated with textured implants, and the time from implant to

TABLE 4. Selected Studies Evaluating Consolidative Autologous Stem-Cell Transplant for Patients in Remission Post CHOP(-like) Chemotherapy

First Author Year	Study[a]	Total Responders	Benefit of ASCT	Response Pre-ASCT CR/PR	Outcome ASCT (*v* No ASCT)	Comment
Abramson et al[39] 2014	Retrospective Multicenter	194	No	CR 100% (by design)	PFS $P = .58$ OS $P = .95$	In CR patients, no benefit of ASCT Point estimates not provided
Cederleuf et al[40] 2017	Registry Danish/Swedish	232	No	CR 100% (by design)	2-year PFS 67% 2-year OS 80%	MVA no benefit of ASCT (including with ALK-pos excluded)
Fossard et al[41] 2018	Retrospective LYSA	269	No	CR/PR 57%	5-year PFS 45% 5-year OS 60%	Analysis by intent to transplant MVA and propensity score-matching, no benefit of ASCT
Park et al[42] 2019	Prospective Multicenter COMPLETE study	119 (nodal)	No	CR 100% (by design)	PFS $P = .23$ 2 year OS 87.6% (*v* 70.2%) $P = .06$	No MVA UVA IPI 2-4 OS superior with ASCT[c]
Garcia-Sancho et al[b,43] 2022	Retrospective Multicenter[d]	174	Yes	CR 100% (by design)	5-year PFS 63% (*v* 49%)[c] OS 5-year 74% (*v* 62%) OS $P = .12$	Analysis in CR/CRu patients only MVA adjusted for stage, PFS/OS benefit
Brink et al[5] 2022	Retrospective Registry (Nodal PTCL <65 years)	219	Yes	CR/PR	Landmark: 5-year OS 78% ASCT (*v* 45%)[c] CR only: 5-year OS 82% ASCT (*v* 47%)[c]	ASCT improved OS in MVA in patients managed 2014-2018 Suggestion of benefit in ALCL and AITL over PTCL-NOS
Savage et al[44] 2022	Prospective (E2 subgroup) Phase III CD30-positive PTCL	114 (CHP-BV) 97(CHOP)	Yes No	CR 100% (by design)	5-year PFS 63% (*v* 46%)[c] 5-year 49% (*v* 51%)	Analysis of patients in CR (adjusted by age, region) Benefit of ASCT in the CHP-BV arm No benefit ASCT in the CHOP arm

NOTE. Estimates are rounded.

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ASCT, autologous stem-cell transplant; BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete remission; CRu, CR unconfirmed; E2, Echelon-2; IPI, international prognostic index; MVA, multivariate analysis; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival; PR, partial remission; PTCL, peripheral T-cell lymphoma; UVA, univariate analysis.

[a]All exclude ALK-positive ALCL, with the exception of Abramson et al[39]: 7% ALK-positive, and Cederleuf: 19% ALK-positive.

[b]Also included extranodal-subtype enteropathy-associated TCL, hepatosplenic TCL, NK/T-cell lymphoma, primary cutaneous gamma delta lymphoma.

[C]Comparison statistically significant.

ALCL is 7-11 years. The overall risk varies in series but is likely between 1:1,000 and 1:10,000.

The most common presentation is a peri-implant effusion, and a large volume should be sent for cytology, flow cytometry including CD30, and molecular testing for a T-cell receptor clone. It is helpful to have a positron emission tomography scan before surgery as postsurgical inflammatory changes can be difficult to distinguish from lymphoma invasion. More than 85% of patients have stage I disease or disease limited to the seroma ± capsule.[46]

Implant removal with complete capsulectomy is recommended. Most are cured with surgery alone with a 5-year disease-specific survival of 95%. For those presenting with more advanced disease, the optimal management is unclear. For patients with incomplete resection, radiation may be considered, and in rare cases, BV has been given in the adjuvant setting. Although patients with BIA-ALCL were not included in ECHELON-2, CHP-BV would be reasonable in those with either lymph node or more distant disease.[46]

THE PRESENT AND FUTURE OF FRONTLINE THERAPY TRIALS IN PTCL

Integration of Epigenetic Therapy in the Frontline Setting: Is It Ready for Prime Time?

With the exception of BV in R/R ALCL, the ORR of approved agents in R/R PTCLs has been modest when considering all subtypes (Table 5). Although infrequent, long-term remissions have been reported as previously described with BV as well as with HDAC inhibitors. In the phase II registration study for romidepsin, the ORR was 25%, CR 15%, and median PFS only 3 months; however, the median duration of response was 17 months in the original report extending to 28 months with longer follow-up.[37,50] Long-term follow-up of the 27 patients with AITL enrolled in the study demonstrated an ORR of 33%, but two-third had a CR, and in four patients, it was maintained CRs for >3 years.[51] A retrospective multicenter series evaluating response to HDAC inhibitors in TFHLs versus PTCL-NOS noted a higher ORR even as a single agent (ORR/CR 56.5%/28.9% *v* 29.4%/19.6%; $P = .0035$).[52] The CR rate deepens using HDAC inhibitors in combination with other agents (ORR/CR 61.1%/38.8% *v* 25%/16.6% in TFHs *v* PTCL-NOS, respectively; $P = .072$).[52] Similar high response rates are seen in TFHL-NOS as observed in AITL. The duration of response in this study was confounded by the use of subsequent allo-SCT in many patients. Clear predictors of response are still under investigation.

Beyond HDAC inhibitors, other epigenetic therapies have demonstrated high response rates in AITL and/or TFHLs. The sensitivity of AITL to the hypomethylating agent azacitidine was first described in a retrospective series of 12 patients, five of which had an associated myeloid neoplasm. The ORR was 75% (CR 50%), and with a median follow-up of 27 months; the median PFS was 15 months, with five patients sustaining a CR for almost 2 years or longer.

Considering the frontline setting, a subgroup analysis of 201 patients with TFHL enrolled on the phase III Ro-CHOP study demonstrated an improved PFS ($P = .046$) providing additional support for enriching a trial population likely to benefit from the novel therapy. This is also highlighted in a phase II study evaluating 5-azacitidine (CC-486) administered before CHOP as priming, and although not subtype-specific, 81% of the patients enrolled had TFHLs. The CR was higher in TFHL (88% *v* 75% for all PTCLs), and with a median follow-up of 21 months, the 2-year PFS was 66%

TABLE 5. FDA-Approved Novel Agents for the Treatment of Relapsed/Refractory PTCLs

Agent	Type	Phase	Indication	ORR/CR (%)	Median DoR (months)	Median PFS (months)	Median OS (months)
Pralatrexate[47]	Anti-folate	II (PROPEL)	PTCL and transformed MF	PTCL 29/11	10.1	3.5	14.5
Brentuximab vedotin[32]	ADC CD30	II	ALCL	86%/57%	12.6[a]	12.6	Not reached
Romidepsin[b,37]	HDAC inhibitor	II	PTCL	PTCL 25/15	17[a]	4	11.3
Belinostat[48]	HDAC inhibitor	II (BELIEF)	PTCL	PTCL 26/11	13.6 —	1.6 —	7.9
Crizotinib[49]	ALK inhibitor	II	ALK-positive ALCL	88%/81%	—[c]	—	—

Abbreviations: ADC, antibody drug conjugate; ALCL, anaplastic large cell lymphoma; BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete remission; DoR, duration of response; HDAC, histone deacetylase; MF, mycosis fungoides; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma.

[a]Updated analyses: romidepsin phase II median follow-up 22.3 months, median DoR 28 months (CR, not reached); BV phase II median follow-up 58 months, median DoR 25.6 months (CR, not reached).

[b]Phase III study romidepsin plus CHOP led to withdrawal of approval of romidepsin for relapsed/refractory PTCL, in the United States, in May 2022 and in Canada March 2023.

[c]DoR assessment limited by censoring.

for all patients (69% for TFHL), with half of the patients also undergoing consolidative ASCT.[53] *TET2* mutations were associated with a more favorable PFS (P = .014), whereas the presence of *DNMT3A* trended toward inferior PFS (P = .83). Grade 3/4 neutropenia occurred in 71.4% despite GCSF use, but febrile neutropenia was 14.3%. Building on this regimen, a randomized phase II study is actively evaluating 5-aza or duvelisib (see below) in combination with CHOP (or CHOEP if <60 years) compared to CHOP/CHOEP alone (1:1:1) in newly diagnosed PTCL in CD30-negative (<10%; Alliance 051902; ClinicalTrials.gov identifier: NCT04803201).

With the potential for higher CR rates with combination therapies and uncertainties around the efficacy of CHOP, chemotherapy-free studies have emerged including in treatment-naïve patients. A phase I study of romidepsin and 5-azacitidine demonstrated an ORR of 73% in R/R T-cell lymphomas.[54] A phase II study followed in PTCL including treatment-naïve and R/R PTCL cohorts.[55] Although there were only 11 newly diagnosed patients (10 evaluable), the ORR was 70% and CR 50%. Considering all patients with TFHL (n = 27), the ORR was 80% and CR 60% and median PFS was 8. 9 months compared with 2.3 months for the remaining histologies.[55] Toxicity was not negligible, with grade 3/4 thrombocytopenia occurred in 48%, grade 3/4 neutropenia in 40%, and febrile neutropenia in 12%. Numerically, the ORR/CR rate was higher with TET2 mutations (69%/53% *v* 40%/20%); however, it did not reach statistical significance. In a separate study, romidepsin and lenalidomide were evaluated in treatment-naïve patients with PTCL ≥60 years or those <60 years and not judged to be a chemotherapy candidate.[56] Of 20 evaluable patients, 13 (65%) had AITL and the ORR was 75% (CR 30%) rising to 85% (CR 38.5%) in AITL. Long-term follow-up is needed to determine the curative potential of non-chemotherapy combination therapy options, but there is a rationale for additional study, especially in TFHLs.

FUTURE DIRECTIONS

For these common PTCL subtypes, we have moved into an era where more personalized therapy can be applied in some settings. CHP-BV is the first therapy to show an OS benefit and represents a new standard for ALCL but has an uncertain role outside of this indication. Genomic insights have highlighted recurrent mutations across TFH PTCLs, and multiple studies show consistently higher than expected response rates to epigenetic therapies with some rare long-term durable remissions. It remains unclear whether the optimal frontline trial design should be adding a novel agent to the CHOP backbone or novel therapy combinations, especially in TFHL, which shows high CR rates, and both approaches are currently under investigation. Nonetheless, modern studies are focused on integrating correlative studies to better understand who benefits from specific therapy to further move away from the one-size-fits-all approach.

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Partnering With All Patients: Ensuring Shared Decision Making and Evidence-Based Management for Underrepresented Groups With Multiple Myeloma

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overview

Several landmark therapeutic advances in multiple myeloma (MM) have led to an unprecedented number of options available to patients and their physicians as shared decision making is attempted. A myriad of factors need to be considered to ensure that patient-, disease-, and treatment-related factors are addressed to arrive at the most appropriate choice for patients at that time in their journey with myeloma. Some of these factors have traditionally remained underaddressed but have a clear association with patient outcomes, leading to underrepresented groups of patients with MM, including the elderly patients, racial-ethnic minorities, and those with specific advanced comorbidities, for example, renal insufficiency. Some of these factors may not be modifiable, but data suggest that they may give rise to implicit or explicit bias and affect treatment decisions. A growing body of literature is bringing these factors to light. However, their incorporation in day-to-day decision making for patients needs to be universal. It is imperative that prospective data are generated for all these and other underrepresented groups such that evidence-based medicine is applicable universally to all patients with MM, irrespective of clinical and sociodemographic factors.

INTRODUCTION

As the understanding and management of multiple myeloma (MM) evolve, considering various patient-, disease-, and treatment-related characteristics to arrive at the most evidence-based, patient-centric decision is imperative. Figure 1 summarizes some of these factors to be considered for informed decision making with patients. Several of these factors are modifiable, whereas others may not be. Practicing evidence-based medicine is associated with superior outcomes in patients.[1] Yet, considering all the patient-, disease-, and treatment-related factors to take the most appropriate evidence-based decision is challenging. Management guidelines for MM have several options available for patients.[2] Previous studies have shown that there are several traditionally underserved and underrepresented patient groups, including older adults, racial-ethnic minorities, and patients with certain comorbidities, for example, those with renal dysfunction. These groups have traditionally not been included in clinical trials; thus, they did not have uniform management guidelines, hence not realizing the true benefit of medical advancements. Partnering with patients to achieve shared decision making, accessing the most appropriate and timely standard-of-care therapeutics, and optimizing clinical trial participation can help MM patient groups on the fringes of health care delivery get included under the umbrella of evidence-based management.

MANAGING MM IN OLDER ADULT POPULATIONS

Age-Related Disparities in MM Incidence and Outcomes

MM is an incurable plasma cell malignancy with incidence and mortality rates disproportionately burdening older adults. With a median age at diagnosis of 69 years, approximately 60% of all newly diagnosed patients will be 65 years and older.[3] Older age at diagnosis means many will also have functional deficits and complex medical comorbidities affecting treatment delivery and tolerability.[4,5] Furthermore, these same older adults are challenged when accessing care because of structural barriers, including lack of transportation, lack of caregiver or other forms of social support, and the influences of ageism which the WHO defines as the "*stereotypes, prejudice, and discrimination towards others or oneself based on age.*"[6,7] Cumulatively, these factors contribute to poor patient-centered outcomes such as quality of life, physical function, and psychological well-being.

Although several potential barriers may limit health care access for an older adult with MM, the unprecedented number of novel therapies and those in the development pipeline have provided increasingly more

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PRACTICAL APPLICATIONS

- The approach to managing older adults with multiple myeloma (MM) requires key consideration of disease- and aging-related factors (assessed using a geriatric assessment or frailty indices) and other facets, such as ageism, which could further limit this population's access to high-quality care.
- Patients' race-ethnicity is not a traditional factor to consider for shared decision making or while generating prospective evidence for MM management, but ample data show that how management decisions are made and how patients access or use health care affect outcomes.
- Patients with MM and advanced comorbidities are frequently excluded from clinical trials, and they may not have an optimal duration of treatment because of lack of appropriate management of adverse events, leading to an impact on their outcomes. A concerted effort to mitigate and manage comorbidities is necessary to provide optimal, evidence-based management and realize the true benefit of therapeutic advancements in all patients.

available treatment options for this population. On the basis of SEER17 2012-2018 data, we have seen an increase in the percentage of people surviving 5 years after a MM diagnosis (relative survival) to 58%. However, there is still a survival gap that exists between older (65 year and older) and younger (younger than 65 years) adults with MM, resulting in only 40% of older adults being alive at 5 years after a MM diagnosis compared with 69% of younger adults with MM. Furthermore, the percentage of early deaths (ie, within 6-12 months of diagnosis) in MM is greatest for older adults.[8] In a recent analysis of 7,512 adults with newly diagnosed MM (NDMM; 2011-2021) and treated primarily in community-based practice settings, 8.3% of adults died within 6 months of diagnosis, with 73% of early deaths occurring in those who are 70 years and older.[9] The disproportionate burden of early and late deaths for this population highlights the growing urgency to address the myriad factors, contributing to the poor survival rates for older adults with MM.

Impact of Ageism

Ageism is prevalent and is associated with poor physical and psychological health outcomes.[10] Among 2,035 predominantly White (71%) community-dwelling adults age 50-80 years participating in the National Poll on Healthy Aging, 94.4% reported regularly experiencing one or more forms of everyday ageism.[10] Although less attention has been given to the effects of ageism in MM, the recent overt and more subtle examples of ageism highlighted during the COVID-19 pandemic (eg, prioritization of COVID-19 resources and the allocation of intensive care unit resources, including ventilatory support during the pandemic's peak, where resources were limited) emphasize the growing and urgent need for more research focused in this area.[11,12] Specifically, in the context of MM, effects of ageism can be viewed through the continued underrepresentation of older adults with MM in clinical trials because of age-based and other restrictive eligibility criteria, as well as provider bias affecting whether these older adults are given the option to enroll in a clinical trial.[13,14] In addition, African American (AA) patients

FIG 1. Informed decision making. Main categories and some specific examples of factors to consider for informed decision making with patients and their caregivers while making evidence-based decisions for patients at any stage of disease.

with MM have incidence (AA: 14 per 100,000 *v* White: 6 per 100,000) and death rates (AA: 6 per 100,000 *v* White: 3 per 100,000) that are twice their White counterparts.[15] These stark disparities create a double disadvantage for older AA patients with MM, who, in addition to the disease- and treatment-related impacts, must also navigate the interactive effects of ageism and structural racism (defined as the unavoidable and unfair inequalities in power, resources, capacities, and opportunities across racial or ethnic groups).[12,16,17]

Management Considerations Among Older Adults With MM

The management of older adults with MM is very complex and requires consideration of not only disease-related characteristics but must incorporate a global assessment of older adults' health, including their treatment preferences and goals (Fig 1). The Comprehensive Geriatric Assessment (CGA) is considered the gold standard in geriatric medicine, capable of capturing the heterogeneity of aging. The CGA assesses multiple domains, including cognition, comorbidities, physical function, polypharmacy, psychological health, social support, and environmental and spiritual components that can affect an older adult's health.[18] This multidisciplinary effort facilitates developing a coordinated care plan informing oncologic care, including participant eligibility in clinical trials.[18,19] In the real world, implementation and dissemination barriers challenge the operationalization and acceptance of CGA-guided approaches and subsequent recommendations.[20] To address these barriers, abbreviated tools such as the International Myeloma Working Group's (IMWG) frailty score,[21] Revised Myeloma Comorbidity Index (R-MCI),[22] and the Facon simplified frailty scale[23] among others have been developed (Table 1). These tools estimate an older adult's fitness level, which occurs on a spectrum ranging from fit to frail. When applied to older transplant-ineligible populations with MM, these frailty scores can predict treatment toxicity, rates of treatment discontinuation, progression-free survival (PFS), and overall survival (OS).[22,29] In the clinical trial setting, these tools are increasingly incorporated to assess the fitness status of patients and, in some circumstances, test fitness-based approaches to assigning MM therapies.[30] A recent systematic review evaluating frailty prevalence and the outcomes of frail patients with MM enrolled in clinical trials found that 42% of trials used the IMWG frailty score and demonstrated high variability in frailty prevalence ranging from 25.1% to 54% in the newly diagnosed setting.

TABLE 1. Myeloma Fitness/Frailty Risk Scores

Frailty Score	Geriatric Domains	Study Design for Score Development	Study Sample Size	Biological Marker	Score Range	Interpretation
IMWG[24]	ADLs IADLs CCI	Retrospective	869	None	0-2	0 (fit) 1 (intermediate fit) 2 (frail)
R-MCI[22]	Age Fried Frailty Lung function Renal function Karnofsky Performance Index	Prospective	801	None	0-9	0-3 (fit) 4-6 (intermediate fit) 7-9 (frail)
Facon Frailty Scale[25]	Age CCI ECOG performance status	Retrospective	1,618	None	0-1 ≥2	1-1 (nonfrail) ≥2 (frail)
Myeloma Research Alliance Risk Profile[26]	Age WHO performance status	Retrospective	2,372	CRP ISS	<−0.256 −0.256 to −0.0283 >−0.0283	<−0.256 (low risk) −0.256 to −0.0283 (medium risk) >−0.0283 (high risk)
Mayo Frailty Index[27]	Age WHO performance status	Retrospective	351	NT-proBNP	0-3	0 (stage 1) 1 (stage 2) 2 (stage 3) 3 (stage 4)
Ancona Vulnerability Score[28]	CCI WHO performance status	Retrospective	266	None	0-2	0 (low) 1 (intermediate) 2 (high)

Abbreviations: ADLs, activities of daily living; CCI, Charlson Comorbidity Index; CRP, c-reactive protein; ECOG, Eastern Cooperative Oncology Group; IADLs, instrumental activities of daily living; IMWG, International Myeloma Working Group; ISS, International Staging System; NT-proBNP, N-terminal pro-brain natriuretic peptide; R-MCI, Revised Myeloma Comorbidity Index.

In comparison, trials in the relapsed/refractory MM (RRMM) setting noted frailty prevalence as high as 73.6%.[25]

Moving Beyond Frailty Scores to Examine Additional Barriers to Care for Older Adults With MM

Despite MM-specific tools such as those noted above and their ability to shape understanding about the heterogeneity in aging phenotype across MM, these tools also have their limitations. One, in particular, is the use of chronologic age within these scoring systems, which is counter to the narrative that chronologic age should be considered separate from biological/functional age and is not a good surrogate for predicting those likely to have the worse MM-related outcomes. Furthermore, using the Charlson Comorbidity Index in the R-MCI could omit MM-specific comorbid conditions.

In clinical practice, we must also consider additional factors, such as an individual's goals and treatment preferences, life expectancy, presence of caregiver support, and other structural barriers to health care access, such as lack of transportation, financial concerns because of under/uninsured status, and fixed/limited incomes in older adults, that could affect their ability to pay for medical services including MM-related and supportive therapies. Furthermore, beyond individual-level factors, we must also acknowledge and find strategies to overcome the effects of ageism. Emerging data, such as a 2022 publication by Allen et al,[10] demonstrate in a national survey of older adults that with an increasing number of everyday ageism–related events, the odds of fair or poor physical health increased by 1.13-fold (95% CI, 1.01 to 1.17; $P < .001$). Furthermore, adults age 65 years and older are more likely than their younger counterparts to have a larger mean amount of everyday ageism (mean, 11.23 [95% CI, 10.80 to 11.66] *v* 9.55 [95% CI, 9.26 to 9.84]; $P < .001$). These findings highlight the potential for compounded harm that results in poor health outcomes among older adults with MM, especially those with advanced chronologic age and low socioeconomic status (SES). Further adverse health outcomes among this population, particularly for older AA adults, can be caused by the effects of structural racism.[24]

Managing MM in Older Adults Requires Acknowledging and Addressing MM and Age-Related Clinical Factors, Social Determinants of Health and the Effects of Ageism, and Structural Racism

Managing an older adult with MM is complex and requires careful consideration of several competing factors. Multilevel and potentially multidisciplinary approaches are necessary to ensure optimal and equitable outcomes for this population. These approaches must be personalized to ensure the ability to deliver tolerable, high-quality MM care that provides maximal therapeutic benefit while preserving function and quality of life. A biomarker-driven approach represents only one dimension of care capable of risk-stratifying patients. Although several studies are underway evaluating high-risk patients with MM, the definitions used across studies vary based on gene expression profile signatures and single or combination genetic abnormalities (eg, double-hit MM).[31] However, for older adults, especially those considered frail, a biomarker-based approach to treatment can potentially lead to overtreatment of these individuals, resulting in treatment-related toxicities, early treatment discontinuation, and declines in overall health and quality of life. Instead, these biomarker-based approaches must be merged with assessments of frailty and other geriatric domains (eg, social barriers to care and the presence of social support) to drive more equitable outcomes for this population.

Treatment Options for Older Adults With MM in the Newly Diagnosed and Relapsed Settings

The range of therapeutic options has continued to increase for older adults who are fit but otherwise ineligible for an autologous stem-cell transplantation (ASCT). These include the daratumumab-based triplet regimen: daratumumab, lenalidomide, and dexamethasone (D-Rd). In the most recent update of the MAIA trial presented during the 2022 American Society of Hematology's annual meeting, after a median follow-up of 64.5 months, PFS was improved with D-Rd versus Rd (median, 61.9 *v* 34.4 months; hazard ratio [HR], 0.55; 95% CI, 0.45 to 0.67; $P < .0001$). Furthermore, the median OS was not reached with D-Rd versus 65.5 months with Rd (HR, 0.66; 95% CI, 0.53 to 0.83; $P = .0003$).[32] Importantly, among those enrolled in the MAIA trial, the median age was 73 years in the D-Rd arm versus 74 years in the Rd arm; 44% of participants were 75 years and older.[32] Subsequently, Facon et al retrospectively assessed the frailty status (IMWG frailty score) of MAIA participants. In the D-Rd arm, 47% were considered frail versus 46% in the Rd arm. Although the median PFS at 36 months was longer for frail patients receiving D-Rd compared with Rd (not reached *v* 30.4 months; HR, 0.62; $P = .003$), it remained shorter than the median PFS observed for nonfrail patients in either arm (not reached *v* 41.7 months; HR, 0.48; $P < .0001$).[33] The data of this trial also underscore the positive focus on including elderly patients with MM in ongoing clinical trials, with some forthcoming clinical trials in the United States specifically focused on this population (S2209; ClinicalTrials.gov identifier: NCT05561387).

Alternative treatment options that could be considered for an older fit adult include the triplet regimen of bortezomib, lenalidomide, and dexamethasone (VRD) on the basis of data from the SWOG S0777 study.[34] However, bortezomib use among older adults requires careful consideration of the toxicity risk. Especially relevant to older adults are neuropathy and the risk of falls. In an analysis of 2,052 older adults with

NDMM, bortezomib was associated with a 36% increased risk of falls (adjusted HR, 1.36; 95% CI, 1.05 to 1.75; $P = .018$).[35] Given these concerns about toxicity, dose-adjusted VRD (VRD-lite) could be considered an alternative treatment approach for some older adults. For those with NDMM and considered to have intermediate fitness, dose-adjusted Rd-R (ie, Rd, followed by maintenance lenalidomide) could be considered.[36] In the relapsed setting, data remain limited, especially for those considered frail using the existing standardized scores (eg, IMWG frailty score). Of further concern are the tolerability of these subsequent lines of therapy and the need for early discontinuation. For example, in the ICARIA study of isatuximab, pomalidomide, and dexamethasone versus pomalidomide and dexamethasone, pomalidomide was reduced in 43% of patients and 335 required reductions in dexamethasone.[37] Furthermore, although studies such as ARROW,[38] ENDEAVOR,[39] and ASPIRE[40] included 25% to 35% of patients considered frail on the basis of the IMWG score, the rates of grade $\geq$3 treatment-emergent effects and cardiac events were higher among the frail population.

Role of Autologous Stem-Cell Transplantation in Older Adults

ASCT remains an integral treatment option for MM, with the existing literature demonstrating improvements in PFS when used in frontline settings.[41] Historically, clinical trial data evaluating the role of ASCT were focused on younger (younger than 65 years) and more fit individuals.[42] However, a growing body of literature demonstrates increasing ASCT use in older adults, particularly those who were 70 years and older.[43] For example, Munshi et al,[43] in an analysis of 2,092 patients 70 years or older registered in the Center for International Blood and Marrow Transplant Research database, showed identical outcomes between older and younger patients who received a single dose of melphalan 200 mg/m^2. However, survival estimates were lower for those who received a single dose of dose-reduced melphalan (140 mg/m^2), a finding attributed to coexisting medical comorbidities. These data are encouraging and can be used to guide provider discussions about the role of ASCT in select older adult populations. Furthermore, providers must be aware of other factors such as insurance status, lack of caregiver support, and, importantly, patient preference as these can also help shape decision making regarding ASCT in older adults.

In the future, ongoing studies such as the phase III Frailty-adjusted therapy in Transplant Non-Eligible patients with newly diagnosed Multiple Myeloma (FiTNEss [UK-MRA Myeloma XIV Trial]),[44] could help address important questions about the role of frailty-adapted approaches for older adults with NDMM. However, more studies are needed to shape the existing therapeutic approaches, including newer cell-based therapies for older frail adults in the relapsed setting.

REAL-WORLD IMPACT OF RACIAL-ETHNIC DISPARITIES IN MM

Although patient race-ethnicity is not traditionally taken into account to arrive at informed, evidence-based management decisions for patients with MM, there is ample evidence that patient race-ethnicity can significantly affect their access to and utilization of health care resources.[45] This can then indirectly affect outcomes, including morbidity and mortality from the disease. Although the incidence of MM is twice in AA patients as compared with White patients, the prevalence pool overwhelmingly comprises White patients.[46] AA patients make up approximately 20% of all patients with MM in the United States. Thus, the vast understanding of MM characteristics, management, and outcomes is among White patients, with gross underrepresentation of racial-ethnic minorities. A focused understanding of MM in AA patients and other racial-ethnic underserved groups is warranted.

Clinical and Biological Characteristics

Several studies have suggested that disease biology and clinical characteristics may be distinct for patients from various racial-ethnic groups.[45,47-49] Patients with MM and African ancestry have been reported to have a lower incidence of certain high-risk mutations, for example, TP53, t(14;16), t(14;20), as compared with their European counterparts.[48,49] At the same time, t(11;14) mutation, which is not considered high-risk, but can have a therapeutic implication with B-cell lymphoma 2 targeting, is seen more frequently in AA patients.[48] Any significant cytogenetic differences have not been reported so far in Hispanic patients as compared with the reference population of White patients.[50] Thus, if there was an exclusive biologically driven therapeutic landscape, AA patients may be expected to have superior survival as compared with White patients, which has not been universally reported, suggesting a larger impact of health care access and utilization. Concerted, prospective efforts to confirm such findings on a large scale, with populations who are enriched for racial-ethnic minorities, are necessary to arrive at firm data and use that to inform therapeutic decisions. Clinical characteristics have been explored among racial-ethnic groups in large databases and show that AA patients are significantly younger than White patients at the time of MM diagnosis and Hispanic patients are even younger as compared with AA patients.[51] This can lead to a difference in age-associated comorbidities, insurance eligibility, and occupation. These in turn can influence treatment choices and eligibility for ASCT, which is considered standard of care for MM in younger fit patients.[52] It has also been reported that myeloma-defining events and myeloma-related complications (hypercalcemia, anemia, and kidney dysfunction) are seen more frequently in AA patients as compared with other

racial-ethnic groups.[45,53] Of note, AA patients are least likely to have myeloma-related bone fractures, considered due to higher bone density seen in them as a race.[45] These findings can be used to triage health care resource utilization and institute targeted interventions. This can also inform timing and choice of therapy in some cases.

Access to and Utilization of Care

Several studies using large national databases including claims data have shown that racial-ethnic minorities have a disparate access to treatment modalities considered cornerstones of MM management, for example, novel therapeutic agents (proteasome inhibitors [PIs], immunomodulatory agents) and SCT. Although the overall utilization of novel therapeutic agents and SCT have increased among all racial-ethnic groups over time, the relative increase has been lesser among AA and Hispanic patients.[45,54,55] Various SCT-focused analyses have reported lowest rate of utilization among Hispanic patients[56] and the age-adjusted odds of receiving SCT being lower among AA patients (as compared with White patients).[57] In another study looking at single-center referral patterns, it was seen that AA patients are referred for a SCT significantly later in their disease course than White patients.[58] Although individual studies may have shown varied results, the undercurrent is that AA and Hispanic patients have lesser and delayed SCT utilization as compared with White patients. Timely utilization of SCT has a significant association with improved PFS in MM,[52] and as such, a delay in receiving SCT or failure to use this modality altogether can lead to inferior outcomes for AA and Hispanic patients with MM.

Similar to SCT utilization, timely access to and utilization of novel therapeutic agents have been the focus of several large studies. As for SCT, the use of novel agents has increased for all patients over time, but the increase in racial-ethnic minorities has been significantly lesser.[55] Furthermore, AA and Hispanic patients have a longer time from MM diagnosis to novel therapy initiation versus White patients (median, 5.2 and 4.6 *v* 2.7 months, respectively).[55] Evaluating some of the novel agents individually, rather alarming trends were noted including significantly delayed initial treatment with bortezomib among Hispanic patients (median, 117 *v* 46-51 days for other races; $P = .025$), no significant increase in the use of lenalidomide among Hispanic patients, and no significant increase in the use of bortezomib among Asian patients.[54] Even after controlling for overall health and potential access barriers, AA patients with MM are significantly less likely to be treated with bortezomib, leading to a potential association with increased hazard of death.[59] Patient race-ethnicity is also associated with disparate patterns of care, including underuse of maintenance therapy and frequent interruptions in treatment among minorities.[60] A major advancement in MM therapeutics has been the approval of chimeric antigen receptor-T (CAR-T) and bispecific antibody treatment, bringing forth a new era of immunotherapy, using T-cell–targeted and engaging agents. Although data on the use of these agents by race-ethnicity are not mature yet, some recent reports presented only in abstract form so far are suggesting at least initially a dismal rate of utilization by racial-ethnic minorities.

Although there may be a complex interplay of factors that are associated with these management patterns and disparities, demonstrating them helps us understand some of the core issues, which can potentially be addressed for universal access to evidence-based care.

Clinical Trials Participation

Clinical trials represent the advancements in medicine and provide access to novel therapies, leading to improvement in PFS and OS over the prevailing standard of care. The need for adequate representation of a diverse patient population in clinical trials is imperative for widespread generalizability of study results. Yet, studies have shown that racial-ethnic minorities are underrepresented in cancer clinical trials, and their accrual rates have not necessarily increased in a meaningful way over time.[53,61,62] This has led to most of the clinical trial participation and, as a result, the knowledge about drug/regimen safety and efficacy stemming from studies among White patients. Specific analyses in MM have shown a similar trend of racial-ethnic minorities being underrepresented in clinical trials.[63] This trend becomes more pressing in MM because of the higher incidence in AA patients and despite that clinical trials falling short of representing the true demographic of patients with MM in the country. The true nature of this disparity becomes evident when these drugs/regimens are used in a widespread populace, and differences in efficacy or toxicity are noted among patients of different racial-ethnic groups, with the lack of prospective clinical trial benchmark data among racial-ethnic minorities.[64-66] Within MM care, there has been widespread attention to this, with some of the recent large clinical trials showing better success in enrolling racial-ethnic minorities. Of note, although a lot of ongoing attention in this field is for AA patients with MM, it would be a missed opportunity to not address other underrepresented groups, for example, Hispanic patients, elderly patients, and those in rural areas. It is likely that several of the similar sociodemographic factors affect these other underrepresented groups as well, just like AA patients with MM. Regulatory, advocacy, academic, and patient support groups, among others, are bringing more attention to the obvious issue of health care disparities in MM care and cancer management at large. Ongoing efforts are aiming to address these disparities by designing clinical trials with more inclusive eligibility criteria and bringing trial access to traditionally underrepresented institutions, which may be

enriched in racial-ethnic minority patients, such that those who are traditionally underrepresented can get a fair shot at clinical trial participation.

Financial Toxicity

SES is an interplay of several sociodemographic factors. It has been postulated that SES of racial-ethnic minority patients with MM affects their OS, presumably because of differences in access and utilization of health care resources.[67,68] It has also been shown that the cost of care is disproportionately higher among racial-ethnic minorities, potentially leading to an intertwined vicious circle of worsening SES. Medicare claims have been reported highest during first 6 months after MM diagnosis for AA patients and at any time after MM diagnosis for Hispanic patients.[35] Over time, Medicare claims have been reported to increase most steadily for Hispanic patients ($P < .001$).[35] In another analysis, the mean adjusted all-cause inpatient, medical, and total monthly costs were significantly higher among Hispanic patients compared with White patients, showing a higher burden of the cost of care on ethnic minorities.[55]

Outcomes

Racial-ethnic disparities in health care access and utilization for patients with MM have been reported extensively. The relationship between patient race-ethnicity and outcomes in MM, both PFS and OS, is an important focus of research. Two findings have been reported in various analyses: (1) OS and myeloma-specific survival (MSS) are different for patients with different race-ethnicities and (2) in equal opportunity situations, for example, clinical trials, single institutions, or Veterans Administration (VA) system, racial-ethnic minorities may have similar or even superior outcomes.

Before other data being available about disease biology and health care access, OS and MSS were noted to be superior in AA patients as compared with White patients. Hispanic patients were noted to have the worst OS in population-level analyses.[51] Other studies also showed superior MSS in AA patients, but OS differences were not noted.[55] If differences in disease biology, as noted above, were the main driver of outcomes, AA patients would be uniformly noted to have superior OS than White patients. Thus, access and utilization seem to be more impactful on disparate outcomes. Pooled analysis from National Cancer Institute–sponsored MM clinical trials showed that despite differences in presentation, disease burden, and risk factors, outcomes (OS and PFS) of White patients and racial-ethnic minorities were similar, suggesting that equal access settings such as clinical trials can benefit outcomes in MM.[53] Subsequently, survival for younger AA patients considered SCT-eligible was reported to be superior to White patients in a large analysis conducted in the VA system.[69] Survival advantage was not noted in the older population, suggesting other factors at play. A more recent analysis from the SEER-Medicare database shows that in a matched cohort analysis, AA patients have better OS than White patients when treated equally, reiterating the importance of providing equal access opportunities to racial-ethnic minorities, the traditionally underserved group.[70]

TREATMENT OPTIONS IN PATIENTS WITH MM AND RENAL IMPAIRMENT

Relevance of Renal Impairment in MM

According to the novel IMWG criteria for symptomatic MM, the definition of renal impairment (RI) is based on either elevated serum creatinine (sCr; >2 mg/dL) or reduced creatinine clearance (CrCl; <40 mL/min), which must be the result of myeloma.[71] At the time of diagnosis, when evaluated by sCr or CrCl, the incidence of RI has been reported at 20%-40%, with a slightly higher proportion over the course of the disease because of worsening of renal function due to the natural history of MM.[72,73] Overall, an acute renal involvement is an independent adverse prognostic factor with a negative impact on OS for patients with MM, especially in terms of increased risk of early deaths and infections.[74] The average level of renal function among general population older than 70 years is at or below the threshold used to define chronic kidney disease (CKD) with an estimated glomerular filtration rate <90 mL/min.[75,76] Therefore, since aging is associated with a gradual deterioration of renal function, the possibility of having patients with MM and also preexisting RI is consistent and notably higher in elderly patients. The elderly population with CKD is representative of a frail group of patients who are more prone to develop renal injury from myeloma and its treatment and are universally underrepresented in clinical trials. A large observational cohort study demonstrated that patients with MM and CKD had an increased risk for mortality, delay in initiating next line of therapy, and incidence of anemia, hypercalcemia, and progression of CKD as compared with patients with MM but without CKD.[77]

Physiopathology of Myeloma Kidney

This etiology of renal injury in patients with MM (myeloma kidney) has been well-described as a secondary event due to multiple clinicopathologic mechanisms involving monoclonal free light chains (FLCs), leading to damage of the renal structures, first in the renal tubules and subsequently in the interstitial space and glomeruli.[78] The foremost final mechanism of kidney disease is the so-called cast nephropathy where the overproduction of FLCs causes direct proximal tubular injury and indirect cast-mediated damage.[79] The interaction of light chains with tubular cells leads to chronic tubulointerstitial inflammation triggered by light chains endocytosis, inducing the release of interleukin-6 (IL-6), IL-8, and monocyte chemoattractant protein-1, finally resulting in NF-kappa-B

intracellular proinflammatory pathway activation.[80] Histologic features seen typically are chronic tubulointerstitial nephritis with distal tubule metachromatic casts (composed of mixed light chains and Tamm-Horsfall protein), frequently surrounded by syncytial giant cells/polymorphonuclear reactive infiltrate.[81]

Supportive Care and Mechanical Approaches

Cornerstones of RI in MM in the emergency setting are adequate hydration and hypercalcemia control (Fig 2). Fluid administration (approximately 2 L/m^2/d) is essential to temporarily dilute clonal light chains concentration in the tubules, decreasing their potential role in inducing cast formation.[82] Potentially nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, loop diuretics, aminoglycosides, angiotensin-converting enzyme inhibitors, or angiotensin II receptor inhibitors should be avoided or withdrawn. Bisphosphonates are essential compounds necessary to prevent and manage MM-related bone disease but have a well-known potential nephrotoxicity because of the possibility of inducing tubular necrosis. Therefore, zoledronic acid and pamidronic acid should be administered carefully in an RI setting and only when CrCl is higher than 30 mL/min while clodronic acid only when CrCl is more than 12 mL/min.[83] In patients with end-stage renal disease who need supportive treatment for bone disease, the fully human monoclonal antibody (MoAb) against RANKL denosumab is alternatively indicated.[84] High cutoff dialysis with a protein-leaking dialyzer (Gambro HCO 1100 dialyzer) can improve the clearance rate of FLC with a theoretical FLC reduction of 35%-70% in the first 2 hours, followed by a gradual reduction in efficacy by a re-equilibration effect because of FLC concentration rebound by other biological compartments.[85] Nevertheless, a randomized trial did not show any significative differences between conventional and high cutoff dialysis, causing questions that remain on the optimal strategy, and the true efficacy of this method for renal recovery in patients with MM.[86] There are no consensus guidelines on the approach for renal replacement therapy (RRT) approach in RI in patients with MM, but it is recommended that RRT should be initiated (in addition to specific anti-MM treatment) as soon as possible, with the

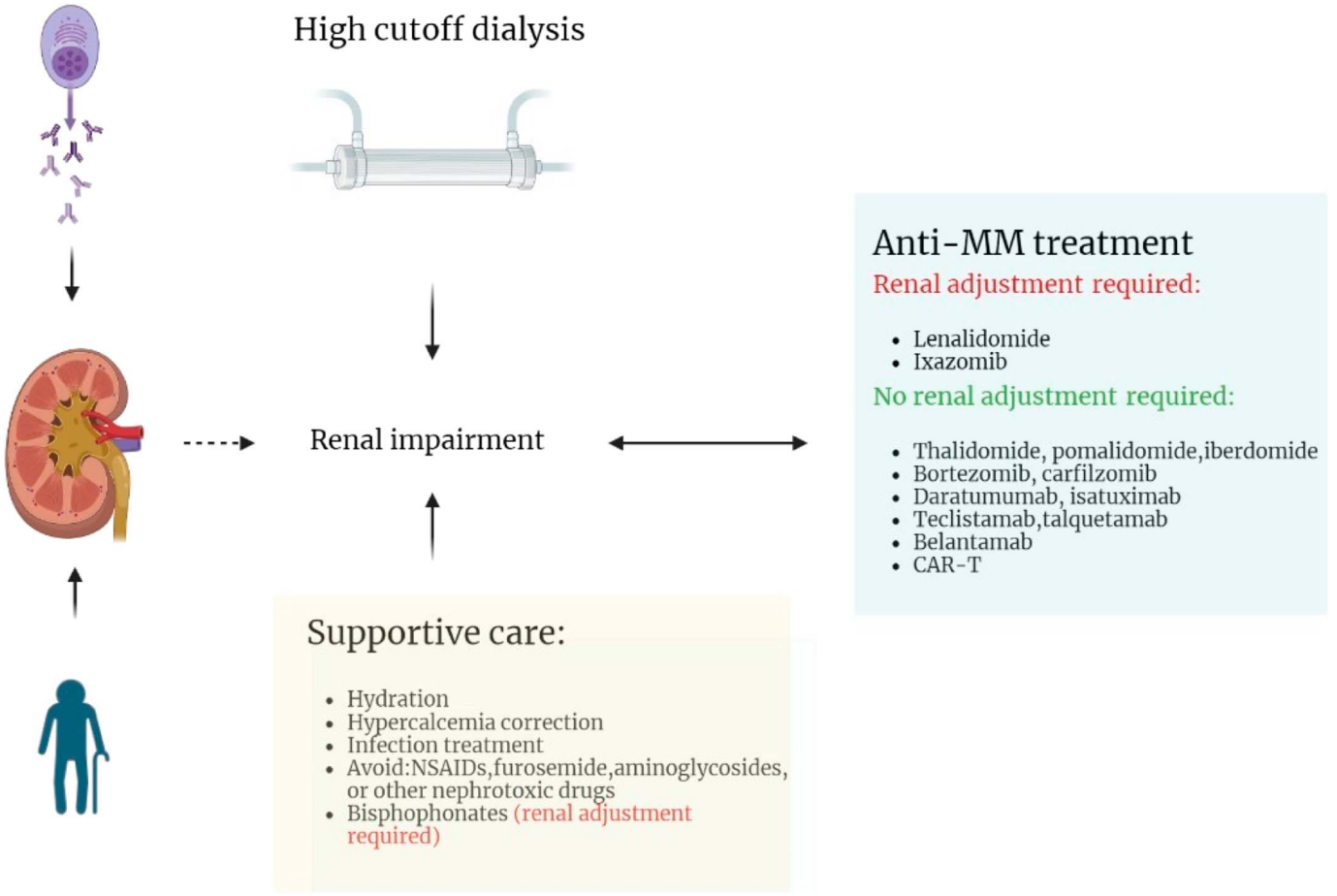

FIG 2. RI in MM. Pathophysiology of disease and factors to consider for management of RI in patients with MM. CAR-T, chimeric antigen receptor-T; MM, multiple myeloma; NSAIDs, nonsteroidal anti-inflammatory drugs; RI, renal impairment.

number of sessions possibly guided by the goal of holding FLC below 500 mg/L, a threshold for triggering tubular injury.[87] Overall, there is a trend toward better renal outcomes with the use of high cutoff dialysis, but no clear data are available on long-term renal and general outcomes because of the lack of randomized clinical trials.[88]

Immunomodulatory Drugs and PI in MM and Renal Insufficiency

Thalidomide is the first-in-class among the immunomodulatory drugs (IMIDs), initially adopted as a single agent and now part of combined induction treatment, with a wider utilization ex-US. Its pharmacokinetics are not affected by renal function impairment since clearance parameters of patients with renal failure are very similar to those reported in patients with normal renal function, and there is no need to modify its dose during dialysis.[89] Lenalidomide, a second-generation IMID, widely adopted in both transplant-eligible and noneligible patients with MM, has a relevant renal excretion requiring dose adjustment in relation to renal function, as moderate, severe, or end-stage renal disease impairs its excretion.[90] Lenalidomide-based regimens have been documented as effective in patients with RI, but with careful CrCl monitoring, as the major toxicity (hematologic) is directly related with impaired lenalidomide renal clearance.[91] A 2011 consensus statement is still a thorough guide for clinicians regarding managing lenalidomide dose (independent of the combination treatment adopted) by CrCl level.[92] The third-generation IMID, pomalidomide, is poorly excreted by kidneys (about 2%), and patients with RRMM even with moderate, severe, or advanced RI show comparable efficacy and safety profile, with a 4-mg recommended starting dose.[93] Iberdomide, a novel CelMod, is not currently FDA-approved, and its activity and safety profile in impaired renal function patients are currently being explored (ClinicalTrials.gov identifier: NCT04933747). Regarding PIs, the first-in-class bortezomib has mainly a hepatic metabolism, with only inactive metabolites undergoing renal excretion.[94] Rapid reduction of disease burden and no significant renal metabolism result in high overall response rates and renal response (reversibility on injury) from this agent.[95,96] Moreover, bortezomib-based treatment is associated with a significant probability of a rapid renal response even in patients under dialysis because of myeloma kidney, with improved survival of patients who became dialysis independent.[97] The second-generation PI, carfilzomib, as well has no influence of renal function on pharmacokinetic parameters, with no need for dose adjustment even in advanced RI.[98] A warning about rare and unpredictable non–myeloma-related renal injury (thrombotic microangiopathy, albuminuria >1 g/day and at least grade 3 acute kidney injury) has been reported.[99] Regarding the only orally available PI, ixazomib, the incidence of grade 3 and 4 adverse events in patients with severe RI or those on dialysis advocates using a reduced dose of 3 mg (instead of 4 mg) in these patients.[100]

Immunotherapy Does Not Get Affected by Renal Function

The treatment of MM has been further revolutionized by the introduction of immunotherapy. This class of drug comprises antibodies with both a targeted action and an indirect immune system (T cells) redirection against MM cells. The significant advantage of these agents is that on the basis of data so far, response rates and PFS with them are not affected by impaired renal function from MM.

Daratumumab and isatuximab are anti-CD38–directed humanized immunoglobulin (IgG) MoAbs with remarkable efficacy in patients with both NDMM and RRMM in combination with dexamethasone, PIs, or IMiDs. Anti-CD38 MoAb administration leads to rapid myeloma cell death by several mechanisms (complement-mediated cytotoxicity, antibody-dependent cytotoxicity, etc). A rapid drop in FLCs after daratumumab administration, with no negative impact on safety even in patients with severe renal injury, has made this agent fundamental in treating RI in MM.[101] Data have now been reported regarding the safety and maintained efficacy of daratumumab in terms of OS, PFS, and MRD-negative rate among both patients with normal and impaired renal function (ClinicalTrials.gov identifier: NCT01985126). Isatuximab, another IgG1 MoAb with a different CD38 target epitope, is a very active anti-MM agent combined with pomalidomide (or carfilzomib) that has also shown no need for dose adjustment in MM patients with RI.[102] Elotuzumab is a humanized immunostimulatory monoclonal IgG1 antibody that has as its target the signaling lymphocyte activation molecule F7 and is approved for use in patients with RRMM in combination with lenalidomide or pomalidomide. Besides the need for lenalidomide dose adjustment in these regimens, elotuzumab safety profile is not affected by RI.[103] Belantamab mafodotin is a first-in-class anti-B-cell maturation antigen (BCMA) immunoconjugate with a humanized IgG1 anti-BCMA MoAb conjugated by a maleimidocaproyl linker to a microtubule-disrupting agent, monomethyl auristatin F. This is being used in a limited fashion with recent withdrawal from the US market. Its single-agent anti-MM activity is not influenced by mild-to-moderate RI, but no data are available for severe RI and clinical trials are underway.[104] Teclistamab is a bispecific BCMA-directed CD3 T-cell engager, which binds BCMA on plasma cells and CD3 on T lymphocyte with the activation of T-cell receptor and resultant tumoricidal activity. There is no indication to reduce the scheduled dose of 1.5 mg/kg weekly of teclistamab by renal function, but prospective confirmatory data are needed.[105] Finally, engineered T cells against BCMA on MM cells (CAR-T) have been a landmark addition to management options for

MM, aiming to provide deep responses and long treatment-free intervals in patients. Similar to other novel immunotherapies, anti-BCMA CAR-T cells have not been reported to have any detrimental effects in patients with RI, although prospective studies establishing their safety and efficacy in MM patients with varying degrees of RI are not yet available.[106] A summary of various strategies in managing MM patients with RI is presented in Figure 2.

CONCLUSION

Lack of universal representation of patients in prospective data generation has led to creation of underrepresented groups in the MM demographic. Although all patients have universally benefitted from a wide range of therapeutic advances in MM, this benefit has been to a disparate extent, with lesser access and benefit realized for some of these traditionally underrepresented groups. Increased awareness of these issues, addressing any implicit or explicit bias, universal inclusion in prospective clinical trials, and day-to-day acknowledgment of these clinical and sociodemographic factors will help in achieving an efficient patient-physician partnership and achieve shared decision making with widespread applicability of evidence-based treatment approaches.

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COVID-19 and Other Viral Infections in Patients With Hematologic Malignancies

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Overview

COVID-19 and our armamentarium of strategies to combat it have evolved dramatically since the virus first emerged in late 2019. Vaccination remains the primary strategy to prevent severe illness, although the protective effect can vary in patients with hematologic malignancy. Strategies such as additional vaccine doses and now bivalent boosters can contribute to increased immune response, especially in the face of evolving viral variants. Because of these new variants, no approved monoclonal antibodies are available for pre-exposure or postexposure prophylaxis. Patients with symptomatic, mild-to-moderate COVID-19 and risk features for developing severe COVID-19, who present within 5-7 days of symptom onset, should be offered outpatient therapy with nirmatrelvir/ritonavir (NR) or in some cases with intravenous (IV) remdesivir. NR interacts with many blood cancer treatments, and reviewing drug interactions is essential. Patients with severe COVID-19 should be managed with IV remdesivir, tocilizumab (or an alternate interleukin-6 receptor blocker), or baricitinib, as indicated based on the severity of illness. Dexamethasone can be considered on an individual basis, weighing oxygen requirements and patients' underlying disease and their perceived ability to clear infection. Finally, as CD19-targeted and B-cell maturation (BCMA)–targeted chimeric antigen receptor (CAR) T-cell therapies become more heavily used for relapsed/refractory hematologic malignancies, viral infections including COVID-19 are increasingly recognized as common complications, but data on risk factors and prophylaxis in this patient population are scarce. We summarize the available evidence regarding viral infections after CAR T-cell therapy.

INTRODUCTION

The COVID-19 pandemic has caused significant morbidity and mortality worldwide, disproportionately affecting patients with impaired immune function, such as those with underlying hematologic or oncologic disease or because of active cancer therapy. Vaccines have emerged as one of the most powerful tools for preventing COVID-19 illness and its complications. The efficacy of vaccination in this patient population, however, can vary. This section summarizes the evidence for COVID-19 prevention with vaccines (including bivalent boosters) and monoclonal antibodies (mAbs) in oncology patients.

COVID-19 INITIAL (MONOVALENT) VACCINES

The pandemic has not only upended the medical community in many ways but has also led to significant advances in vaccine development. With billions of COVID-19 vaccine doses administered worldwide, the safety and efficacy of these vaccines in preventing severe disease and death have been demonstrated. As of December 2022, there were 242 vaccine candidates worldwide, with 50 approved for use with a variety of immunogens used. The prefusion-stabilized spike protein of the SARS-CoV-2[1] is the most used vaccine antigen. This review will focus primarily on vaccinations currently approved in the United States (Table 1). The three types of vaccines approved or authorized in the United States include nucleic acid, protein subunit, and viral vector delivery systems. Nucleic acid (messenger RNA or mRNA) and viral vector vaccines use cellular processes to make the conformationally appropriate protein (spike) to elicit a protective immune response while protein subunit vaccines deliver the immunogen directly.

Of the four vaccines approved in the United States, two use mRNA technology. Pfizer-BioNTech's Comirnaty (BNT162b2) was approved by the US Food and Drug Administration (FDA) in August 2021 for individuals age 16 years and older after receiving FDA Emergency Use Authorization (EUA) in December 2020 after demonstrating efficacy at preventing mild-to-moderate COVID-19.[2] BNT162b2 is currently approved for individuals age 12 years and older for a primary series of two doses separated by 3-8 weeks and for age 6 months to 11 years under EUA, with trials assessing a primary series of three vaccine doses.[3]

Moderna's Spikevax (mRNA-1273) is the second mRNA vaccine also granted EUA in December 2020

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PRACTICAL APPLICATIONS

- Patients with blood cancer are at elevated risk of morbidity and mortality from COVID-19.
- Vaccination remains the most important line of defense against COVID-19, including among patients with blood cancer.
- Outpatient and inpatient evidence-based treatments are available to decrease the morbidity and mortality of COVID-19 among patients with blood cancer.
- Viral infections, especially respiratory viruses, are prevalent in the later phase after chimeric antigen receptor (CAR) T-cell therapy, when lymphopenia and hypogammaglobulinemia become common.
- Mortality after COVID-19 infection in CAR T-cell recipients remains high, and prevention with adequate mask wearing and social distancing and repeated booster doses of mRNA vaccines to maximize T-cell response are part of ongoing consensus recommendations.

and full approval for individuals age 18 years and older in January 2022. The primary series has two doses 4 weeks apart for all age groups, with a vaccine efficacy of 94% to prevent mild-to-moderate COVID infection.[4] The CDC recommends that males age 12-39 years receiving the second dose of the primary series can consider increasing duration until 8 weeks after the first dose to minimize the risk of myocarditis.[5] Myocarditis is reported as a complication in both mRNA vaccines, more common in males, those younger than 30 years, and after the second dose of the vaccines.[6,7] Limitations in mRNA vaccines include the need for storage at freezer temperatures, which can, unfortunately, constrain access or hinder distribution in some settings. Dosages for children are different than those for adults, which will not be covered here in detail.

The third approved vaccine is Johnson & Johnson's Janssen (Ad26.COV2.S) virus vector vaccine, a replication-incompetent adenovirus 26 vector, which was authorized in February 2021. The initial one-shot strategy led to ease of administration and uptake; however, vaccine efficacy against severe critical disease was lower (85%),[8] and several months after EUA, concerns about reports of severe cerebral venous sinus thrombosis related to vaccine-induced antiplatelet factor-4 antibodies prompted a pause on the vaccine (which was eventually lifted).[9] However, in December 2021, the CDC recommended a preference for mRNA vaccinations. Ultimately, guidance on use emerged stating that the vaccine is available for adults 18 years and older who request the vaccine or have a contraindication to other vaccination types and should not be given to persons with a history of thrombosis with thrombocytopenia or heparin-induced thrombocytopenia.

The fourth vaccine created by Novavax (Nuvaxovid and Covovax NVX-CoV2373) is a recombinant, protein-adjuvanted vaccine that in studies has performed similarly to mRNA vaccines (90% efficacy in clinical trials[10,11]) and was the fourth COVID-19 vaccination to receive EUA in the United States in July 2022 for individuals age 12 years and older, two doses 3-8 weeks apart.

The speed with which these vaccines emerged partly relates to different manufacturing processes, with the mRNA platform being the nimblest. The challenges in manufacturing are a significant consideration as public health authorities plan future updates to these vaccines and determine the clinical importance of the vaccine insert/antigen matching the circulating stain as closely as possible, an issue the community routinely debates with the annual influenza vaccine.

VACCINE RESPONSE IN IMMUNOCOMPROMISED HOSTS AND ADDITIONAL VACCINE DOSES

Because of many studies demonstrating lower vaccine effectiveness and decreased or absent neutralizing antibody response in patients with underlying hematologic malignancy or receiving B-cell depleting therapies,[12-15] the Advisory Committee on Immunization Practices advised immunocompromised patients who received mRNA vaccination two-dose series to receive a third mRNA vaccine dose as part of their primary series 4 weeks after the second dose or a first dose of mRNA vaccine if Ad26.COV2.S was

TABLE 1. Approved/Authorized SARS-CoV-2 Vaccines in the United States

Name of Vaccine	Date EUA Issued for Primary Series in Adults	Date of FDA Approval	Delivery System
Pfizer-BioNTech Comirnaty BNT162b2[92]	December 11, 2020	August 23, 2021	mRNA
Moderna Spikevax mRNA-1273[93]	December 18, 2020	May 31, 2022	mRNA
Johnson & Johnson Janssen Ad26.COV2.S[94]	February 27, 2021		Viral vector
Novavax Nuvaxovid & Covovax NVX-CoV2373[95]	July 13, 2022		Protein subunit

Abbreviations: EUA, Emergency Use Authorization; FDA, US Food and Drug Administration.

given previously.[16] Patients are considered immunocompromised with the use of active chemotherapy, hematologic malignancy, hematopoietic stem-cell or solid organ transplant (SOT), untreated HIV with CD <200, moderate-to-severe primary immunodeficiency, or immunosuppressive therapy (including but not limited to the use of rituximab, steroid equivalent of prednisone >20 mg/day once daily for >14 days).[17] Those with hematologic malignancy, specifically those receiving anti-CD20 agents, often fail to develop neutralizing antibodies to COVID-19 and are at high risk for COVID-19–associated complications.[18,19] In these patients, the emergence of COVID-19–specific T-cell responses is associated with clinical improvement, pointing out the importance of redundancy in adaptive immune responses.[19] Given the many logistical challenges in assessing T-cell responses, many immunologic assessments of vaccine-elicited immune responses have focused on neutralizing and binding antibodies. In other immunosuppressed populations, such as those who have received a SOT, observational studies have demonstrated higher immune responses and vaccine efficacy with a three-dose mRNA initial series compared with two doses.[20-23]

Other strategies to consider improving immune responses to vaccination include holding immunosuppression around the timing of vaccination or strategically timing vaccination to target periods of lower immunosuppression or breaks in therapy (eg, 4 weeks before rituximab administration[24] and in SOT, decreasing mycophenolate mofetil dosing at the time of vaccination[25]). Finally, revaccination with primary series should be considered for any individual 3 months after undergoing hematopoietic stem-cell transplantation or chimeric antigen receptor (CAR) T-cell therapy.[26]

BOOSTERS (MONOVALENT AND BIVALENT)

Waning of immune responses associated with increased breakthrough infections has been observed after the completion of the primary vaccination series.[27,28] This led to broad recommendations for vaccine booster immunizations in the late summer of 2021. Subsequent work has raised questions about the frequency of booster immunizations, given an improved understanding of the durability of protection. It is important to carefully assess the significance of breakthrough infections as these are mainly mild-to-moderate illnesses with persistent strong protection against severe illness and death.

Another important consideration is the viral evolution that has occurred, allowing the virus to better adapt to the human host and transmit more efficiently, as well as to escape dominant immune responses. With new emerging variants that can escape previous immune responses, such as the Omicron variants, rapid global spread occurs. The emergence of new variants, which can partially escape previous immunity, raises important considerations for vaccine development and which vaccine antigen(s) should be in the vaccines used.

For example, the emergence of the Omicron variants and concern for decreased efficacy of the original vaccine antigens in use led the FDA on August 31, 2022, to provide EUA for the bivalent mRNA vaccine boosters (Pfizer bivalent if 5 years and older and Moderna 6 months and older) that target the Omicron BA.4/5 variants and deauthorize the original monovalent vaccine antigen. This decision was based mainly on immunologic data demonstrating improved Omicron-directed neutralizing antibody immune responses and dominance of the Omicron variants circulating in the community. Notably, other communities, such as the United Kingdom, authorized the BA.1 component rather than BA.4/5.

These vaccines contain equal parts of the spike protein sequence from the initial ancestral strain and BA.4/5 strains of the Omicron variant (B.1.1.529). They can be administered 2 months after completing the primary series or monovalent boosters from any of the four vaccine regimens listed above (only mRNA boosters are currently available).[29] Since approval, bivalent boosters have been shown to provide additional protection against severe infection during Omicron waves that emerged in late 2021, even in those previously vaccinated and boosted, with vaccine effectiveness similar to mRNA vaccines and conferring an increase in Omicron-neutralizing antibodies.[30,31] Furthermore, bivalent mRNA boosters have demonstrated protection in the immunocompetent against symptomatic disease for at least 3 months in the fight against ever-evolving variants, most recently, Omicron BA.2-related sublineage XBB.1.5, which emerged in early 2023, although overall low population uptake of bivalent boosters has been noted (approximately 10% of the eligible population).[32] It remains difficult to tease out the importance of the vaccine antigen matching the circulating strains versus the waning of immunity over time as to the drivers of booster-associated protection. Efficacy data on these strategies should be forthcoming.[33]

The impact of waning immunity and long-standing vaccination strategies are not yet known. In the future, it will be important to weigh the goals of achieving high serum-neutralizing antibody levels and long-standing cellular immunity against booster fatigue and the need for clear, consistent communication. Future recommendations regarding booster doses will require robust supporting evidence to achieve what we define as success (eg, preventing hospitalizations and death).[34,35]

MONOCLONAL ANTIBODIES FOR PREVENTION OF DISEASE IN ONCOLOGY PATIENTS

mAbs have been demonstrated to have a role in preventing COVID-19 infection in patients at high risk of severe disease

as either pre-exposure or postexposure prophylaxis (such as those with household contacts who are infected with COVID-19). mAbs function as passive immunity as an antibody cocktail containing different antibodies targeting the spike protein, such as the receptor-binding domain. Given the risk of viral escape, using two antibodies can minimize the mutational escape of the virus and prolong the utility of a given mAb cocktail. During the pandemic, availability, cost, and logistics of outpatient administration of mAbs were barriers to widespread use; however, the emergence of escape mutants is an even larger barrier to these therapies. Intramuscular AZD7442 (tixagevimab and cilgavimab—Evusheld), a combined mAb, was authorized for EUA in December 2021[36] after the initial study showed a relative risk reduction of symptomatic COVID-19 of 83% at 6 months in those who had an inadequate vaccine response.[37] Further studies confirmed this protective effect[38,39] and showed increased protection with higher doses, adjusted in guidance.[40] This was the only mAb approved for pre-exposure prophylaxis until January 23, 2023, when the FDA revised the EUA to limit use, as the new nonsusceptible Omicron subvariants (XBB.1.5, BQ.1.1) were projected to be more than 90% of infections in the United States.[41] As such, there are currently no approved mAbs for pre-exposure prophylaxis.

Postexposure prophylaxis, like pre-exposure prophylaxis, was previously authorized by EUA by the FDA for mAb casirivimab-imdevimab (REGEN-COV)[42] and bamlanivimab-etesevimab[43] to prevent SARS-CoV-2 infection in select individuals older than 12 years. Casirivimab-imdevimab decreased the risk of developing symptomatic and asymptomatic infection and reduced the duration of symptoms and high viral load in household contacts.[44] Bamlanivimab alone was assessed in nursing home residents to reduce the risk of developing COVID-19.[45] Although these therapies were effective during surges of cases with delta variants, with the onset of the Omicron subvariants, both treatments are rendered ineffective and thus are no longer supported by EUA. No current mAb therapies are currently available for clinical use for circulating variants.

In addition to vaccination strategies, it is essential to implement other measures to reduce the risk of COVID-19 in oncology patients. These measures include social distancing, mask wearing, and hand hygiene. Oncology clinics may also consider implementing telemedicine and other virtual care options to reduce the risk of exposure to the SARS-CoV-2 virus in the clinical setting. All household members should also be vaccinated to enhance the cocooning of vulnerable patients. Ultimately, a multifaceted approach that includes vaccination, nonpharmacologic interventions, and close monitoring of oncology patients is necessary to prevent and manage COVID-19 in this vulnerable population.

COVID-19 MANAGEMENT IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Vaccination is the most important tool to decrease morbidity and mortality from COVID-19, but not all patients accept or have access to complete vaccination. Additionally, as discussed above, some patients with blood cancer remain at risk of severe COVID-19 despite being fully vaccinated.

This section reviews the management of adult patients with blood cancer and COVID-19, focusing on outpatient management and implications for ongoing cancer treatment. The COVID-19 field continues to evolve rapidly, and review articles are at risk of needing to be updated soon after publication. Fortunately, high-quality, evidence-based guidelines, including three living guidelines, are available on this topic (Table 2).

OUTPATIENT MANAGEMENT

Severe COVID-19 is defined as SARS-CoV-2 infection with hypoxemia, respiratory distress (respiratory rate >30), and/or severe pneumonia on imaging (>50% infiltrates).[46,47] Patients with mild-to-moderate COVID-19, who are at high risk of progression to severe COVID-19, should be

TABLE 2. Evidence-Based Guidelines on the Management of COVID-19

Organization	Title	Living[a]	Link
WHO	WHO Therapeutics and COVID-19: living guideline	Yes	https://app.magicapp.org/#/guideline/nBkO1E https://www.bmj.com/content/370/bmj.m3379
National Clinical Evidence Taskforce	Australian guidelines for the clinical care of people with COVID-19	Yes	https://app.magicapp.org/#/guideline/L4Q5An/section/L0OPkj
IDSA	IDSA Guidelines on the Treatment & Management of Patients with COVID-19	Yes	https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
NIH	NIH COVID-19 Treatment Guidelines	No	https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/
NICE	COVID-19 rapid guideline: managing COVID-19	No	https://www.nice.org.uk/guidance/ng191

Abbreviations: IDSA, Infectious Diseases Society of America; NICE, National Institute for Health and Care Excellence; NIH, National Institutes of Health.
[a]Living guidelines are updated as new evidence becomes available.

TABLE 3. When to Consider Antiviral Treatment in Patients With Active or Previous Blood Cancer and Symptomatic, Mild-to-Moderate COVID-19

COVID-19 Treatment Recommended[a]	Reasonable to Consider COVID-19 Treatment[a]	May Not Need Treatment for COVID-19
Age older than 65 years Unvaccinated Partially vaccinated and/or last shot >6 months prior Vaccinated, but anticipate poor response to vaccination because of immunodeficiency, past administration of B-cell–depleting therapy, hypogammaglobulinemia, etc On active treatment for blood cancer Within 2 years of stem-cell transplant or CAR-T therapy Solid organ transplant HIV with CD4 count <200 ≥1 additional comorbidity on CDC list[49] Living in long-term care	Absence of risk factors in column 1 and age 50-64 years	None of the risk factors in column 1 or 2 and able to follow-up in the event of clinical deterioration

NOTE. This table considers inclusion criteria of relevant randomized clinical trials, CDC systematic review of risk factors, and National Institutes of Health guidelines.[46,49-52,59] Decisions to treat should be made using a shared decision-making framework.
Abbreviations: CAR, chimeric antigen receptor; CDC, Centers for Disease Control and Prevention.
[a]COVID-19 treatment should only be offered in the absence of known contraindications to treatment.

considered for outpatient, antiviral treatment.[46-48] Table 3 outlines an approach to risk stratification in patients with hematologic malignancy informed by National Institutes of Health guidance, CDC risk criteria, and inclusion criteria from relevant trials.[49-52] The most important and consistently identified risk factor of severe COVID-19 is older age. An active or recent diagnosis of blood cancer, cancer treatment (especially B-cell–depleting treatments), immunodeficiency, transplant (cellular or solid organ), cellular therapy, >1 major comorbidity, and absent, incomplete, or distant (>6 months prior) vaccination are all associated with a higher risk of severe COVID. It is anticipated that most patients followed in blood cancer clinics will have risk features for severe COVID-19.

Figure 1 illustrates a pragmatic, evidence-based approach to outpatient management of adult patients with blood cancer and symptomatic, mild-to-moderate COVID-19. In the absence of contraindications, nonhypoxemic patients with risk features for progression to severe COVID-19 should be offered antiviral therapy if presenting within 5-7 days of symptom onset. All patients with blood cancer and mild-to-moderate COVID-19 should receive supportive care and be counseled regarding symptoms that should trigger an urgent reassessment. Where available, telehealth-based COVID-19 monitoring clinics can be helpful.

At the time of writing, the recommended first-line treatment for symptomatic, higher-risk outpatients with mild-to-moderate COVID-19, presenting within 5 days of symptom onset, is nirmatrelvir plus ritonavir (NR).[46,47] NR received emergency use authorization from the FDA in December 2021 after the EPIC-HR clinical trial showed that among unvaccinated patients, without a known history of COVID-19, presenting for treatment within 5 days of symptom onset, a 5-day course of NR reduced the 28-day rate of COVID-19 hospitalization, and/or death from COVID-19 from 6.3% to 0.77% with a number needed to treat (NNT) of 18.[50] Although prospective data are lacking in a vaccinated/naturally immune population, large real-world observational studies suggest that NR remains beneficial in this setting, reducing the risk of hospitalization or death, albeit with a higher NNT.[53-55] A large, ongoing UK randomized clinical trial (RCT) is expected to shed further light on the efficacy of NR in a vaccinated population.[52]

Importantly, patients with severe renal or hepatic dysfunction are not eligible for NR. Ritonavir (R) is also an inhibitor of CYP3A4, and drug interactions can complicate or prevent its use. Many treatments for hematologic malignancy have important interactions with R (eg, BTK inhibitors, tyrosine kinase inhibitors, and venetoclax). Clinicians should consult their local pharmacist regarding potential interactions and/or access available drug interaction databases such as the Liverpool Drug Interaction Database[56] or the University Health Network online reference on NR drug interactions in oncology.[57]

Intravenous (IV) remdesivir represents an alternative to NR in eligible patients presenting within 7 days of symptom onset. In an RCT of nonhypoxemic, unvaccinated, higher-risk outpatients, remdesivir reduced the risk of hospitalization or death within 28 days from 5.3% to 0.7% with an NNT of 22.[51] A small number of patients in this trial had immune compromise and/or cancer (4.1% and 5.3%, respectively). As with NR, prospective data on the efficacy of remdesivir in a vaccinated and/or naturally immune population are lacking, and the NNT is likely higher in this context. Like NR, remdesivir is not recommended in patients with a creatinine clearance of <30 mL/min, although some experts suggest that it can be used with caution and close monitoring. However, the main barrier to remdesivir is

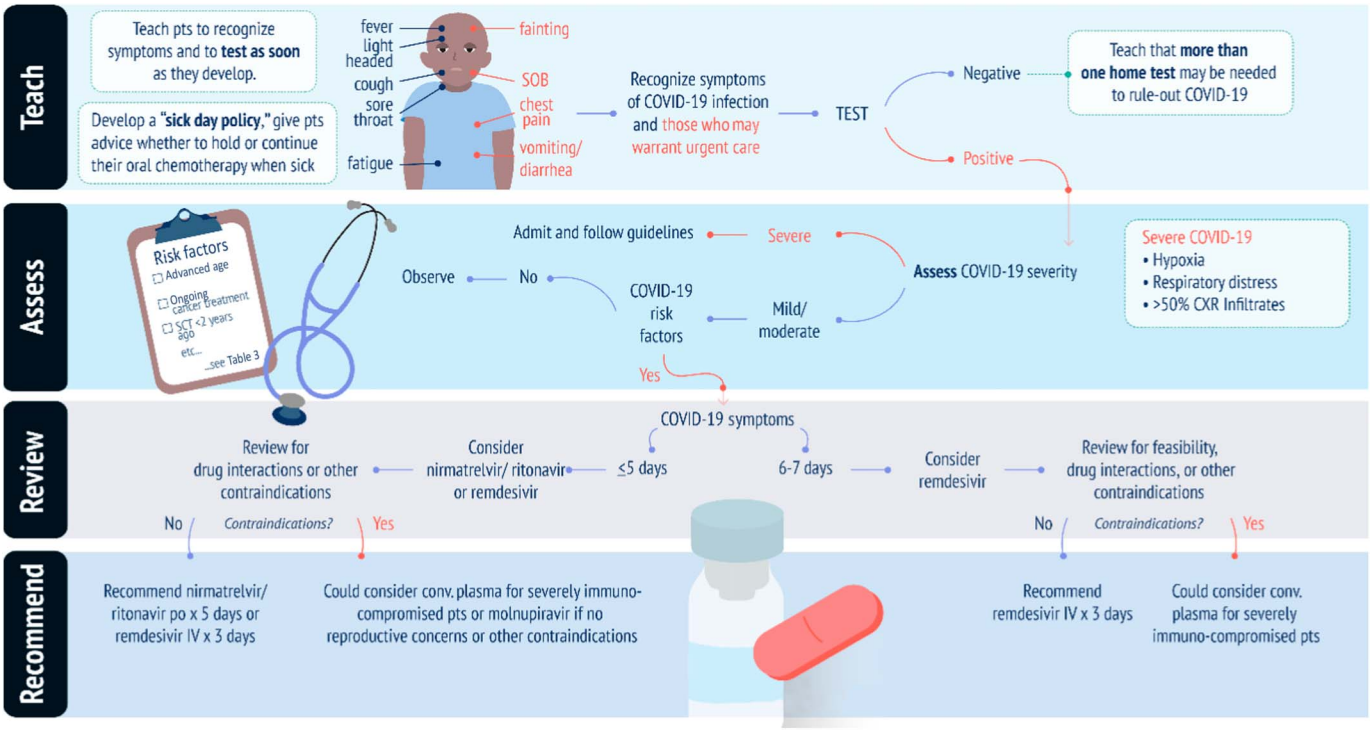

FIG 1. Approach to outpatient management of patients with blood cancer and COVID-19. conv., convalescent; CXR, chest x-ray; IV, intravenously; po, orally; pts, patients; SCT, stem-cell transplant; SOB, shortness of breath.

operational. The drug requires three consecutive days of IV administration started within 7 days of symptom onset—a challenge for many clinics which operate 5 days a week and may not have the capacity to safely isolate patients with COVID-19 from other immunocompromised patients with cancer.

When neither NR nor remdesivir is available nor appropriate, some guidelines[46,48] recommend molnupiravir. The MOVe-OUT study reported that among higher risk, outpatients with mild-to-moderate COVID-19, presenting within 5 days of symptom onset, hospitalization/death within 29 days decreased from 9.7% to 6.8% (NNT of 34) with a 5-day course of oral molnupiravir.[58] Vaccinated patients were excluded from this trial; 74.1% of included patients had no evidence of past infection, and only 2% of participants had cancer. In addition, a recent large RCT of molnupiravir in higher-risk, vaccinated patients showed limited benefit with hospitalization rate and/or death of 1% in both arms.[59] Additionally, there is concern about the mutagenic potential of this drug.[48] Nonetheless, it remains an option for selected high-risk outpatients with blood cancer who have contraindications to NR and remdesivir.

As previously discussed, mAbs were recommended for the outpatient treatment of COVID-19; however, in vitro data show that these agents are not effective against newly dominant SARS-CoV-2 variants, and thus, they are no longer recommended.[46,48] There are some data suggesting benefit from high-titer convalescent plasma, among immunocompromised outpatients, particularly those without an effective response to vaccination. However, data are mixed[48] and operational challenges limit this therapy's routine use, even in resource-rich environments.

Emerging outpatient therapies for COVID-19 are not yet approved for clinical use but may become available in the coming months and years. Oral analogs of remdesivir are under active investigation, and a recent RCT reported that VV116 (one such analog) is noninferior to NR in reducing symptoms among patients with mild-to-moderate COVID-19.[60] mAbs targeting regions of the SARS-CoV-2 virus that tend to be highly conserved are also under investigation.[61] In addition, a single subcutaneous injection of pegylated interferon (IFN) lambda was recently reported to reduce hospitalizations/emergency department visits, when given within 7 days of symptom onset.[62] This trial contained mostly higher-risk patients, patients infected with the Omicron variant (40%), and vaccinated patients (83% were at least partially vaccinated). Viral evolution is unlikely to overcome IFN's mechanism of action. However, data will be required among immunosuppressed patients, such as those with blood cancer, as the hepatitis C literature suggests that some immunocompromised patients are less responsive to IFN.[63]

INPATIENT MANAGEMENT

Patients who have mild-to-moderate COVID-19 and are hospitalized for other reasons should be managed in the same manner as outpatients with mild-to-moderate COVID-19. Excellent evidence-based guidelines are available regarding the management of patients with severe COVID-19 (Table 2), and a detailed discussion of the evidence is outside of the scope of this review. Briefly, a 5-day course of IV remdesivir is recommended in patients who require conventional oxygen support, but not among those requiring high-flow oxygen or mechanical ventilation. A 10-day course of low-dose (6 mg daily) dexamethasone is generally recommended in patients with hypoxemia; the course can be shortened in those ready for early discharge. Notably, patients with blood cancers were not represented in trials of dexamethasone in moderate-to-severe COVID-19,[64,65] and potential benefits need to be weighed against the risks of additional immunosuppression in this vulnerable population. In patients with critical COVID-19, evidence supports the addition of tocilizumab (or an alternate interleukin-6 receptor blocker) or baricitinib (a JAK inhibitor).[46-48]

Therapeutic anticoagulation is recommended for nonpregnant hospitalized patients who require oxygen and have D-dimer levels above the upper limit of normal in the absence of excess bleeding risk.[46] All other patients should receive prophylactic anticoagulation. The recommendation for therapeutic anticoagulation is based on three randomized controlled trials that demonstrated improvements in mortality as a secondary outcome, thrombosis and/or mortality as a composite outcome, or organ-support free days.[66-68] These trials included <10% patients with cancer. Special considerations in patients with hematologic malignancy include the possibility of thrombocytopenia, increased risk of thrombosis, and increased risk of bleeding with therapeutic anticoagulation compared with other patients.

APPROACH TO CANCER TREATMENTS

In most cases, holding immunosuppressive cancer therapy in patients with acute COVID-19 infection is appropriate. However, it is acknowledged that with some aggressive blood cancers, there can be competing causes of morbidity and mortality and that in some situations, cancer treatment may take precedence. When deciding to hold versus continue cancer treatment, clinicians should consider factors such as the urgency of cancer treatment, the intention of treatment (curative versus palliative), the anticipated depth of immunosuppression, the severity of COVID-19 symptoms, and the patient's risk of progressing to severe COVID-19. Decisions regarding when to resume cancer treatment depend on symptom resolution, local infection control practices, and the urgency of cancer treatment. In some cases, polymerase chain reaction (PCR) cycle threshold values (the number of PCR cycles required to reach threshold of positivity) and chest imaging may help the clinician distinguish between active COVID-19 infection and a residual positive test from resolved infection. Workup should be undertaken to assess for persistent COVID-19 infection, opportunistic infection or coinfection, and/or complications of COVID-19 in those with ongoing symptoms. Patients with suspected persistent infection should be discussed with local infectious disease experts.

VIRAL INFECTIONS AFTER CAR T-CELL THERAPIES

Patients receiving CD19- or BCMA-directed CAR T cells are at increased risk of infectious complications because of a combination of effects related to previous and concurrent therapies. On-target effects of the lymphodepletion (LD) chemotherapy and adoptive T cells include the depletion of B cells and plasma cells, leading to selective aplasia and subsequent hypogammaglobulinemia, loss of the endogenous helper T-cell repertoire, and reduced ability to mount an adaptive response to viral infections.[69] Interventions to mitigate CAR T-cell–associated toxicities, including treatment of cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) with corticosteroids and tocilizumab, also contribute to immune dysregulation and an increased risk of infection. Furthermore, all currently available commercial CAR T-cell therapies for B-cell non-Hodgkin lymphoma (B-NHL) or multiple myeloma are approved for patients with multiply relapsed or refractory disease, with patients' previous treatments further contributing to baseline depleted antibody repertoire and reduced ability to mount viral-specific neutralizing antibodies.[69] The CAR construct has an indirect impact on infectious risk—CD28-based constructs confer a higher risk of severe CRS and ICANS that often require greater dose intensity of steroids and/or anticytokine therapies to manage compared with 4-1BB–based constructs; BCMA-directed constructs produce a more profound B-cell and plasma cell depletion, leading to greater degrees of hypogammaglobulinemia and loss of viral-specific humoral repertoire.[70] In a retrospective single-institutional study of infectious outcomes after anti-BCMA and anti-CD19 CAR T-cell therapies, the incidence of viral infections in the first year was much higher in patients receiving anti-BCMA CAR T cells (53% *v* 20%, respectively).[71]

EPIDEMIOLOGY AND RISK FACTORS FOR VIRAL INFECTIONS POST-CAR T-CELL INFUSION

Data on infectious complications following after T-cell therapy have been derived primarily from single-center retrospective studies and scant adverse event reporting provided from registry trials and are difficult to interpret because of the wide variability in patient characteristics and center-specific antimicrobial and antiviral prophylaxis use. In contrast to bacterial pathogens that predominate early

TABLE 4. Summary of Data on Viral Infectious Complications From CAR T-Cell Therapy

Reference	CAR T-Cell Product(s) Received	No.	Disease	Time Point	Viral Infection Incidence, No. (%)	Type
Abramson et al[96]	Lisocabtagene maraleucel	269	R/R B-cell lymphoma	12 months	4 of 269 (1), (grade ≥ 3 infections)	Coronavirus CMV JC virus Parainfluenza virus
Locke et al[97]	Axicabtagene ciloleucel	108	R/R B-cell lymphoma	12 months	11 of 108 (10)	CMV HHV-6 Hepatitis B Herpes simplex Influenza Parainfluenza Rhinovirus Varicella zoster
Logue et al[77]	Axicabtagene ciloleucel	85	R/R B-cell lymphoma	≤30 days	12 of 85 (14)	Influenza Rhinovirus Respiratory syncytial virus
				>30 days	19 of 85 (22)	
Wittmann Dayagi et al[98]	CD19.CD28.3z CAR T-cells	88	R/R B-cell lymphoma	≤30 days	14 of 85 (16)	BK virus CMV Enterovirus Epstein-Barr virus
				>30 days	2 of 85 (2)	
Baird et al[75]	Axicabtagene ciloleucel	41	R/R B-cell lymphoma	≤30 days	8 of 41 (19.5)	BK virus CMV HHV-6 Respiratory viruses (respiratory syncytial virus, rhinovirus) Varicella zoster virus
				>30 days	10 of 41 (24.4)	
Wudhikarn et al[69]	Axicabtagene ciloleucel, tisagenlecleucel	60	R/R B-cell lymphoma	≤30 days	10 of 60 (17)	Adenovirus BK virus Coronavirus CMV Human metapneumovirus Influenza virus Norovirus Parainfluenza Rhinovirus Varicella zoster virus
				>30 days	17 of 60 (28)	
Hill et al[76]	CD19.41BB.3z.EGFRt CAR T-cells	133	R/R B-cell lymphoma B-cell ALL	≤28 days	11 of 133 (8.3)	BK virus Coronavirus CMV Human metapneumovirus Influenza Parainfluenza Rhinovirus
Kambhampati et al[71]	CD19 CAR-T cells	49	R/R B-cell lymphoma	12 months	27 of 49 (55)	
Munshi et al[99]	Idecabtagene vicleucel	54	R/R Myeloma	12 months	15 of 54 (28)	
Kambhampati et al[100]	BCMA CAR T-cells (JCARH125, BB2121, BB21217, JNJ-4528)	55	R/R Myeloma	12 months	25 of 55 (53)	

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CMV, cytomegalovirus; HHV-6, human herpesvirus 6; JC, John Cunningham; R/R, relapsed/refractory.

when neutropenia is most prevalent (often designated within the first 30 days postinfusion), viruses are more prevalent after day +30 when lymphopenia and hypogammaglobulinemia become two critical components of immune dysfunction.[72] The cumulative incidence of viral infections in patients undergoing CD19 and BCMA CAR T-cell therapies over the first year postinfusion ranges from 8.3% to 28% and 28% to 53%, respectively (Table 4).

Risk factors for viral infections identified in multivariate analyses include previous autologous or allogeneic stem-cell transplant, receipt of bridging therapy, and receipt of steroids or tocilizumab postinfusion.[73] Prolonged CD4 T-cell lymphopenia, B-cell aplasia, and hypogammaglobulinemia affect up to 46% of patients at day +90 and have variably been associated with increased infection density.[74,75] Opportunistic viral respiratory pathogens appear to be the most common late infection after CAR T-cell infusion, with rhinovirus being the most common pathogen identified.[69,75,76] This may be related to CAR T-cell recipients transitioning back to the community early after treatment. Less common infections include herpes simplex virus (HSV) and varicella zoster virus (VZV) reactivation, given the near universal prophylaxis with acyclovir, but have been described in association with stomatitis, cutaneous eruptions, encephalitis, hepatitis, esophagitis, pneumonitis, or bone marrow suppression.[69,75,76] Human herpesvirus 6 reactivation has been associated with encephalitis, bone marrow suppression, and pneumonitis in case reports.[74,77] Although data are limited, symptomatic cytomegalovirus reactivation appears to be uncommon while asymptomatic viremia may be more prevalent than previously recognized.[75,78] Routine monitoring is not currently advised, except in high-risk patients (eg, after allogeneic transplant or `exposure to high-dose/long-term corticosteroids). Progressive multifocal leukoencephalopathy due to JC virus has been reported in a patient with relapsed large B-cell lymphoma 1 year after CAR T-cell therapy.[79] Finally, CAR T-cell manufacturing and subsequent treatment are feasible and safe in patients with hepatitis B virus (HBV),[80,81] hepatitis C virus,[82] and HIV[83,84] infections, provided adequate treatment leads to undetectable viral loads before apheresis and starting LD.[85] A cohort of 70 patients identified as chronic HBV carriers before receiving CAR T-cell therapy demonstrated no significant difference in toxicity and response when compared with patients without HBV.[86]

COVID-19 (SARS-CoV-2) IN CAR T-CELL PATIENTS

Patients with hematologic malignancies undergoing cellular therapy are among the highest risk group of developing severe SARS-CoV-2 infection and having prolonged viral clearance time of up to 2 months.[87] Data from the European Hematology Association (EHA) reported an incidence of COVID-19 of 4.8% with a median time from CAR T-cell therapy to infection of 169 days. Severe illness was observed in 67%, and COVID-19–related mortality was around 50%, which is significantly higher compared with the case fatality ratio of 1.8% in the general US population.[88,89] Another study also reported a high mortality rate of 45% at 6 months after COVID-19 diagnosis.[90] Mortality after SARS-CoV-2 infection in CAR T-cell recipients was also higher than in stem-cell transplant recipients (approximately 32%),[91] likely because CAR T-cell recipients have on average higher comorbidity burdens. Lymphopenia was an independent factor correlating with the degree of COVID-19 severity. Prevention with adequate mask wearing, social distancing, and repeated booster doses of mRNA vaccines to maximize T-cell response is part of ongoing consensus recommendations.[26]

ANTIVIRAL PROPHYLAXIS IN CAR T-CELL PATIENTS

Primary data are lacking on the optimal regimen and duration for antimicrobial prophylaxis after CAR T-cell infusion, and thus, current guidance is based on expert opinion.[72,75] Acyclovir is recommended from the initiation of LD chemotherapy for HSV prophylaxis. The duration of acyclovir use should be for at least a year or until CD4 lymphocyte counts recover to >200 cells/μL. Patients who are hepatitis B carriers (HBs Ag–positive or detectable HBV DNA in blood) should strongly consider prophylaxis with entecavir or tenofovir for at least 6 months, along with surveillance for reactivation by checking liver function test and HBV DNA. In patients who have a history of hepatitis B infection (HBs Ag and HBV DNA–negative, anti-HBc Ab immunoglobulin G–positive), surveillance with testing for HBV DNA and liver function test every 1 -3 months can be considered as an alternative to prophylaxis. Immunoglobulin levels should be measured routinely, and IV or subcutaneous immunoglobulin replacement can be considered to maintain serum levels >400 mg/dL in adults to reduce the risk and severity of sinopulmonary infections.

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Older Adults With Newly Diagnosed AML: Hot Topics for the Practicing Clinician

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overview

Over the past decade, our understanding of AML pathogenesis and pathophysiology has improved significantly with mutational profiling. This has led to translational advances in therapeutic options, as there have been 10 new US Food and Drug Administration (FDA) approvals for AML therapies since 2017, half of which target specific driver mutations in *FLT3*, *IDH1*, or *IDH2*. These new agents have expanded the therapeutic armamentarium for AML, particularly for patients who are considered ineligible for intensive chemotherapy with anthracycline- and cytarabine-containing regimens. These new treatment options are relevant because the median age at diagnosis is 68 years, and outcomes for patients older than 60 years have historically been dismal. However, the optimal approach to incorporating novel agents into frontline regimens remains a clinical challenge, particularly with regard to sequencing of therapies, considering the role of allogeneic hematopoietic stem cell transplantation and managing toxicities.

INTRODUCTION

Mutational profiling has dramatically improved our understanding of AML biology, culminating in landmark updates in disease classification and risk stratification from the World Health Organization (WHO)[1] and the International Consensus Classification (ICC)[2] in 2022. Both nomenclatures remove an arbitrary 20% blast cutoff for AML diagnosis if there is a disease-defining genetic alteration, underscoring the importance of disease biology in accurate risk prognostication. The European LeukemiaNet (ELN) also updated their risk stratification[3] to specify the favorable prognostic impact of *CEBPA* bZIP domain mutations,[4-6] denote that *FLT3* internal tandem duplication (ITD) mutations are intermediate risk regardless of variant allelic frequency (VAF) or *NPM1* status,[7] and consider myelodysplasia-related genetic alterations as adverse risk.[8-13] With 10 new FDA approvals for AML therapies since 2017, the approach to frontline therapy has become substantially more nuanced as these classification changes have prompted a more personalized approach to frontline therapy and patient selection for allogeneic hematopoietic stem-cell transplantation (alloHCT). This is particularly relevant for older patients or those who are ineligible for intensive chemotherapy (IC), because their outcomes have improved only marginally over the past several decades.[14,15] Here, we discuss the emerging role of novel intensive and nonintensive combination therapies that are established or under active investigation for genetically and biologically diverse subsets of patients with AML, toxicities associated with treatment, and the role of allogeneic hematopoietic stem cell transplantation.

MIX AND MATCH: INTEGRATING BCL2, FLT3, AND IDH1/2 INHIBITORS INTO FRONTLINE ACUTE MYELOID LEUKEMIA THERAPY

Mutation-Agnostic Approach to AML

Although recent advances in AML treatment have revolved around targeting specific driver mutations, the majority of newly diagnosed patients still lack a targetable lesion in the frontline setting. Thus, optimizing a mutation-agnostic approach to treatment is critical (Fig 1A). The standard frontline approach for fit patients with AML over the past 40 years has been anthracycline- and cytarabine-containing IC.[16-18] Although IC can elicit complete remission (CR) in approximately 60%-70% of patients younger than 60-65 years,[19-24] relapse rates remain high. The addition of gemtuzumab ozogamicin, an antibody-drug conjugate targeting CD33, to traditional IC has expanded therapeutic options for patients, although the survival benefit seems limited to those with favorable-risk core binding factor AML.[25] Thus, optimizing therapies for patients with intermediate- and adverse-risk host and disease factors has been a significant focus of therapeutic development. The incorporation of venetoclax-based therapies into AML management has proven to be transformative given its synergistic activity with hypomethylating agents (HMA)—either azacitidine or decitabine[26-28]—and low-dose cytarabine (LDAC).[29-31] As venetoclax potently triggers apoptosis through BCL2 inhibition,[32] its combination with IC may also allow for an amplification of tumor cell death.[33]

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PRACTICAL APPLICATIONS

- Treatment of older patients with AML involves complex decisions taking into consideration age, fitness, treatment tolerability, quality of life, and social support.
- Increased treatment options have allowed patients to live longer compared with historically dismissal outcomes.
- Integrating BCL2, FLT3, and IDH1/2 inhibitors allows for increased efficacy while minimizing toxicity compared with cytotoxic chemotherapy.
- Management of side effects of these novel agents requires personalized care for each patient.
- By improving outcomes and minimizing toxicity with incorporation of BCL2, FLT3, and IDH1/2 inhibitors, more patients may be able to proceed to allogeneic stem-cell transplant.

Venetoclax-based combinations have become the frontline standard for patients ineligible for IC. In the VIALE-A study,[26] patients with newly diagnosed AML had a median age of 76 years and were randomly assigned to receive azacitidine/venetoclax or azacitidine/placebo. The addition of venetoclax significantly improved both CR/CR with incomplete hematologic recovery (CRi) rates (66.4% *v* 28.3%) and median overall survival (OS, 14.7 months *v* 9.6 months). Furthermore, with long-term follow-up at a median of 43.2 months, patients for whom treatment achieved CR/CRi with measurable residual disease (MRD) negativity had a median OS of 34.2 months.[27] Patients in the VIALE-C study[31] also had a median age of 76 years and were randomly assigned to receive LDAC/venetoclax or LDAC/placebo with improved CR/CRi rates seen in the venetoclax group (48% *v* 13%). A 2-year follow-up from the landmark study demonstrated that the addition of venetoclax to LDAC led to a statistically significant improvement in median OS compared with LDAC/placebo (8.4 months *v* 4.1 months).[29,30] LDAC has also been studied in combination with the Hedgehog pathway inhibitor, glasdegib[34,35]; however, responses rates and OS are inferior to venetoclax-based regimens for patients ineligible for IC.

While the efficacy of venetoclax-based combinations was initially observed in those who were ineligible for IC and alloHCT, recent evidence suggests HMA/venetoclax therapy may serve as an effective bridge to alloHCT. Pollyea et al[36] found that patients older than 60 years who received azacitidine/venetoclax had a significantly improved median OS if they underwent alloHCT compared with no alloHCT (not reached [NR] *v* 17.2 months). Patients who underwent alloHCT had similar OS at 12 months whether their induction regimen consisted of azacitidine/venetoclax or IC.[37] For patients younger than 60 years, there are no prospective data demonstrating superiority of one regimen over another;

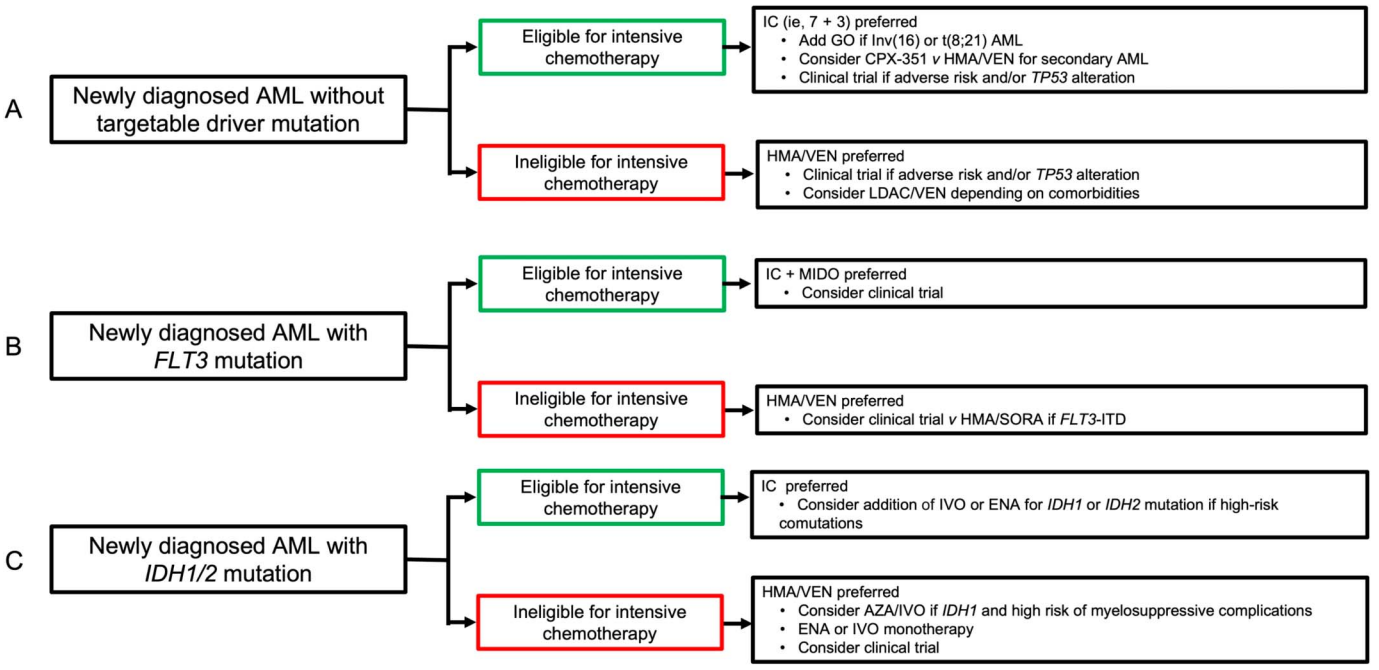

FIG 1. Approach to frontline therapy in AML. Treatment algorithm of AML induction therapy is shown. AZA, azacitidine; ENA, enasidenib; GO, gemtuzumab ozogamicin; HMA, hypomethylating agent; IC, intensive chemotherapy; ITD, internal tandem duplication; IVO, ivosidenib; LDAC, low-dose cytarabine; MIDO, midostaurin; SORA, sorafenib; VEN, venetoclax.

however, two randomized phase III studies evaluating IC versus HMA/venetoclax are ongoing (ClinicalTrials.gov identifiers: NCT04801797, NCT05177731). Retrospective data suggest that, for the overall population, there may not be significant differences in outcomes between IC and HMA/venetoclax, but selected subsets may benefit from a specific treatment strategy on the basis of mutation profile.[36-38]

Unfortunately, patients with *TP53* alterations have similarly dismal outcomes with IC or HMA/venetoclax with a 2-year survival under 15%[39] and a median OS under 6 months after alloHCT in eligible patients.[40,41] Notably, in the absence of *TP53* alterations, azacitidine/venetoclax seems to be active in patients with adverse-risk cytogenetics[42] or other high-risk mutations (ie, *ASXL1* and *RUNX1*)[38,43,44] and confers a survival benefit compared with azacitidine alone. However, several studies have demonstrated that, in the presence of *TP53* alterations, there is no significant duration of remission (DOR) or OS benefit to HMA/venetoclax compared with HMA despite significantly improved rates of CR/CRi.[26,28,42,45,46]

CD47 is a ubiquitously expressed glycosylated cell surface protein that provides an antiphagocytic don't-eat-me signal in normal cells and is overexpressed on leukemic cells promoting immune evasion.[47-49] Recent studies of the CD47 monoclonal antibody magrolimab (Hu5F9G4) demonstrate early clinical efficacy in AML harboring adverse genetic features including TP53 mutations. In a phase Ib study of patients with untreated AML and ineligible for IC,[50] treatment with azacitidine/magrolimab yielded CR/CRi rates of 56%, noting that 27% of patients had *TP53* mutations. In a phase Ib/II study of azacitidine/venetoclax/magrolimab for patients with adverse-risk AML,[51] CR/CRi rates were 63% and 86%, and 1-year OS rates were 53% and 83%, in patients with newly diagnosed AML with or without *TP53* mutations, respectively. Survival was very attenuated in patients with relapsed/refractory (R/R) AML, especially in those with previous venetoclax exposure, but a comparison of patients with *TP53* mutations treated with the magrolimab triplet versus doublet HMA/venetoclax cohorts demonstrated a significant median OS improvement (10.4 months *v* 3.5 months). Ongoing phase III studies are investigating the efficacy of azacitidine/magrolimab versus azacitidine/venetoclax or IC in patients with untreated *TP53*-mutant AML (ClinicalTrials.gov identifier: NCT04778397) as well as magrolimab/azacitidine/venetoclax versus azacitidine/venetoclax in patients with untreated AML who are ineligible for standard IC (ClinicalTrials.gov identifier: NCT05079230). Other CD47-targeting antibodies are under investigation but are not as far along in clinical development as magrolimab.

For patients considered to be candidates for IC, DiNardo et al[52] examined the efficacy of venetoclax in combination with fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF), and idarubicin (FLAG-Ida) in a phase Ib/II study of adult patients with R/R or newly diagnosed AML. In the newly diagnosed AML arm, 29 patients with a median age of 45 years were initially enrolled, of whom 38% had adverse-risk disease. Patients received a median of two cycles of FLAG-Ida with venetoclax 400 mg once daily on days 1-14. The time to hematopoietic recovery was 31 days in the newly diagnosed AML group; aside from myelosuppression, the major toxicity of this regimen was infectious complications; nevertheless, the 30-day mortality was 0%. Ultimately, composite CR (CRc) was observed in 90% of patients with newly diagnosed AML, of whom 96% had MRD negativity. At 12-month median follow-up, the DOR was NR, and 94% of patients with newly diagnosed AML were still alive. Notably, 69% of patients with newly diagnosed AML were able to proceed to alloHCT with 24-month follow-up data demonstrating similar outcomes with median event-free survival (EFS) and OS not yet reached.[53] These findings support the feasibility of adding venetoclax to FLAG-Ida in AML in younger patients who are candidates for IC with preliminary response rates and survival surpassing those of historical cohorts and notably high rates of pretransplant MRD negativity. Although myelosuppression and infectious complications were prevalent, short-term mortality was low in this selected group of younger patients. However, caution is advised in older patients or those unfit for IC. This trial (ClinicalTrials.gov identifier: NCT03214562) is ongoing and will provide insight into future combinations with IC.

FLT3-Mutant AML

FLT3 mutations are present in 25%-32% of newly diagnosed AML cases with ITD mutations seen more frequently than tyrosine kinase domain (TKD) mutations.[54,55] Despite the development of FLT3 inhibitors (FLT3i), which have improved the outcomes for these patients, the prognostic impact of *FLT3*-ITD seems to be worse regardless of VAF or *NPM1* status. Therefore, these patients should be considered for transplant in first remission, if eligible.[56-60] Type I FLT3i are active against TKD and ITD variants while type II FLT3i are active only against ITD variants. With two FDA-approved FLT3i (midostaurin and gilteritinib) and two more in clinical development (quizartinib and crenolanib), optimizing combination therapies with FLT3i is an area of active investigation (Fig 1B).

The first approved FLT3i was midostaurin on the basis of the RATIFY trial.[61] This phase III trial randomly assigned adult patients younger than 60 years with newly diagnosed *FLT3*-mutant AML to receive midostaurin or placebo in combination with standard IC and consolidation with high-dose

cytarabine. Both groups had CR rates of 50%-60%, although the addition of midostaurin improved median EFS (8.2 months *v* 3 months) and median OS (74.7 months *v* 25.6 months). Follow-up studies observed that patients who received midostaurin had a deeper molecular remission and were more likely to ultimately receive alloHCT,[62,63] emphasizing the durable benefit in survival despite similar CR rates after induction. Moreover, another study combining midostaurin with IC in patients with newly diagnosed *FLT3*-mutant AML up to age 70 years recapitulated these findings.[64,65] CR/CRi rates after induction were similar across age groups, and most patients were able to proceed to alloHCT. The median EFS was 14.5 months and 11.7 months, and the median OS was 57.3 months and 22.7 months in the younger and older age groups, respectively. Of note, midostaurin is not approved as a single agent because of a paucity of data supporting its use for post-consolidation maintenance[60,62-64]; thus, in clinical practice, midostaurin is recommended exclusively in combination with IC and consolidation for younger patients with newly diagnosed *FLT3*-mutant AML.

While midostaurin is the only FLT3i currently recommended for frontline use in combination with IC, newer-generation, specifically targeted FLT3i are being studied in this context. Gilteritinib, which is already FDA-approved for R/R *FLT3*-mutant AML, was combined with 7 + 3 in a phase I study (ClinicalTrials.gov identifier: NCT02236013) of patients with newly diagnosed AML[66] and was noted to confer CRc rates of 81.8%. Of patients with *FLT3* mutations, the median DOR was 14.1 months, and the median OS was NR. Given these findings, two ongoing trials are studying gilteritinib versus midostaurin in addition to IC and consolidation (ClinicalTrials.gov identifiers: NCT04027309, NCT03836209). Although neither quizartinib nor crenolanib has been approved by the FDA, recent clinical trials have shown them to be effective when combined with frontline IC. Despite underwhelming results with quizartinib in R/R AML in the QuANTUM-R study,[67] the QuANTUM-FIRST study[68] suggests that it may have a role in newly diagnosed *FLT3*-ITD AML. This study enrolled patients up to age 75 years with newly diagnosed *FLT3*-ITD AML and randomly assigned them to receive quizartinib or placebo in combination with IC, consolidation, and maintenance. CR/CRi rates were slightly better in the quizartinib arm (71.6% *v* 64.9%), although DOR was significantly improved (38.6 months *v* 12.4 months), as was median OS (31.9 months *v* 15.1 months). A follow-up study also demonstrated a deeper molecular remission compared with the placebo arm[69] similar to midostaurin. If quizartinib gains FDA approval, it would add to the available agents specifically targeting *FLT3*-ITD mutations in older patients, although it does not target *FLT3*-TKD. Recent data on the use of crenolanib in combination with 7 + 3 in patients with newly diagnosed *FLT3*-mutant AML showed CR/CRi rates of at least 75%, regardless of age, ITD or TKD mutation, comutation group (except for *TP53*), *FLT3* VAF, ELN risk group, or the presence of hyperleukocytosis.[70] Moreover, MRD negativity was observed in 94% of evaluable patients, and median OS for the study population was NR at a median follow-up of 45 months. Thus, the pending data from the QuANTUM-FIRST study and ongoing trials assessing other frontline combinations with quizartinib (ClinicalTrials.gov identifiers: NCT04209725, NCT04047641), crenolanib (ClinicalTrials.gov identifier: NCT03258931), and gilteritinib (ClinicalTrials.gov identifiers: NCT04027309, NCT03836209) will potentially expand the options of FLT3i. These agents consistently seem to deepen response when combined with IC and may consequently be effective tools to improve durability of remissions, particularly if pretransplant MRD negativity can be achieved, as this has been shown to improve outcomes.[71-76]

For patients with *FLT3* mutations who are not eligible for IC, low-intensity regimens remain the standard of care. However, pooled data from VIALE-A[26] and a phase Ib HMA/venetoclax study[28] demonstrated that patients with *FLT3*-ITD had a median OS of only 9.9 months, compared with 19.2 months in those with *FLT3*-TKD despite CR/CRi rates exceeding 60% in both groups.[77] These data suggest that the efficacy of HMA/venetoclax is modest in patients with *FLT3*-ITD AML. Moreover, trials combining gilteritinib[78] or midostaurin[79] with HMA have not yielded encouraging results to date. The LACEWING trial randomly assigned patients with newly diagnosed *FLT3*-mutant AML to receive azacitidine/gilteritinib versus azacitidine alone[78]; although patients in the doublet arm had a two-fold improvement in CRc rates, the median OS was similar between both arms (9.82 months *v* 8.87 months). Despite these discouraging findings, other studies suggest synergy between FLT3i and venetoclax.[80-82] A phase II trial evaluated the use of triplet therapy (decitabine/venetoclax/FLT3i) in older patients with newly diagnosed *FLT3*-mutant AML and all adult patients with R/R *FLT3*-mutant AML. In the newly diagnosed AML cohort, the CRc rate was 92% with high rates of MRD negativity in responders. At a median follow-up of 14.5 months, median OS was NR in newly diagnosed patients (2-year OS estimated at 80%). Recent data from a trial studying azacitidine/venetoclax/gilteritinib demonstrated potency with 95% of patients with newly diagnosed AML achieving CR with an estimated 1-year OS of 80%.[83] Longer follow-up data from this study (ClinicalTrials.gov identifier: NCT04140487) and another trial investigating azacitidine/venetoclax/quizartinib (ClinicalTrials.gov identifier: NCT03661307) are pending. Thus, there may ultimately be a role for triplet FLT3i-based therapy as a lower-intensity option for patients with newly diagnosed *FLT3*-mutant AML, particularly if they have ITD.

When considering the role of FLT3i as maintenance after alloHCT, the National Comprehensive Cancer Network

(NCCN) considers sorafenib, midostaurin, and gilteritinib as options. Although frontline use of sorafenib has marginal benefit,[84,85] the SORMAIN trial[86] noted that its use as maintenance after alloHCT was associated with a 25%-30% improvement in 2-year relapse-free survival (RFS) and OS compared with placebo in patients with *FLT3*-ITD AML; these findings have since been independently corroborated.[87] An important caveat is that only nine patients in the SORMAIN trial were treated with frontline midostaurin, and none had received HMA/venetoclax.[86] Thus, while these results are certainly compelling, the gastrointestinal and skin toxicities often make long-term use challenging. Data on quizartinib for *FLT3*-ITD mutations[69] and gilteritinib seem promising, but neither is FDA-approved for this indication. A press release of the MORPHO trial (ClinicalTrials.gov identifier: NCT02997202) announced on March 9, 2023, that maintenance with gilteritinib after alloHCT for patients with *FLT3*-ITD AML did not reach primary end point of RFS over placebo,[88] although final data release is pending.

IDH1- and *IDH2*-Mutant AML

IDH1 and *IDH2* mutations are reported at a frequency of 7%-14% and 8%-19%, respectively, in AML.[89,90] Inactivating mutations in the catalytic domain of isocitrate dehydrogenase lead to buildup of the oncometabolite 2-hydroxyglutarate,[91,92] which is associated with epigenetic changes seen in AML and other malignancies.[93,94] The prognostic impact of *IDH1/2* mutations is controversial although canonically, *IDH2* mutations are thought to be relatively favorable while *IDH1* mutations confer worse outcomes.[95,96] The approval of ivosidenib, enasidenib, and olutasidenib has expanded therapeutic options for patients with R/R AML, and recent studies have been examining how to best incorporate these agents into the frontline setting (Fig 1C).

Ivosidenib or enasidenib has been studied in combination with 7 + 3 (or bioequivalent dose of idarubicin) in patients with *IDH1/IDH2* mutations throughout induction, consolidation, and maintenance.[97] The addition of either agent to 7 + 3 did not prolong count recovery and were generally well-tolerated. CRc rates in an updated report were 78.3% with ivosidenib and 73.6% with enasidenib, which are improved compared with historical controls of IC alone with these mutations.[98] Median OS was NR in the ivosidenib arm and was 25.6 months in the enasidenib arm. These data provide clinical equipoise for incorporating IDH-targeting agents into the frontline setting with IC, especially if a patient has high-risk comutations; however, in the absence of head-to-head studies, these data should be interpreted cautiously, and it should be noted that neither of these therapies are currently approved for frontline use with IC.

Both ivosidenib and enasidenib have also been studied for use as a low-intensity monotherapy for newly diagnosed AML. In studies of patients with newly diagnosed *IDH1*- or *IDH2*-mutant AML and ineligible for IC, ivosidenib[99] or enasidenib[100] monotherapy achieved CRc rates of 42.4% or 21%, respectively, with a median OS of 12.6 months or 11.3 months, respectively. Only ivosidenib is FDA-approved for frontline monotherapy use, although response rates and OS for either as single agents are modest, especially considering that patients with *IDH1/2* mutations seem to be very sensitive to azacitidine/venetoclax with outcomes similar to those achieved with IC.[101] In patients with these mutations, CR/CRi rates were reported at 79% with a median OS of 24.5 months when treated with azacitidine/venetoclax; responses and survival were comparably better with *IDH2* mutations versus *IDH1* mutations. Moreover, combinations of enasidenib and HMA in patients who are ineligible for IC have not been shown to significantly improve OS compared with HMA alone (22 months *v* 18.6 months),[102] suggesting that HMA/venetoclax should still be considered to be a first-choice low-intensity option for patients with *IDH2* mutations. For patients with *IDH1* mutations, however, the data are more compelling for azacitidine/ivosidenib as a reasonable alternative. In the AGILE study,[103] patients with newly diagnosed *IDH1*-mutant AML had significantly improved median OS when treated with azacitidine/ivosidenib compared with azacitidine alone (24 months *v* 7.9 months), leading to FDA approval of this regimen. Nevertheless, azacitidine/venetoclax should still be considered first for frontline low-intensity therapy in *IDH1*-mutant AML given comparatively improved CR rates, more familiarity with its use, and the consistent ability to bridge eligible patients to alloHCT. However, in patients who may be at high risk of myelosuppressive complications with HMA/venetoclax, azacitidine/ivosidenib is a suitable alternative. It is unknown whether responses with azacitidine/venetoclax can be improved with triplet combinations of ivosidenib or enasidenib, and increased toxicity in this older population is concerning. In an exploratory study of patients with *IDH1* mutations, patients receiving HMA/venetoclax/ivosidenib had CRc rates similar to that of venetoclax/ivosidenib, although they had a significant improvement in MRD negativity (86% *v* 25%), which was associated with a significant improvement in OS.[104] However, additional data from studies combining ivosidenib and enasidenib with azacitidine and/or venetoclax (ClinicalTrials.gov identifiers: NCT04092179, NCT03471260) will be needed to formally determine the utility of triplet regimen–incorporated *IDH1/2* inhibitors.

MANAGING THE TOXICITIES AND SUPPORTIVE CARE ASSOCIATED WITH NOVEL ACUTE MYELOID LEUKEMIA AGENTS

In 2018, the landmark VIALE-A trial led to accelerated FDA approval of venetoclax in combination with azacitidine, decitabine, or LDAC for patients with newly diagnosed AML aged at least 75 years or younger than 75 years with one of

several qualifying comorbidities (full approval occurred in 2020).[26] In relatively short order, a new standard of care was implemented across the world for the majority of patients with AML who are deemed ineligible for IC. Currently, the NCCN AML Guidelines give a category 1 recommendation for the combination of venetoclax and a HMA—either azacitidine or decitabine—as the preferred frontline regimen for IC-ineligible patients regardless of the presence of actionable mutations. The sole exception is the recent addition of the IDH1 inhibitor, ivosidenib, given in combination with azacitidine for patients with mutated *IDH1*.[105] In this section, we will focus on the practical management of patients deemed IC-ineligible who receive either venetoclax or ivosidenib in combination with HMA.

Although not the primary focus of this section, it is worth noting that the determination of fitness as it pertains to eligibility for IC is a rapidly evolving field. This determination should not be made solely on the basis of age but should incorporate an assessment of performance status, medical comorbidities, and disease biology.

HMA With Venetoclax

Starting therapy. Although administration of a HMA does not require central venous access, it is recommended for patients who require frequent lab monitoring and transfusion support before achieving remission. Previous studies have demonstrated similar toxicity profiles and efficacy of azacitidine relative to decitabine,[28] and they are likely interchangeable when used in combination with venetoclax. Peripheral intravenous (IV) administration can be considered for selected patients who have robust baseline hemoglobin and platelet counts or do not mind frequent skin pricks. Subcutaneous administration of azacitidine is another alternative; however, it is often poorly tolerated given the high prevalence of severe thrombocytopenia in patients with AML and the associated hematomas that can result from subcutaneous injections.

As the incidence of febrile neutropenia may be as high as 50% during treatment, antibacterial and antiviral prophylaxis is recommended.[106] Mold-active azole (posaconazole, voriconazole, or isavuconazole) should also be considered based on duration of previous neutropenia and regional susceptibilities to fungal infections, with appropriate venetoclax dose adjustments if azoles (or other strong CYP3A4 inhibitors) are used. Dose adjustments for concomitant azole administration[107] and other situations are shown in Table 1. Although the incidence of tumor lysis syndrome (TLS) with HMA/venetoclax in AML is low when the WBC count is not elevated,[108] adequate hydration and allopurinol prophylaxis are still routinely recommended for the first cycle of therapy but can be safely discontinued if there is no evidence of TLS and clearance of bone marrow blasts. Accordingly, inpatient hospitalization is not required for initiation of therapy but should be considered if frequent outpatient monitoring is challenging, if expedited treatment is necessary, or if the patient may be at increased risk for complications on the basis of leukocytosis (WBC >25 K/μL), impaired renal function, or other comorbid conditions. WBC count must be brought down to <25 K/μL with hydroxyurea or cytarabine before initiating therapy to minimize tumor lysis.

Common toxicities associated with this regimen include nausea, vomiting, fatigue, decreased appetite, diarrhea, and/or constipation.[26,28] Accordingly, antiemetics, antidiarrheals, and/or promotility agents are routinely prescribed on an as-needed basis on initiation of therapy.

Initiation of venetoclax includes a 3-day ramp-up. In the absence of any indications for dose adjustments, venetoclax is given as 100 mg once on day 1, 200 mg once on day 2, and 400 mg once daily on day 3 and beyond.[26]

TABLE 1. Dose Adjustments of Venetoclax on the Basis of Metabolism

Metabolic Interaction	Examples[a]	Dose Reduction (%)	New Daily Dose (mg)[b]
Strong CYP3A4 inhibitors	Clarithromycin, itraconazole, ketoconazole, voriconazole, HIV protease inhibitors	75	100
	Posaconazole	≥75	70-100
Moderate CYP3A4 inhibitor	Aprepitant, cimetidine, ciprofloxacin, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, verapamil	50	200
P-glycoprotein inhibitor	Amiodarone, carvedilol, cyclosporine, dronedarone, quinidine, ranolazine, verapamil	50	200
Strong CYP3A4 inducers	Carbamazepine, efavirenz, phenytoin, rifampin	—	Avoid use
Child-Pugh C cirrhosis		50	200
Renal impairment		None	400

[a]Examples listed are not exhaustive of all inhibitors, inducers.
[b]Dose administsered once daily.

Monitoring on treatment and restaging. The most common grade 3/4 adverse events associated with this combination include neutropenia, thrombocytopenia, and anemia. These can be especially profound in patients with antecedent hematologic malignancies or with baseline marrow hypocellularity. Accordingly, until remission is achieved, the majority of patients will require at least twice weekly monitoring of blood counts with readily available transfusion support when needed. Similarly, frequent monitoring of chemistries and uric acid should be obtained early on to monitor for TLS and other electrolyte derangements.

Unlike with HMA monotherapy, responses with the combination of HMA/venetoclax are typically achieved quickly, with a median time to response of approximately 1 month. Since the majority of patients will begin treatment with cytopenias and nearly all patients will have cytopenias by the end of the first cycle, in the absence of clear signs of persistent disease, it is essential to obtain a restaging bone marrow evaluation before cycle 2. This is performed to determine whether cytopenias are therapy-related or due to persistent disease. There is no standard for when bone marrow biopsies are performed after cycle 1 and vary by institution; this ranges from days 14 to 28. These early bone marrow biopsies help identify the significant proportion of patients in whom clearance of marrow blasts is rapid. Identifying these patients early is crucial as continuation of venetoclax without a temporary pause or a delay in the subsequent cycle may result in prolonged aplasia and a higher risk of serious infectious complications.

If patients are in CR—defined as <5% blasts—irrespective of hemoglobin or platelet count after cycle 1, it is recommended to pause venetoclax and delay initiation of the second cycle for up to 14 days or until recovery of neutropenia to less than grade 3 (ie, an absolute neutrophil count >1 K/μL). The effect of venetoclax is most pronounced on neutrophils, so normalization of platelets with persistent neutropenia is often an indicator that the neutropenia is therapy-related. If persistent disease (>5% marrow blasts) is found on the restaging biopsy, treatment should continue without delay and without a change in the venetoclax to the schedule, with plan for a repeat biopsy before the third cycle.

Management of postremission myelosuppression. Once remission is achieved, the main challenge in successfully keeping patients on continued treatment is the recurrence of grade 3/4 hematologic toxicities, most notably neutropenia. To avoid this issue, the vast majority of patients should only receive venetoclax between 14 and 21 days once remission has been achieved. If prolonged or severe cytopenias are recurrent after achieving remission, the recommendation is to decrease the number of days of venetoclax per cycle rather than change the dose of venetoclax. Although data are limited, it does not seem that a shorter duration of venetoclax postremission compromises durability of response.[109-112] Additional strategies for limiting the depth and duration of cytopenias postremission include reduction in the dose or number of days of HMA therapy and the use of supportive G-CSF for grade 3/4 neutropenia.

If cytopenias worsen at any point during the course of treatment or do not respond to dose pauses/adjustments, a repeat marrow evaluation is recommended to rule out disease progression.

HMA With Ivosidenib

Although some of the best responses to HMA/venetoclax are in patients with mutated *IDH2*, evidence suggests that those with mutated *IDH1* may respond less well.[101] Although the NCCN guidelines give a category 1 recommendation for HMA/venetoclax in patients with an IDH2 mutation, enasidenib—which targets the *IDH2* mutation—is also included as a potential monotherapy in the frontline setting on the basis of a phase I/II trial demonstrating a median OS of 11.3 months.[100] Ivosidenib monotherapy was initially approved for newly diagnosed IC-ineligible patients with mutated *IDH1* in 2019, although more recently the combination of ivosidenib and azacitidine gained approval on the basis of results from the phase III AGILE trial. In this trial, the combination of azacitidine plus ivosidenib yielded a median OS of 24 months, as compared with 7.9 months with azacitidine alone. When starting ivosidenib and azacitidine for newly diagnosed AML, management principles are similar to those that apply to starting HMA/venetoclax, including antimicrobial prophylaxis and close monitoring for hematologic, metabolic, and infectious complications. However, there is generally less myelosuppression associated with ivosidenib-based therapy. Similar to venetoclax-based therapy, dose reductions are recommended in patients receiving strong CYP34A inhibitors; ivosidenib should be reduced by 50% to a dose of 250 mg once daily in patients receiving strong CYP3A4 inhibitors. Key differences between venetoclax-based and ivosidenib-based therapy include the time-to-response assessment, the risks of QT prolongation, and differentiation syndrome (DS).

Monitoring on treatment and restaging. Prolongation of the QT interval on ECG is a known complication of ivosidenib. It is recommended to minimize the concomitant use of other QT-prolonging agents and to obtain ECGs before starting therapy, weekly for the first 3 weeks on therapy, and then monthly thereafter. For prolongation of the QTc interval >480 milliseconds, it is recommended to ensure electrolytes are repleted and to interrupt ivosidenib until the QTc returns to <480 milliseconds. Should the QTc prolong to >500 milliseconds, electrolyte repletion and interruption of ivosidenib are recommended, with subsequent reduction of

the dose from 500 mg once daily to 250 mg once daily after the QTc has returned to <480 milliseconds. This assumes there are no other culprit drugs that may be contributing to QTc prolongation that can be discontinued.

Perhaps the most notable and important-to-recognize toxicity of ivosidenib either alone or in combination with azacitidine is DS. A high index of suspicion for DS is necessary since it is commonly misdiagnosed as either disease progression or infection. In combination with azacitidine for newly diagnosed IC-ineligible patients, ivosidenib led to DS in 14% of patients, with 4% of patients experiencing DS ≥grade 3. Symptoms of DS most commonly include leukocytosis, peripheral edema, fever, dyspnea, effusions, hypotension, hypoxia, rash, and increased creatinine. In addition to hospitalization for concurrent workup of infection and disease progression, management of DS should be initiation of dexamethasone 10 mg IV or orally every 12 hours. If concomitant noninfectious leukocytosis is observed, hydroxyurea may be warranted; volume overload should be managed with diuretics. Importantly, corticosteroids and hydroxyurea should only be tapered after complete resolution of symptoms and after a minimum of 3 days. If severe symptoms of DS persist for more than 48 hours after initiation of corticosteroids, interrupt ivosidenib until signs/symptoms resolve.

Unlike venetoclax-based therapy, median time to best response with the combination of ivosidenib and azacitidine is approximately 4 months; accordingly, restaging marrow evaluations should generally occur after 3-4 cycles of azacitidine or at time of hematologic recovery. In the absence of clear signs of disease progression, it is recommended to continue ivosidenib and azacitidine for at least six cycles given the potential for late responses. When used as a single agent, ivosidenib achieved a CRc rate of 42.4% and median OS of 12.6 months.[99] Monotherapy with ivosidenib may have a lower risk of febrile neutropenia but a higher risk of diarrhea and leukocytosis. Posterior reversible encephalopathy syndrome has been reported rarely with the use of ivosidenib.

Other agents/combinations in development. There are multiple novel agents and combinations currently under study, including frontline FLT3i,[113,114] oral HMAs,[115,116] and triplets combining HMA, venetoclax, and targeted agents. At present, these are recommended only in the context of a clinical trial.

Palliative care and advanced care planning. The landscape of therapeutic options available to patients with newly diagnosed AML is rapidly evolving as many patients who choose to undergo therapy will have better outcomes than those who receive supportive care alone. Nonetheless, for all newly diagnosed IC-ineligible patients with AML, the goal of therapy remains palliative/life-prolonging rather than curative. Accordingly, we strongly recommend the early incorporation of specialty palliative care for discussion of advance care directives and for symptom management expertise. All treatment decision plans should be made in conjunction with the patient and their stated goals.

WHAT IS THE ROLE OF ALLOGENEIC STEM-CELL TRANSPLANT FOR OLDER PATIENTS WITH ACUTE MYELOID LEUKEMIA IN 2023?

Older Patients With AML: Transplant or Not?

Survival outcomes among older patients with AML remain dismal over the past several decades mainly because of the general higher disease risk, coexisting comorbidities, compromised performance status, and the inability to deliver curative intent, consolidative alloHCT to most of these patients.[117] AlloHCT is more effective over time compared with non-HCT therapies for selected older patients with AML who can achieve disease control and who have adequate level of fitness, although early treatment-related mortality should be acknowledged.[118-120] However, how to identify, expand, and optimize this population of older patients remains quite challenging without any standardization. This has become the subject of intense debate encompassing many intricate topics such as dynamic disease risks, aging biology, and the impact of treatment, long-term survival versus the early risk of death, and perhaps most importantly, patients' own perspectives on risks, quality of life, and available resources.[121-123] In fact, a recently reported, 8-year longitudinal, multicenter study of 692 older patients with AML highlighted these complexities. While alloHCT utilization was associated with a reduced risk of death, the benefit disappeared after accounting for age, comorbidity burden, disease risks, frailty, depression, and impaired function and quality of life, suggesting that alloHCT improves survival only for selected older patients who are healthier and noninfirmed.[124] Although it might be easier for clinicians to simply present all these findings and describe the population statistics, it is equally important to appreciate that each older alloHCT candidate is unique, and perspectives from all parties, including the physician, the patient, family/caregivers, and local institution, should be considered.

AlloHCT likely will continue to be an integral part of AML therapy for the foreseeable future because of its graft-versus-leukemia mechanism of action, curative potential for an older patient population which historically has the worst outcome, and, importantly, the rapidly improving transplant outcomes including older patients.[125] This notion is supported by several registry-based and prospective studies, including the most recent CIBMTR study of 1,321 older patients with AML transplanted in the contemporary era of 2007-2017. In this analysis, the 3-year OS ranged from 40% to 50%, and disease-related risk factors, rather

than increasing chronologic age, were the major determining factors for survival.[126] However, despite these findings, clinical ageism, or treatment decision on the basis of chronologic age alone, has been the most common barrier for referring older patients for consideration of alloHCT.[127] This is also supported by a recent study examining trends and factors associated with alloHCT utilization among Medicare beneficiaries with AML from 2010 to 2016. Mau et al[128] found that alloHCT utilization rate within 1 year of diagnosis had increased gradually over time from 11.9% in 2010 to 20% in 2015 and estimated that there was an unmet need of 43%-44% of older patients with AML who could benefit from alloHCT. Nevertheless, there are many reasons to believe that the future will be brighter.

Novel AML Therapies as Bridge to AlloHCT

As discussed in earlier sections of this review, AML treatments, especially for the older patient population, are rapidly expanding and evolving. These novel agents and their rational combinations are generally better tolerated than traditional intensive induction therapies such as 7 + 3 and are generally more effective, especially in combination, than the meager historical 30%-40% CR rate seen in older patients.[129] Although not considered curative, these regimens can produce high rate and high-quality remissions in older patients which potentially allow safer bridging to alloHCT. For example, older patients with AML who received induction with the novel agent CPX-351 (liposomal daunorubicin and cytarabine) and subsequently went to alloHCT had superior OS and reduced transplant-related mortality as compared with older patients who were induced with 7 + 3, followed by alloHCT.[130] This suggested that CPX-351 not only improved disease control by allowing more patients to proceed to transplant but also improved treatment tolerability and reduced subsequent nonrelapse mortality of alloHCT. Similarly, the combination of venetoclax with azacitidine could successfully bridge older patients with AML to alloHCT, resulting in superior survival compared with maintenance therapy alone in a single-institution study,[36] and single-agent ivosidenib could induce remission in older patients with AML with *IDH1* mutations, thus enabling subsequent alloHCT in otherwise ineligible candidates.[131] Finally, novel agents with significant antileukemia activity continue to emerge such as anti-CD45 Iodine (^{131}I) Apamistamab (IOMAB-B), which has been incorporated into salvage/conditioning treatment to bridge to transplant with encouraging results and is currently being evaluated for approval.[132]

Selecting the Older Candidate: Role of Geriatric Assessment

How do we select the appropriate older candidate? We need to consider disease risks, treatment response, patient preference, and findings from the comprehensive geriatric assessment (GA), which is a multidimensional, multidisciplinary, and holistic approach to evaluate an older person's functional and cognitive ability, physical mobility, mental health, and socioenvironmental circumstances to identify frailty and age-related vulnerabilities.[133] GA plays an important role in the management of older patients with AML including risk stratification at diagnosis, longitudinal (re) assessment, and potential guidance on treatment intensity and supportive care.[134,135] In the setting of alloHCT, GA has been increasingly used for pretransplant evaluation, optimization, and peritransplant management of older patients with hematologic malignancies.[136] Several common geriatric deficits including functional impairment, cognitive impairment, and polypharmacy have been shown to be associated with alloHCT outcomes including survival and treatment-related toxicities.[136] Importantly, a GA-guided, outpatient clinic-based, multidisciplinary and multifaceted, pretransplant optimization program for older patients has been shown to effectively reduce transplant-related mortality and improve survival in a pre- and poststudy design.[137] A similar pretransplant optimization program has been described at Duke University which found that 52% of patients had resolution of at least one GA deficit from the initial visit to pretransplant admission visit.[138] These findings strongly support the utility and value of GA and GA-guided, pretransplant management and optimization programs and may likely be adoptable to the post-transplant setting. Despite these advances, however, many barriers exist to fully

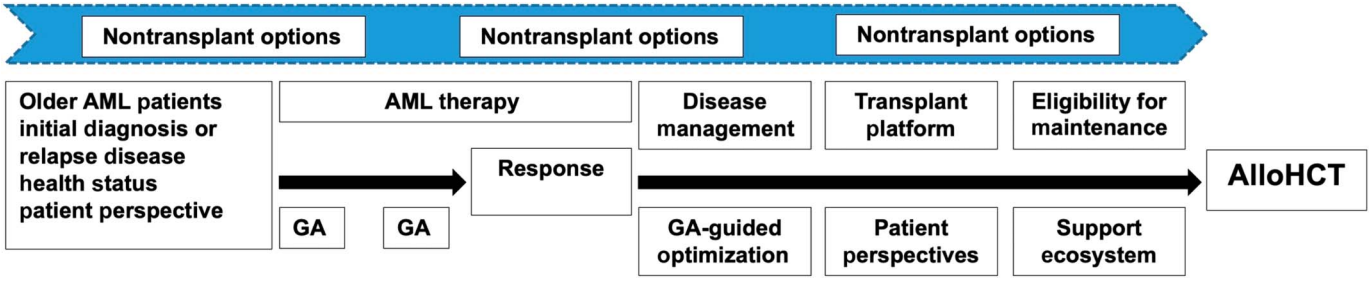

FIG 2. Integration of GA and alloHCT for older patients with AML. alloHCT, allogeneic hematopoietic stem-cell transplantation; GA, geriatric assessment.

integrate GA into transplant practices including physician perception, time constraints, staffing limitations, financial costs, and knowledge base.[139]

Expanding Horizons in AlloHCT Technology and Platforms

Importantly, the field of alloHCT is advancing steadily with improved outcomes in recent years, especially for older patients.[126,140,141] These improvements are largely attributed to the development of reduced-intensity and nonmyeloablative conditioning regimens,[142,143] advances in supportive care including newer antimicrobials such as letermovir,[144] better prophylaxis and treatment of graft-versus-host disease,[145] and more recently, increased donor choices across the human leukocyte antigen match barrier.[146] Specifically, for older patients with AML, a treosulfan-based conditioning regimen with reduced toxicity and improved antileukemia activity, as well as novel antibody-based conditioning strategies may further improve tolerability of alloHCT.[132,147] Finally, the role of maintenance therapy post-alloHCT may be of heightened importance among older patients with AML to reduce the risk of relapse, given the generally higher disease risk and lower intensity of conditioning even with MRD (MRD+) before alloHCT.[74,148] Oral agents are generally preferred given ease of administration and available evidence from the post hoc analysis of a registration trial.[149]

Integrating GA and AlloHCT Into the Total Therapy for Older Patients With AML

We are entering a new era of personalized treatments for older patients with AML with innovate, effective, and low-toxicity induction strategies; increased ability to bridge to the curative intent alloHCT for selected patients; improved donor selection and transplant platforms; and highly individualized peritransplant care to manage nononcologic geriatric issues.[150] Central to the care of older patients with AML is to incorporate early, longitudinal GA, and GA-guided management to prevent treatment-related decline[151] and to combine GA with disease risk assessment for early transplant evaluation to maximize the chance of cure for selected older patients. This likely will be a dynamic population of patients that could be expanded or preserved with appropriate GA-guided care across the treatment continuum. We propose here to incorporate GA and alloHCT as parts of total therapy for older patients with AML (Fig 2).

CONCLUSION

AML is a very complex and heterogeneous disease as evidenced by the expansion of genetic and cytogenetic qualifiers in the updated WHO and ICC classification systems. Although outcomes continue to improve on the basis of novel therapies, understanding of toxicities, and improvements in alloHCT, the long-term OS is still dismal, and we need to do better. In this regard, standardization of MRD assessment would help tailor subsequent treatment after CR and also predict relapse. Equally important is appropriate diagnostic cytogenetic, molecular, and mutational testing to understand baseline mutations and repeating this testing at relapse to understand clonal evolution. Our goal as clinicians is to optimize timing, combination, and sequence of therapy while taking physiologic age into consideration and maximizing objective measures of quality of life. This includes early assessment of GA before treatment, during treatment, and pre- and post-alloHCT. Integration of multidisciplinary services such as physical and occupational therapy, nutrition, social work, and palliative care will also insure care of the whole patient with regard to physical, social, and emotional well-being. By combining precision oncology to use the best testing with optimal treatments, we will continue to make progress in this scientifically interesting yet challenging disease.

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Management Considerations for Patients With Primary Refractory and Early Relapsed Diffuse Large B-Cell Lymphoma

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Overview

Most patients with diffuse large B-cell lymphoma (DLBCL) will be cured with up-front chemoimmunotherapy, but 30%-40% of patients will experience relapsed disease. Historically, salvage chemotherapy followed by autologous stem-cell transplant (ASCT) was the mainstay of treatment for these patients. However, research has demonstrated that patients with primary refractory or early relapsed (R/R; high-risk) DLBCL do not benefit from ASCT, prompting investigation into other options. With the advent of chimeric antigen receptor (CAR) T-cell therapy, treatment of R/R DLBCL has changed dramatically. With positive outcomes in the TRANSFORM and ZUMA-7 trials with manageable toxicity profiles, approval was obtained for lisocabtagene maraleucel (liso-cel) and axicabtagene ciloleucel (axi-cel) as second-line therapies for high-risk R/R DLBCL. However, these trials required patients to be medically fit for ASCT. In PILOT, liso-cel was deemed a reasonable treatment option for R/R transplant-ineligible patients. We recommend either axi-cel or liso-cel for fit patients with high-risk R/R DLBCL or liso-cel for unfit R/R patients as a second-line therapy. If CAR T-cell therapy is not an option, we recommend consideration of either ASCT if the patient has chemosensitive disease and is fit or clinical trial if the patient is unfit or has chemoresistant disease. If trials are not an option, alternative treatments are available. With the advent of additional therapies such as bispecific T-cell–engaging antibodies, the treatment landscape of R/R DLBCL may be upended. There continue to be many unanswered questions in the management of patients with R/R DLBCL, but given the promise of cellular therapies, outcomes are more optimistic in this group with historically dismal survival.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease with a 5-year overall survival (OS) ranging from 79.5% for stage I disease to 54.7% for stage IV disease, with a median 5-year OS of 64.6%.[1] Although two thirds of patients with DLBCL are cured with up-front immunochemotherapy regimens, such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), up to 30%-40% of patients will either have progression of disease during or at the end of up-front therapy (ie, primary refractory) or relapse after initial response.[2,3] Historically, the treatment of relapsed/refractory (R/R) DLBCL has been salvage chemotherapy followed by autologous stem-cell transplant (ASCT). Although ASCT has the potential to be curative, patients with primary refractory or early relapsed disease often do not reach the same levels of success with ASCT. Recent clinical trial advances and drug approvals in transplant-eligible and transplant-ineligible patients with R/R DLBCL have unleashed several novel therapeutics providing more efficacious options with manageable toxicity profiles. This review will outline these advances and highlight a proposed algorithm for the management of patients with primary refractory and early relapsing (high-risk R/R) DLBCL.

ASCT: NOT A ONE-SIZE-FITS-ALL APPROACH FOR R/R DLBCL

In 1995, the Parma trial reported results of a phase III trial evaluating fit patients younger than 60 years with relapsed intermediate- or high-grade lymphoma by the Working Formulation classification who had attained a complete response (CR) for at least 4 weeks to initial induction doxorubicin-based therapy. Salvage chemotherapy with two cycles of DHAP (dexamethasone, high-dose cytarabine, and cisplatin) followed by ASCT with carmustine, etoposide, cytarabine, cyclophosphamide, and mesna conditioning was superior to salvage chemotherapy alone with respect to 5-year event-free survival (EFS) rate (46% *v* 12%) and OS rate (53% *v* 32%). This trial solidified the role of ASCT as the standard of care in patients with second-line relapsed DLBCL and refractory patients although that group was not specifically studied.[4] Subsequently, as the phase III trials, CORAL and LY12 investigated different salvage chemotherapy regimens with some incorporating rituximab, such as rituximab, ifosfamide,

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PRACTICAL APPLICATIONS

- Although most patients with diffuse large B-cell lymphoma will be cured with up-front chemoimmunotherapy, 30%-40% of patients will relapse. Although autologous stem-cell transplant offered a second chance at a durable remission, primary refractory and early relapsed diffuse large B-cell lymphoma (DLBCL) had an extremely poor outcome.
- On the basis of randomized controlled trials, chimeric antigen receptor (CAR) T-cell therapy with axicabtagene ciloleucel or lisocabtagene maraleucel (liso-cel) is now the recommended second-line treatment for patients who are medically fit with primary refractory and early relapsed disease.
- For unfit patients with relapsed/refractory DLBCL, we recommend treatment with liso-cel therapy if available and if not, participating in a clinical trial with treatments such as bispecific T-cell engagers (BITE), or treatment with an approved agent such as tafasitamab with lenalidomide, polatuzumab-vedotin with bendamustine and rituximab, R-GemOx, or loncastuximab tesirine.
- There remain many areas for research in DLBCL including optimizing options for bridging therapy, sequencing of treatments, such as CAR T-cell and BITE therapy, and when to treat a patient who may experience a complete response during salvage chemotherapy while awaiting CAR T-cell therapy.

carboplatin, and etoposide, R-DHAP, and gemcitabine, dexamethasone, and cisplatin, and demonstrated similar efficacy across all salvage regimens.[5,6]

An important finding of the CORAL and LY.12 trials was that patients with primary refractory disease or relapsed disease within 12 months after diagnosis had significantly inferior outcomes compared with patients who relapsed after 12 months. The CORAL study highlighted that patients with R/R DLBCL within 12 months of diagnosis with previous exposure to rituximab had dismal outcomes with a 3-year progression-free survival (PFS) of only 23%.[5]

The REFINE study looked further in-depth at why patients in the rituximab era might have primary treatment failure. In this multicenter retrospective study of nearly 300 patients, ultra-high-risk features were defined as having primary progressive disease while on first-line treatment (defined as progressive disease by clinical or radiologic assessment during or within 6 weeks of completion of chemoimmunotherapy), an intermediate-high or high National Comprehensive Cancer Network International Prognostic Index score at the time of primary treatment failure, or *MYC* translocation. Of the entire cohort, patients with ultra-high-risk features had a predicted 2-year overall survival (OS) of 13.6%. Of the 132 patients who underwent ASCT, 2-year OS was directly related to the number of high-risk features, with the OS of 74.3% for patients with no ultra-high-risk features and only 10.7% for patients with two to three ultra-high-risk features.[7]

Another multicenter retrospective review of 117 patients examined the impact of double-hit (defined as *CMYC* and either *BCL2* or *BCL6* gene rearrangements) and double-expressor (defined as overexpression of *CMYC* and *BCL2* protein) status on ASCT outcomes in patients with R/R DLBCL. Both double-hit and double-expressor lymphomas were associated with poor PFS, and double-hit lymphoma was associated with poor OS post-transplantation. Notably, for patients with double-hit status, the 4-year PFS and OS were only 28% and 25%, respectively, and the 4-year PFS was 0% for both double-expressor and double-hit status.[8]

SCHOLAR-1 was an international, multicohort study that retrospectively evaluated outcomes in patients with refractory DLBCL. This analysis demonstrated that patients who were primary refractory, were refractory to two or more lines of therapy, or relapsed within 1 year of an ASCT had an overall response rate (ORR) of 26% (CR, 7%) to the next line of therapy, and the median OS was 6.3 months. Only 20% of patients were alive after 2 years.[9]

Thus, ASCT may be a potentially curative approach for some patients with R/R DLBCL; however, high-risk subgroups such as those with primary refractory disease, those with early relapse, and patients who meet the REFINE ultra-high-risk factors and double-hit gene rearrangements warrant a different therapeutic modality.

A NEW PARADIGM IN R/R DLBCL TREATMENT

Chimeric antigen receptor (CAR) T-cell therapy is a novel treatment strategy that has improved outcomes in patients with relapsed lymphomas. CAR T-cell therapy is an immune effector cell therapy where autologous T cells are genetically engineered to target CD19 antigen on lymphoma cells. Patients awaiting CAR T-cell therapy may require bridging therapy, which often comprises glucocorticoids or additional chemotherapy to maintain disease control until the products can be engineered. Before CAR T-cell infusion, patients receive lymphodepleting chemotherapy, often with fludarabine and cyclophosphamide. On the basis of phase II pivotal trials, three CAR-T constructs, namely, axicabtagene ciloleucel (axi-cel), lisocabtagene maraleucel (liso-cel), and tisagenlecleucel (tisa-cel), were initially approved by the US Food and Drug Administration (FDA) for third-line treatment of R/R LBCL (large B-cell lymphoma), demonstrating excellent responses and durable PFS and OS.[10-12] In the

ZUMA-1 trial, 111 patients with R/R LBCL were enrolled. axi-cel was administered to 91% of the cohort. The ORR was 82% with a CR rate of 54%. The 18-month OS was 52%.[10] In the TRANSCEND trial, patients with R/R LBCL were enrolled to assess the efficacy and safety of liso-cel therapy. Of the 344 patients enrolled, 78.2% received at least one dose of liso-cel. The ORR was 74% with a CR rate of 54%. The median OS was 21.1 months after a follow-up of 17. 5 months.[12] In the JULIET trial, 93 patients with R/R DLBCL were enrolled and all patients received tisa-cel therapy. The ORR was 52% with a CR rate of 40%.[11] Long-term results with over a 4-year follow-up for ZUMA-1 demonstrated a median OS of 25.8 months with a 4-year OS rate of 44% hinting at a possible cure for a subset of R/R DLBCL.[13] At a median follow-up of 40.3 months for JULIET, the ORR was 53%, with 39% of patients achieving a CR.[14] These trials demonstrated the safety, efficacy, and durability of response of CAR T-cell therapy as a third-line therapy for patients with R/R DLBCL. Given that a significant proportion of patients with heavily pretreated DLBCL achieved a durable response after CAR T-cell therapy, it was intuitive to explore the efficacy and safety of CAR T-cell therapy in the second-line high-risk R/R DLBCL setting, thus creating a paradigm shift in the treatment of DLBCL.

TREATMENT OF FIT PATIENTS WITH HIGH-RISK PRIMARY REFRACTORY AND EARLY RELAPSING DLBCL

While ZUMA-1, TRANSCEND, and JULIET demonstrated the benefit of CAR T-cell therapy after two or more lines of treatment, three pivotal phase III trials, ZUMA-7, TRANSFORM, and BELINDA, explored the use of axi-cel, liso-cel, and tisa-cel, respectively, in the second-line setting in transplant-eligible patients with primary refractory and early relapsing (high-risk R/R) DLBCL against standard investigator choice (SOC) salvage chemotherapy, followed by high-dose chemotherapy and ASCT.[15-17] ZUMA-7 and TRANSFORM met their primary end point of EFS and demonstrated superiority with manageable toxicity of CAR T-cell therapy compared with ASCT. BELINDA did not show superiority of CAR T-cell therapy to SOC. Table 1 outlines key features of these three clinical trials.

The ZUMA-7 and TRANSFORM trials showed strikingly similar efficacy for axi-cel and liso-cel compared with SOC. With a median follow-up of 24.9 months, axi-cel therapy achieved superior EFS (8.3 months *v* 2 months), ORR (83% *v* 50%), and CR (65% *v* 32%) compared with SOC.[15] In the TRANSFORM trial, the primary end point of EFS was significantly improved in the liso-cel group (10.1 months) compared with SOC (2.3 months). liso-cel therapy was associated with a higher CR (66% *v* 39%) and a longer median duration of response (not reached *v* 14.5 months) when compared with SOC. A statistically significant improvement in PFS was observed in the liso-cel group (stratified hazard ratio [HR], 0.41; 95% CI, 0.25 to 0.66; $P = .0001$).[16] The primary analysis at a median follow-up of 17.5 months continues to demonstrate excellent outcomes for liso-cel over SOC.[18] In both studies, adverse events were similar in the CAR T-cell therapy and SOC arm with the exception of more neutropenia in the CAR T arm; however, this did not translate into higher incidence of febrile neutropenia. With respect to toxicities of special interest, grade 3 or higher cytokine release syndrome (CRS) and neurotoxicity (NT) were seen in 6% and 21%, respectively, in the ZUMA-7 study and in 1% and 4%, respectively, in the TRANSFORM study.

Altogether, the abovementioned data resulted in FDA approval of axi-cel and liso-cel for second-line treatment in fit patients with primary refractory and early relapsed large-cell lymphoma in 2022.[19-21] After almost two and a half decades of suboptimal outcomes, CAR-T cell therapy represents a new standard of care for patients with high-risk R/R DLBCL.

TREATMENT OF UNFIT PATIENTS WITH R/R DLBCL

A key inclusion criterion for the trials discussed earlier was that patients had to be medically fit to be considered for ASCT in the SOC arm. Given that a large proportion of patients with R/R DLBCL may not be eligible for transplant on the basis of age or medical comorbidities, this begs the question of what is the ideal treatment for transplant-ineligible patients with R/R disease. The PILOT study, a phase II trial investigating the efficacy of liso-cel, recruited patients with R/R DLBCL who were considered ineligible for ASCT. Specifically, patients had to meet one of the following criteria: age 70 years or older, an Eastern Cooperative Oncology Group (ECOG) performance status of 2, receipt of one previous line of therapy containing an anthracycline and a CD20-targeted agent, a diffusing capacity of the lung of 60% or less, a LVEF of $<50\%$, a creatinine clearance of <60 mL/min, or transaminases two times the upper limit of normal. Seventy-four patients underwent leukapheresis, with 61 receiving liso-cel therapy. Baseline characteristics were relevant for a median age of 74 years, 26% had an ECOG of 2, and 42% had an age-adjusted IPI score of ≥ 2. Fifty-four percent of patients had refractory disease, 21% relapsed within 1 year of first-line treatment, and 25% relapsed 12 months after first-line treatment. The primary end point was ORR. With a median follow-up of 12.3 months, the ORR was 80% (95% CI, 68 to 89; $P < .0001$) and the CR rate was 54%. The median PFS was 9.03 months (95% CI, 4.17 to not reached [NR]), and the EFS was 7.23 months (95% CI, 3.22 to 22.60). Among patients who achieved CR, the median PFS was 22.60 months (95% CI, 12.98 to NR) and the EFS was 22.60 months (95% CI, 12.98 to NR). Cytokine release syndrome was seen in 38%, and NT was seen in 31%, mostly of low grade. No grade 4 or grade 5 CRS/NT was reported. Treatment-related adverse events were similar to those previously reported, and there were

TABLE 1. Phase III CAR T-Cell Therapy Outcomes

Characteristic	ZUMA-7	TRANSFORM	BELINDA
Definition of EFS	Time from randomization to the earliest date of disease progression, the commencement of new therapy, death from any cause, or a best response of stable disease up to and including the response on the day 150 assessment after randomization	Time from randomization to death because of any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first	Time from randomization to stable or progressive disease at or after the week 12 assessment or death at any time
Total No. of patients	359	184	322
Bridging therapy	Dexamethasone ≤40 mg daily for ≤4 days	One cycle of R-ICE, R-GDP, or R-DHAP (63%)	>1 cycle of R-ICE, R-GDP, R-DHAP, or R-GemOx (83%)
CAR T-cell product	axi-cel	liso-cel	tisa-cel
Costimulatory domain	CD28	4-1BB	4-1BB
Gene transfer	Retrovirus	Lentivirus	Lentivirus
Median time from trial registration to CAR (days)	29	34	52
Patients receiving CAR, %	94	97	96
SOC regimen	R-ICE, R-GDP, R-DHAP, R-ESHAP	R-DHAP, R-ICE, R-GDP	R-ICE, R-GDP, R-DHAP, R-GemOx
Patients receiving ASCT, %	36	46	32
Crossover	Not allowed	Allowed (51%)	Allowed (51%)
Median follow-up, months	25	6.2	10
mEFS, months	8.3 *v* 2[a]	10.1 *v* 2.3[a]	3 *v* 3
HR EFS	0.39 ($P < .0001$)	0.34 ($P < .001$)	1.07 ($P = 1.07$)
ORR	83% *v* 50%[a]	86% *v* 48%[a]	46.3% *v* 42.5% Week 12 assessment
CR rate	65% *v* 32%	66% *v* 39%[a]	28% *v* 28%
Grade ≥ 3 any treatment-related AE	91% *v* 83%	34% *v* 43%	74.7% *v* 85.6%
CRS	6%	1%	5%
ICANS	21%	4%	3%

Abbreviations: ASCT, autologous stem-cell transplant; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; EFS, event-free survival; liso-cel, lisocabtagene maraleucel; HR, hazard ratio; ICANS, immune effector cell neurotoxicity syndrome; ORR, overall response rate; PR, partial response; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-ESHAP, rituximab, etoposide, methylprednisolone, high dose cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, dexamethasone, and cisplatin; R-GemOx, rituximab, gemcitabine, oxaliplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; SOC, standard investigator choice; tisa-cel, tisagenlecleucel.

[a]Denotes statistically significant value.

TABLE 2. US Food and Drug Administration–Approved Regimens for Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Regimen	Trial	No. of Patients	Median Previous Lines of Therapy	ORR (%)	CR Rate (%)	Median PFS or EFS (months)	Median Overall Survival (months)
axi-cel	ZUMA-7[15]	359	One	83	65	8.3 EFS	NR
liso-cel	TRANSFORM[16,18,21]	184	One	86	66	10.1 EFS	NR
	PILOT[22]	74	One	80	54	9.03 PFS	NR
Tafasitamab + lenalidomide	L-MIND[23]	81	Two	57.5	43	11.6 PFS	33.5
Loncastuximab tesirine	LOTIS-2[24]	184	Three	48.3	24.1	4.9 PFS	9.9
Pola-BR	NCT02257567 [25]	118	Two	25	20	9.5 PFS	12.4

Abbreviations: axi-cel, axicabtagene ciloleucel; CR, complete response; EFS, event-free survival; liso-cel, lisocabtagene maraleucel; NR, not reached; ORR, overall response rate; PFS, progression-free survival; Pola-BR, polatuzumab-vedotin with bendamustine and rituximab.

no study-associated deaths.[22] PILOT demonstrated that liso-cel can be an effective time-limited option for transplant-ineligible patients with R/R DLBCL. The Food and Drug Administration approved liso-cel for adult patients with LBCL who have refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem-cell transplantation (HSCT) because of comorbidities or age.[20]

Although our recommendation for unfit patients with early relapse and primary refractory DLBCL would be to proceed with liso-cel, we understand that not all physicians and patients have access to this therapy for a variety of reasons (bridging therapy, manufacturing time, availability of slots for apheresis, access to CAR-T center, lack of caregiver). For transplant-ineligible patients without access to CAR T-cell therapy, we recommend participation in a clinical trial whenever possible. If a clinical trial is not available, then one could consider other FDA-approved regimens in R/R DLBCL such as tafasitamab with lenalidomide, polatuzumab-vedotin with bendamustine and rituximab (pola-BR), R-GemOx, or loncastuximab tesirine (Table 2). The data behind these treatments are reviewed below.

In the L-MIND trial, patients with R/R DLBCL ineligible for ASCT were treated with tafasitamab, a humanized anti-CD19 monoclonal antibody (12 mg/kg weekly for three 28-day cycles and then every 14 days until progression) in combination with lenalidomide (25 mg daily on days 1-21 of a 28 day cycle for 12 cycles) as a second-line treatment. Importantly, when the recruitment began, patients with primary refractory disease defined as no response or progressive disease within 3 months of frontline therapy were excluded. Eighty-one patients were enrolled, with 56% of patients older than 70 years; 75% of patients had stage III-IV disease, with 51% having an IPI score of $\geq$3; and 92% had an ECOG of 0-1; 18.5% of patients had primary refractory disease, 41.3% had rituximab-refractory disease, and 43.8% were refractory to their last line of treatment. After a median follow-up of 35 months, the ORR was 57.5% and the CR rate was 43%, with a median PFS of 11.6 months (95% CI, 6.3 to 45.7) and median OS of 33.5 months (95% CI, 18.3 to NR). For patients achieving a CR, median PFS and median OS were not reached. The most common grade 3 or greater treatment-related adverse events were neutropenia (49.4%), thrombocytopenia (17.3%), and febrile neutropenia (12.3%).[23,26]

Polatuzumab-vedotin is a CD79b-targeted antibody-drug conjugate with a payload of monomethyl auristatin E (MMAE), a microtubule inhibitor. In a phase Ib/II trial, pola-BR was compared against BR alone in ASCT-ineligible patients with R/R DLBCL. In previous studies, BR alone in this patient population had a median PFS of 3.6-6.7 months.[27,28] For this trial, patients with R/R DLBCL after at least one previous line of therapy were included. One hundred eighteen patients were enrolled, with 67 patients receiving therapy with pola-BR. In the pola-BR group, 82.5% had an ECOG of 0-1, with a median age of 67 years, and 45% had three or more previous lines of therapies. Of the patients receiving pola-BR, 25% had failed a previous ASCT and 30% had an insufficient response to previous therapy. After a median follow-up of 22.3 months, the PFS was 9.5 months (95% CI, 6.2 to 13.9) in the pola-BR versus 3.7 months (95% CI, 2.1 to 4.5) in the BR-alone group (HR, 0.36; 95% CI, 0.21 to 0.63; $P < .001$), and OS significantly improved, with pola-BR patients surviving 12.4 months versus BR patients surviving 4.7 months (HR, 0.42; 95% CI, 0.24 to 0.75; $P = .002$).[25]

In a retrospective review of 196 transplant-ineligible patients with R/R DLBCL, it was found that R-GemOx was a promising and well-tolerated regimen. Patients were eligible if they had progressive or stable disease during a treatment or relapse/progression within 1 year of last treatment. The breakdown between primary refractory and early relapsed was not specified. The median age was 72 years, with 63% of patients having an IPI score of $\geq$3. Sixteen percent of patients had undergone ASCT. Fifty-eight percent received R-GemOx as a second-line treatment, 23% received it as a third-line treatment, and 19% received it as a fourth-line

treatment or later. With a median follow-up of 22 months, 33% of patients achieved a CR and the median PFS was 5 months with a median OS of 10 months. There was no statistically significant difference in PFS or OS on the basis of whether R-GemOx was given in the second- or subsequent-line setting.[29]

Loncastuximab tesirine is an antibody-drug conjugate comprising a humanized anti-CD19 antibody conjugated to a cytotoxic alkylating agent, SG3199.14, which is internalized by CD19-expressing B cells to then deliver the payload, which causes interstrand DNA cross-links preventing DNA replication causing apoptosis. In the phase II LOTIS-2 trial, patients with two or more lines of treatment for DLBCL or primary refractory disease were enrolled. Of 184 patients enrolled, 39% had primary refractory disease, 24% had relapse within 3 months of first-line therapy, and 39% had relapse within 6 months of first-line therapy. The median age was 66 years, with 10% having double- or triple-hit DLBCL. The ORR was 48.3% (95% CI, 39.9%-56.7%), the median PFS was 4.9 months, and the median OS was 9.9 months. The CR rate was 24.1%, and of patients in a CR, 57% continued in a CR at the time of data cutoff.[24]

IMPLEMENTING CAR T-CELL THERAPY IN SECOND LINE FOR HIGH-RISK R/R DLBCL—ONGOING CONTROVERSY AND UNANSWERED QUESTIONS

After the approval of CAR T-cell therapy as a second-line therapy, many experts have debated if ASCT is a thing of the past for patients with high-risk R/R DLBCL who show a response (CR/PR) to salvage chemotherapy. The studies exploring CAR-T versus ASCT trials randomly assigned patients before initiating salvage therapy given historically poor rates of chemosensitivity for these subgroups and thus were not designed to answer this question. On the basis of the data outlined earlier, it is reasonable to state that patients with primary refractory, ultra-high-risk by REFINE criteria and double-hit lymphomas do not appear to benefit from ASCT even if they demonstrate chemosensitivity.

However, the best strategy for early relapsed DLBCL remains unclear, with some favoring CAR T-cell therapy and others recommending ASCT for chemosensitive patients. In a retrospective review of the Center for International Blood and Bone Marrow Transplant Research (CIBMTR) registry, the efficacy of ASCT was compared with that of CAR T-cell therapy in patients with DLBCL in a partial response after salvage chemotherapy. Four hundred eleven patients with early relapsed DLBCL were identified, with 266 having undergone ASCT while in a partial response and 145 having undergone CAR T-cell therapy. Early relapse for this population was defined as relapse or progression in $\leq$1 year from original diagnosis. The 2-year PFS was 52% for patients receiving ASCT while in a PR and was 42% for patients undergoing CAR T-cell therapy (P = .05). The 2-year OS rate was 69% in patients undergoing ASCT compared with the OS rate of 47% in those undergoing CAR T-cell therapy (P = .004). The incidence of relapse or progression was lower in the ASCT group compared with the CAR T-cell group at both 1-year (34% *v* 45%) and 2-year (40% *v* 52%) follow-ups.[30] It is important to recognize that the ASCT patients were less heavily pretreated than CAR T patients. This was a retrospective review, introducing mortality time bias. In TRANSFORM, EFS was also examined for patients who crossed over to liso-cel therapy. Of the 46 patients who crossed over, 10 had undergone ASCT. With a median follow-up of 4.1 months, the EFS was 3.4 months and the ORR was 48%, with a CR rate of 39% and OS of 7.8 months.[16] This demonstrates that although liso-cel was effective, its efficacy is less pronounced when used in the third-line setting compared with the second-line setting.

Another unanswered question is if a patient is intended to receive CAR T-cell therapy but is in a CR to salvage therapy, should that patient still receive this therapy? In a retrospective review of patients with DLBCL treated at eight academic centers receiving axi-cel or tisa-cel therapy, it was found that of 364 patients receiving CAR T-cell therapy, 33 patients received therapy in a CR (nine axi-cel, 24 tisa-cel). Of this subset of patients, 26 had measurable disease at the time of leukapheresis and went into CR after bridging therapy, with most patients receiving systemic therapy (20 patients). With a median follow-up of 16 months, 39.3% of patients had relapsed. The 1-year EFS and OS of patients were 59.6% and 81.3%, respectively, indicating that CAR T-cell therapy continued to be effective treatment even for patients in a CR at the time of T-cell infusion. In addition, the development of CRS and ICANS in this patient subset was much lower than that in patients with residual disease at the time of CAR T-cell treatment, demonstrating safety in this population.[31] This was also supported by TRANSFORM as there were nine patients who were in a CR at the time of liso-cel infusion and demonstrated favorable outcomes.

Until better prediction tools are available to determine chemosensitivity, we recommend CAR T-cell therapy in second line for patients with primary refractory and early relapsed DLBCL. However, it is reasonable to consider ASCT in early relapsed DLBCL if patients do not have access to CAR T-cell therapy or are being evaluated for consolidation therapy after having achieved a CR/PR to salvage therapy.

Often patients with R/R disease will need prompt access to treatment, but CAR T-cell production takes on average anywhere from 3 to 4 weeks. This delay in therapy necessitates the importance of establishing optimal bridging therapies. Typical therapies are steroids, salvage chemotherapy (RICE, R-GemOX, RDHAP), or polatuzumab with a preference for combination with rituximab therapy. However, this may change with the POLARIX trial. In POLARIX,

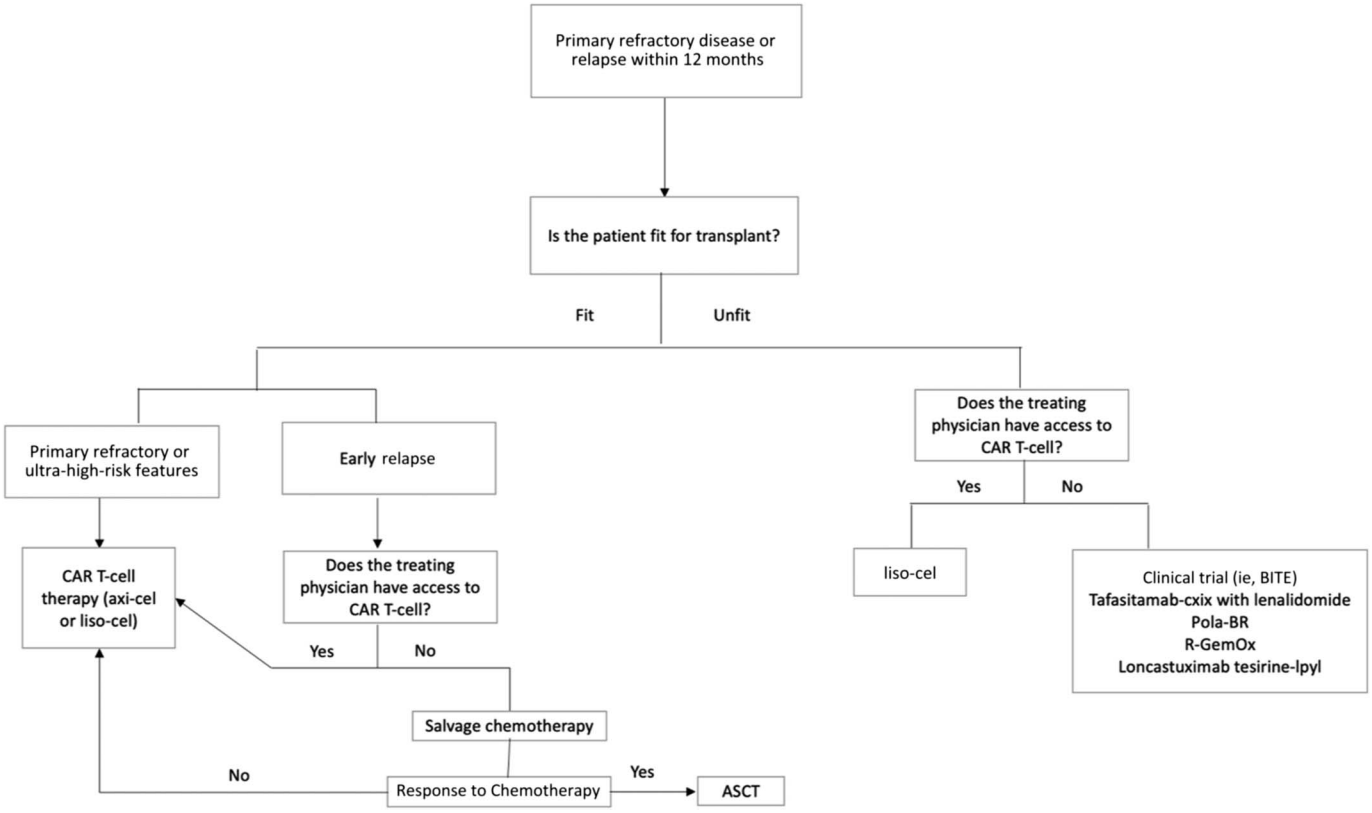

FIG 1. Proposed algorithm for treatment of primary refractory and early relapsing DLBCL. ASCT, autologous stem-cell transplant; axi-cel, axicabtagene ciloleucel; BITE, bispecific T-cell engagers; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; pola-BR, polatuzumab-vedotin with bendamustine and rituximab; R-GemOx, rituximab, gemcitabine, oxaliplatin.

investigators compared frontline therapy in patients with untreated DLBCL with R-CHOP or pola-R-CHP. With a median follow-up of 28.2 months, pola-R-CHP patients were more likely to be alive without progression (76.7% *v* 70.2%). OS at 2 years was not significantly different between the groups (88.7% *v* 88.6%).[32] If pola-R-CHP receives approval for frontline treatment of intermediate- to high-risk DLBCL, it would prevent its use as a bridging agent. More research is required to determine ideal bridging strategies.

LOOKING INTO THE HORIZON

Although CAR T-cell therapy seems promising for the treatment of R/R DLBCL, novel strategies for treatment that may circumvent issues with production and cost are underway. Bispecific T-cell engagers (BITEs) targeting CD20 are off-the-shelf therapies that have demonstrated excellent results. There are at least four BITEs currently being studied in clinical trials, including mosunetuzumab, glofitamab, epcoritamab, and odronextamab, with glofitamab and epcoritamab having the most mature data in R/R DLBCL for review.

Glofitamab is a BITE that binds in a 2:1 fashion to C20 on B cells and CD3 on T cells, imparting greater potency. In a phase I trial of 171 patients with NHL who had undergone at least one line of treatment with no further options, 42.7% of patients had DLBCL, the median age was 64 years (range 22-85), and patients on average had three previous lines of therapy. For patients with aggressive NHL histologies, the ORR was 48% with a CR rate of 33.1%. CRS occurred in 50.3% of all patients, with most patients experiencing grade 1 (21.6%) or grade 2 (25.1%) CRS.[33] In the phase II trial, patients were treated with glofitamab for 12 cycles or until disease progression. In the cohort of 154 patients with a median follow-up of 12.6 months, 39% of patients had a CR with a median time to CR of 42 days. Seventy-eight percent of CRs were ongoing at 12 months. The 12-month PFS was 37%.[34] Recent data demonstrated that time-limited treatment with glofitamab can result in durable CR for patients with relapsed DLBCL. Of 61 patients with heavily pretreated DLBCL who had received glofitamab for 1 year with a median follow-up of 18.1 months, a majority of patients (45) remained in CR.[35]

Epcoritamab is a BITE that targets CD3 on T cells and CD20 on B cells and is subcutaneously administered. In a phase I/II trial, 157 patients with DLBCL or other aggressive NHL with two or more lines of therapy, who were ineligible for ASCT, were recruited. Patients received a median of three

lines of therapy (range, 2-11), 61.1% had primary refractory disease, and 75.8% were refractory to two or more lines of therapy; 38.9% had received previous CAR T-cell therapy. The ORR was 63.1% with a CR rate of 38.9%. Overall, epcoritamab was demonstrated to be tolerable, with the most common adverse events being CRS (49.7%), injection site reaction (19.7%), and neutropenia (17.8%).[36] While further research must be performed to compare BITEs with the standard of care, they hold promise as an off-the-shelf option for patients with DLBCL who are not transplant or CAR T-cell therapy candidates.

CONCLUSIONS

Although most patients with DLBCL are cured with first-line rituximab and anthracycline-based immunochemotherapy, a significant subset of patients experience R/R disease. With the proven benefit of CAR T-cell therapy in transplant-eligible and transplant-ineligible patients with high-risk R/R DLBCL, it is our recommendation that CAR T-cell should be the treatment of choice in patients with R/R DLBCL, if available. For patients who are medically fit with early relapse for whom CAR T-cell therapy is not an option, salvage chemotherapy with ASCT is a reasonable consideration. For medially unfit patients, we recommend treatment with liso-cel or other alternative therapies. We propose the algorithm in Figure 1 for the treatment of high-risk R/R DLBCL. Many questions remain on the impact of prolonged immunosuppression with CAR T-cell therapy, including long-term infection risk and response to vaccination. With the impending regulatory approval of BITEs, the proposed paradigm in this review may be entirely shifted in the coming years. BITE therapy has proven to be effective in early trials and holds promise as a treatment option that may be more widely available to patients as an off-the-shelf option compared with CAR T-cell therapy. While more time will be required to allow these data to mature, it would be reasonable to refer patients with relapsed disease after CAR T-cell therapy to BITE therapy. It is unclear if patients receive BITE before CAR T-cell therapy if T-cell exhaustion would limit response to CAR T-cell therapy. Given historically dismal outcomes of patients with R/R DLBCL, the rise of novel therapies including CAR T-cell therapy and BITEs holds great promise for treatment options for this historically neglected patient population.

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Practical Management of Richter Transformation in 2023 and Beyond

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overview

While the past decade has witnessed unprecedented progress for patients with chronic lymphocytic leukemia (CLL), outcomes for patients with Richter transformation (RT) remain dismal. Multiagent chemoimmunotherapy regimens, such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, are commonly used, although outcomes are far poorer than observed with the same regimens used in de novo diffuse large B-cell lymphoma. The revolutionary targeted therapies approved for CLL, such as inhibitors of Bruton tyrosine kinase and B-cell leukemia/lymphoma-2, have limited activity in RT as monotherapy, and initial promising activity of checkpoint blockade antibodies was also eventually found to be ineffective as monotherapy for most patients. Over the past few years, as outcomes for patients with CLL improved, there has been a growing focus of the research community on improving our biological understanding of the underlying pathophysiology of RT and on translating these new insights into rational combination strategies that are poised to improve therapeutic outcomes. Here, we present a brief overview of the biology and diagnosis of RT, as well as prognostic considerations, before providing a summary of the data supporting various therapies that have been recently studied in RT. We then turn our attention to the horizon and describe several of the promising novel approaches under investigation to treat this challenging disease.

INTRODUCTION

While the past decade has witnessed unprecedented progress in the outcomes for patients with chronic lymphocytic leukemia (CLL), outcomes for patients with Richter transformation (RT; also known as Richter's syndrome) unfortunately remain dismal. The prognosis for this disease is nearly as poor as it was when it was first identified nearly 100 years ago. It was first described by the American pathologist Dr Maurice Richter in 1928 as a reticular cell sarcoma[1] and the condition was later named in his honor in 1964.[2] Incremental progress was made with the utilization of multiagent chemoimmunotherapy (CIT) regimens, such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), although outcomes are far poorer than observed with the same regimens used in de novo diffuse large B-cell lymphoma (DLBCL). The revolutionary targeted therapies approved for CLL, such as inhibitors of Bruton tyrosine kinase (BTK) and B-cell leukemia/lymphoma-2 (BCL-2), have limited activity in RT as monotherapy, and initial promising activity with checkpoint blockade antibody monotherapy was also eventually found to be ineffective for most patients. There is cause for optimism, however. Over the past few years, as outcomes for patients with CLL improved, there has been a growing focus of the research community on improving our biological understanding of the underlying pathophysiology of RT and on translating these new insights into rational combination strategies that are poised to improve therapeutic outcomes. Here, we present a brief overview of the biology and diagnosis of RT, as well as prognostic considerations, before providing a summary of the data supporting various therapies that have been recently studied in RT. We then turn our attention to the horizon and describe several of the promising novel approaches under investigation to treat this challenging disease.

BIOLOGY

The development of RT involves a complex interplay between genetic, epigenetic, immunologic, and tumor microenvironmental factors. Retrospective studies have demonstrated that certain genetic features of a patient's CLL are associated with increased risk of development of RT. These include the presence of *TP53* aberrancy,[3] *NOTCH1* mutation,[4,5] and certain BCR stereotypes,[6] specifically subset 8 immunoglobulin heavy chain (IGHV 4-39).[7,8]

Advancements in the genetic, epigenetic, and transcriptomic profiling of RT have been made in recent years, leading to new insights into the biology of this challenging disease.[9] Owing to limited availability of primary patient samples and RT-derived cell lines, reliable murine models provide an important avenue of interrogating the biological complexities of RT. Recently, multiplexed in vivo CRISPR-Cas9 B-cell editing of recurrent CLL loss-of-function genetic drivers was

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PRACTICAL APPLICATIONS

- Signs/symptoms that should raise clinical suspicion for Richter transformation (RT) include development of a rapidly enlarging lymph node, new fevers, drenching night sweats, unintentional weight loss, and/or persistent lactate dehydrogenase elevation.
- Diagnostic work-up of suspected RT should include a positron emission tomography-computed tomography scan, biopsy of the most fluorodeoxyglucose-avid lymph node, expert hematopathology review, and, if possible, determination of IGHV clonality.
- Chemoimmunotherapy remains the most commonly used initial therapy for RT, with nonrandomized data supporting the addition of venetoclax; allogeneic hematopoietic cell transplantation does provide a chance for long-term remission.
- Significant advancements in the genetic, epigenetic, and transcriptomic profiling of RT have been made in recent years, and these new biological insights have begun to inform the design of trials investigating targeted regimens in RT.
- Such trials investigating targeted agents include Bruton tyrosine kinase inhibitors, venetoclax, immune checkpoint blockade, chimeric antigen T cell, and bispecific antibodies in various combinations, and these studies will likely pave the way for new targeted therapeutic options for RT.

shown to recapitulate the process of transformation from an indolent CLL into a large cell lymphoma.[10] This model provides a robust system in which to interrogate novel therapies as well as study potential disease resistance mechanisms; such preclinical studies may prove pivotal to informing the design of early-phase clinical trials for RT.

Several recent large genomic studies from patients' primary samples have also generated new understanding about the genetic events that underlie the transformation of CLL to RT.[11-14] In one study, paired CLL and RT whole-exome sequencing data from 52 patients yielded identification of RT-specific somatic driver mutations (including *IRF2BP2*, *SRSF1*, *B2M*, *DNMT3A*, and *CCND3*) and additional characteristics including certain recurrent copy number alterations and whole-genome doubling.[13] In another study, genome-wide sequencing was performed on serial samples from patients with CLL from the years preceding the diagnosis of RT and at time of diagnosis of RT. In a striking finding, in one patient, the malignant RT clone was identified 19 years before the time of diagnosis.[12] This phenomenon of early seeding was seen across several other patients studied. Additional genetic alterations were observed over time, suggesting a complex interplay between clonal selection and evolution.[12] Beyond genetic studies, advancements are also being made using functional precision medicine techniques. For example, a novel assay to interrogate apoptosis, BH3 profiling, was recently applied to primary CLL and RT samples, revealing insights into differences in survival dependence of these cells on various antiapoptotic proteins.[15] These inroads into the processes and pathways underpinning the development of RT will hopefully provide sound rationales for new therapeutic approaches in the future.

DIAGNOSIS

RT can occur at any point in the disease course of a patient with CLL, including in previously untreated patients on observation and even as an initial presentation of CLL; however, such cases are rare, and the vast majority of RT occurs in patients either on active CLL treatment or progressing after previous treatment. Early in the development of targeted therapies for CLL, there was some concern that RT may be developing more frequently on the newer drugs compared with patients treated with CIT alone. With additional research, this proved not to be the case—for example, a study by the German CLL Study Group retrospectively analyzed the incidence of RT across their portfolio of chemotherapy and CIT trials and found the rate to be in the range of 4%,[16] and in other retrospective analyses of patients with CLL treated with targeted therapies, the rate of RT similarly averages about 4%.[17-20]

The diagnosis of RT requires both appropriate clinical suspicion and diagnostic evaluation. Patients who develop RT may present with B symptoms (fevers, drenching night sweats, unintentional weight loss), new physical deterioration, rapid and/or discordant growth of a particular lymph node conglomerate, and/or a sudden and significant rise in lactate dehydrogenase (LDH). As CLL disease progression is usually indolent, the pace of these changes can be a major clue that RT is present, and in such patients, prompt diagnostic testing to evaluate for RT is warranted. In a large retrospective study of patients with CLL treated with ibrutinib, independent prognostic variables that increased the likelihood of the development of RT at disease progression were progression on active treatment, elevated LDH, and lymphadenopathy without lymphocytosis.[21]

An important initial diagnostic step is to obtain a positron emission tomography-computed tomography (PET/CT) scan, as lymphadenopathy because of CLL typically has a low level of fluorodeoxyglucose (FDG) avidity. Highly FDG-avid nodes should prompt suspicion for RT; however, the

differential diagnosis in such cases also includes transformation events not classically categorized as RT, including Hodgkin transformation (HT) and plasmablastic lymphoma. Additionally, patients with CLL are at increased risk for second malignancies, including solid tumors, so this must also remain in the differential diagnosis. Once the PET/CT is performed, a biopsy should be directed to the site of highest FDG avidity, even if this is not the most accessible site for biopsy. For example, a patient with low-moderately FDG-avid inguinal lymphadenopathy but with a highly FDG-avid retroperitoneal lymph node conglomerate should have a biopsy of the retroperitoneal mass, as biopsy of an inguinal node that shows CLL could be falsely reassuring and does not rule out the presence of RT elsewhere. Typically, a tissue biopsy completed through a core needle approach by an interventional radiologist is sufficient to make the diagnosis of RT, although an inconclusive biopsy result in the setting of a case with high clinical suspicion for RT should prompt consideration of either repeat core needle biopsy or, if feasible, excisional surgical biopsy. Occasionally, patients with RT will present with rapidly evolving cytopenias, and in that case, a bone marrow biopsy can be helpful to make the diagnosis of RT.

It should be noted that pathologic diagnosis of RT can be challenging, particularly in patients with *TP53*-aberrant CLL and those who are progressing on targeted agents, such as BTK inhibitors. In such cases, a main diagnostic confounder can be accelerated CLL, which can mimic RT, but requires a different therapeutic approach (ie, using CLL-directed therapy instead of RT-directed therapy). To be considered RT, the biopsy must demonstrate sheets of large B cells by immunohistochemistry. One retrospective study found that nearly 20% of cases described as RT locally could not be confirmed on central pathologic review,[22] so, when possible, it is encouraged to send a biopsy in a patient with CLL suspected to have RT for pathologic review at a center with specialized hematopathologists. Molecular characterization, including clonal relatedness through IGHV analysis, should be determined whenever possible as this has important prognostic implications (see below).

An important nuance to appreciate when interpreting the results of PET/CT scans when RT is suspected is that the predictive value of FDG avidity may vary depending on the type of previous therapy. For example, in patients treated only with previous CIT, the sensitivity and specificity of PET/CT with SUV values >10 were high at 91% and 95%, respectively.[23] By contrast, in a prospective study of 167 patients who progressed after ibrutinib or idelalisib and underwent a PET/CT as part of the screening evaluation for a clinical trial of venetoclax treatment, the sensitivity and specificity of SUV ≥10 were only 71% and 50%, respectively.[24] Several of the patients in this study with high SUVs that were concerning radiographically for RT underwent lymph node biopsy and were found to have accelerated CLL. These patients were then spared undergoing more aggressive CIT regimens used in RT, which are generally ineffective for accelerated CLL, and could instead be treated with standard-of-care CLL-directed therapies, which are recommended for the effective management of accelerated CLL. Thus, the decreased predictive power of PET/CT in the targeted agent era further emphasizes the crucial role that histological diagnosis plays in making a diagnosis of RT.

PROGNOSIS

The prognosis for RT remains dismal, with retrospective studies consistently reporting a median overall survival (OS) of only 6-12 months.[16,25-28] Although data in the targeted therapy era are more limited, the outcomes do not appear to be improving. For example, in a multicenter, retrospective cohort of 71 patients with CLL who developed RT while receiving treatment with a novel agent (mostly, BTKi or venetoclax), the median OS was only 3.5 months.[29]

An important feature of RT that ties together both pathophysiology and prognosis is the clonal relation to the preexisting CLL. Clonality can be determined by comparison of the *IGH V-D-J* gene rearrangement. About 80% of RT is clonally related, whereas 20% of RT is clonally unrelated.[3,30] IGHV gene sequencing is a reliable way to assess clonal relationship, but if not available, then comparison of kappa versus lambda restriction can, in some cases, provide at least some insight into the potential clonal relationship. A difference in light chain restriction suggests the RT is not clonally related. Clonality has significant implications for prognosis. One retrospective analysis demonstrated that patients with clonally unrelated RT had a median survival of approximately 5 years, whereas clonally related RT had a much shorter median OS of only 14 months.[3] Closely intertwined is the observation that the number of lines of previous CLL-directed therapy is associated with prognosis.[26,28] In a large, single-center, retrospective analysis, CLL-treatment–naïve patients who developed RT had a median OS of 46.3 months compared with a median OS of only 7.8 months in previously treated patients with CLL who developed RT.[28]

The RS score is a prognostic scoring system, which was built from a retrospective analysis of 130 patients with RT treated at MD Anderson Cancer Center and identified five characteristics that were independent predictors of shorter survival: Zubrod performance status >1, LDH >1.5 times the upper limited of normal, platelet counts $<100 \times 10^9$/L, tumor size ≥5 cm, and >1 previous therapy.[25] This score was subsequently validated in two independent cohorts where survival outcomes indeed stratified by this RS score.[3,26]

Notable subsets of CLL transformation are Hodgkin lymphoma and a cutaneous-only form of RT. Patients with HT have a more favorable prognosis than transformation to DLBCL. In a multicenter retrospective analysis of 94 patients

with transformation to HL, the 2-year OS after HT diagnosis was 72%; in those patients who received standard doxorubicin, bleomycin, vinblastine, and dacarbazine–based therapy, responses were durable, with a reported median OS of 13.2 years.[31] Cutaneous-only RT is a rare extranodal presentation of RT, with literature limited to case reports and case series, but may have a more indolent nature if confined only to the skin.[32]

MANAGEMENT

Approach in Clinical Practice

CIT, with the regimen of R-CHOP, remains the most commonly used initial treatment for RT in clinical practice. R-CHOP was initially investigated prospectively in a phase II study of 15 patients, which reported an overall response rate (ORR) of 67% (complete response [CR] rate of 7%).[33] Responses were generally not durable, with a median progression-free survival (PFS) of only 10 months. Investigation of ofatumumab in combination with CHOP yielded similar results, with an ORR of 46% (CR rate 27%) and median PFS of 6 months.[34] Additional cytarabine-based CIT regimens have been explored,[35] including the combination of oxaliplatin, fludarabine, cytarabine, and rituximab.[36,37] In these studies, the alternate CIT regimen did not significantly improve efficacy and was associated with considerable toxicity. The ORR with the regimen of rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) was reported to be 39%, with a PFS of 3.5 months and median OS of only 5.9 months.[38] In total, although no regimen has been demonstrated to achieve superiority (or inferiority) compared with R-CHOP, on the basis of the historical management of DLBCL, the most commonly used first-line treatment for RT remains R-CHOP.

Role of Transplant

For patients who achieve a remission to initial therapy, hematopoietic cell transplantation (HCT) presents an opportunity for potential long-lasting remission, although prospective data in this area are limited. One of the first studies to report on outcomes of allogeneic HCT (alloHCT) and autologous HCT (autoHCT) in RT was a single-institution retrospective study of 20 patients who underwent HCT as either a consolidative therapy or a salvage therapy.[25] For patients who underwent alloHCT while in remission, the estimated 3-year OS was encouragingly about 75% (although with a small sample size of only seven patients). Notably, the estimated 3-year OS was only 27% for those patients who responded to initial therapy but did not proceed to alloHCT, highlighting the potential benefit of proceeding to alloHCT in remission.

A subsequent retrospective analysis examined alloHCT and autoHCT in patients with RT and reported a 3-year PFS rate of 45% in those undergoing autoHCT versus 27% in alloHCT.[39] However, notably 82% of patients were in remission at the time of autoHCT versus only 60% of those undergoing alloHCT. Recent retrospective studies of patients with RT undergoing alloHCT have reported outcomes ranging from a 4-year PFS of 39%[40] to a 2-year PFS of 65% with reduced-intensity conditioning.[41] One of the largest recent retrospective studies of alloHCT in patients with RT (118 patients) demonstrated that disease status at the time of HCT was significantly associated with outcomes.[42] The 3-year PFS of patients in CR at the time of alloHCT was favorable at 66%, whereas it was 43% in patients in PR at the time of HCT and only 5% in patients with resistant disease. In this study, the 3-year PFS of patients who underwent autoHCT was 48%. Notably, there have been no prospective studies directly comparing autologous versus allogeneic transplantation; however, given that patients with RT have concomitant CLL and alloHCT as opposed to autoHCT can achieve durable remissions for CLL, alloHCT with reduced-intensity conditioning remains the preferred transplantation approach.

New Directions of Treatment for RT

The emergence of targeted therapies that are being effectively used in CLL and across the spectrum of B-cell non-Hodgkin lymphomas (NHL) has raised the hope that these drugs may also improve outcomes for RT. Here, we will first review the data on targeted therapies investigated as monotherapy, which have ranged from small-molecule inhibitors to immunotherapies, including immune checkpoint inhibitors, bispecific antibodies, and chimeric antigen receptor T-cell (CAR-T) therapy. We will then summarize combination strategies with available data.

Targeted Agent Monotherapies

BCL-2 inhibition. One of the first pathways to be explored with targeted agent monotherapy in RT was the intrinsic (mitochondrial) pathway of apoptosis, which is governed by the interaction of the BCL-2 family of proteins. In the phase I study of the oral BCL-2 inhibitor venetoclax, a dedicated cohort of seven patients with RT was included.[43] Three of the seven patients achieved response, suggesting some biological activity of the drug in this disease; however, these responses were for the most part relatively short-lived, and therefore, although the study was a proof of principle that BCL-2 inhibition (BCL-2i) has activity in RT, it also suggested that future studies using BCL-2i to treat RT should use the drug as part of a combination strategy.

BTK inhibition. **Covalent BTK inhibitors.** Although covalent BTK inhibitors, such as ibrutinib, acalabrutinib, and zanubrutinib, have revolutionized the treatment armamentarium for CLL,[44-46] the outcomes for patients with RT treated with these agents as monotherapy remain less promising. For example, in a small, retrospective series of four patients with RT treated with ibrutinib, three achieved response (one CR,

two PR), but the median treatment duration was only 6.1 months,[47] and in another case series of two patients, one patient had excellent disease response whereas the other patient had primary refractory disease to ibrutinib.[48]

In a phase I/II study of acalabrutinib that enrolled 25 patients with RT, while the ORR was 40%, the median duration of response (DOR) was only 6.2 months and median PFS was short at 3.2 months.[49] The activity of zanubrutinib as montherapy in RT was recently reported in 13 patients, with eight patients (62%) achieving a response (two patients achieved a CR). The median PFS and OS were favorable at 17.3 months and 29.3 months, respectively.[50]

Noncovalent BTK inhibitors. Pirtobrutinib and nemtabrutinib are noncovalent BTK inhibitors that have been studied in RT. These drugs inhibit BTK through distinct pharmacologic properties compared with covalent BTK inhibitors,[51] and they thereby have the potential to be used effectively in settings of BTKi resistance in CLL (ie, C481S-mutant *BTK*). Pirtobrutinib, a highly selective BTKi with a long half-life that enables continuous BTK inhibition, was investigated as monotherapy in RT in a dedicated cohort of the phase I/II BRUIN study. In recently reported results of 75 response-evaluable patients, the ORR was 52% with a CR rate of 10%.[52] Despite these encouraging response rates, the median PFS was short at 3.7 months. As seen across a total cohort of 773 patients including those with other B-cell malignancies, pirtobrutinib was well-tolerated, with low rates of severe adverse events (AEs). Interestingly, although these patients were relatively heavily pretreated with a median of four lines of previous CLL and RT therapy, the median OS was 13.1 months. This substantially longer median OS than median PFS suggests that pirtobrutinib may effectively serve as a bridge to other therapies such as allogeneic transplantation, which have the potential to provide durable benefit for some patients.

The results for six patients with RT treated with nemtabrutinib were reported in the BELLWAVE-001 study, with an encouraging ORR of 50% (three patients achieved a PR).[53] This noncovalent BTKi binds with similar potency to C481-mutant *BTK* and wild-type *BTK* but is less selective than pirtobrutinib, additionally having activity against SRC, ERK, and AKT; notably, it can also inhibit signaling downstream of PLCγ2.[54] In the recently reported results of a phase II expansion study across B-cell malignancies, the toxicity profile included fatigue, constipation, dysgeusia, cough, nausea, and pyrexia as the most common treatment-related AEs.[55]

Immune-Based Therapeutic Approaches as Monotherapies

PD-1 blockade. Given the high expression of PD-1 on RT cells, there is a promising rationale for investigation of immune checkpoint blockade in RT. Single-agent pembrolizumab was initially reported to have moderate activity in a small case series of nine patients with RT-DLBCL.[56] The ORR was 44% (one patient achieved a CR) with a median OS of 10.7 months, and immune-related AEs, including liver toxicities and pneumonitis, were observed in only a small proportion of patients. In a subsequent phase II study of pembrolizumab monotherapy in RT (KEYNOTE-170), the results were less promising. In 23 patients, the ORR was only 13% (4% CR) with a median PFS of 1.6 months and median OS of 3.8 months.[57] Notably, two of the three patients who responded had classical Hodgkin lymphoma histology rather than DLBCL. Thus, PD-1 blockade as monotherapy is unlikely to provide meaningful benefit in RT. Given the immune dysfunction inherent in CLL, if a future role is to be identified for checkpoint blockade in RT, it is likely that it will be as part of a combination strategy where the combination partner is able to help reduce the CLL-driven immune suppression and thus allow the checkpoint blockade to enhance antitumor immunity (see below).

Anti–CD19-directed CAR-T therapies. Given anti-CD19 CAR-T therapy can be effective even in patients with highly refractory de novo DLBCL,[58] there is a strong rationale to explore this approach in RT. To our knowledge, to date, there are no robust prospective data on the utility of CAR-T in RT specifically, although the early results available do appear to hold some promise. One small prospective study investigating an institutionally produced CD19-directed CAR-T product enrolled eight patients with transformed CLL.[59] Of the six patients with DLBCL-RT, four achieved a CR. For the four patients who responded, at a median follow-up of 5.5 months (range, 4-10 months), all were alive at last follow-up, and two patients underwent alloHCT. Additional data supporting the potential role of anti-CD19 CAR-T therapy in RT include an early report of axicabtagene ciloleucel (axi-cel) in which one patient achieved a PR, but response duration was only 1 month,[60] and a study of the product JCAR017 in which five patients with RT were treated and three patients achieved a response on day 28 restaging (two CRs, one PR).[61] In a recent institutional retrospective cohort review of the use of commercially available axi-cel, eight of nine patients responded, including five patients who achieved a CR.[62] One patient proceeded to a consolidative alloHCT, although the median follow-up was only 6 months. The expected CAR-T–associated AE of cytokine release syndrome (CRS) was observed in all patients (for eight patients, $\leq$ grade 2; one patient with grade 4 CRS). Immune effector cell–associated neurotoxicity syndrome of $\geq$ grade 3 occurred in three patients. A prospective study of the anti-CD19 CAR brexucabtagene autoleucel (brexu-cel) that includes patients with relapsed/

refractory (R/R) RT is now enrolling (ZUMA-25; ClinicalTrials.gov identifier: NCT05537766).

Bispecific antibodies. Bispecific T-cell–engaging antibodies (BsAbs), which contain a tumor antigen-binding domain and a CD3-binding domain, are designed to bring tumor cells in close proximity to effector T cells, thereby leading to direct tumor cell lysis. There are three BsAbs with reported efficacy in RT at present: blinatumomab, glofitamab, and epcoritamab. The phase II BLINART study investigated blinatumomab, a CD19/CD3 BsAb, in previously untreated DLBCL-RT and used a PET-CT response-adapted approach, whereby patients who did not achieve a CR after two initial cycles of R-CHOP proceed to induction with blinatumomab.[63] In 39 patients who initiated treatment with R-CHOP, 25 went on to receive blinatumomab, with an ORR of 36% (9/25). In another phase II study of blinatumomab in RT, nine patients were treated, with two patients achieving a response (one CR, one PR); the median survival was 10.3 months.[64]

Glofitamab and epcoritamab are CD20/CD3-targeting BsAbs. Glofitamab, a bivalent antibody with two anti–CD20-binding domains, has demonstrated highly promising efficacy in heavily pretreated patients with de novo DLBCL.[65] The phase I study included 10 patients with RT, of whom six patients were evaluable for efficacy; three achieved a CR, and two achieved a PR.[66] Epcoritamab is a monovalent CD20/CD3 BsAb that has also demonstrated a high level of efficacy in R/R de novo DLBCL.[67] An expansion cohort of the ongoing EPCORE CLL-1 phase Ib/II study specifically enrolled patients with RT. Six of the 10 patients responded, with five of those six patients achieving CR.[68] Glofitamab and epcoritamab are both well-tolerated for most patients, with the most notable AE of this class of therapies being low-grade CRS. Larger numbers of patients with longer follow-up will be needed to understand the potential for using BsAbs in RT, but the initial data do appear to be promising.

ROR1-targeting antibody-drug conjugate. The receptor tyrosine kinase-like orphan receptor 1 (ROR1) is a transmembrane oncofetal protein present on the surface of CLL and RT cells,[69] and investigations of ROR1-targeting antibodies are underway. One potential advantage of this target is that it is not expressed on other normal hematopoietic cells, including B cells, so this approach has the potential to be less immunosuppressive. The WAVELINE-001 study investigated zilovertamab vedotin, an anti-ROR1 ADC containing the antimicrotubule agent monomethyl auristatin E (MMAE) as a payload, in patients with NHL. Recently reported results included seven patients with RT, four of whom responded, with a median DOR of 2.8 months.[70] Treatment-related AEs included neutropenia, fatigue, nausea, and peripheral sensory neuropathy, consistent with the expected profile of an MMAE-containing ADC.

Novel Agent Therapies—Combination Approaches

Given the highly refractory nature of RT, and the modest activity seen with all monotherapies explored to date, to our knowledge, achievement of durable disease remission will likely require a combination therapeutic approach; there are several such strategies currently under investigation. Some build on the current standard-of-care CIT backbone while others are entirely based on combinations of targeted agents, and many incorporate immune-based approaches. In the following sections, we will focus primarily on those studies with available results, and we also include some discussion of ongoing studies without results reported yet. Figure 1 provides an overview of the spectrum of combination studies in RT.

Combination of novel agents with CIT. There are several studies investigating novel agents in combination with a CIT backbone; we recently published the results of a multicenter, phase II study of venetoclax in combination with dose-adjusted EPOCH-R, with venetoclax added via an accelerated ramp-up in cycle 2.[71] The rationale of this approach is that because venetoclax demonstrated some single-agent activity in RT,[43] it may have the potential to make RT cells more primed to undergo apoptosis. By combining venetoclax with CIT, we hypothesized that there would be a chemosensitization effect that enhanced the already established activity of CIT to treat RT. In the 26 patients enrolled, the ORR was 61.5% with a CR rate of 50%, and in the 20 patients who received venetoclax (six patients did not proceed beyond the first cycle of CIT alone), 65% (13/20) achieved CR. The OS in all patients was 19.6 months; eight patients successfully proceeded to consolidative alloHCT with 11 remaining on venetoclax monotherapy maintenance. Toxicity with the R-EPOCH backbone was notable for hematologic and infectious complications, particularly in older patients and those with preexisting medical comorbidities. To assess whether keeping the venetoclax but deintensifying the CIT backbone might lead to better tolerability while still preserving the potential for chemosensitization, a new cohort investigating venetoclax plus R-CHOP (VR-CHOP) is ongoing. With the promising results from the initial VR-EPOCH cohort, using VR-EPOCH or VR-CHOP for a fit patient with RT is a reasonable consideration in clinical practice, given that all the agents are already approved and accessible for use in patients with CLL.

Another approach being evaluated is the combination of BTKi with CIT. Given that acalabrutinib did have some single-agent activity as described earlier and was also well-tolerated in patients with RT, it was hypothesized that it could be efficacious to add it to a CIT backbone to improve the quality of response. The ongoing STELLAR trial is a randomized study investigating the combination of

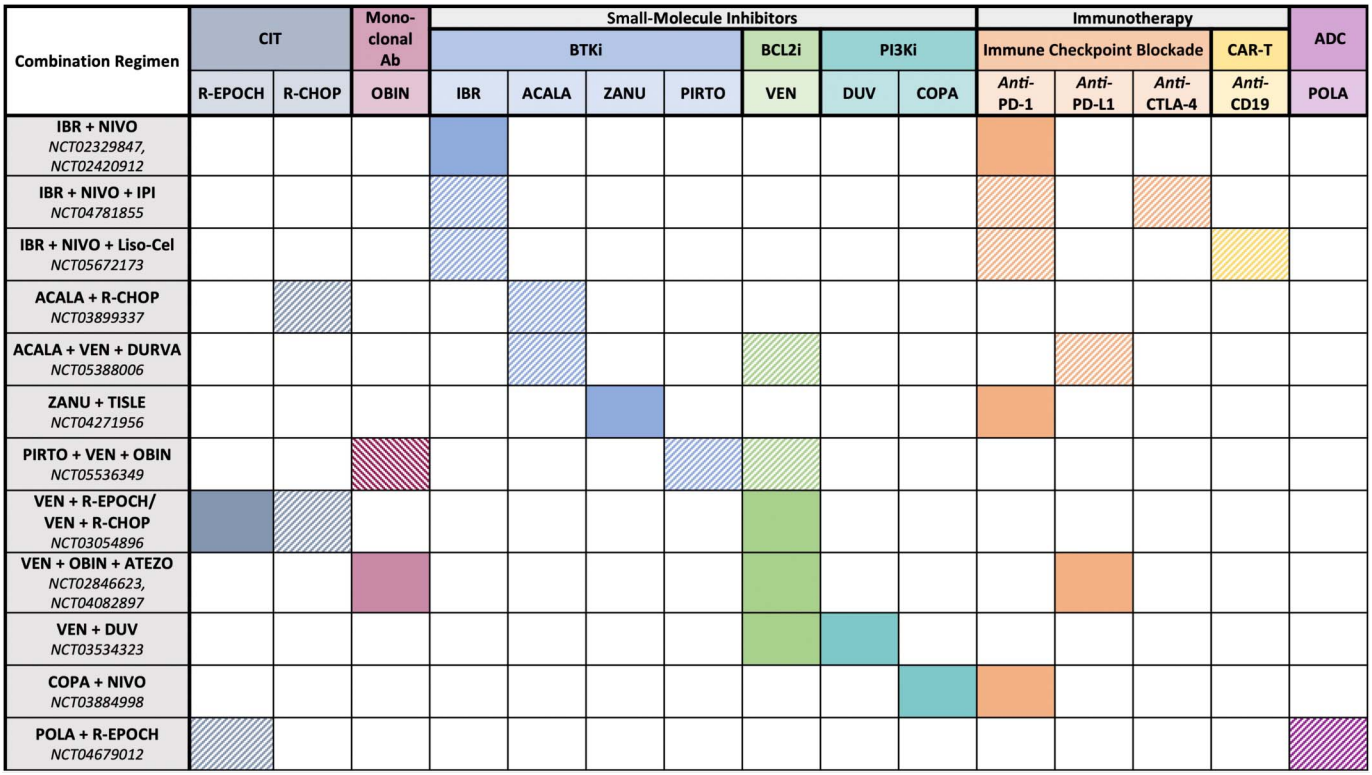

FIG 1. Novel agent combination treatment regimens under investigation for the treatment of Richter transformation. Solid fill indicates results reported. Hashed lines indicate trial enrollment ongoing with no reported results yet. Ab, antibody; ACALA, acalabrutinib; ADC, antibody-drug conjugate; ATEZO, atezolizumab; BCL2i, B-cell leukemia/lymphoma-2 inhibitor; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell; CIT, chemoimmunotherapy; COPA, copanlisib; CTLA-4, cytotoxic T-cell lymphocyte-4; DURVA, durvalumab; DUV, duvelisib; IBR, ibrutinib; IPI, ipilimumab; Liso-cel, lisocabtagene maraleucel; NIVO, nivolumab; OBIN, obinutuzumab; PIRTO, pirtobrutinib; POLA, polatuzumab vedotin; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin ; TISLE, tislelizumab; VEN, venetoclax; ZANU, zanubrutinib.

acalabrutinib and R-CHOP versus R-CHOP alone in RT.[72] This trial is particularly noteworthy given that, to our knowledge, it will be the first randomized, controlled trial dedicated solely to RT ever to be reported.

Combination of BCL-2i with phosphoinositide 3-kinase inhibition. Rationale for this combination includes preclinical data demonstrating that phosphoinositide 3-kinase (PI3K) inhibition enhances the functional dependence of CLL cells on the protein BCL-2 for their survival.[73] In addition, analysis of primary CLL cells from patients treated with the delta/gamma PI3Ki duvelisib suggested increased sensitivity to venetoclax.[74] Furthermore, preclinical studies in RT-patient-derived xenograft models demonstrated synergistic effects of the combination of venetoclax and duvelisib.[75] We are currently conducting an ongoing phase I/II study of duvelisib and venetoclax in patients with R/R CLL and RT. Four of the eight patients with RT enrolled thus far have responded, with two of those four achieving CR. Two of the responders proceeded to cellular therapy (one with CAR-T and one with alloHCT) and have had durable remission, suggesting the potential of regimens, such as BCL-2i and PI3Ki, as a bridge to therapies with curative potential.[76]

Combination of small-molecule inhibitors with immune checkpoint blockade. Preclinical studies demonstrated enhanced antitumor effects when combining BTK inhibitors with PD-1/PD-L1 blockade,[77] and, to our knowledge, there have been two studies to date that have reported results of the combination of ibrutinib and nivolumab. The first included 20 patients with RT as part of a larger phase II study investigating this combination in several B-cell malignancies.[78] Patients were required to have received at least one previous line of RT-directed therapy, and previous ibrutinib treatment was an exclusion criterion. The ORR was promising at 65%, with 10% of patients achieving CR; however, the median DOR and PFS were short at 6.9 and 5.0 months, respectively. A second phase II study investigated the combination of ibrutinib and nivolumab in patients with either previously untreated or R/R RT.[79] Of the 24 patients enrolled, 58% were previously untreated for RT, although 54% (13/24) had received a previous BTKi. The ORR was 42% with a CR rate of 34%, and a median OS of

13 months; however, efficacy outcomes did differ by previous treatment status, with the median OS for the 14 patients who were treatment-naïve for RT being 24.1 months compared with 9.1 months in the 10 patients who had R/R disease.

The CLL-RT1 trial similarly investigates the combination of BTKi with PD-1 blockade, but with the second-generation covalent BTKi zanubrutinib and the PD-1 inhibitor tislelizumab.[80] This phase II multicenter trial has now completed enrollment (estimated enrollment 57 patients), and in preliminary efficacy results of seven patients, three patients were reported to have responded (one CR, two PR), with a median and OS of 2.9 months and 15.4 months, respectively.[50]

A different approach currently under investigation is a combination of the pan-PI3K inhibitor copanlisib with nivolumab in an ongoing phase I study that has now enrolled 14 patients with RT.[81] In this heavily pretreated patient population, the ORR was 29% (two CR and two PR). This study additionally includes patients with transformed follicular lymphoma, and across all 19 efficacy-evaluable patients, the median time on treatment was 3 months (range, 1-20 months). The most common grade 3-4 AEs in all 22 patients in the study were hematologic (neutropenia, lymphopenia, anemia, thrombocytopenia), and nonhematologic grade 3-4 AEs included hypertension (14% of patients) and diarrhea (9% of patients).

Investigation of the triplet of atezolizumab (PD-L1 blockade), venetoclax, and obinutuzumab is ongoing in two studies. In the multicenter international study MOLTO, preliminary safety results of 14 patients have been reported with the most common AEs being hematologic.[82] A separate single-institution phase II study of this combination has reported promising preliminary efficacy results.[83] Of eight patients enrolled, seven patients had previously untreated RT and all responded (five CR, two PR), with a median PFS of 13.0 months. Three patients successfully proceeded to a consolidative alloHCT.

CONCLUSION

In summary, the practical management of RT in 2023 still utilizes long-standing historical approaches to treatment while leveraging new targeted therapies. As shown in Figure 2, appropriate clinical suspicion should prompt diagnostic work-up, with a biopsy essential for diagnosis. Given the histopathologic challenge RT presents, expert pathology review should be obtained whenever possible. We strongly encourage clinical trial enrollment—even in the frontline setting—given the historically poor outcomes with CIT regimens. For patients who are fit, alloHCT represents the only proven modality that can provide highly durable remission at present, with outcomes associated with the depth of response entering transplant. Thus, in such patients, the primary goal of frontline treatment is to achieve CR before transplant, leveraging novel agents if needed (Fig 2).

Notably, much of the current approach management of RT is based on either single-arm studies or retrospective data, with no randomized-controlled trials reported to date, to our knowledge. Furthermore, in nearly all prospective studies either reported or ongoing, the sample sizes are limited, thus establishing that a clear new standard of care in RT will likely remain challenging in the near future. In the longer term, if the field is able to coalesce around a limited number of the most promising regimens, randomized phase III studies will be needed to define a true standard-of-care approach.

While RT remains one of the largest clinical unmet needs in the field of B-cell NHL, the new biological insights over the past few years have the potential to usher in a new era of effective targeted therapeutics. Parallel advancements in the development of novel targeted agents in the clinic provide the opportunity to leverage our increased understanding of the biological mechanisms underlying this disease to pursue rational, effective targeted agent combinations. These encouraging developments bring renewed hope that improved outcomes in RT may be on the horizon.

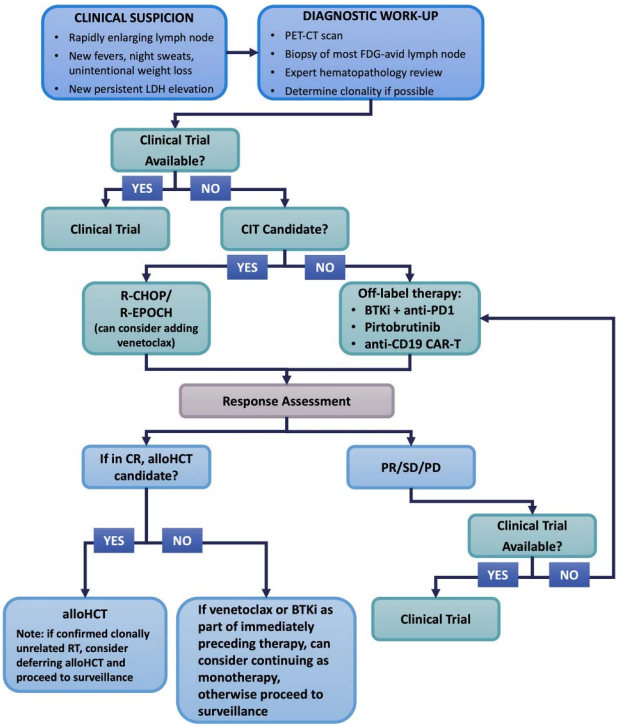

FIG 2. Summary of the practical management of Richter transformation in 2023. alloHCT, allogeneic hematopoietic cell transplantation; BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CIT, chemoimmunotherapy; CR, complete response; FDG, fluorodeoxyglucose; LDH, lactate dehydrogenase; PD, progressive disease; PET-CT, positron emission tomography-computed tomography; PR, partial response; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; RT, Richter transformation; SD, stable disease.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Spotlight on Small-Cell Lung Cancer and Other Lung Neuroendocrine Neoplasms

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overview

Lung neuroendocrine neoplasms (NENs) encompass a spectrum of neoplasms that are subdivided into the well-differentiated neuroendocrine tumors comprising the low- and intermediate-grade typical and atypical carcinoids, respectively, and the poorly differentiated, high-grade neuroendocrine carcinomas including large-cell neuroendocrine carcinomas and small-cell lung carcinoma (SCLC). Here, we review the current morphological and molecular classifications of the NENs on the basis of the updated WHO Classification of Thoracic Tumors and discuss the emerging subclassifications on the basis of molecular profiling and the potential therapeutic implications. We focus on the efforts in subtyping SCLC, a particularly aggressive tumor with few treatment options, and the recent advances in therapy with the adoption of immune checkpoint inhibitors in the frontline setting for patients with extensive-stage SCLC. We further highlight the promising immunotherapy strategies in SCLC that are currently under investigation.

INTRODUCTION

Lung neuroendocrine neoplasms (NENs) account for up to 25% of all lung cancers and can be subdivided into (1) well-differentiated neuroendocrine tumors (NETs, 2%), comprising low-grade typical and intermediate-grade atypical carcinoids (ACs), and (2) poorly differentiated, high-grade neuroendocrine carcinomas (NECs) including large-cell neuroendocrine carcinomas (LCNECs, 3%) and small-cell lung carcinoma (SCLC, 20%). Each of these lung NEN subtypes shows different behavior in terms of clinical presentation, prognosis, and etiology. SCLC and LCNEC are smoking-related, displaying aggressive biologic behavior, whereas highly metastatic tumors with poor prognosis, typical carcinoids, and ACs have thus far an unclear association with smoking and are less aggressive, with longer survival.[1,2] Although the incidence and prevalence of lung NETs have increased markedly in recent years,[3] LCNEC and pulmonary carcinoids are still the rare entities of lung NENs and, consequently, considered orphan diseases because of the limited basic biological and clinical knowledge.

MORPHOLOGICAL FEATURES

On the basis of the recent WHO histological classification of thoracic tumors,[1] SCLC is a malignant epithelial tumor composed of small cells with scant cytoplasm, finely granular nuclear chromatin, and absence of or inconspicuous nucleoli, with a high mitotic count and frequent necrosis. Most SCLCs express neuroendocrine (NE) markers. Combined SCLC has an additional component of non–small-cell lung carcinoma (NSCLC), which may include large-cell neuroendocrine carcinoma (LCNEC), adenocarcinoma, squamous cell carcinoma, large-cell carcinoma (LCC), spindle cell carcinoma, or giant cell carcinoma. In the case of LCNEC, large cells should make up $\geq$10% of the tumor for it to be classified as combined SCLC/LCNEC or combined SCLC and LCC. LCNEC is a high-grade NSCLC with NE morphology and a mitotic count of $>$10 mitoses/2 mm^2, which expresses one or more NE immunohistochemical markers. Combined LCNEC is an LCNEC with components of adenocarcinoma, squamous cell carcinoma, or spindle or giant cell carcinoma. Finally, carcinoid tumors are NE malignancies with a well-differentiated organoid architecture. There are two subtypes: typical carcinoids (carcinoid tumors with $<$2 mitoses/2 mm^2 and lacking necrosis) and ACs (carcinoid tumors with 2-10 mitoses/2 mm^2 and/or foci of necrosis, usually punctate; Fig 1).

Contrary to gastrointestinal/pancreatic NETs, where the proliferation marker Ki-67 is used to stratify patients for therapeutic decisions, its main role in lung NENs is to help distinguish NETs from NECs in small biopsies. Documenting Ki-67 for lung NETs may also be useful in the metastatic setting. Otherwise, mitotic counts and necrosis remain the main diagnostic criteria in primary resected lung NET basically because definite cutoffs for Ki-67 are yet to be identified.[1]

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PRACTICAL APPLICATIONS

- Recent biological findings push toward a future morphomolecular classification, although they have not yet fully translated into novel therapeutic options for all subtypes.
- The optimal systemic treatment for patients with stage IV large-cell neuroendocrine carcinoma is yet to be defined, with both small-cell lung carcinoma (SCLC) and non–small-cell lung carcinoma systemic therapy regimens commonly used in practice.
- Biologic subtypes are classified by differential expression of transcription regulators, such as ASCL1 (achaete-scute homolog 1), NEUROD1 (neurogenic differentiation factor 1), and POU2F3 (POU class 2 homeobox 3), or low expression of all three transcription factor signatures accompanied by an inflamed gene signature and may have therapeutic implications.
- Combined PD-L1 inhibitors and platinum-doublet chemotherapy improve overall survival in all patients with extensive-stage SCLC and may preferentially benefit patients with the SCLC-I subtype.
- Bispecific T-cell engagers and chimeric antigen receptor T cells designed against unique SCLC tumor antigens, such as DLL3, are novel immunotherapeutic strategies to overcome deficiencies in antigen presentation, which are common in SCLC.

UNRAVELING THE BIOLOGY AND MOLECULAR FEATURES OF LUNG NENS

Molecular Features of Lung NETs (pulmonary carcinoids)

Unlike lung NECs (SCLC and LCNEC), NETs present with a low mutational rate, frequent alterations in chromatin-remodeling genes, and rare mutations in *TP53* and *RB1*.[4-7] *MEN1*, *EIF1AX*, and *ARID1A* are significantly mutated genes, with 5% of patients affected by MEN1 syndrome.[8,9] Although lung NETs are considered as a single entity, a recent multiomic study by Alcala et al[10] suggests that these tumors comprise three distinct molecular groups (Fig 1). Carcinoid A1 tumors have high levels of *ASCL1* and *DLL3* and enrichment for *EIF1AX* mutations. Carcinoid A2 tumors have low levels of *SLIT1* and *ROBO1*. More than 80% of patients with A1 and A2 tumors are alive >10 years. Carcinoid B tumors have high levels of UGT and CYP genes, *ANGPTL3*, and *ERBB4* and low levels of *OTP* and *TTF1*. These tumors are also enriched for *MEN1* alterations. Only 60% of patients with carcinoid B tumors survive >10 years. These molecular subtypes do not strictly correlate with the morphological classification, although enrichment for typical (A1 and A2) and atypical (B) carcinoids was observed. The existence of these molecular groups was confirmed in an independent series.[11-13]

A recent single-cell study has shown that lung NETs are characterized by an immune microenvironment of noninflammatory monocyte-derived myeloid cells, and a stromal microenvironment constituted of vascular cells and CAF-like myofibroblasts.[14] This study also showed that the abovementioned molecular clusters are not driven by immune or stromal cells, but rather represent tumor intrinsic features. However, they seem to be associated with enrichment for distinct tumor microenvironment cell types, such as monocytes, in cluster B and dendritic cells in cluster A1.

The molecular findings have not yet translated into novel therapeutic options. Currently, only everolimus (a mammalian target of rapamycin inhibitor) has been approved by the US Food and Drug Administration and European Medicines Agency for advanced, progressing, nonfunctional, pulmonary, and digestive NETs (approved in 2016).[15]

Evidence for Novel Morphological Variants and Biological Entities

According to the thoracic WHO classification, lung NETs are divided into grade 1 typical carcinoids and grade 2 ACs.[1] This grading in the lung is based on the mitotic count, with a maximum of 10 counts per 2 mm^2 for ACs. Beyond this ceiling, lung NENs are by default classified as LCNECs. However, recent findings suggest the existence of additional entities that might not completely fit into the current classification (Fig 1). Understanding the implications of these new entities is crucial because the distinction between lung NETs and NECs determines the most appropriate clinical management: Surgical resection is the standard for localized tumors, mostly NETs, while chemoimmunotherapy is preferred for advanced NECs.

The grade 3 lung NETs, a highly proliferative emerging variant. Despite the abovementioned criteria, there have been several reports of lung NENs with classically carcinoid morphology (bland, uniform cytology, and absence/focal necrosis) but higher mitotic counts (>10/2 mm^2).[16-20] These NENs also present with higher Ki67 levels than expected for lung NETs (>30%), a marker of proliferation. The presence of *MEN1* mutations and the absence of *RB1* and *TP53* alterations further support their relationship with carcinoids. However, these tumors appear to be highly aggressive, showing higher rates of postsurgical recurrence, as compared with the recurrence rate for conventional ACs (approximately 20-30%). Interestingly, in the digestive system, a similar subgroup of highly proliferative yet well-differentiated NET has been recently recognized, named

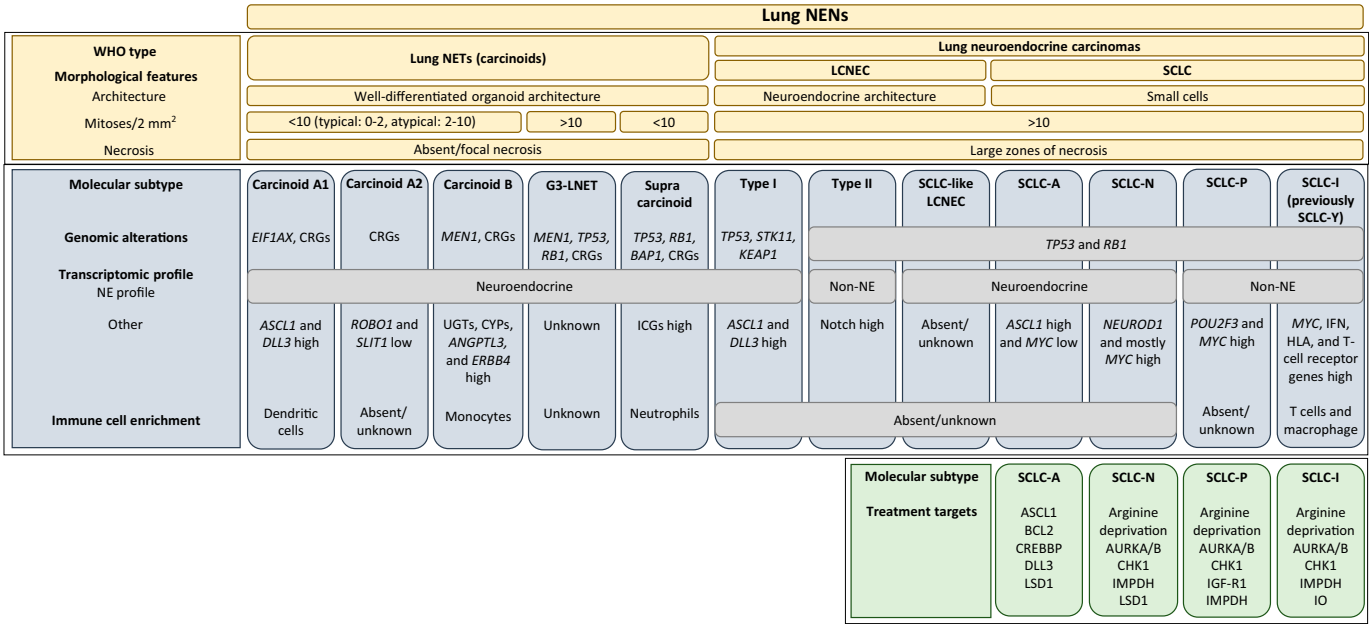

FIG 1. Morphological molecular spectrum of lung NENs. The current classification of lung NE neoplasms, subdivided into tumors (typical and atypical carcinoids) and carcinomas (LCNEC and SCLC) is depicted in orange. Diagnostic morphological features areas are described in the WHO Classification of Tumours.[1] Molecular subtypes of each WHO type are described in blue, including characteristic genomic alterations and gene expression profiles, NE profile (on the basis of whole-transcriptome analyses or immunohistochemsistry of characteristic NE markers), and immune cell enrichment.[6,10-13,16-20,43,46] Treatment targets for SCLC subtypes are depicted in teal.[39] SCLC-I (previously SCLC-Y) may also be known as *ASCL1*/*NEUROD1*/*POU2F3*-negative SCLC. Note, G3-LNET (grade 3 lung NET), and supracarcinoids are emerging morphological and biological entities, respectively, with uncertain economic alterations because of low numbers; CRGs, chromatin remodeling genes; ICGs, immune checkpoint genes; IO, immuno-oncology; LCNEC, large-cell neuroendocrine carcinoma; NE, neuroendocrine; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; SCLC, small-cell lung carcinoma.

well-differentiated NETs of grade 3.[21,22] In contrast, in the lung setting, they are classified as LCNEC with morphologic features of carcinoid tumor, nomenclature likely to remain until more data for these tumors can be accumulated.[23]

Supracarcinoids, an emerging biological entity. Although the mitotic count for typical carcinoids and ACs separates two grades of the same disease entity, it is strongly believed that lung NETs and NECs are biologically separate entities on the basis of the distinct genomic profiles found in molecular studies.[24] Surprisingly, Alcala et al[10] identified six samples morphologically classified as ACs that fell into the molecular cluster of LCNEC. They were named supracarcinoids. Supracarcinoids also displayed poor survival (10-year overall survival [OS] of 33%), similar to LCNEC, and a particular immune pattern of high levels of immune checkpoint receptors and ligands and high neutrophil content. These features may represent potential diagnostic and therapeutic candidates for this group of aggressive lung NETs. Simbolo et al[11] also identified four ACs that fell into clusters enriched for LCNECs, supporting the existence of supracarcinoids. The discovery of supracarcinoids suggests that the molecular link between lung NETs and NECs, especially between ACs and LCNECs, might be subtler than initially believed.[25] In line with this, the work of Pelosi et al[26,27] supported the possibility of progression or transition from lung NET to NEC in both the lung and the thymus. In agreement with this idea, a recent study revealed that well-differentiated insulinoma tumors could dedifferentiate and acquire a progenitor-like molecular phenotype, resulting in the development of invasive metastasis-like primary pancreatic NETs. These data demonstrate that dedifferentiation is a mechanistically and temporally separable step in the multistage tumorigenesis of pancreatic islet cells.[28]

Whether grade 3 NETs and supracarcinoids are indeed the same variant discovered through different approaches and what are the implications of their existence for the clinical management of the patients would require designed-for-purpose follow-up studies in larger series.

LCNECs

Molecular studies have shown the existence of two major groups of LCNECs.[6,16,29] The first, named type I LCNEC, displays a NSCLC-like genomic profile (mutations in *STK11*, *KEAP1*, *KRAS*, and other RAS pathway gene alterations) and a NE transcriptomic profile (*ASCL1*-high/*DLL3*-high/*Notch*-low). The second, named type II LCNEC, carries an SCLC-like genomic profile (*TP53* and *RB1* mutations) and a non-NE transcriptomic profile (*ASCL1*-low/*DLL3*-low/*Notch*-high).

A small subset of LCNECs presented with both the genomic (*TP53* and *RB1* mutations) and transcriptomic profiles of SCLC being therefore considered as SCLC-like. These data suggest that LCNEC represents a distinct entity that harbors a unique combination of genomic and transcriptional programs (Fig 1). On the basis of this, LCNEC may indeed be the result of phenotypic convergence of tumor groups derived from distinct cells of origin.[6,16,29] This translates in a vast heterogeneity of LCNEC at both molecular and histological levels. Indeed, combined LCNECs account for 20%-25% of resected LCNECs.[30] Although any non-NE NSCLC histological type may be present, the most frequent co-occurrence is with adenocarcinoma. Genomic studies show that LCNEC and NSCLC components are clonally related, supporting the concept of phenotypic divergence rather than a collision phenomenon.[29]

The optimal systemic treatment for patients with stage IV LCNEC is yet to be defined, with both SCLC and NSCLC chemotherapy regimens commonly used in practice.[31] Of note, given the rare tumor type, clinical trials tailored for patients with LCNEC are lacking, especially in the era of immunotherapy.[32] The abovementioned molecular findings encouraged further retrospective studies that found differences in prognosis and therapeutic outcomes to SCLC-like and NSCLC-like chemotherapy regimens of patients on the basis of the molecular subtype of their LCNEC tumor. However, these studies showed contradictory findings, and the global response to chemotherapy was generally quite poor.[33,34] These findings highlight the unmet need to find novel therapeutic options for these patients.[15,35] An example of such therapeutic options includes the effective targeted agent sotorasib against LCNEC harboring *KRAS G12C* mutations.[36] DLL3 targeted therapy may represent another promising opportunity for stage IV LCNEC, given the high percentage (74%) of *DLL3* expression in these advanced tumors.[37]

SCLC

SCLC was once defined as a homogeneous disease marked by mutational alterations associated with tobacco-related carcinogenesis; however, this has evolved with discovery of morphologic, epigenetic, and transcriptomic heterogeneity. DNA sequencing data demonstrate a high tumor mutation burden,[4,38] with near universal loss of the tumor suppressor genes *TP53* and *RB1*.[5] In preclinical studies, loss of function of TP53, RB1, and NOTCH lock NE progenitors into a self-renewal program and thereby contribute to tumorigenesis and transformation to SCLC.[39] Most recent studies have revealed distinct subsets such as the identification of subsets of MYC-driven SCLC,[40-42] with metabolic heterogeneity that suggested arginine deprivation as a potential therapeutic vulnerability for MYC-driven SCLC. Further work has led to the classification of transcription factor–defined subsets that include the subtypes SCLC-A, SCLC-N, SCLC-P, and SCLC-Y, defined by increased expression of achaete-scute homolog 1 (*ASCL1*), neurogenic differentiation factor 1 (*NEUROD1*), POU class 2 homeobox 3 (*POU2F3*), or low expression of all three transcription factor signatures accompanied by an inflamed gene signature, respectively.[43]

SCLC-A is the dominant subtype, with high expression of NE markers including chromogranin A and synaptophysin.[44] The SCLC-N subtype was previously referred to as the variant type with more loosely aggregated cells and decreased expression of NE markers. Numerous other genes are differentially regulated among these two subtypes, including high *MYCL*, *BCL2*, *SOX2*, and *DLL3* in SCLC-A and high *MYC*, *INSM1*, and *HES6* in SCLC-N. SCLC-P was identified as defining a previously unappreciated non-NE, tuft-cell variant of SCLC.[45] The fourth subtype driven by the transcription factor YAP1 proposed a partial solution to these unclassified tumors and has been shown to correlate with high expression of interferon-γ response genes, a T-cell–inflamed phenotype, and high expression of HLA and T-cell receptor genes.[46] However, YAP1 protein expression as measured by immunohistochemistry was more variable and did not distinctly identify this subtype.[47] It is now also referred to as SCLC-I for *ASCL1*/*NEUROD1*/*POU2F3*-negative profile with an inflamed gene signature.[43] Recent studies have called into question whether these represent separate subtypes altogether, and further classification is ongoing.[43,47]

In addition, for the complexity of the heterogeneity of these SCLC tumors, studies have shown not only intertumoral heterogeneity but also intratumoral heterogeneity and how this may influence development of chemoresistance in preclinical models. These subtypes are fluid, and more than one transcriptional subtype may exist within a tumor or shifts in subtypes may occur during therapy as a potential driver of chemoresistance.[43,48-50] To highlight this, these subtypes may not be static but are driven from a pulmonary neuroendocrine cell of origin to the classic *ASCL1*+, *NEUROD1*+, and then *YAP1*+ subtype by dynamic changes in notch signaling driven by MYC.[49] Several studies demonstrated that MYC expression and the non-NE SCLC phenotype increase after chemotherapy treatment while NE identity decreases. This has been associated with development of resistance to chemotherapy with platinum and etoposide.[51] In addition, SCLC-A can evolve to a different subtype, such as SCLC-N or SCLC-Y.[49] The mechanisms underlying or leading to plasticity are under investigation.

Real-world multiomic characterization of SCLC subtypes using comprehensive molecular profiling was performed in 437 samples from patients with SCLC and high-grade NE lung carcinomas. In this study, tumors were categorized into

five subgroups (SCLC-A/N/P/Y and SCLC-mixed) on the basis of the relative expression of the four transcription factors, resulting in 35.7% of SCLC-A, 17.6% of SCLC-N, 6.4% of SCLC-P, 21.1% of SCLC-Y, and 19.2% of SCLC-mixed samples. SCLC-Y was associated with the highest expression of T-cell inflamed, NK cell, and STING pathway signatures.[52]

Given the challenges in obtaining tissue biopsies in patients with SCLC, utilization of cell-free DNA to assess the methylation profile of SCLC[53] has emerged as a promising tool in subtyping and disease monitoring, including facilitating analyses of plasticity and interconversion between subtypes as a mechanism of acquired resistance. Machine learning determined 366 differentially methylated regions and was validated on patient-derived xenograph samples. In a cohort of 56 cell-free SCLC DNA samples, 3% were classified as *ASCL1*+, 13% were classified as *NEUROD1*+, and 14% were classified as being double negative. Methylation scores of high versus low were applied to patient samples on the basis of median cutoff, and patients with low scores had significantly longer median OS than patients with high scores (20.6 *v* 8.5 months, two-sided log-rank test, $P = .00015$).[53]

More recently, characterization of the tumor immune microenvironment (TIME) among transcriptomic subtypes of SCLC provided insight into patient selection for immune checkpoint inhibitors.[54,55] Using matched SCLC tumor samples from endobronchial ultrasound transbronchial needle aspirates and peripheral blood mononuclear cells (PBMCs), Best et al[54] found distinct immune checkpoint and cytotoxic signature profiles within each transcriptomic subtype of SCLC. SCLC-N had the lowest expression of immune-related genes, whereas SCLC-P had the highest. A range of immune-related gene expression was observed across SCLC-A tumors. These findings were recapitulated in a second study, which demonstrated a statistically significant association of SCLC-N and an immune cold phenotype.[55] Furthermore, the TIME of SCLC-N had more Tregs and fewer CD8+ T cells compared with other subtypes.[55]

CURRENT STATUS OF THERAPEUTIC INTERVENTIONS: A FOCUS ON SCLC

In recent years, several therapeutic advances have been made in NE tumors. An in-depth discussion on therapies for NENs is beyond the scope of this study. In this section, we focus on the evolving treatment landscape and exciting developments of immunotherapies in SCLC.

SCLCs are characterized by rapid tumor growth and early metastatic spread for which systemic therapy is necessary for all stages of disease. A summary of studies involving immune checkpoint inhibitors, including both positive and negative studies, is provided in Table 1. Clinical studies of single-agent PD-1 and PD-L1 inhibitors in relapsed/refractory SCLC had disappointing results with low response rates and no improvements in survival.[56-58] It appears that PD-L1 inhibitors need to be given in combination for SCLC. The addition of PD-L1 inhibitors to platinum-doublet chemotherapy demonstrated improvements in survival of patients with extensive-stage (ES) SCLC in several studies, which is currently the standard first-line therapy.[59,60-65] The IMpower133 study is a phase III study randomly assigning patients with ES-SCLC to chemotherapy with or without the PD-L1 inhibitor, atezolizumab.[59] Patients receiving atezolizumab and chemotherapy had a statistically significant improvement in OS of 12.3 months compared with 10.3 months in patients receiving chemotherapy alone (hazard ratio [HR], 0.70; 95% CI, 0.52 to 0.91). The CASPIAN study, which investigated chemotherapy with or without durvalumab, demonstrated similar improvements in survival (median OS 13.0 *v* 10.3 months; HR, 0.73; 95% CI, 0.59 to 0.91).[61] Interestingly, the addition of pembrolizumab demonstrated only statistically significant improvement in progression-free survival, but not OS.[62] The negative result of this study was felt to be related to complexity of the statistical design and overperformance of the control group. The benefits of PD-L1 inhibitors were generally thought to be a class effect.[59,61--65] Despite this milestone achievement, the absolute benefit of PD-L1 inhibitors was modest.

Efforts to combine checkpoint inhibitors to improve outcomes were met with disappointing results (Table 1). The CASPIAN study included a group that was treated with chemotherapy, durvalumab and tremelimumab, a cytotoxic T-lymphocyte–associated protein-4 checkpoint inhibitor.[61,66] Unfortunately, patients receiving the quadruplet derived no statistically significant benefit compared with chemotherapy alone (HR, 0.82; 95% CI, 0.68 to 1.00). Similarly, the combination of ipilimumab and nivolumab failed to demonstrate any improvement in survival when used as maintenance therapy or in patients with relapsed/refractory SCLC.[67,56] Efforts at combining PD-1 inhibition with another coinhibitory checkpoint, T-cell immunoglobulin and ITIM domain (TIGIT), also failed. Despite correlative data showing high polio virus receptor expression on SCLC, a natural ligand to TIGIT, the phase III SKYSCRAPER-02 study failed to improve survival over standard therapy (HR, 1.04; 95% CI, 0.79 to 1.36).[68]

The use of poly ADP-ribose polymerase (PARP) inhibitors was hypothesized to increase tumor immunity through DNA damage–induced innate immunity.[69] Unfortunately, clinical trials of combined PARP and PD-L1 inhibition failed to improve responses in previously treated SCLC (Table 1).[70,71] In a phase II study of relapsed/refractory SCLC, treatment with olaparib and durvalumab had an overall response rate (ORR) of 10.5%.[70] However, treatment with PD-L1

TABLE 1. Clinical Studies of PD-L1 Checkpoint Inhibitors in Small-Cell Lung Cancer

Study	Phase	Regimen	Median PFS	Median OS	Other	FDA/EMA Approved
PD-L1 inhibitors—first line and maintenance						
IMpower133 Horn et al[59]	III	Atezolizumab, chemotherapy *v* Chemotherapy[a]	5.2 months *v* 4.3 months (HR, 0.77; *P* = .02)	12.3 months *v* 10.3 months (HR, 0.70; *P* = .007)	18-month OS rates: 34% *v* 21%	Yes
CASPIAN Paz-Ares et al[61]	III	Durvalumab, chemotherapy *v* Chemotherapy[a]	5.1 months *v* 5.4 months (HR, 0.78)[b]	13.0 months *v* 10.3 months (HR, 0.73; *P* = .005)	18-month OS rates: 34% *v* 25%	Yes
KEYNOTE-604 Rudin et al[62]	III	Pembrolizumab chemotherapy *v* Chemotherapy[a]	4.5 months *v* 4.3 months (HR, 0.75; *P* = .002)	10.8 months *v* 9.7 months (HR, 0.80; *P* = .02)[c]	24-month OS rates: 23% *v* 11%	No
ECOG-ACRIN EA5161 Leal et al[63]	II	Nivolumab, chemotherapy *v* Chemotherapy[a]	5.5 months *v* 4.6 months (HR, 0.65; *P* = .01)	11.3 months *v* 8.5 months (HR, 0.67; *P* = .04)		No
Capstone-1 Wang et al[65]	III	Adebrelimab, chemotherapy *v* Chemotherapy[a]	5.8 months *v* 5.6 months (HR, 0.67, *P* < .001)	15.3 months *v* 12.8 months (HR, 0.72; *P* = .002)	24-month OS rates: 31% *v* 17%	No
Astrum-005 Cheng et al[66]	III	Serplulimab, chemotherapy *v* Chemotherapy[a]	5.7 months *v* 4.3 months (HR, 0.48)[b]	15.4 months *v* 13.3 months (HR, 0.63; *P* < .001)	24-month OS rates: 43% *v* 8%	No
CheckMate-451 Owonikoko et al[67]	III	Nivolumab *v* Placebo	1.9 months *v* 1.4 months (HR, 0.67)[b]	10.4 months *v* 9.6 months (HR, 0.84)[b]		No
Combined checkpoint inhibitors—first line or maintenance						
SKYSCRAPER-02 Rudin et al[68]	III	Atezolizumab, tiragolumab, chemotherapy *v* Chemotherapy	5.4 months *v* 5.6 months (HR, 1.11; *P* = .35)	13.6 months *v* 13.6 months (HR, 0.79; *P* = .79)		No
CASPIAN Goldman et al[58]	III	Durvalumab, tremelimumab, chemotherapy *v* Chemotherapy	4.9 months *v* 5.4 months (HR, 0.84)[b]	10.4 months *v* 10.5 months (HR, 0.82; *P* = .045)	18-month OS rates: 30.7% *v* 25%	No
CheckMate-451 Owonikoko et al[67]	III	Ipilimumab, nivolumab *v* Placebo	1.7 months *v* 1.4 months (HR, 0.72)[b]	9.2 months *v* 9.6 months (HR, 0.92; *P* = .37)		No
Checkpoint inhibitors in relapsed/recurrent SCLC						
CheckMate-331 Spigel et al[57]	III	Nivolumab *v* Chemotherapy[d]	1.4 months *v* 3.8 months (HR, 1.41)[b]	7.5 months *v* 8.4 months (HR, 0.86; *P* = .11)	12-month OS rates: 37% *v* 34%	No
CheckMate-032 Ready et al[56]	I/II	Ipilimumab, nivolumab	1.5 months	4.7 months	24-month OS rate: 17%	No
KEYNOTE-028, KEYNOTE-158 Chung et al[58]	I/II	Pembrolizumab	2.0 months	7.7 months	24-month OS rate: 13%	No
Thomas et al[70]	II	Olaparib, durvalumab	1.8 months	4.1 months		No
Chu et al[74]	I/II	BMS-986012, nivolumab	2.1 months	18.7 months	24-month OS rate: 39%	No

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SCLC, small-cell lung carcinoma.

[a]Chemotherapy refers to a standard platinum doublet with cisplatin/carboplatin and etoposide.

[b]Where a *P* value is not reported, statistical significance was not formally tested in the clinical study.

[c]*P* value does not meet predefined threshold of statistical significance.

[d]Chemotherapy refers to oral or intravenous topotecan or amrubicin.

inhibitors alone is known to have low response rates in the relapsed/refractory setting. Ongoing studies will further investigate the potential for PARP inhibitors in earlier line settings and in combination with radiation or temozolomide, which appeared synergistic, independent of PD-L1 inhibition (ClinicalTrials.gov identifiers: NCT04728230, NCT03830918). Mutations in *SLFN11* were recently identified as a biomarker of response to PARP inhibitors and may refine patient selection.[72,73]

An agent that has demonstrated preliminary efficacy in combination with nivolumab is the ganglioside fucosyl-GM1 antibody BMS-986012. In a phase I/II study of BMS-986012 with or without nivolumab, the combination demonstrated synergistic effect with an objective response rate of 38% in

previously treated SCLC (Table 1).[74] Although the mechanism of synergy remains elusive, the combination is being further investigated in a first-line randomized phase II clinical study (ClinicalTrials.gov identifier: NCT04702880).

Despite the modest benefits of immune checkpoint inhibitors in SCLC, a subset of patients appeared to derive durable benefits. In the IMpower133and CASPIAN studies, the 2-year OS rate is almost doubled in the immunotherapy group.[59,60,61,75] The 3-year OS rate in the CASPIAN study was an impressive 17.6%.[75] Furthermore, in the pooled analysis of the KEYNOTE-028 and KEYNOTE-158 studies in which patients with relapsed/refractory SCLC were treated with pembrolizumab, the subset of responders had a remarkable duration of response ranging from 4.1 to >36 months.[58] Thus, characterization of the tumor and host immune interactions is necessary for successful development of immunotherapeutic approaches in SCLC.

Lack of Predictive Biomarkers and the Tumor Immune Microenvironment

SCLC is a particularly immune cold cancer.[76-78] Transcriptomic analysis of human SCLC samples demonstrated a particularly low CD45+ T-cell infiltration compared with lung adenocarcinomas. Furthermore, the TIME of SCLC was enriched for immunosuppressive monocytes and macrophages.[55] In retrospective studies, the only factor that demonstrated a positive association with response was CD8+ T-cell infiltration.[79-83] These observations partly explain the limited benefits of PD-L1 inhibitors in SCLC and the poor correlation with known biomarkers in other cancer types.

The incidence of PD-L1 expression is low in SCLC. In the biomarker analysis of the IMpower133 study, 53% of patients had PD-L1 expression ≥1%, but only 21% had PD-L1 expression ≥5% on tumor or immune cells.[60] There was no association between PD-L1 expression, response, and survival. Similarly, high tumor mutational burden, which associates with response across several different tumor types, did not confer any advantage in SCLC.[60]

To understand the clinical relevance of SCLC subtypes as a way to refine patient selection, an exploratory analysis was conducted using data from the IMpower133 study. Interestingly, similar trends toward the benefit of atezolizumab plus chemotherapy were observed across all subtypes, including the immune cold SCLC-N subtype.[43] Instead, a fourth subtype, SCLC-I (*ASCL1*, *NEUROD1*, and *POU2F3* low), benefitted preferentially from the addition of atezolizumab.[43] Among 49 patients with SCLC-I subtype, the median OS for those receiving atezolizumab plus chemotherapy compared with chemotherapy alone was 18 and 10 months, respectively (HR, 0.56). Using a similar method of classification, exploratory analysis of the CASPIAN study demonstrated strikingly similar results.[84] Patients with the SCLC-I subtype had a median OS of 17.6 months with durvalumab plus chemotherapy compared with 11.3 months with chemotherapy alone.[84] Corresponding to improved survival, gene expression profiling using an 18-gene panel also demonstrated the expression of inflamed T-cell markers in the SCLC-I subtype.[43,84]

Future Developments in Immunotherapeutics

The heterogeneity in TIME of SCLC suggests that a more selective approach is needed for successful drug development. Ongoing studies involve combinations of PD-L1 inhibitors that have demonstrated efficacy in other tumor types. For example, combined PD-L1 and vascular endothelial growth factor inhibitors, effective in hepatocellular carcinomas and renal cell carcinomas, is thought to be synergistic through modulation of myeloid-related immunosuppression.[85-87] Other studies investigate the role of PARP and ataxia telangiectasis and rad-3 related inhibitors in potentiating the effect of PD-L1 inhibitors through DNA damage–induced immunity.[69] Other novel immunotherapies under active investigation for SCLC are summarized in Table 2.

Defective major histocompatibility complex 1 (MHC) antigen presentation is an emerging hypothesis of resistance to immunotherapy in SCLC. Mutations in *β2 microglobulin*, a component of MHC-I, and transcriptional suppression of MHC-I were described as a mechanism of acquired resistance to checkpoint inhibitors in Merkel cell carcinomas and melanoma.[88,89] In SCLC, comparative analysis of gene expression profile of surgically resected SCLC demonstrated that expression of genes related to tumor immunity, such as MHC, *β2 microglobulin*, and *CXCL9*, was associated with long-term survival of longer than 4 years.[80]

Epigenetic therapy may reverse deficiencies in antigen presentation by modulating large areas of transcription programs. In preclinical studies, polycomb repressive complex 2 (PRC2) was found to have a key role in direct repression of MHC-I antigen presentation.[90] Inhibition of PRC2 by inhibiting enhancer of zeste homolog 2 (EZH2), its catalytic component, restored cell surface MHC-I expression. In genetically engineered mouse models, treatment with EZH inhibitors was associated with induction of MHC-I transcription, proinflammatory cytokine production, and T-cell activation.[90] EZH inhibitors are currently investigated as monotherapy or in combination with immunotherapy in SCLC.

T-cell engagers and chimeric antigen receptor T-cell (CAR-T) therapy are novel approaches in overcoming defective MHC antigen presentation.[91] The binding of tumor antigen and CD3 by a T-cell engager creates a cytolytic synapse that allows T-cell activation without MHC-dependent antigen presentation. The tumor antigen delta-like ligand 3 (DLL3) is an attractive therapeutic target

TABLE 2. Active Clinical Trials Investigating New Immunotherapies for Small-Cell Lung Carcinoma

Trial	Investigational Drug	Phase	Line	End Point
PD-1 and VEGF inhibitors				
NCT05384015	Pembrolizumab, lenvatinib, chemotherapy	II	First line	Safety PFS
PD-1 and PARP inhibitors				
NCT03958045	Rucaparib, nivolumab	II	First line	PFS
NCT04624204	Pembrolizumab, olaparib	III	Limited stage	PFS OS
NCT04728230	Olaparib, durvalumab, chemotherapy, radiation	I/II	First line	Safety
NCT03830918	Niraparib, atezolizumab, temozolomide	I/II	≥second line	Safety PFS
PD-1 and ATR inhibitors				
NCT04699838	Ceralasertib, durvalumab, chemotherapy	II	First line	PFS
PD-1 and fucosyl-GM1 antibody				
NCT04702880	BMS-986012, nivolumab, chemotherapy	III	First line	PFS
EZH2 inhibitors				
NCT05353439	Tazemetostat, pembrolizumab, topotecan	I	≥second line	Safety
NCT03460977	PF-06821497	I	≥second line	Safety
DLL3 T-cell engagers				
NCT05060016	Tarlatumab	I	≥second line	ORR
NCT05361395	Tarlatumab, atezolizumab/durvalumab, chemotherapy	Ib	First line	Safety
NCT05619744	RO7616789	I	≥second line	Safety
NCT04429087	BI764532	I	≥second line	Safety
NCT04471727	HPN328	I/II	≥second line	Safety
DLL3 CAR-T				
NCT05680922	LB2102	I	≥second line	Safety
Innate/NK cell–targeting therapies				
NCT04101357	BNT411 (TLR7 agonist), atezolizumab, chemotherapy	I/II	First line	Safety
NCT05652686	PT217	I	≥second line	Safety

Abbreviations: ATR, ataxia telangiectasis and rad-3 related; CAR-T, chimeric antigen receptor T-cell; NT, natural killer; ORR, overall response rate; OS, overall survival; PARP, poly ADP-ribose polymerase; PFS, progression-free survival; VEGF, vascular endothelial growth factor.

in SCLC.[92] DLL3 is expressed in >80% of SCLC but uncommonly expressed in normal cells, thus minimizing the potential for toxicity.[92] Tarlatamab is a DLL3 bispecific T-cell engager that is being actively investigated in clinical studies. In the phase I dose escalation study of tarlatamab, 64 patients with previously treated SCLC had a confirmed partial response rate of 13% across all dose levels and a disease control rate of 43%.[93] HPN328, a trispecific DLL3 T-cell engager that binds DLL3, CD3ε, and albumin, also reported positive preliminary results.[94] In nine patients with previously treated SCLC, the ORR across dose levels to HN328 was 33%. A highly promising therapeutic approach and several other DLL3-targeting T-cell engager therapies are under investigation (Table 2).

The innate immune system also plays an important role in immune surveillance and may be particularly important in tumors with downregulated MHC.[95] In a study using matched SCLC tissue and PBMCs, natural killer (NK) cell infiltration was found to be significantly reduced in the tumor. Furthermore, in mouse studies, depletion of NK cells, but not CD8+ T cells, resulted in increased SCLC dissemination to the liver and lungs.[54] Therapeutics strategies to target the innate immune system include toll-like receptor (TLR) agonists, stimulator of interferon gene (STING) agonists, cytokines, engineered monoclonal antibodies with preferential Fcγ receptor binding to enhance antibody-dependent cellular cytotoxicity (ADCC), and CAR-NK therapy.[95] Although early in development, therapies

aimed at enhancing NK cell immunity may become important for SCLC in the future.

CONCLUSION

The increasing role of gene expression profiling in lung NEN studies is particularly striking. In carcinoids, it has led to the discovery of three distinct molecular subtypes with prognostic values and supracarcinoids.[10] In LCNEC, NE and non-NE transcriptomic profiles have been identified, also associated with specific genomic alterations.[6,16] Finally, although SCLC genomic profiles are quite homogeneous, the high transcriptomic diversity has translated into four molecular subtypes defined by the relative expression of three key transcription regulators.[43,47,62]

Identifying biologically homogeneous tumor subtypes is appealing, as one might expect more similar clinical course and response to therapy, and one valuable methodology to uncover such phenotypes is the average gene expression over all cells in the tumor (including the tumor microenvironment). In this regard, the multitask evolution of cancer theory is a powerful framework to describe, using gene expression data, how tumors evolve and face selection tradeoffs between biological functions.[96] Tumors that specialize in a particular task could be more sensitive to drugs that impair that task, and actionable driver mutations may also tune gene expression levels toward specialization in specific tasks. Together, these analyses can generate hypotheses around the therapeutic vulnerabilities of these emerging lung NEN subtypes,[96] which should help to concentrate and speed up therapeutic research, eventually producing biologically based targeted treatments that could improve clinical outcomes for patients with these rare diseases.

In parallel with advances in understanding the molecular biology of lung NENs, developments in immunotherapeutics have improved outcomes in patients. The combination of PD-L1 inhibitors and chemotherapy improves survival in SCLC across clinical studies, a first advancement in many decades for this disease. Research for predictive biomarkers is ongoing and will guide design of rationale combinations build upon the backbone of chemo-immunotherapy. The identification of molecular subtypes has led to enthusiasm in the field since exploratory studies suggest correlation with clinical outcomes. Further refinement in subclassifications may assist in selecting patients for clinical trials. Finally, better characterization of the tumor-host immune interactions can lead to the development of novel therapeutic strategies for lung NENs.

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LUNG CANCER

Treatment Decisions for Resectable Non–Small-Cell Lung Cancer: Balancing Less With More?

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Overview

For patients with non–small-cell lung cancer (NSCLC), the outcomes for patients with resectable disease are historically poor compared with other solid organ malignancies. In recent years, there have been significant advances in multidisciplinary care, which have resulted in improved outcomes. Innovations in surgical oncology include the use of limited resection and minimally invasive techniques. Recent data in radiation oncology have suggested refinements in pre- and postoperative radiation therapy, resulting in optimization of techniques in the curative setting. Finally, the success of immune checkpoint inhibitors and targeted therapies in the advanced setting has paved the way for inclusion in the adjuvant and neoadjuvant settings, resulting in recent regulatory approvals for four regimens (CheckMate-816, IMpower010, PEARLS, ADAURA). In this review, we will provide an overview of the seminal studies informing advancements in optimal surgical resection, radiation treatment, and systemic therapy for resectable NSCLC. We will summarize the key data on survival outcomes, biomarker analyses, and future directions for perioperative studies.

INTRODUCTION

Non–small-cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide, with an estimated 1.8 million lung cancer deaths in 2020.[1] Unfortunately, most patients (60%-70%) present with late-stage disease and treatment is not delivered with curative intent.[2] However, even for patients with early-stage disease, NSCLC poses a significant clinical challenge with a propensity for distant metastasis and early relapse.[3] Given the high risk of relapse for patients with resectable NSCLC, improving the outcomes for these patients has been a focus of multidisciplinary research in recent years.

The early-stage NSCLC space is separating into two populations, with distinct clinical and research questions. In very early-stage disease (stage IA1-IA2), the questions center around the extent of resection and the ability to do less without compromising oncologic outcomes. In patients with stage IB-IIIA disease, there is a far greater risk for recurrence and although surgery remains central to treatment, the approach is multimodality and the questions focus on how to safely combine systemic therapy, radiation, and surgery together for greatest benefit. Pivotal trials have investigated the role of postoperative radiation therapy (PORT) in patients with high-risk resected NSCLC. Defining the population that may benefit from PORT while minimizing cardiopulmonary toxicity remains a challenge. Immune checkpoint inhibitors (ICIs), targeting PD-1, PD-L1, or cytotoxic T-cell lymphocyte (CTLA)-4, have transformed outcomes for advanced solid organ malignancies particularly in diseases such as melanoma, NSCLC, and renal cell carcinoma.[4] This has resulted in long-term survival (>5 years) for a subset of patients with these malignancies. More recently, there have been studies investigating the use of ICIs in early-stage NSCLC (adjuvant or neoadjuvant), with the goal of improving the current limited benefits of perioperative systemic chemotherapy.

Herein, we will summarize the current standard of care in the perioperative management of resectable NSCLC. We will review the most recent evidence exploring optimal surgical resection, radiation therapy (RT), and the use of neoadjuvant and adjuvant systemic therapies in resectable NSCLC.

RESECTION OF LOCALIZED LUNG CANCER

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New evidence on the extent of resection. Lobectomy was the gold standard for treatment of all early-stage tumors since the 1995 publication by the Lung Cancer Study Group (LCSG) of their randomized trial comparing lobectomy with limited resection for stage I NSCLC. This trial demonstrated a significant increase in local

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PRACTICAL IMPLICATIONS

- Recent progress in the management of patients with resectable non–small-cell lung cancer (NSCLC) has resulted in improved outcomes.
- Sublobar resection is now a recognized standard of care for patients with stage 1A1 or 1A2 resectable NSCLC.
- Postoperative radiation therapy is associated with significant cardiopulmonary toxicity and is reserved for patients with high-risk features (eg, R1 or R2 resection).
- Adjuvant and neoadjuvant systemic therapy has evolved to now include immune checkpoint inhibitors and targeted therapies with approval of four regimens (CheckMate-816, IMpower010, PEARLS, and ADAURA).

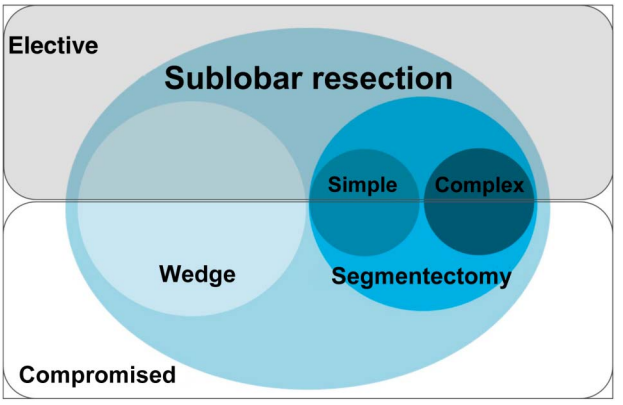

FIG 1. Surgical resection in non–small-cell lung cancer. Sublobar resections include wedge or segmentectomy (simple or complex), elective procedures in those with adequate physiologic reserve, and compromise procedure in those who could not tolerate lobectomy.

recurrence with sublobar resection and set the standard in surgical care for early-stage NSCLC for 25 years.[5] The trial is now felt to represent a different era with limited staging technology, and the results may not be fully applicable today. The landmark LCSG trial completed accrual in the 1980s before the full integration of computed tomography (CT) scans or F-labeled fluorodeoxyglucose (FDG)-positron emission tomography (PET) into NSCLC staging, and neither was required for enrollment. The increased accuracy and availability of cross-sectional imaging and added staging precision with FDG-PET have rekindled interest in sublobar resections. These advances also coincide with better understanding of the heterogeneity of biology in early-stage disease and the full spectrum of adenocarcinoma subtyping.[6]

Over the past 2 decades, numerous large database studies, single-institutional retrospective studies, and meta-analyses have demonstrated equivalency of oncologic outcomes of sublobar resection compared with lobectomy for select patients with stage IA NSCLC[7-9] and suggested the importance of tumor size, grade, and histologic subclassification when deciding between a sublobar resection and lobectomy.[10,11] Unfortunately, retrospective work in this arena is challenging since the decision between procedures can be affected by patient comorbidity. Sublobar resection can be used as an elective procedure in patients with adequate physiologic reserve for lobectomy or as a compromise procedure in patients who could not tolerate lobectomy. Most large databases do not include pulmonary function data or information on surgical intent. Adding to the challenge is the fact that sublobar resection is an umbrella term that includes segmentectomy and wedge and now segmentectomy can be broken down into simple and complex segmentectomy (Fig 1).

Two large prospective randomized trials comparing lobectomy with sublobar resection for stage IA NSCLC reported results in the past 2 years and will guide surgical care for early-stage care for decades to come. Each trial required CT and FDG-PET for staging and limited tumor size to <2 cm, smaller than the 3-cm size limit for the LCSG trial.

JCOG0802/WJOG4607. The Japanese trial, JCOG0802/WJOG4607, randomly assigned 1,106 patients between lobectomy and segmentectomy (wedge resections were not allowed) and noted equivalent short-term surgical outcomes between procedures with no differences in surgical approach, length of procedure, blood loss, hospital stay, morbidity, or mortality.[12] The primary outcome, 5-year overall survival (OS), was superior in the segmentectomy arm (hazard ratio [HR], 0.663; 95% CI, 0.47 to 0.92), and a trend toward improved survival was noted in all subgroups evaluated.[13] Surprisingly, the difference in pulmonary function tests at 1-year postoperative were smaller than anticipated (–8.5% *v* –12.0%). Local recurrences were more common in the segmentectomy group (6.9% *v* 3.1%), but most were salvageable and did not lead to mortality. The most notable mortality benefit for segmentectomy was related to fewer deaths from other cancers (including second primary lung cancers) and from nonmalignant disease. This suggests an overall health benefit to preserved lung parenchyma.

CALGB/Alliance trial 140503. The trial from North American cooperative group CALGB/Alliance randomly assigned 697 patients to lobectomy or sublobar resection. Sublobar resection could be segmentectomy or wedge resection, a distinct difference from the JCOG0802/WJOG4607 trial. It also noted no differences in short-term perioperative morbidity or mortality between lobectomy and sublobar resection.[14] The primary end point was disease-free survival (DFS), and at a median follow-up of 7 years, no difference was

reported (63.6% *v* 64.1%; HR, 1.01; 95% CI, 0.83 to 1.24) in 2022.[15,16] Similarly, no difference in OS was noted (80.3% *v* 78.9%; HR, 0.95; 95% CI, 0.72 to 1.26). Nearly 60% of the sublobar resections in this trial were wedge resections. Subgroup analysis of outcomes stratified by the type of sublobar resection are expected in the spring of 2023.

Intraoperative lymph node evaluation. One thing that these two trials had in common was the importance placed on complete lymph node evaluation when considering a sublobar resection. Pathologic nodal stage is the most significant prognostic factor in resectable NSCLC. Each of these trials preregistered patients before the day of surgery, but random assignment was performed during the operation, after confirmation of N0 status by means of frozen section evaluation of hilar and mediastinal lymph nodes. This step of frozen section lymph node evaluation before performing a planned sublobar resection is not common in clinical practice and causes some to question the validity of results if this step is not integrated as routine operative care.

Intraoperative nodule localization. The need to precisely localize small nonpalpable lung nodules within segmental boundaries for surgical resection is now a major concern and has driven an explosion in novel localization technologies. These fall into five basic categories: (1) preoperative 3D imaging platforms; (2) intraoperative imaging adjuncts, such as thoracoscopic ultrasound; (3) physical markers, such as hook wires, fiducials, and microcoils; (4) parenchymal dyes or tattoos delivered via a bronchoscope; and (5) molecular targeting agents, which are delivered systemically, collect in the tumor, and can be visualized intraoperatively with fluorescence imaging. Use of these novel techniques is greatly facilitated by hybrid operating rooms that contain cone beam CT, fluoroscopy, and molecular imaging capability. Although early in development, these technologies show promise. Further refinement will broaden their utility and will stimulate advancement of safer and more precise operative techniques.

Conclusion. Care for early-stage NSCLC is becoming more personalized with a more tailored approach to resection. An important aspect of this is the new evidence supporting sublobar resection for well-selected peripheral stage I tumors <2 cm. Appropriate use of sublobar resection places increased importance on operative lymph node evaluation and tumor localization.

ROLE OF RADIATION IN RESECTABLE LUNG CANCER

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Introduction. Surgical resection is the cornerstone of treatment of all operable early-stage NSCLC, and (neo) adjuvant chemotherapy has been the standard of care in stage IB-IIIA NSCLC for over 20 years.[17,18] However, even with major changes in the therapeutic management of these operable patients, the risk of a recurrence is still high especially in stage III: up to two thirds of them present a relapse and 20% to 40% of those patients present with a locoregional failure.[19]

The role of PORT was evaluated in several trials performed in the 70-90s, all conducted with radiation techniques nowadays considered obsolete, such as Cobalt, in the pre–3D conformal radiotherapy era.[20,21] The PORT meta-analysis, published in 1998, showed a detrimental effect of PORT of 7% on OS at 2 years.[21] Subgroup analyses suggested that this adverse effect was greatest for pN0-N1 patients, whereas for those with pN2 disease, there were possible benefits that needed further evaluation and no clear evidence of an adverse effect.[21] The PORT meta-analysis is felt to represent a different era, with both surgical and radiotherapy techniques having evolved (expanding indications for video-assisted thoracoscopic surgery, widespread use of 3D conformal radiotherapy, in the 2000s) and the preoperative staging dramatically improved with the FDG PET-CT scan and brain imaging.

Despite the low evidence level, PORT continued to be proposed to patients at high risk of locoregional failure: in the case of incomplete resection (R1-R2 disease) or completely resected N2 disease. Its use was supported by several large database studies and a meta-analysis of the PORT phase III trials, suggesting that modern PORT might confer an advantage in OS after adjuvant chemotherapy, possibly because of a lower cardiopulmonary toxicity.[22-27]

Lung ART and PORT-C. Two phase III randomized trials comparing the outcomes of PORT in patients with completely resected stage III N2-positive NSCLC have been recently published: the Lung Adjuvant Radiotherapy Trial (Lung ART) and the PORT-C.[28,29] The multi-institutional European Lung ART trial randomly assigned 501 patients (treated between 2007 and 2018) to PORT after the completion of surgery or surgery and adjuvant chemotherapy (252 patients in the PORT group and 249 patients in the control group).[28] Pretreatment staging included FDG-PET-CT scan in 91% of patients. The majority of patients received pre- and/or postoperative chemotherapy (96%). In the PORT group, 89% had 3D conformal RT and 11% had intensity-modulated radiation therapy (IMRT). At a median follow-up of 4.8 years, there was no significant in DFS between groups (HR, 0.86; 95% CI, 0.68 to 1.08). The median DFS was 30.5 months and 22.8 in the PORT group and in the control group, respectively. The 3-year OS was similar in the two arms (67% in the PORT arm *v* 69% in the control arm). Of the 296 patients with DFS events, 36 (25%) had a mediastinal relapse and 105 (73%) had a distant relapse in the PORT arm versus 70 (46%) and 98 (64.5%) in the control arm, respectively.

The PORT-C trial randomly assigned 364 patients coming from a single center (treated between 2009 and 2017) to PORT after the completion of surgery and adjuvant chemotherapy (184 patients in the PORT group and 180 in the control group).[29] Pretreatment staging details (FDG-PET-CT scan use) were not reported. The majority of patients (89.3%) were treated with IMRT. At a median follow-up of 46 months, according to an intention-to-treat analysis, the median DFS for patients in the PORT arm and observation arm was 22.1 months and 18.6 months, respectively (3-years DFS: 40.5% in the PORT arm *v* 32.7% in the observation arm [HR, 0.84; 95% CI, 0.65 to 1.09]). The median OS was not reached in the PORT arm and was 81.5 months in the observation arm. The 3-year OS rates were 78.3% in the PORT arm and 82.8% in the observation arm. The 3-year exclusive local recurrence rates significantly differ in the two arms, with 9.5% in the PORT arm and 18.3% in the observation arm.

In both trials, the beneficial effect of PORT in terms of locoregional control did not translate into an increased OS. Even if most patients in Lung ART died of recurrence (155), 18 patients died because of cardiopulmonary diseases and 16 were in the PORT group. As in other studies on lung cancer, there is a risk of additional cardiopulmonary toxicity.[19]

PORT in high-risk patients. Retrospective analyses have identified several possible risk factors for recurrence such as multi-station N2 disease, extracapsular nodal extension, disease in highest removed mediastinal node, lymph node ratio (number of involved nodes/number of explored nodes), and/or inadequate nodal resection.[30-32]

In the Lung ART trial, review of the surgical and pathologic reports was performed according to the definition of complete resection (CR), proposed by the International Association for the Study of Lung Cancer.[32] Thus, by applying this refined definition of CR, going beyond lung tumor margins, to include the status of most distant nodes, nodal capsule, and the performance of an adequate mediastinal lymph node exploration, the percentage of patients having a R0 resection decreased from 99% to 28%.[29] Prognostic factors for DFS include quality of resection, extent of mediastinal involvement, and lymph node ratio.[28] With regard to OS, the extent of nodal involvement is a significant prognostic factor, whereas PORT is not.[28] Secondary analyses of the Lung ART trial may contribute to identifying subgroups where PORT may be effective in terms of tumor control with minimal morbidity.

As there are no randomized data exploring specifically the role of PORT in cN2 resected patients after preoperative chemotherapy, it will be interesting to explore this subgroup of patients (20% of the whole cohort of Lung ART patients). Their relapse rate seems to be high even after CR.[33]

Concerning R1 and R2 resection, two National Cancer Data Base analyses suggest that PORT (alone or in association with chemotherapy) was associated with improved OS.[34,35] Therefore, chemoradiation (sequential or concurrent) is recommended after R1 and R2 resection by the European Society of Medical Oncology, American Society for Radiation Oncology, and ASCO.[36,37]

PORT toxicity. The meta-analyses showed higher cardiopulmonary toxicity and noncancer-related deaths, probably because of less modern techniques, larger volumes, and larger fraction doses in the included studies.[36] Recent evidence highlighting the importance of heart dose in thoracic RT in NSCLC has been published. In particular, a higher dose to some cardiac substructures (such as left anterior descending coronary artery) seems to be correlated with a poorer OS in a recently published reanalysis of the RTOG 0617.[38-40] A systematic review of all dosimetry studies publishing heart doses between 2013 and 2020 showed that mean heart doses were lower with particle therapy and active respiratory motion management, whereas the use of IMRT had no effect in reducing heart doses.[41]

Excess of cardiopulmonary toxicity of the PORT arm was observed in the Lung ART trial, which will be more thoroughly analyzed, with longer-term follow-up. Such analyses of toxicity patterns are awaited as they concern fit patients with cardiovascular comorbidities having received multimodality treatment including surgery. Even if the standard of care for patients with stage IIIA N2 NSCLC may change in the near future, including immunotherapy and surgery, we need long-term follow-up data.

Furthermore, cardiovascular comorbidities may play a synergistic (negative) role not only in radiation but also in other treatments especially when combined.[42]

Perspectives. Evaluation is warranted of more modern radiation techniques such as proton therapy, systematic use of cardiac segmentation, active respiratory management, or any other technique that may select patients who benefit from PORT and reduce cardiopulmonary toxicity. Circulating tumor DNA and other dynamic biomarkers may identify those patients at higher risk of recurrence and potentially those who may benefit from PORT. Ongoing and future trials might clarify which subgroup of patients could benefit from PORT with minimal long-term toxicity.

PERIOPERATIVE SYSTEMIC THERAPY IN NSCLC

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History. Initially published in 2004, the IALT trial randomly assigned patients with resected NSCLC to an adjuvant

cisplatin-based doublet chemotherapy versus observation.[43] In this study, patients received 3-4 cycles of cisplatin in combination with one of either etoposide, vindesine, vinblastine, or vinorelbine. Treatment with the cisplatin doublet was associated with an improved OS of 4.4% at 5 years. After this, the LACE meta-analysis (published in 2008) pooled data from five randomized clinic trials totaling 4,854 patients. This demonstrated a statistically significant improvement of 5.4% in 5-year OS with adjuvant platinum-based chemotherapy.[44] Together, these studies established adjuvant platinum-based chemotherapy as the standard of care for patients with resected stage II-IIIA NSCLC. In the neoadjuvant setting, the NATCH trial investigated three cycles of neoadjuvant versus adjuvant carboplatin/paclitaxel for patients with resectable NSCLC.[45] In the neoadjuvant arm, a greater proportion of patients completed planned therapy (97% *v* 66.2%). Despite this improved treatment exposure, there was no significant difference in DFS or OS between groups. Despite this, a meta-analysis of 15 randomized controlled trials demonstrated that preoperative chemotherapy improves OS and DFS for patients with resectable NSCLC.[18] Taken together, both neoadjuvant chemotherapy and adjuvant chemotherapy are considered options for patients with resectable NSCLC. The critical benefit of adjuvant therapy is the prioritization of the definitive portion of the treatment paradigm (surgery).[46] The benefits of neoadjuvant systemic therapy include early treatment of micrometastatic disease, in vivo assessment of response to systemic therapy, and the increased likelihood of completion of all planned systemic therapies, as demonstrated in the NATCH trial.[45] Furthermore, it provides enhanced tissue for translational research. The recent trials introducing targeted therapies and ICIs into perioperative care represent an exciting advancement. ICIs differ in their mechanism of action compared with chemotherapy, and there is early evidence that neoadjuvant therapy with the primary tumor in place may result in larger and broader pools of T-cell clones directed to tumor antigens and that pathologic tumor response correlates with the robust nature of the T-cell response, which could represent an added benefit of neoadjuvant therapy unique to ICI.[47]

Adjuvant immune checkpoint inhibitors in NSCLC. In the phase III IMpower010 study (n = 1,005), 1 year of adjuvant atezolizumab was compared with best supportive care for patients with resected stage IB-IIIA NSCLC.[48] All patients received adjuvant chemotherapy, and patients whose tumors had known alterations in *EGFR/ALK* were eligible for inclusion. In the intention-to-treat (ITT) population, there was a significant improvement in DFS (HR, 0.81; 95% CI, 0.67 to 0.99). Those whose tumors had a PD-L1 score of >50% appeared to derive the majority of the benefit (HR, 0.43; 95% CI, 0.27 to 0.68). Serious adverse events were uncommon, with 11% of patients suffering from grade 3+ adverse events in the atezolizumab arm. By contrast, in the phase III PEARLS trial (n = 1,177) which investigated the use of adjuvant pembrolizumab, adjuvant chemotherapy was not mandated.[49] DFS was significantly improved in the pembrolizumab ITT population compared with placebo (DFS = 53.6 months *v* 42 months; HR, 0.76; 95% CI, 0.63 to 0.91). Unlike in the IMpower010 study and somewhat counterintuitively, the subgroup that demonstrated the most benefit were those whose tumors had a PD-L1 of 1%-49% (HR, 0.67; 95% CI, 0.48 to 0.92) or harbored EGFR mutations (HR, 0.44; 95% CI, 0.23 to 0.84). However, these subgroups were small. In both studies, OS data are currently immature.

Both studies suggest significant activity of ICIs in the adjuvant setting. The European Medicines Agency (EMA) has licensed adjuvant atezolizumab for patients with a tumoral PD-L1 score of >50% only, whereas the US Food and Drug Administration (FDA) has licensed both atezolizumab and pembrolizumab for patients with a tumoral PD-L1 score of >1% and all-comers, respectively.

NEOADJUVANT IMMUNE CHECKPOINT INHIBITOR MONOTHERAPY

There are 11 phase I and II studies published to date (see Table 1), which have investigated the use of neoadjuvant ICIs without chemotherapy for patients with resectable NSCLC.[50-60] Most of these investigated the use of neoadjuvant ICI without any postoperative therapy. Approaches included the combination of PD-1/PD-L1 with a CTLA-4 inhibitor (NEOSTAR), with stereotactic body radiation (Altorki et al) or with novel agents (NEOCOAST).[50,52,60] These studies demonstrated major pathologic response (MPR) rates ranging from 7% to 50%. The incidence of adverse events was consistent with the known safety profile of ICIs, with the incidence of G3-5 adverse events ranging from 10% to 30%.

NEOADJUVANT CHEMOIMMUNOTHERAPY

There have been five single-arm studies (see Table 2) reported to date investigating neoadjuvant ICI combined with chemotherapy, which include the use of nivolumab, atezolizumab, toripalimab, durvalumab, and sintilimab.[62-66] In these small studies, patients received 2-4 cycles of neoadjuvant platinum doublet-based chemotherapy and an ICI. Most of these studies included patients with stage IB-IIIA NSCLC (see Table 2), and the MPR rate ranges from 22.6% to 83%. Particular highlights include NADIM study enrolled 46 patients with resectable stage IIIA NSCLC, where patients received nivolumab + carboplatin + paclitaxel. In this study of high-risk patients, the MPR rate was an impressive 83% (38 of 46). Moreover, the 1-year DFS was 77% (35 of 46). Although 96% (43 of 46) of patients had a treatment-related adverse event during therapy, only 30% (14 of 46) had a grade 3+ adverse event.

TABLE 1. Neoadjuvant Immunotherapy Studies

Name	Phase of Study	No. of Participants	Treatment	Stage	No. of Patients With ALK/EGFR/ROS1 Mutations	MPR Rate	DFS
NCT02904954 Altorki et al[50]	II	34 32 surgery	Neoadjuvant: (1) durvalumab once every 3 weeks x 2 doses *v* (2) durvalumab once every 3 weeks x 2 doses + SBRT Optional adjuvant durvalumab once every 4 weeks x 12 months	I-IIIA (I/II/IIIA) Arm 1: 41/24/35% Arm 2: 24/41/35%	EGFR+ Arm 1: 4/17 (23%) Arm 2: 4/17 (25%)	Arm 1: 0/17 Arm 2: 8/17 (47%) MPR, excl EGFR = 8/13 (61.5%)	—
MK3475-223 Bar et al[51]	I	10 (interim)	200 mg pembrolizumab once every 3 weeks x 2 doses	I-II	—	4/10 (40%; 95% CI, 16.7 to 68.8)	—
NEOSTAR study Cascone et al[52]	II	44 33 surgery	Neoadjuvant: nivolumab 3 mg/kg once every 2 weeks *v* nivolumab 3 mg/kg once every 2 weeks + ipilimumab 1 mg/kg once every 6 weeks x 1 dose	I-IIIA	—	Overall Arm 1: MPR 5/23 (22%) Arm 2: MPR 8/21 (38%) Undergoing resection Arm 1: MPR 5/21 (24%) Arm 2: MPR 8/16 (50%) Arm 1: CR 2/21 (10%) Arm 2: CR 6/16 (38%)	
Forde et al[53]	II	21 (20 underwent resection)	Nivolumab 3 mg/kg once every 2 weeks x 2 doses	I-IIIA	—	MPR 9/20 (45%)	73% PFS at 18 months (95% CI, 53 to 100)
Gao et al[54]	I	40 37 surgery	Sintilimab 200 mg IV once every 3 weeks x 2 doses	IA-IIIB		MPR 15/37 (41%) pCR 6/37 (16.2%)	—
LCMC3 Kwiatkowski et al[55]	II	180 144 surgery	Atezolizumab 1,200 mg once every 3 weeks x 2 doses	IB-IIIB	7 EGFR, 1 ALK: no MPR	MPR 30/144 (21%) pCR 10/144 (7%)	
NEOMUN study Eichhorn et al[56]	II	15 (interim)	Pembrolizumab IV 200 mg once every 3 weeks x 2 doses	II-IIIA		MPR 4/15 (27%)	
Bott et al[57]	I	22 enrolled, 20 underwent surgery	Nivolumab, 3 mg/kg, 4 and 2 weeks preresection	I-IIIA		MPR 9/20 (45%)	
IoNESCO study Wislez et al[58]	II	50 46 treated 43 surgery	Durvalumab 750 mg once every 2 weeks x 3 doses preoperatively	IB-IIIA		Median residual viable tumor = 37% (stopped early because of excess postoperative mortality)	
TOP 1501 Tong et al[59]	II	35 30 treated 25 surgery	Pembrolizumab 200 mg once every 3 weeks x 2 doses preoperatively, 4 doses postoperatively	IB-IIIA		MPR 7/25 (28%) R0 88%	
NEOCOAST Spicer et al[60]	II	84	Durvalumab 1,500 mg once every 4 weeks x 1 dose Durvalumab + oleclumab 3,000 mg once every 2 weeks x 2 doses Durvalumab + monalizumab 750 mg once every 2 weeks x 2 doses Durvalumab + danvatirsen 200 mg once daily on days 1, 3, and 5 of week 0, followed once weekly x 4 doses	I-IIIA	—	Oleclumab (19%) Monalizumab (30%) Danvatirsen (31%) Durvalumab (11%)	

Abbreviations: CR, complete resection; DFS, disease-free survival; IV, intravenous; MPR, major pathologic response; pCR, pathologic complete response; PFS, progression-free survival; R0, resection with negative surgical margins; SBRT, stereotactic body radiotherapy.

TABLE 2. Neoadjuvant Chemoimmunotherapy Studies

Name	Phase of Study	No. of Participants	Treatment	Stage	No. of Patients With ALK/EGFR/ ROS1 Mutations	MPR Rate	DFS
CheckMate-816 Forde et al[61]	III	358	Neoadjuvant: nivolumab 360 mg IV + platinum-doublet chemotherapy once every 3 weeks for 3 cycles *v* chemotherapy once every 3 weeks for 3 cycles	IB-IIIA	No ALK/AGFR alterations per inclusion criteria	pCR ITT (24% *v* 2.2%); $P < .0001$ MPR ITT (36.9% *v* 8.9%) ORR (53.6% *v* 37.4%)	Median EFS of 31.6 months (nivolumab + chemotherapy) *v* 20.8 months (chemotherapy) with a HR of 0.63
NADIM study Provencio et al[62]	II	46	Carboplatin (AUC 6), paclitaxel 200 mg/m^2, and nivolumab 360 mg once every 3 weeks for 3 cycles followed by nivolumab once every 2 weeks for 1 year (240 mg every 2 weeks for 4 months, followed by 480 mg every 4 weeks for 8 months)	IIIA-IIIB		MPR 34/41 (83%) pCR 26/41 (63%)	77.1% of patients alive and progression-free at 24 months
NEOTPD01 Zhao et al[63]	II	33 30 surgery	IV toripalimab 240 mg, carboplatin (AUC 5) + pemetrexed 500 mg/m^2 or nab-paclitaxel 260 once every 3 weeks for 3 cycles	IIIA or IIIB		MPR 20/30 (66%) pCR 15/30 (50%)	
Atezo + chemotherapy Shu et al[64]	II	30 enrolled 29 resected	Neoadjuvant: atezolizumab IV 1,200 mg on day 1; nab-paclitaxel 100 mg/m^2 on days 1, 8, and 15; and carboplatin (AUC 5) on day 1 every 21 days for 2-4 cycles	IB-IIIA		MPR 17/30 (57%; 95% CI, 37 to 75)	
Neoscore Qiu et al[65]	II	60 55 surgery	Neoadjuvant: carboplatin AUC 5 and nab-paclitaxel 260 mg/m^2; pemetrexed 500 mg/m^2 and sintilimab 200 mg IV once every 21 days for 2-3 cycles, then 1 year of postoperative maintenance sintilimab	IB-IIIA		MPR 12/29 (44.1%) with 3 cycles 7/26 (26.9%) with 2 cycles	
SAKK 16/14 Rothschild et al[66]	II	68 55 surgery	Neoadjuvant: cisplatin 100 mg/m^2 and docetaxel 85 mg/m^2 once every 3 weeks for 3 cycles followed by durvalumab 750 mg once every 2 weeks for 2 cycles Adjuvant: durvalumab 1 year after surgery	IIIA		MPR: 34/55 (62%) CR: 10/55 (18%)	EFS 73% (90% CI, 63 to 82)

Abbreviations: CR, complete resection; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; ITT, intention to treat; IV, intravenous; MPR, major pathologic response; ORR, overall response rate; pCR, pathologic complete response.

One phase II study and one phase III study have been reported to date investigating neoadjuvant nivolumab + chemotherapy versus neoadjuvant chemotherapy alone for three cycles preoperatively. The NADIM-II study enrolled patients with resectable stage IIIA disease, whereas the phase III CheckMate-816 study included patients with stage IB-IIIA resectable NSCLC.[61,67] Both studies excluded patients with activating *EGFR/ALK* mutations. In the NADIM-II study, pathologic complete response (pCR) rates were significantly higher compared with chemotherapy alone (36.2% *v* 6.8%, *P* = .0071) and similarly for both MPR (52% *v* 14%) and objective response rates (74% *v* 48%). In addition, there was a significant improvement in OS at 24 months in the experimental arm (85.4% *v* 64.8%; HR, 0.37; 95% CI, 0.14 to 0.93). In the CheckMate-816 study, pCR with the addition of nivolumab to chemotherapy alone were 24% versus 2% and this effect was seen across prespecified subgroups.[61] Moreover, MPR was significantly improved with the addition of nivolumab (36.6% *v* 2.2%) compared with chemotherapy. In preliminary results, there was a trend toward an OS improvement with the addition of ICI to chemotherapy (HR, 0.57; 95% CI, 0.38 to 0.87). In both studies, there was a higher incidence of grade 3+ adverse events in the experimental arms (24%-33% *v* 10%-11%). There was no unexpected surgical morbidity or mortality observed in these studies.

ADJUVANT AND NEOADJUVANT THERAPIES FOR PATIENTS WITH EGFR/ALK ALTERATIONS

For patients whose tumors harbor an activating *EGFR* mutation, the success of first- and second-generation tyrosine kinase inhibitors (TKIs) in the metastatic setting resulted in a number of trials investigating their role in the adjuvant setting with disappointing results.[68,69] In the ADAURA study, adjuvant use of the third-generation TKI, osimertinib, was investigated for patients with resected stage IB-IIIA *EGFR*-mutant NSCLC. In this study, adjuvant chemotherapy was recommended but not mandated and patients were randomly assigned to 3 years of osimertinib versus placebo.[70] A total of 682 patients were randomly assigned in this study, 410 of whom received adjuvant chemotherapy. This study demonstrates a DFS benefit in favor of osimertinib (HR, 0.20; 95% CI, 0.14 to 0.3). In the osimertinib group, 90% of patients were alive and disease-free at 24 months compared with 44% in the placebo group. OS data remain immature. This regimen has been approved by both the FDA and EMA.

First-generation *EGFR* TKIs have also been investigated in five phase II studies in the neoadjuvant setting in a total of 124 patients.[71-75] The primary end point in each of these studies was objective response rate, which ranged from 42% to 58.3%. These encouraging data have resulted in the ongoing phase III NEOADAURA study, which is

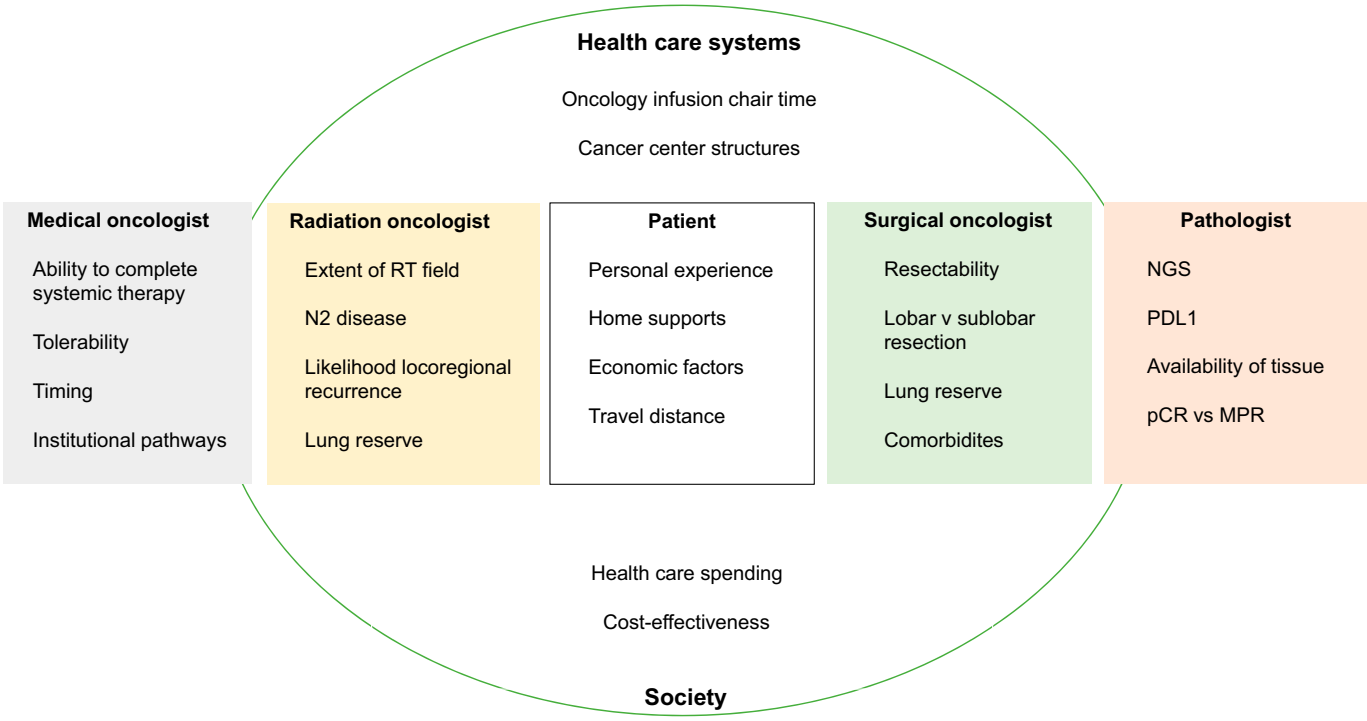

FIG 2. Factors in selection of perioperative approaches in non–small-cell lung cancer. MPR, major pathologic response; NGS, next-generation sequencing; pCR, pathologic complete response; RT, radiotherapy.

investigating neoadjuvant osimertinib for patients with resectable NSCLC.[76] For patients with *ALK*-rearranged NSCLC, case studies and small trials have demonstrated activity with neoadjuvant crizotinib and alectinib.[77,78] The phase III ALINA study is currently underway and will investigate the role of adjuvant alectinib in patients with resected *ALK*-rearranged NSCLC.[79] Finally, the ongoing phase III ALCHEMIST study offers biomarker analysis and targeted therapy for patients with stage IB-IIIA resected NSCLC (erlotinib, crizotinib, nivolumab, pembrolizumab + chemotherapy) and may provide further data in this field.

OPTIMAL SYSTEMIC THERAPY FOR RESECTABLE NSCLC: WHICH APPROACH IS BEST?

FDA-/EMA-approved regimens for patients with resectable NSCLC now include adjuvant atezolizumab/pembrolizumab, neoadjuvant nivolumab with chemotherapy, and adjuvant osimertinib. The decision as to which approach to pursue is influenced by patient preference, performance status, disease staging, presence of tumoral *EGFR/ALK* alterations, PD-L1 status, and institutional pathways (see Fig 2).

DISCUSSION

In this article, we have reviewed advances in the multidisciplinary management of patients with resectable NSCLC.

The CALGB/Alliance Trial and the JCOG0802/WJOG4607 study have both demonstrated that sublobar resection is a standard of care for select patients with stage IA1/IA2 NSCLC. It is hoped that this de-escalation of therapy may improve our patients' quality of life by preserving pulmonary parenchyma associated with the more extensive lobar resection. In clinical practice, the development of surgical pathways equivalent to both these studies may be challenging (eg, intraoperative frozen sections of nodal stations). Despite this, it is likely that sublobar resection will become a new standard of care for a select group of patients with NSCLC. Further developments in the surgical management of NSCLC include the increasing role of minimally invasive surgery, which now plays a key role in current surgical practice. De-escalation of surgical resection may be a component of future clinical trials for patients with NSCLC.

Given the high rates of relapse after resection of NSCLC, the benefits of adjuvant PORT have been investigated in several contemporary clinical trials (most recently, Lung ART and PORT-C). Evaluating the benefits of historical prospective studies has been challenging given the emergence of modern radiotherapy techniques associated with improved treatment accuracy and lower toxicity. The risk of cardiopulmonary toxicity post-PORT remains a clinical challenge and may negate some of the survival benefits with regard to disease control and mortality. Despite this, PORT is recommended for a subset of patients with high-risk resected NSCLC (R1/R2 resection) and it may play a role in patients with other high-risk features. Modern radiotherapy techniques such as proton therapy or systematic use of cardiac segmentation may allow the delivery of doses necessary for tumor cell death while preserving surrounding normal tissues. Future prospective work will likely investigate these modern techniques in conjunction with the recent advances seen in surgical and medical oncology.

With three new FDA regimens approved in the perioperative setting, ICIs are undoubtedly a new standard of care for patients with resectable stage IB-IIIA NSCLC. The conflicting subgroup analyses of PEARLS and IMpower010 raise questions regarding the role of PD-L1 status as a predictive biomarker in this setting, differenced in the study populations, and differing efficacy of PD-1 and PD-L1 inhibitors. Given the shorter treatment duration and convincing EFS benefit in CheckMate-816, this neoadjuvant regimen may be favored. Looking to the future, we eagerly await OS data for the studies already reported. There are ongoing randomized phase III studies investigating nivolumab (ANVIL) and durvalumab (AEGEAN) in similar settings to IMpower010 and PEARLS.[80] Beyond this, novel approaches may involve de-escalation of therapy for those who have a pCR at the time of surgery and the use of ctDNA for treatment selection, monitoring, and even duration.

We are fortunate to work in an era with clinical advances in the management of NSCLC, resulting in tangible improvements in outcomes for patients. Critical questions remain with regard to the most appropriate conditions for sublobar resection, the need for intraoperative staging, and the optimal timing and choice of systemic agents to achieve the best outcomes for our patients. To date, the evidence supports the utilization of these advances, but defining a therapeutic strategy for each patient is increasingly complex (see Fig 1). Given this increasing complexity, decisions regarding perioperative approaches must be made in a collaborative multidisciplinary manner.

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Family Matters: Germline Testing in Thoracic Cancers

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Overview

Most thoracic cancers arise via a series of stepwise somatic alterations driven by a well-defined carcinogen (ie, tobacco or asbestos for lung cancer and mesothelioma, respectively). A small proportion can emerge on a background of pathogenic germline variants (PGVs), which have the property of heritability. In general, PGVs may be initially suspected on the basis of the presence of specific clinical features. Such gene × environment interactions significantly increase the risk of developing lung cancer (1.5- to 3.2-fold). PGVs have been discovered involving the actionable driver oncogene, epidermal growth factor receptor (EGFR), with an *EGFR* T790M PGV rate of 0.3%-0.9% in the nonsquamous non–small-cell lung cancer subtype. Its appearance during routine somatic DNA sequencing in those patients who have not had a previous tyrosine kinase inhibitor should raise suspicion. In patients with sporadic mesothelioma, *BAP1* is the most frequently mutated tumor driver, with a PGV rate between 2.8% and 8%, associated with a favorable prognosis. *BAP1* PGVs accelerate mesothelioma tumorigenesis after asbestos exposure in preclinical models and may be partly predicted by clinical criteria. At present, routine germline genetic testing for thoracic cancers is not a standard practice. Expert genetic counseling is, therefore, required for patients who carry a PGV. Ongoing studies aim to better understand the natural history of patients harboring PGVs to underpin future cancer prevention, precise counseling, and cancer management with the goal of improving the quality and length of life.

BASICS OF GERMLINE TESTING AND APPROACHES TO GENETIC COUNSELING IN THORACIC CANCER

The vast world of clinical cancer genetics has changed rapidly over the past several years, which one could argue, began with the 2013 Supreme Court of the United States ruling that companies may not patent genes.[1] That ruling and the use of next-generation sequencing allow many laboratories to offer genetic testing at a reduced cost and to sequence multiple genes at a reduced cost. As a result, there has been an increase in the use of genetic tumor profiling to drive treatment options and therapy.[2] With this expansion, the approaches to germline genetic testing and their uses have changed over a brief period. These changes have occurred throughout many tumor types; however, germline genetic testing has yet to be integrated as the standard of care in the thoracic setting.[3,4]

What Is Genetic Counseling?

Genetic counseling is not a therapy nor counseling in the traditional sense of the word. According to the National Society of Genetic Counselors, "genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease."[5] In the cancer setting, genetic counselors help patients understand the genetic make-up of their cancer, how this genetic make-up affects treatment, future cancer risks, and risk to other family members. Therefore, it is imperative that cancer genetic counselors have a thorough understanding of not only genetics but also cancer. It is often the first time in a patient's journey that they are allotted the time to fully understand their disease.

Suspecting an Inherited Mutation in a Thoracic Cancer

Although all cancers have a genetic origin, not all cancers are hereditary. Around 5%-10% of all cancers are hereditary in nature.[6] Some key features to consider when identifying a potentially inherited cancer include an early age of onset, bilateral/multifocal disease, more than one cancer diagnosis in an individual, aggressive or rare tumor, family history, and ethnicity.[7] In addition, the tumor's genetic profile highlights a potential germline or inherited alteration. For this reason, ASCO guidelines suggest that oncologists inform patients that an incidental germline variant could be identified before ordering a genomic tumor profile.[8] For example, if a genetic tumor profile reveals a mutation in *TP53* with a variant allele fraction ≥40%, this may suggest a germline mutation in *TP53* rather than a somatic alteration. However, not all germline mutations are present in a tumor, so there may still be a need for germline genetic testing even after the genetic profiling of a tumor.[8-10]

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PRACTICAL APPLICATIONS

- The National Comprehensive Cancer Network lacks specific guidelines for managing lung cancer patients with genetic mutations and little mention of genetic testing (Table 1). Standardizing genetic testing can improve patient care, reduce disparities, and ensure all patients receive the same level of care. Genetic testing in the thoracic setting can identify mutations to guide treatment options, identify at-risk family members, and facilitate data sharing for a more comprehensive understanding of inherited cancer syndromes. Collaboration can lead to identifying new targets for therapy and screening modalities, ultimately improving patient care, and promoting access and equity in health care.
- The prevalence of genetic variants that increase the risk of lung cancer is high. Germline profiling of patients with lung cancer may affect their management, including screening recommendations and clinical trial opportunities. As testing becomes cheaper and more available, it is likely that germline profiling will improve our understanding of the interactions between pathogenic germline variants and lung cancer development and between genetic polymorphisms and treatment outcomes.
- BAP1 mutations are associated with an increased risk of developing mesothelioma and other types of cancers, such as uveal melanoma and renal cell carcinoma. Testing for these mutations can help identify individuals and family members who may be at increased risk of developing these cancers and allow for earlier surveillance and intervention. Genetic counseling can help these individuals understand their risk and make informed decisions about genetic testing and cancer screening. Overall, BAP1 germline testing in patients with mesothelioma can provide important information for cancer risk assessment, treatment decision making, and genetic counseling.

Genetic Counseling in the Thoracic Setting

Through the emergence of genetic tumor profiling, we are discovering new associations with not only known DNA repair genes and tumor suppressor genes but also within genes that were not typically associated with cancer (eg, *NOTCH1* and *RECQL1*).[2,4,11] This crossover between subspecialties within genetic counseling is changing the scope of practice and increasing the need for experts who understand this crossover.

As routine germline genetic testing in the thoracic setting is not the standard in the United States, counseling of patients is different compared with solid tumors such as breast or colon cancer. Unlike other tumor settings, patients with thoracic cancers have somatic mutation testing before germline testing. Genetic counselors need to have a thorough understanding of the somatic alterations in thoracic tumors and their interpretation. Somatic alterations may reveal germline mutations that are not obvious by tumor type or family history alone, which are known as an anticipated incidental finding.[12] These results are often frustrating and confusing to a patient who is already suffering from a cancer diagnosis. This is especially true in the thoracic setting where little has been studied regarding known germline variations.

Once a risk of thoracic cancer is identified in the family, there is little known regarding the standard of care for screening of thoracic cancers in the United States. This lack of standard of care makes it difficult to offer patients guidance in screening and relies heavily on small case studies as guides to screening.[13] This can often leave the patient with more anxiety and stress. In addition, insurance coverage for screening in these instances is often denied, which can also be an additional financial burden placed on the family.[14-16]

HEREDITARY LUNG CANCER

Lung cancer is the most common cause of cancer mortality worldwide. In fact, the combined annual mortality from colorectal, pancreatic, and breast cancers is less than the annual mortality from lung cancers alone in the United States.

Most lung cancers are thought to be related to environmental risk factors, such as cigarette smoking or radon exposure. Genes associated with nicotine addiction and polymorphisms in genes, which inadequately metabolize cigarette-containing carcinogens when expressed, contribute to lung cancer development. These genes, which are inherited, would not be considered pathogenic germline variants (PGVs). However, their relation to lung cancer development indicates that many, if not most, lung cancers have a genetic link contributing to their development.

PGVs are inherited genes that sometimes predispose individuals to cancer. In this section, we discuss the inherited genes that place individuals at risk of developing lung cancer that would not be referred to as PGVs. We also discuss PGVs that predispose individuals to developing lung cancer.

Genetic Pathogenic Variants and Lung Cancer Risk Among Smokers

Smokers with a family history of lung cancer in a first-degree relative have a much higher chance of developing lung

cancer than those without. Investigators from the International Lung Cancer Consortium evaluated almost 50,000 lung cancer cases and controls and their family histories.[17] Overall, individuals who have a first-degree relative with lung cancer had a 1.5-fold increase in risk. Among smokers who had a first-degree relative with lung cancer, the risk was 3.2-fold higher. These data suggest that germline genetic characteristics increase the susceptibility of developing lung cancer when exposed to toxins in tobacco. The association between chronic obstructive pulmonary disease (COPD) and the development of lung cancer,[18] adjusted for tobacco exposure, also suggests that lungs damaged from tobacco exposure are more susceptible to the development of lung cancer. A parental history of COPD is associated with an increased risk of developing COPD.[19]

These associations may, in part, be explained by the activity of nicotine acetylcholine receptors, which are a family of ligand-gated cation channels activated endogenously by acetylcholine and exogenously by chemicals, such as nicotine. A single-nucleotide polymorphism (SNP) in one of its subunits is associated with a significant increase in nicotine dependence and the development of lung cancer.[20] It is hard to distinguish the increase in tobacco consumption due to this SNP versus the potentially direct, negative biological effect of lung cancer development resulting from this polymorphism because the receptors in individuals harboring this polymorphism have been associated with both cell proliferation and apoptosis.

Hereditary Lung Cancer With EGFR Pathogenic Variants

Acquired somatic point mutation T790M of the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) domain confers resistance to first- and second-generation oral EGFR inhibitors.[21] Although some activating mutations of the TK domain are incompatible with normal embryonic development, the T790M is a proven *EGFR* PGV.[22] Tumor interrogation revealing an *EGFR* T790M in the lung cancer of a patient who was not previously exposed to tyrosine kinase inhibitor therapy suggests that this is an *EGFR* T790M PGV and should prompt referral for genetic counseling according to the current National Comprehensive Cancer Network (NCCN) guidelines.

Similarly, the NCCN guidelines (Table 1) suggest that if a mutation is identified in a lung cancer that is not a typical lung cancer somatic mutation, and particularly if the mutational allelic frequency of that gene suggests the identified alteration represents an incidental PGV, these patients with lung cancer should be considered for genetic counseling.

Interestingly, most of the adenocarcinomas associated with this PGV do have a second somatic activating mutation of the *EGFR* TK domain.[23] Lung cancers associated with the *EGFR* T790 PGV represent 0.3%-0.9% of all cases of nonsquamous NSCLC.[4] On the basis of a review of the literature and an analysis of a large family, Gazdar et al concluded that the lifetime risk likelihood of developing NSCLC in individuals harboring an *EGFR* T790M PGV is very high. The authors reported 19 lung cancer cases developing among 29 carriers. This extremely elevated risk justifies a discussion about family genotyping and screening for lung cancer for those carriers of the *EGFR* T790M gene. The use of magnetic resonance imaging, starting as early as age 20 years was suggested by Gazdar et al,[8] although no established penetrance statistics or screening recommendations are currently available.

TABLE 1. NCCN Guidelines for Hereditary Cancer Testing

NCCN Guidelines Version 3.2023 for Hereditary Cancer Testing
General Testing Criteria
Testing is clinically indicated in the following scenarios:
Individuals with any blood relative with a known P/LP variant in a cancer susceptibility gene
Individuals meeting the criteria below but who tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) and are interested in pursuing multigene testing
A P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline
To aid in system therapy and surgical decision making
Individuals who meet LFS testing criteria or Cowden syndrome/PHTS testing criteria or Lynch syndrome
Testing *may* be considered in the following scenario (with appropriate pretest education and access to post-test management):
An individual of Ashkenazi Jewish ancestry without additional risk factors
Personal history of serous endometrial cancer

Abbreviations: LFS, Li-Fraumeni syndrome; NCCN, National Comprehensive Cancer Network; P/LP, pathogenic/likely pathogenic; PHTS, PTEN hamartoma tumor syndrome.

Lung adenocarcinomas that develop in never smokers and have an activating *EGFR* mutation are more common among female patients and those of Asian ethnicity.[24] This suggests that polymorphisms that predispose to *EGFR* somatic mutations might be found more commonly in these groups. Currently, these polymorphisms or the mechanism of tumorigenesis in these patients is not well-understood but warrants further investigation.

Another poorly understood association is that between Li-Fraumeni syndrome (LFS) and *EGFR*-mutated lung cancer. LFS is a cancer susceptibility syndrome associated with a *TP53* PGV. Individuals with LFS are at a particularly elevated risk of developing sarcomas, leukemia, brain tumors, adrenal cortical carcinoma, breast cancer, choroid plexus tumors, and lung adenocarcinomas. European investigators[25] identified 22 patients with lung cancer and Li-Fraumeni

syndrome. Of 25 patients, 17 (68%) had an activating *EGFR* mutation, of which 15 had the most common exon 19 deletion or L858R. Of note, one additional patient had a *ROS-1* fusion. Only two of these patients were former smokers, and 76% had stage IV disease on presentation.

Breast cancers associated with Li-Fraumeni syndrome have been correlated with higher rates of human epidermal growth factor receptor 2 (HER2) overexpression.[26] This association suggests that HER family-driven carcinogenesis is associated with the increased chromosomal instability in the context of a *TP53* PGV. A novel germline *HER2* G660D PGV has been reported in a Japanese family with familial lung adenocarcinomas.[27]

Presence of Pathogenic Variants in the General Lung Cancer Population

Universal germline testing of all patients with lung cancer would be justified if identified PGVs were to have an implication for the screening or management or implications for their families. The other reason to perform such analysis or pharmacogenomic profiling for polymorphisms is to understand the factors influencing the natural history of lung cancer. For example, patients who have advanced adenocarcinoma of the lung may have prolonged disease control on maintenance pemetrexed. It is unknown whether these patients have a somatic mutation profile that predicts the observed prolonged response or that remarkable benefit is that related to a polymorphism or PGV that affects the efficacy of the pemetrexed.

Although a discussion of the pros and cons of broad germline testing in patients with cancer is beyond the scope of this review, readers are directed, for example, to the recent excellent discussion using GI malignancies as the model proposed by Hampel and Yurgelun.[28] Germline testing is considered the standard of care for all or many patients with ovarian, pancreatic, colorectal, breast, and prostate cancers. Investigators from Memorial Sloan Kettering evaluated the germlines of 12,000 patients diagnosed with advanced cancer.[29] In their study, 9% of the patients had a likely pathogenic/pathogenic (LP/P) variant. The most common PGVs identified were in *BRCA1/2*, *CHEK2*, *ATM*, mismatch repair genes and *PALB2*. Lung cancer was under-represented in their germline analysis, and results of this group were not reported. Investigators from China analyzed 1,026 patients with lung cancer and performed a germline analysis using a 58-gene next-generation sequencing panel.[30] When combining pathogenic (P) and likely pathogenic (LP) variants, they found a PGV prevalence of 4.7%. The most common PGVs were in *BRCA2*, *CHEK2*, and *ATM*.[31-33]

In another study, 7,788 patients with lung cancer were evaluated for PGVs.[34] The diagnosis prompting germline testing was lung cancer, and the gene panel chosen was based on the clinician's choice. In this study 1,161 patients with a LP/P variant, with a prevalence of 14.9%. The most common were in *BRCA2* (2.8%), *CHEK2* (2.1%), *ATM* (1.9%), *TP53* (1.3%), *BRCA1* (1.25), and *EGFR* (1%). The high-prevalence results appeared to suggest that the germline tests were ordered because the clinician was suspicious of a PGV, not on the basis of the lung cancer diagnosis but rather the personal or family histories of these patients with lung cancer. However, patients without and with personal or family histories of non–lung cancers had similar rates of these variants (14.5% *v* 16%, respectively).

Although it is likely that the true percentage of PGVs in the lung cancer population is lower than the 14.9% observed in this study raised the question of whether PGVs other than *TP53* and *EGFR T790*, such as *BRCA2* and *CHEK 2*, should be considered—or at least further studied—as lung cancer predisposing.

Another interpretation of this findings is that patients diagnosed with lung cancer are inadequately considered for germline testing before their diagnosis. In other words, if the patients in this study were tested because of their personal or family histories of non–lung cancer, provided these patients were evaluated in other clinics before their diagnosis of lung cancer, providers in those clinics either were unaware of the personal or family histories that should prompt referral for genetic counseling or did not adequately assess whether these patients had personal or family histories suggesting a high pretest probability of carrying a PGV. A family history must be part of a comprehensive lung cancer evaluation, and when such history suggests the possibility a germline variant that may affect cancer development, the prevalence of 15% justifies germline analysis testing.

Small-cell lung cancer represents around 10% of the lung cancer population. Inherited susceptibility has been identified by germline whole-exome sequencing of 87 patients, 43.7% of whom had 42 PGVs involving 35 cancer-predisposing genes. The results were independently cross-validated, including PGVs involving *RAD51D*, *CHEK1*, *BRCA2*, and *MUTYH*.[35]

GERMLINE ALTERATIONS AND INHERITED PREDISPOSITION IN MESOTHELIOMA

Exposure to asbestos has long been the principal environmental carcinogen causally associated with the etiology of mesothelioma. However, a substantial body of data has emerged over the last five decades that implicates germline predisposition as a component of risk associated with this cancer.

A case-control study in the 1970s hinted at familial clustering in a cohort of 52 female patients, in whom it was observed that the parental risk of cancer was significantly greater in cases compared with controls, raising the

possibility of germline predisposition.[36] This finding was also observed independently[37,38] reinforcing this possibility.

Robust confirmation of heritable transmission followed a genetic epidemiological analysis involving six generations and 526 individuals in the Cappadocia region of Turkey, in which the rate of mesothelioma in the villages of Jarain and Tuzkoy was as high as 50% and unrelated to the abundance of erionite asbestos in both affected and unaffected neighboring villages.[39] Genetic predisposition modulates sensitivity to asbestos. This was inferred in the Cappadocia study on the basis of the finding that family members born and raised outside of these villages did not develop mesothelioma.

Genome-Wide Association Studies

It is probable that mesothelioma has a heritable polygenic component, in common with other multifactorial conditions. However, progress in identifying polygenic risk has been hindered by the requirement for very large sample sizes. Genome-wide association studies have been conducted in case-control samples in Italy,[40] with 407 cases and 389 asbestos-exposed controls, and in Australia,[41] with 428 cases and 1,269 controls. Neither study identified SNPs with associations stronger than chance expectation. However, the study conducted in Italy reported suggestive signals in regions previously associated with somatic mutations in mesothelioma, including *SLC7A14*, *THRB*, *CEBP350*, *ADAMTS2*, *ETV1*, *PVT1*, and *MMP14*. Neither study succeeded in directly replicating the results of the other, although the study conducted in Australia reported suggestive associations in *SDK1* with some evidence of replication in the study conducted in Italy.

The recent emergence of large national biobanks has increased the number of genotyped cases available, albeit with lower quality data on asbestos exposure. Unpublished genome-wide association study (GWAS) results are available on the Internet for the UK Biobank,[42] with 165 cases and 361,029 controls (http://www.nealelab.is/uk-biobank), and FinnGen,[43] with 298 cases and 259,583 controls (https://www.finngen.fi). Again, these studies have not identified associations stronger than chance expectation and have not replicated the strongest signals from other GWAS.

GWAS data allow the estimation of heritability from ostensibly unrelated individuals, providing evidence for the presence of polygenic associations. In the UK Biobank, this was estimated at 0.7734 with SE 0.358[44]; however, this estimate is likely to be numerically unstable given the limited sample size. In view of the dominating environmental risk from asbestos exposure, any polygenic heritability is likely much smaller but is not ruled out by the UK Biobank estimate.

Currently then, sample sizes remain insufficient for reliable identification of common germline variants increasing mesothelioma risk. However, meta-analysis of extant results with integration of data from multiple biobanks[45] may soon allow greater progress in this area.

BAP1 and Predisposition to Mesothelioma

BRCA1-associated protein (BAP1[46]) is one of the most frequently mutated tumor suppressors in patients with mesothelioma. It functions as a deubiquitinating enzyme and subunit of the polycomb transcriptional repressor complex. BAP1 PGVs (^Fig 1) are associated with a loss of BAP1 nuclear localization, which is critical for DNA repair, chromatin assembly, or transcription.[47] Because the carboxy terminus of the BAP1 protein contains the nuclear localization signal, all truncating mutations are pathogenic and the truncated BAP1 protein is found in the cytoplasm.

A link between BAP1 and germline susceptibility was identified in connection with metastatic uveal melanoma, renal cancer, cutaneous melanoma, and basal cell carcinomas.[48,49] Approximately one third of carriers develop two to seven malignancies in their lifetime, with malignant mesotheliomas being frequent.[49-56]

BAP1 germline mutations were originally found in two families with a high incidence of mesothelioma.[57] Genealogic studies traced a common ancestor from the 1700s associated with a large BAP1 cancer syndrome kindred over nine generations.[58] Biallelic inactivation (ie, a second hit) can arise after both germline and subsequent somatic alterations. Recently, however, germline whole BAP1 gene deletion has been found in a family.[59] Preclinical studies have shown that the onset of mesothelioma after asbestos exposure is accelerated in germline BAP1(±) mice, consistent with a gene × environment interaction.[60,61]

In patients, germline BAP1 mutation affects a fraction of patients with mesothelioma, originally reported at 8% (2 of 26) in the first reported series,[57] with some studies reporting low or absent germline BAP1 alterations.[62] *The Clinical and Histopathologic Characteristics of BAP1 Mutations study* (ClinicalTrials.gov identifier: NCT01773655) recently reported the prevalence of pathogenic BAP1 germline mutations to be 5 of 180, which were found exclusively in those patients predicted by the following clinical screening criteria: (1) a personal or family history of choroidal nevus, uveal melanoma, melanoma, mesothelioma, renal cancer, or cholangiocarcinoma; (2) a history of cancer in >two first-degree relatives; (3) no known history of asbestos exposure; and (4) age younger than 50 years at diagnosis.[63] These results confirm the low rate of pathogenic BAP1 germline mutations in patients with mesothelioma.

The prognosis for patients diagnosed with germline BAP1 mutation is particularly good. In a series of 79 patents, this

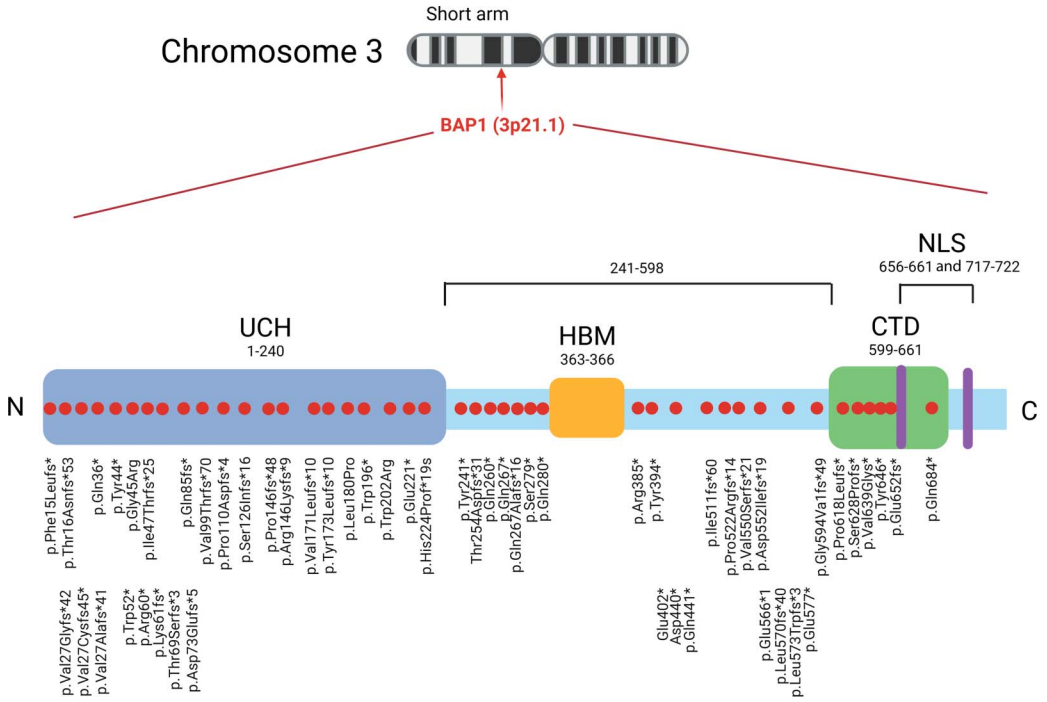

FIG 1. A schematic summarizing reported *BAP1* PGVs in patients with mesothelioma. Mutation hotspots are evenly distributed across multiple protein domains (red dots). CTD, C-terminal domain; HBM, host cell factor 1–binding domain; NLS, nuclear localization signals; PGV, pathogenic germline variant; UCH, ubiquitin carboxyl-terminal hydrolase domain.

was 9 years versus 8 months across all stages in the SEER cohort.[64] Another study showed a 7-fold increase in survival for germline *BAP1* mutations in patients with mesothelioma.[65]

The penetrance of the heterozygous nonfunctional *BAP1* allele in the clinically confirmed families has reached 100%; approximately one third of carriers develop two to seven malignancies in their lifetime, with malignant mesotheliomas being frequent.[49-56] Interestingly, 9.7% to 12% of all patients with mesothelioma have shown to acquire pathogenic germline mutations, which most affects *BAP1*.[64,66,67] These alterations are more common in young individuals and those who have a family history of the disease.

Pleural and peritoneal mesotheliomas may develop simultaneously or years apart in *BAP1* mutation carriers.[47,68] Affected people also develop benign melanocytic intradermal tumors and malignancy around 20 years earlier than the same malignancies occurring sporadically.[58,64,65,69]

Mesotheliomas are among the less aggressive cancers that develop in germline *BAP1* mutation carriers.[47] The median survival for mesothelioma in these patients is 5-7 years after diagnosis, with 26% of patients surviving 10 or more years.[64,69] Depending on the histology, the median survival for sporadic mesothelioma ranges from 6 to 24 months.[70]

Genetic Counseling and Mesothelioma

One of the greatest differences when counseling patients in the thoracic setting is when a patient has a diagnosis of mesothelioma. As previously mentioned, mesothelioma can be associated with mutations in *BAP1*, which can be inherited or somatic. Many patients with mesothelioma are involved with litigation when it comes to their personal diagnosis of mesothelioma due to exposure to asbestos. Many of these patients are rightfully concerned that if a germline mutation is identified, this can be used against them. That is, the defense could argue that the asbestos exposure had little to no effect on cancer diagnosis and that the cause of the cancer was due to an underlying predisposition to mesothelioma. Although it is a standard practice to discuss the Genetic Information Non-Discrimination Act (GINA) with all patients, this litigation area of concern is specific to patients with mesothelioma.[63] It is imperative that genetic counselors discuss this potential with patients so that they can make the best decision for themselves regarding genetic testing. Viable alternative options may (1) include a decline in germline genetic testing or (2) choose to undergo genetic testing under a research study to keep this information separate from their medical record.

Prospective studies have been designed to help underpin cancer prevention, precise counseling, and cancer

management in patients with germline BAP1 mutation. These include a study enrolling 500 patients with a family history suggestive of hereditary *BAP1* is being investigated, as well as individuals with variants that are known to be or are potentially pathogenic or of uncertain significance (ClinicalTrials.gov identifier: NCT04792463 due for completion in 2026). The goal is to develop novel screening, prevention, and treatment strategies by investigating the prevalence of germline *BAP1* in mesothelioma as well as melanoma, renal cell carcinoma, cholangiocarcinoma, hepatocellular carcinoma, meningioma, and basal cell carcinoma (BAP1 syndrome cancers).

Long-term Follow-up of Mesothelioma Patients and Their Family Members with Germline Mutations in BAP1 and Other Genes (ClinicalTrials.gov identifier: NCT03830229 due for completion in 2027) is an observational study designed to characterize the clinical history of malignant mesothelioma in 1,000 patients and their first-degree relatives who have a *BAP1* or *TP53* mutation. The study will use periodic MRI scans and breast, skin, and ocular examination.

A study designed to improve how people with known or suspected BAP1 mutations are monitored over time (ClinicalTrials.gov identifier: NCT04431024 due for completion in 2038) will recruit 800 participants to undergo dual-energy computed tomographic imaging, longitudinal noninvasive (liquid) biopsy, and minimally invasive surgical surveillance. Participants are eligible if they are older than 30 years, with a history of any malignancy, are with a germline *BAP1* mutation involving *BAP1*, or are a first- or second-degree relative of someone with a known germline *BAP1* mutation. Tumor tissue, blood, saliva, or buccal swab specimens will be sampled for genetic analyses to explore the biological mechanisms associated with the favorable prognosis of germline *BAP1* mutation.

SUMMARY

Routine germline genetic testing for thoracic cancers is not currently the standard practice; however, ongoing studies aim to better understand the natural history of patients with PGVs to improve their clinical management.

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Antibody-Drug Conjugates for Lung Cancer: Payloads and Progress

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overview

Antibody Drug Conjugates (ADCs) are a novel class of therapeutic that structurally comprise an antibody directed at a tumor epitope connected via a linker to a cytotoxic payload that have shown significant antitumor activity across a range of malignancies including lung cancer. In this article we review the pharmacology of ADCs, describe results of trials with ADCs directed at targets in lung cancer including Trophoblast cell-surface antigen 2(TROP2), HER3, MET, Carcinoembryonic antigen-related cell adhesion molecular 5(CECAM-5) and HER2. Trastuzumab Deruxtecan (also known as DS-8201a or T-DXd) an ADC directed at HER2 recently became the first ADC to receive FDA approval in lung cancer, on the basis of its activity in tumors with HER2 mutations, demonstrated in the Destiny-Lung01 and Lung02 trials.

INTRODUCTION

The historical roots of antibody-drug conjugates (ADCs) trace back to the early 20th century when Paul Ehrlich conceived of a more targeted delivery of anticancer therapy termed the magic bullet.[1] Indeed, a century of advancement in the fields of biochemistry, pharmacology, and immunology has converged and led to the development of these novel therapeutic agents that demonstrate clinically meaningful activity with immense potential to alter the treatment paradigm in non–small-cell lung cancer (NSCLC). The rationale of ADCs is simple: selectively target cancer cells and deliver concentrated cytotoxic payloads through an antibody-mediated process, effectively sparing normal tissue and inflicting increased damage to tumors. In addition to the direct cytotoxic effects, additional innate and adaptive immune mechanisms may further potentiate anticancer effects both regionally and systemically.[2] As such, modern ADCs have been developed to maintain pharmacodynamic stability in the compartment of systemic delivery (ie, the blood), preferentially bind to a target antigen expressed on cancer cells leading to accumulation within the tumor compartment, become internalized by the target cell, and release cytotoxic levels of the chemotherapy payload. This precise delivery mechanism may ultimately lead to an increased therapeutic index of the corresponding payload compound, in theory limiting what may otherwise be toxic effects at equivalent systemic doses. These agents have had increasing impact in both solid tumor and hematologic malignancies, with recent advances in the treatment of oncogene-driven and non–oncogene-driven NSCLC.[3,4] Here, we provide an overview of the pharmacology of design of ADCs and review advances with ADCs directed at targets in lung cancer including trophoblast cell-surface antigen 2, HER3, MET, carcinoembryonic antigen-related cell adhesion molecular 5 and discuss developments in targeting HER2 leading to the approval of trastuzumab deruxtecan (T-DXd) for *HER2* mutation–positive NSCLC.

THE ABCs OF ADCs

Design of ADCs

Three key elements of ADC design include the antibody, linker, and payload. Each of these components have undergone significant refinement in recent decades, culminating in more clinical activity and tolerability, but also leading to important variability and distinctions between ADCs.

Antibody and antigen target. Selecting an appropriate target and consequently designing a corresponding antibody against this target are essential aspects to successful ADC development. An ideal protein target is one that is highly expressed on the cell surface of cancer cells, with limited expression levels on nonmalignant tissues.[5] Current targets of ADCs, including HER2,[6] TROP2,[7] and HER3,[8] exhibit higher expression levels on tumor cell surfaces compared with normal tissue, albeit to varying degrees. This variability in expression patterns between malignant and nonmalignant cells may in part explain some of the on-target toxicities noted with these agents. In addition, the heterogeneity of antigen expression within a given tumor may be another important consideration.[9,10]

Another key factor to be considered is rate of antigen turnover or cycling on tumor cell surface. Preclinical

PRACTICAL APPLICATIONS

- Traztuzumab deruxtecan (T-DXd) is the first antibody-drug conjugate (ADC) approved for lung cancer on the basis of activity in patients with *HER2* mutation–positive non–small-cell lung cancer demonstrated in the DESTINY-Lung01 and DESTINY-Lung02 trials.
- ADCs directed at additional targets, including TROP-2, HER3, MET, CEACAM5, and DLL2, are being clinically evaluated in a range of settings as monotherapy and in combination with other agents including immunotherapy.
- Although ADCs will likely become established as additional treatment options for lung cancer, there remains a need to develop strategies for optimal patient selection and to overcome resistance to treatment.

studies have suggested that high turnover rates of ADC targets on tumor cells may increase internalization and delivery of cytotoxic payload intracellularly, thereby increasing cytotoxic killing.[11]

The antibody component of ADCs is predominantly humanized to limit immune-mediated elimination seen with murine monoclonal antibodies. The immunoglobulin G (IgG) class is the predominant antibody backbone for several immune-based oncologic therapies, including ADCs. Further isotype subclassifications of IgG (IgG1, IgG2, IgG3, and IgG4) lead to variability in antibody half-life, constant and hinge regions, and interaction with immune effector cells via differences in Fcγ-receptor (FcγR) affinity.[12] The majority of ADCs use an IgG1 antibody, given its extended serum half-life and FcγR-binding affinity associated with complement-mediated cytotoxicity and antibody-dependent cellular cytotoxicity.[13] Alternative IgG subclasses, such as IgG3, may have greater immunogenicity[14] but are limited by a shorter half-life.[15] In comparison, IgG2 and IgG4 subclasses have apparent equivalent half-life duration to IgG1, although with limited capacity for FcγR-mediated activation of immune effector cells.[16]

Linker. The linker is a biochemical compound that connects the antibody to the cytotoxic payload. The linker serves two major roles that directly affect both toxicity profile and activity of the ADC. First, the linker maintains ADC stability within the systemic compartment, typically the bloodstream. Linker instability in this setting can lead to inappropriate or premature release of the cytotoxic payload and significant toxicity, particularly given the potent concentration of these compounds. Conversely, an effective linker must also successfully release the cytotoxic payload once the ADC is internalized by the targeted cell. Without successful delivery of the cytotoxic payload, the clinical activity of the ADC can be quite muted.[17]

Linkers are broadly categorized into either cleavable or noncleavable on the basis of the corresponding mechanism of payload release.[18] Cleavable linkers are engineered to degrade and release the cytotoxic payload on the basis of certain intracellular factors, such as acidity, glutathione reduction, or presence of lysosomal proteases leading to peptide cleavage.[19,20] Gemtuzumab ozogamicin, which was the first US Food and Drug Administration (FDA)–approved ADC, uses a hydrazine-based acid cleavable linker that is pH-sensitive,[21] while investigational agent mirvetuximab soravtansine incorporates a reducible disulfide linker.[22] Several FDA-approved ADCs including trastuzumab deruxtecan,[3] sacituzumab govitecan,[23] and enfortumab vedotin[24] are designed with peptide-based cleavable linkers.[25] Noncleavable linkers, by contrast, are formed by nonreducible bonds with amino acid residues of the connected antibody, leading to greater stability within the bloodstream.[26] The main method of payload release for noncleavable linkers is through lysosomal-dependent degradation of the entire antibody-linker complex. Of note, this lysosome-based degradation can affect payload permeability because of retention of charged amino acid residues.[27] Beyond the intracellular release of payloads, preclinical studies have suggested that release of cytotoxic payload into the tumor microenvironment may play an important role in ADC function,[28] a term known as bystander effect.[29-31]

Payload. The payload component of the ADC potentiates cytotoxic effects on the target cell after internalization and release by the linker. Earlier, ADCs incorporated more conventional chemotherapeutic agents, such as methotrexate.[32] However, these ADCs, comprising lower-potency payload compounds, showed limited efficacy compared with conventional chemotherapy delivery. More modern ADCs contain payloads consisting of higher-potency chemotherapy agents, with IC50s (denoting half maximal inhibitory concentration) in the nanomolar and picomolar range.[33] Although such concentrations could be administered through traditional systemic routes, a narrow therapeutic window limits their clinical utility. General categories of these cytotoxic payloads include antimicrotubule agents (ie, DM1) and agents that exert DNA damage such as topoisomerase I inhibitors (ie, SN-38).[34] Several of these compounds were discovered decades prior; however, their clinical potential was limited at the time by their narrow therapeutic window.

Pharmacology

A key factor in the pharmacologic profile and clinical activity of ADCs relates to the drug-antibody ratio (DAR). The DAR is the average number of payload moieties attached to each monoclonal antibody. FDA-approved ADCs have DARs

ranging from 2 to 8.[35] Although ADCs with higher DARs have expectedly greater in vitro potency, preclinical studies suggest they may be subject to more rapid hepatic clearing and carry less favorable toxicity profiles, ultimately lowering their therapeutic index.[36] ADC manufacturing may use various methods, whereby cytotoxic drug is conjugated to either lysine or cysteine residues present along the accompanying monoclonal antibody. The pattern of conjugation may be performed in a more random or controlled manner, with the former leading to variability of DAR and resulting batch effect.[37] More recent manufacturing practice incorporates controlled, site-specific conjugation at predetermined positions along the antibody, decreasing the level of heterogeneity among the final ADC product.[38]

The variability of ADC design, with the key biochemical components detailed above, can translate to differences in the pharmacokinetics (PK) and pharmacodynamics (PD). The majority of the total ADC is comprised by the antibody portion, with the PK of the ADCs, thereby significantly influenced by the properties of the antibody backbone.[39] Target-specific binding, Fc receptor–dependent recycling, and Fc effector functions—all of which are largely affected by the antibody component of ADCs—can dictate the PK and PDs of these agents. In addition to the antibody component of the ADC, other elements such as the linker, site of conjugation, and cytotoxic payload carry their own PK considerations. Conjugation status of the linker, including site of conjugation, may affect the PK of the ADCs through effects on stability while the ADC is within circulation or after internalization. More unstable linkers may lead to a faster decline in antibody concentrations while the half-life of ADCs with more stable linkers may more resemble that of unconjugated monoclonal antibodies.[40] Finally, while the cytotoxic payload component may not fully determine the PK of the corresponding ADC, its mechanism of action can affect the therapeutic index, which is important when investigating and determining appropriate dosing regimens.[41]

ANTIBODIES FOR EVERYBODY: TARGETS AND TOXICITIES OF ADCs IN LUNG CANCER

In NSCLC, additional treatment options after failure of immunotherapy combinations and after development of acquired resistance to targeted therapy in molecularly driven subtypes are clearly needed. In this context, ADCs are a rapidly emerging class of therapies that are currently being explored across a range of targets in the metastatic setting with promising early results.

ADC Targets and Therapeutics in NSCLC

Here, we briefly review the current ADC targets in NSCLC and the preliminary efficacy and toxicity of ADCs agents, excluding HER2-targeting ADCs that are discussed separately below (Table 1).

Trophoblast cell-surface antigen 2. Trophoblast cell-surface antigen 2 (TROP-2) is a glycoprotein transmembrane calcium signal transducer present in more than 50% of lung adenocarcinoma and squamous cell carcinoma, associated with poor survival.[51-53]

Datopotamab deruxtecan. Datopotamab deruxtecan (Dato-DXd) is an anti–TROP-2 ADC linked to topoisomerase I inhibitor deruxtecan via a cleavable linker. The phase I TROPION-PanTumor01 trial included an NSCLC expansion cohort where 180 previously treated patients unselected for TROP-2 expression received Dato-DXd 4, 6, and 8 mg/kg every 3 weeks. Although objective response rate (ORR) and median progression-free survival (PFS) were similar across all dose levels (25% and 6 months, respectively), treatment-emergent adverse events (TEAEs) including nausea, mucositis, and asthenia were more frequent at higher levels. It is noteworthy that interstitial lung disease (ILD) occurred in 19 patients (11%) and seemed to be dose-dependent.[23,43,54]

Dato-DXd also achieves encouraging 35% ORR and 9.5 months median duration of response in 34 NSCLC previously treated patients with actionable genomic alterations.[55] The phase Ib TROPION-Lung02 trial is evaluating Dato-DXd 4 and 6 mg/kg combined with pembrolizumab with or without platinum agents in both previously untreated and pretreated patients with metastatic NSCLC without actionable genomic alterations. In 33 response-evaluable first-line patients, the ORR was 54% (62% with doublet and 50% with triplet therapy) and the most frequent TEAEs included stomatitis and nausea. To date, no grade 4 or 5 ILD events have been considered as Dato-DXd drug-related.[4] Dato-DXd 6 mg/kg every 3 weeks is currently being explored in multiple settings, including a phase III versus docetaxel in pretreated advanced NSCLC without actionable genomic alterations (TROPION-Lung01; ClinicalTrials.gov identifier: NCT04656652). Dato-DXd is also being evaluated as first-line therapy for patients with advanced/metastatic NSCLC with PD-L1 expression $\geq$50% in the phase III TROPION-Lung08 trial comparing Dato-DXd in combination with pembrolizumab versus pembrolizumab monotherapy (ClinicalTrials.gov identifier: NCT05215340).

Sacituzumab govitecan. Sacituzumab govitecan (SG) is an anti–TROP-2 antibody linked to the topoisomerase inhibitor SN-38 by a cleavable linker. The phase I/II IMMU-132-01 basket trial included 495 patients with treatment-refractory solid tumors regardless of TROP-2 expression evaluating SG at 8, 10, 12, and 18 mg/kg on days 1 and 8 of 21-day cycles. Relevant TEAEs included gastrointestinal (nausea, diarrhea, and vomiting) and hematologic (febrile neutropenia and

TABLE 1. Clinical Data With ADCs in Lung Cancer (excluding HER2-directed ADCs)

Target	Agent	Study	Sample Size—Patients (No.)	Treatment (RP2D or RDE)	ORR, No. (%)	Median PFS, months (95% CI)	Median OS, months (95% CI)	Safety and Toxicities (%)	References
TROP-2	Dato-DXd	Phase I, dose-escalation and expansion study	180	6 mg/kg every 3 weeks	25	6 (NE)	NE	Grade 3 stomatitis (2%), nausea (1%), neutropenia (1%). ILD by independent adjudication any grade: 4 mg/kg 10% (one grade 1, three grade 2, one grade 3), 6 mg/kg 4% (two grade 2), and 8 mg/kg 15% (three grade 1, five grade 2, one grade 3, three grade 5	Meric-Bernstam et al,[42] Spira et al,[43] Garon et al[44]
	SG	Phase I/II basket trial	54	10 mg/kg D1 D8 every 3 weeks	16.7	4.4 (3.6 to 9.7)	16.8 (9.0 to 21.9)	Grade 3 nausea (3.6%), diarrhea (7.9%), vomiting (2.8%) grade 3 anemia (10.3%) Neutropenia: grade 3 28.9%, grade 4 13.5% Febrile neutropenia: grade 3 4.2%, grade 4 1.0%	Bardia et al[23]
HER3	HER3-DXd	Phase I dose-escalation/ expansion study	57 (EGFRm) 47 (EGFRwt)	5.6 mg/kg every 3 weeks	39 (EGFRm) 28 (EGFRwt)	EGFRm 8.2 (4.4 to 8.3) EGFRwt 5.4 (3. 9 to 12.7)	NE	Grade 3 thrombocytopenia 30%, anemia 9%, neutropenia 19%, Adjudicated treatment-related ILD 7% (two grade 1, one grade 2, one grade 3)	Janne et al[45] Steuer et al[46]
MET	Teliso-V	Phase I dose-escalation/ expansion study	16 c-MET+ by IHC	2.7 mg/kg every 3 weeks	18.8	5.7 (1.2 to 15.4)	NE	Grade 3 fatigue (14.3%), grade 3 anemia (7.1%), grade 3 neutropenia (7.1%) grade 3 hypoalbuminemia (4%), grade 3 peripheral edema (2.1%), grade 3 hypophosphatemia (2.1%)	Strickler et al[47]
		Phase II	136 c-MET+ by IHC: OE ≥25% 3+	1.9 mg/kg every 2 weeks	36.5	NE	NE	Any grade AEs: peripheral sensory neuropathy (25%), nausea (22.1%), hypoalbuminemia (20.6%)	Camidge et al[48]
CEACAM-5	TUSA	Phase I dose-expansion study	92 CEACAM+ by IHC: 64 high 28 moderate	100 mg/kg every 2 weeks	20.1 (high) 7.1 (moderate)	NE	NE	Grade 3 keratopathy (10.9%), dyspnea (11%), asthenia (4.3%)	Gazzah et al[49]
B7-H3	I-DXd	Phase I dose escalation/ expansion study. SCLC cohort	19	12 mg/kg every 3 weeks	58	NE	NE	Grade 3 anemia (19%), neutropenia (7%), nausea (3%), pneumonia (3%). Any grade IRR 32%, one grade 3, one case of grade 5 ILD	Doi et al[50]

Abbreviations: ADCs, antibody-drug conjugates; AEs, adverse events; Dato-DXd, datopotamab deruxtecan; HER3-DXd, patritumab deruxtecan; I-DXd, ifinitamab deruxecan; IHC, immunohistochemistry; ILD, interstitial lung disease; IRR, infusion-related reaction; m, mutant; NE, not evaluated; OE, overexpression; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RDE, recommended dose for expansion; RP2D, recommended phase II dose; SCLC, small-cell lung cancer; SG, sacituzumab govitecan; Teliso-V, telisotuzumab vedotin; TUSA, tusamitamab ravtansine; wt, wild-type.

anemia) toxicity. Dose reductions were required in 32% of patients. On the basis of these data, the dose of 10 mg/kg was selected for further development. Interestingly, the presence of homozygosity of the UGT1A1 *28 allele (*28/*28; 9.3% of patients) was associated with an almost two-fold increase in incidence of neutropenia.[23] The IMMU-132-01 study included a single-arm expansion cohort of 54 patients with previously treated NSCLC achieving an ORR of 17% and a median PFS of 5.2 months. More than 90% of the 26 assessable archival tumor specimens were positive for TROP-2 by immunohistochemistry (IHC).[54] Currently, the phase III EVOKE-01 trial is evaluating SG versus docetaxel in patients with advanced NSCLC EGFR and those with ALK wild type after immunotherapy and platinum-based chemotherapy (ClinicalTrials.gov identifier: NCT05089734).

Human epidermal growth factor receptor 3. Human epidermal growth factor receptor 3 (HER3) is a member of the HER family. Its heterodimerization with other tyrosine kinase receptors (TKR) including other HER family members and MET leads to activation of oncogenic pathways. HER3 has gained attention as an important contributor to EGFR/HER2-targeted therapy resistance.[8,56-59]

Patritumab deruxtecan. Patritumab deruxtecan (HER3-DXd) is a HER3-targeted ADC linked to deruxtecan via a tetrapeptide-based cleavable linker. A phase I trial included patients with metastatic EGFR-mutated NSCLC with previous EGFR tyrosine kinase inhibitor (TKI) therapy. Among the 57 patients receiving HER3-DXd 5.6 mg/kg every 3 weeks, the ORR was 39% and median PFS was 8.2 months. Responses were observed in patients with known and unknown mechanisms of resistance and across a multiple range of HER3 expression. Common grade $\geq$3 TEAEs included thrombocytopenia and neutropenia. ILD, although present, was an uncommon phenomenon (5%, no patients with grade >3).[45] In a cohort of 26 patients with previously treated advanced NSCLC without identified genomic diver alterations, HER3-DXd was associated with an ORR of 26.9% and a median PFS of 4.2 months.[46] An ongoing phase III trial is currently comparing HER3-DXd versus platinum-based chemotherapy in metastatic advanced EGFR-mutated patients after failure of EGFR TKI therapy (ClinicalTrials.gov identifier: NCT05338970).

MET. MET is a tyrosine kinase inhibitor that is activated through several mechanisms including amplification, exon 14 skipping mutations, and overexpression in NSCLC. These diverse mechanisms have made MET an attractive option for ADC development.[60-62]

Telisotuzumab vedotin. Telisotuzumab vedotin (Teliso-V) is an ADC composed of a c-MET–binding antibody linked to monomethyl auristatin E, a microtubule inhibitor. In a phase I trial, of 16 patients with c-Met–positive NSCLC who were treated with Teliso-V 2.4 to 3.0 mg/kg, ORR was 18.8%. The recommended phase II dose was established at 2.7 mg/kg every 21 days.[47] The LUNGMAP substudy S1400K included 28 previously treated patients with squamous histology and c-MET positive tumors. Pneumonitis was an unanticipated toxicity (two grade 5 events), and the 9% ORR failed to meet the prespecified response, leading to trial discontinuation.[63] The phase II LUMINOSITY trial aimed to identify the population best suited to receive Teliso-V. Patients with c-MET overexpression by IHC were included, and a total of 136 patients were treated with Teliso-V. In patients with nonsquamous EGFR wild-type tumors, a promising 36.5% ORR was achieved. The most common AEs included neuropathy (25%), hypoalbuminemia (21%), and nausea (22%).[48] A phase III randomized trial is currently comparing Teliso-V versus docetaxel in previously treated c-MET overexpressing, EGFR wild-type nonsquamous NSCLC (ClinicalTrials.gov identifier: NCT04928846). Teliso-V in combination with erlotinib has also been studied in 28 patients with MET-positive *EGFR*-mutant advanced NSCLC with previous EGFR-TKI achieving a promising ORR of 32% and a median PFS of 5.9 months.[64]

Carcinoembryonic antigen-related cell adhesion molecular 5. Carcinoembryonic antigen-related cell adhesion molecular 5 (CEACAM5) is a glycoprotein member of the CEA gene family and seems to promote cell proliferation and migration.[65,66]

Tusamitamab ravtansine. Tusamitamab ravtansine (TUSA) is a CEACAM5 monoclonal antibody linked to the maytansinoid warhead DM4. In a phase I clinical trial, 31 patients with metastatic solid tumors were included in the dose-escalation part. The maximum tolerated dose of 100 mg/m^2 every 2 weeks was selected for further investigation.[67] The NSCLC dose expansion evaluated two cohorts according to CEACAM5 expression by IHC. Ninety-two previously treated patients were included (64 high expressors, 28 moderate). The ORR was higher in the high-expressor cohort (20.3%). The most common grade $\geq$3 TEAEs included keratopathy (10.9%), dyspnea (11%), and asthenia (4.3%).[49] An exploratory analysis of patients with long-term treatment exposure has revealed that responses to TUSA may be durable and could not be related to CEACAM5 expression by IHC.[68] An ongoing randomized phase III study is comparing docetaxel versus TUSA in previously treated patients with metastatic nonsquamous NSCLC with CEACAM-positive tumors (ClinicalTrials.gov identifier: NCT04154956).

ADCs in Small-Cell Lung Cancer

The treatment landscape of ADCs in small-cell lung cancer (SCLC) is also evolving. Molecules such as delta-like protein 3 (DLL3), CD56, and even TROP-2 have been

evaluated as targets for ADC development.[69] Rovalpituzumab tesirine, a DLL-3–targeting ADC, failed to improve efficacy outcomes compared with topotecan or as maintenance after first-line therapy.[70,71] CD56 is the target of lorvotuzumab mertansine, an ADC with a maytansinoid payload. Its combination with first-line platinum-based chemotherapy was evaluated in a phase I/II trial. Safety was a concern, as peripheral neuropathy was present in 29% of patients and showed increased toxicity, including a higher incidence of serious infections with fatal outcomes.[72] Sacituzumab govitecan has also been analyzed in 62 patients with refractory SCLC included in the IMMU-132-01 trial. SG showed an ORR of 19%, a median PFS of 5.7 months, and a median OS of 7.1 months.[23] Ifinatamab deruxtecan (DS-7300a, I-DXd), a B7-H3–targeting ADC with a potent DNA topoisomerase I inhibitor, showed promising results in 19 patients with refractory SCLC, achieving 58% ORR. The most common TEAEs were nausea, anemia, and infusion-related reaction. I-DXd is currently being evaluated in a phase II clinical trial of patients with previously treated SCLC (ClinicalTrials.gov identifier: NCT05280470).[50]

HER2 HOMECOMING: THE JOURNEY TO TRASTUZUMAB DERUXTECAN

Alterations in the human epidermal growth factor receptor 2 (HER2, also known as ERBB2) in NSCLC have been described through three mechanisms: (1) gene mutation, (2) gene copy number gain or amplification, and (3) HER2 protein overexpression.[73-77] *HER2* mutations (*HER2*m) are typically in-frame insertions in exon 20 (96%), occur in 1%-4% of NSCLC, and are more frequent in never-smokers and in adenocarcinoma.[73-77] *HER2* gene amplification is present in 2%-5% of NSCLC. The prognostic value of *HER2* gene amplification in NSCLC is unclear.[78] HER2 protein overexpression is found in 10%-30% of NSCLC with the specific frequency depending on the cutoff score used.

Evolution of HER2-Directed Therapies

Nonselective HER2 tyrosine kinase inhibitors. Nonselective HER2 TKIs such as dacomitinib, afatinib, and neratinib have yielded inconsistent results with ORR ranging from 0% to 19% and have been associated with substantial toxicity limiting clinical utility.[79-81]

Trastuzumab with and without chemotherapy. Trastuzumab is a monoclonal immunoglobulin humanized murine antibody that binds to extracellular subdomain IV of HER2 and inhibits HER2 homodimerization, preventing HER2-mediated signaling.[82] Cappuzzo et al[83] first demonstrated activity of trastuzumab in combination with chemotherapy in a pretreated patient with *HER2* exon 20–mutant NSCLC. A small single-arm phase II study of trastuzumab monotherapy in pretreated NSCLC patients with HER2 alterations yielded disappointing results with an ORR of 0% (95% CI, 0 to 26) although the disease control rate (DCR) and mPFS were 70% and 5.2 months, respectively.[84] The EUHER2 retrospective cohort study analyzed the effects of HER2-targeted drugs given with chemotherapy in pretreated NSCLC patients with *HER2* exon 20 mutations and reported an ORR of 50.9% and mPFS of 4.8 months in the chemotherapy-trastuzumab combination group.[85] The phase IIa MyPathway basket trial assessed the activity of combination trastuzumab and pertuzumab (a recombinant humanized monoclonal antibody that inhibits dimerization of HER2 and HER3 15) in 27 patients with HER2-amplified/overexpressed NSCLC, demonstrating a modest ORR of 25.9%.[86]

ADCs in HER2 NSCLC. Two ADCs targeting HER2, first ado-trastuzumab emtansine and more recently trastuzumab deruxtecan, have been evaluated in NSCLC (Table 2).

Ado-Trastuzumab Emtansine

Structural features and chemistry. Ado-trastuzumab emtansine (also known as T-DM1) is the first ADC targeting the HER2 receptor that links trastuzumab with a tubulin polymerization inhibitor maytansinoid (DM1) via the noncleavable linker, maleimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (or SMCC), to a lysine residue of the antibody.[95] The noncleavable linker improves stability in systemic circulation, and drug release occurs through lysosomal degradation of the antibody leading to intracellular cytotoxic drug release and is not expected to have substantial bystander effect.[5,95]

Clinical data in NSCLC. In a phase II study in 15 patients with pretreated *HER2* exon 20–mutant (47%) or overexpressed (53%) NSCLC, T-DM1 was reported to have limited efficacy with the mPFS and median overall survival (mOS) of 2.0 months and 10.9 months, respectively.[87] Grade 3 or 4 TEAEs were observed including thrombocytopenia (40%) and hepatotoxicity (20%). T-DM1 demonstrated modest activity in the HER2 overexpressing cohort in a phase II study that recruited 49 patients with HER IHC 2+ and 3+, with the ORR of 0% and 20%, respectively.[89] PFS was comparable between the two cohorts, 2.6 versus 2.7 months, and mOS was 12.2 versus 15.3 months, respectively.

In a subsequent phase II basket trial reported by Li et al,[88] 18 patients with pretreated *HER2*m lung adenocarcinomas were treated with T-DM1 3.6 mg/kg intravenously every 3 weeks resulting in an ORR of 44% and mPFS of 6 months. Responses were observed in those with HER2 exon 20 mutation, including two patients who had concurrent *HER2* amplification. A phase II study of T-DM1 in 22 patients with *HER2* exon 20 mutation NSCLC reported an ORR of 38.1% with a DCR of 52.4%. mPFS and mOS were 2.8 months and 8.1 months, respectively.[90] T-DM1 was well tolerated with 18.2% reported to have grade 3 thrombocytopenia. T-DM1 demonstrated promising activity in HER2 NSCLC, particularly in those who harbor *HER2* exon 20 mutation.

TABLE 2. Clinical Data With HER2-Targeting Antibody-Drug Conjugates in NSCLC

Agent	Study	Population and HER2 Alteration Type	Sample Size—Patients With NSCLC (No.)	Treatment	ORR, No. (%)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Safety and Toxicities (%)	References
T-DM1	Phase II, single arm	HER2 IHC 2/3+ and FISH+ or exon 20 mutation Previous lines of therapy	15	3.6 mg/kg every 3 weeks	1/7 HER2 mutation+ (6.7) 0/8 IHC or FISH+ (0)	2.0 (1.2 to 4.0)	10.9 (4.4 to 12.0)	Grade 3-4 thrombocytopenia (40%), grade 3 hepatotoxicity (20%), grade 3 acute renal failure (7%)	Hotta et al[87]
	Phase II, single-arm basket trial	HER2 mutation Previous lines of therapy	18 (11 with exon 20 mutation)	3.6 mg/kg every 3 weeks	44	5.0 (3.0 to 9.0)	—	Grade 3 anemia (6%), no grade 4 or 5 toxicities	Li et al[88]
	Phase II, single arm	HER2 IHC 2/3+ Previous lines of therapy	49 (IHC 2+ n = 29; IHC 3+ n = 20)	3.6 mg/kg every 3 weeks	0/29 IHC 2+ (0); 4/20 IHC 3+ (20)	IHC 2+ 2.6 (1.4 to 2.8); IHC 3+ 2.7 (1.4 to 8.3)	IHC 2+ 12.2 (3.8 to 23.3) IHC 3 + 15.3 (4.1 to NE)	Grade 3 infusion reaction (2%), thrombocytopenia (2%), anemia (2%), grade 4 seizure (2%)	Peters et al[89]
	Phase II, single arm	HER2 mutation Previous lines of therapy	22	3.6 mg/kg every 3 weeks	38.1	2.8 (1.4 to 4.4)	8.1 (3.5 to 13.2)	Grade 3 thrombocytopenia (18.2%)	Iwama et al[90]
T-DXd	Phase I dose-expansion study	HER2 overexpressing or mutant Multiple pretreated solid tumors	18/60 (11 with HER2 mutations, 8 were exon 20)	6.4 mg/kg every 3 weeks	10/18 overall (55.6) 8/11 in HER2-mutant (72.7)	11.3 (7.2 to 14.3)	NR	Grade 5 respiratory failure (1. 7%), grade 5 DIC, febrile neutropenia, and abnormal hepatic function (1.7%)	Tsurutani et al[91]
	DESTINY-Lung01 Two cohorts, phase II, two arm	HER2 IHC 2/3+ (without known HER2 mutation) Previous lines of therapy	90 (49 in cohort 1 and 41 in cohort 1a)	Cohort 1: 6.4 mg/kg every 3 weeks Cohort 1a: 5.4 mg/kg every 3 weeks	26.5% (cohort 1) 34.1% (cohort 1a)	5.7 (cohort 1) 6.7 (cohort 1a)	12.4 (cohort 1) 11.2 (cohort 1a)	Independently adjudicated drug-related ILD (any grade) occurred in 20.4% (two grade 1, five grade 2, three grade 5; cohort 1) and 4.9% (one grade 1, one grade 5; cohort 1a) of patients	Smit et al,[92] Nakagawa,[93] Li et al[3]
	DESTINY-Lung01 Cohort 2. phase II, single arm	HER2 mutation Relapsed/refractory cohort	91	6.4 mg/kg every 3 weeks	50/91 (54.9)	8.2	18.6	Adjudicated drug-related ILD occurred in 25 (27.5%) patients (grade 1—3; grade 2—16; grade 3—4; grade 5—2)	
	DESTINY-Lung02 phase II, two arm	HER2 mutation Relapsed/refractory cohort	80 (52 treated at 5.4 mg/kg; 28 treated at 6.4 mg/kg)	5.4 mg/kg every 3 weeks ORR 6.4 mg/kg every 3 weeks (2:1 random assignment)	53.8% 42.9%	NR	NR	Adjudicated drug-related interstitial lung disease (any grade) occurred in 5.9% and 14.0% of patients receiving T-DXd 5.4 or 6.4 mg/kg, respectively	Goto et al[94]

Abbreviations: DIC, disseminated intravascular coagulation; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; ILD, interstitial lung disease; NE, not evaluable; NR, not reached; NSCLC, non–small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Trastuzumab Deruxtecan (T-DXd/DS-8201a)

Structural features and chemistry. [fam-] Trastuzumab deruxtecan (also known as DS-8201a or T-DXd) is a new-generation HER2-targeting ADC structurally composed of a humanized anti-HER2 IgG1 monoclonal antibody, a tetrapeptide-based cleavable linker, and a novel cytotoxic topoisomerase I inhibitor (DXd) payload.[95,96] As with TDM-1, the anti–HER-2 antibody component has the same amino acid sequence as trastuzumab; however, it has been engineered with distinctive features that potentially enhance its therapeutic activity. The linker and a self-immolative amino methylene spacer used in T-DXd reduce hydrophobicity and provide stability in the systemic circulation. The cytotoxic payload, a campthothecin topoisomerase I inhibitor, binds and stabilizes the triple complex with DNA topoisomerase 1 and DNA inducing DNA damage and apoptosis of cells. Furthermore, T-DXd exhibits a high DAR of approximately 8, almost two-fold higher than T-DM1 (DAR of 3-4), hence delivering a more potent cytotoxic payload. In addition, as a result of T-DXd's highly membrane-permeable payload, T-DXd can exert a bystander effect, thus allowing antitumor activity in heterogeneous and HER2-low tumors.[30,95]

Preclinical antitumor activity. T-DXd was evaluated preclinically across a range of HER2-expressing cell lines and patient-derived xenograft models and compared with T-DMA.[96] T-DXd had antitumor activity across a range of models with different HER2 expression levels, including KPL-4 (strong positive), JIMT-1 (moderate positive), Capan-1 (weak positive) because of its bystander effect, whereas T-DM1 was only effective against the KPL-4 model.[95,96] Pharmacokinetics were favorable with low release rates into plasma indicating its stability in the circulation.

Clinical studies of trastuzumab deruxtecan. In the phase I dose-escalation study of T-DXd, 24 patients with advanced breast and gastric or esophageal tumors received initial intravenous T-DXd between 0.8 and 8.0 mg/kg (n = 3 for each of 0.8, 1.6, 3.2, and 8.0 mg/kg doses; n = 6 for each of 5.4 and 6.4 mg/kg), and dose-limiting toxicities were assessed over a 21-day cycle.[97] The MTD of T-DXd was not reached, and the recommended phase II dosing (RP2D) was 5.4 or 6.4 mg/kg given every 3 weeks. The most common TEAEs are mild-to-moderate gastrointestinal and hematologic events. ORR was 43%, across the study including patients with low HER2–expressing tumors. PK analysis confirmed high stability of the linker payload in systemic circulation. In the phase III DESTINY-Breast03 trial, T-DXd demonstrated significantly greater efficacy compared with T-DM1 in previously treated HER2 metastatic breast cancer with 75.8% of patients alive without disease progression at 12 months versus 34.1%, with a hazard ratio for progression or death from any cause of 0.28.[98] ORR was 79.7% for T-DXd compared with 34.2% for T-DM-1. Adjudicated drug-related ILD was 10.5% with T-DXd and 1.9% in T-DM1.[98]

Trastuzumab deruxtecan in HER2 NSCLC. In the first-in-human dose-expansion clinical study investigating T-DXd, 60 heavily pretreated patients with HER2 expressing nonbreast/nongastric or *HER2*m solid tumors demonstrated encouraging antitumor activity.[91] T-DXd seemed particularly active in patients with *HER2*m NSCLC with an ORR of 72.7% and mPFS of 11.3 months.[91] This was associated with an overall acceptable safety profile, but safety signals were raised with two fatal outcomes, one of which was associated with treatment-related respiratory failure.

The phase II DESTINY-Lung01 study evaluated T-DXd in two NSCLC cohorts: HER2 overexpressing and *HER2*m tumors.[3,92] In the updated analyses reported by Li et al,[3] T-DXd 6.4 mg/kg showed robust activity in a HER2m cohort that was refractory to standard therapy, resulting in an ORR of 55% and median DoR of 9.3 months; median PFS and mOS were 8.2 months and 17.8 months, respectively. Of note, 26% of patients had adjudicated drug-related ILD with two deaths. In the subsequent DESTINY-Lung02 trial, patients with *HER2*m mNSCLC were randomly assigned to T-DXd 5.4 mg/kg or 6.4 mg/kg. Interim results demonstrated encouraging results in a heavily pretreated population, with ORRs of 53.4% in the 5.4 mg/kg cohort and 42.9% in the 6.4 mg/kg cohort.[94] There were lower frequency of adjudicated drug-related ILD (5.9% *v* 14.1%) and lower frequency of dose interruptions (13.9% *v* 30%) in the 5.4 mg/kg group.[94] The results of DESTINY-Lung01 and Lung02 trials resulted in the FDA approval for T-DXd 5.4 mg/kg dosing as new standard-of-care treatment for patients with previously treated *HER2*-mutant NSCLC. An ongoing phase III trial, DESTINY-Lung04, is evaluating T-DXd in the first-line setting for mNSCLC patients with *HER2* exon 19 or 20 mutations (ClinicalTrials.gov identifier: NCT05048797).

Despite the promising clinical results with T-DXd in the treatment resistant/refractory population, safety signals had been raised with drug-related ILD/pneumonitis. The precise pathophysiology of T-DXd–associated ILD/pneumonitis is unclear, but potential mechanisms include direct cytotoxic pulmonary injury and immune-mediated lung injury. Pooled analyses have identified potential risk factors to T-DXd–associated ILD/pneumonitis, such as higher T-DXd dose, low baseline oxygen saturation, presence of certain baseline lung comorbidities, and moderate-to-severe renal impairment.[99] Early detection of drug-related ILD/pneumonitis is key with proactive patient education and monitoring, and if drug-related ILD/pneumonitis is detected, then a multidisciplinary management approach should be adopted.[99] T-DXd treatment should be interrupted for all grade 1 and beyond ILD/pneumonitis and should not

be rechallenged if a patient experienced grade 2 or greater severity. The safety profile of T-DXd will be further defined as we obtain more real-world data on the incidence, diagnosis, and management of T-DXd–associated ILD/pneumonitis.

CONCLUSION

Advances in the fields of chemistry, pharmacology, and immunology have led to the development of ADCs that now demonstrate clinically meaningful activity in subsets of patients with lung cancer. In August 2022, T-DXd 5.4 mg/kg was approved by the FDA for patients with previously treated *HER2*m metastatic NSCLC marking the first approval of an ADC for lung cancer. This accelerated approval was based on the results from the DESTINY-Lung01 and DESTINY-Lung02 trials, which demonstrated frequent and durable tumor responses in previously treated *HER2*m metastatic NSCLC. ADCs directed at additional targets, including TROP-2, HER2, HER3, MET, and CEACAM5, are now being explored as monotherapy and in combination with other agents. As we begin to understand the nuances in ADC and tumor interactions, refine the design and chemistry of ADCs, develop strategies for patient selection, as well as toxicity management, and understand mechanisms of resistance, it is likely that ADCs will become incorporated into treatment paradigms for a broad spectrum of patients with NSCLC.

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Expanding the Reach and Grasp of Lung Cancer Screening

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overview

Low-dose computer tomographic (LDCT) lung cancer screening reduces lung cancer–specific and all-cause mortality among high-risk individuals, but implementation has been challenging. Despite health insurance coverage for lung cancer screening in the United States since 2015, fewer than 10% of eligible persons have participated; striking geographic, racial, and socioeconomic disparities were already evident, especially in the populations at greatest risk of lung cancer and, therefore, most likely to benefit from screening; and adherence to subsequent testing is significantly lower than that reported in clinical trials, potentially reducing the realized benefit. Lung cancer screening is a covered health care benefit in very few countries. Obtaining the full population-level benefit of lung cancer screening will require improved participation of already eligible persons (the grasp of screening) and improved eligibility criteria that more closely match up with the full spectrum of persons at risk (the reach of screening), irrespective of smoking history. We used the socio-ecological framework of health care to systematically review implementation barriers to lung cancer screening and discuss multilevel solutions. We also discussed guideline-concordant management of incidentally detected lung nodules as a complementary approach to early lung cancer detection that can extend the reach and strengthen the grasp of screening. Furthermore, we discussed ongoing efforts in Asia to explore the possibility of LDCT screening in populations in whom lung cancer risk is relatively independent of smoking. Finally, we summarized innovative technological solutions, including biomarker selection and artificial intelligence strategies, to improve the safety, effectiveness, and cost-effectiveness of lung cancer screening in diverse populations.

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EXPANDING THE REACH AND GRASP OF LUNG CANCER SCREENING

Lung Cancer Is Endemic

With an estimated annual global incidence of 2.2 million, 1.8 million annual deaths, and projections for a sequential increase in coming decades, lung cancer remains the oncologic public health challenge of this age.[1] Lung cancer was the most common cause of cancer deaths in men in 93 of 185 countries, and in women in 25 countries[1] and in all quintiles of the country-level global Socio-demographic Index.[2] In the United States, although the aggregate incidence of and mortality from lung cancer have sequentially reduced since the 1990s for men and the 2000s for women, the pattern of improvement is geographically heterogeneous.[3] Striking geographic disparities in per capita lung cancer statistics exist, exemplified by clusters of countries with static or rising incidence and mortality rates.[4]

In the United States, the aggregate 5-year survival with a lung cancer diagnosis is only 23% because most patients have advanced-stage disease at the time of diagnosis. Specifically, 40%-50% of patients have distant disease at diagnosis, with a 5-year survival of 7%, and 20%-30% have been diagnosed with regional disease, with a survival of approximately 30%. Only 20%-30% of patients are diagnosed with localized lung cancer when the 5-year survival is approximately 60%.[1] The aggregate 5-year survival of >90% for breast cancer, >60% for colorectal cancer, and >95% for prostate cancer can be partly attributed to the implementation of effective screening programs that promote early detection.[1] The relatively poor aggregate 5-year survival challenges us to do more to diagnose lung cancer at an early stage.

The Recent History of Low-Dose Computer Tomographic Lung Cancer Screening in a Nutshell

After the prospective observational Early Lung Cancer Action Project (ELCAP) cohort studies revealed that low-dose computer tomographic (LDCT) screening significantly redistributes lung cancer to an early stage at diagnosis,[5,6] the randomized controlled National Lung Screening Trial (NLST) corroborated the stage shift and revealed a 20% reduction in lung cancer–specific mortality and 7% reduction in all-cause mortality.[7] Initially published in 2011, the NLST led to the 2013 US Preventive Services Task Force (USPSTF) grade B recommendation, which made LDCT lung cancer

PRACTICAL APPLICATIONS

- Despite two large randomized controlled trials proving its efficacy in reducing lung cancer mortality, lung cancer screening by low-dose computer tomographic scanning has been poorly implemented, with fewer than 10% of eligible persons screened in the United States and no implementation in most countries.
- Expanding access to screening for currently eligible persons requires social policy-, organization-, provider-, and patient-level interventions.
- Eligibility criteria for screening also need to be optimized to better overlap with the persons who develop lung cancer.
- The global population of people who never smoke but develop lung cancer warrants exploration of screening approaches for people whose lung cancer risk is defined by other factors, besides smoking, as is being explored in East Asia.
- Rapidly emerging biomarker and artificial intelligence approaches have great potential to improve the safety, efficiency, and cost-effectiveness of screening but will need rigorous validation in diverse populations.

screening eligible for insurance coverage,[8] followed by the 2015 Medicare Coverage Decision that established annual LDCT lung cancer screening a covered health care benefit.[9] A gradual aggregate national redistribution of lung cancer to earlier stage at diagnosis has already become evident in the United States since 2015.[10]

Corroboration of the NLST findings by the Dutch-Belgian lung cancer screening trial (NELSON), which reported a 24% reduction in lung cancer–specific mortality in a smaller cohort, with a lower eligible age limit and less intense tobacco use history, led the USPSTF to relax screening eligibility criteria in 2021, lowering the age limit from 55 to 50 years and the cigarette smoking requirement from 30 to 20 pack-years.[11,12] The Medicare Coverage Decision of 2022 essentially adopted these changes (with an upper eligibility age limit of 77 years, rather than 80 years).[13] This is the good news.

The bad news is that lung cancer screening is proving to be a tremendous implementation challenge. By most estimates, fewer than 10% of eligible persons have participated in any lung cancer screening and a systematic review and meta-analysis of 21 studies reported adherence to subsequent screening cycles ranging from 46% to 69%, significantly lower than the 95% reported in the NLST.[14-16] However, in the first one million screened from 2015 to 2019 in the American College of Radiology (ACR) registry, adherence to annual screening was only 22.3%.[17,18] Furthermore, disparities in access have emerged. For example, there is a striking geographic mismatch between state-level per capita lung cancer mortality and location of ACR-registered screening facilities.[14,19] Of the top 10 states in the lung cancer incidence and mortality leaderboard, Kentucky is listed in the top for lung cancer screening implementation.[14] Indeed, the other nine states atop the incidence and mortality leaderboard are in the bottom half of the implementation leaderboard.[14,15] Very few countries have adopted LDCT screening as a covered health care benefit. Most countries in the European Union continue to evaluate the cost-effectiveness and feasibility of various implementation approaches.[20,21]

Implementation Challenges

Barriers to attaining the full population-level benefit of early lung cancer detection can be broadly categorized as factors that inhibit the full adoption of LDCT screening for currently eligible patients (which we refer to as the grasp of LDCT screening) and eligibility criteria limitations that prevent extension to the breadth of the population at risk (the reach of LDCT screening). Using the socioecological model of health care, factors that inhibit the grasp of lung cancer screening can be categorized into policy-, institution-, provider-, and patient-level barriers (Table 1). Because lung cancer in the United States is a disease associated with a relative socioeconomic disadvantage, the populations at greatest risk are particularly challenged by these barriers.

The US populations at greatest risk of lung cancer reside in the Mississippi Delta and the Appalachian Valley regions that include the preponderance of states that made the political decision to not expand Medicaid access under the Affordable Care Act (ACA), despite having higher proportions of uninsured and underinsured persons (public policy-level barriers).[14,15,22] These regions are largely rural, have fragmented health care delivery systems, and have the lowest density of ACR-accredited LDCT screening facilities (institutional-level barriers).[14,19] Regardless of the region, awareness of the value, risks and benefits of lung cancer screening among primary care providers, and various other specialists involved in implementing screening varies significantly (provider-level barriers).[23] Finally, persons eligible for lung cancer screening, that is, those with a history of tobacco use, are more likely to have a lower level of education and be from indigent and minoritized populations (person-level barriers).[24]

The implementation challenge is exacerbated by the triple-jump concept: Unlike other cancers for which screening is recommended (breast, cervical, colorectal), which identify

TABLE 1. Barriers and Solutions to Lung Cancer Screening Implementation Using the Socioecological Framework for Health Care

Level	Examples of Multilevel Barriers to the Reach and Grasp of Lung Cancer Screening in the United States, Solutions
Social policy	1. Health insurance coverage for lung cancer screening (a) USPSTF recommendations: 2013 and 2021. B recommendation created a pathway to insurance coverage for LDCT lung cancer screening in the United States; expanded eligibility criteria[8,12] (b) Medicare Coverage Decision: 2015 and 2022. Established lung cancer screening as a covered health care benefit; expanded coverage eligibility criteria mostly for persons 65 years or older[9,13] (c) Affordable Care Act: Eliminated co-pays for cancer screening tests, including LDCT lung cancer screening (d) Additional proposed solutions: (i) Provide health insurance coverage and consider co-pay elimination for screening-related downstream testing (ii) Extend benefits to persons in the 11 non-Medicaid expansion states[22] 2. Lack of quality standards Future solution: Establish performance benchmarks, for example, HEDIS measure for lung cancer screening.[42] 3. Social stigma related to lung cancer and smoking Public campaign to eliminate stigma associated with lung cancer.[54]
Institutional	1. Infrastructure Provision of low-dose CT screening facilities[14,19,43,44] 2. Financial structure for investment in screening facilities Assistance to build a business case for investment in early lung cancer detection infrastructure, for example, LungPLAN[45] 3. Processes (a) Candidate identification, shared decision making, feedback, promoting adherence to subsequent testing[46,47] (b) Screening team recruitment, engagement, and oversight[46,47] (c) Interdisciplinary interactivity[46,47] 4. Quality control and program effectiveness (i) Implementation structure: centralized *v* hybrid *v* decentralized[48-50] (ii) Implementation of tobacco control programs[43,46] (iii) Future: response to HEDIS measure[42]
Provider	1. Primary care provider level Awareness, engagement, support[43,46,47,53] 2. Radiologist level Support, proficiency, dedicated versus general radiology support[47] 3. Multidisciplinary specialist support Key clinician stakeholder engagement—pulmonologists, surgeons, medical and radiation oncologists, nurses, navigators; proficiency; dedication[43,46] 4. Clinician sensitivity Stigma, nihilism, cultural sensitivity[54] 5. Quality control. (i) Lung-RADS scoring system for radiologists[46,47] (ii) Future: response to HEDIS measure (primary care providers)[42]
Patient	1. Knowledge, attitudes about smoking, lung cancer, screening, health care 2. Nihilism[54] 3. Social networks and influence on beliefs and attitudes

Abbreviations: HEDIS, Healthcare Effectiveness Data and Information Set; LDCT, low-dose computer tomography; LungPLAN, Projecting Lung Assessment Needs; Lung-RADS, Lung CT Screening Reporting and Data System; USPSTF, US Preventive Services Task Force.

eligible populations solely on the basis of age (think of the long jump), participation in LDCT lung cancer screening requires determination of eligibility on the basis of age and smoking intensity (pack-year history) and quit duration (akin to the much more difficult triple jump). Indeed, when one factors in the additional structured requirements for documented shared decision making, smoking cessation counseling and (previously, but now abrogated) participation in a lung cancer screening registry to get reimbursed, lung cancer screening may be more analogous to a steeplechase. This complexity has contributed to both organization- and physician-level delays in adoption.

However, even if all eligible persons were to suddenly undergo lung cancer screening, the 2021 USPSTF eligibility criteria would still exclude a large proportion of patients who are diagnosed with lung cancer (Fig 1). In a regional cohort, of 1,858 patients with lung cancer, only 54% would have been deemed eligible for screening by the USPSTF 2021 criteria.[25] This includes 15% who never smoked, those younger than 50 years or older than 80 years, and the great preponderance of patients who either quit smoking more than 15 years earlier or develop lung cancer at lower levels of cigarette smoke exposure. Women and racial minorities, such as Black persons and Hawaiian Islanders, are at

higher risk of lung cancer at lower levels of cigarette use.[26] Indeed, when population-level race and sex-stratified lung cancer incidence are crossed with eligibility for LDCT screening (the incidence:eligibility ratio), striking differences according to race and sex become clearly evident.[27] These eligibility criteria limitations, which restrict the reach of lung cancer screening, also exacerbate preexisting race-based disparities in population-level lung cancer outcomes.[28-32] Hence, there exists the dual need to improve the implementation of lung cancer screening for those currently eligible and to improve selection criteria to accurately match the screened population to the disease population.

BUILDING A STRONGER NET: IMPROVING THE UPTAKE OF LUNG CANCER SCREENING

Building a stronger net for current lung cancer screening-eligible populations will require eliminating access barriers; improving the effectiveness of embedded tobacco cessation programs; and improving the adherence to subsequent testing recommendations, including subsequent screening tests throughout the period of eligibility. The socioecological model of health care can also be used to categorize interventions to strengthen the net (Table 1).

Policy-Level Interventions

Expansion of eligibility criteria. The USPSTF 2013 lung cancer screening eligibility criteria were derived from the NLST. It quickly became evident that the selection criteria needed to enrich a clinical trial population for persons at sufficiently high risk to prove the efficacy of LDCT screening were not necessarily optimal for selecting the full range of patients who develop lung cancer (Fig 1). By one estimate, only 20%-30% of the US population with lung cancer would have qualified for screening using the NLST eligibility criteria.[33] The USPSTF 2021 criteria modifications were designed to expand the reach of screening by lowering the age of eligibility and the intensity of tobacco exposure in the hope that this would narrow the inadvertent race- and sex-based access disparities, given that women and Black persons, two demographic populations that benefit especially well from LDCT screening,[11,28,32] are at risk of lung cancer at a young age and with less intense cigarette use.[34] However, lowering the age of eligibility from 55 to 50 years may not alleviate the race-based disparity as much as projected because of access barriers in the pre-Medicare age population that often lacks health insurance coverage.[35-40]

In addition to expanding the eligibility criteria, the 2022 Medicare Coverage Decision eliminated the requirement for participation in a defined registry and loosened the requirements for test ordering, conducting required shared decision making and smoking cessation counseling, thereby alleviating some of the organization- and provider-level barriers.[13] This should strengthen the grasp of screening among the eligible population (Table 1).

Expanding insurance coverage. The segments of the population most at risk of lung cancer also face greater challenges in accessing preventive care.[24,41] Large proportions of this population are either uninsured or underinsured (such as by Medicaid). The 11 non-Medicaid expansion states as of March 2023 (AL, FL, GA, KS, MS, NC, SC, TN, TX, WI, WY) are all in the top half of the US per capita lung cancer incidence and mortality leaderboard.[14,15,22] Most of the states also have greater than average proportions of socioeconomically disadvantaged persons who are most likely to lack employment-based health insurance. Insurance limitations also present an indirect barrier to access because of co-pays and costs associated with the diagnostic response to a positive screening test. Thus, additional policy-level interventions are needed to expand the reach and grasp of lung cancer screening, especially in the populations at greatest risk (Table 1).

Quality benchmarking. There are no existing institutional or provider quality measures for lung cancer screening, but with the support of the American Cancer Society and the American Lung Association, the National Committee for Quality Assurance has committed to developing a Healthcare Effectiveness Data and Information Set (HEDIS) measure for lung cancer screening.[42] This measure, which should become available by 2026, will incentivize health care organizations and primary care providers, the main gatekeepers to screening access, to engage in the implementation challenge.

Institution-Level Interventions

Provision of screening infrastructure. The infrastructure for lung cancer screening requires investments in facilities, equipment, and workforce.[43,44] Prevailing nihilism about lung cancer adversely influences the willingness to make these investments. However, for US institutions, the National Lung Cancer Roundtable and the ACR developed a customizable, user-friendly, financial management program, Projecting Lung Assessment Needs (LungPLAN), to help program managers make a business case to justify this investment by estimating the personalized return on investment relevant to unique aspects of the institution's service population.[45]

Successful lung cancer screening also relies on the development of processes to identify eligible candidates, invite them for the required shared decision making, and conduct tobacco cessation counseling for those who smoke. Investment in case management resources to communicate test results, development of infrastructure and processes for safe and effective decision making, and promotion of adherence to subsequent screening cycles are key features of high-functioning screening programs.[46,47] Because the

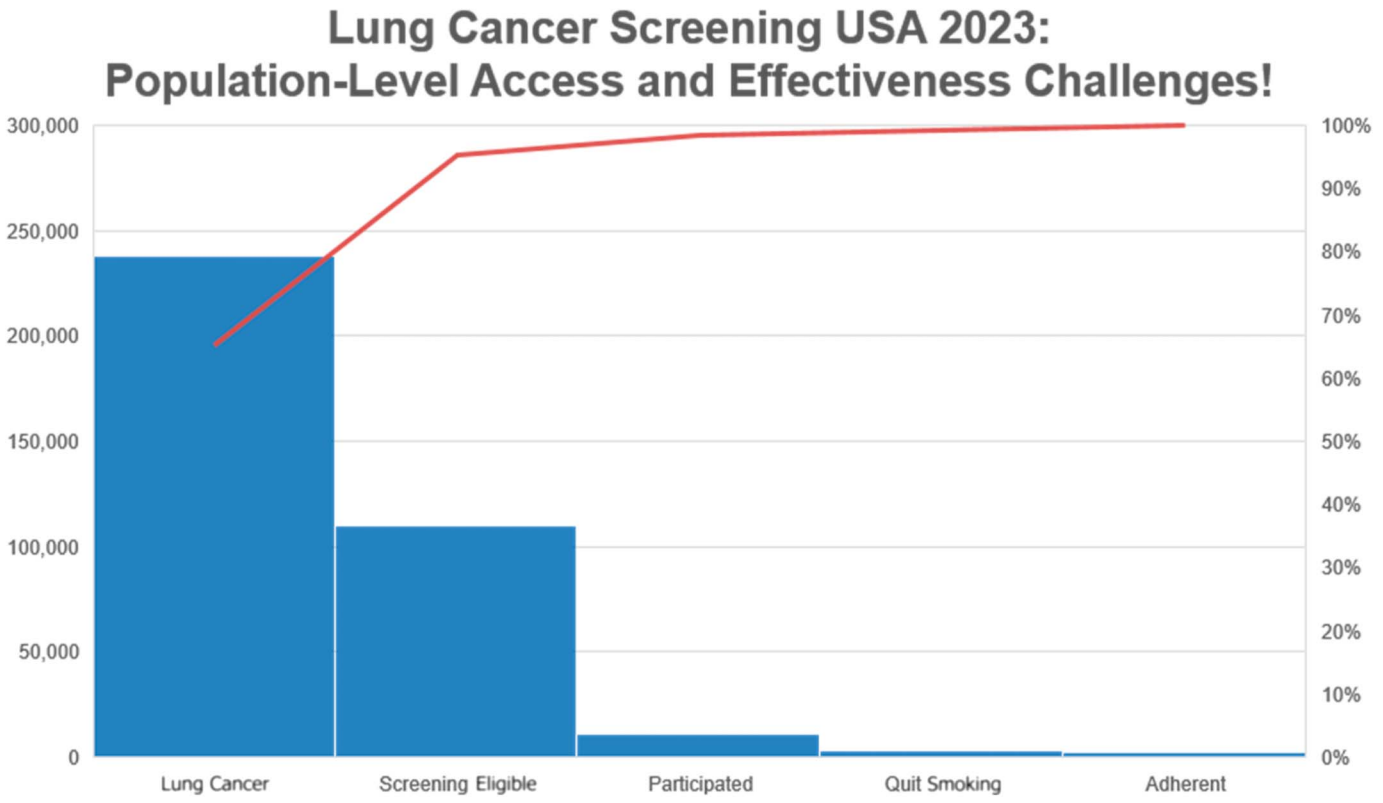

FIG 1. Estimated levels of attrition in access to lung cancer screening for patients with lung cancer, US population estimates. Estimates are based on projected 2023 US lung cancer statistics,[3] 50% screening eligibility among patients with lung cancer,[25] 10% screening participation rate,[14,15] 67% active smoking among screening participants,[25,17,18] and 22% adherence to subsequent screening cycles.[17,18]

greatest stage shift from LDCT comes with subsequent (incidence) screening cycles after the initial (prevalence) scan, the low adherence rates uncovered in the ACR registry highlight the need for a structured approach to developing lung cancer screening programs.[17,18]

Program structure. Lung cancer screening programs could be decentralized, hybrid, or centralized.[48] Decentralized models rely on individual referring providers to order screening tests and manage results. Centralized programs assume responsibility for the shared decision making, tobacco cessation management, communication of results, and promotion of adherence to subsequent management recommendations. In hybrid models, some elements of patient management are centralized while other aspects remain the responsibility of the referring provider. Adherence may be better in centralized programs.[49,50]

Complementary approaches to early lung cancer detection. Institutions can also develop processes to promote guideline-concordant management of incidentally detected lung nodules, an alternative pathway to early lung cancer detection. Such lung nodule programs are relatively agnostic to the smoking history and, therefore, bypass the implementation barriers raised by the triple-jump phenomenon.[25] They provide access to early detection to approximately five times more patients with lung cancer than LDCT screening programs, with greater demographic diversity, including more Black persons, more underinsured persons, and more patients who would not qualify for screening by the current criteria, including patients who have never smoked cigarettes.[25,51,52]

Provider-Level Interventions

Poor provider awareness of lung cancer screening availability, benefits, safety, and eligibility criteria represents another major barrier. After initial skepticism, the American Academy of Family Practice endorsed lung cancer screening in April 2021, as evidence consistently corroborated the safety and effectiveness in diverse care delivery environments.[53] Programs to avoid the stigma associated with lung cancer, including ongoing efforts to avoid the use of stigmatizing language (eg, emphasis on personhood and avoiding referring to persons who smoke as smokers), and eliminate clinician nihilism about lung cancer are likely to improve patient and provider engagement in promoting screening.[54] The multidisciplinary specialist interactions necessary for safe and effective implementation of screening can also be challenging.[46,47] Creating incentives

for the key clinicians to engage screening, such as the proposed HEDIS measure for primary care providers, will help.

Patient-Level Interventions

Campaigns to raise public awareness of the benefits, effectiveness, and safety of lung cancer screening, eliminating stigma, self-blame, and nihilism among persons whose lung cancer risk is defined by their smoking history, are important aspects of improving the grasp of lung cancer screening by increasing the likelihood of participation and adherence.[54] However, given the complexity of lung cancer screening and management of lung cancer, patients need the agency of supportive providers, care delivery systems, and social policies to fully derive the benefits of early lung cancer detection.

CASTING A WIDER NET IN ASIA: AN INTERNATIONAL CASE STUDY IN EXPANDING LUNG CANCER SCREENING ELIGIBILITY

Epidemiology and Risk Factors of Lung Cancer in Asia

Asia has the highest lung cancer disease burden, accounting for 58.5% of worldwide lung cancer incidence and 60.7% of worldwide lung cancer mortality.[55] In East Asia, the prevalence of lung cancer in people who do not smoke is high, including mostly women with lung cancer (Fig 2).[56] As a result, different screening strategies have been explored among Asian populations, which are tailored to the regional risk patterns. Significant resources have been spent on studying the increased risk of lung cancer among Asian populations who have no smoking history. Age, family history of lung cancer, history of other cancers, second-hand or passive smoking, and indoor and outdoor air pollution are likely important risk factors (Fig 3). In addition, exposure to occupational or environmental lung carcinogens, such as radon, asbestos, and silica, and pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), tuberculosis (TB) and pulmonary fibrosis, are other risk factors of lung cancer.

A study from India showed that adenocarcinoma histology is significantly associated with exposure to indoor air pollution (second-hand smoke or fuel used for cooking).[57] A meta-analysis also showed that history of pulmonary TB at a young age is an independent risk factor of lung cancer, regardless of smoking history.[58] In addition, a study group from Japan also showed that second-hand smoke exposure is a significant risk factor of lung cancer.[59] In South Korea, BMI was also regarded as a predictive factor for the development of lung cancer.[60] However, no other risk factors were exclusively found in patients with lung cancer who had never smoked. This suggests the diverse impact of the different risk factors and a potential contribution from genetic factors.

Risk prediction models for people who do not smoke. The accumulated evidence of increasing lung cancer risk in people who never smoked creates a need to identify populations whose high risk is independent of smoking, who might benefit from lung cancer screening. The PLCO2014 model is analogous to the PLCO2012 model but focused on US populations who never smoked. The prediction model has seven component variables—age, education, race, BMI, COPD, personal history of cancer, and family history of lung cancer. The AUC was 0.662, but these predictors were not reparameterized to people who do not smoke.[61] Warkentin et al developed a model from a UK cohort, which included age, sex, family history of lung cancer, personal cancer history, and lung function as predictors. The AUC was 0.694. Only age and sex were reliable predictors after reparameterization.[62]

Some models are focused on Asian people who do not smoke. Wu et al[63] developed a model on the basis of Taiwanese prospective cohort data. The predictors included age, sex, BMI, family history of lung cancer, pulmonary function (maximum mid-expiratory flow), and two serum biomarkers—alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA). The AUC of 0.806 looks good, but this needs further validation. Chien et al[64] developed the Taiwanese Never-Smoker Female—Simple Questionnaire (TNSF-SQ) model, which focuses on women. Unlike previous models, they also considered gene polymorphism in addition to common predictors. The reported AUC in this model was 0.714; education level, BMI, family history of lung cancer, and COPD were regarded as significant predictors. In a prospective lung cancer screening cohort study under the framework of the Cancer Screening Program in Urban China (CanSPUC), Guo et al[65] developed a risk prediction model for individuals who did not smoke. They identified several common risk factors including age, sex, family history of lung cancer, and history of TB. The study design and results of these prediction models are summarized in Table 2.

Current guidelines and recommendations on lung cancer screening eligibility in Western populations focus mainly on people who smoke. There are considerable differences between Asian and Western patients with lung cancer; lung cancer risk factors seem to differ between the two populations (Figs 2 and 3). The implementation of lung cancer screening should be tailored to the population at risk and to the resources available to local health care systems. To further continue the discussion, a steering committee was formed with 19 lung cancer experts from 11 Asian countries across different specialties to develop consensus on the most affordable and accessible lung cancer screening approaches for Asian populations.

In their consensus statement, the committee considered several risk factors that are related to Asian populations and

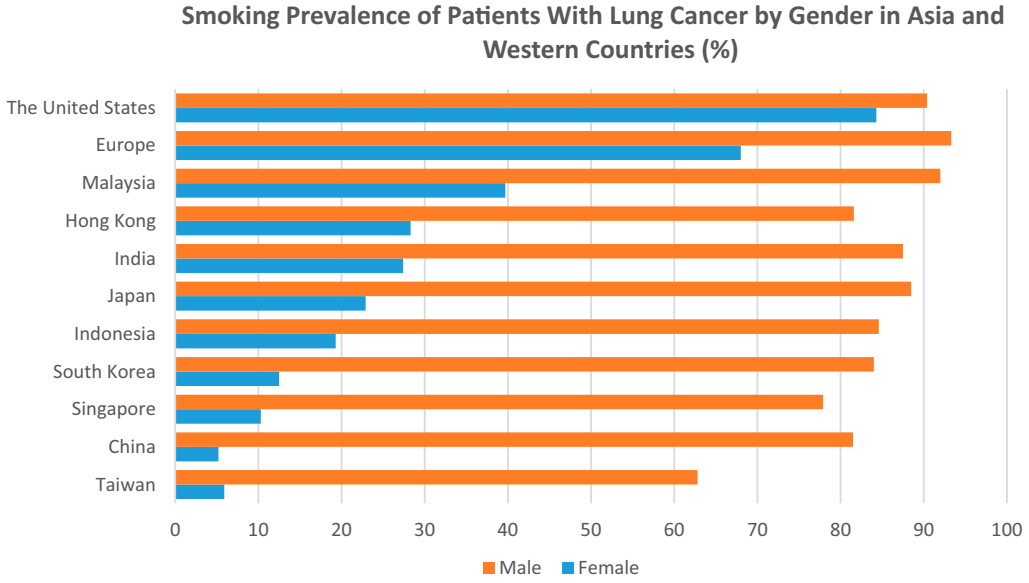

FIG 2. Smoking prevalence of patients with lung cancer by sex in Asian and Western countries.

recommended for high-risk individuals (defined by the smoking history, years since smoking cessation, and family history of cancer) to receive LDCT screening. For people who actively smoke or have quit smoking, they recommended that individuals age 50-75 years or with a smoking history of ≥20 pack-years or who quit smoking ≤15 years earlier should receive LDCT screening. For people who never smoked, individuals with a family history of lung cancer were also recommended for LDCT screening. The recommended frequency of LDCT screening was once a year for those with any screening-detected abnormality and persistent exposure to risk factors and a history of smoking ≥20 pack-years.

Lung cancer screening in people who do not smoke, but who have other risk factors. In the Taiwan Lung Cancer Screening in Never-Smoker Trial (TALENT), LDCT screening was conducted in people who never smoked, but who were, nevertheless, deemed to be at high risk for other reasons.[58] People age 55-75 years with one of the following risk factors were eligible: a family history of lung cancer in up to third-degree relatives, exposure to passive smoking, TB or COPD, cooking time-years index of 110 or greater (cooking index: 2/7 × days cooking by pan-frying, stir-frying, or deep-frying in 1 week × years cooking), and poor ventilation. The study revealed family history, especially in first-degree relatives, as the most prominent risk factor of lung cancer in people who

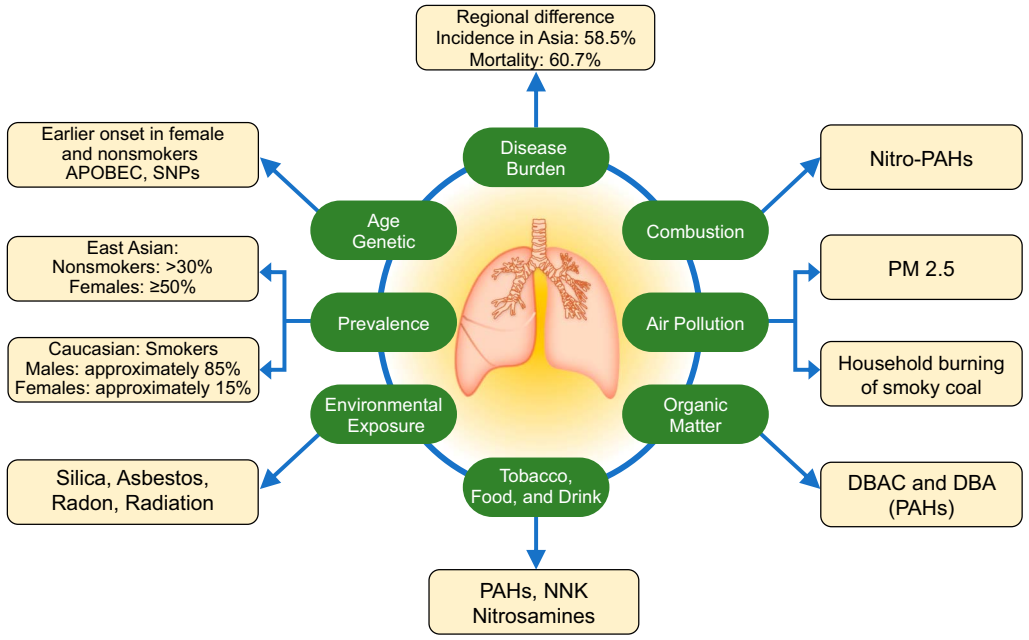

FIG 3. Risk factors of lung cancer in people who smoke and people who never smoked. APOBEC, apolipoprotein B mRNA editing enzyme catalytic polypeptide; DBA, dibenz[a,h]anthracene; DBAC, dibenz[a,h]acridine; NNK, nicotine-derived nitrosamine ketone; PAH, polycyclic aromatic hydrocarbon; PM, particulate matter; SNP, single nucleotide polymorphism.

TABLE 2. Descriptive Summary of Selected Lung Cancer Risk Prediction Models

Reference	Tammemägi et al[61]	Wu et al[63]	Warkentin et al[62]	Chien et al[64]	Guo et al[65]
Model name	PLCOall2014	MMIRA	Not named	TNSF-SQ	Not named
Cohort design	Prospective	Prospective	Prospective	Case-control, age-matched	Prospective
Population	American	Taiwanese	European	Taiwanese	Chinese
No. of people who had never smoked, lung cancers	N = 69,183; 110 lung cancers	N = 281,111; 525 lung cancers	N = 218,892; 165 lung cancers	5,343 controls, 1,341 lung cancer cases	N = 107,382; 158 lung cancers
Analyzing model	Logistic regression	Cox regression	Fine and Gray competing risk regression	Conditional logistic regression	Cox regression
AUC	0.662	0.806*	0.700, 0.694, and 0.722 for the 3-, 5-, and 7-year lung cancer risk, respectively	0.714	0.668, 0.678, and 0.685 for the 1-, 3-, and 5-year lung cancer risk, respectively
Predictors	Age, education, BMI, COPD, personal history of cancer, and family history of lung cancer	Age, sex, BMI, pulmonary function, family history of lung cancer, AFP, and CEA	Age, sex, personal cancer history, family history of lung cancer, and lung function	Education, BMI, COPD, and family history of lung cancer	Age, sex, education, family history of lung cancer or tuberculosis, and without a history of hyperlipidemia

Abbreviations: AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; COPD, chronic obstructive pulmonary disease.

did not smoke.[66] The first screening round of TALENT showed a lung cancer detection rate of 2.65%, which is higher than that in NLST and NELSON. Importantly, 96.5% of the patients were detected with stage 0-I lung cancer.[66]

On the basis of TALENT, the Government of Taiwan initiated biennial nationwide LDCT lung cancer screening for high-risk patients, including people age 50-74 years with a smoking history of >30 pack-year, who agree to quit smoking, and women age 45-74 years and men age 50-74 years who have never smoked but have a history of lung cancer in first-degree relatives. Among 22,451 screened individuals from July 1, 2022, to December 26, 2022, 36% were people who smoked, 60% did not smoke but had a family history of lung cancer, and 4% had both risk factors; 160 individuals had histologically confirmed lung cancer, of whom 86.3% were in stage 0-I.[67] The preliminary results were consistent with TALENT, supporting the feasibility of LDCT screening for lung cancer in people who never smoked, who, nevertheless, had other risk factors of lung cancer. This supports expanding the lung cancer screening eligibility criteria in East Asia, where the prevalence of lung cancer is relatively high in people who do not smoke.

SHARPENING OUR TOOLS: THE NEXT WAVE OF EARLY DETECTION TECHNOLOGIES

Early Detection Biomarkers

Other possible solutions to improve the grasp and reach of lung cancer screening lie in novel technologies that use blood, breath, and image-based biomarkers. A myriad of diagnostics companies and academic groups from around the world are pursuing the development of blood-based early detection tests that examine analytes in the blood, such as DNA, RNA, exosomes, proteomics, and circulating tumor cells. However, all blood-based assays face a common hurdle: the early-stage cancers are small and secrete only a small amount of analytes that are extremely difficult to detect in peripheral blood.

DNA assays are the farthest in clinical development and are designed to detect a variety of DNA characteristics, such as specific oncogenic mutations, methylation patterns, and fragmentation patterns (Table 3). Some DNA assays are being developed to screen for multiple types of cancers simultaneously (the so-called multicancer detection assays or MCDs). To our knowledge, to date, MCD data have been presented in the context of case-control studies and single-arm prospective studies in average-risk adults, as opposed to populations at high risk of certain cancers by virtue of some clinical or demographic feature other than age.

The two largest prospective studies of MCDs presented thus far are the DETECT-A study, using an older version of the MCD assay now being developed by Exact Sciences, and the PATHFINDER study, using the MCD assay developed by Grail.[68,69] DETECT-A screened 10,000 women between age 65 and 75 years, and PATHFINDER screened a little more than 6,600 people age 50-85 years. Both studies were designed to assess the feasibility of conducting MCD screening, rather than to evaluate clinical effectiveness. In DETECT-A, nine patients were diagnosed with lung cancer

TABLE 3. Selected DNA-Based Assays to Detect Early-Stage Lung Cancer

Author	Aspect of DNA Assessed	Multicancer *v* Lung Cancer Assay	Type of Study	Commercial Name of Assay (company[ies] involved)
Jamshidi et al[77] (CCGA substudy 1)	Multiple methods explored	Multicancer	Case-control	Galleri (Grail)
Liu et al[78] (CCGA substudy 2)	Methylation	Multicancer	Case-control	
Klein et al[79] (CCGA substudy 3)	Methylation	Multicancer	Case-control	
Schrag et al[69]	Methylation	Multicancer	Prospective single-arm study	
Cohen et al[80]	Specific mutations (and proteins)	Multicancer	Case-control	CancerSEEK (Thrive); now acquired and being reworked (Exact Sciences)
Lennon et al[68] (DETECT-A)	Specific mutations (and proteins)	Multicancer	Prospective single-arm study	
Cristiano et al[81]	Fragment size	Multicancer	Case-control	Delfi
Mathios et al[70]	Fragment size	Lung cancer	Case-control	
Chabon et al[82]	Specific mutations	Lung cancer	Case-control	Lung-CLiP
Liang et al[83]	Methylation	Lung cancer	Case-control	—
Nguyen et al[84] (K-DETEK)	Methylation and fragment size	Multicancer	Prospective single-arm study	SPOT-MAS (Gene Solutions)
Gao et al[85] (THUNDER)	Methylation	Multicancer	Case-control	ELSA-seek (Burning Rock Dx)
Wang et al[86]	Fragment size	Lung cancer	Case-control	—

on the basis of abnormal blood test signal, including one patient with stage I lung cancer and two patients with stage II lung cancer (the remaining six patients diagnosed with lung cancer had more advanced-stage disease). In PATHFINDER, one patient was diagnosed with advanced lung cancer on the basis of abnormal blood test signal. While these initial results have raised concern among some that MCD tests may be less adept at finding patients with early-stage cancer eligible for surgery, it is important to remember that the current understanding of MCD testing and how to best implement it is still nascent, and many additional much larger studies are ongoing and planned. In addition, the definitive metrics by which to view the successes of MCD testing should likely take into account all cancer subtypes diagnosed by this single test rather than thinking singly about each cancer. To guide the development of MCD assays and the metrics to compare them with other screening tests, the US National Cancer Institute is launching a new cooperative group called the Cancer Screening Research Network specifically to study MCD tests and assess for cancer-specific and overall survival effects via randomized clinical trials in larger populations.

Another approach, taken by Delfi Diagnostics, is to focus on the development of a circulating tumor DNA assay for lung cancer specifically, with the concept of using a blood-based assay to guide patients not currently involved in lung cancer screening toward LDCT imaging on the basis of a high-risk blood test result. Thus far, only retrospective case-control data have been published using this assay, but there are ongoing prospective trials accruing.[70]

Because lung cancers are located proximally to exhaled breath emitted from the lungs, analysis of volatile organic compounds contained in exhaled breath is also attractive to technology developers looking to discover better ways to diagnose early-stage lung cancer.[71,72] While many mass spectrometry-based platforms have been described in this space, variables, such as comorbidities, diet, recent gum use, and recent smoke inhalation, can affect the reliability of the assay.[73,74] Interestingly, some breeds of dogs are also trained to detect the smell of lung cancer. Yet, none of these breath-based methods have been tested in large-scale clinical trials.[75,76] Details of selected publications on DNA-based assays in the development of early-stage lung cancer detection are provided in Table 3.

Radiomics and Artificial Intelligence

Finally, machine learning and artificial intelligence techniques can be applied to imaging studies to assist with lung cancer detection. Some machine learning approaches have focused on computer-aided diagnostics, which try to ensure that radiologists notice worrisome lung nodules while reading films.[87,88] A recent publication about a different application of machine learning by Mikhael et al describes the Sybil algorithm, which takes the entire volume of an LDCT scan and uses the data to predict the risk of future lung cancer, extending 6 years into the future.[89] Trained on thousands of scans from the NLST cohort, Sybil was then validated on independent LDCT cohorts from Mass General Hospital (standard US-based lung cancer screening in people with a positive tobacco history) as well as from Chang Gung Hospital

in Taiwan (consisting of people with both positive and negative tobacco history). The Sybil model can accurately predict future lung cancer risk in both of these diverse validation cohorts, raising the possibility that such a tool could be used to select people who are at the highest risk of lung cancer in future, regardless of smoking history. This is a distinct strategy from some of the clinical risk models discussed earlier, which focus on gathering known clinical and demographic risk factors for each patient. Sybil does not require clinical or demographic information, but likely integrates these and many other features visible to the computer through patterns in the computed tomography images to provide a personalized risk assessment founded on pattern recognition from thousands of previous scans. Further clinical validation in prospective studies is needed to determine the optimal strategies to implement deep learning models, such as Sybil, in lung cancer screening. In addition, as Sybil and other radiology-based deep learning models are developed and implemented, significant care will be required to ensure that the models have been tested in diverse populations and that model performance across a variety of technical image acquisition parameters has been studied.[90,91]

SUMMARY

Evidence from two large randomized trials, the NLST and NELSON, demonstrated that LDCT screening of persons at high risk of lung cancer significantly reduced lung cancer mortality. This proof of principle that lung cancer screening saves lives now challenges us to implement safe, effective, and equitable screening programs that will provide the benefit of early detection to the diverse global population of patients with lung cancer, at a cost that is acceptable to policymakers. Innovation in optimizing selection criteria (such as risk calculators); implementing supplementary pathways for early detection (such as programs to promote guideline-concordant management of incidentally detected lung nodules); expanding eligibility criteria to include additional risk factors (such as family history and genetic associations); and leveraging technology to enhance the efficiency, safety, and cost-effectiveness of screening (such as DNA-based biomarkers and artificial intelligence algorithms that can extend the value of digital imaging beyond the limitations of the human eye) are exciting solutions currently being explored. These relatively new fields of research and commercial endeavor are likely to accelerate progress into a world in which few people die of lung cancer within the next couple of decades.

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A Brain, A Heart, and the Courage: Balancing Benefit and Toxicity of Immunotherapy in Melanoma

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Overview

The overall survival of advanced melanoma has improved dramatically. Immunotherapies, specifically checkpoint inhibitors, have played a large role in this improvement. These agents have also shown benefit in the adjuvant setting, are approved for treatment of resected stage II, III, and IV melanoma, and play an evolving role in the neoadjuvant setting. Although generally well tolerated, immune-related adverse events occur and can be severe. Here we focus on some severe and potentially long term toxicities, including cardiovascular and neurologic toxicities. Our understanding of the acute and long-term toxicities of immune checkpoint inhibitors continues to evolve. Oncologists must continue to balance cancer risk and treatment-related toxicities.

INTRODUCTION

The treatment and prognosis of melanoma continues to evolve. Over the past decade, the overall survival (OS) rate of advanced unresectable disease has improved from approximately 20% at 5 years to as high as 50%.[1-3] While immunotherapies have always played a role in the treatment of melanoma, the advent of immune checkpoint inhibitors (ICIs) has increased the percentage of patients surviving and duration of survival. ICIs have come with familiar toxicities (vitiligo and thyroid dysfunction) seen with other immunotherapies such as high-dose interleukin-2. However, toxicities such as hypophysitis and other immune-related adverse events (IrAEs) are distinct. IrAEs require prompt and expert management with treatment holds and immunosuppression, typically with high-dose glucocorticoids. Although most of these toxicities have been considered acute, with the growing number of patients treated with ICI and surviving with prolonged follow-up, there is an evolving understanding of both acute and long-term IrAEs. As these agents are being investigated and used in earlier-stage disease, the balancing of toxicity with cancer risk continues to be a challenge. We propose that this should be performed on a case-by-case basis and a thorough discussion should occur with each patient, especially in the adjuvant setting.

IMMUNE CHECKPOINT INHIBITORS

ICI refers to therapeutic agents that affect the positive or negative regulatory markers of the immune system (Fig 1). Currently, all anticancer agents approved by the US Food and Drug Administration are antagonistic antibodies against negative regulators of the immune system. In melanoma, the ICI agents currently approved in the metastatic setting include ipilimumab (anti–cytotoxic T-lymphocyte–associated protein [CTLA]-4), nivolumab and pembrolizumab (anti–PD-1), atezolizumab (anti–PD-L1), and relatlimab (anti-LAG3). These agents are approved as single agents or in combination in advanced disease; ipilimumab, nivolumab, and pembrolizumab are approved as monotherapy for the adjuvant treatment of resected stage III and IV melanoma. Most recently, pembrolizumab was approved for the treatment of resected stage II melanoma. Ipilimumab has demonstrated an OS and recurrence-free survival (RFS) benefit in resected stage III melanoma; however, at higher doses (eg, 10 mg/kg), there is associated severe toxicity.[4,5] For anti–PD-1 agents in the adjuvant setting, the known benefit at this time is RFS; OS was similar for nivolumab compared with ipilimumab, and data remain immature for pembrolizumab in stage II and III.[6-8] Recent preliminary data support a role for anti–PD-1 in the neoadjuvant setting.[9] Duration of ICI treatment in melanoma is determined by treatment intent, tolerance, and response. In the advanced unresectable setting, treatment typically continues until maximal benefit or maximal toxicity, with discontinuation considered at completion of 2 years of treatment. In the adjuvant setting, treatment is for 1 year in the absence of progression and unacceptable toxicities.

IrAEs are attributed to dysregulation of the immune system, resulting in immune attack on normal organs/tissues, as CTLA-4 and PD-1 play a role in immune self-

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PRACTICAL APPLICATIONS

- Immune checkpoint inhibitors (ICIs) carry potential acute and long-term toxicities.
- Cardiac and neurologic immune-related adverse events can be life-threatening and are important to recognize and manage promptly in consultation with specialists.
- Benefits of ICI therapy must be weighed against the risks, and shared decision making between the patient and the physician is recommended.

tolerance. These can be unpredictable, can affect a broad range of organs from the skin to the brain, and can range from mild to fatal.[10] The incidence, timing, frequency, and severity of IrAEs vary according to the ICI agent, dose, and if used alone or in combination.[11-13] The highest-risk regimen is the combination of CTLA-4 and PD-1 therapies with the greatest incidence in the first 3 months of treatment. The mechanisms of IrAEs continue to be investigated and overall are poorly understood. Given the variety of inflammatory cell infiltrates seen histologically, multiple mechanisms are likely.[14] Although there are data to suggest a correlation between the incidence of IrAEs and antitumor efficacy, severe toxicities are not required for benefit and may affect outcomes.[15] Acute management includes holding ICI (temporarily or permanently depending on the IrAE(s)), glucocorticoid administration, and supportive measures. Additional immunosuppressive agents may be needed depending on IrAE severity and response/control achieved with steroids. The rate of fatal toxicities is approximately 1.2%.[16] Typically, IrAEs occur during active treatment; however, there is growing understanding that the risk of toxicities continues after active dosing.[17-24] The exact duration of toxicity risk after ICI cessation is unclear but can persist for at least several months to possibly years. In addition, there is a possibility of permanent end-organ damage—best understood with ICI-induced endocrinopathies. As our understanding of the mechanisms of IrAEs increases, our understanding of their management will also.

Consideration of several factors is integral to the decision to treat with ICI: patient factors including comorbidities, functional status, pre-existing immune alteration (autoimmune conditions, transplant), and disease factors such as stage and extent of disease and potential ICI benefit. Areas of ongoing need and research include prediction models that not only predict those patients who will benefit from ICI but also those at greatest risk of toxicities. Here, we discuss some severe and long-term IrAEs to consider in the decision to treat patients with ICI. A thorough discussion of potential risks and benefits and shared decision making with the patient and the physician are recommended.

A HEART: CARDIAC TOXICITY OF IMMUNOTHERAPY

ICIs are associated with acute and chronic cardiovascular toxicities.[14,25] Acute events include myocarditis, pericarditis, vasculitis, arrhythmia, and other forms of cardiomyopathy, including Takotsubo cardiomyopathy (Fig 2).[26] Recently, more chronic issues after ICI therapy have been observed, including late-onset heart failure and atherosclerotic cardiovascular disease.[27]

ICI myocarditis is a relatively infrequent but potentially fatal IrAE, particularly among patients receiving combination ICI therapy. The incidence of ICI myocarditis has been reported to be between 0.27% and 1.14%.[28,29] However, mortality can be as high as 50%.[30] The main risk factor is combination ICI therapy. In the VigiBase, a WHO pharmacovigilance database, the combination of anti–CTLA-4 and anti–PD-1/PD-L1 antibodies was associated with a more than four-fold higher risk than either monotherapy (reporting odds ratio [OR], 4.31; 95% CI, 2.86 to 6.38).[30] Importantly, there has been an increased reporting of ICI myocarditis in the past decade, consistent with increased ICI use for cancer therapy and increased recognition of this new syndrome.[31,32] Although female sex has been identified as a risk factor for ICI myocarditis in some studies, case series of ICI myocarditis suggest higher prevalence in men.[33,34] Other risk factors for ICI myocarditis are still under investigation.

ICI myocarditis often presents with nonspecific symptoms, including chest pain, shortness of breath, palpitations, lightheadedness, and generalized weakness.[35,36] Acute coronary syndrome, pulmonary embolism, and alternative diagnoses must be ruled out. Patients with ICI myocarditis can have pre-existing coronary artery disease, which may delay or confound the diagnosis and portend a poorer outcome.[37] The median time to onset was 30 days (interquartile range, 18-60 days) after initial exposure to ICIs.[30] ICI myocarditis can occur simultaneously with other IrAEs, especially myositis. Up to one third of patients can have skeletal muscle symptoms, such as myalgia, diplopia, muscle weakness, and a myasthenia-gravis (MG)–like syndrome.[36] Importantly, severe myositis and MG-like cases can be associated with ventilatory failure because of respiratory muscle weakness. Conversely, patients who present with myositis must also be evaluated for myocarditis.[38] ICI myocarditis can be proarrhythmogenic, even when left ventricular function remains normal. Ventricular arrythmia, complete heart block, and low-voltage and pathologic Q waves are serious electrocardiographic changes and are associated with mortality.[39] On the other hand, even fulminant cases of ICI myocarditis can have preserved cardiac function. Pharmacologic and genetic models of ICI myocarditis have been generated, which recapitulate the clinical and pathologic syndrome seen in humans. These models have provided insights into

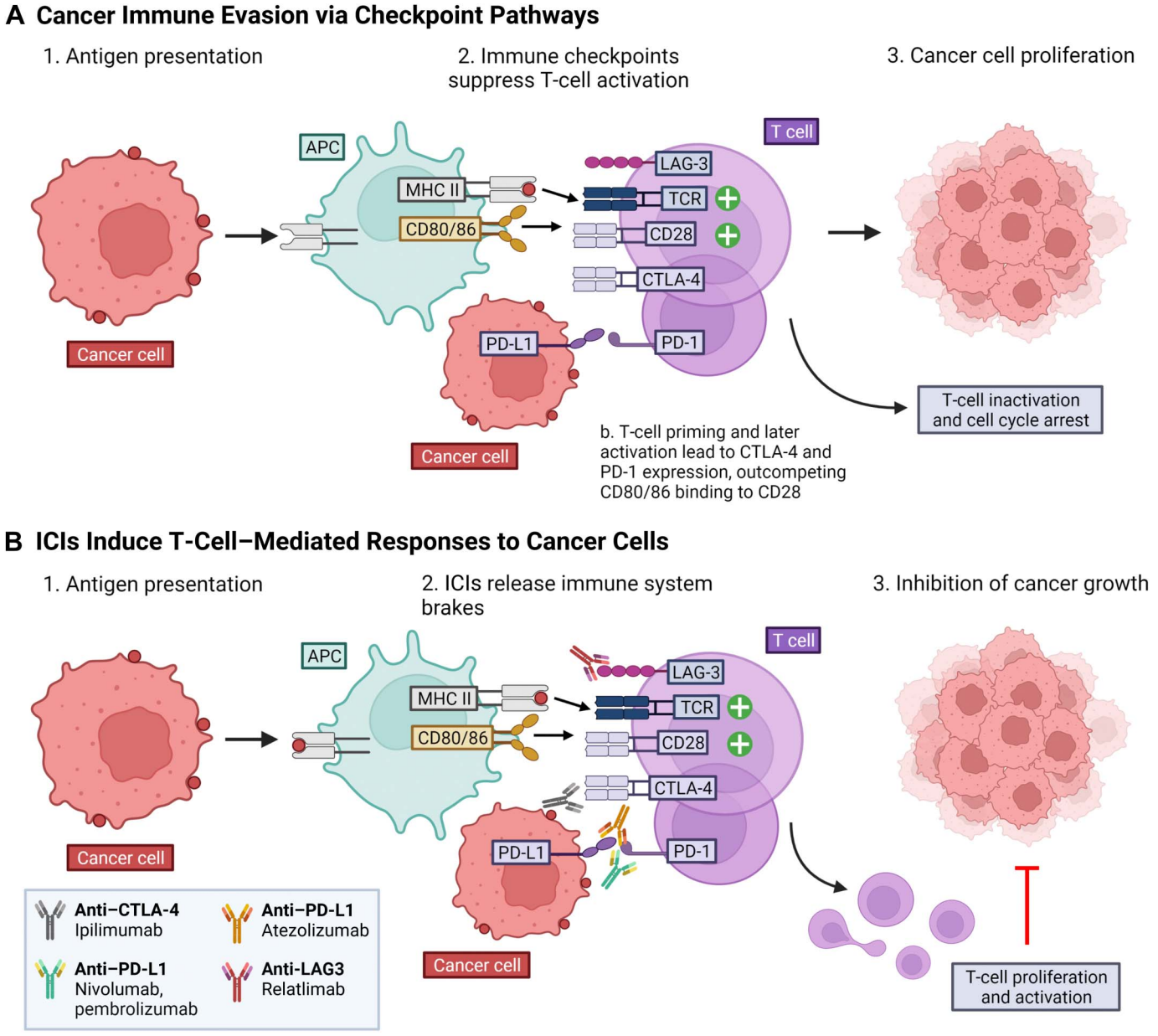

FIG 1. (A) Mechanism of immune evasion by tumor cells. (B) Mechanism of ICIs. The inset box indicates ICIs currently approved for melanoma. APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ICI, immune checkpoint inhibitor; LAG, lymphocyte activation gene; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor. Created with BioRender.com.

underlying pathophysiology and diagnostic and therapeutic options for patients.[40] For example, in a genetic model, activated cytotoxic CD8+ T cells targeting alpha-myosin are necessary for the development of myocarditis.[28,40-42] In addition, both Janus kinase inhibition and CTLA-4 immunoglobulin fusion protein ameliorate the disease in mice, providing biologically plausible treatment options in patients.[43]

Diagnosis of ICI myocarditis requires clinical vigilance and comprehensive evaluation, including exclusion of other cardiac diagnoses. Endomyocardial biopsy yields the most definitive diagnosis by showing infiltration of immune cells coupled with cardiomyocyte death.[44,45] Diagnosis may be alternatively made by supporting evidence and advanced cardiac imaging, including cardiac magnetic resonance (CMR).[37] Modified Lake-Louise criteria of CMR for myocarditis have been proposed to diagnose other forms of acute myocarditis (such as viral myocarditis).[46] These criteria include T1/T2 mapping and the presence of late gadolinium enhancement (LGE). However, in biopsy-proven ICI myocarditis, only 35% of patients had LGE and 26% had

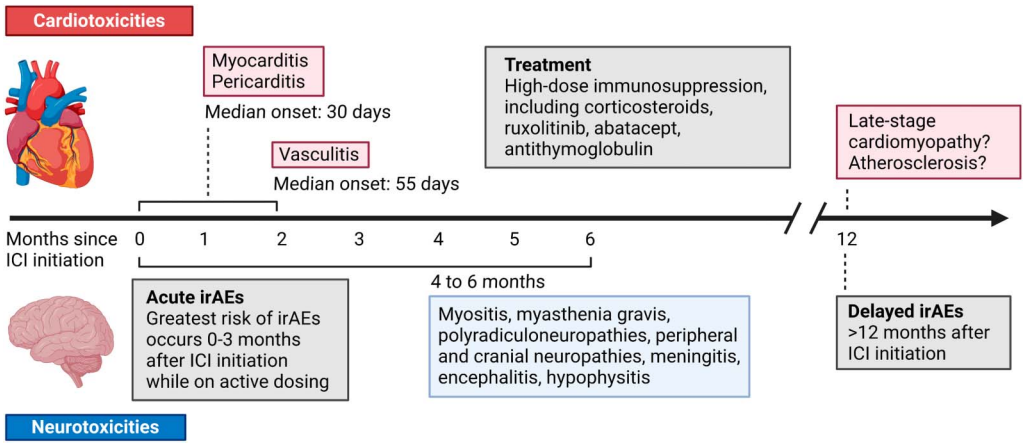

FIG 2. Toxicities timeline. ICI, immune checkpoint inhibitor; IrAE, immune-related adverse event.

elevated T2-weighted signal consistent with myocardial edema.[47] The addition of tissue characterization with T1 and T2 mapping only modestly improved diagnostic sensitivity for ICI myocarditis. In a retrospective study of clinically or pathologically diagnosed ICI myocarditis, only 48% of patients met both main T1 and T2 criteria of modified Lake-Louise criteria.[48] In addition, this study did not include relevant controls such as baseline abnormalities. In separate studies, 10%-30% of patients have abnormal CMR images even before ICI administration.[49,50] These results suggest the need for additional research to identify novel imaging tools for the diagnosis of ICI myocarditis and myocarditis.

When ICI myocarditis is suspected, ICI therapy should be held; prompt immunosuppression is recommended.[14,25] Patients should be hospitalized for diagnostic workup and telemetry monitoring. Most groups recommend high-dose corticosteroids (1-2 mg/kg of methylprednisolone every 12-24 hours) within 24 hours of the presentation. Other groups have advocated for higher doses of corticosteroids (methylprednisolone 500-1,000 mg once daily for 3-5 days) followed by 1-2 mg/kg methylprednisolone every 12-24 hours.[25] After clinical improvement, intravenous corticosteroids can be switched to an oral formulation and slowly tapered for at least 4-6 weeks. Of note, corticosteroid-resistant/corticosteroid-dependent myocarditis occurs in up to 60% of patients.[51] Case series describe multiple options of second-line immunosuppressants. Recently, the combination of ruxolitinib and abatacept has been shown to significantly reduce the mortality from 60% to 3% in patients with severe ICI myocarditis with respiratory muscle failure.[43] Although plasmapheresis has been used in case series, given the long half-life of ICIs, plasmapheresis may only remove ICIs in blood, but residual ICIs still bind with target receptors, maintaining a high receptor occupancy and proinflammatory effect.[52] Tumor necrosis factor (TNF)-alpha inhibitors are generally not recommended because of risks associated with heart failure.[53]

Baseline assessment before ICI initiation and surveillance on ICI treatment for myocarditis are other areas of investigation. Many cardiology groups recommend a baseline troponin test and electrocardiogram before ICI therapy.[25,36] However, the effectiveness of routine surveillance after initiation of ICI remains controversial. In the post hoc analysis of the JAVELIN Renal 101 Trial, a frontline study in kidney cancer, 20.4% of patients receiving ICI had an abnormal Troponin T level at baseline, whereas 13% who had a normal troponin T level at baseline developed higher levels during ICI therapy. However, in the ICI treatment group, only six myocarditis cases (of 434 patients—1.4%) were adjudicated as probable or definite ICI myocarditis.[54] Troponin level at baseline among patients with cancer can be elevated because of multiple factors including chronic kidney disease.[25,55] Additional studies are needed for more specific biomarkers associated with myocarditis.

ICI therapy can induce pericarditis (reporting OR, 3.8; 95% CI, 3.08 to 4.62) and vasculitis (reporting OR, 1.56; 95% CI, 1.25 to 1.94) (Fig 2).[30,56] The median time to onset is between 30 and 55 days, similar to ICI myocarditis.[30] Patients with pericarditis may present with sharp, pleuritic chest pain, aggravated by lying down or deep breathing and relieved by leaning forward. ICI pericarditis and pericardial effusion can result in cardiac tamponade, leading to heart failure and cardiogenic shock. The management of ICI pericarditis also includes ICI cessation and corticosteroid initiation.[25] Colchicine or nonsteroidal anti-inflammatory drugs may be added as an adjuvant treatment.[57] ICI vasculitis is overall rare but can occur in small and large vessels. Temporal arteritis, a commonly reported ICI vasculitis, can involve the aorta and its branches (reporting OR, 12.99; 95% CI, 8.12 to 20.77).[30] Patients can present with headache, monocular visual loss, diplopia, jaw claudication, and asymmetric blood pressure/pulses. The definitive diagnosis needs a temporal artery biopsy.[26] Visual loss related to ICI temporal arteritis can reach 27.8%.[30]

While much of the above discussion is regarding anti–CTLA-4 and anti–PD-1/PD-L1 therapies, recent data suggest increased risk of myocarditis in patients receiving other combinations including relatlimab and nivolumab, which carries a slightly higher incidence of ICI myocarditis (1.7%) compared with nivolumab monotherapy (0.6%).[58,59] Another consideration is the combination of ICIs with cytotoxic chemotherapy or targeted therapies, which may carry intrinsic cardiovascular risks.[60,61] In the JAVELIN Renal 101 Trial, patients were randomly assigned to avelumab (anti–PD-L1) with axitinib (anti-VEGFR inhibitor) versus single-agent sunitinib (anti-VEGFR inhibitor) alone. 7.1% of patients receiving avelumab and axitinib had major cardiovascular events, including cardiac death, myocarditis, myocardial infarction, and cerebral stroke, compared with 3.9% in the sunitinib arm.[54] Further investigation is important to understand and manage toxicities seen with ICI combinations and in ICI combined with different cancer therapies.

As patient survival improves, chronic cardiovascular toxicities, such as smoldering myocarditis, late-onset heart failure, and accelerated atherosclerosis after ICI therapy, have become emerging issues.[27] Currently, there is limited understanding about these more chronic cases. It is reasonable to consider that chronic sequalae of ICI myocarditis may evolve to cardiomyopathy.[24] In a single-center study, patients receiving ICIs had a three-fold greater risk of myocardial infarction, coronary intervention, and ischemic stroke compared with patients with cancer not treated with ICIs, with corresponding increases in aortic plaque volumes.[62] Preclinical mouse models deleting the gene for PD-1 (*Pdcd1*$^{-/-}$) or PD-L1/-L2 (*Pd-l1/2*$^{-/-}$) also showed accelerated atherosclerosis and enhanced inflammatory infiltrations in the arterial plaques.[63,64] The association between atherosclerotic disease and ICI needs to be validated in larger cohorts, but if these findings are true, these would have significant implications for the growing number of cancer survivors treated with ICI and support optimization of cardiovascular risk factors.[24] An ABCDE algorithm has been proposed to prevent cardiovascular disease in patients with breast and prostate cancers and was accepted by the National Comprehensive Cancer Network (NCCN) guideline committee for all cancer survivors.[65-67] A similar approach could be considered in patients receiving ICI. Given that recent studies implicate atherosclerosis as a late complication of ICI therapy, pre-existing cardiovascular diseases and risk factors, such as hypertension, diabetes, hyperlipidemia, and smoking, should be identified and managed.[25]

A BRAIN: NEUROTOXICITY OF IMMUNOTHERAPY

Neurologic immunotherapy-related adverse events (NirAEs) are becoming more common as an increasing number of cancers are treated with ICIs. Neurologic complications include a wide range of conditions, affecting virtually every level of the nervous system including the muscle, neuromuscular junction, peripheral nerve, plexus, spinal cord, and brain (Fig 2). To further complicate matters, more than one level of the nervous system may be implicated (eg, myasthenia gravis can occur with myositis), and although NirAEs can resemble the classical neurologic syndromes, they often have other features (eg, elevated CSF WBCs in what otherwise resembles classical Guillain-Barre Syndrome [GBS]) that may complicate the diagnosis. This is a poorly studied area, and there are no clinical trials regarding optimal treatment and limited studies regarding pathogenesis.

NirAEs occur in 1.5%-7.2% of patients treated with ICIs.[68-70] A large retrospective national database examined over 50,000 reports of immunotherapy-related adverse events, and 7.2% were NirAEs.[71] Stage III and IV melanoma incidence in the United States is estimated to be 1.5 and 0.9 per 100,000 persons, respectively; assuming that all these patients are treated with ICIs, approximately 150-600 patients with newly diagnosed melanoma per year will have NirAEs.[72,73] With stage II melanoma having an incidence of 2.4 per 100,000 persons, extending ICI therapy to this group doubles this number to approximately 300-1,200.[74] With the rapidly expanding use of ICIs, this emphasizes the need for oncologists to recognize, diagnose, and treat these syndromes quickly and the importance of consultation with neurologists.[75]

The major risk factors for NirAEs include the use of anti–CTLA-4 antibody alone or in combination with anti–PD-1/PD-L1 antibodies. One study found that the frequency of severe NirAEs was 2.8% in combination therapy, 2.2% with anti–CTLA-4, and 1% with anti–PD-1/PD-L1 therapy.[68] Among adverse events related to the recently approved relatlimab, no NirAEs were found other than hypophysitis.[58] History of an NirAE is also a risk factor. Age >60 years also confers a higher incidence of fatal NirAEs[71]; there is a suggestion that specific NirAEs are associated with specific ICIs. For example, myasthenia gravis tends to occur more often after anti–PD-1/PD-L1 treatment, whereas meningitis tends to occur more frequently after anti–CTLA-4 monotherapy. Peripheral neuropathy may occur more frequently in patients with melanoma.[76] Preexisting active neurologic diseases or neurologic autoimmune diseases predispose patients to NirAEs. ICI use should be considered carefully in patients with neurologic paraneoplastic syndromes,[77] a history of or active multiple sclerosis,[78] myasthenia gravis,[79] or amyotrophic lateral sclerosis.[80] Hence, we recommend avoiding ICIs in patients with active or severe neurologic disease and particularly neurologic autoimmune disease. Laboratory parameters have not been found to predict risk for NirAEs. One study found that patients with the *HLA-B*27:05* allele may be at an increased risk for autoimmune encephalitis triggered by atezolizumab.[81] Thus far, a specific HLA

subtype, single-nucleotide polymorphism (SNP), or other biomarker has not been found to predispose to or predict NirAEs.

The pathophysiology of NirAEs is unknown; however, both humoral and cell-mediated autoimmune mechanisms are proposed. In murine models, deletion of CTLA-4 on follicular T-helper and T-regulatory cells resulted in defective suppression of B-cell–mediated autoimmunity.[82] In another preclinical study, CTLA-4 blockade induced a CNS paraneoplastic syndrome.[83] Meanwhile, PD-1 knockout mice were used in an experimental autoimmune encephalomyelitis model and showed the expected proliferation of CNS-derived T-cell lymphocytes.[84] Nerve and muscle biopsies are rarely performed on patients with NirAEs, often because of fulminant onset and feasibility, which further limits our understanding. As pathogenic mechanisms of NirAEs are further researched, rational treatments for NirAEs will emerge.

The most common NirAEs are myositis, myasthenia gravis or other neuromuscular junction syndromes, polyradiculoneuropathies (which include GBS and other variants) and peripheral neuropathies, cranial neuropathies, meningitis, encephalitis, and hypophysitis (Table 1). The very rare neurologic paraneoplastic syndromes, such as limbic encephalitis, may occur after ICI therapy, but there are few data.[87] In general, NirAEs are very complex, difficult to recognize or diagnose, may result in permanent deficits even with prompt treatment, and require involving a neurologist as soon as possible, ideally one familiar with ICI toxicities.

There are several points about possible NirAEs that we emphasize here.

- Patients have multiple potential causes of neurologic signs/symptoms. Melanoma, as well as other tumors, can metastasize to the CNS causing neurologic symptoms. Since melanoma can metastasize to virtually any organ, it makes it very difficult to determine whether a new neurologic sign/symptom is due to an ICI toxicity or damage from another cause. Patients might have had previous therapies (targeted therapy, radiation, or surgery) that may have caused neurologic side effects. Concomitant medications, for example, corticosteroids, may induce a severe myopathy, further complicating assessment.
- The temporal relationship between the initiation of ICI and the onset of neurologic symptoms/signs can be long. Most NirAEs tend to appear within 4-6 months of initiation of ICIs. Currently, to be considered related to immunotherapy, they should generally occur within 12 months of the last infusion.[88] The occurrence of a concomitant non-NirAE and/or a robust tumor response may correlate with ICI neurotoxicity.[89]
- Consult a neurologist early and urgently if possible. Even experienced neurologists in major cancer centers find these disorders to be complex at least in part because many involve multiple areas of the nervous system (eg, muscle, neuromuscular junction, etc) at once. Shortness of breath or ventilatory issues, facial or bulbar symptoms, and ascending weakness require emergent evaluations.
- Many NirAEs are overlapping syndromes. The classifications listed in Table 1 are descriptive but not definitive. There can be a collection of symptoms and findings from several classical neurologic syndromes that may defy previous definitions. NirAEs can have several features that are atypical for a non-ICI–related GBS, for example. Non-ICI–related GBS commonly has an albuminocytologic dissociation, whereas the ICI-mediated counterpart commonly has CSF pleocytosis.[85]

Diagnostic features, key findings, and treatment recommendations are summarized in Table 2 to reflect the consensus recommendations of the NCCN, Society for Immunotherapy of Cancer, and ASCO.[14,92,93] Corticosteroids are usually used first starting at high doses for 2 weeks followed by a taper over no <4 weeks to avoid rebound of IrAEs. In many cases, these patients require hospitalization and intravenous steroids are used in conjunction with close monitoring. Corticosteroid-refractory cases are not uncommon and may require addition of other agents; discussion with a neurologist and consideration of other immunosuppressants is prudent. These include intravenous immunoglobulin, plasmapheresis (plasma exchange), rituximab (RTX), or oral immunosuppressants such as mycophenolate or azathioprine.[91] In some case reports, RTX been found to be useful for refractory cases of MG.[94] These are based on case reports or small case series and experience in treating the corresponding non-ICI–induced neurologic condition. There are no randomized studies comparing these immunosuppressant modalities to help choose the best treatment.

The prognosis is variable. Most patients recover with corticosteroids; one series found that 74% of patients had demonstrated neurologic recovery with corticosteroids alone.[95] Of all the NirAEs, ICI-induced myasthenia gravis is the most serious with an approximate 40% fatality rate, much higher than idiopathic myasthenia gravis, which is fatal in only about 2% of cases.[96,97] This may be due to the concurrent myocarditis and myositis in ICI-associated myasthenia gravis. On average, other NirAEs have lower fatality rates of 6%-12%, but these are still high compared with other IrAEs.[38] Importantly, courses of corticosteroids do not undo the antitumor effects of ICIs, but it remains unclear whether longer courses of steroids may affect cancer outcomes since ICIs dramatically suppress interferon-γ and a host of other cytokines necessary for a response.[68]

TABLE 1. Summary of the Clinical Associations, Signs/Symptoms, and Pitfalls of the Most Common Neurologic Immunotherapy-Related Adverse Events; Consult Neurology Early

Syndrome	Clinical Associations	Signs/Symptoms	Pitfalls/Notes
Myositis	Older patients	Myalgias, ocular/bulbar/limb girdle/axial muscle weakness	Approximately 25% with resp. failure; may occur with myocarditis/MG ↑ CK in approximately 33% of patients but may not correlate with severity Ddx: hypothyroid myopathy and noninflammatory myopathies
MG	Older patients and anti–PD-1/PD-L1 use	Fatigable weakness with respiratory/bulbar involvement	Urgent PFTs (FVC and NIF), consider ICU and rule out myocarditis and cardiac involvement Up to 50% may be seronegative Ddx: Lambert-Eaton syndrome
Polyradiculoneuropathies (AIDP, AMAN, Miller-Fischer, etc) and peripheral neuropathies	Melanoma and anti–CTLA-4 use	Progressive sensory/motor deficits May be rapidly ascending in GBS (ie, AIDP, AMAN, Miller-Fischer, etc)	Urgent PFTs, dysautonomia, and resp. failure can occur Ddx: chemotherapy-related neuropathy, metabolic neuropathy
Cranial neuropathies	ICI combinations	Facial weakness and hearing loss; if other cranial nerves are involved, consider LMD or Miller-Fischer variant	Ddx: LMD, chemotherapy-induced facial palsy, Miller-Fischer variant of GBS (Gq1b ABs)
Aseptic meningitis	Melanoma, young patients, anti–CTLA-4 use	Altered mental status, fever, headache, nausea/vomiting	LP to rule out infectious causes or LMD
Encephalitis	Lung cancer, anti–PD-1/PD-L1 use	Altered mental status, psychiatric disturbances, seizures, movement disorders	Ddx: metabolic encephalopathy, infectious encephalitis, PRES, rarely paraneoplastic syndrome
Hypophysitis	Anti–CTLA-4 use	Headaches, weakness, fatigue, weight loss, confusion, visual field deficit	Nonspecific symptoms, requires high clinical suspicion MRI brain fine cuts through pituitary; check serum markers of endocrine function

NOTE. Adapted from the studies by Vogrig et al[85] and Zhao et al.[86]

Abbreviations: AB, antibody; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; CK, creatine kinase; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; Ddx, differential diagnosis; FVC, forced vital capacity; GBS, Guillain-Barre syndrome; ICI, immune checkpoint inhibitors; ICU, intensive care unit; LMD, leptomeningeal disease; LP, lumbar puncture; MG, myasthenia gravis; MRI, magnetic resonance imaging; NIF, negative inspiratory force; PFT, pulmonary function test; PRES, posterior reversible encephalopathy syndrome; Resp., respiratory.

Rechallenge with ICIs in a patient who has already experienced NirAEs is controversial and must be determined on a case-by-case basis. Although NirAE-specific data are limited, studies have shown that up to 40% of patients may experience recurrent immune-related adverse events after rechallenge.[98] Patients with a high risk of cancer morbidity or mortality and minor residual neurologic sequelae stand the best chance of benefiting, whereas those with a history of severe and refractory NirAEs are poor candidates for rechallenge. Although current guidelines recommend against it, cautious rechallenge may still be considered when other treatment options are limited and the NirAEs had been minor (≤grade 2).[93]

NirAEs are uncommon but potentially fatal complications from ICIs. Early/urgent neurologic consultation for patients with symptoms/signs is critical. The current diagnostic labels for NirAEs may ease communication but are not definitive as many NirAEs involve several levels of the neuroaxis and/or have features that are distinct from classical corresponding neurologic syndromes. Balancing risks and benefits is important. In some patients with active immune-related neurologic disease or with options for alternative cancer treatments, the risks of ICIs may outweigh the benefits. Consensus treatment guidelines are useful for treatment decisions. There is a significant need for basic and clinical research in this area.

THE COURAGE: MANAGING STEROID-REFRACTORY AND LONG-TERM EFFECTS OF IMMUNOTHERAPY

Most IrAEs have been attributed to acute inflammatory changes. The greatest risk is typically in the first 3 months of treatment and while on active dosing; early IrAEs occur within the first year of treatment. IrAEs, for the most part,

TABLE 2. Summary of Diagnostic Workup, Findings, and Treatment Recommendations for the Most Common Neurologic Immunotherapy-Related Adverse Events

Condition	Diagnostic Workup	Findings	Treatment
Myositis	CK, AST/ALT, GGT, ESR, CRP, aldolase, ANA, anti-CCP PFTs Consider myositis ABs and rheumatology consultation Consider MRI of affected muscles EMG/NCS and possibly muscle Bx ECHO, EKG, and troponins Consider MRI of the brain and spine	Serum CK usually ↑, but may be normal in approximately 1 of 3 cases Myositis ABs may be positive MRI of affected limbs often shows T2 hyperintensity EMG/NCS often shows myopathic findings, and muscle Bx shows inflammatory infiltrates MRI brain and spine may show enhancement of paraspinal muscles, muscles of mastication, and/or extraocular muscles	Hold ICI Consult neurology and rheumatology Grade 2 toxicity: consider NSAIDs and oral prednisone Grades 3 and higher: consider hospitalization and IV glucocorticoids IVIG, PLEX, RTX, or INX Long-term, might consider azathioprine or mycophenolate
MG	Similar workup as myositis above Also AchR, MuSK, LRP4, VGCC, and antistriated muscle ABs Obtain repetitive nerve stimulation and consider single-fiber EMG Consider MRI brain and spine to rule out any CNS involvement	Can coexist with myositis/cardiomyopathy AB-positive in 50%-60% of cases Repetitive nerve stimulation is positive in up to 80%, whereas single-fiber EMG is highly sensitive (>95%)	Hold ICI Consult neurology and/or pulmonology Pyridostigmine and IV glucocorticoids Consider IVIG, PLEX, or RTX Avoid beta-blockers, fluoroquinolones, and IV magnesium
Polyradiculoneuropathies (AIDP, AMAN, Miller-Fischer, etc) and peripheral neuropathies	B12, folate, A1c, TSH, ESR, ANA, SPEP/UPEP, ANCA, CK Consider antiganglioside and anti-MAG ABs Consider paraneoplastic AB panel MRI of L-spine, LP EMG/NCS and possibly nerve Bx PFTs	Can be axonal or demyelinating polyneuropathy on EMG/NCS Antiganglioside and paraneoplastic ABs are sometimes positive MRI of L-spine can show nerve root enhancement LP can show albuminocytologic dissociation or lymphocytic pleocytosis	Hold ICI Consult neurology Consider pregabalin/duloxetine for symptoms of pain Initiate oral or IV glucocorticoids May also consider IVIG
Cranial neuropathies	Recommend similar serum testing to peripheral neuropathy Obtain MRI brain w/wo contrast LP	MRI brain w/wo contrast often shows cranial nerve enhancement LP with elevated protein and pleocytosis	Hold ICI Consult neurology Oral or IV glucocorticoids, eye patching to prevent corneal abrasions
Aseptic meningitis	LP (basic CSF studies, oligoclonal bands, meningoencephalitis panel, fungal panel, cytology) MRI brain and whole spine w/wo contrast EEG if seizures suspected	LP with pleocytosis/elevated protein but negative microbiologic studies with normal cytology MRI brain often shows meningeal enhancement	Hold ICI Consult neurology Oral or IV glucocorticoids until CSF viral PCR results are negative Can consider IVIG, RTX, or PLEX

(Continued on following page)

TABLE 2. Summary of Diagnostic Workup, Findings, and Treatment Recommendations for the Most Common Neurologic Immunotherapy-Related Adverse Events (Continued)

Condition	Diagnostic Workup	Findings	Treatment
Encephalitis	Similar to workup for meningitis Obtain autoimmune encephalitis and paraneoplastic panels in both serum and cerebrospinal fluid TPO ABs	MRI brain can show mesial temporal lobe enhancement in 25% of cases Anti-Hu, anti-Ma2, anti–NMDA-R, and anti-CASPR2 paraneoplastic ABs are sometimes found	Similar treatment considerations as meningitis above If no improvement despite steroids/IVIG/PLEX after 2 weeks, consider RTX
Hypophysitis	MRI brain w/wo contrast Pituitary hormone panel	Homogenously enlarged pituitary gland can be seen Anterior hypopituitarism is often seen	Consider consulting neurology and/or endocrinology Responds to corticosteroids Consider hormone replacement (levothyroxine, testosterone, etc) once adrenal axis is stable Consider NSAIDs for headache

NOTE. Adapted from the studies by Burton et al[90] and Reynolds and Guidon.[91]

Abbreviations: AB, antibody; AchR, acetylcholine receptor; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; Bx, biopsy; CASPR2, contactin-associated protein-like 2; CCP, cyclic citrullinated peptide; CK, creatine kinase; CRP, C-reactive protein; ECHO, echocardiogram; EMG/NCS, electromyography/nerve conduction studies; ESR, erythrocyte sedimentation rate; GGT, gamma glutamyl-transferase; ICI, immune checkpoint inhibitor; INX, infliximab; IV, intravenous; IVIG, intravenous immunoglobulins; LP, lumbar puncture; LRP4, LDL receptor–related protein 4; MAG, myelin-associated glycoprotein; MG, myasthenia gravis; MRI, magnetic resonance imaging; MuSK, muscle-specific kinase; NMDA-R, N-methyl D-aspartate receptor; NSAID, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction; PFT, pulmonary function test; PLEX, plasma exchange; RTX, rituximab; SPEP, serum protein electrophoresis; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; UPEP, urine protein electrophoresis; VGCC, voltage-gated calcium channel; w/wo, with/without.

have been treated as acute phenomena and were rarely long-lasting or permanent. Delayed IrAEs and chronic or long-term IrAEs are a newer concept. The first report describing long-term IrAEs was in patients with melanoma treated with single-agent ipilimumab; they reported mainly endocrinopathies, dermatologic IrAEs, and a delayed presentation of diarrhea.[17] Similar long-term toxicities were also described in patients with melanoma, renal cell carcinoma, and non–small-cell lung cancer treated with PD-1/PD-L1 inhibitors as monotherapy or in combination.[18] Chronic toxicities were more frequent with combination ICI and again included endocrinopathies, thyroid dysfunction was the most common at 10.6%. But also included were arthritis, neuropathy, dermatologic issues, and pneumonitis. They also reported radiation necrosis in 25% of patients who received cerebral radiation after starting ICI. More recently, another group reported on 118 patients with melanoma treated with PD-1 or PD-1 with CTLA-4 antibodies and included those on and off active ICI.[21] In this retrospective, multisite analysis, the incidence of delayed IrAEs, defined as an onset of >12 months from ICI initiation, was 5.3%, with the most common toxicities being colitis, rash, and pneumonitis. The majority were grade 1 and 2; however, 39% were ≥grade 3/4. There were two grade 5 delayed IrAEs (encephalitis and multiorgan IrAEs) The most common organ/sites with severe delayed toxicities included colon, liver, kidneys, and nervous system. Seventy-four percent of patients were still receiving PD-1 therapy at the onset of the delayed IrAE, 12% were within 3 months of the last ICI dose, and 14% were > 3 months from the last ICI dose.

Long-term consequences of ICI treatment may range from end-organ damage after acute IrAEs to chronic IrAEs or delayed/long-term IrAEs. IrAEs can occur after active dosing has stopped, and the end point for risk of IrAEs remains unknown, but appears to extend for at least 1 year if not longer.[17-24] At this time, definitions are still being considered/refined and are dependent on treatment duration. One group proposed the following definitions for IrAEs associated with anti–PD-1 treatment in the adjuvant setting: acute IrAEs were during treatment, delayed started after ICI cessation, and chronic persisted for >12 weeks after discontinuation.[19] They reported a delayed IrAE incidence of 43.2%, the majority in nonvisceral organs, such as

endocrine and salivary glands, joints, and skin. The majority of these chronic toxicities were grade 1 or 2 and persisted; many were symptomatic, and additional treatment was needed. Another group defined long-term IrAEs as 12 weeks to <12 months, and chronic IrAEs as >12 months since last ICI treatment.[22] This group reported long-term IrAEs in 51.9% and chronic IrAEs in 35.5%, a similar pattern involving joints, skin and endocrine glands, and a negative impact on quality of life. Risk factors for chronic IrAEs appear to overlap with risk factors for any IrAE and include combination ICI, pre-existing autoimmune conditions, and previous solid organ transplant.[18,23,24]

Two hypotheses regarding mechanisms for chronic IrAEs have been proposed by Johnson et al:[24] burnout and smoldering inflammation. Burnout is characterized as inflammation that leads to permanent damage of cells and/or organs, as seen with ICI endocrinopathies. Currently, a variety of endocrinopathies can be seen and are typically irreversible: hypothyroidism, hypopituitarism, adrenal insufficiency, and insulin-dependent DM. Less common and less well-understood endocrinopathies include pancreatic insufficiency and gonadal deficiency. Although ICI has been thought to have little impact on fertility, endocrinopathies and possible gonadal damage remain ripe for additional investigation; this has growing importance as the number of ICI-treated cancer survivors of child-bearing age/potential increases.[99] Other examples could include vitiligo and pneumonitis, with reports of persistent imaging findings at least 1-2 years from the symptom onset.[100] Neuropathies, as discussed earlier, could also fall into this category.

The other proposed mechanism is smoldering inflammation, such as in arthritis.[24] These IrAEs can flare after ICI has been stopped and appear to resemble chronic autoimmune conditions. Bowel inflammation could fall under both possible mechanisms.[101] With chronic IrAEs, the findings on imaging or symptoms may be more indicative of end-organ damage rather than ongoing inflammation. It is critical to attempt to understand if there is ongoing inflammation as this affects the decision for continuous use of steroids or other immunosuppressive agents versus monitoring. Tissue sampling in some circumstances can be of benefit in this setting.[102] The presence of chronic IrAEs also factors into a decision to rechallenge after IrAEs. If there is end-organ damage but not necessarily ongoing inflammation, rechallenge could be reasonable.

Steroid-refractory describes an inadequate response to steroids in autoimmune and other conditions, but its definition can vary on the basis of disease and organ. With respect to IrAEs, this can refer to an improvement in IrAE but ongoing dependence on high doses of steroids or limited IrAE improvement on steroids. As described above, it is possible that some steroid-refractory IrAEs may not be reflective of ongoing inflammation but rather end-organ damage. If inadequate response to initial steroid therapy is observed, rapid addition of a second-line agent is recommended to manage acute IrAEs. This is best delineated in ICI enterocolitis where anti–TNF-alpha agents are used if inadequate response is observed within the first 3-7 days.[14] For other IrAEs, second-line therapy is influenced by the typical management of the correlating autoimmune condition. Collaboration between subspecialists and oncologists is critical to determine clinical management. Immunosuppression also comes with infectious complications/risks such as opportunistic infections and other long-term risks such as cataracts, steroid myopathy, hyperglycemia and steroid-induced diabetes, decreased bone density and fracture risk, and others.[14,103,104] Although treatment of IrAEs with steroids and other immunosuppressive agents does not appear to reverse anticancer activity in the short term, the impact of prolonged steroid courses and aggressive immunosuppression should be considered.

Another approach for categorizing IrAEs is the time to resolution as the majority are expected to be temporary. Ghisoni et al[20] performed a retrospective analysis of all grade 2 or higher IrAEs in patients with lung cancer or melanoma treated at a single institution over 8 years. The incidence of at least 1 ≥grade 2 IrAE was 52.4%; 6.9% started 1 year after ICI initiation. The median duration of all IrAEs was 98 days. An IrAE duration of >6 months occurred in 35.2% and was ongoing at data cutoff or death in 40.3%. No significant correlation was found between the onset and risk of chronic IrAEs and baseline characteristics. Another report of 161 patients with melanoma treated with ICI noted that IrAEs were permanent in 41%, long-term in 9.3%, and transient in 21.1%, whereas 28.6% had no IrAEs.[23] Permanent toxicities were more common with CTLA-4 with PD-1 therapy compared with monotherapy and primarily involved the skin and endocrine glands. Treatment for long-term or permanent IrAEs was required in 32.9% of patients at ≥6 months from ICI cessation, and 2.5% of patients had a fatal IrAE.

It is important to acknowledge and counsel patients and families regarding potentially fatal IrAEs, which range from 0.4% to 1.2%.[16] As aforementioned, the toxicities that carry the highest mortality include myocarditis and NirAEs. Often, these occur early in the course of ICI treatment and rechallenge is contraindicated. A registry study from a single institution in France reported a similar grade 5 rate (1.3%) and reported very severe IrAEs (grade 4 and 5) typically seen early after ICI initiation.[105] Interestingly, these occurred with PD-1/PDL-1 monotherapy in 33 of 34 cases.[105] The ability to predict severe or life-threatening toxicities is an area of ongoing research that would have a great clinical impact. Investigation of patient factors that affect the development of IrAEs and organ specificity is ongoing.[106]

Correlations with certain SNPs and HLA types have been noted but are limited by small sample sizes and varied clinical scenarios. Recently, one group reported the presence of a germline *NLRC5* missense mutation in 9 of 13 tumors from patients who developed ICI insulin-dependent DM, not found in type 1 DM.[107]

CONCLUSION

Our understanding of the duration and extent of IrAEs and associated morbidity(ies) continues to advance. To balance known and unknown risks of ICI and known and unknown benefits, shared decision making between the treating physician and the patient is recommended. This includes a thorough discussion of potential toxicities, including fatal IrAEs, typical management strategies, and the importance of early reporting and prompt intervention. This may also include a discussion of long-term or delayed IrAEs and of unknown risks, such as the potential increased risk of atherosclerosis and infertility. In advanced unresectable melanoma, OS benefit from ICI is clearly established. In the adjuvant setting, the known benefit for adjuvant PD-1 is recurrence-free-survival. For patients with good prognosis and/or higher risk for IrAEs, long-term or severe IrAEs, it is important to balance these ICI risks with potential benefits of ICI therapy. This strategy is applicable to all histologies and treatment scenarios.

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Neoadjuvant Immunotherapy in Melanoma: The Paradigm Shift

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Overview

Clinical stage III melanoma, defined as resectable RECIST measurable nodal disease with or without in-transit metastases, represents approximately 15% of new melanoma diagnoses every year with additional cases presenting as recurrent nodal disease following previous treatment of a primary melanoma. The standard of care for patients with resectable clinical stage III melanoma is surgical resection, consisting of therapeutic lymph node dissection and/or resection of in-transit disease and consideration of adjuvant systemic therapy and occasionally adjuvant radiation. These patients have high rates of regional recurrence and progression to metastatic disease postsurgery, highlighting the need for better treatment options. With the success of immune checkpoint inhibitors in both the adjuvant and metastatic settings, the use of these agents in the neoadjuvant setting has been an emerging area of research interest. In this chapter, we will discuss the rationale for neoadjuvant immunotherapy; review impactful clinical trials; and define response monitoring, surgical considerations, emerging therapies, and unanswered questions for neoadjuvant therapy as a recent paradigm shift in the management of clinical stage III melanoma.

BACKGROUND

Rationale for Neoadjuvant Immunotherapy

Patients with clinical stage III melanoma represent a high-risk patient population with suboptimal long-term outcomes from up-front surgery and adjuvant medical therapy.[1,2] The rationale for neoadjuvant immunotherapy stems from the concept that administration of immune checkpoint inhibitors (ICIs) while the primary tumor is still present will result in a more robust systemic antitumor immune response compared with what is seen in the adjuvant setting.[2] This phenomenon was first demonstrated preclinically[3] and then in two separate clinical trials demonstrating increased ability to generate tumor-specific CD8 T cells, resulting in improved clinical outcomes for neoadjuvant- versus adjuvant-treated patients.[4,5] With neoadjuvant therapy, the assessment of response to treatment is feasible after surgical resection, which provides useful prognostic data from tissue pathology, including intratumoral T-cell expansion, presence of tertiary lymphoid structures, and percentage of viable tumor cells.[6-9] In a pooled analysis, Menzies et al showed that pathologic complete response (pCR) correlated with improved recurrence-free survival (RFS) and disease-free survival (DFS) and suggested that pCR should be an early surrogate primary end point for clinical trials. Moreover, detecting poor response enables altering the planned adjuvant therapeutic regimen, and obtaining pCR provides the option for potentially de-escalating further treatment.[2] Neoadjuvant immunotherapy provides an opportunity to better understand the tumor microenvironment while the patient is on an active treatment[2] and allows for biomarker exploration of the applied therapy. On the other hand, particularly for surgically resectable disease, potential disadvantages of the neoadjuvant approach include disease progression delaying or precluding surgical resection and treatment-related adverse events that might delay or complicate the operation. Nonetheless, a neoadjuvant approach to high-risk stage III disease is an exciting paradigm shift supported by an increasing body of clinical data (Fig 1).

The Paradigm Shift

OpACIN-neo. The Optimal Adjuvant Combination Scheme of Ipilimumab and Nivolumab in Melanoma Patients (OpACIN)-neo trial was inspired by the preceding OpACIN trial, in which one arm evaluated neoadjuvant ipilimumab 3 mg/kg, with nivolumab 1 mg/kg resulting in a 30% pCR rate and 90% grade 3-4 toxicities. OpACIN-neo addressed the increased toxicity by altering neoadjuvant dosing of ipilimumab and nivolumab. Patients in arm A received ipilimumab 3 mg/kg and nivolumab 1 mg/kg once every three weeks for two cycles (n = 30), those in arm B received ipilimumab at 1 mg/kg dose and nivolumab at 3 mg/kg dose once every three weeks for two cycles (n = 30), and those in arm C received ipilimumab at 3 mg/kg dose once every three weeks for two cycles

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PRACTICAL APPLICATIONS

- Patients with clinical stage III melanoma have high risk of disease recurrence despite up-front surgery and adjuvant systemic therapy
- Neoadjuvant therapy allows for rapid assessment of pathologic and radiographic response as well as safety data and interrogation of biospecimens collected across the continuum of treatment
- Assessment of response to neoadjuvant therapy can help personalize postoperative treatment approaches
- Any pathologic response to neoadjuvant immunotherapy seems to confer superior survival outcomes
- Neoadjuvant therapy can serve as a useful platform for new drug development and clinical trials of new agents and combinations, and can provide useful information to help inform decisions on the promise of novel therapeutics

followed by nivolumab at 3 mg/kg dose once every two weeks for two cycles (n = 26). Grade 3 or 4 adverse events were observed in 40%, 20%, and 50% of arms A, B, and C, respectively, and the pathologic response rate (defined as pCR, near pCR, and partial pathologic response [pPR]) was 80%, 77%, and 65%, respectively.[10,11] Although there was no observed association between Interferon (IFN-γ) and tumor mutation burden (TMB), Blank et al[12] reported that patients who exhibited both elevated IFN-γ and TMB had a 100% partial pathologic response rate and no recurrence at 2 years.

Nivolumab-relatlimab. The combination of nivolumab-relatlimab was used in unresectable melanoma in the RELATIVITY-047 trial, and the same agents were used in the neoadjuvant setting in patients with resectable clinical stage III or oligometastatic stage IV melanoma.[13,14] Patients received two cycles of neoadjuvant nivolumab and relatlimab at fixed doses of 480 mg and 160 mg, respectively, every 4 weeks, followed by surgical resection, and then 10 doses of adjuvant nivolumab-relatlimab combination. The trial included 30 patients treated with a pCR rate of 57% and pathologic response rate of 70%. No grade 3 or 4 adverse events were observed in the neoadjuvant setting. The radiologic response rate was 57%. The 1- and 2-year RFS was 100% and 92%, respectively, for patients who had any pathologic response, and 88% and 55%, respectively, for patients who did not exhibit a pathologic response (P = .005).[14] The authors reported a significantly greater quantity of CD8+ tumor-infiltrating T cells, increased tumor cell PD-L1 expression, higher rate of T-cell clonality, and higher levels of lymphoid markers among patients who responded versus nonresponders.[15,16]

SWOG S1801. The Southwest Oncology Group (SWOG) S1801 trial was a randomized phase II trial that compared adjuvant and neoadjuvant pembrolizumab among patients with clinical stage III or oligometastatic, resectable stage IV melanoma. Patients who received adjuvant therapy underwent surgery first followed by 18 doses of pembrolizumab at a dose of 200 mg every 3 weeks (n = 159) while patients who received neoadjuvant therapy received three doses of preoperative pembrolizumab followed by surgery and then 15 doses of adjuvant pembrolizumab (n = 154). Patients were required to undergo planned surgical resection; therapeutic lymph node dissection (TLND) for the stage III patients, regardless of response to neoadjuvant therapy; and no de-escalation of surgery occurred. At 2 years, event-free survival (EFS), defined as disease progression or toxicity that prevented a participant from having a surgery, adjuvant therapy not initiated within 84 days of surgery, postoperative relapse, or death due to any cause, was 72% and 49% for neoadjuvant and adjuvant pembrolizumab, respectively. Treatment-related adverse event rates were similar among both treatment arms. On local review, 21% of neoadjuvant participants with submitted pathology reports achieved a pCR.[5]

Neoadjuvant Immunotherapy Response Assessment

Objective response assessment. Neoadjuvant trials enrolling patients with RECIST 1.1 measurable disease allow for the assessment of both radiographic and pathologic response. In clinical trials, outcome measures are based on image-based trial end points and include objective response rate, progression-free survival, and EFS. EFS is often defined as time from random assignment to any of the following events: progression of disease that precludes surgery, local or distant recurrence, or death due to any cause. Analogous to DFS in the adjuvant setting, EFS assessment in the neoadjuvant setting accounts for early progression to nonsurgically treatable diseases.[17] Clear guidelines exist for pathologic response assessment on the basis of the 2016 and 2017 International Neoadjuvant Melanoma Consortium (INMC) meetings, which defined pCR as the "absence of residual invasive cancer … after evaluation of the completely resected specimen." Other pathologic substages, including near pCR (>0% but ≤10% viable tumor), pPR (>10% to ≤ 50% viable tumor), and no pathologic response (pNR; >50% viable tumor), have also been widely used, which depend on the calculation made by the reporting pathologist on the total tumor area affected at baseline.[7] Some studies use major pathologic response (MPR) to denote both patients with pCR and near pCR, and any

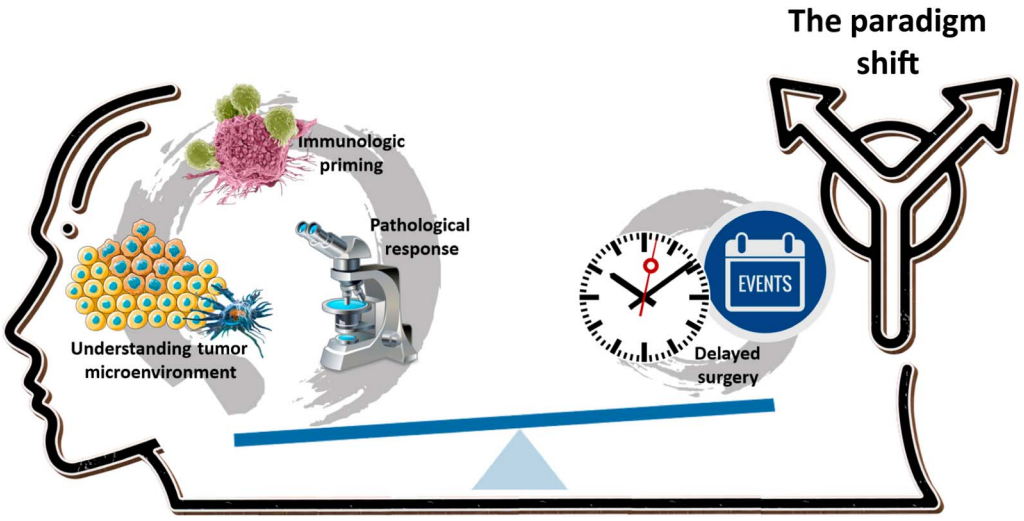

FIG 1. The paradigm shift: potential advantages of neoadjuvant immunotherapy.

pathologic response is defined as patients with pCR, near pCR, and pPR.

Historically, the critical end point correlating with durable clinical efficacy emphasized pCR on the basis of chemotherapy trials in patients with breast cancer.[18-20] This phenomenon also appears important in the context of neoadjuvant BRAF/MEK therapy. In the INMC pooled analysis, in patients with stage III melanoma, achieving only a pCR after neoadjuvant BRAF/MEK inhibitor therapy, but not a pPR, was associated with improved RFS[8,21,22] with a median follow-up of 20.9 months. Patients who had near pCR or pPR exhibited outcomes that were similar to nonresponders. Data from neoadjuvant immunotherapy suggest that any pathologic response is associated with favorable durable clinical outcomes.[8,11,23,24] Although few patients with a pCR to immunotherapy experience recurrence, recurrences have also been observed among patients with a pCR to targeted therapy.[8,16] Additionally, this trend of any pathologic response correlating with improved clinical outcomes after neoadjuvant immunotherapy was paralleled in studies of other malignancies, including lung cancer, head and neck squamous cell carcinoma, and Merkel cell carcinoma,[25-27] further supporting that a pCR, while preferable, is not essential in the setting of neoadjuvant immunotherapy.

Potential prognostic biomarkers. The relationship between pathologic response and preoperative clinicopathologic traits is being investigated in several studies, and collection of serial biospecimens is strongly encouraged. On the basis of the OpACIN-neo study showing improved outcomes in patients with high baseline IFN-γ levels, the DOMINI study was designed to ascertain response of domatinostat, nivolumab, and ipilimumab in IFN-γ low and IFN-γ high stage III melanoma. Domatinostat is a selective class I histone deacetylase inhibitor that can enhance IFN-γ expression, and the goal was to convert tumors that have low IFN-γ expression pretreatment to a high IFN-γ expressing phenotype, thus potentially enhancing the tumor response.[28] Single-agent nivolumab was highly effective in patients with baseline high IFN-γ expression while in patients with low IFN-γ expression, even triplet therapy was not sufficient to improve pathologic outcomes. Although this study failed to show improved outcomes with the experimental agent, it highlights an innovative biomarker-based trial design to optimize the treatment approach depending on baseline tumor characteristics.[16]

Surgical Considerations

The surgical oncologist plays a pivotal role in the multidisciplinary team caring for patients with high-risk stage III melanoma. Surgical oncologists are uniquely suited for assessing resectability that involves both the technical feasibility of operation (defining disease extent, describing nodal matting, and fixation to adjacent structures) and the likelihood of meaningful clinical benefit from an operation. Surgeons are therefore critical in determining appropriate patient selection for this approach as well as for ensuring cohesion from presentation through neoadjuvant treatment to response assessment, surgery, postoperative care, and outcomes.

Impact of neoadjuvant treatment on operative management and perioperative care. Initial concerns raised around the neoadjuvant approach centered on loss of disease control, potentially precluding curative surgical resection of disease. Evidence to date suggests that regional disease progression to unresectability has not been an issue. Instead, approximately 5% of patients enrolled in neoadjuvant trials with stage III disease on initial assessment have been found to progress to distant metastatic disease at restaging imaging following neoadjuvant systemic therapy before surgery,

sparing this small percentage of patients an unnecessary operation.[8,29] A second theoretical drawback to neoadjuvant therapy might be a negative effect on the technical conduct of the operation. This has been evaluated prospectively with structured surgeon surveys within the NeoACTIVATE neoadjuvant trial (ClinicalTrials.gov identifier: NCT03554083) for high-risk resectable stage III melanoma testing combinatorial neoadjuvant therapy regimens on the basis of BRAF status.[30] In this study, patients had a median largest lymph node size of 4 cm, a median three affected nodes, and 50% had fixation to adjacent structures at presentation. The investigators found that while surgeons most often assessed the degree of difficulty of operation as greater than the usual TLND, the operation was deemed more difficult than baseline impression in only 17% of cases and easier in one quarter of cases. As different neoadjuvant regimens are tested in patients with disease that may be cured with an operation, it is critical to evaluate the impact of neoadjuvant treatment on the technical conduct of the operation. As such, these survey instruments have been adapted and incorporated recently into the INMC guidelines.[29] A third consideration is the effect of potential irAEs on time to operation (surgical delay), perioperative management, and postoperative complications. The treatment team needs to be aware of irAEs as well as the likely chronology for emergence of the most frequent and impactful irAEs to inform appropriate preoperative evaluation and perioperative management. Assessment for endocrine, liver, and cardiac abnormalities should be done preoperatively. Patients on systemic steroids for an irAE should be deferred for operation until they are improving (grade 1), and steroids are being tapered. Steroid treatment is not a contraindication to proceeding to operation but does incrementally increase the risk of wound complications.[29] Additionally, the team needs to consider that some irAEs develop at later time points[31-33] (in recently reported neoadjuvant trials, approximately one third of irAEs emerge beyond week 12) and may confound perioperative management such as when hypotension secondary to hypophysitis may emerge in the postoperative period and erroneously be attributed to sepsis or other postsurgical cause.[34]

Response assessment before operation. Following completion of neoadjuvant therapy, the primary purpose of preoperative imaging is to assess for distant metastatic spread of melanoma, as systemic progression of disease would render a TLND futile from the standpoint of cancer control. Suspicious new lesions should be biopsied whenever feasible, as immunotherapy-related changes—particularly growth of distant lymph node due to expansion of lymphocytes—can resemble metastatic disease on both computed tomography and positron emission tomography imaging.

In addition to evaluating for distant metastases, preoperative imaging provides information on response of the tumor-positive lymph node(s) to neoadjuvant treatment. However, it is critical to note that radiographic responses (RECIST or iRECIST) frequently do not correlate with pathologic responses seen at the time of the operation. For example, in the OpACIN-neo study testing neoadjuvant ipilimumab and nivolumab, the radiographic response rate (CR + PR) per RECIST 1.1 was 52%, while the pathologic response rate (pCR, near pCR, or pPR) was 74%.[11] These results demonstrate that it is entirely possible for a patient to have stable disease or even progression radiographically and yet still have a favorable pathologic response to neoadjuvant therapy, thus highlighting the critical role for surgical resection after completion of neoadjuvant therapy.

In short, response assessment after neoadjuvant therapy is critical for identifying patients who will not benefit from TLND because of either distant disease progression or rapid regional progression involving encasement of critical structures. However, radiographic response alone should not serve as a surrogate for pathologic evaluation of the lymph node basin as a predictor of the efficacy of neoadjuvant treatment.

Tailoring treatment. As mentioned earlier, one of the many compelling advantages of neoadjuvant immunotherapy for patients with surgically resectable high-risk stage III melanoma is the potential opportunity to tailor treatment on the basis of response. De-escalation of the extent of TLND has been occurring before the availability of efficacious systemic therapies to test in the neoadjuvant setting, largely because of significant improvements in cross-sectional imaging over time. Thus, before operation, surgeons can now more accurately define the anticipated extent of nodal disease. Current cancer surgery guidelines endorse less extensive TLNDs for patients with melanoma, including two- versus three-level axillary dissection and superficial (inguinofemoral) versus radical (inguinofemoral plus external iliac and obturator) lymph node dissection for appropriately selected patients.[35] With neoadjuvant therapy, further de-escalation of the extent of operation for clinical stage III melanoma, on the basis of treatment response, is now being explored. The MemaLoc substudy within the OpACIN-neo trial evaluated pathologic response in the index lymph node (defined as the largest metastatic node) and the remainder of the lymph nodes in the TLND specimen in 12 patients and reported concordance in all cases.[36] The results of this substudy and the high pathologic response rates seen in OpACIN-neo supported opening the study's PRADO extension cohort to further explore de-escalation of both the surgical and adjuvant therapies on the basis of response to neoadjuvant treatment. Primary end points of PRADO included pathologic response rate and 24-month RFS for patients with a MPR ($\leq$10% viable tumor) treated per protocol that omitted TLND and adjuvant therapies for this patient group, on the basis of the potential of neoadjuvant therapy to eradicate

subclinical micrometastatic disease and the durable responses seen after cessation of immunotherapy among responders to ICI for advanced disease.[34] The index lymph node was marked at baseline with a magnetic, radioactive, or sonographically visible marker and retrieved at the first operation in 90 of 94 patients, which included retrieval of >1 lymph node (range, 2-7) in 40%, highlighting the feasibility of this approach. Among 60 patients with a MPR treated with limited surgery, after a median follow-up of 28 months, there were four regional recurrences, all among patients with two or more FDG-avid nodes on baseline scans, resulting in a failure to meet the primary RFS end point (null hypothesis not rejected in case of >1 recurrence). These four patients proceeded to delayed TLND, and one patient later developed a distant recurrence. Thus, although attempts are being made to de-escalate treatment on the basis of neoadjuvant response, this is still experimental and further work must be done to adequately identify patients eligible for de-escalation approaches.

Neoadjuvant Therapy Beyond PD-1, Anti–Cytotoxic T-Cell Lymphocyte-4, and Lymphocyte Activation Gene-3 (LAG-3) Checkpoint Inhibitors

Despite the excellent efficacy of single-agent anti-PD01, anti–PD-1 therapy in combination with either anti–cytotoxic T-cell lymphocyte-4 (CTLA-4) or anti–LAG-3,[11,14,23,24] a significant number of patients do not respond; to address this, new treatment options are being investigated in the neoadjuvant setting. One major advantage of the evaluation of novel combination therapies in the neoadjuvant setting is the use of pathologic response as a trial end point that provides rapid evaluation on efficacy and facilitates testing of multiple hypotheses, even in the one trial.

Oncolytic Viruses

Talimogene laherparepvec (T-VEC) is a genetically modified oncolytic herpes simplex virus type 1 used for unresectable IIIB-IVM1 melanoma.[37] A phase II study compared neoadjuvant T-VEC followed by surgery to surgery alone in patients with resectable stage IIIB-IVM1a melanoma. One hundred fifty patients were enrolled and divided into two arms. In total, 17.1% of patients achieved a pCR after neoadjuvant treatment with T-VEC; however, 19 (25%) patients in the T-VEC arm did not undergo surgery, primarily (58% of cases) because of progressive disease.[38]

A phase II clinical trial (ClinicalTrials.gov identifier: NCT04330430) is currently underway to assess the effectiveness of a combination treatment of T-VEC and nivolumab in the neoadjuvant setting for patients with stage IIIB-IVM1a melanoma. Participants will receive four intralesional injections of neoadjuvant T-VEC, in combination with nivolumab every two weeks from cycle 2. This trial is expected to be completed by the end of 2023. Another phase II trial (ClinicalTrials.gov identifier: NCT03842943) is evaluating the use of T-VEC in combination with an anti–PD-1 treatment in patients with stage III disease. Twenty-eight patients will be recruited for the study and will receive T-VEC injections into palpable lymph nodes every three weeks for six months or until complete response of target tumors concomitant with pembrolizumab every three weeks for six months and adjuvant pembrolizumab for one year following surgery.

New oncolytic viruses are also being evaluated in the neoadjuvant setting. A phase Ib trial is evaluating the use of recombinant human GM-CSF herpes simplex virus intratumoral injection (OrienX010) in combination with the recombinant humanized anti–PD-1, toripalimab, as a neoadjuvant treatment for patients with resectable stage III and IV (M1a) melanoma.

BRAF-Targeted Therapy

Several studies have evaluated combined BRAF and MEK inhibition alone or in combination with immunotherapy. Two different phase II clinical trials have studied neoadjuvant dabrafenib plus trametinib followed by the same adjuvant therapy.[21,22] Long et al reported the outcomes of a single-arm clinical trial involving 35 patients with resectable stage IIIB-C melanoma receiving 12 weeks of neoadjuvant and 40 weeks of adjuvant dabrafenib and trametinib. All patients achieved an imaging response, and 49% of them had a complete pathologic response.[22] The second study compared neoadjuvant plus adjuvant dabrafenib and trametinib versus standard-of-care physicians' choice in patients with resectable III or oligometastatic stage IV melanoma randomly assigning patients 2:1 favoring the targeted therapy arm. Fourteen patients received 8 weeks of neoadjuvant and adjuvant treatment with trametinib and dabrafenib while seven patients were randomly assigned to the standard-of-care physicians' choice arm. pCR was observed in 58% of patients who received neoadjuvant therapy with dabrafenib and trametinib. Although this was a small study after a median follow-up of 18.6 months, 71% of patients treated with targeted therapy were alive, whereas no patients of the standard-of-care group survived. The median EFS was 19.7 months in the treatment arm compared with 2.9 months in the standard-of-care arm.[21]

BRAF Therapy and Immunotherapy

Triple therapy of neoadjuvant anti–PD-1 and BRAF plus MEK inhibitors has been recently presented at ASCO 2022. In the NeoTrio study, 60 patients with stage III melanoma were randomly assigned to one of three different arms and received 6 weeks of neoadjuvant treatment. Participants in the ALONE arm received two courses of pembrolizumab, the SEQ arm received one week of dabrafenib and trametinib followed by two cycles of pembrolizumab, and the CON arm received pembrolizumab concomitant with dabrafenib and trametinib. After surgery, patients had 46 weeks of the same assigned treatment to complete a total of

12 months. Patients in the CON arm had the best outcomes, with 80% achieving a pathologic response and 50% pCR. The ALONE and SEQ arms had 30% and 20% pCR, respectively. After a median follow-up of 20 months, none of the patients who achieved pCR in the ALONE and SEQ arms had recurrence while only one in the CON arm showed progressive disease.

Two clinical trials, NeoPele (ClinicalTrials.gov identifier: NCT04207086) and NeoACTIVATE (ClinicalTrials.gov identifier: NCT03554083), are investigating the combination of immunotherapy and targeted therapy as neoadjuvant treatment for resectable melanoma. The NeoPele is a phase II, single-arm clinical trial, currently exploring combined lenvatinib and pembrolizumab. Lenvatinib is a potent multiple tyrosine kinase inhibitor that selectively suppresses vascular endothelial growth factor and fibroblast growth factor receptors.[39] This dual inhibition can affect T cells by decreasing the expression of PD-1, CTLA-4, and Tim-3.[40] Furthermore, combination therapy with lenvatinib and anti–PD-1 significantly inhibited tumor growth in murine models associated with increased influx of T cells, including $CD8^+$ T cells.[41] This trial will enroll 40 patients with histologically confirmed diagnosis of resectable stage IIIB, IIIC, or IIID cutaneous or unknown primary melanoma (excluding in-transit or satellite metastases). Patients will receive neoadjuvant pembrolizumab and lenvatinib for 6 weeks and, after surgery, adjuvant pembrolizumab alone for 46 weeks. In addition, the study NeoPeLeMM (ClinicalTrials.gov identifier: NCT05545969) and the study NCT04622566 are investigating this combination as neoadjuvant treatment in patients with resectable mucosal melanoma.

The NeoACTIVATE trial (ClinicalTrials.gov identifier: NCT03554083) is a nonrandomized phase II trial that enrolled 30 patients with high-risk stage III melanoma in two arms. Patients in arm A received neoadjuvant vemurafenib and cobimetinib for up to three cycles associated with atezolizumab starting from the second cycle while patients in arm B received atezolizumab and cobimetinib. Following TLND, adjuvant atezolizumab was administered every 3 weeks for up to eight cycles in both groups. These two arms of the study have completed accrual, with results expected soon.

Combinations Targeting Multiple Immune Checkpoints

Targeting multiple immune checkpoint receptors has shown improved efficacy in different trials (see above). Tiragolumab is a monoclonal antibody that targets T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT), an inhibitory receptor found on T cells and natural killer cells. TIGIT activates an inhibitory signaling pathway in T cells by suppressing the phosphoinositide 3 kinase/mitogen-activated protein kinase signaling pathways.[42] Given promising data on the combination of tiragolumab with atezolizumab, in patients with metastatic non–small-cell lung cancer, this combination is being pursued in NeoACTIVATE arm C. Patients in arm C will receive neoadjuvant atezolizumab and tiragolumab every 21 days for up to four cycles followed by surgery and adjuvant atezolizumab.

The Morpheus-Melanoma trial (ClinicalTrials.gov identifier: NCT05116202) is currently underway to evaluate efficacy, safety, and pharmacokinetics of different combinations simultaneously that may enhance antitumor activity, including inhibitors of LAG-3, TIGIT, and PD-1. Cohort 1 will include patients with stage III melanoma with clinical lymph node metastasis. Patients will be randomly assigned to receive neoadjuvant treatment for 6 weeks in one of three experimental arms or a comparator arm of combined ipilimumab and nivolumab. The three experimental arms will study RO7247669, which is a bispecific anti–PD-1 and anti–LAG-3, atezolizumab plus tiragolumab, and RO7247669 plus tiragolumab. The simultaneous evaluation of several combinations in the Morpheus-Melanoma trial is a promising approach to accelerate the development of novel neoadjuvant therapies in patients with resectable melanoma.

Unanswered questions. Despite the intriguing clinical data on neoadjuvant therapy for clinical stage III melanoma, a number of unanswered questions remain.

1. What is the right choice of agent(s) for neoadjuvant therapy? Thus far, robust data exist for neoadjuvant single-agent anti–PD-1, ipilimumab and nivolumab, and nivolumab and relatlimab[5,10,11,14] with emerging data on triplets and injectable agents. These regimens have not been compared head-to-head; thus, selecting the best regimen poses a challenge. Ultimately, the choice of regimen will be determined by patient and tumor characteristics. Although there is growing evidence supporting neoadjuvant therapy in an off-protocol manner, participation in clinical trials is recommended for patients with clinical stage III melanoma when possible.

2. What is needed to change surgical clinical practice? Current evidence suggests that further refinement of criteria for selecting patients for limited surgical resection for potentially surgically curable disease is needed before this approach can be adopted safely as the standard of care. A phase III randomized controlled trial comparing TLND with more limited lymph node surgery for patients with high-risk stage III melanoma who have a MPR to neoadjuvant therapy, perhaps also guided by blood or tissue biomarkers, would be ideal. Feasibility of this approach also requires scalable adoption of the INMC pathology assessment of immunotherapy-treated lymph nodes to categorize pathologic response and agreement from pathologists. In view of the substantially lower (21%) pCR rate in SWOG 1801

TABLE 1. Clinical Trials of Neoadjuvant Treatment for Patients With Resectable Melanoma

Reference	Phase	Stage	Neoadjuvant	Adjuvant	Patients	pCR (%)	Relapse After pCR	Near PCR (%)	Relapse After Near pCR	Grade 3-4 Toxicities (% of patients)	2-Year RFS (%)	2-Year EFS (%)	2-Year DMFS (%)	2-Year OS (%)	Other Outcomes
Tarhini et al[44]	I	IIIB-C	Ipilimumab 3 or 10 mg/kg once every three weeks i.v. for two doses and HDI 20 MU/m^2/d i.v. 5 d/wk for 4 weeks followed by 10 MU/m^2/d s.c. 3 d/wk for 2 weeks	Ipilimumab 3 or 10 mg/kg i.v for two doses and HDI at the same s.c. dose for 46 additional weeks	30	32	1/9	7.1	0/2	25 events[a]	60.7% at 32 months	NA	NA	89	mPFS NR. PFS 86% and 79% at 6 and 12 months
Najjar et al[45]	Ib/II	IIIB-C, IV	Pembrolizumab 200 mg i.v. for two doses and HDI 20 MU/m^2/d i.v., 5 d/wk for 4 weeks followed by 10 MU/m^2 3 days a week for 2 weeks	Pembrolizumab 200 mg i.v. every 3 weeks and interferon-alfa-2b 10 MU/m^2/d s.c. 3 days per week for 46 weeks	30	43	0/13	13.3	1/4	46 events[a]	NA	NA	NA	NA	mRFS and mOS NR
Huang et al[24]	Ib	IIIB-C, IV	Pembrolizumab 200 mg i.v., single dose	Pembrolizumab 200 mg i.v. every 3 weeks for up to 1 year	29	18.5	0/5	11.1	0/3	7 events[a]	NA	NA	NA	NA	DFS at 1 year 63%. mDFS NR
Patel et al[5] (SWOG S1801)	II	IIIB-C, IV	Pembrolizumab 200 mg i.v. once every 3 weeks for three doses	Pembrolizumab 200 mg i.v. every 3 weeks for 15 doses	154	21	NA	0	—	<2	NA	72	NA	NA	HR for OS, 0.63
			Nil	Pembrolizumab 200 mg i.v. every 3 weeks for 18 doses	159	—	—	—	—	<2	NA	49	NA	NA	
Amaria et al[21]	II	IIIB-C, IV	Nivolumab 3 mg/kg i.v. once every 2 weeks up to 4	Nivolumab 3 mg/kg i.v. every 2 weeks for 13 doses	12	25	0/3	NA	—	8	80% at 20.5 months	NA	67% at 22.6 months	76% at 24.6 months	mOS NR in both arms
			Ipilimumab 3 mg/kg i.v. and nivolumab 1 mg/kg i.v. once every 3 weeks up to three doses	Nivolumab 3 mg/kg i.v. every 2 weeks for 13 doses	11	45	0/5	NA	—	73	90% at 14.9 months	NA	91% at 17.2 months	100% at 24.4 months	
Blank et al[12] (OpACIN trial)	Ib	IIIB-C	Nil	Ipilimumab 3 mg/kg and nivolumab 1 mg/kg every 3 weeks for four doses	10	—	—	—	—	90	60	60	NA	80	Two patients in the NAT and four patients in AT relapsed
			Ipilimumab 3 mg/kg and nivolumab 1 mg/kg i.v. once every 3 weeks for two doses	Ipilimumab 3 mg/kg and nivolumab 1 mg/kg every 3 weeks for two doses	10	33.3	0/3	33.3	0/3	90	80	80	NA	90	
Rozeman et al[11] (OpACIN-neo trial)	II	III with macroscopic lymph node metastases	Ipilimumab 3 mg/kg plus nivolumab 1 mg/kg i.v. once every 3 weeks for two doses	Nil	30	47	0/14	23	0/7	40	90	90	NA	93	mRFS and mEFS NR
			Ipilimumab 1 mg/kg plus nivolumab 3 mg/kg i.v. once every 3 weeks for two doses	Nil	30	57	0/17	7	0/2	20	78	74	NA	95	
			Ipilimumab 3 mg/kg i.v. once every 3 weeks for two doses followed by 2 nivolumab 3 mg/kg once every 2 weeks	Nil	26	23	0/6	23	0/6	50	83	81	NA	96	
Reijers et al[34] (PRADO trial)	II	IIIB-D	Ipilimumab 1 mg/kg and nivolumab 3 mg/kg i.v. once every 3 weeks for two doses	If ≤10% viable tumor: TLND and adjuvant omitted	99	49	3/48	12	1/12	30	85	80	89	95	mRFS, EFS, DMFS, and OS NR
				If >10 to ≤50% viable tumor: TLND only											
				If >50% viable tumor: TLND and adjuvant therapy											
Amaria et al[14]	II	IIIB-IIID, IV	Relatlimab 160 mg and nivolumab 480 mg i.v. once every 4 weeks for two doses	Relatlimab 160 mg i.v. and nivolumab 480 mg i.v. every 4 weeks for 10 doses	30`	57	0/17	7	0/2	26	82	81	NA	88	

(Continued on following page)

TABLE 1. Clinical Trials of Neoadjuvant Treatment for Patients With Resectable Melanoma (Continued)

Reference	Phase	Stage	Neoadjuvant	Adjuvant	Patients	pCR (%)	Relapse After pCR	Near PCR (%)	Relapse After Near pCR	Grade 3-4 Toxicities (% of patients)	2-Year RFS (%)	2-Year EFS (%)	2-Year DMFS (%)	2-Year OS (%)	Other Outcomes
Amaria et al[21]	II	IIIB-C, IV	Nil	Standard of care	7	—	—	—	—	—	NA	0	0	Approximately 65%	mEFS 2.9 *v* 19.7 months mOS NR in both arms. mDMFS NR in D-T arm *v* 7.7 months in SoC
			Dabrafenib 150 mg twice per day and trametinib 2 mg per day for 8 weeks p.o.	Dabrafenib plus trametinib p.o. up to 44 weeks	14	58	1/7	0	—	61.5	NA	Approximately 45%	Approximately 70%	Approximately 85%	
Long et al[22] (NeoCombi trial)	II	IIIB-IIIC	Dabrafenib 150 mg twice per day and trametinib 2 mg per day for 12 weeks p.o.	Dabrafenib plus trametinib p.o. up to 40 weeks	35	48.6	8/17	NA	NA	29	43.4	NA	60% at 30.6 months	93.8%	mRFS 23.3 months mOS NR
Dummer et al[38]	II	IIIB-IVM1a	Intralesional T-VEC for six cycles. First dose 4 mL of 10E6 p.f.u./mL, from second dose 3 up to 4 mL of 10E8 p.f.u./mL	Nil	76	17.1	3/13	NA	NA	5.5% presurgery, 12.3% postsurgery	29.5	NA	33.7	88.9	EFS at 3 year 50.3% *v* 32.7%
			Nil	Nil	74	—	—	—	—	5.8% postsurgery	16.5	NA	19.5	77.4	

Abbreviations: AT, adjuvant therapy; DMFS, distant metastasis-free survival; EFS, event-free survival; HDI, high-dose interferon; HR, hazard ratio; i.v., intravenous; NA, not available; NAT, neoadjuvant therapy; NR, not reached; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; RFS, relapse-free survival; s.c., subcutaneous; SoC, standard of care; TLND, therapeutic lymph node dissection.

[a]Toxicity only reported by the number of events.

compared with the pCR rate following neoadjuvant doublets (57%) in the OpACIN-neo (most active arm) and relatlimab-nivolumab studies (both with even higher rates of MPR of 63%-64%), another important consideration is whether the optimal neoadjuvant approach should focus on achieving high pCR rates to drive de-escalation of operation (and adjuvant therapies). More mature RFS data from existing studies may help address this question and provide future guidance. Technical considerations also need to be addressed, including best practices to broadly improve short- and long-term surgical outcomes as well as continued structured assessment of the effect of various neoadjuvant regimens on the conduct of the operation. Extensive fibrosis from a robust response to treatment may hinder even limited surgical resection and confound intraoperative assessment of the extent of disease. As we await further advances in the field, data from ongoing trials, and exploration of new strategies for accurate assessment of extent of disease following neoadjuvant immunotherapy, the gold standard operation for clinically evident stage III melanoma remains TLND.

3. Is adjuvant therapy required after neoadjuvant treatment?

In addition to the neoadjuvant phase, most trials have included an adjuvant phase to complete a total of one year of systemic therapy, analogous to current adjuvant therapy regimens. Currently, there is no clear consensus regarding whether the adjuvant phase of therapy is essential or can be omitted and there is no clarity on which patients are ideal for omission of therapy. The use of adjuvant therapy also effects RFS data and can make data harder to interpret. In an attempt to lessen planned surgical and adjuvant therapy approach, the PRADO trial omitted TLND and adjuvant medical therapy in patients achieving MPR. Patients with pathologic partial response underwent TLND only, whereas patients with pNR underwent TLND and adjuvant systemic therapy with or without synchronous adjuvant radiotherapy. In this trial, Blank et al showed that TLND and all adjuvant therapies were omitted in 59 of 60 patients with major pathologic response, and the 24-month relapse-free survival and distant metastasis-free survival rates were 93% and 98% in patients with MPR, 64% and 64% in patients with pPR, and 71% and 76% in patients with pNR, respectively.[11] In patients with pPR having surprisingly poorer outcomes than patients with pNR, the omission of the adjuvant medical therapy does not appear to be optimal for this patient population. This trial opens a new future perspective where the extent of pathologic response from neoadjuvant therapy may direct the decision of whether incorporation of an adjuvant phase is needed,[14] as is being evaluated in the NADINA trial (ClinicalTrials.gov identifier: NCT04949113).

While this approach needs further investigation, to develop a standard and permit cross-trial comparisons, the INMC recommends that neoadjuvant clinical trials include a conventional postoperative adjuvant phase, which may or may not include the drug(s) under investigation, to complete a total duration of 1 year of systemic therapy.[43] Better understanding of the role of adjuvant phase in neoadjuvant immunotherapy remains an ongoing area of research interest to be further investigated in future studies.

CONCLUSION

Patients with clinical stage III melanoma represent a group at high risk for disease recurrence after up-front surgery and adjuvant systemic therapy. Through the work of the INMC, standard guidelines for trial design, patient selection, study end points, and pathologic response criteria have been implemented. Both preclinical and clinical trials have demonstrated improved EFS/RFS outcomes for patients treated in the neoadjuvant setting versus the adjuvant setting. Additionally, patients with any pathologic response to neoadjuvant immunotherapy have durable responses, including improved RFS. There are a number of ongoing and planned trials (Table 1) to explore the efficacy of novel agents or combinations with the goals of improving clinical outcomes, lowering toxicity, and evaluating new drug assets. While there are a number of ongoing questions regarding the neoadjuvant approach, the data thus far support the paradigm shift of considering neoadjuvant therapy for patients with clinical stage III melanoma.

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Evolving Management of Stage IV Melanoma

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overview

Significant advancements have been made in the treatment of advanced melanoma with the use of immune checkpoint inhibitors, novel immunotherapies, and BRAF/MEK-targeted therapies with numerous frontline treatment options. However, there remains suboptimal evidence to guide treatment decisions in many patients. These include patients with newly diagnosed disease, immune checkpoint inhibitor (ICI)–resistant/ICI-refractory disease, CNS metastases, history of autoimmune disease, and/or immune-related adverse events (irAEs). Uveal melanoma (UM) is a rare melanoma associated with a poor prognosis in the metastatic setting. Systemic treatments, including checkpoint inhibitors, failed to demonstrate any survival benefit. Tebentafusp, a bispecific molecule, is the first treatment to improve overall survival (OS) in patients with HLA A*02:01–positive metastatic UM.

EVOLVING MANAGEMENT OF STAGE IV AND UNRESECTABLE MELANOMA

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ICIs and targeted therapy have improved survival for patients with newly diagnosed metastatic melanoma. Recently, a new ICI combination, nivolumab (nivo) and relatlimab (rela), was approved for patients with metastatic melanoma after demonstrating efficacy in untreated patients. The numerous treatment options available for patients with metastatic disease have complicated the decisions faced by physicians and patients. In addition, more and more patients are receiving therapy earlier in the course of their disease, in the neoadjuvant or adjuvant setting, so that they have potentially resistant disease when metastasis is found.

Early studies on the use of ICIs in the treatment of metastatic melanoma showed significant improvements in progression-free survival (PFS) and OS over previously available therapies. PD-1 inhibitors, such as pembrolizumab (pembro) and nivo,[1,2] and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, such as ipilimumab (ipi), function by preventing inactivation of T-lymphocyte activity by cancer cells, leading to improved immune system activation and targeting of neoplastic cells. Ipi was the first agent to be associated with an improvement in survival in metastatic melanoma with a response rate of 11% (95% CI, 6.3 to 17.4). Nivo and pembro were demonstrated to have even greater benefit with response rates in the 30%-40% range, and the greatest initial response rate of 58% (95% CI, 45.9 to 68.5) is observed when PD-1 inhibition is combined with CTLA-4 inhibition.[3,4] These results were found to be consistent across different patient cohorts, but some factors including tumor PD-L1 status and *BRAF* mutation status have trends that are sometimes used to help make initial treatment selection.[3,4]

Recent development of the LAG-3 inhibitor, rela, expanded options for the treatment of metastatic melanoma. LAG-3 is a cell surface molecule that functions as a negative regulator of T-cell proliferation and function, and rela is a first-in-class lymphocyte activation gene 3 protein (LAG-3) blocking antibody that prevents T-cell inactivation by tumor cells. The 2022 study RELATIVITY-047 showed that combination of rela/nivo had twice the median PFS and a 25% reduction in risk of disease progression (PD) or death compared with nivo alone (hazard ratio [HR], 0.75; P = .006). The benefits observed with nivo/rela were similar to the benefits observed in combination PD-1/CTLA-4 therapy although the response rates on both arms were lower at 43% and 32%, respectively.[5]

The selection of frontline therapy for patients with metastatic disease is often based on patient characteristics and preferences. As a result, the autoimmune toxicities associated with different regimens play a huge role. While the rate of grade III/IV treatment-related AEs associated with single-agent PD-1 inhibition is roughly 10%-14%, the rate of grade III/IV treatment-related AEs associated with combination of ipi/nivo is roughly 55% and must be considered when selecting patients to receive this regimen. The rate of grade III-IV AEs observed with nivo/rela is somewhere between single-agent PD-1 inhibition and combination therapy at 18.9%.

Modifications in the dosing of combination of ipi/nivo regimens have shown some effectiveness in reducing the incidence of high-grade AEs associated with ICI

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PRACTICAL APPLICATIONS

Participants should be able to

- discuss selection of frontline therapy for metastatic melanoma,
- understand the choices for patients progressing after frontline therapy,
- select proper therapy for patients with melanoma brain metastases,
- understand the unique nature of uveal melanoma and its therapy, and
- support the enrollment on well-designed clinical trials to improve future therapy for metastatic melanoma.

treatment. The CheckMate 511 study found that using flipped-dose ipi/nivo (nivo 3 mg/kg plus ipi 1 mg/kg every 3 weeks for four doses followed by nivo maintenance) lowered the incidence of grade III-V AEs by 14% ($P = .006$) with overlapping OS and PFS curves.[6] However, the data with this regimen are much less mature than those with regular dose ipi/nivo, leading some clinicians to be concerned that responses might not be as durable.

Approximately 40%-50% of melanomas are found to have a mutation in the *BRAF* gene at the V600 location, and there have been numerous studies focused on the use of targeted BRAF and MEK inhibition in treatment of melanomas.[7-10] *BRAF* and *MEK* are both genes functioning in the mitogen-activated protein kinase (MAPK) signal transduction pathway, leading to increased cell division and proliferation, and, when mutated, become overactive with resultant tumor growth. The *BRAF* inhibitors vemurafenib (vem) and dabrafenib (dab) have efficacy as monotherapies in metastatic melanoma with *BRAF* V600E or V600K mutations. However, acquired resistance to *BRAF* inhibitors often develops due to aberrant reactivation of the MAPK pathway. Studies have shown that combining dab with the *MEK* inhibitor trametinib (tram) leads to improvements in treatment response in this population of patients, when compared with dab alone, because of delayed emergence of resistance.[7] These benefits have been observed even in long-term treatment, as evidenced in a 5-year landmark analysis showing long-term survival, particularly in patients with favorable baseline prognostic features.[8] Other combinations of BRAF/MEK inhibitors have also demonstrated benefit in the treatment of melanoma, which include vemurafenib with cobimetinib and encorafenib with binimetinib.[9,10] However, the combination of *BRAF/MEK* regimens is not without side effects and treatment with them carries a rate of grade III-IV AEs of 55% although side effects often respond quickly to treatment holds or reduction.

The question of which therapy, ICIs or targeted therapy, to start in patients with advanced *BRAF* V600 E/K–mutant melanoma was recently answered by two trials: the DREAMSeq and SECOMBIT trials. The DREAMSeq trial investigated optimal sequencing of treatment for patients with *BRAF* V600E/K–mutant melanoma by comparing ipi/nivo followed by dab/tram at progression against dab/tram followed by ipi/nivo at progression.[11] The study found that starting with ipi/nivo was associated with higher 2-year OS and durability of disease response versus the inverse sequence of dab/tram followed by ipi/nivo in all clinical subgroups examined. Recent tumor biology studies have suggested that resistance to *BRAF/MEK* inhibitor therapy results in a locally immunosuppressive tumor environment, preventing effective antigen presentation and immune system activation, and that initial treatment with immunotherapy may actually enhance responsiveness to targeted therapies among *BRAF*-mutated cancers. This study concluded that among patients with metastatic melanoma and *BRAF* V600E/K–mutated tumors, ipi/nivo should be considered the preferred first-line therapy for the majority of patients and has cemented ICI as the first-line choice for all patients with melanoma regardless of mutation status.[11] The SECOMBIT study was a phase II trial that randomly assigned patients to a combination of ipi/nivo, enco/bini, or enco/bini for 8 weeks, followed by ipi/nivo. It found a 3-year OS of 54% (95% CI, 41 to 67) for enco/bini as initial therapy, 62% (95% CI, 48 to 76) for ipi/nivo as initial therapy, and 60% (95% CI, 58 to 72) for a short course of targeted therapy followed by immunotherapy.[12] This trial confirms the benefit of starting patients with *BRAF* V600 mutations on immunotherapy. It also provides an alternate approach to be used in patients started on targeted therapy who did well with a switch at 8 weeks to immunotherapy.

Trials have been performed looking at the combination of ICI with *BRAF/MEK* inhibition. One such study, evaluating the efficacy of triplet therapy with dabrafenib/trametinib/pembro, found that this regimen conferred longer PFS and durability of response, although with greater toxicity than dabrafenib/trametinib alone (with a grade III-V AE rate of 58%).[13] Another trial examined vemurafenib, cobimetinib, and atezolizumab in combination and demonstrated a PFS benefit over targeted therapy alone.[14] However, the clinical application of triplet therapies has been limited by high toxicity rates and lack of comparison with ipi/nivo, nivo/rela, or single-agent ICI treatment. Further studies are ongoing on how best to combine immunotherapy with *BRAF/MEK*-targeted therapy.

The question that clinicians are faced with when discussing immune checkpoint inhibition with patients who have newly diagnosed metastatic melanoma is which ICI regimen to start. The options include single-agent PD-1 inhibition, combination of ipi/nivo at normal dosing or flipped dosing, and combination of nivo/rela. Each of these regimens have different levels of efficacy and different rates of severe

autoimmune toxicities. Factors that are used to make the decision include *BRAF* mutation, location of metastasis, symptoms associated with melanoma, and the underlying fitness and comorbid medical issues of patients. In addition, many patients have received ICI in the neoadjuvant or adjuvant setting before being diagnosed with metastatic disease, and this influences treatment choice (Table 1).

As noted earlier, many patients with metastatic melanoma are diagnosed after treatment with neoadjuvant or adjuvant PD-1 inhibition and thus have disease resistant to PD-1 inhibitor therapy. In patients previously treated with PD-1 inhibition alone, studies have demonstrated that the combination of immunotherapy with ipilimumab and nivolumab is more effective than ipilimumab alone with a rough response rate of 30% (95% CI, 18.4 to 40.6).[15,16] Data for nivolumab and relatlimab in patients who progressed on previous PD-1 inhibition are poor with a response rate of 12% (95% CI, 8.8 to 15.8).[17] Thus, in patients who progressed on adjuvant therapy, the combination of ipi/nivo would be predicted to have the highest response rate.

Trials testing novel agents in combination with PD-1 inhibition in initial treatment of patients with metastatic melanoma have had mixed success. Although Lag-3 inhibition was successful, three recent trials aimed at increasing tumor immune infiltrate all failed to improve treatment over PD-1 inhibition alone. These include an IDO inhibitor (epacadostat), a modified injectable herpes virus (talimogene laherparepvec), and a modified interleukin-2 (IL-2) agonist (bempegaldesleukin). Current frontline clinical trials are testing PD-1 inhibition in combination with HDAC inhibition, novel immunotherapies, vaccines, and many other agents. There are also efforts to test the administration of tumor-infiltrating lymphocytes (TILs) in treatment-naïve patients. TIL therapy involves extraction of infiltrating lymphocytes within tumors, ex vivo outgrowth and expansion of these cells, and adoptive transfer of the cells back to the patient with preparative lymphodepleting chemotherapy and IL-2. Objective responses have been observed among approximately one third of patients, and even in patients with heavily pretreated disease, and it was shown to be superior to single-agent ipilimumab in PD-1–refractory patients.[18-20]

Given the severe immune toxicities associated with ICIs, there are several important frontline trials looking at adding drugs to the combination of ipilimumab and nivolumab to reduce side effects. The addition of granulocyte-macrophage colony-stimulating factor to ipilimumab was previously shown to decrease toxicity, and a current study is testing this with the combination of ipi/nivo.[21] Ongoing studies are showing some promise in the use of tocilizumab, an IL-6 inhibitor, to reduce immune-related adverse effects, after finding increased expression of IL-6 in tumor tissue from patients treated with immune checkpoint inhibitors (ClinicalTrials.gov identifier: NCT03999749).

CHALLENGING SCENARIOS IN STAGE IV MELANOMA

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PD-1–Refractory Melanoma: Current Approaches and Future Considerations

Anti–PD-1 ICIs, both as a monotherapy and as a combination with either anti-CTLA4 or anti-LAG3 agents, provide robust and durable response rates in a large percentage of patients with advanced melanoma and are now a widely accepted backbone of frontline treatment, regardless of *BRAFV600* mutational status.[5,22-24] However, a large percentage of patients exhibit either primary resistance or acquired resistance after anti–PD-1 therapy.[25] The management of these patients presents an unmet need.[25,26]

Although continuous enrollment on prospective clinical trials remains the encouraged approach, we already have important insights available. The phase II SWOG S1616 trial focused on patients who exhibited a complete lack of response to anti–PD-1 (or PD-L1) monotherapy by treating them with ipi alone or in combination with continuous nivo. A significant PFS benefit was observed with the combination of ipi/nivo compared with ipi monotherapy (HR, 0.63; 90% CI, 0.41 to 0.97; $P = .037$) with the 6-month PFS of 34% and 13%, respectively.[27] This study also noted intriguing enhancement of intratumoral CD8+ cells in the tumor microenvironment (TME) with the combination of ICIs, particularly among those with a response, suggesting that anti-CTLA4 ICI may reverse primary resistance to the PD-1/L1 blockade. An additional prospective effort combining low-dose ipi (1 mg/kg every 3 weeks for four doses) with pembro in patients who progressed on anti–PD-1/L1 monotherapy noted a median PFS and OS of 5 and 24.7 months, respectively, and a duration of response of 16.6 months (95% CI, 7.9 to not reached).[16] These observations support consideration of combination of ipi plus anti–PD-1 in patients exhibiting resistance to frontline anti–PD-1 monotherapy. A reasonable alternative currently used for patients exhibiting primary or secondary resistance to anti–PD-1 ICI (without CNS involvement) includes the combination of nivo/rela. This is based on a promising signal of enhanced objective response rates (ORRs) and disease control rates of 12% and 45%, respectively, in a phase I/II patient cohort with advanced melanoma that progressed on or after previous anti–PD-1.[5,28] However, these data remain relatively immature awaiting long-term follow-up.

Targeted *BRAF* plus *MEK* inhibition is an approved therapy for patients with anti–PD-1-refractory *BRAFV6000*-mutant melanoma. *BRAF/MEK* inhibitors are commonly used in

TABLE 1. Treatments for Metastatic Melanoma

Line of Therapy	Patient Characteristics		First Choice of Regimen	Alternate Option	
First line	*BRAF*-mutant, reasonable PS	Brain metastasis, symptomatic metastasis, high M stage, high LDH	Ipilimumab and nivolumab	Nivolumab and relatlimab	Clinical trial first choice whenever available!!
	BRAF wt, reasonable PS	No brain metastasis, lower M stage	Nivolumab and relatlimab	Ipilimumab and nivolumab	
	Poor PS, autoimmune disorders	No brain metastasis	Single-agent PD-1 inhibition	BRAF/MEK inhibition if *BRAF V600*–positive	
	Progression on adjuvant PD-1 therapy		Ipilimumab and nivolumab	Nivolumab and relatlimab[a]	
Second line	Previous ipilimumab and nivolumab		BRAF/MEK inhibition if *BRAF V600*–positive	Nivolumab and relatlimab[a]	
	Previous PD-1 alone or nivolumab and relatlimab	Reasonable PS for additional therapy	Ipilimumab and nivolumab	BRAF/MEK inhibition if *BRAF V600*–positive	

Abbreviations: LDH, lactate dehydrogenase; M, metastasis; PS, performance status; wt, wild-type.
[a]Response rate for nivolumab/relatlimab post–PD-1 inhibition is 12%, which must be discussed when considering this regimen.

patients (1) who are considered ineligible for further ICI agents, (2) who require rapid disease control, and/or (3) who progress on combination of ICIs. The latter scenario is founded on early signals, suggesting CTLA-4 resistance in those previously receiving anti-PD1 plus anti-LAG3 regimens, with further validation needed.[29] Additional support for subsequent *BRAF/MEK* inhibition includes a post hoc analysis of the phase III (KEYNOTE-006) trial, where subsequent *BRAF/MEK* inhibition in patients with advanced melanoma who progressed on pembro achieved an ORR of 30.5% (95% CI, 19.2 to 43.9).[30] Given the suboptimal outcomes of targeted agents when compared with ICI regimens in the frontline setting, alternative options are needed in the anti-PD1 refractory setting.[31,32]

The underlying biology responsible for ICI resistance in melanoma is complex and remains a field of active investigation.[25,33,34] The TME appears to play a crucial role in the immunologic suppression by (1) lack of T-cell priming, (2) immune tolerance, (3) stromal adaptations, and (4) enhanced exhaustion of antitumoral CD8+ T cells with concurrent upregulation of regulatory T cells.[33] Given the high mutational burden associated with melanoma, the utilization of advanced single-cell spatial profiling of non–T-cell-inflamed and low interferon-γ expressing (cold) tumors is anticipated to provide neoepitope targets to be recognized by T lymphocytes and provides the basis of peptide vaccine therapies.[35] This approach has recently led to US Food and Drug Administration (FDA) fast-track approval of a personalized neoepitope vaccine (EVX-01) combined with anti–PD-1 (pembrolizumab) in the phase II study (KEYNOTE-D36).[36] Finally, although not FDA-approved at the time of this publication, an exciting non-ICI treatment option for patients with anti–PD-1 refractory melanoma includes adoptive cell therapy with TILs. A phase II trial with an autologous, centrally manufactured TIL (lifileucel) has observed an ORR of 36% (95% CI, 25 to 49), with 41.7% of these lasting for more than 24 moths and a median OS of 17.4 months, in a heavily pretreated patient cohort with PD-1–refractory melanoma.[19] A randomized phase III (M14TIL) trial comparing TIL therapy with ipilimumab monotherapy noted an ORR of 49% (95% CI, 38 to 60) vs 21% (95% CI, 13 to 32) along with a median PFS of 7.2 vs 3.1 months, respectively, in a cohort of patients with mostly PD-1 monotherapy–refractory melanoma.[20] Finally, a plethora of alternative approaches for patients with PD-1–refractory melanoma are ongoing.[23,37]

CNS Involvement

Metastatic disease involving CNS portends a poor prognosis. Melanoma brain metastases (MBM) occur at high rate (40%-60%) and account for approximately 54% of melanoma deaths.[38] This high-risk subset remains underrepresented in trials given exclusion of MBM in major clinical trials to date. However, retrospective and small prospective studies dedicated to this group revealed important observations leading to substantial improvements in response and survival for certain subsets of patients.[38-40]

The phase II COMBI-MB trial, with *BRAF/MEK* combination (dabrafenib plus trametinib) in patients with *BRAFV600* mutation, achieved intracranial responses in 58% (95% CI, 46 to 69) of patients with asymptomatic and treatment-naïve disease, a median duration of response of 6.5 (95% CI, 4.9 to 10.3) months, a mPFS of 5.6 (95% CI, 5.3 to 7.4) months, and an OS of 10.8 (95% CI, 8.7 to 19.6) months.[41] Additional studies involving *BRAF* and *MEK* inhibitors at higher doses (ClinicalTrials.gov identifier: NCT03911869) or in combination with ICIs (ClinicalTrials.gov identifiers: NCT03625141 and NCT04511013) and novel agents

(ClinicalTrials.gov identifier: NCT02159066) for patients with *BRAFV600*-mutant MBM are ongoing.[38]

In patients with asymptomatic MBM, a phase II trial with anti-CTLA4 (ipilimumab) achieved intracranial disease control at 12 weeks in 24% with a median OS of 7 months (95% CI, 4.1 to 10.8).[42] A phase II trial with anti-PD1 (pembrolizumab) noted an ORR of 22% and a median OS of 17 months (95% CI, 10 to not reached) in a similar population.[43] Similar response rates (20%; 95% CI, 7 to 41) were observed in the phase II (ABC) trial using anti–PD-1 (nivolumab) for patients with asymptomatic MBM.[44] Five-year intracranial PFS and OS rates of 46% and 51% for the ipi/nivo ABC trial arm, compared with 15% and 34% for nivolumab monotherapy in the asymptomatic patient cohort, were observed. The combination of ipilimumab plus nivolumab phase II (CheckMate 204) trial observed an ORR of 54% (95% CI, 43.3 to 63.5) and a 36-month intracranial PFS of 54% (OS 72%) for patients with asymptomatic MBM.[45,46] Given the durable intra- and extracranial response and survival rates observed in these two trials, up-front combination of ICIs (ipilimumab plus nivolumab) is currently considered an optimal approach for patients with asymptomatic MBM. This combination is preferred over frontline targeted therapy in patients with asymptomatic MBM and *BRAFV600* mutation, supported by expert consensus and prospective and real-world analyses.[31,32,47,48] Prospective trials are ongoing to elucidate the additional benefit of ICI combined with stereotactic radiosurgery (SRS) or *BRAF/MEK* (ClinicalTrials.gov identifier: NCT04511013).[40,49-53]

Patients with symptomatic MBM, requiring >10 mg daily prednisone-equivalent steroids, exhibited substantially worse response and survival rates in all trials where such cohorts were included.[40,46] These likely reflect a larger disease burden, need for larger doses of systemic steroids, and unique TME.[38] Responses to ICI are reduced in those with exclusively intracranial disease, suggesting that ICI may augment CD8+ T-cell trafficking via peripheral immune T-cell expansion to achieve a more robust intracranial response.[40,54] Development of relevant biomarkers is an area of ongoing research.[26,55]

Additional Considerations: Autoimmune Disease

Given the systemic autoinflammatory pathophysiology associated with irAEs, patients with an underlying autoimmune disease have historically been excluded from major clinical trials and therefore are largely under-represented within the currently available prospective data, supporting ICIs in a variety of cancer subtypes.[56] A systematic review of patients with cancer (mostly melanoma) and concurrent autoimmune disease noted 41% experienced a flare of their underlying condition, 25% developed de novo irAEs, and 9% experienced both preexisting flares and de novo events upon initiation of ICI, with a signal of anti-CTLA4 ICI more commonly associated with flares of the underlying disease and anti-PD1 ICI triggering new irAEs.[56] Importantly, there was no observed difference in irAE rates in those with active compared with inactive pre-existing autoimmunity at the time of ICI initiation, and although irAEs were controlled without the need to discontinue ICI in more than half of the patients, the rates of grade 5 irAEs were higher than the general population at 2.4%.[56] Additional cohort studies observed that 71% of patients with underlying autoimmune diseases developed either worsening of their pre-existing condition or a new irAE on initiation of ICI.[57] This study also noted a trend in reduced PFS in those with autoimmune flares and irAEs compared with those without such events, mostly in patients requiring systemic immunosuppressants and/or ICI discontinuation.[57] The high doses of systemic glucocorticoids, especially in the early phases of ICI initiation, may blunt the response to ICI that is historically associated with patients who develop irAE compared with those who do not.[58-60] These observations suggest that the use of systemic glucocorticoids, although oftentimes required in the management of severe irAE, should be considered judiciously in those experiencing low-grade irAE events and/or indolent autoimmune conditions especially in the early phases of ICI initiation.[58,61-64]

UVEAL MELANOMA: CHANGING PARADIGMS OF TREATMENT

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UM is the most common primary intraocular malignancy in adults, albeit a rare melanoma subtype, characterized by the absence of *BRAF*, *NRAS*, or *KIT* mutation but recurrent, mutually exclusive, and early oncogenic mutations in the Gαq pathway (mostly *GNAQ/11*)[65]; the inactivation of these Gα proteins results in activation of downstream signaling cascades, including the MAPK, PI3K-AKT, and YAP pathways.[66]

Despite a highly effective management of the ocular tumor, up to 50% of patients develop metastases by hematogenous dissemination, with occult micrometastases before the detection of the primary eye tumor. The liver is the first site of metastasis in more than 90% of patients.[67] Because of limited efficacy of available regional and systemic therapies, OS is poor and the historical median OS is 1 year after the first metastatic event.[68,69] Until recently, no systemic treatment had demonstrated any survival benefit. In January 2022, tebentafusp became the first systemic therapy to receive regulatory approval in this treatment-resistant cancer.

Tebentafusp is a T-cell–redirecting bispecific fusion protein HLA A*02:01–restricted, using a high-affinity T-cell receptor targeting glycoprotein 100 (gp100), a melanocyte

lineage–specific antigen highly expressed on UM cells, and fused to an anti-CD3 single-chain variable fragment. Once bound to the gp100-HLA complex, tebentafusp recruits and activates polyclonal T cells through CD3 ligation to release cytokines and cytolytic mediators.[70]

In the open-label, phase III, IMCgp100-202 trial, 378 HLA A*02:01–positive patients with first-line systemic metastatic UM were randomly assigned (2:1) to receive tebentafusp or the investigator's choice of pembrolizumab (82%), ipilimumab, or dacarbazine. After a median follow-up of 14 months, the improvement in OS was highly significant, with an estimated median OS duration of 21.7 months in the tebentafusp group versus 16 months in the control group and a 1-year OS rate of 73% versus 59% (HR, 0.51; 95% CI, 0.37 to 0.71; $P < .001$).[71] This unprecedented result is weighted by a modest although significant benefit in PFS (median PFS 3.3 *v* 2.9 months; 31% *v* 19% at 6 months; HR, 0.73, 95% CI, 0.58 to 0.94; $P = .01$) and a low ORR of 9% versus 5%.

Moreover, an OS benefit was observed in patients with best objective response of RECIST 1.1 PD on tebentafusp compared with the control group (HR, 0.43) and who continued tebentafusp beyond initial radiographic progression. According to the protocol, 109 patients received tebentafusp beyond progression and 39 had a clinical benefit (ORR or SD >3 months); the OS benefit was sustainable after adjusting for all covariates (HR, 0.7).[72] Investigations are underway to understand the decoupling of RECIST-based radiographic assessment and OS benefit: There is a need for new measures of clinical activity with this new class of immuno-oncology therapies and for predictive biomarkers of response or resistance.

Indeed, the underlying practical question is closely related to the optimal way to monitor tebentafusp treatment: (1) in patients with stable disease for uninterrupted months or years of weekly infusions and (2) in patients with RECIST or irRECIST PD in the absence of any disease symptoms or treatment-related AEs. What is the optimal duration of treatment? Which discontinuation rules can be outlined?

Because of the lack of correlation between survival benefit and OR rate and a weak PFS gain in tebentafusp versus the investigator's choice, an update of the 202 trial with longer follow-up is very much awaited.

UM has a very low mutational burden, making analysis of circulating tumor DNA (ctDNA) challenging.[73] In a single-arm, phase II trial of tebentafusp in 127 previously treated patients with metastatic UM, 84% with evaluable serum samples had detectable ctDNA at baseline and on treatment, measured with multiplex PCR followed by next-generation sequencing for major UM-specific genes (*GNAQ*, *GNA11*, *SF3B1*, *PLCB4*, *CYSLTR2*, *EIF1AX*). The magnitude of ctDNA reduction after 9 weeks of tebentafusp correlated with improvement in OS using a logarithmic scale ($R^2 = 0.88$, $P < .0001$): 14% of patients achieved complete ctDNA clearance, including patients with a best response of PD.[74] TILs and tumor necrosis may mimic a radiographic progression with changes in tumor size because of immune infiltration and activation rather than tumor growth; further studies are needed to confirm that ctDNA is a surrogate marker more accurate than imaging response criteria to assess tebentafusp benefit in patients with metastatic UM. ctDNA results from the prospective phase III trial 202 are required before ctDNA analyses can be added to routine clinical practice to early identify patients benefiting most from tebentafusp.

Assessment of OR by RECIST or irRECIST criteria underestimates the clinical benefit from tebentafusp treatment. Considering growth kinetics and providing a quantitative evaluation of tumor volume changes over time on the basis of the sum of the largest target lesion diameters, the tumor growth rate may provide additional information compared with standard RECIST criteria on the basis of unidimensional assessment of target lesions.[75]

Moreover, the mechanism of action and the safety profile of tebentafusp may encourage trials combining or sequencing tebentafusp with other systemic treatments. Preclinical data suggest that tebentafusp induces and potentiates antigen cross-presentation by dendritic cells.[76] The changes induced by tebentafusp in the tumor TME may increase the efficacy of the checkpoint blockade; this is attested by post-tebentafusp biopsies showing increased expression of PD-L1 and PD-1. To investigate the outcomes from patients treated with checkpoint inhibition (CPI), pre- or post-tebentafusp may help to build the next prospective clinical trials in UM.

Regional therapies could also be tested with tebentafusp in selected patients with UM with a limited metastatic disease, combining clinical outcomes and immunologic end points.

Finally, adjuvant and/or neoadjuvant studies should be launched in the near future for patients at high risk of metastasis through international collaborations and networks including the Collaborative Ocular Oncology Group, the International Rare Cancer Initiative, EURACAN, and Patient Advocacy Groups as Cure OM and Melanoma Patient Network Europe.[77]

IMC-F106C, a new bispecific molecule targeting an HLA A*02:01–restricted epitope of PRAME, the most broadly expressed cancer testis antigen in many tumors, such as lung, ovarian, endometrial, or melanoma, is currently tested as a single agent and in combination with CPI (ClinicalTrials.gov identifier: NCT04262466). Preliminary results showed durable RECIST partial responses and ctDNA response in PRAME-positive patients across multiple tumor types, including UM.[78]

A major limitation of immune-mobilizing monoclonal T-cell receptor against cancer (ImmTAC) molecules is HLA restriction. Main ImmTACs target HLA A*02, which is represented at its highest frequency (around 45%) in the White population.[79] For patients with metastatic UM who are not HLA A*02:01–positive, current options are locoregional strategies focused on the liver, alone or combined with systemic therapies, depending on the extent of metastases; CPI in monotherapy or combination with no evidence of survival benefit; or a clinical trial.[66]

One alternative for half of patients with HLA A*02:01–negative UM could be the development of ImmTACs targeting peptides on other HLA alleles. Other challenges for T-cell–engaging bispecific molecules include selecting the most relevant targets, achieving optimal dosing, reaching higher efficacy, and overcoming tumor resistance.[80]

Giving the immunosuppressive hepatic microenvironment in UM metastases, exploration of new immunotherapy strategies to enhance antitumor immune response is of high interest. Cellular therapies with autologous TILs harvested from UM metastases demonstrated an ORR of 35% in 20 evaluable patients in a single-center phase II study, but survival data are lacking.[81]

LAG-3 is a negative regulator of T cells, leading to immune escape of cancers through T-cell dysfunction and immune exhaustion.[82] Single-cell RNA sequencing showed that most CD8 cytotoxic T cells in UM expressed LAG3 at a high level and correlated with high risk of metastasis.[83,84] A single-arm, Simon, two-stage, phase II trial of relatlimab and nivolumab in patients with metastatic UM is recruiting (ClinicalTrials.gov identifier: NCT04552223).

The combination of MDM2 inhibitor APG-115 with pembrolizumab has demonstrated synergy in vitro via depletion of M2 macrophages from the TME as a result of p53 activation and is tested in a phase I/II study in solid tumors (ClinicalTrials.gov identifier: NCT03611868), showing encouraging results in UM.[85] Two phase II studies combining lenvatinib and pembrolizumab in patients with CPI-naïve metastatic UM are also recruiting (ClinicalTrials.gov identifiers: NCT05308901 and NCT05282901).

Multiple other emerging strategies are being investigated, including agents targeting protein kinase C, a downstream element of the Gαq signaling pathway. After disappointing results with first-generation sotrastaurin[86] and limited activity of second-generation LXS196/IDE196 in monotherapy,[87] the combination of IDE196/darovasertib with crizotinib showed a promising ORR of 31% in 35 evaluable patients (ClinicalTrials.gov identifier: NCT03947385).[66]

Focal adhesion kinase inhibitors target YAP oncogenic activation related to *GNAQ/11* mutations and are currently evaluated in monotherapy or in combination with MEK inhibitors (ClinicalTrials.gov identifiers: NCT04109456 and NCT04720417).

DYP-688 is a first-in-class PMEL17 targeting antibody-drug conjugate (ADC), a melanocyte lineage protein highly expressed in cutaneous and UM. On ADC binding to PMEL17 on the target cells, the linker is cleaved to release SDZ475, which inhibits *GNAQ/11* oncogenic signaling, resulting in dose-dependent apoptosis. A multicenter phase I/II trial is recruiting patients with metastatic UM and other *GNAQ/11*-mutant melanoma (ClinicalTrials.gov identifier: NCT05415072). Epigenetic approaches and combination of regional and systemic therapies are also developed.[66]

Finally, patient preferences need to be integrated into clinical trials, with the aim of improving patient satisfaction regarding information and supportive care, through tailored patient-reported outcomes[88] and dedicated studies (ClinicalTrials.gov identifier: NCT04728113).

CONCLUSIONS

The frontline treatment for advanced melanoma has significantly evolved in recent years with considerable improvement in disease response and survival. Currently approved first-line treatment options include PD-1 inhibition on its own, combination of nivo/rela, combination of ipi/nivo, and combination of *BRAF/MEK* inhibitors. Future research into biomarkers for treatment selection and tools such as ctDNA to monitor efficacy of therapy will help guide treatment selection.

Challenges remain for treatment of patients with CKI-refractory disease, progression after CKI combinations, CNS involvement, and both pre-existing and acquired autoimmune conditions where clinical trials should be prioritized. Randomized prospective data now exist for anti-CTLA4 (ipi) combined with anti-PD1 (nivo) and for TILs in patients with melanoma resistant to frontline anti-PD1 monotherapy. Data for other second-line options, including TCR engagers and personalized neoepitope vaccines, are eagerly anticipated. The optimal approach to patients with MBM who do not respond or are unable to receive ipi/nivo combination is unknown. dab/tram combination therapy is effective for patients with *BRAF* V600–mutated tumors, but the long-term durability of responses remains suboptimal. Better therapy strategies are needed for patients with pre-existing autoimmune conditions and those who develop higher-grade irAEs on ICI therapies, aiming to preserve the efficacy without worsening both acute and chronic toxicities.

UM is a distinct disease from its skin counterpart. It has a dismal prognosis and does not respond readily to existing therapies. Recent advances in our understanding of its

genomic and immunologic characteristics, driven by dedicated, international collaborations, have resulted in novel promising treatment strategies. Tebentafusp is the first-ever FDA-approved therapy, specifically in UM, improving OS. For the sake of our patients, we hope for more breakthroughs in the near future.

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Patient-Reported Outcomes in Pediatric Patients With Cancer

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overview

Patient-reported outcomes (PROs) are reported directly by the patients about their own health. The objective of this article was to provide an overview of PROs in pediatric cancer, to describe how PROs can be incorporated into pediatric cancer clinical trials, and to discuss how PROs can guide symptom management treatment choices in pediatric oncology. Pediatric patient self-report provides a distinct voice in describing their experience compared with family caregiver or clinician report. Thus, every effort should be made to allow children to self-report symptoms, functioning, and other quality-of-life impacts and to use that data to inform treatment decision making. In addition to its incorporation into routine clinical care, it is also important to incorporate PROs into clinical trials to understand the patient experience of treatment toxicities and their impact on quality of life. Key considerations include clearly articulated PRO aims, selection of outcomes, choice of PRO measures, and frequency of PRO assessments. Once PROs are integrated into routine clinical care, it will be important to enable evidence-based symptom management. Strategies should be based on clinical practice guidelines (CPGs). Development and adaptation of care pathways on the basis of CPGs is one approach to standardize evidence-based symptom management at individual institutions. PROs are important to pediatric patients with cancer and their families. Self-report should be emphasized wherever possible. Approaches to enable PRO reporting into routine clinical care and enable preventative and therapeutic actions for symptom management are important. These efforts will optimize quality of life for pediatric patients with cancer.

INTRODUCTION

Pediatric patients with cancer have excellent survival outcomes related to improved treatment strategies including immunotherapy and more precise risk stratification.[1] This accomplishment can be attributed to multicenter clinical trials and evidence-based standardization of cancer treatments. However, such standardization has not been achieved across cancer care settings, including supportive care.[2] Supportive care encompasses all aspects of care apart from that related to the cancer diagnosis and treatment and includes quality of life, organ toxicities, and infectious complications as examples. One aspect that is important to patients, their families, their treating clinicians, and researchers is patient-reported outcomes (PROs).[3]

PROs are reported directly by the patients about their own health and include subjective outcomes, such as physical function, pain, nausea, and fatigue.[4] In pediatric cancer, PROs are important because neither clinicians nor caregivers provide concordant ratings compared with those reported by the patients themselves.[5] However, many gaps remain before PROs can be implemented into routine clinical practice and influence clinical actions to address them. The objective of this review was to provide an overview of PROs in pediatric cancer, to describe how PROs can be incorporated into pediatric cancer clinical trials, and to discuss how PROs can guide treatment choices in pediatric oncology. Figure 1 provides an overview of these issues.

Listen to the Children: Giving Children a Voice in Reporting on Their Health-Related Quality of Life

Health-related quality of life (HRQOL) is a broad multidimensional construct that describes the impact of cancer and its treatments on the lives of children in terms of physical, mental, and social well-being.[6-8] As most of the HRQOL domains are subjective in nature,[9] children self-reporting on their HRQOL (ie, PROs) is essential to minimize child suffering and improve tolerance of treatments. If the treating clinicians are aware of what the child is experiencing, they can implement symptom management strategies to make sure the child can continue cancer treatment or consider treatment modification to a less intensive regimen. As a result, the child will receive the maximum benefit from the anticancer treatments.

In adult cancer settings, it is generally accepted that patients should self-report on their HRQOL impact

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PRACTICAL APPLICATIONS

- Patient-reported outcomes (PROs) are reported directly by patients about their own health.
- Pediatric patient self-report provides a distinct voice in describing their experience compared with family caregiver or clinician report, and thus, every effort should be made to allow children to self-report their symptoms, functioning, and other quality-of-life impacts.
- Incorporation of PROs into clinical trials provides critical information about toxicities and the tolerability of treatment; important considerations when evaluating PROs in clinical trials include clearly articulated PRO aims, selection of PROs, choice of PRO measures, and frequency of PRO assessments.
- For routine clinical care, symptom management should be based on clinical practice guidelines; development and adaptation of care pathways is one approach to standardize evidence-based symptom management at individual institutions.

using PRO measures. However, in pediatric settings, there is not the same level of buy-in that the child can provide valid information on their HRQOL despite the existence of well-validated PRO measures, such as the National Institutes of Health's (NIH's) Patient-Reported Outcome Measurement Information System (PROMIS) Pediatric measures,[10,11] the National Cancer Institute's (NCI's) Pediatric PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE),[12,13] and the Symptom Screening in Pediatrics Tool (SSPedi).[14-16] Table 1 shows examples of PRO measures that assess multiple HRQOL dimensions. The lower acceptance of PROs in pediatric settings may be due to a lack of awareness of these PRO tools. However, there is a perception that clinician- and family caregiver-proxy reports are sufficient for understanding the child's experiences. Thus, our focus for this section is to examine the extent to which the child provides a distinct voice in describing their HRQOL impact from cancer and treatment. Multiple studies have examined this issue[22-25]; we will summarize some illustrative studies below.

In one of the largest studies to date, Freyer et al[5] examined the level of concordance among the triad of the children, their family caregivers, and their treating clinicians for reporting symptomatic adverse events (AEs) associated with cancer treatment. The total sample included 438 children with 41% between age 7 and 12 years, 30% between age 13 and 15 years, and 29% between age 16 and 18 years. The sample was diverse in terms of sex, race, and cancer types. Most children (92%) were reporting on symptomatic AEs associated with recently received chemotherapy within the past 1-2 weeks, with the remaining children receiving radiation therapy (6%) or hematopoietic cell transplant (2%). The agreement between children and their family caregivers ranged from good for more observable symptoms such as vomiting (weighted kappa = 0.60) to fair for more

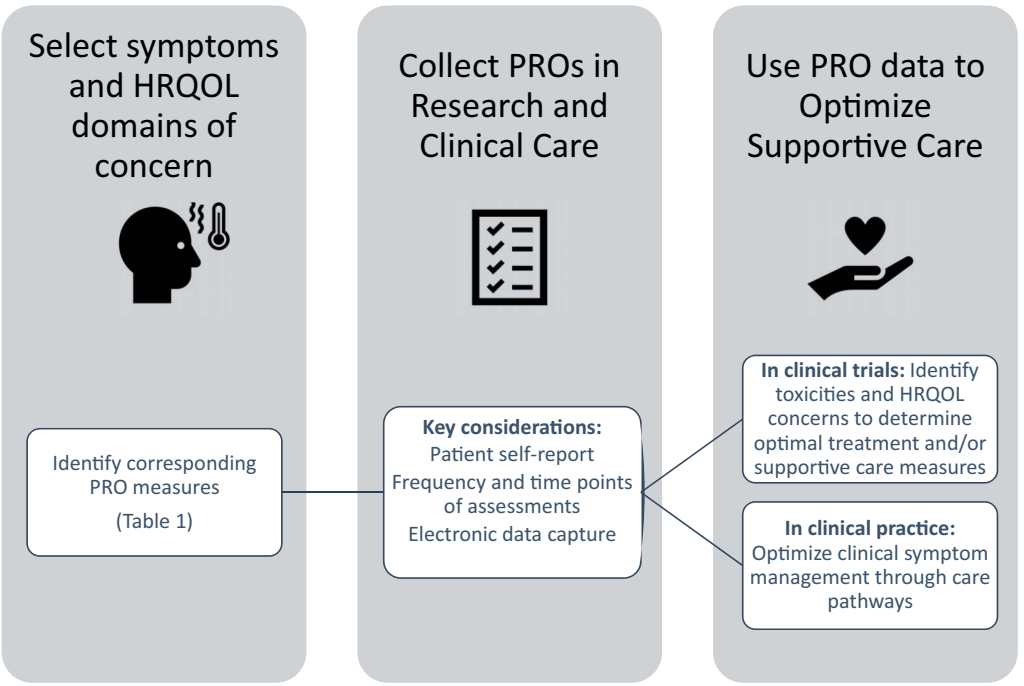

FIG 1. Optimal incorporation of PROs in pediatric oncology research and clinical care. HRQOL, health-related quality of life; PROs, patient-reported outcomes.

TABLE 1. Examples of Patient-Reported Outcome Measures Commonly Used in Pediatric Patients That Capture Multiple Aspects of HRQOL

Patient-Reported Outcome Tool	Age Validated for Self-Report (years)	Constructs Measured
Patient-Reported Outcome Measurement Information System (PROMIS) Pediatric measures[10,11]	8-17	Symptoms, functioning, HRQOL
Pediatric Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (Pediatric PRO-CTCAE)[12,13]	7-18	Symptomatic adverse events
Symptom Screening in Pediatrics Tool (SSPedi)[14-16]	8-18	Bothersome symptoms
Mini-SSPedi[17]	4-7	Bothersome symptoms
Memorial Symptom Assessment Scale[18,19]	7-12; 10-18	Symptoms
Pediatric Quality of Life Inventory (PedsQL)[20]	8-18	HRQOL
KidScreen[21]	8-18	HRQOL

Abbreviation: HRQOL, health-related quality of life.

unobservable symptoms such as depression (weighted kappa = 0.24). The agreement between children and their treating clinicians ranged from fair for more observable symptoms such as anorexia (0.35) to poor for unobservable symptoms such as fatigue (weighted kappa = 0.11) and depression (weighted kappa = 0.15). Across all 15 symptomatic AEs reviewed in the study, consistently clinicians reported significantly lower symptomatic AE grades than children, with family caregivers reporting grades closer but still not similar to the children's self-reports.

Using the same participants from the study of Freyer et al,[5] Maurer et al[26] examined performance status ratings, which are important for determining eligibility for clinical trials. On average, clinicians reported statistically significant better performance status than family caregivers ($P < .01$) using the Lansky Play-Performance Scale (LPPS). Approximately 63% of clinicians placed the child in a higher LPPS level than the caregivers. Using a LPPS threshold of 60 that is commonly used for clinical trial eligibility, 25.6% of clinicians would have deemed a child eligible, but the caregivers reported LPPS scores below the threshold. Moderate correlations were found between the family caregivers' LPPS ratings and the children's self-reported physical function (via PROMIS; $r = 0.45$) and between the clinicians' LPPS ratings and the children's self-reported physical function ($r = 0.35$).

Both the studies summarized above are consistent with other studies and together demonstrate a clear picture that children provide a distinct voice in reporting how cancer and cancer treatment affect their lives physically, mentally, and socially. Every effort should be made to allow children to self-report their HRQOL and to use that data to inform treatment decision making. Most PRO measures are validated for children as young as 8 years as that is a typical age when children can read PRO questions independently.[27] Some PRO measures have been adapted to be completed by children as young as 4-5 years.[15] In a recent survey among 376 pediatric oncology clinicians with at least 2 years of experience treating children with cancer, 99% reported that 6- to 7-year-old children are able to describe their subjective symptoms by 3-4 months postdiagnosis (58% at the time of diagnosis) and 84% of clinicians reported that 4- to 5-year-old children are able to describe their symptoms by 3-4 months postdiagnosis (19% at the time of diagnosis).[28] For 4- to 7-year-old children, almost all clinicians (>97%) reported they would likely use the children's self-reported symptom data for managing the child's symptoms if the data were collected from a validated PRO measure. An advantage of mini-SSPedi (age 4-7 years)[17] and SSPedi (age 8-18 years) is the availability of an audio function that allows the entire instrument or specific questions to be read aloud to the child. As a promising approach to facilitate young children to self-report symptoms, co-SSPedi is a structured dyadic approach in which the child voices symptoms first, and their assessment is supported by their family caregiver.[29,30]

Together, there is strong evidence and support for allowing children to self-report their HRQOL impact and to use that information to inform cancer care. The number of questions that can be included and the frequency of administration are likely to vary by age and acuity of illness such that clinically important PROs can be identified while minimizing patient burden for completing questionnaires. We also want to recognize that both the family caregivers' perspectives and the treating clinicians' perspectives are important in understanding the HRQOL impact on the children. The differences in ratings and scores do not suggest that one reporter is right and the others are wrong. Instead, their reports reflect different experiences and perspectives with the common goal among all to improve the children's HRQOL. Thus, we must learn how to use all three voices to inform care for the children, importantly valuing the children's perspectives that have typically been ignored.[31] There is additional value to learn how to use the family

caregivers' and clinicians' reports, particularly at times when the child is too ill or unable or unwilling to self-report their HRQOL. Recognizing the value of PRO measures for capturing the distinct voices of the children, subsequent sections of this article focus on integrating PROs in clinical trials and how clinicians should respond to PROs whether obtained during routine clinical care or during trials.

Incorporation of PRO Aims and Outcomes in Pediatric Clinical Trials

Rationale for PRO incorporation in pediatric cancer clinical trials. It is not only important to measure PROs during clinical care but also to measure PROs during the conduct of clinical trials. As iterative cooperative group trials have led to tremendous improvements in survival for many pediatric malignancies,[1] many current clinical trials focus on risk-stratified care to reduce treatment toxicities and improve HRQOL for those diseases with excellent outcomes. Other clinical trials seek to improve outcomes for difficult-to-treat diseases through the addition of novel therapeutics, many with poorly described toxicities. Incorporation of PRO aims, measures, and outcomes is critical to understanding the patient experience of these toxicities and the impact of therapy on symptoms and HRQOL during and after treatment. PRO measures can help answer primary study questions about tolerability where there may be similar efficacy between treatment arms, and PROs can help determine what supportive care interventions are needed and when to use them. As described above, it is particularly important that clinical trials incorporate direct patient reporting as clinician and family caregiver reports frequently do not align with the patient experience of toxicities or HRQOL.[5,32] Yet, PRO aims and measures have often been excluded from pediatric clinical trials. Only four of 17 recent drug trials of novel agents in pediatric oncology included PROs,[33] and other studies suggested that PROs are incorporated in <20% of pediatric and adolescent and young adult (AYA) clinical trials.[34,35] In the following sections, we suggest key considerations for optimizing the inclusion of PROs in pediatric cancer clinical trials.

Determination of PRO aims and how they contribute to a study's overarching aims. Early consideration of PROs is important starting from the concept development stage. After identifying key study outcomes and goals, we consider whether some of these outcomes may be best captured by direct patient report or whether a combination of clinical data complimented by PROs may be helpful. For example, in studies that incorporate novel agents in combination with cytotoxic chemotherapy where study outcomes of interest include understanding the added toxicities of novel agents to combination therapy, both clinician-reported and patient-reported toxicities should be used. PRO aims should be structured and written in the same format as disease response and survival aims. They must be clear, specific, and measurable, and their role in determining the primary trial outcome should be clearly apparent. Instead of referring to PROs broadly, we recommend selecting and describing the primary PRO(s) of interest in the aims, even if a more comprehensive battery of PROs will be collected. Moreover, as with any concept to be measured, PROs should only be incorporated in clinical trials if their collection will contribute to a specific study aim.

Optimal measures and outcomes. Similar to the challenges of determining which laboratory studies and biospecimens should be collected in a clinical trial, consideration must be paid to ensuring that all necessary PRO data are collected while minimizing participant burden. The outcomes of interest should be determined before the selection of optimal PRO measures (Table 1). However, it is worth considering the inclusion of some PRO batteries both to allow comparison of PROs across studies over time and to ensure that unexpected toxicities are not overlooked. The NCTN AYA PRO task force recommends inclusion of PROMIS health status short forms to address core HRQOL domains and the PRO-CTCAE and Pediatric PRO-CTCAE to capture symptoms and toxicities, across all AYA clinical trials.[36]

In cross-network clinical trials that enroll both children and adults, there are many existing validated and reliable tools within the public domain that have aligned pediatric and adult measures such as PROMIS.[37] PROMIS measures have well-established psychometric properties in both pediatric and adult oncology populations including responsiveness to change over time.[38-40] The Pediatric and Adult PROMIS measures have been shown to be comparable conceptually across the age continuum with no evidence of differential item functioning on the basis of age.[41] Similarly, PRO-CTCAE and its corresponding pediatric version, the Pediatric PRO-CTCAE, were designed for use in clinical trials to identify patient experience of symptomatic AEs and their change over time. Both the NCI and the Food and Drug Administration have endorsed the use of the Pediatric PRO-CTCAE in pediatric clinical trials.[13,42] These tools can be used to measure patient reports of the frequency, severity, and interference of core symptoms, and additional potential toxicities of interest can also be assessed on the basis of specific treatments. Other study-specific questions can be addressed through the inclusion of other validated measures and items.

Time points of collection. In clinical trials, the frequency and specific time points of PRO collection should be driven by the research question, and decisions need to be made about whether the outcome of interest is the change in PROs over time or the difference between PROs at a given moment in time. For example, in a current cross-network

osteosarcoma trial evaluating the optimal surgical approach to pulmonary metastatic osteosarcoma (COG AOST2031), we are comparing the patient experience of pain between a thoracoscopic approach and open thoracotomy immediately postoperatively and several weeks postoperatively. A study of postoperative pain in adults with lung cancer found that those who underwent a thoracoscopic procedure had significantly less pain immediately postoperatively, but the difference in pain scores between groups decreased over time.[43] Therefore, we were careful to select our time points of interest to ensure that we do not inadvertently miss a clinically important difference in the patient experience by measuring pain at the wrong time.

Ensuring sufficient number of time points and PRO collection beyond active therapy and into survivorship are also important considerations to ensure meaningful data. However, in clinical trials, frequent assessments may prove overly burdensome to respondents and may result in nonparticipation and missing data. Thus, it is important to balance frequent assessments to identify changes in PROs against feasibility and respondent burden. Furthermore, large time lapses between PRO assessments or extending PRO assessments far into the post-treatment period come with concerns of losing patients to follow-up or decreased engagement.[44]

PRO data collection strategies and the role of electronic data collection. Historically, paper-and-pencil data collection has been used in pediatric clinical trials despite the associated inefficiencies of data collection and data entry and despite patient preference for electronic data capture (EDC).[45] PROMIS, PRO-CTCAE, and SSPedi have electronic data collection options that can be completed on a patient's own computer, smartphone, or tablet. EDC also allows for central PRO collection, thereby substantially minimizing individual participating site burden. The NCTN AYA Task Force and the Children's Oncology Group have recently devoted substantial resources and efforts to develop and pilot an EDC strategy using the REDCap platform in several cross-network trials. However, electronic data collection, particularly in pediatric clinical trials, requires further research. Unanswered questions include the optimal strategy for ensuring direct patient report from younger children who may not have their own electronic device. There is also some concern that EDC may not be as successful for some particularly vulnerable populations.[46] Finally, although central EDC relieves some of the site burden in PRO data collection, individual sites may be unaware of concerning symptoms reported by patients using PRO measures. Future PROs collected via EDC in cooperative group clinical trials may consider using existing strategies to report back worrisome patient-reported toxicities to clinicians, particularly those that may require timely intervention such as uncontrolled severe pain.

Who are we missing? Throughout these efforts to incorporate PROs in pediatric cancer clinical trials, we must continually ask ourselves whose voices may be missing. Optimal strategies for including the concerns of very young patients and ways of ensuring participation and representation of vulnerable populations with differential access to, or comfort with, EDC are warranted. Furthermore, although adult PRO measures have available translations in numerous languages, translations of pediatric PRO measures are greatly lacking and limit our knowledge of the experiences of many children. Despite these ongoing questions and challenges, PRO collection in pediatric clinical trials plays an important role in our understanding of toxicities, treatment tolerability, and long-term outcomes of treatments investigated in clinical trials. The following section examines how symptoms identified by PRO measures should be addressed in health care delivery settings.

How PROs Can Guide Symptom Management Treatment Choices in Pediatric Oncology

Approaches to prevent and treat symptoms. Whether PROs are identified during routine clinical care or during conduct of a clinical trial, it is important that clinicians act on these reports. More specifically, action to prevent and treat toxicities and concerns identified through PROs is critical to optimizing supportive care and symptom burden. One of the many challenges to symptom control is the multitude of possible symptoms, with each one having its own unique evidence base to guide preventative and therapeutic options. Furthermore, the number of studies being published continues to grow exponentially.[47] As oncologists must be aware of advances in cancer diagnosis and treatment, it is not reasonable to expect them to also keep pace with advances in supportive care. Thus, to optimize symptom prevention and treatment, approaches are required to facilitate evidence-based clinical care. These approaches should be clinical practice guideline (CPG) development[48] and tools to facilitate implementation of CPGs into clinical practice, such as care pathways. They will lead to the standardization of symptom management and are likely to improve outcomes for patients, similar to that achieved related to protocolization of cancer treatment improving cancer outcomes.[49]

The current status of symptom intervention is likely poor in pediatric cancer care. For example, one study examined the medical records of 168 pediatric patients age 8-18 years who self-reported severely bothersome symptoms using SSPedi.[50] Interventions were uncommonly provided. The following severely bothersome symptoms were never treated: thinking or remembering things, changes in how your body or face look, tingly or numb hands or feet, changes in taste, or diarrhea. Failure to provide treatments when concerning symptoms are identified through PROs may be related to lack of awareness of effective strategies to manage symptoms.

Symptom prevention and treatment should be based on CPGs. CPGs are documents that include statements focused on facilitating health care–related decisions, with the goal of optimizing the care of individual patients.[51] Steps involved in CPG creation include conducting a systematic review of the literature and convening an expert guideline panel to balance the benefits and downsides of different treatment options to arrive at recommendations.[52] It is important that CPGs are developed using robust methodologies to ensure recommendations are based on available evidence. CPGs may make strong or conditional recommendations. A strong recommendation is made when the benefits of a treatment approach clearly outweigh the downsides or vice versa. In this situation, clinicians usually should adopt that action as a matter of policy (or not adopt it in the case of a strong recommendation against an intervention). Conversely, a conditional recommendation is made when the benefits and downsides of an intervention are closely matched or when there is considerable uncertainty about their estimates. In this case, institutions may choose to adopt or not adopt that intervention routinely or may leave decision making to individual clinicians and patients.

In pediatric cancer supportive care, it is common to hear the phrase "there is no evidence." However, unless one searches for CPGs, it is likely that clinicians will not be aware of CPGs developed to manage symptoms. One effort specifically conducted a systematic search for CPGs related to symptom management. It used a pragmatic approach to first evaluate repositories known to include methodologically appropriate CPGs. If CPGs were not identified, a systematic review was then conducted.[53] CPGs were identified for 14 of the 15 symptoms included in SSPedi, with the absence of a CPG directed at anger.

Thus, CPGs have been developed for many symptoms. However, they can be difficult to use directly to influence care. Furthermore, recommendations in CPGs require adaptation to individual institutions to consider available resources and culture. One mechanism to facilitate CPG-consistent care may be development, adaptation, and implementation of care pathways.

Development of care pathways. Care pathways are documents developed to improve clinical care that contain best practices with respect to the management of a group of patients.[54] We previously described one approach to care pathway conceptualization and development.[55] We envisioned that development of care pathways for institutional use could include two steps. First, the CPGs could be directly translated to care pathways, and this translation could include options for subsequent adaptation. This step would result in a single version of a care pathway template for each symptom. Second, the template care pathway would then need to be adapted for each institution. Consequently, there could be numerous adapted care pathways for each symptom.

The first step in creating a template care pathway was to first identify all CPGs focused on that clinical condition.[53] Once these CPGs were identified, recommendations would then be used to populate the care pathway template. The templates had a common structure across all symptoms consisting of prevention, assessment, and treatment sections. In populating the template, we created visual cues for strong vs. conditional recommendations to ease the process of adaptation by institutions. We also provided a list of possible resources that institutions could consider during the adaptation process. For example, psychosocial resources could include psychiatry, psychology, social work, art therapy, chaplaincy, child life services, music therapy, or recreational therapy. For relevant symptoms, each institute could choose from this list or could add additional resources dependent on those available at their institution.

Adaptation of care pathways. We previously described our experience in adapting template care pathways for symptom management at 10 institutions participating in a cluster randomized clinical trial comparing routine symptom screening and implementation of care pathways vs. standard of care.[56] In this early experience, we implemented the following four steps (Fig 2): preparation, initial care pathway

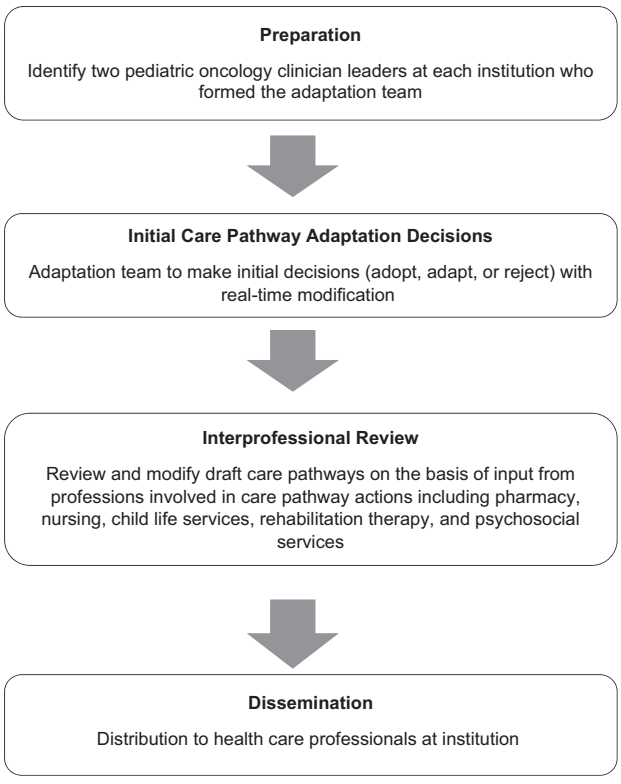

FIG 2. Overview of care pathway adaptation steps.

decision making, interprofessional review, and dissemination. The preparation phase involved identifying two pediatric oncology clinicians to lead the adaptation effort; they formed the local adaptation team. We chose two clinicians to reduce the work and ease the decision-making process, with a goal of making the procedure more feasible.

The second phase consisted of the main work of the adaptation process. For this phase, we worked through each template care pathway sequentially, where each template care pathway represented a single symptom. We reviewed each template recommendation and asked the adaptation team to decide whether to adopt, adapt, or reject the statement. We accomplished this process over a series of videoconference calls, and we modified the template in real time to enable the local adaptation team to reflect on the modifications made and further edit them as required. Examples of adaptations included modifying the language to reflect wording used at that institution, choosing first-line medications, describing medications using the brand name or generic name, and indicating consulting services or investigations. This process resulted in draft adapted care pathways that were institution specific.

The third phase consisted of interprofessional review. The adaptation team distributed the draft care pathways to representatives from disciplines involved in the care pathway actions such as pharmacy, nursing, and psychosocial resources. Their feedback was incorporated into the care pathways, and these were finalized. In this study, they were uploaded to a website named Supportive care Prioritization, Assessment and Recommendations for Kids (SPARK), which focuses on enabling routine symptom screening and encouraging CPG-consistent care for their management.[57-59] The final phase consisted of dissemination where the link was distributed to all health care professionals at that institution.

Future steps. Although the described process is one example of how to encourage evidence-based actions for symptom prevention and treatment, there are several areas that require investigation. First, although this approach standardizes symptom management at an institution, we do not yet know whether clinicians will follow their care pathways or whether these care pathways improve patient outcomes. However, we believe that standardizing supportive care on the basis of CPGs has distinct advantages in itself. Second, there are likely to be approaches that can improve clinician adherence to their local care pathways. Identifying the optimal approaches should be a focus for investigation. Third, although the described approach was feasible in that it was successfully accomplished at all institutions within the context of a trial, it was relatively labor intensive. Identifying approaches that are less resource intensive will be important to achieve a sustainable long-term solution.

CONCLUSIONS

PROs are important to pediatric patients with cancer and their families. Self-report should be emphasized wherever possible. Approaches to enable PRO reporting into routine clinical care and enable preventative and therapeutic actions for symptom management are important. Consequently, facilities should consider adopting the collection of specific PROs during routine clinical care and should identify approaches to implement CPG-consistent interventions to prevent and manage bothersome symptoms. These efforts will optimize quality of life for pediatric patients with cancer.

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Fear of Saying No (FOSNO): Setting Boundaries With Our Patients and Ourselves

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overview

Cancer is an inherently complex and intense medical condition that often requires prolonged treatment and surveillance over years. Treatments can lead to frequent side effects and anxiety, requiring constant communication and follow-up with patients. Oncologists have the unique privilege of developing close relationships with their patients that evolve through the course of their disease. The advent of newer technology and the changing landscape of medicine have drastically altered how oncologists now manage patient needs. These changes have allowed for much quicker and closer communication but are not without personal and professional challenges. Some may wonder how accessible they can and should be to their patients—essentially, the boundaries they may place to protect their own identities and well-being. An oncologist might wonder how much of their personal contact information they should provide to patients and how often they should be available for questions and discussions when away from the clinic without impairing their relationship. Here, we define and explore the role of boundaries in medicine, and review common ethical dilemmas that oncologists face daily when trying to balance patient care and lives outside of medicine. Although we recognize there is no clear single solution, we will propose possible approaches to setting boundaries and potential pitfalls.

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BACKGROUND

Some have said that to join the oncology profession is to answer a noble calling. This calling is embodied by supporting people at their most vulnerable, uncertain, and complex moments and cocreating a path forward that meets their goals, preferences, and values. This is all while balancing the intricacies of a complex health system inherently difficult to navigate, both as a patient and health care professional. Navigation of such a path is hallmarked by expertly balancing both science and art and refining these skills over a lifetime as a professional craft. Although much attention is given to honing scientific, clinical, and administrative knowledge of delivering cancer care, professionals should also allow for self-reflection. Although cancer care at its best is delivered by compassionate and available oncology professionals, how do we ensure that such an impassioned work force can professionally complete the duties of this noble calling while also thriving as individuals?

Discussions of oncology professionals' thriving in the current era starts with acknowledging some difficult truths. First, being an oncology professional is hard. It is hard because of the principle of volatility, uncertainty, complexity, and ambiguity (VUCA). VUCA was first introduced by the US Army War College after the terrorist attacks in 2001 to reflect on the rapid changing pace of the post-9/11 world.[1] They noted four areas of change: (1) unprecedent information generation, (2) the need to respond to multiple stakeholders, (3) inability to always anticipate changes or guarantee outcomes, and (4) less resources than ideally would exist. Sound familiar? Although on a different level of importance than national security, the everyday existence of an oncology professional is swimming in VUCA across many realms, from clinical decision-making to navigating professional development. Oncology is in a new era, with unprecedented growth in the number of treatment options, patients diagnosed with and surviving cancer, and employed oncologists. The former two highlight the immense cognitive burden placed on oncology clinicians. For example, the National Science Foundation estimates that nearly 2.6 million science and engineering articles are published annually across the globe.[2] If we assume that only 0.1% of those apply to oncology practice, it results in seven articles per day for each of 365 days for a person to read. The latter is important because for many newly employed oncology professionals, the locus of control for individual and practice decisions has shifted from clinicians to administrators and from communities to central hubs. Such evolutions in cancer care delivery require an intentional and dedicated focus on the oncology professionals' well-being not only as the means to an end but also as an end in and of itself.

BOUNDARIES 101

The American Psychological Association defines a boundary as a psychological demarcation that protects

PRACTICAL APPLICATIONS

- Oncology is a demanding profession, asking a great amount of those practicing in the field. The demands and complexities of oncology practice, combined with devotion of oncology clinicians, can make setting personal boundaries challenging, which can then lead to negative outcomes for clinicians (including harms to well-being, compassion fatigue, and burnout).
- Oncology clinicians can set boundaries while still meeting ethical practice standards as long as they do not abandon patients.
- Setting boundaries while still providing high-quality patient care can be challenging, and each individual oncology clinician may ultimately set personal boundaries slightly differently.
- Setting boundaries may ultimately allow clinicians to be more present and engaged while working, have more satisfaction with their work, and maintain personal well-being.

the integrity of an individual or group or helps the person or group set realistic limits on participation in a relationship or activity.[3] They expand that in psychotherapy this is an important limit that is usually set by the therapist as part of the ground rules in treatment and may be placed on topics of discussion or physical limits.[3] These definitions easily translate into medicine—to protect both the patient and the physician and their professional medical relationship. As oncologists, and frankly as individuals, most of us do not often consider setting ground rules in our professional practices (or personal lives), relying more on the inherent standards of social norms in communicating and interacting. Although with multifaceted cultures and socioeconomic backgrounds, there are no well-defined norms.

Boundaries are a vital form of individual self-preservation, both in personal and professional aspects of life. They protect our beliefs and values, preserve our priorities, and maintain our well-being. Dr Brené Brown describes them simply as "what's ok and what is not ok."[4] In his webinar on burnout for the American Medical Association (AMA) Steps Forward program, Dr Kevin Hampton describes boundaries as limits or margins that allow room for some give and take.[5] In her commentary, Mammoliti[6] compares the physician to a masterpiece in a museum and describes the ropes as boundaries used to protect and preserve the piece of art from eager visitors while still allowing them to enjoy the piece. We can argue that to functional as effective human beings, we must have some degree of boundaries. Boundaries create predictability, and in medicine where there are more often gray areas of uncertainty, this can provide security and sustainability.[6] Simply put, boundaries are enablers to being present and successful within, and between, many roles. The need for boundaries assumes the multidimensionality of a human being and the need to live as an authentic self—as an oncology professional and beyond.

Historical Boundary Standards

In the past, boundaries in medicine have been called on to highlight transgressions in professional behavior. Thus, the boundaries themselves were the edges of appropriate behavior, and focus on them was to call out the need for clear distinctions between professional practice and personal crossings.[7-9] Most previous literature also focuses on this topic of misconduct and is predominately in the form of commentaries, editorials, or opinion pieces. The AMA, for example, is quite explicit in stating that such relationships between physicians and patients are unethical, hearkening to the vulnerability of patients, the inherent power imbalance between patients and physicians, and the conflict of interest that would exist for a physician who also had a romantic/sexual relationship with their patient.[10] The AMA goes even further to state such relationships with former patients may also be unethical, as would similar relationships with key third parties, such as patients' family members or surrogates or others with a key role in the clinical encounter or in health care decision making.[10] By similar reasoning, the AMA also cautions against physicians treating themselves or their family members, owing to the complexity (and inherent conflict) in playing dual roles (eg, as clinician and relative), and to the lack of objectivity caring for a family member can cause.[10]

Where Do We Stand on Boundaries in Medicine?

To some degree, boundaries were a natural consequence of physical, geographic, and technological limitations and barriers. Distance between patients and medical centers limited how frequently they could be seen. The lack of more advanced means of communication including internet access and cellular devices meant that patients could only reach their provider through on call or after-hours phone numbers, pagers, and operator services. In some parts of the country, particularly rural communities, providers visited and cared for patients directly in their own homes (house calls). However, there appears to be a clear generational shift in medicine. Although house calls still occur in some parts of the country and in some practices and specialties, care has moved mostly to distinct health care settings. Now, the health care continuum transcends all locations. With laptops, cell phones, and messaging devices, time and location are no longer natural barriers. Telemedicine visits allow patients to been seen essentially anywhere at any time.

Imagine ending your clinic day, finishing notes, answering the last few emails, and logging out of the computer. Once you get home, you receive an email alert on your phone from a patient inquiring about medication side effects. Do you answer? Do you leave it to the next day? Do you forward it to your colleague on call or your nurse? These are all questions that may arise amid greeting family, preparing dinner, paying bills, or catching up with old friends.

There are few specific institutional guidelines on how to establish and maintain boundaries, most relying on generalized recommendations. There may also be misconceptions of what it means to have boundaries or guardrails for oneself. This does not mean that one is less professional or effective as a clinician.[11] Having limits allows for more emotional and cognitive flexibility. Having boundaries should not interfere with maintaining exceptional patient care. It should, however, create a healthier working environment and solidify the patient-provider relationship by leaving less ambiguity and uncertainty in communication and practice.

With shifting medical care, physicians are now taking on more off the beaten path tasks—records collections, prior authorizations (PAs), patient transportation through the hospital, and uploading outside imaging. By setting more clear boundaries and expectations, perhaps these tasks could be delegated to other members of the health care team. Some may argue that these tasks are being taken on because of a lack of support staff, resources, or finances, and by completing them, they can hasten patient care. Although they are fully capable of these tasks, we question: Is this the most efficient and productive use of physician time and resource? These are tasks that then detract from the physician's focus on patient care, and in oncology, these moments can be vital. Most of us want to do all we can for our patients, going above and beyond our call of duty, but eventually we may reach a point where we have no more of ourselves to give. In many ways, throwing all of yourself into patient care may mean you give less of yourself to everyone who needs you. In a recent viewpoint, Nadkarni et al[12] describe how accountability is a part of one's professional duty as a physician, but what often becomes overlooked is accountability to oneself. This idea of making sacrifices across many aspects of personal and professional life is not new, and being an advocate for our patients is a worthy part of our calling to medicine.[13] However, it is equally important to recognize our limitations and find a balance on the pendulum that swings between apathy and martyrdom.

More recently, experiences during the COVID-19 pandemic highlighted the importance of personal and professional boundaries. Medical professionals left the clinic or hospital while carrying home the looming threat of possible viral transmission to their families and friends. They left home each day with lingering concerns of childcare, pet care, job security, and adequate goods and supplies needed for home. There no longer seemed to be any safe spaces to decompress and reprioritize. The endless amounts of morbidity and mortality during the early periods of the pandemic further ignited the flames of burnout and declining mental health. A study published in *Mayo Clinic Proceedings* reported that rates of burnout in US physicians increased from 38.2% in 2020 to 62.8% in 2021.[14] These few years established the importance of physicians having guardrails—for security, safety, and well-being. We know that more resilient and emotionally aware physicians who can care for themselves are much more effective caregivers for their patients.[15-17] However, blurring boundaries across personal and professional settings and the lack of some communication restrictions may make work-life balance more difficult, contributing to compassion fatigue and burnout.[18]

ETHICAL CONSIDERATIONS REGARDING BOUNDARIES IN HEALTH CARE

Identifying how best to create boundaries while still providing high-level patient care can be challenging, and for many, it can represent a personal ethical dilemma. Is there a way to create such boundaries so that we can protect our own personal well-being while still providing the level of patient care that is so important in oncology? Furthermore, is it definitive that such boundaries will have a negative impact on the care we provide? Perhaps even more importantly, how can/should we ethically navigate the creation of these boundaries for ourselves while understanding that not all will necessarily support this? Although data are likely and sorely lacking in this area, this struggle has the potential to cause significant clinician distress. Furthermore, many clinicians express concern that such boundaries will affect patient satisfaction scores and/or how they are viewed/treated by their colleagues. As a result, guidance on the ethics of boundaries in oncology clinical practice is much needed.

In recent years, with the growth of many physicians' presence on social media, the AMA and the American College of Physicians have expanded their guidance regarding professional boundaries to the social media space.[19] In this realm, they argue that not only individual physicians must take care to maintain appropriate professional boundaries online but they also have a responsibility to alert their colleagues who they see acting unprofessionally online and even to potentially report such activity to appropriate authorities if the colleague does not take what is seen to be appropriate action.[10] Notably, the increasing presence of oncologists on social media in recent years has led to publication of several oncology-specific guidelines for professional social media use, but training on how to handle certain issues that may arise is still lacking.[11,18,20,21]

These standards might strike some as obvious or as a low bar, but they speak to the way that health care has changed in recent decades. Although we still occasionally learn of cases in which a clinician is found to be having an inappropriate relationship with a patient, the focus largely has changed to questions regarding how one can—or even should—maintain boundaries (with patients, with colleagues, with academia, etc) in the interest of one's own well-being, work-life balance, and safety. So then, in this modern consideration of boundaries, we must ask what is ethically obligatory? Just as not having a sexual relationship with a patient is an ethical obligation in the former conceptualization, what do we consider to be ethically obligatory today? Or, put in another way, what do we consider to be the low bar of boundary setting in modern health care?

Ethical Obligations

When considering such questions, it is important to distinguish what we consider to be ideal versus a minimum standard. In caring for a patient, there are often several reasonable treatment options, all of which meet a certain threshold of acceptability (eg, likelihood of survival with a favorable quality of life). In such settings, standard practice is not to obligate the option that is best but instead to choose one of these different options above the defined threshold by a process of shared decision making.[22]

Similarly, when considering boundaries, individuals are not expected (or obligated) to do what might be ideal for every patient or for their professional life. This ultimately would lead to a complete dissolution of boundaries, to loss of work-life balance, and likely to significant harm to individual well-being. Instead, as we further recognize the hazards of burnout, the importance of well-being and the challenges related to setting boundaries (both with patients and otherwise), individuals should consider what is ethically obligatory for themselves—the low bar when considering such boundaries.[23]

On this point, ethical guidelines and the law are quite clear. The ethical obligation—the low bar of professional boundaries—is nonabandonment. Modern Western ethical standards are clear that clinicians must not abandon patients, and legal standards, although variable state-to-state, similarly deem patient abandonment to be a form of medical malpractice.[24-27] Abandonment occurs when a clinician-patient relationship has been established, the clinician stops the treatment abruptly (without giving the patient time to seek an alternative care provider), and that cessation of care causes harm (or potential harm). Many hospitals and health systems provide guidance for their own clinicians and patients regarding this obligation of nonabandonment, often within the patient bill of rights or code of conduct.

That is not to say, however, that this obligation of nonabandonment requires either a loss of boundaries or personal integrity. Clinicians certainly are not required to continue to provide care to patients who are physically or verbally abusive, to provide treatments they find to be disproportionately harmful, to be available at all hours, or to take part in procedures to which they are personally opposed. Instead, as long as the patient's care can be safely transferred to another clinician/institution, these professional obligations can be met.

Finding the Ethically Optimal Boundary

So, if a complete lack of boundaries is at one end of the spectrum and patient abandonment at the other, where between those two poles lies the ethically optimal boundary that one can set for themselves? Unfortunately, this is a challenging task that likely varies from one individual to the next, depending on their own needs and values, as well as the circumstances under which they are trying to set these boundaries (eg, family considerations, institutional culture/support, clinical/academic focus, etc). Overall, most will likely wish to identify the way to set boundaries that allows them to provide the clinical care (and complete additional academic work, if applicable) that meets the standards of their own personal professional ethics while maintaining enough balance to be able to not only continue to fulfill that professional role but also to maintain job satisfaction and a globally fulfilling life.

BOUNDARY SETTING AND WELL-BEING

Nearly every stop along the oncology professionals' journey requires making choices between a professional aspiration and a personal goal. Akin to the Star Wars' Mandalorian way of life, for oncology professionals pushing limits to do more, better, and faster is our ethos—It is the way. Oftentimes pursing these goals means that personal needs are ignored—in college, a party is skipped to take a graduate school entrance exam; in residency or fellowship training, a birthday party is missed to conduct research; and as an attending, one excuses themselves from a dinner at the beck and call of a pager. These departures from normal life are so commonplace that oncology has its own culture. Professionals are expected to do one more thing, for a little bit longer with the tensile strength of a superhuman rubber band, stretching and bending with an unwavering agreeableness and affability. And to depart from this way of being can call into question work ethic and dedication from external parties and can force individuals to question their own suitability for the work. At the intersection of professional commitment, personal thriving is a boundary, which is only produced from intentional boundary setting.

Although the need for boundaries is universal, how those boundaries are created and used is individual- and context-dependent, an almost Goldilocks-like endeavor. For example, the types of boundaries required for a medical oncologist with on-call duties will vary from a shift-based oncology infusion

nurse. Similarly, they differ between a medical oncology fellow and a division chief. They also change through different phases of life and career. Despite different roles and expectations, all professionals should allow for the development and enforcement of personal and professional boundaries that balance common principles of respect of self, duty to others, and autonomy to decide. Critical to boundary setting is both a balance of duty and self-care alongside ensuring agency so that professionals play the leading role in developing, ensuring, and evaluating boundaries set for themselves. Fundamentally, as Simone's[28] legendary axiom is to suggest, the employer/institution does not love the employee back to the extent that sacrifices, rewards, and loyalty are equal. Professionals must own the discussion regarding setting boundaries for themselves with their employers, colleagues, and constituencies (eg, patients and clients). As can naturally occur, external forces with their own interests will pull for more from employees; gently discussing partnering around boundaries can ensure that both sides will achieve a win-win.

Importantly, boundary setting is not an event, but rather a process with continued refinement through feedback. Such feedback must involve data from the individual professional, their world, and their employer. Curiosity and intentionality are needed. Curiosity leads to questions like "What would be possible if I did less of XX and more of YY?" and "How might a close friend reflect on how I'm handling my competing demands?" Intentionality manifests as regular review of self-efficacy and effectiveness, and whether any tradeoffs in the development of boundaries are resulting in unfulfilled professional goals or leading to harm. Careful attention must be paid to balance the pendulum so that wide swings from apathy to martyrdom are avoided. For neither lead to professional nor personal success, and both are associated with an individual leaving an employer or the field altogether.

How Boundary Setting Promotes Trust

Frequently professionals worry that boundary setting will lead to missed opportunities. In the lay world, the term FOMO is used to denote fear of missing out. FOMO is the emotional response to the belief that important opportunities are being missed. In the oncology content, a more suited term may be FOSNO which is the fear of saying no. Similar worries to FOMO exist with FOSNO so that creating a personal boundary for oneself (by saying no) may lead to a sense of shirked obligation, guilt of not being agreeable, or fear of reprisal. For many, advancement into the upper echelons of clinical practice and administration has meant a certain agreeableness to increasing responsibilities, with a sense that delayed gratification will be a debt paid off at a future time. And naturally during times of training and learning, such approaches of saying yes many more times than declining an opportunity are valued and needed. This is because the process of evaluating an opportunity is also an important skill to attain as a learner. However, as one progresses in their career, a different decision model and accept/decline ratio may be needed. Such an evolved approach will serve to build trust, even as professionals may worry the opposite.

Zenger and Folkman[29] discuss in The 3 Elements of Trust the importance of consistency to developing trust with external parties. Readers with children need to only look as far as employing different consequences for children within a family for the same transgression—and the lobbying of unfairness that will follow—to understand the relationship between consistency and trust. More than words, people evaluate us by our actions. And those actions must be aligned with our stated intentions and must honor commitments and keep promises. Ultimately, trust bestowed by colleagues, patients, and our families/communities stems from our ability to follow through, with each stakeholder (eg, patient, colleague, and family member) evaluating the consistency of our actions from their lens. Thus, trust is hurt both when we do not respond to a patient with cancer in pain who was directed to page us when in extremis and when a clinical page takes us away from an anniversary toast expected by our parent—all while striving to be an excellent clinician and loving child.

Many times, trust is lost when we fall victim to the fundamental attribution error. Oversimplified, this results from individuals judging themselves by their intentions and others judging them by their actions, take for example, the well-meaning junior faculty member who agrees to write from scratch a comprehensive review article for a special journal series coedited by her mentor. Because of a prescheduled vacation, caregiving responsibilities of a parent, and rounding on hospital service, the one-month deadline comes and goes without completion of the manuscript. The junior faculty member had intended to demonstrate agreeableness, being a good mentee, and a team player. However, she is judged by her actions, and the relationship between herself and her mentor is strained, and trust is broken. In this, we must be mindful that good intentions of being everything to everybody is laudable in theory but oftentimes leads to disappointment in follow through. Such disappointment is understandable, and in some way, it may be inevitable. However, such a scenario is yet another reminder of the importance of sometimes saying no.

Keys to Boundary Setting

Oncology professionals are challenged with embodying multiple roles during their career. Rarely is one only a clinician, only an administrator, or only a researcher. Commonly, lines blur, responsibilities get added or taken away, and competence is awarded with further roles and work. We have found that through this process, the following five

activities help build consistency of action and trust in behavior. Table 1 further explores common issues in boundary setting and recommendations.

Be intentional with intentions. Closer alignment of intentions to planned actions requires knowing one's own intentions for professional advancement and personal success. This requires first knowing the coins of the realm that lead to success. For example, in academic medicine, the three coins are the 3 R's—relationships, resources, and results. Put another way, who you know and work with, what grants and other capital you have, and what publications, presentations, and other deliverables you disseminate. For our mentees, we recommend that any opportunity they consider must contribute to at least two of these. Such a consideration is dependent on the person and the situation. For example, a fellow who is looking to secure a faculty position at his training institution and whose career interest is becoming a pancreatic cancer expert may strongly consider an opportunity to join the health system pain control task force that has the division chief as the task force chair (pursing a relationship with her) and a GI oncologist as member (to offer to work with the faculty member on a QI project commissioned by the task force). With these objectives clear and appropriate planning to attend the meetings, the oncology fellow has the critical intentionality to participate in such a group. Frequently, opportunities are compelling because of mere FOMO, with only one of three coins attained. Self-reflection will reveal that this happens more than we may appreciate.

Consider the rule of 1Os. In oncology, everything seems important, urgent, and necessary. And yet, few issues are long-lasting. To achieve a sense of objectivity, we like to incorporate a rule that considers whether an issue will remain top of mind in 10 minutes, 10 hours, 10 days, 10 weeks, 10 months, or 10 years. Such a frame of thinking provides perspective regarding the cognitive and emotional bandwidth an issue should take and whether a new mental boundary is needed to deprioritize something in the

TABLE 1. Examples of Common Boundary Issues and Recommendations

Examples	Recommendations
Time	Set time limits For patient encounters, conversations and encounters with friends, checking work-related emails and messages outside work, administrative tasks Use a timer to monitor time more objectively Focus on 3 Rs—relationships, resources, and results to prioritize time and activities
Communication	Outline a communication care plan Clear and direct expectations on how to reach you, when you can be reached (including days and times), instances on when to use this mode of access versus others, if other team members should be included This communication plan can be for both patients and colleagues
Being honest about priorities, abilities, and limitations	Say no (respectfully) To seeing repeatedly late patients (without an appropriate excuse) or patients who are physically, emotionally, and verbally abusive To repeatedly completing tasks that interfere with direct patient care To an opportunity or task that is nonurgent and pulls you away from a commitment or obligation outside work
Being intentional and consistent	Stick to the boundaries and expectations you set Try to avoid contradicting your own expectations and boundaries. If you say you do not want to be contacted after a certain time and will not answer messages, do not respond to messages past that time Delay sending the email—not all messages need an immediate response Compare practice data to benchmarks, such as HER usage after hours
Empower/educate colleagues, junior faculty, and trainees	Vent and provide a safe space for self-reflection for yourself and others Inspire other oncology professionals, particularly trainees and junior faculty, to comfortably set boundaries without guilt or fear
Advocate for change	Provide direct, specific feedback to your institution and help in the process of developing better guidelines/safeguards to suit provider needs

moment. For example, a medical oncologist may receive an autogenerated email from the clinical practice office that patient satisfaction scores from the last month are in, and he received 4.9 of 5 from 85 patient surveys. Although this communication may risk the oncologist being distracted in thinking about why a perfect 5.0 did not occur and not mentally present during a family meal, the rule of 10's may help. In this case, likely the time effect of the less-than-perfect score will likely not affect the oncologist for more than 10 days (as new scores will come in) and thus with perspective, the oncologist can focus back on his family.

Have everything. Oftentimes boundaries are difficult to accomplish because of seeking it all, a mystical future state where a person has everything, everywhere, all at once (not to be confused with the Oscar-winning film). In truth, many highly motivated and accomplished persons can achieve excellence in every aspect or domain of their career but likely not all at one time. Personified, this is the adage you can have it all, just not all at the same time. We recall mentors who are world-renowned thought leaders in oncology and whose publication cadence slowed during the critical years of child-rearing. When the children left home, the investigator could push harder on the publication gas pedal with the newly found time afforded by fewer baseball games and theme park visits. In truth, careers are marathons, not sprints. The average retirement age for physicians is nearly 70 years, which means decades of being in the same profession (a feat accomplished by few outside of medicine and certain professional fields).[30] Rarely are doors permanently shut, and as referred to above: Do missed opportunities fall in the 10-year category?

Have work/life balance mentors. Many oncology professionals recognize the benefits of having career mentors who focus on professional development, skills attainment, relationship building, and overall career guidance. And yet, few have an identified person in their life who is asking questions like what are you stopping to take on that new work?, is that something you could do later?, or what parts of your life outside of work may be affected by that new work responsibility? For some, one mentor can simultaneously focus on the brake and the gas, the work and the life. But for many, it takes those who are not conflicted by success on one side to genuinely guide about the other. In our experience, many oncology professionals surround themselves with a mix of career and work/life mentors to bring several perspectives and inquisitive questions to their mentee's portfolio of obligations.

Find/review/embody meaning and purpose. Inherent to the oncology profession is an immense privilege from standing side-by-side with those experiencing a life-changing diagnosis and lending a hand. All in the profession have felt a profound calling, informed by personal or professional experiences, that required harnessing significant time and energy to improve the human experience. To temper the importance and sacrifice would be disingenuous to the journey and the cause. Yet, in bringing our whole selves to this work, we must be fueled by experiences outside of work. William Osler was an avid reader of philosophy and biographies. Anthony Fauci runs marathons. Cliff Hudis surfs in the summer and skis in the winter.

CONCLUSIONS

Medicine is a profession of caring—caring for others and caring for ourselves. At the end of the day, we are all on the same team, working toward the same ultimate purpose of patient care. And yet that process of caring, of being proximal to the suffering of others, can leave a residue on us. It is described by the analogy of standing next to a waterfall, and not having time to dry off. If the waterfall is the distress to which we bear witness, why should we not be intentional of stepping away and creating a boundary between the waterfall and the dry space a little bit away? We challenge all oncology professionals to take a moment of self-reflection and consider their limits—for their patients and loved ones, but mostly for themselves.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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From Boring to Bravo! Using Learning Science to Create Memorable Presentations

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overview

The practice of oncology continues to evolve over time. Educators find themselves in a position where they are no longer able to teach a topic in its entirety. Moreover, the rapid expansion of information available through research and discovery in the field of oncology makes it difficult for learners to process the constant barrage of new content. Lecturers continue to impart knowledge using didactic techniques, often trying to include as much material as possible in the time permitted. The question becomes: In the face of an impossibly large field, how can one assist learners in learning, and retaining, what is most important? The science of learning continues to develop, and we now recognize that there are ways to teach that optimally facilitate the retention and application of knowledge. By using these strategies, educators can make it easier for learners to absorb and retain key information. This article will touch upon several such techniques: cognitive load optimization, analogy, contrasting cases, elaboration, and just-in-time telling. By applying these methods to didactic presentations, educators can ensure that their lessons are heard, understood, and ultimately transformed into something unforgettable.

OPENING SCENARIO

A lecturer is excited to deliver a talk to oncology fellows about colon cancer. This single lecture is the main didactic session dedicated to colon cancer within the whole fellowship curriculum. The lecturer is determined to include as much information as possible to ensure that everything is covered. After many hours, they produce slide after slide, replete with clinical trials and Kaplan-Meier curves, and while the text is small, they are pleased that the fellows will have all the data!

The morning of the lecture, the fellows sip their coffee and eagerly await the teachings of one of their favorite clinic attendings. Five minutes into the 60-minute talk, the fellows' eyes start to glaze over, and they start checking their phones. Another 5 minutes pass, and some eyes are drifting closed. The lecturer ponders: Why do the fellows seem so disinterested? They love learning from me in clinic! And I put so much work into preparing this lecture! What went wrong?

In today's fast-paced world where attention spans are mere seconds to minutes, it can be challenging to captivate learners for the duration of an entire lecture. Moreover, the rapid pace of new scientific and clinical discoveries in oncology can be overwhelming. Educators are no longer in a position to teach the entire field of oncology and are thus faced with teaching learners how to synthesize and apply knowledge within a rapidly evolving landscape. Medicine often finds itself using old methodologies of information dissemination including PowerPoint presentations with seemingly endless content for learners to absorb in a brief period. Conferences use darkened rooms with hours of information delivery in the hopes of sharing important data for clinicians to apply within their own practices.

The study of how people learn has evolved over time. For example, although individuals can learn through multiple modalities, care must be taken when combining delivery systems. Reading written words on a slide is associated with diminished recall, simply because the simultaneous task of absorbing information by reading and listening limits the learner's ability to do either one well.[1] As another example, while learning objectives can set the stage at the beginning of a session, additional strategies are needed to help learners identify the key learning points that they should recall at the session's conclusion.[2]

As you will read, an understanding of learning science can improve an educator's ability to disseminate information to learners effectively, thereby promoting their ability to retain and apply knowledge. By determining your session's desired outcomes, you can choose the tools that will be most effective for information delivery. Are you looking to further knowledge acquisition and memorization? Ensure conceptual understanding? Or have learners problem solve? By starting with those basic questions, you can inform your chosen approaches.

For example, when asked to recall a list of words, subjects remember those at the beginning and those at the end.[2] You can take advantage of these primacy and

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PRACTICAL APPLICATIONS

Tips to make your presentation more memorable:

- Avoid overloading slides with information and emphasize key teaching points.
- Avoid distractions so learners can focus on important content.
- Use contrasting cases to highlight key differences between concepts and analogies to emphasize similarities. These help learners make connections with known elements in their long-term memory.
- Expose learners to problem-solving before a lecture; this will help with their conceptual understanding.
- Create a space of psychological safety which will promote learning, elaboration, and interaction, leading to greater comprehension.

recency effects by selecting which information to emphasize at the beginning and end of your presentation. The take-home points can be cemented at both of these opportune moments. If there is key information that your audience must recall, you can assist them in meeting that goal simply by adjusting the timing of your information delivery.

Our ability to integrate information into long-term memory is optimized when such principles are used. While this article will focus specifically on the transformation of a didactic talk, it is important to recognize that this information can be applied in numerous teaching settings including classroom lectures, ward rounds, and small group sessions. By applying the elements that make the most sense for your session type and desired learning outcomes, you can improve the learning experience and achieve those outcomes with greater ease.

COGNITIVE LOAD THEORY AND ITS APPLICATION TO TEACHING

The well-intentioned, knowledgeable, and popular teacher described in this article's Opening Scenario could have engaged their learners more effectively with increased attention to cognitive load (CL). CL theory (Fig 1), originally described in the 1980s by John Sweller[3] and now one of the most commonly referenced learning theories, depicts working memory as a bottleneck for learning. The working memory can only process limited amounts of information at a given time, so much of the sensory input that enters the working memory is quickly forgotten while only a small subset is encoded into long-term memory for later retrieval. The process of encoding information from working memory into long-term memory storage is called learning. For someone to learn, their working memory must have sufficient capacity to process the desired information. If working memory capacity is exceeded before the desired information enters the working memory, the information will not be learned.

CL is the mental effort required to perform a cognitive task, such as learning from a lecture.[4] If a learner's CL exceeds their working memory capacity, learning will not be optimal. Learners encounter three sources of CL during a cognitive experience such as a lecture (Fig 2): intrinsic load (IL), extraneous load (EL), and germane load (GL). IL is the mental effort that the *task itself* requires sitting in the classroom (in-person or virtually), listening to the lecturer, and viewing the slide content. A key example of IL is the level of the lecture's content. A straightforward and simple lecture intended for senior fellows will impose a very different amount of IL for a junior resident. IL should be *optimized* such that early learners encounter relatively simple learning tasks while advanced learners can handle more complex learning tasks. EL is the mental effort required to navigate *distractions* unrelated to the lecture's content. Examples of EL include slide elements (eg, excessive animation), presenter elements (eg, excessive gesticulation or saying "umm" frequently), and external elements (eg, noise in the room or texts/e-mails related to patient care). EL should be *minimized* as much as possible. GL is the mental effort left over after IL and EL are accounted for that can be devoted explicitly to *learning*. GL should be *promoted* to enhance learning.

Educators can use strategies to optimize IL, minimize EL, and promote GL.[5] To optimize IL, educators should target teaching to the intended learner's level. For example, an early first-year fellow may not yet know enough about the principles of colon cancer diagnosis and treatment to be able to internalize and critique multiple clinical trials. Thus, it may behoove a lecturer to limit the amount of clinical trial data presented to early learners of oncology and focus instead on key principles. Similarly, limiting the number and scope of learning objectives to be achieved during a lecture will help focus learners on the key points to take away. The amount of information to be included in a lecture should be reasonable for the time allotted rather than attempting to fit

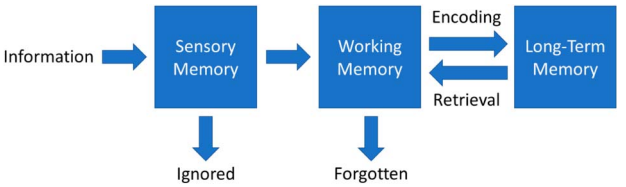

FIG 1. How incoming information is processed according to cognitive load theory.

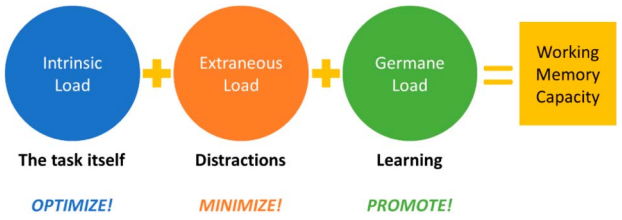

FIG 2. The three sources of cognitive load, their definitions, and associated teaching goals.

an excessive amount of content into a limited timeslot, which will result in a rushed presentation and/or overly packed slides. It is better to present learners with less information that they can actually learn, rather than overloading their working memory with excessive data such that little is retained.

To minimize EL, educators should make efforts to reduce or eliminate learner distractions whenever possible. These distractions may be elements a lecturer can control, such as eliminating redundant text or unrelated visuals on slides, making sure the lecturer's e-mail is closed so it does not make sounds during the presentation, or reducing the occurrence of a lecturer's distracting movement such as a nervous foot tap. External factors such as noise may be more difficult to control, but simple interventions such as closing the door to the room to reduce hallway sounds and asking learners to silence their phones can be helpful. Systemic interventions, such as fellowship programs providing clinical coverage for fellows during educational time to eliminate distracting clinical communications, can be challenging to implement but make a large difference in EL.

To promote GL, educators should use strategies to prompt learners to engage with the key learning points whenever possible. Examples include summarizing key points repeatedly, visually highlighting key points on slides, incorporating active and interactive learning opportunities such as polling the learners and facilitating group discussion, connecting new knowledge to information the learners have seen before, and applying learning to clinically relevant scenarios. Incorporating clinical cases with interactive questions and discussion into a lecture will enhance learning beyond what a series of slides with clinical trial data can do.

So what could the lecturer from the Opening Scenario have done from a CL perspective to engage their learners more effectively while teaching about colon cancer? Instead of trying to include excessive content in the talk, they could have boiled the lecture down to three concrete learning objectives covering, for example, principles of staging, treatment, and prognosis. They could have focused their slides on key principles and take-home points, supported by a smaller number of figures, instead of presenting many Kaplan-Meier curves in a row. They could have asked a colleague for feedback on their talk ahead of time to catch any distractions because of their slides or presenting style that they may not recognize. Perhaps most importantly, they could have incorporated clinical cases with interactive questions to promote discussion and application of the material. Preparing and delivering a lecture with attention to CL takes more effort on the part of the educator but pays off for the learners who will retain the information and apply their learning to patient care.

HOW TO ACE TEACHING THROUGH ANALOGY, CONTRASTING CASES, AND ELABORATION

There are many different learning science principles that, when implemented properly, can enhance the teaching and learning experience. In this section, we will focus on three that are essential for creating an effective oncology presentation that is easy to understand and follow.

Analogy

Analogy is defined as drawing a comparison between two things. When applying this concept within the educational environment, it requires the identification of similarities between two or more dissimilar examples.[6,7] Depending on the level of learner, the context and the topic of the presentation, there are different methodologies that may be considered.

In the first approach, the educator remains the guide and facilitates comprehension by creating a comparison with a familiar situation or process and then clearly explaining the application.

For example, as Katz describes, when trying to teach about the lymphatic system and its physiologic implications, one might consider comparing it with an alarm system. Just like the wiring system and sensors of an alarm system, so too the lymphatic system has channels and lymph nodes that permit the body to detect an infection or injury and mount an immune response. Further explanations may add that lymph nodes are like detection stations for the system, and this can be a path down in which cancer cells may easily travel.[8]

In the second methodology, one can ask learners to generate their own explanations on the basis of a given analogy. As an example, consider the biology and mechanisms of action of oncology drugs, specifically, immune checkpoint inhibitors. Consider having two aligned figures, one with an image of a brake pedal with a foot being lifted off the brake and a second with a cancer cell with PD-L1 on the surface along with an immune T cell with PD-1 on the surface. After providing these images in parallel, one can then ask learners to explain the mechanism of action of immune checkpoint inhibitors. By analyzing the analogous foot and brake pedal,

learners can conceptually understand that immune checkpoint inhibitors release the brakes so that the immune system can attack the cancer cells.

This self-generation of the explanation, when used with analogy, is considered an even more effective learning tool. Engaging learners in this way not only teaches them to think in analogies but also allows them to analyze the material deeply and facilitate their comprehension. Benjamin Franklin said it best: "Tell me and I forget, teach me and I remember, involve me and I learn."

While analogy helps the learner comprehend a new concept through comparison with a known entity, teachers must be careful to avoid anchoring bias. It can be difficult for a learner to understand that while two situations may have multiple similarities, they are still different. We explain this further in the next learning principle, contrasting cases, which focuses on learning through the appreciation of the differences between two concepts.[7]

Contrasting Cases

As the name implies, contrasting cases identify differences between two or more somehow similar examples or concepts. In teaching, contrasting cases highlight distinctive features of a particular concept and help the learner understand these distinctions by focusing on their relevant differences.[6,7]

With the rapid evolution of the field of oncology over the past two decades, the learning principle of contrasting cases has become one of the most useful tools. In a world with multiple therapeutic options and treatment decisions that depend on many variables, guidelines and management pathways can be overwhelming. As oncology educators, we must guide our learners to discern the key distinctive features that govern therapeutic decision making. Contrasting cases permit learners to understand these critical elements and facilitate the comprehension of what may seem to be abstract concepts.

Table 1 lists some examples of contrasting cases. Each example can be implemented using tables, figures, or other means. As with analogies, contrasting cases can be guided by the instructor or learners can be asked to develop their own contrasting cases. By having learners recognize key differences and determine the impact on an outcome, contrasting cases create deep understanding.

Ultimately, whether asking learners to recognize similarities between a new concept and a familiar example (analogy) or distinctive differences between similar examples (contrasting cases), educators will find the application of these techniques straightforward (Fig 3). While useful in lectures, these principles can also be integrated into prework (see the Just-in-Time Telling section) or postlecture assignments after a presentation to ensure learners have grasped key concepts and their implications.

TABLE 1. Examples of Using Contrasting Cases in Oncology Presentations

Teaching TNM classification: how to show a learner that T can mean multiple things	T in colon cancer means depth of invasion *v* T in breast or lung cancer means tumor size
Teaching the impact of cancer staging	Two cases with similar clinical presentations: Case 1: TNM stage 1 with curable treatment options Case 2: TNM stage 4 with palliative treatment options
Teaching the differences between two oncology drugs for one type of cancer	Drug A: indication, toxicity, dosing Drug B: indication, toxicity, dosing

Elaboration

Elaboration is defined as making connections between new information and prior knowledge to improve memory. In the context of teaching, elaboration helps encode new knowledge and transfers it from the working memory into long-term memory where information can be retained and retrieved at a later time.[6,9] Finding ways to connect new material to prior known information, even if seemingly unrelated, can help improve transfer of the new information into long-term memory.

Elaboration can be accomplished through numerous mechanisms. For instance, one might group similar elements together to facilitate their recall or discuss a connection between new information and knowledge the learners have covered previously. Elaboration is analogous to building a house: A strong knowledge base forms the foundation on which new information can be added.[9,10]

For elaboration to be effective, it must be tailored to the learner's level. The strategies used in an oncology presentation for medical students will need to be different than those provided in a presentation to an audience of certified

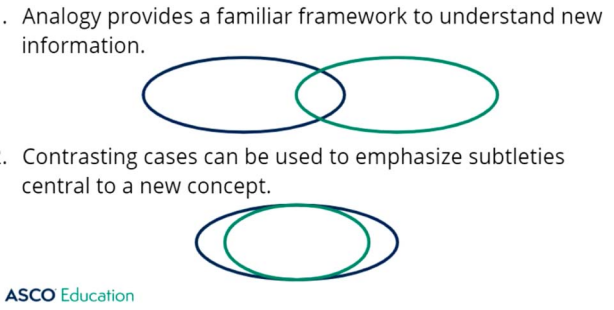

FIG 3. Difference between the principles of analogy and contrasting cases.[7]

oncology providers. Table 2 lists some known and suggested examples of elaboration strategies that a speaker can use to enhance their presentations for a variety of audiences.[9]

JUST-IN-TIME TELLING: MEETING YOUR LEARNERS WHERE THEY ARE

Opening Scenario Revisited

The beloved clinic attending applies learning science to their lecture and revamps their presentation to optimize CL and adds case-based scenarios with audience response questions. The learners participate a bit more to answer the audience response poll questions, but many responses are incorrect. The teacher reviews the postclass survey, and the students rated the relevance of the content covered as average with some below average scores as well. The teacher seeks additional feedback.

In this section, we will discuss the learning science principle of just-in-time telling (JiTT). This principle, when used to design a session, affords learners both an appreciation for the relevance of a topic to their training and useful and applicable knowledge.[6] The scenario described above illustrates a challenge that can arise when learners have not experienced a particular clinical situation in advance of the didactic session and therefore may not perceive how the didactic content will be applicable to their clinical practice.

JiTT requires learners to have experienced the content first before hearing or discussing it in a didactic session.[6] This type of learning happens organically during clinical rotations where the learner sees a patient on their own and develops an assessment and plan before presenting to their attending. Applying this learning science principle to a classroom setting is more challenging but can be adapted and implemented with preplanning. The three steps that can be applied to facilitate conceptual understanding using JiTT are (1) designing a prework exercise to provide experience with the content in advance of class, (2) creating a safe learning climate right at the beginning of the session, and (3) selecting interactive experiences that will enhance engagement and learning (Fig 4).

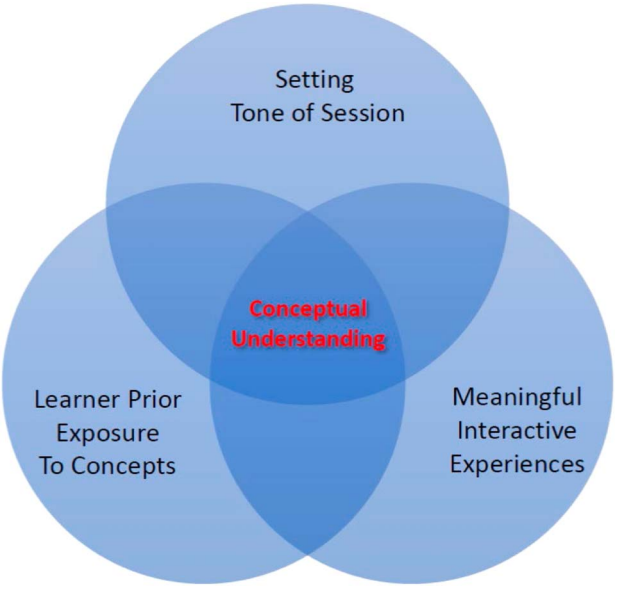

FIG 4. Key elements required to promote conceptual understanding with just-in-time telling. Bottom-left circle: Step 1 takes into account the prior knowledge learners bring to the session and the time they have available for prework. Top circle: Step 2 represents the need to directly talk to the learners about learning climate and create a safe space to make mistakes. Bottom-right circle: Step 3 emphasizes the goal of creating meaningful interactive experiences that enhance learning and help learners apply the knowledge. The goal of conceptual understanding represented in the center of the diagram is learners walking away from the session with more usable knowledge and an appreciation for why it is important.

Step 1: designing the prework. This step is important for meeting the learners where they are because the amount of time available for prework will vary based on the stage of training. The flipped classroom is an established approach that works well in settings such as medical schools where learners have protected time to read and analyze information in advance of the session.[11] By contrast, assigning a series of flipped classroom exercises to a fellow on an intense inpatient rotation would run the risk of increasing CL and being perceived as a burden. In our teaching scenario where the audience consisted of clinical fellows, the teacher could instead send a few discussion questions ahead of time to prime the fellows in advance of the class discussion with minimal preparation time required.

An additional point to consider is that learners at the same level of training will still have variability in their experiences and prior knowledge.[12] There may be more consistency in the setting of a fellow lecture on colon cancer, but having an awareness that not all fellows will have had the same exposure to colon cancer is important.

Step 2: setting the tone. Taking time to establish an inclusive and safe environment at the beginning of class is important to encourage participation. It is a standard part of PowerPoint presentations to start with a learning objectives

TABLE 2. Examples of Elaboration Strategies in Oncology Presentations

• Grouping similar ideas into categories that are familiar to learners
• Reviewing a new US Food and Drug Administration drug approval within the context of the standard of care
• Having learners relate new concepts to their own experiences after a presentation
• Using familiar mnemonics or acronyms to assist in memorization of new material

slide, but a teacher may not always pause and set the tone for interactions during the class. One strategy to encourage participation is to explicitly state that the most important aspect you are looking for is learners actively engaging with the clinical cases being discussed and sharing what they know, rather than placing the emphasis on giving the right answer. If the learners fear that they will be judged for giving a wrong answer, they will hold back from participating when they are unsure.

Establishing a safe learning environment will help learners be willing to ask questions and discuss content that they are still trying to master. As depicted in Figure 2, not all content that learners are previously exposed to will make it into long-term memory, and the learners will realize what they have not fully understood as they try to generate answers to discussion questions in class.

Incorrect answers from learners are helpful for guiding teachers to focus on areas where the class needs more practice. One strategy to make learners feel comfortable giving an incorrect answer is to provide a contrasting case in which the answer they provided would be the correct answer.[6] In the business literature, the concept of psychological safety has been described as benefiting the whole team, and in our educational environment, it will similarly benefit the whole class in moving toward conceptual understanding.[13]

Step 3: designing interactive experiences. The first two steps focused on the preparation for the class discussion, and now our focus will turn to optimizing the interactive classroom activities. A commonly used approach is adding board review questions to a fellow lecture. While this does add interaction and can be used in a pretest and post-test manner to gauge understanding of key points, it is not guaranteed to generate discussion. In our scenario, the learners answered the poll question on their phones but did not engage in further discussion of the answers.

It can be tempting to stay with traditional board review multiple-choice questions since they are readily available and represent a format familiar to teachers. However, this strategy alone may not be enough to spark discussion. In an ideal situation, all learners would have protected time to read and prepare for class, but for clinical fellows, time is often limited. An alternative approach faculty can consider is carving out protected time during the session for learners to read a key article or work through case scenarios. The case-based learning format could be used to give the learners opportunity to grapple with the content during class and work through cases with faculty guidance.[14] While some case-based learning experiences are longer, even a brief time dedicated to learners working on a clinical case scenario would aid in their understanding of the didactic content.

Finally, faculty can ask learners questions in class to facilitate interaction and elaboration, such as what is something you have seen in clinic or on the wards related to this? These types of questions do not have a right or wrong answer, and faculty can adapt their session on the basis of learner responses.

TABLE 3. Picking the Right Learning Science Tool

Desired Outcome	Learning Science Tool
Conceptual understanding	Analogy
	Just-in-time telling
Memory	Elaboration
	Cognitive load optimization
Discovery	Contrasting cases

Adapted from Schwartz et al.[6]

Opening Scenario Revisited

The lack of response in this scenario could have been related to any of the three steps. The faculty member reflected afterward that they dove right into the learning objectives and content without clearly establishing a psychologically safe learning environment. The faculty member also noted they were uncomfortable with the silences and did not pause long enough for the learners to generate a response.

Adding interactive exercises is a good strategy, but if the exercise is not well designed to promote interaction or not accompanied by a tone of psychological safety, silence can ensue and detract from the session. By taking the time to allow learners to wrestle with the content before a didactic talk, and by creating a safe space and interactive opportunities in the classroom, educators can improve learner understanding and recall of key concepts (Fig 4).

CONCLUSION

The incorporation of learning science can truly transform your presentations. By applying these straightforward principles, you are helping learners focus on achieving a deep understanding rather than forcing them to work harder only to achieve the same, or inferior, results.

Remember the importance of optimizing CL to improve the transfer of new information into long-term memory. By minimizing extraneous elements and keeping IL manageable, your learners will be able to process and appreciate the most important pieces of information without losing them in the fray. In today's world of oncology, where an endless amount of information is available to learners with only a few clicks of a mouse, the emphasis of education must be on facilitating distillation by highlighting the most important content.

- Keep the information on slides limited.
- Avoid complexity of figures.
- An image while you speak is worth a 1,000 words.
- Limit distractions.

When considering *analogy* and *elaboration* to communicate new information, remember that associating new concepts with elements that are already familiar will improve understanding and recall.

- Relate new information to elements that are already familiar.
- Use situations that allow learners to make associations they can easily comprehend.
- Help learners to organize the information into groups or to use meaningful acronyms.

When applying knowledge to a different scenario, *contrasting cases* can facilitate understanding. Providing examples that are almost but not quite the same highlights the subtle differences, thereby augmenting understanding. However, changing multiple elements can be confusing and dilute the key message.

- Discriminate one element at a time.
- Allow learners to understand the impact of a key difference or feature.

JiTT, which upends traditional expectations for classroom teaching, provides learners with information beforehand followed by an in-class application exercise. When learners are forced to problem solve in class on the basis of assigned prework, they develop context for the content and an improved ability to apply their new knowledge.

- Ensure learners have contact with the material before the classroom discussion.
- Create a space of psychological safety to facilitate open discussion and interaction.
- Create meaningful interactive experiences.

Our closing message is simple: By using appropriate educational tools grounded in learning science, you will assist your learners in transferring new information into their long-term memory. You will make it stick. Your learners will then be able to recall key information and apply it to future scenarios such as clinical care. Consider your learners' level of training and your desired learning outcomes and then pick the best tool(s) to accomplish your goals (Table 3). As we look to the future of oncology, we must recognize that our efficacy as clinicians, researchers, and educators is measured by our ability to adapt and integrate new knowledge as it becomes available. Learning science principles are critical for the optimization of teaching and learning in today's environment of unbounded oncologic discovery. As educators, we must incorporate these principles to help learners navigate this vast field. It all starts with you.

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Structural Sexism and Cancer Care: The Effects on the Patient and Oncologist

Bridget P. Keenan, MD, PhD[1]; Elizabeth Barr, PhD[2]; Elizabeth Gleeson, MD, MPH[3]; Caprice Christian Greenberg, MD, MPH[3]; and Sarah M. Temkin, MD[2]

overview

Despite progress toward equity within our broad social context, the domains of gender as a social, cultural, and structural variable continue to exert influence on the delivery of oncology care. Although there have been vast advances in our understanding of the biological underpinnings of cancer and significant improvements in clinical care, disparities in cancer care for all women—including cisgender, transgender, and gender diverse women—persist. Similarly, despite inclusion within the oncology physician workforce, women and gender minorities, particularly those with additional identities under-represented in medicine, still face structural barriers to clinical and academic productivity and career success. In this article, we define and discuss how structural sexism influences both the equitable care of patients with cancer and the oncology workforce and explore the overlapping challenges in both realms. Solutions toward creating environments where patients with cancer of any gender receive optimal care and all physicians can thrive are put forward.

DEFINING STRUCTURAL SEXISM

Over the past 50 years, the availability of educational and employment opportunities for women has led toward societal advancement and gender equity.[1] Despite advances in the understanding and treatment of cancer, disparities persist across cancer care and the oncology workforce.[2] Structural sexism or systematic gender inequality in power and resources influence and perpetuate inequities for women within the health care system.[3] Defining certain terms surrounding structural sexism is essential to understand the concept. The terms sex and gender are often conflated but refer to distinct categories. Sex and gender are multidimensional constructs in which sex refers to anatomical and physiological traits (sex traits) and gender is a social construct on the basis of expressions and social and cultural expectations associated with sex.[4] As a social and structural variable, gender encompasses multiple domains beyond gender identity: gender roles, gender relations, and power.[4] Structural sexism can be measured at the macro, meso, and micro levels. The macro level refers to institutional sexism such as policies, cultural norms, and distributions of resources; the meso level refers to patterns of behavior and organizational practices; and the micro or individual level refers to the gendered perception of self.[3]

Both patient care and physicians' careers are negatively affected by structural sexism (Fig 1). Exposure to sexism at multiple levels is associated with more chronic conditions, worse self-rated health, and worse physical functioning for women.[3] A supportive workplace environment for physicians who are women is critical for women's health equity, in part because clinicians who are women are more likely to provide health care to women.[5] Despite the inclusion of women in medicine for over a generation, gender equity has been slow to materialize. Nearly half of women medical students report experiences of sexual harassment during medical school, rates substantially higher than in other STEMM graduate programs.[6] Progress in the rate of advancement of women into higher levels of faculty rank, department chairs, and cancer center directors has been limited.[7,8] Physicians who are women start with lower salaries than their counterparts who are men, and the gender wage gap continues to widen even when adjusted for factors such as rank and experience.[9,10] Differences in the work environment, leadership opportunities, and the accumulation of wealth are associated with decreased career satisfaction and higher rates of burnout for women oncologists.[11,12]

Structural sexism cannot be addressed without consideration of other forms of structural systems of discrimination and inequity that also affect patients with cancer and oncologists. Intersectionality is a framework for understanding how multiple socially constructed identity categories (ie, race, ethnicity, and gender) overlap and interact at the individual and institutional level to create disparate outcomes for

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PRACTICAL APPLICATIONS

- Structural sexism, the unequal distribution of resources and power, remains a challenge in oncology and negatively affects both physicians and patients.
- Structural sexism results in the deprioritization of specialties predominately populated by women physicians and patients and stalled progress in cancers affecting women.
- Policy and institutional solutions are needed to combat structural sexism and improve cancer care for all.

individuals and communities.[13] Structural sexism amplifies other institutional barriers such as structural racism, ableism, heterosexism, and classism, and individuals with multiple marginalized identities may be more affected by these compounding systematic forces.[14] Women who belong to groups that are under-represented in medicine face further structural challenges in addition to structural sexism; for example, Black and Latinx/Hispanic women are vastly under-represented in the specialties of medical, surgical, and radiation oncology.[15,16] This further affects patient care as diverse clinical teams are associated with increased patient satisfaction and perceived quality of care.[17,18]

Interpersonal factors that act as barriers to gender equity have been described extensively elsewhere.[19,20] To date, attempts to address the interpersonal sources of inequities have been insufficient.[21] Although implicit bias training can increase bias awareness,[22,23] reports on long-term successes of bias training are scant.[24,25] Rather than putting the onus on those affected by sexism to fix themselves, combatting structural sexism in cancer care demands the generation of specific structural solutions to foster equity related to the delivery of cancer care.

HOW CONSIDERATIONS OF SEX AND GENDER INFLUENCE CANCER CARE

Cancer incidence and outcomes are influenced by a variety of biologic, social, environmental, and economic conditions, including sex and gender.[26] The differences in cancer diagnosis and outcomes between men and women are multifactorial and poorly understood, but most likely reflect differences in both endogenous factors and exogenous factors. Both sex, as a biological variable, and gender, as a social, cultural, and structural variable, act to influence health. Historically, a 70-kg male patient was used to define

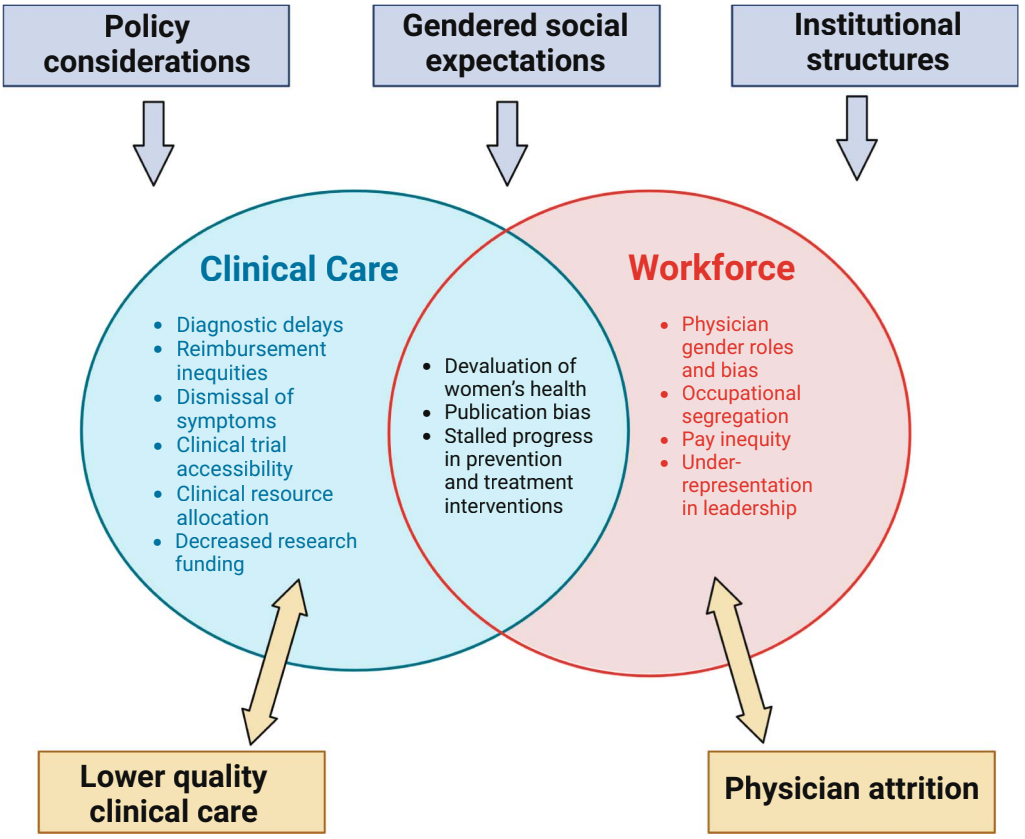

FIG 1. Structural sexism affects both oncology workforce and clinical care. Top arrows demonstrate the forces contributing to structural sexism in clinical care, physician workforce, and both domains; bidirectional arrows show the downstream outcomes which further amplify structural sexism. Created with Biorender.

the average patient in medicinal education, practice, and biomedical research.[27] Both sex and gender, therefore, influence the structure of cancer care delivery, affecting how patients receive care.

Among the components that define sex, anatomy most noticeably influences epidemiologic differences in cancer risk, treatment, and outcomes (Fig 2). Cancer incidence and mortality (male:female ratio of 1.15 and 1.37, respectively) are higher in the male US population, reflecting differences in life expectancy and sex-specific cancer disease site risk.[28] Variations in incidence and mortality by sex additionally exist across disease sites that are not sex-specific. Higher cancer risk in male patients for most cancer sites except thyroid and gallbladder persists even after adjustment for known risk factors.[28-30]

Beyond anatomy, other domains of sex exert influence across cancer biology and clinical care. Sex differences in molecular and genomic alterations have been described across cancer disease sites in specific genes, including actionable mutations, such as mismatch repair genes, and mutation signatures.[31,32] Gonadal steroid hormones alter cancer risk and outcomes, and hormonal modulation is a common component of cancer therapy.[33] Although the influence of circulating estrogen, progesterone, and androgens is primarily implicated in cancers of reproductive organs, these hormones influence tumor vasculature, stroma, and other aspects of the tumor microenvironment.[34,35] Total body water, lipid composition, and metabolism influence the pharmacodynamics and pharmacokinetics of chemotherapy agents, potentially altering efficacy and adverse events.[36,37] Differences in the male and female innate and adaptive immune responses have been well-established.[38] Distinct sex-specific immune features across multiple cancer types and differences in response and adverse events with immuno-oncology treatments have been demonstrated.[33,37,39,40] The reduction of risk of death was twice as large for male patients compared with female patients according to a meta-analysis that pooled results from 20 randomized trials of immune checkpoint inhibitors.[40]

The multiple dimensions of gender similarly influence cancer care and affect patients with cancer. Gender identity and a sense of femininity link postmastectomy breast reconstruction to an improved quality of life.[41] Cultural expectations about behavior as they are associated with certain sex traits influence cancer risk behaviors (eg, indoor tanning, cigarette smoking, and physical inactivity). Conformation to gender norms of masculinity or femininity related to these behaviors contributes to cancer incidence

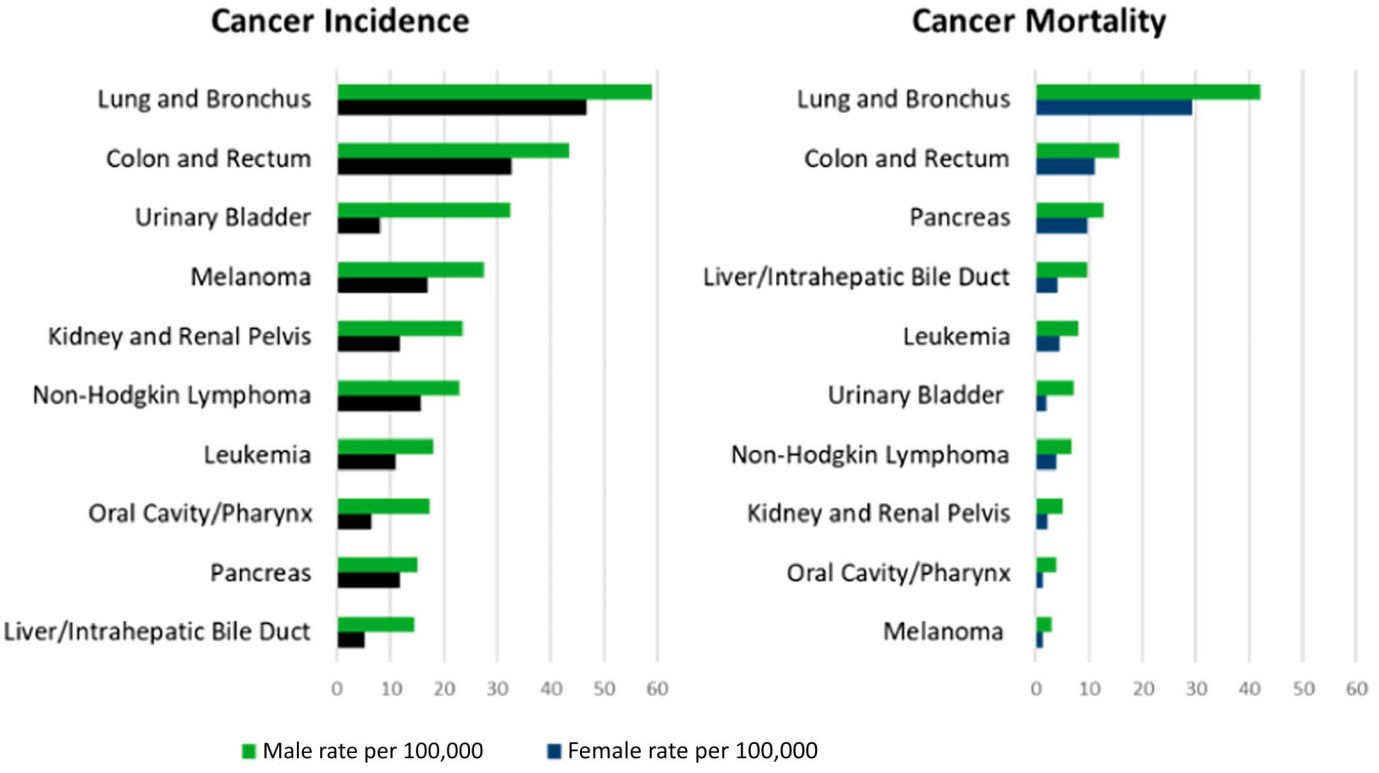

FIG 2. Age-adjusted cancer incidence and mortality rates in the United States including the years 2016-2020. Bars represent incidence and mortality rates for 100,000 male patients (green) or 100,000 female patients (blue) for the indicated cancer type. Created by SEER*Explorer.

differences between men and women.[42] Gendered assumptions that women are emotional, sensitive, and even hysterical affect the way that physical pain symptoms are interpreted by health care professionals.[43] Gender bias in the patient encounters within the health care system can lead to diagnostic delays and is significantly associated with longer diagnostics intervals in six of 11 non–sex-specific disease sites (bladder, colorectal, gastric, head and neck, lung, and lymphoma) without comparable diagnostic delays for men in any of those disease sites.[44] Repeated exposures to gender-based inequities at the individual, relational, and institutional levels accumulate and are associated with a diagnosis of chronic conditions and worse overall health.[3] The presence of comorbidities and decreased performance status are well-known factors which are negatively associated with cancer outcomes.

Access to cancer care and the patient experience differ for women compared with men. Women are more likely to have health insurance than men but less willing to incur out-of-pocket costs influencing their availability and choices in therapies.[45] Financial toxicity perpetuates health disparities in access and quality cancer treatment.[46] Although women with cancer are more likely to have a caregiver than men, caregivers to male patients are more likely to be a spouse, whereas caregivers to female patients are more likely to be a child.[47] Psychosocial support from the health care team is valued more by women than men.[48]

Gender additionally influences how we think about sex and sex-specific conditions and disorders. Stigma contributes to nonadherence with breast and cervical cancer screening for persons from sexual and gender minority communities.[49] Dismissal of symptoms of postmenopausal bleeding by health care professionals is commonly reported by women ultimately diagnosed with endometrial cancer.[50] Ovarian cancer has been historically labeled a silent killer, although nearly three fourths of patients have documented symptoms in the year before their diagnosis.[51] The care of gynecologic cancers has historically been siloed from the care of other disease sites, leaving significant infrastructure barriers to care for patients with these malignancies.[52,53]

Sex and gender may act independently of each other and in ways that can complement, enhance, diminish, or negate the other's influence on cancer risk, treatment, and outcomes.[54] Similarly, sex and gender may interact with other social factors, such as race, ethnicity, socioeconomic status, and educational attainment to affect cancer outcomes.[55] The influence of structural determinants of health, including health insurance status, geographic distance from specialty care, and transportation barriers, generally disadvantage patients with cancer from under-represented and underserved communities.[3] Presumably resulting from the intersection of multiple social and structural factors, cervical and endometrial cancer, two female-specific disease sites, have among the largest racial disparities for Black women of solid tumor types.[56] Patients with gender nonconforming identities have been shown to have lower rates of cancer screening and increased cancer mortality.[57,58]

Within the scientific literature and health policy domains, sex and gender are often used imprecisely in language and/or conflated. A recent analysis of oncology trials between 2012 and 2019 used to support FDA drug approval demonstrated that sex and gender terminologies were used inconsistently in 76% of reporting of results. None of the 128 evaluated studies described how sex and gender information was collected or assessed. Although 89% of survival data for non–sex-specific cancer sites was disaggregated by sex, no study presented disaggregated toxicity data by sex or gender.[59] Without disaggregation by sex and gender of research data, an analysis and understanding of how sex differences and gender inequalities affect health is not possible. Inattention to sex and gender in research, imprecision in language and reporting, and inadequate enforcement of journal and funder policies reflect a larger system of gender inequity that devalues women's bodies, health, and experiences.

Gender inequity is also reflected in disparities in National Institutes of Health (NIH) funding for diseases that affect women. For many diseases that affect primarily one sex, the funding pattern favors those that primarily affect men. With respect to burden of the disease within the population, female-dominant diseases are statistically more likely to be underfunded compared with male-dominant diseases.[60,61] Although there is an association between burden of disease and NIH funding, historic funding for a condition or disease is the factor most strongly associated with continued funding, thereby perpetuating male bias in biomedical research.[62] Disproportionately low NIH funding to gynecologic cancers compared with other cancer disease sites has been described.[60,63,64] Over time, persistent disparities in funding and research resources can lead to gaps in the evidence base for screening, diagnosis, and treatment of female-specific cancers, as well as limiting the pipeline of researchers invested identifying novel therapeutics for those diseases.

Reproducibility and generalizability of cancer clinical trials depend on the enrollment of populations representative of the population for which interventions are intended. Historically, exclusion of women from clinical trials rested on the gendered construction of a normal study participant as a 70-kg male patient, concerns that the normal hormonal fluctuations of the menstrual cycles might interfere with study results, and fears that enrollment of subjects capable of pregnancy might potentially lead to a teratogenic fetal exposure. The requirement that NIH-funded researchers

enroll racial and ethnic minorities and women, including women of childbearing age, into clinical research trials was codified into Federal law in the NIH Revitalization Act of 1993.[65] Although women make up approximately half of participants in NIH-sponsored research today, disparities in cancer clinical trial enrollment persist. For non–sex-specific trials completed between 2003 and 2016, female patients were underenrolled. Female enrollment to lung and pancreatic cancer trials was under 10% during this time frame while they represent over 40% of the new diagnoses.[66]

Oncology drug development depends on phase I trials made up of small cohorts of patients receiving escalating doses. In a recent analysis of National Cancer Institute (NCI)–supported phase I trials (between 2000 and 2019), similar numbers of male and female participants were enrolled and outcomes, including survival and adverse events, were similar between men and women. However, there are multiple selection biases in clinical trials enrollment that favor male participation in all phases of drug development.[67] Women are more likely than men to have multiple chronic conditions[68]; hemoglobin levels are generally lower in women, which could potentially preclude women from participation[69]; and financial toxicity related to clinical trials enrollment may disproportionately affect women's accrual.[70] Without representative populations of women participating in clinical research, the applicability of doses and efficacy of anticancer agents to the broader population of women may result in over- or undertreatment as well as excess treatment-related toxicity.

Few peer-reviewed journals are centered around the health needs of women. Publications in women's health journals remain primarily focused on reproductive health with an emphasis on obstetrics.[71] Within the broader publication community, women's health research has been shown to be less publishable—and when published, less impactful—than research focused on men.[72] Research focused on cancer care for women is also more often performed by women than men adding to other publication biases.

THE IMPACT OF STRUCTURAL SEXISM ON THE ONCOLOGY WORKFORCE

Just as the intersection of gender, power, and status affects patient care, structural sexism has wide-ranging effects on the oncology workforce. The physician identity was created by men as medicine was historically a profession performed by men.[73] The culture of medicine today reflects this history with value assigned to typically masculine traits and characteristics such as authority, objectivity, and rationality. More characteristically feminine behaviors such as acts of compassion or bidirectional communication are infrequently built into health care systems, incentivized, or rewarded.[73] The consideration of sex and gender as a binary has resulted in unique challenges, such as emotional distress, harassment, and fear, for physicians with nonconforming gender identities.[74,75] In 2021, 35.2% of practicing oncologists identified as women.[19] Yet despite large numbers of women practicing in oncology-focused specialties, women in oncology face many of the same challenges encountered by women in the larger medical community.

Gender bias or assumptions about roles, behaviors, and interactions on the basis of presumed sex are pervasive in society and medicine. Gender-biased beliefs are equally held by men and women,[76] health care professionals, and the general public.[77] Resulting from these wider societal expectations, women practicing medicine juggle a disproportionate share of household management and childcare tasks compared with their male colleagues in addition to their work as physicians.[78] Occupational gender bias, including the association of men as physicians, is identified early in childhood.[79] Gender segregation in medicine occurs at the specialty level with women tending to choose communal specialties that involve the care of women and children.[23] The specialties with the largest representation of women in the oncology workforce reflect this gendered specialty divide as 54% of gynecologic oncologists and 69% of breast surgeons are women.[80-82]

The culture of medicine—a hierarchical power structure, history of male dominance, long hours, and ample access to private spaces—makes gender-based harassment in medicine more pervasive than in other science or professional fields.[6] While explicit discrimination and sexual harassment are declining, implicit gender bias remains prevalent and can have equivalently detrimental effects over time compared with explicit discrimination.[6,83] In a recent survey of ASCO members, 70% reported having experienced sexual harassment in the past year. These experiences were more common in women compared with men (80% *v* 56%) and included gender harassment, unwanted sexual attention, and sexual coercion.[84] Inclusion of women into a specialty does not necessarily lead to decreasing rates of gender harassment. Within general surgery residencies, increasing percentages of women correlates with higher rates of gender discrimination and sexual harassment.[85] Most gynecologic oncologists (64%) report workplace gender discrimination.[86] Behaviors of these volumes, reported from such a variety of sources that include authority figures, patients, staff, and other hospital employees, suggest social forces beyond the individual level that drive gender-based harassment.[87,88]

Role congruity theory when applied to gender and medicine proposes that women will be positively evaluated when they are perceived as feminine (not a physician); however, being perceived as a woman often leads to being unrecognized as

an expert. This double bind leaves women challenged as to whether they should prioritize likeability or recognition for their expertise.[81,89] Biases held by patients and coworkers lead to the frequent misidentification of physicians who are women as nurses, support staff, or other nonphysician health care professionals leaving women to choose between laughing it off or asserting their role.[90,91] Women are less likely than men to be introduced using professional titles in a variety of setting including while speaking at grand rounds[92] and when receiving messages from patients communicating through the electronic medical record.[93] Despite representing 35.6% of physician membership within oncology professional societies, women were found to receive only 24% of the physician awards suggesting exceptional performance may be less likely to be recognized or rewarded in women.[94] Each of these seeming small undermining acts, behaviors, or dismissals accumulate, create additional work for women who are physicians to justify their skill and proficiency, and contribute to the leadership gap in medicine.[95-97]

Leadership in oncology remains disproportionately male. Over half of women practicing oncology perceive their gender to adversely affect their job promotion.[98] Within academic medical departments in gynecology and radiation oncology, a disproportionately low number of women hold the rank of full professor or department chair.[99-101] Within radiation oncology, there remains an under-representation of women in chair positions despite higher levels of grant funding for women.[102] At NCI-designated cancer centers, cancer center leadership teams are made up of predominantly White men, with women holding only 16% of cancer center director positions.[8,100,103] Women remain underrepresented in the currency of academics—women are less likely than men to publish in the senior author position, less likely to be included in authorship of clinical trials, and less likely to hold editorial positions in oncology journals.[104,105] These and other opportunities and activities can be thought of as markers of influence.[106] They coalesce and synergize to define leadership in oncology, and if, for each marker, women are less likely to be considered or awarded, stereotypes about women being less fit for leadership are perpetuated.

Gender pay gaps, arguably the most objective and transparent representation of differing value assigned to work performed by women, persist in all fields of oncology.[80,107,108] Across professions, the separation of jobs as performed primarily by women or men, or occupational segregation, explains much of the gender wage gap.[109] Men and women earn less in professions predominated by women compared with those where men are in the majority. The declines typically occur after the entry of women into previously male-dominant occupations signifying a devaluing of the same work when performed by women.[110,111] This trend has been demonstrated in medical fields including endocrinology, surgery, and gynecology.[81,110,112]

Numerous other gender-related factors explain observed differences in salary. Our current approach to physician compensation approach devalues an approach to practice favored by women (whether due to patient and coworker expectations or gender identity as a woman)—engagement in more patient-centered care and longer visits.[113,114] Female-specific procedures reimburse on average 28% lower than the comparable procedure in a male patient, a so-called double discrimination for women physicians who primarily care for breast or gynecologic malignancies.[114,115] Compensation in specialty care is most often dependent on new patient referrals. Although doctors are more likely to refer to specialists of the same gender, a bias toward referrals to men persists even with increasing representation of women within a specialty.[116,117] Patient complications lead to sharp drops in referrals to specialists who are women (and all women physicians) but not to men.[118] Women are more likely to be referred patients with complex psychosocial problems who require more time in the office and are less likely to generate procedural revenue.[11] In aggregate, women are doing more work for each work unit assigned compared with men.

SURMOUNTING THE CHALLENGE OF STRUCTURAL SEXISM IN CANCER CARE

The multiple domains of gender amplify one another leading to many barriers for patients with cancer and the oncology workforce. The downstream effects of structural sexism negatively influence the quality of care and innovation in research and are evidenced by persistent disparities in outcomes for patients with cancer and the continued barriers to career satisfaction and advancement for all oncologists, who identify as women—including cisgender, transgender, and gender diverse women—despite several decades of inclusion. Women with additional underrepresented identities are further disadvantaged by the intersection of structural sexism with other structural factors that influence health.

To overcome the challenges related to structural sexism, organizational and structural changes are required. Several cancer research and care organizations, such as European Society for Medical Oncology and ASCO, have put forth leadership development initiatives for oncologists of all backgrounds, advocated for policies advancing health equity for patients with cancer, and put forth best practices for caring for gender minority patients with cancer.[15,26,119,120] The following solutions are put forward toward creating a more equitable work and supportive clinical environment for the betterment of oncologists and patients with cancer.

- Individual oncologists should examine their own motivations, biases, and practices related to the delivery of equitable medical care to all patients.
  - Interventions to best implement and reward empathetic, trauma-informed (inclusive of recognizing and responding to the effects of traumatic stress and promoting patient safety, empowerment, and healing), and person-centered care are urgently needed across oncology care delivery environments.
- Incorporate sex and gender education in medical school, postgraduate oncology training, and continuing medical education such that the concepts are well understood by clinicians and the oncology workforce.
- Interrogate and disaggregate data from quality improvement projects by patient and health care professional gender to identify areas in need of improvement.
- Ensure inclusion of sex and gender considerations, diverse populations of researchers (including women), and patients throughout the research continuum—from hypothesis generation to study design, analysis, interpretation, and dissemination of results.
- Encourage the use of precise and accurate terminology about sex and gender in interpersonal communication, patient charts, reporting of research results, and health education related to cancer.
  - Avoid use of stigmatizing language (eg, hysterical, aggressive, and bossy) when discussing patients and colleagues and opt for gender-neutral terms when possible (eg, upset, assertive, and goal-directed).
- Enhance flexibility. Alternate schedules, job sharing, and family-friendly policies allow patients and health care professionals with any gender to better integrate cancer care with other responsibilities and ensure continuity of care.
- Enact term limits for leadership positions within organizations, professional societies, and journals. Term limits spur succession planning and innovation.
- Create cultures of inclusion and excellence, through ensuring transparent and fair metrics for patient care, administrative tasks, and research.
- Ensure transparent and fair metrics for recruitment, retention, promotion, and salary.

Equity is important to everyone, and diversity improves health care and research outcomes. Dismantling structural sexism is one piece of improving care delivery in cancer care, and the cancer research enterprise can benefit individuals of all genders and improves the health of communities of people affected by cancer.

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SARCOMA

Local Therapies for Metastatic Sarcoma: Why, When, and How?

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overview

Management of patients with advanced sarcoma has been evolving in recent decades, from a one-fit-all perspective to a more refined, personalized, and multidisciplinary approach. In parallel, the evolution of local therapies (radiotherapy, surgical and interventional radiology techniques) has contributed to the improvement of survival of patients with advanced sarcoma. In this article, we review the evidence regarding local treatments in advanced sarcoma, as well as its integration with systemic therapies, to provide the reader a wider and deeper perspective on the management of patients with metastatic sarcoma.

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INTRODUCTION

Soft-tissue sarcomas (STSs) describe a heterogeneous group of soft-tissue tumors with the WHO Handbook separating more than 60 subtypes. Being diagnosed at an early stage and achieving a complete (R0) resection of the primary tumor, the patients' prognosis might be excellent. However, metastatic tumor spread is common and may affect all parts of the body with the lungs as the predominant location[1] (Figure 1). Improved insight into tumor biology of sarcomas has resulted in significantly improved prognosis of patients over the past decade.[2]

THE CONCEPT OF OLIGOMETASTASES AND ITS IMPACT ON CLINICAL DECISION MAKING

If metastatic sarcoma presents with multiple bilateral lung metastases, systemic treatment is the treatment of choice. However, a considerable proportion of patients might have disseminated cancer with a limited number of metastases—each *per se* accessible to local treatment. For a wide spectrum of cancerous diseases including sarcoma, such an approach offers long-term survival by local treatment.[2,3] This subset of patients were called oligometastatic by Hellman and Weichselbaum in 1995.[4,5] The concept has been refined since and now also defines oligorecurrent and oligoprogressive disease.[6] The number of metastases has long been considered as one of the defining factors of oligometastatic disease (OMD), and the terms were consented to be applied by medical societies such as European Organisation for Research and Treatment of Cancer (EORTC) and ESTRO.[7] Disease characteristics and burden, time interval to the primary tumor, and other aspects were agreed on[7,8] to allow better comparison of trial results from surgery or radiation oncology for OMD. However, a systematic literature review on the completeness of reporting showed that the overwhelming publications show significant deficits.[9] A decade ago, miRNA clusters were in the focus of translational research of OMD.[10] Nowadays, the immune environment or epigenetic changes are at the forefront of research.[3,11-13]

Stereotactic radiotherapy, thermal ablation, surgical resection and refined systemic treatment options contribute to long-term survival of patients with metastatic STS. These highly selective procedures should only be administered after decision making in a multidisciplinary sarcoma board.

RADIATION THERAPY IN METASTATIC SARCOMA: MODALITIES, INNOVATION, AND CONSIDERATIONS ACROSS THE AGES

Historically, local control with conventional radiation for gross disease in sarcomas is quite poor, with limited available reports suggesting only 20%-30% local control at 2-5 years. Because of the relative radioresistance and chemoinsensitivity of sarcomas, patients with limited metastatic disease and otherwise expected longer-term survival are generally referred for consideration of surgery if metastases-directed local therapy is being considered. Prospective, randomized data for observation versus lung metastasectomy are unlikely to be obtained, but numerous series demonstrate a consistent 20% 5-year survival for patients with metastatic sarcoma to lung who are able to undergo surgical resection. Although there is almost certainly a selection bias in these series, surgical metastasectomy is generally an accepted practice for patients with OMD, especially if the lung is the only site of disease.

In contrast, pediatric sarcomas, such as Ewing, rhabdomyosarcoma, and synovial, tend to be chemosensitive and sensitive to moderate doses of radiation. For more than 20 years, it has been a standard

PRACTICAL APPLICATIONS

- Patients with advanced sarcoma could benefit from local therapies, and the multidisciplinary management of metastatic patients has probably played a role in the improvement of outcome in this population.
- Surgical resection of metastasis can provide selected patients prolonged disease control. In this article, the indications for metastasectomy are reviewed.
- New radiotherapy techniques such as stereotactic body radiotherapy are able to achieve local disease control in selected patients with metastatic sarcoma and can be an alternative to metastasectomy in patients not suitable for surgery.
- Systemic drugs combined with radiotherapy seek to increase the efficacy of radiation. Existing preclinical and clinical data on the combination of trabectedin plus palliative radiotherapy (30 Gy in 10 fractions) showed synergy and very interesting data in terms of overall response rate and outcome.

practice to attempt to consolidate patients with newly diagnosed pediatric sarcoma with comprehensive metastatic-directed therapy when feasible. Retrospective analysis of prospective pediatric studies and single-institution retrospective reviews consistently demonstrate a 20% survival in patients with metastatic pediatric sarcomas.[14-16] A closer review of the data reveals that survival generally improves to closer to 30%-40% for patients who received comprehensive metastatic-directed therapy, whereas in patients who did not receive comprehensive therapy, survival ranges from 0% to 10%.

In an attempt to improve the feasibility of metastatic-directed therapy in pediatric patients with newly diagnosed Ewing and rhabdomyosarcoma, stereotactic body radiotherapy (SBRT) and hypofractionated (higher dose over fewer days) radiation regimens was introduced into prospective COG study AEWS1221. 40 Gy in five fractions was recommended for bone metastases up to 5 cm in size. Alternative schedules were also allowed if 40 Gy in five fractions was not considered feasible secondary to toxicity concerns of nearby organs at risk (OAR). Although the primary end point, impact of insulin growth factor 1 inhibition, was negative, the OS for patients on AEWS1221, a study which limited to patients with metastatic Ewing sarcoma, was 36%. Analysis of impact of SBRT on metastatic site-directed therapy is ongoing.

A similar philosophy was adopted for patients with rhabdomyosarcoma on ARST1431. Prescription dose for this tumor, felt to be more radiosensitive, was 35 Gy in five fractions, with alternative fractionation schedules allowed. Although analysis is still ongoing, the recommended schedule has been continued on the currently open rhabdomyosarcoma study ARST2031. In the recently completed nonrhabdomyosarcoma adult and pediatric joint protocol evaluating pazopanib in addition to radiation and surgery for sarcomas, COG-NRG ARST1321, metastatic site-directed therapy was advised for all metastatic sites with either surgery or radiation. Radiation dose and fractionation was left to the discretion of the investigators. In the currently open osteosarcoma study AOST2031, patients with newly diagnosed metastatic osteosarcoma are recommended to receive comprehensive metastatic site-directed therapy as part of protocol therapy. Although it is expected that most patients will receive surgical metastatectomy, 50 Gy in five fractions is being recommended for metastatic sites including lung that are not amenable to surgical resection. Outcomes for SBRT in pediatric sarcomas have been reported in single-institutional series and a multi-institutional pilot study, and the safety and efficacy for pediatric patients receiving SBRT are demonstrated in the relapsed setting.[17,18] Local control was excellent for patients with Ewing and rhabdomyosarcoma. Osteosarcoma local control was slightly inferior suggesting that higher doses are necessary for durable local control in that disease.

With improvement in radiotherapy techniques such as SBRT that allow high-dose radiation to be delivered safely, radiation has been reintroducing as a potential modality for metastatic-directed therapy in adult sarcomas. Although for the most part patients are directed to surgery when feasible, for patients in whom surgical resection would be morbid or who are not otherwise surgical candidates, SBRT has been used to provide durable local control. Studies of lung, spine, and brain radiosurgery all demonstrate 85%-98% local control at 1-5 years, with many patients in the series experiencing prolonged survival.[19,20] Improved local control is associated with higher radiation doses, such that doses should exceed 100 Gy BED for the goal of ablative therapy.

For patients in whom ablative doses are not possible, generally because of toxicity concerns of adjacent OAR, attempts to achieve the highest dose possible are still justified as conventional palliative doses have very limited efficacy in sarcomas. Combination therapy with surgery and/or interventional radiology procedures can be considered as well for patients with good performance status or limited therapeutic options.

SBRT and modern IMRT for metastases in these populations have been very well tolerated. Pain flare can be seen with ablative doses of radiation, attributed to rapid

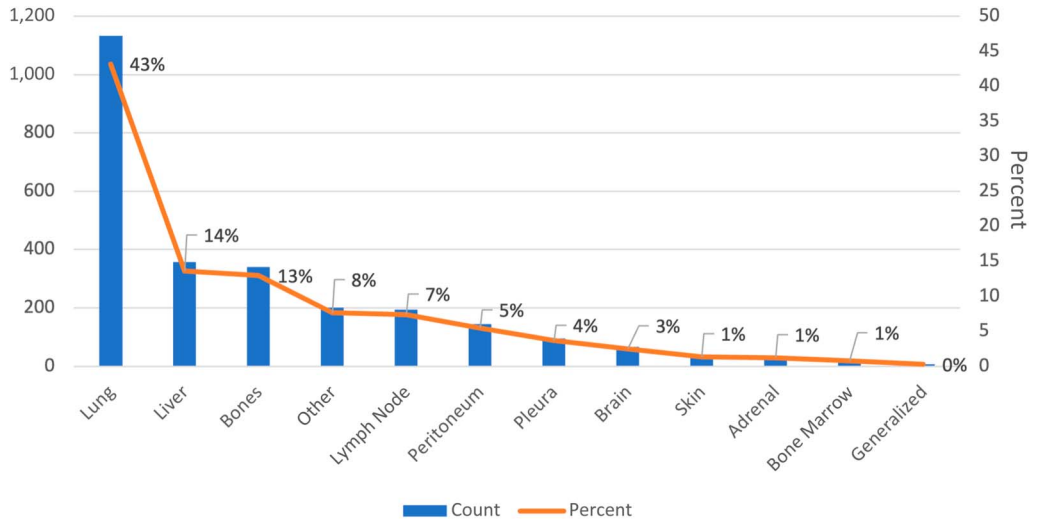

FIG 1. Frequency distribution and percentage of localizations of primary metastases (without gastrointestinal stromal tumor, N = 2,625).

tumor lysis. Treatment or pretreatment with short-course steroids can mitigate pain flares with SBRT. Radiation pneumonitis is rare but associated with ultracentral tumors, very large tumors, or multiple courses of treatment. Bone insufficiency fractures are a risk after all forms of radiotherapy but maybe a higher risk after ablative doses. Most studied are vertebral compression fractures which can occur in as high as 30% of patients as soon as 1 month after RT but can also be a late complication. For patients with features that are high risk for subsequent fracture, early intervention with vertebroplasty, with or without cryoablation if necessary to make room for safe cement placement, is recommended within 3 months of radiation. Other toxicities are generally mild and reversible (radiation dermatitis, fatigue).

Although the results of SBRT and hypofractionated ablative dose RT are encouraging, we await the results of the multiple prospective pediatric studies for both local control and acute and long-term toxicities. Although data are more limited in adult sarcomas, preliminary data more commonly in the relapsed setting suggest that high-dose SBRT provides durable local control and is an alternative to surgical metastasectomy for patients in whom surgical resection is not possible. Prospective studies in adults with newly diagnosed sarcomas are needed to evaluate the benefit of early, aggressive metastatic site-directed therapy similar to the current standard in pediatric sarcomas, to determine the safety and efficacy of this approach.

THE ROLE OF SURGICAL THERAPY FOR STS METASTASES

The recommendation to resect sarcoma metastases is often difficult because no results from randomized studies are available. The decision might depend on the subjective assessment and experience of the treating surgeon regarding extent and radicality of the intervention. In the case of surgery for recurrent metastases or when the patient's general condition is impaired, other ablative procedures can also be considered. Therefore, the indication for surgery should be made in a multidisciplinary tumor board.

The lung is the main location of sarcoma metastases accounting for about 40%, liver and bone account for 13% each, peritoneum and lymph node metastases develop at rates of 7%, and other locations are detected at even lower rates.[21,22] Thus, most publications on surgery of sarcoma metastases address the lung. The history of pulmonary metastasectomy dates back to 1882.[23] Most of the patients with pulmonary metastases are asymptomatic, and the lesions are detected during follow-up visits. Symptoms such as hemoptysis, cough, or shortness of breath are uncommon. Pain related to pulmonary metastases is only expected through chest wall invasion or a pneumothorax because of rupture of the pleural surface covering the metastasis.

Treatment Results of Lung Surgery and Influencing Factors

Numerous case series and reviews of the literature dating back over decades address very different patient scenarios.[23] A recent systematic review included series published after 2010 with at least 25 patients after metastasectomy and could analyze eight publications with 1,004 patients. Primary tumors were leiomyosarcoma (20%), synovial sarcoma (16%), and liposarcoma (6%), whereas the group of malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma (UPS)/undetermined STS accounted for 42% of the cases[24]; an extract of the data is shown in Table 1. In median, two lung metastases were resected at one time; the recurrence rate was 34% in one series and around 80% in both others. Patients can be offered a 90% chance of complete (R0) resection combined with a low complication rate (average of 10.8% in three series

TABLE 1. Extraction of Data From Eight Publications Evaluated in a Systematic Review[24]

Variable	Average	Worst	Best	Data NA
OS (median, months)	42	33.2	79.5	—
5-year-survival rate	35%-50%	8.5%	58%	1
DFS (median, months)	20	6.8	27	2
R0 resection rate	89%	74%	97%	1
No. of metastases. resected (median)	2	1	40	1
DFI to primary tumor (median, months)	16	9	30	2
Type of surgery, % minimally invasive	24%	0	29%	0
Recurrence rate	81%	82%	79%	5
Repeat pulmonary metastasectomy	34%	42%	16%	2
Complication rate	10.8%	14.7%	9.1%	5
Mortality	1.2%	3%	0%	2

Abbreviations: DFI, disease-free interval; DFS, disease-free survival; NA, not available; OS, overall survival.

reporting data), and operative mortality in six series was very low with 1.2%. The median overall survival (OS) after surgery ranges from 33 to 79.5 months. Depending on intensity of follow-up, the disease-free interval (DFI) is around 20 months. It did not matter whether an open or a minimally invasive procedure was performed. No relevant differences in R0 rates and DFI could be observed.[23] With more refined thoracoscopic procedures and improved computed tomography (CT) staging, the surgical approach can be easily adapted to the individual patient.

Seven of eight series evaluated prognostic factors with inconsistent results. Only DFI >12 months and solitary versus multiple nodules were mentioned in 6 of 7 reports. Like in other series, potential prognostic factors include a wide range from leiomyosarcoma subtype, neutrophil count, or response to preoperative chemotherapy.[23,25]

The recently published evidence-based German guideline on STS[26] states that surgical resection of pulmonary metastases of STS is encouraged and indicated, if

1. R0 resection of all pulmonary metastases is expected.
2. There are no signs of local tumor recurrence at the site of the primary tumor that cannot be controlled locally.
3. Prior pulmonary metastasectomy is no contraindication.
4. The patients' quality of life should play an important role in the decision making and, less invasive and better tolerable procedures should be preferred.
5. In metachronously resected lung metastases, there is no indication for additive chemotherapy.
6. Resection of pulmonary metastases with palliative intent is not recommended and should be reserved for exceptional cases with severe symptoms.
7. In case of the presence of extrapulmonary metastases, surgical removal of pulmonary metastases must be an interdisciplinary decision in an individual case.

Magnitude of the Effect of Surgery Versus Nonsurgical Management and Chance of Long-Term Survival

A propensity-matched comparison of 1,578 patients treated from 1998 to 2015 with metachronous metastases from extremity and trunk STS tried to quantify the effect of metastasectomy on OS.[27] Patients from two European centers had myxofibrosarcoma in 29%, synovial sarcoma in 13%, and UPS in 10% as the most common histological subtypes. OS was significantly longer in 68 patients undergoing metastasectomy than in 67 patients who did not (10-year OS, 23% *v* 4%; hazard ratio [HR], 0.34; 95% CI, 0.22 to 0.53; $P < .0001$). The effect prevailed after weighting of the data to control for the higher prevalence of favorable prognostic factors in the surgery group (adjusted 10-year OS, 17% *v* 3%; log-rank $P < .0001$; HR, 0.33; 95% CI, 0.20 to 0.52; $P < .0001$). Five-year OS was 27.8% in patients who had and 14.5% in patients who had not undergone metastasectomy within the first 3 months after diagnosis of a metastasis ($P < .0001$).

The potential benefit of surgical intervention was consistent across important clinical subgroups such as Eastern Cooperative Oncology Group status, metachronous interval more or less than 12 months, or age younger or older than 70 years at metastasis diagnosis. However, the benefit of metastasectomy was stronger in patients with a single metastasis (HR, 0.21) than in patients with multiple metastases (HR, 0.44). The results are more encouraging than those published a decade ago with a 5-year OS of 17%.[28]

A multistate modeling of 443 patients integrated multiple risk factors as local recurrence, metastases, and clinical end points into a single statistical model to avoid that the Kaplan-Meier method may overestimate actual long-term survival. With a median follow-up of 6 years, 84%, 52%, and 23% of patients had being followed for more than 1, 5, and 10

years, respectively. The 15-year cumulative incidences of local recurrence, distant metastasis, and death from any cause, using a competing risk analysis, were 16% (95% CI, 11 to 22), 21% (95% CI, 17 to 26), and 55% (95% CI, 44 to 67), respectively.[29] Patients who experienced a local recurrence were more likely to develop distant metastasis (HR, 8.4; 95% CI, 4.3 to 16.5; $P < .001$) and to die (HR, 3.4; 95% CI, 2.1 to 5.6; $P < .001$). The occurrence of distant metastasis was associated with a strong increase in the risk of death (HR, 12.6; 95% CI, 8.7 to 18.3; $P < .001$). Distant metastasis occurring after a long DFI was not associated with a more favorable prognosis with respect to mortality. The relative decrease in the adverse effect on mortality for 1-year delay of distant metastasis is 0.9 (95% CI, 0.7 to 1.1; $P = .28$).

Aggressivity of surgical treatment is a significant contributor of long-term survival. A group of 97 patients treated for stage III STS could be split into 61 patients (62.9%) who survived for more than 5 years followed up with a median of 7.3 years (range, 5.0-17.3 years). The median survival of the 36 short-term survivors was 1.3 years (range, 0.3-3.3 years), and these patients underwent less aggressive treatment against recurrence, particularly less surgical resection of metastatic disease.[30]

The more the scenario of OMD is fulfilled (no history of polymetastatic disease) the earlier the indication for surgical therapy is on safe ground. Pulmonary has the potential to result in long-term survival[2,23]

Surgical Treatment of Nonpulmonary Metastases

All sites of the body can be targets of metastases from sarcoma, for example leiomyosarcoma tend to show a higher rate of metastases to the liver and soft tissues.[31] Metastases to the skeleton are more often detected in myxoid-round cell and dedifferentiated liposarcoma.[32] Data on resection of sarcoma metastases at such sites are scarce. The likelihood of nonpulmonary metastasis (NPM) occurring in the absence of lung metastasis is low and affects roughly 10% of all patients developing metastases. Malignant periferal nerve sheath tumor, angiosarcoma, rhabdomyosarcoma, synovial sarcoma, and myxoid liposarcoma were six times more likely to develop initial NPM than other subtypes of STS with an odds ratio of 6 (95% CI, 1.93 to 18.65; $P < .01$[33]). For resection of liver metastases, a systematic review summarizes six studies on 212 patients dating back to 1982.[34] The largest series with 128 patients resected for non-GIST liver metastases (49% leiomyosarcoma) in 1998-2015 reports 5-year OS rate of 49.3% and RFS of 14.9% with no difference in OS or RFS between histological subtypes.[35]

Brain metastases from sarcoma are a rare event but can develop in all subtypes including GIST. In alveolar soft part sarcoma, they are often detected at initial diagnosis. A systematic review analyzed 10 studies published from 1994 to 2020 on the treatment of brain metastases of STS, and 269 patients underwent metastasectomy. With a follow-up between 14 and 29 months, the median OS ranged from 7 to 25 months.[36] Similar to the view of neurosurgeons, resection may be a realistic treatment option in patients with up to three metastases and is particularly indicated in symptomatic lesions.[37] A randomized controlled trial of preoperative versus postoperative stereotactic radiosurgery for surgically resectable brain metastases is ongoing (ClinicalTrials.gov identifier: NCT04474925).

Regarding lymph node metastases, the overall incidence is reported to be 4.2%.[38] Clear cell sarcoma (16%), epithelioid sarcoma (13%), angiosarcoma (6.1%), and synovial sarcoma (3.8%) are subtypes with the highest incidences.[38,39] It is important to consider which age cohorts are being studied.[40] Prognostically, it was reported that surgical resection of isolated lymph node metastases results in better OS than resection of pulmonary metastases[41,42]

In summary, the recommendation for surgery in NPM should only be done following an interdisciplinary discussion, if an R0 removal of all metastases can be performed and in the abscense of uncontrolled local recurrence. Resection of liver metastases with palliative intent is not recommended. Metastases from other sites may be surgically removed on a case-by-case basis and after multidisciplinary tumor board discussion.[26]

Communication Skills

In the discussion with the patient one should avoid the palliative (systemic treatment) versus curative (surgery) perspective. Surgical removal of metastases should render the patient free from disease postoperatively. This might turn out that it did cure the patient. More realistically it offers the opportunity for long-term disease control—until the detection of a (hopefully late) recurrence.[43] This strategy opens the door for a shared decision making on the basis of realistic assumptions. A French study of patients with metastatic sarcoma demonstrated that 39 of 436 patients (9%) were still alive 5 years after diagnosis of metastases with a median survival of 12 years.[2]

Future Aspects

Two emerging factors might positively influence the contribution of surgical treatment in the future: control of the surgical effect on the metastatic cell load via cDNA as it is already applied for sarcoma subtypes such as GIST or Ewing sarcoma. Monitoring cDNA could provide a tool to better combine local and systemic treatments.[44-46] Technical development brings CT-guided surgery of pulmonary nodules to the hybrid operation theater. The more widespread use of nonintubated videothoracopy-assisted, uniportal lung

resection should further add to patient-tailored surgical procedures of very low morbidity.[47,48]

INCORPORATING SYSTEMIC THERAPIES WITH LOCAL MODALITIES IN METASTATIC SARCOMA

As previously stated, systemic treatment is the mainstay of therapy in patients with advanced/metastatic unresectable STS.[49] Although patients with metastatic sarcoma still have a poor prognosis, expected median OS in this population has clearly increased in the past decades, from around 12 months[50] to nearly 2 years in more recently published clinical trials.[51,52] The incorporation of several second-line options (trabectedin, pazopanib, and eribulin) to the therapeutic armamentarium has contributed to this increase in OS, but the better refinement in patients' management, with a multidisciplinary approach, even in the advanced setting, has also played a role. This multimodal view has allowed us incorporating local therapies to systemic drugs, maximizing symptom and disease control options.

When designing the first line of therapy of a patient with advanced STS, treatment objective is a relevant issue to be discussed and defined upfront to better select the proper treatment modality. In the case of patients with asymptomatic unresectable disease, systemic therapy with anthracyclines or, in selected patients, close follow-up could be the treatment of choice. However, there are patients in whom a multimodal approach can be indicated or needed. Patients with OMD at diagnosis, for example, could be candidates to a more intense first line, that is, anthracycline-based combinations, to maximize the possibility of achieving an objective response,[53] with the aim of facilitating a subsequent surgical resection. It is especially important to discuss with the patients the risk of a higher toxicity for these more intense approaches, as anthracycline combinations present significantly higher risk of grade 3-4 adverse events, especially hematologic, when compared with doxorubicin alone.

Patients with symptomatic lesions could also be candidates to local therapy of the symptomatic lesion in combination with systemic treatment. Palliative surgeries can be necessary in the context of unresectable metastatic disease, for example in the case of bleeding or ulcerated primary tumors. Despite the absence of prospective evidence, the combination of chemotherapy and definitive radiotherapy of the primary tumor may also be an option in patients with metastatic sarcoma and unresectable primary tumors (especially in symptomatic tumors). In the case of concomitant chemoradiotherapy, with anthracyclines and ifosfamide, the experience in the localized setting showed a higher risk of grade 4 thrombocytopenia, something that has to be taken into account, especially given the palliative setting.[54]

Beyond first line, several drugs are used and/or approved in the second and further lines: ifosfamide, gemcitabine combinations, trabectedin, pazopanib, eribulin, and dacarbazine. With the exception of specific drugs in specific histologic subtypes (ie, high-dose ifosfamide, which can induce responses in a high proportion of patients with synovial sarcoma,[55,56] or gemcitabine combinations, especially active in leiomyosarcoma and undifferentiated pleomorphic sarcoma[57,58]), the chances of obtaining an objective response with these drugs is lower than 10%.[59-61] This is relevant because, consequently, the chances of achieving symptomatic benefit with chemotherapy alone in those patients with symptomatic disease are scarce.

As previously discussed, radiotherapy is a useful tool in the metastatic setting for disease and symptom control. Systemic therapies, in addition to contribute to obtain systemic disease[62] control, can potentiate the effects of radiotherapy, acting as radiosensitizers. Several mechanisms have been described, by which systemic drugs can enhance the activity of radiotherapy: induction of DNA damage (ie, cisplatin induces DNA adducts, making cells more vulnerable to RT), interaction with relevant cell processes (such as angiogenesis), or modulation of cell cycle (to synchronize cells and induce cell cycle arrest in the most radiosensitive cell cycle phase [G2/M]). In sarcoma, there are scare data on systemic therapies (beyond anthracyclines and ifosfamide) and its concurrent administration with RT. Haas et al[62] tested in a small phase I study the concurrent administration of preoperative pazopanib and radiotherapy in patients with high-risk localized STS. Although no patients showed radiological responses, pathological response in >95% of the tumor volume was found in four of 10 tumors in the surgical specimens. However, this experience is difficult to extrapolate to the metastatic setting. Although the toxicity profile in the previous study was the expected for pazopanib (grade 3-4 adverse events mainly related with hepatotoxicity), there could be some concerns in the advanced disease setting in terms of toxicity. The previous study was developed in patients with tumors in limbs or trunk wall, but the main location for metastatic disease in sarcoma is lungs. Pneumothorax has been described as adverse event in a proportion of patients treated with pazopanib,[63] and, in the absence of specific studies in the metastatic setting, the concurrent use of pazopanib and radiotherapy should be taken with caution.

Trabectedin is another drug approved for the therapy of patients with pretreated advanced STS. Several mechanisms of action have been described for trabectedin: immunomodulatory effects by its interaction with tumor infiltrating macrophages, transcriptional modulation and DNA damage induction (by its ability to bind the minor grove of DNA), and interestingly, effects on cell cycle, inducing accumulation of cells in G2/M.[64] This latter confers trabectedin radiosensitizing properties, something that was already described in preclinical models a couple of decades ago.[65] The combination of trabectedin and radiotherapy in sarcoma was

explored in the TRASTS trial, a phase I/II academic study sponsored by the Spanish Group for Research in Sarcoma, with the collaboration of Italian and French Sarcoma Groups. The cohort A of this study explored the safety and efficacy of the combination of trabectedin and radiotherapy (with the regimen of 30 Gy in 10 fractions, considered a low-dose, palliative regimen) in patients with metastatic sarcoma. This study showed that this regimen is safe, being the adverse events observed those expected for trabectedin alone, with the exception of some cases of transient pneumonitis in RT fields. In terms of efficacy, the regimen showed a very interesting activity, with 60% of the patients included in the cohort achieving RECIST objective responses according to a central radiological review. In addition to this, outcome was also interesting in terms of progression-free survival (PFS), with 9.9 months for the phase II part, whereas median OS had not been reached at the time of the analysis.[66] Beyond this study, the experience in 40 patients with advanced STS treated with the same combination of study has also been published.[67] In this nonselected, real-life population, the combination of trabectedin and radiotherapy was able to induce objective responses in one third (32.5%) of the patients included in the series. The median PFS in this series exceeded 7 months, and the median OS was almost 2 years, very interesting data for a pretreated advanced STS population. The translational studies performed within TRASTS trial confirmed in sarcoma the finding of the synergy between trabectedin and RT, already observed in carcinoma cell lines. Of note, cell cycle modulation (G2/M accumulation) had its peak at 12 hours after trabectedin administration. This finding provides a potential explanation for the better results found in the TRASTS study when compared with the real-life series, in which the start of RT was delayed for more of 24 hours in up to one third of the patients. With all these data, the recommendation would be to start RT as soon as possible after the end of trabectedin cycle, to maximize the synergy between both therapeutic tools.

This regimen constitutes an attractive alternative for patients with advanced STS, especially those who need a dimensional reduction to obtain symptomatic relief. Currently, the phase II multicohort Synergias Study (ClinicalTrials.gov identifier: NCT05131386) is exploring the activity of this combination not only in STS but also in bone and small-cell sarcomas, with a special focus in quality-of-life items.

CONCLUSIONS

Treatment of patients with advanced STS is challenging, and patient survival in this setting has still a wide margin of improvement. Although outcome is still poor, globally the situation has improved in the past decades, and the median OS has almost doubled for these patients. Several circumstances could explain this improvement: First, more second-line systemic options are available. Second, the fact that the multidisciplinary management of the localized setting has been translated to patients with advanced STS, as local therapies can also be considered for these patients. Medical oncologists, together with surgeons, radiotherapy oncologists, and interventional radiologists, are responsible of designing the best management for each patient in an individual basis. The final aim of this multimodal approach should be to provide the best outcome with the best quality of life, always integrating and respecting patient preferences. Technical advances in the past decades have brought less invasive surgical procedures, refined RT techniques such as SBRT, and interventional radiology therapeutic options which, added to systemic therapies in selected patients, have enlarged the therapeutic perspectives of this population. In addition, the improvements in the knowledge on the molecular background of the different histological subtypes and the knowledge on the mechanisms of action of the several available drugs have also added a new layer in the refinement of the management of advanced disease.

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SARCOMA

Bad to the Bone: Emerging Approaches to Aggressive Bone Sarcomas

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overview

Bone sarcomas are rare heterogeneous tumors that affect patients of all ages including children, adolescent young adults, and older adults. They include many aggressive subtypes and patient groups with poor outcomes, poor access to clinical trials, and lack of defined standard therapeutic strategies. Conventional chondrosarcoma remains a surgical disease, with no defined role for cytotoxic therapy and no approved targeted systemic therapies. Here, we discuss promising novel targets and strategies undergoing evaluation in clinical trials. Multiagent chemotherapy has greatly improved outcomes for patients with Ewing sarcoma (ES) and osteosarcoma, but management of those with high-risk or recurrent disease remains challenging and controversial. We describe the impact of international collaborative trials, such as the rEECur study, that aim to define optimal treatment strategies for those with recurrent, refractory ES, and evidence for high-dose chemotherapy with stem-cell support. We also discuss current and emerging strategies for other small round cell sarcomas, such as *CIC*-rearranged, *BCOR*-rearranged tumors, and the evaluation of emerging novel therapeutics and trial designs that may offer a new paradigm to improve survival in these aggressive tumors with notoriously bad (to the bone) outcomes.

INTRODUCTION

Primary bone sarcomas are rare heterogeneous tumors that make up <1% of cancers. They include a number of aggressive subtypes. Many groups of patients have poor outcomes, and they have seen little improvement over recent years. Increased collaboration and improved understanding of tumor biology have revealed promising therapeutic targets and contributed to defining treatment strategies. This review focuses on emerging approaches to therapy in these tumors.

Systemic Approaches Across the Spectrum of Chondrosarcoma

Chondrosarcomas (CSs) are rare mesenchymal neoplasms defined by the production of an abnormal cartilaginous matrix. They represent approximately 25% of all primary malignant bone tumors and have diverse morphological features and clinical behavior. Conventional chondrosarcoma (cCS) accounts for 85%-90% of CSs. Non-cCS variants include mesenchymal chondrosarcoma (MCS), dedifferentiated chondrosarcoma (DCS), and clear cell CS (Table 1).[1] These are a challenging group of tumors with limited standard-of-care systemic options, lack of prospective evidence for management, and poor outcomes in patients with metastatic or unresectable disease. Here, we discuss current management and emerging systemic therapies.

Current management. cCSs primarily arise in the medulla of the bone (central CS). Most CSs are solitary but are occasionally multifocal in syndromic patients with underlying multiple osteochondromas and enchondromatosis.[2] Grade 1 cCSs or atypical cartilaginous tumors have low metastatic potential,[3] whereas grade 2 and 3 cCSs are more aggressive with higher metastatic potential and reduced 10-year survival. Surgical excision is the primary treatment modality of CS. Conventional chemotherapy has very limited activity in patients with advanced cCS and is not recommended.[4]

Occasionally, cCS dedifferentiates into a high-grade aggressive sarcoma, DCS, which is associated with dismal outcomes.[3] Approximately 20% of patients with DCS present with metastatic disease, with a median overall survival (mOS) of <9 months.[5] On the basis of several studies with small patient numbers, a survival advantage for neoadjuvant or adjuvant chemotherapy in DCS has been demonstrated.[6-8] Conversely, retrospective data from the European Musculo-Skeletal Oncology Society group did not demonstrate an obviously improved survival with adjuvant chemotherapy.[9] Despite these relatively limited and conflicting data, chemotherapy is often considered for patients with DCS in the adjuvant and advanced setting, with anthracycline-based chemotherapy regimens most commonly used.[10]

MCS is a very rare distinct subtype that affects younger patients. MCS is composed of undifferentiated small

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PRACTICAL APPLICATIONS

- Due to the rarity and complexity of aggressive bone sarcomas, patients should be managed in expert sarcoma centers.
- In conventional chondrosarcoma (cCS), chemotherapy is not the standard of care, but novel therapeutic targets are under evaluation, and patients should be considered for clinical trial entry where possible.
- Recent clinical trials have defined standard of care for patients with localized Ewing sarcoma (ES), but trials for patients with metastatic or recurrent ES have failed to demonstrate a significant improvement in survival.
- Retrospective analyses have provided insights into management and outcomes of other small round cell sarcomas, including *CIC*- and *BCOR*-rearranged sarcomas; however, controversies remain regarding the optimal treatment strategy for these patients.
- Multitargeted tyrosine kinase inhibitors (MTKI) have demonstrated efficacy in several bone sarcomas, including ES and osteosarcoma, and ongoing trials aim to define their place in therapy.
- The current system of identifying new agents for bone sarcomas is limited to those that exhibit responses or prolong event-free survival (EFS) in those with measurable disease, thereby not addressing resistant residual populations that lead to relapse.
- Current promising strategies focus on different mechanisms, such as targeting altered cell cycle, DNA damage repair mechanisms, surface proteins, and kinases, and improving immune responses.

round cells (SRCs) and variable amounts of well-differentiated hyaline cartilage and is characterized by the presence of a specific gene fusion between *HEY1 and NCOA2*.[11] For localized disease, surgery is the mainstay of treatment. Tumors are typically radiosensitive, and adjuvant radiotherapy is recommended particularly for large tumors.[2] This high-grade, aggressive neoplasm is typically chemosensitive. Adjuvant anthracycline-based chemotherapy is associated with a significant reduction in recurrence and death.[12] The consensus of many groups is to use Ewing sarcoma–like treatment regimens, although, to our knowledge, no randomized studies have been performed. Metastatic disease at presentation (10% of cases) is more common than in cCS[6] and is the strongest prognostic indicator.[13] There are phase II data indicating a role for trabectedin in advanced disease.[14] Other rare variants include periosteal CS and clear cell CS. These are low-grade variants with no specific systemic therapeutic options.

Targets and novel systemic treatment options in CS. There is an urgent need for new targeted therapies in CS, particularly for those with advanced and metastatic disease. Increased understanding of biology has provided the rationale for novel therapeutics, but historically clinical translation has been disappointing, including that of Hedgehog inhibitors that yielded great promise preclinically but failed to demonstrate a survival benefit in two large phase II clinical trials.[15-18] In addition, because of the rarity of the disease and heterogeneity of the natural history of CS, with relatively indolent disease observed in a proportion of patients, lack of standardization of inclusion criteria and lack of random assignment make the interpretation of benefit challenging. There are currently no targeted therapies approved for CS; however, increasing evidence and ongoing clinical trials hold promise for the future.

Pazopanib is a multitargeted tyrosine kinase inhibitor (MTKI) that has shown clinical benefit in patients with CS. Prolonged stability of disease has been seen in patients with progressive CS,[19] and phase II trial data demonstrated a median progression-free survival (mPFS) of 7.9 months (95% CI, 3.7 to 12.6).[20] However, pazopanib is not licensed for treatment of cCS, and although frequently used in the management of advanced metastatic disease in the United States, it is not currently available in many countries in Europe. The REGOBONE trial, which evaluated the MTKI regorafenib, across bone sarcomas, demonstrated encouraging results in the cCS cohort, with an improved mPFS of 19.9 weeks in the regorafenib arm compared with 8 weeks in the placebo arm; however, this small trial did not meet its primary end point.[21] There is anecdotal evidence that MTKIs may offer disease control in MCS, but data from clinical trials are lacking.[22]

IDH1 and *IDH2* mutations are the most common mutations found in CS, first described by Amary et al in 2011, in 56% of CS. These mutations are thought to be an early event in the pathogenesis of disease as they are present in enchondromas, through to cCS and DCS, and in patients with both solitary and multiple neoplasms.[23] Mutations in the *IDH1/2* genes are some of the best described genetic alterations linking oncogenesis and metabolism and hence a potential therapeutic avenue in multiple cancers, including CS. Preclinical data were encouraging, showing that drug inhibition of IHD1 (with AGI-5198) reduced the production of 2-HG by up to 90% in *IDH1/2*-mutant CS cells.[24-26] However, only a moderate decrease in viability was observed in some mutant *IDH1* cell lines and tumor models.[26] Outcomes from clinical trials have been mixed.

TABLE 1. 2020 WHO Classification and Features of Select Bone and SRC Tumors

Tumor Subtype	Clinical Features	Molecular Features
Chondrogenic tumors		
Central atypical cartilaginous tumor, grade 1 (ACT/CS1)	ACT = appendicular skeleton (long + short tubular bones) CS1 = axial skeleton (flat bones including pelvis, scapular and skull base) Primary conventional central ACT/CS1—arise centrally in bone without benign precursor Secondary conventional central ACT/CS1—arise centrally in bone in association with a preexisting enchondroma	*IDH1* or *IDH2* mutation (50% primary; 78% secondary)
Secondary peripheral atypical cartilaginous tumor, grade 1	Adults Age: 20-40 years Flat bones and appendicular skeleton	Germline *EXT1* or *EXT2* mutation
Central chondrosarcoma grade 2 and 3	Adults Third to sixth decades of life Bones of extremity or pelvis	*IDH1* or *IDH2* mutation (50%) *RB1* pathway alteration (86%) *TP53* mutation (20%-49%) *COL2A1* (45%), *YEATS2* (12.3%), *EGFR* (19%), *NRAS* (18%), *CDKN2A* (rare) mutations
Dedifferentiated chondrosarcoma	Adults Median age: 59 years (range, 15-89 years) Long bones, pelvis, and scapula	*IDH1* or *IDH2* mutation (50%-87%) *TP53* mutation (20%-49%)
Mesenchymal chondrosarcoma	Adults Second and third decades of life Bone, soft tissue, intracranial	*HEY1—NCOA2* fusion
Periosteal chondrosarcoma	Adults, peak incidence third decade of life Usually located in the metaphysis of long bones (distal femur, humerus)	*IDH1* or *IDH2* mutation
Clear cell chondrosarcoma	Adults Epiphysis of long bones (femoral and humeral head)	Diploid genome *P53* overexpression in the absence of mutation
Undifferentiated SRC sarcomas of bone and soft tissue		
Ewing sarcoma	Children to young adults, peak incidence in adolescents Bones of extremity or pelvis	*FET-ETS* fusion (*EWSR1-FLI1* 85%, *EWSR1-ERG* 10%)
CIC-rearranged sarcoma	Children and adults, peak incidence in the third decade Soft tissue of extremity, trunk, head/neck, retroperitoneum Aggressive course with poor response to chemotherapy	Fusions of *CIC-DUX4* (95%), *CIC-FOXO4*, *CIC-LEUTX*, *CIC-NUTM1*, *CIC-NUTM2A* (rare)
BCOR-rearranged sarcoma	Children, AYA, predilection in males Long or flat bones (*BCOR*-ITD, soft-tissue tumors of trunk, head/neck, retroperitoneum) Outcomes more favorable than those of *CIC*-rearranged sarcomas	Fusions of *BCOR-CCNB3* (most common), *BCOR-MAML3*, *BCOR3-ZC3H7B*, and *BCOR*-ITD
EWSR1–non-ETS sarcoma	Children and adults *EWSR1-NFATC2*: 4:1, long bones: soft tissue *FUS-NFATC2*: exclusively long bones *EWSR1-PATZ1*: soft tissue of the chest wall or abdomen	Fusions of *EWSR1-NFATC2*, *FUS-NFATC2*, *EWSR-PATZ1*

Abbreviations: AYA, adolescent young adult; ITD, internal tandem duplication; SRC, small round cell.

The phase I study of ivosidenib (ClinicalTrials.gov identifier: NCT02073994) in solid tumors with an *IDH1* mutation showed good oral exposure, a long half-life with persistent plasma 2-HG inhibition observed in *IDH1*-mutant tumors, and an acceptable toxicity profile.[27,28] In the CS cohort, there were encouraging results with a mPFS of 5.6 months (95% CI, 1.9 to 7.4).[28] The phase I/II study of IDH1 inhibitor olutasidenib (ClinicalTrials.gov identifier: NCT03684811) recruited 23 patients with CS. The phase I/II study of the US Food and Drug Administration approved IDH2 inhibitor enasidenib[29] in solid tumors including CS (ClinicalTrials.gov identifier: NCT02273739) and completed accrual in 2018. The dual inhibitor of IDH1/2, vorasidenib (ClinicalTrials.gov identifier: NCT02481154), is also under investigation in CS. The efficacy results of these trials are eagerly awaited.

Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) receptor (DR4 or DR5) agonists are promising cancer therapeutics as they selectively induce apoptosis in cancer cells. Monoclonal antibodies targeting DR5 are under development. Among them, INBRX-109 appears promising for CS with a phase I trial demonstrating favorable disease control and objective response rates and a mPFS of 7.4 months.[30] An international randomized phase II trial is ongoing.[31]

The immune microenvironment of CS remains poorly understood. Immunohistochemical analysis of CS tissue microarrays reported PD-L1 expression in around 40% of patients with DCS, with expression exclusively in dedifferentiated components of the tumors and an absence in cCS and MCS.[32] Biomarkers predictive of response, however, are lacking. The phase II SARC 028 study investigated the use of pembrolizumab in advanced bone and soft-tissue sarcoma. Among five patients with CS enrolled, one patient with DCS achieved a partial response (PR).[33] In a phase II study assessing pembrolizumab with doxorubicin in patients with advanced anthracycline-naïve sarcoma, three of eight patients with CS had a PR to therapy.[34] The phase I/II ImmunoSarc study investigating sunitinib and nivolumab in advanced bone and soft-tissue sarcoma demonstrated the initial evidence of activity in DCS; recruitment in this cohort is ongoing.[35] Further ongoing immunotherapy agent trials are detailed in Table 2.

The PI3K-AKT-mTOR pathway is highly active in CS[37,38]; however, activating mutations in the pathway are very rare.[39] Preclinical evidence has indicated the activity of inhibitors to a number of these kinases in CS.[40,41] Furthermore, a small retrospective clinical study of the mTOR inhibitor sirolimus plus cyclophosphamide in patients with unresectable CS showed disease control with preliminary results from a phase II trial of the combination also demonstrating disease stability.[42]

The second most frequent mutation in cCS and DCS occurs in the *TP53* gene (20%-50%).[43,44] Overexpression of TP53 or its alteration correlates with higher histologic tumor grade suggesting a role in tumor progression.[45] TP53 remains undruggable. Other frequently aberrated genes in CS relate to the cell cycle control process, and the retinoblastoma protein pathway, with loss of expression of cyclin-dependent kinase 2A/B (CDKN2A and CDKN2B) commonly seen in high-grade cCS.[43] These provide a rationale for patient inclusion in studies evaluating CDK4/6 inhibitors such as abemaciclib (ClinicalTrials.gov identifier: NCT04040205). Similar agents, however, have failed as monotherapy across multiple cancer types; thus, it remains undetermined whether there is utility for patients with CS.

Finally, epigenetic dysregulation may represent a potential barrier for tumor progression and target for therapeutic intervention with CS demonstrating high sensitivity to histone deacetylase (HDAC) inhibition independent of isocitrate dehydrogenase mutation status in *in vitro* models.[46] Additionally, a combination of a DNA methyltransferase inhibitor and the HDAC inhibitor, suberanilohydroxamic acid, impaired the proliferation of CS models *in vitro* and in xenograft models, leading to an ongoing combination phase II study (ClinicalTrials.gov identifier: NCT04340843).

Controversies in Managing High-Risk and Relapsed Ewing Sarcoma and Other SRC Sarcomas

Ewing sarcoma (ES) is a SRC sarcoma that is molecularly defined by the presence of a *FET* (most commonly *EWSR1*)-*ETS* fusion.[47] More broadly, the family of other undifferentiated SRC sarcomas encompasses those with *EWSR1*–non-*ETS* fusions and *BCOR* or *CIC* rearrangements (Table 1).[1,48] Although treatment of ES, including chemotherapy and surgery and/or radiation, has evolved over the past few decades leading to improved survival for a subset of patients, progress has halted for others. Controversies remain in the management of high-risk ES and other SRC sarcomas, in part driven by an incomplete understanding of their high-risk biological features and their relatively lower incidence, which have limited the feasibility of rigorous clinical trials for the smaller high-risk ES populations and rarer SRC sarcoma subtypes. Principles surrounding several such controversies are presented here, providing a foundation of both evidence and remaining questions for future studies in the endeavor to improve outcomes in these high-risk sarcomas.

Frontline chemotherapy for Ewing sarcoma. Building on a series of trials over the previous few decades, the landmark randomized phase III studies AEWS0031 and EURO EWING 2012 (EE2012) established the use of vincristine, doxorubicin, and cyclophosphamide (VDC) alternating with ifosfamide and etoposide (IE) in a biweekly interval compressed dosing schedule as standard-of-care frontline

TABLE 2. Overview of Relevant Completed and Ongoing Clinical Trials in CS

Trial	Trial Phase	Intervention	Drug Class	Type of Tumor	Status + Efficacy
Schwartz et al[36]	II	Cixutumumab + temsirolimus	IGF-1R antibody and mTOR inhibitor	STS Bone sarcoma CS (n = 38)	Completed mPFS: 5.2 months mOS: 13.6 months
Tawbi et al[33]	II	Pembrolizumab	PD-1 inhibitor	STS Bone sarcoma CS (n = 5)	Completed mPFS: 8 months mOS: 12 months
Chow et al[20]	II	Pazopanib	MTKI	CS (n = 47)	Completed mPFS: 7.9 months mOS: 17.6 months
Tap et al[28]	I	Ivosidenib	IDH1 inhibitor	CS (n = 21)	Completed mPFS: 5.6 months mOS: NA
Pollack et al[34]	I/II	Pembrolizumab + doxorubicin	PD-1 inhibitor	Advanced anthracycline-naïve sarcoma; CS (n = 4)	Completed mPFS: not reported mOS: not reported
Duffaud et al[21] REGOBONE	II	Regorafenib	MTKI	CS (n = 46)	Completed mPFS: 5 months mOS: 11.7 months
Italiano et al[17]	II	Vismodegib (GDC-0449)	Hedgehog inhibitor	Advanced CS	Completed mPFS: 3.5 months mOS: 12.4 months
Wagner et al[18] CTOS	II	IPI-926	Hedgehog inhibitor	Advanced CS	Completed mPFS: 3.7 months
NCT02273739	I/II	Enasidenib	IDH1 inhibitor	All solid tumors	Completed in 2018, no results presented
NCT03277924 ImmunoSarc	I/II	Sunitinib with or without nivolumab	Antiangiogenic PD-L1 inhibitor	Cohort 6: dedifferentiated CS	Ongoing
NCT04521686	I	LY3410738	IDH1 and IDH2 inhibitor	Basket trial with IDH1/2 mutations	Ongoing
NCT04762602	I	HMPL-306	IDH1 and IDH2 inhibitor	Basket trial with IDH1/2 mutations	Ongoing
NCT04278781	II	AG-120	IDH1 inhibitor	Advanced/metastatic or recurrent CS with IDH1 gene mutation	Ongoing
NCT03684811	I/II	Olutasidenib (FT-2102)	IDH1 inhibitor	Basket trial with IDH1 mutation	Ongoing
NCT04950075 Chawla et al[30]; CTOS 2022	II I	INBRX-109	Tetravalent DR5 agonistic antibody	CS	Ongoing Phase I mPFS: 7.6 months
NCT04040205	II	Abemiciclib	CDK4/6 inhibitor	Bone and soft-tissue sarcoma with CDK pathway alteration	Ongoing
NCT02821507	II	Sirolimus and cyclophosphamide	mTOR inhibitor and chemotherapy	Unresectable myxoid liposarcoma and CS	Ongoing Preliminary results
NCT04340843	II	Belinostat and SGI-110 (Guadecitabine) or ASTX727	HDAC inhibitor Antimetabolites	Unresectable and metastatic conventional CS	Ongoing

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; CS, chondrosarcoma; HDAC, histone deacetylase; IDH, isocitrate dehydrogenase; IGF-1R, insulin-like growth factor 1 receptor; mOS, median overall survival; mPFS, median progression-free survival; MTKI, multityrosine kinase inhibitor; mTOR, mammalian target of rapamycin; NA, not available; OS, overall survival; STS, soft tissue sarcoma.

chemotherapy for patients with localized ES, with an associated 5-year event-free survival (EFS) of 73% for AEWS0031 and a 3-year EFS of 67% for EE2012.[49-52] Several retrospective studies have further demonstrated the feasibility of interval compressed VDC/IE in adults with localized ES, with an estimated median 5-year EFS of 79%

and toxicity similar to that observed in trials with primarily pediatric enrollment.[53,54]

Studies over the past several decades, however, have failed to identify novel frontline therapeutic combinations to improve outcomes in metastatic ES. Although early studies using a VDC backbone in metastatic ES observed a response rate of 73%, only 30% of patients remained disease-free after 3 years.[55] The addition of IE, the antiangiogenic combination of vinblastine and celecoxib, or the IGF-1R inhibitor, ganitumab, to a VDC backbone, intensification of chemotherapy dose or schedule, or use of high-dose chemotherapy (HDC) with autologous stem-cell transplant (SCT) have not demonstrated a convincing improvement in EFS beyond this unacceptably low benchmark.[49,56-62] As new therapeutic strategies are desperately needed in metastatic ES, controversies remain in the optimal management of these high-risk patients beyond the use of a VDC chemotherapy backbone.[183,184]

Second- and subsequent-line chemotherapy in Ewing sarcoma. Outcomes in recurrent ES are poor, with fewer than 20% of patients surviving beyond 5 years, and chemotherapy options remain limited in this setting. The rEECur trial, a multiarm, multistage, phase II/III randomized study, compared survival and toxicity of four chemotherapy regimens in recurrent ES. Using a probability-based Bayesian approach and multiple pairwise comparisons, gemcitabine and docetaxel (GD) and irinotecan and temozolomide (IT) arms were closed in first- and second-interim assessments, respectively, because of observed lower overall response (OR) and shorter EFS.[63,64] Topotecan and cyclophosphamide (TC) and high-dose ifosfamide (IFOS) were then compared in a phase III analysis, with findings demonstrating a survival benefit in favor of IFOS.[65] The results from pairwise comparisons (Table 3) confirmed that GD in recurrent ES was associated with the poorest outcomes. Other comparisons favored greater EFS and OS with the use of TC over IT and with IFOS over TC, but demonstrated more favorable OS with IT compared to IFOS. However, some pairwise comparisons included a small number of patients, which may limit interpretation of these findings.[66] This framework efficiently studied the activity of these four regimens in recurrent ES. As IFOS, TC, and IT are all active regimens, the choice of therapy for second-line or beyond in recurrent ES should include consideration of individual patient factors and goals of care. The use of carboplatin and etoposide is now being explored in an ongoing arm of the rEECur study, and a new arm evaluating the combination of IFOS and lenvatinib is soon to open.

MTKIs are another established therapy option in recurrent ES. With targets including VEGF (vascular endothelial growth factor), PDGF (platelet-derived growth factor), KIT and RET, treatment with regorafenib in this population was associated with the mPFS of 11.4-14.8 weeks and OS of 34.9-53 weeks in recent trials, REGOBONE and SARC024.[67,68] Use of cabozantinib, a MTKI with targets including MET and VEGF, was associated with PRs in 25.6% of patients and a best response of stable disease (SD) in an additional 48.7% of patients. mPFS and OS were 4.4 and 10.2 months, respectively, in the CABONE trial.[69]

Despite the value of data obtained on short-term outcomes from these select studies, acknowledgment of the low rates of long-term survival in recurrent ES is critical, and accordingly, clinicians should support clinical trial enrollment in this setting when feasible.

HDC and SCT in ES. The use of HDC, in combination with autologous SCT (auto-SCT), has been an active area of interest, investigation, and debate for several decades. Multiple retrospective and single-arm studies, despite differences in initial conditioning therapy, have shown promising outcomes in patients with high-risk and refractory ES.[70-79]

For primary metastatic disease, several studies have explored the use of multiagent induction chemotherapy, followed by local control and consolidation HDC/SCT. With this approach, the Italian and Scandinavian Sarcoma Groups (ISG/SSG) observed 5-year EFS and OS rates of 43% and 52%, respectively.[80] A similar study from the Société Française des Cancers de l'Enfant demonstrated a 5-year EFS of 37% and OS of 38%.[81] Further analysis revealed that patients with lung-only metastases had an encouraging EFS rate of 52%, whereas the presence of bone metastases, without bone marrow involvement, was associated with an EFS rate of 36%. Using this framework in patients with bone, bone marrow, or multifocal metastases, which included induction of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE)/vincristine, dactinomycin, and ifosfamide (VAI) and HDC with busulfan/melphalan before auto-SCT, the Euro-EWING R3 99 trial observed a 3-year EFS of 27% and OS of 34%.[62] However, none of those trials were randomized. Other studies exploring HDC and auto-SCT for patients with newly diagnosed metastatic disease revealed less encouraging results.[82] Among these, the randomized controlled R2Pulm trial studied the use of HDC/SCT in patients with lung-only metastatic disease but showed no benefit for the strategy over standard chemotherapy in combination with whole-lung irradiation, and toxicity, not surprisingly, was greater for those who received HDC/SCT.[83] The EuroEwing2008 also failed to demonstrate a benefit for the addition of treosulfan/melphalan in patients with very high-risk ES.[58]

Use of HDC/SCT has also been evaluated in patients with localized ES and poor response to induction therapy. The ISG/SSG group III protocol observed a 5-year EFS rate of 72% in poor responders who received intensified treatment with HDC/SCT, which compared favorably to those with a

TABLE 3. Available Data From rEECur Study

Chemotherapy Regimen	First Interim Analysis (18)	Second Interim Analysis (19)	Phase III Assessment[a] (third interim analysis) (20)
Gemcitabine/docetaxel (n = 72) (*v* regimens A, B, C)	ORR: 11.5% mPFS: 3 months (95% CI, 1.6 to 8.0) mOS: 13.7 months (95% CI, 10.1 to 23.9) Pairwise comparisons favored other arms for ORR and PFS		
Irinotecan/temozolomide (n = 127) (*v* regimens A, B)		ORR: 20% mPFS: 4.7 months (95% CI, 3.4 to 5.7) mOS: 13.9 months (95% CI, 10.6 to 18.1) Pairwise comparisons favored other arms for ORR, PFS, and OS	
Topotecan/cyclophosphamide (n = 162)			ORR: not reported mEFS: 3.5 months (95% CI, 2.1 to 5.1) mOS: 10.5 months (95% CI, 7.2 to 15.0)
High-dose ifosfamide (n = 78)			ORR: not reported mEFS: 5.7 months (95% CI, 3.8 to 6.9) mOS: 16.8 months (95% CI, 11.3 to 20.9)

NOTE. Regimens A, B, and C included irinotecan/temozolomide, cyclophosphamide/topotecan, and high-dose ifosfamide. Regimens A and B included cyclophosphamide/topotecan and high-dose ifosfamide.

Abbreviations: mEFS, median event-free survival; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate.

[a]Data are presented for third interim analysis on the basis of data presented at the ASCO 2022 Plenary Session.

poor response who received only standard therapy (33%), although again patients were not randomly assigned.[84] The R2Loc trial, a randomized study of HDC (busulfan/melphalan) and auto-SCT versus standard seven cycles of VAI for high-risk patients (with localized disease and a poor response to induction therapy), resulted in significant improvements in rates of 3-year (69% *v* 56.7%) and 8-year (60.7% *v* 47.1%) EFS and 3-year (78% *v* 72.2%) and 8-year (64.5% *v* 55.6%) OS.[85] More severe acute toxicities were seen in the HDC groups. The impact of HDC in patients receiving interval compressed VDC/IE is currently unknown, and its use, particularly in the United States, remains limited.

Although no randomized trials have explored the use of HDC in recurrent ES, several retrospective studies have, including one of 196 patients with relapsed or refractory ES, that reported superior post-relapse survival and mOS in patients who received HDC (67.9% at 2 years and 76 months, respectively) in comparison with those who received non-HDC chemotherapy (20.5% at 2 years and 10.5 months).[86] Other retrospective studies have reported similar outcomes among patients with relapsed ES treated with HDC and auto-SCT.[87] Until prospective randomized studies can help answer the question of benefit from HDC and auto-SCT in recurrent ES, Windsor et al[86] proposed a prognostic scoring system that, with validation, may help guide clinical decision making in this population.

Finally, there has been some interest in exploring allogeneic transplantation in patients with ES. However, data supporting its use remain limited and, in at least one study, did not appear to improve outcomes over auto-SCT.[88]

Management of other SRC sarcomas. Non-ES SRC sarcomas, including *EWSR1*–non-*ETS* fusion, *CIC*-rearranged, *BCOR*-rearranged, and unclassified round cell sarcomas, share a degree of morphologic or clinical similarity to ES but are now recognized as unique molecularly defined sarcoma subtypes (Table 1).[1,48,89] As such, the question arises of whether treatment of these other SRC sarcomas should mirror that of ES or whether tailored approaches are needed.

Most common of these, *CIC*-rearranged sarcomas often present as a deep soft-tissue tumor in the extremity and are associated with a more aggressive clinical course than ES, with an estimated 3-year OS rate of 56.5% and 20.4% in localized and advanced disease, respectively.[89-91] The optimal approach to chemotherapy in *CIC*-rearranged sarcomas is yet to be defined as most reports in the literature are based on retrospective cohorts or case series, but there is recognition that these tumors are minimally responsive to chemotherapy. Both the GRACefUl collaboration and a

retrospective French study explored chemotherapy response rates across *CIC*-rearranged sarcomas, reporting similar OR in patients whether treated with an ES-based therapy (VDC/IE or VIDE; 46%-57.9%) or a soft-tissue sarcoma–based regimen (doxorubicin, ifosfamide, mesna; 30%-56%). However, a long-term survival plateau was observed in patients with metastatic *CIC*-rearranged sarcoma treated with ES-based therapy, with three patients surviving for up to 48 months.[91] Smith et al[93] and Connolly et al[94] additionally reported on a small number of cases of metastatic *CIC*-rearranged sarcomas with prolonged survival after treatment with ES-based chemotherapy. Patients with recurrent *CIC*-rearranged sarcomas have limited therapeutic options, with clinical benefit (SD + PR) from several sarcoma-based therapies observed in only 8 of 37 patients studied in the GRACefUI collaboration, although PRs were reported in two patients using gemcitabine-based chemotherapy in the aforementioned French study.[91,92]

BCOR-rearranged sarcomas are the second most common SRC sarcoma, with a tendency to arise from long and flat bones in the majority of cases and a strong male predilection (Table 1).[1,48] These are genomically distinct from ES but display patterns of chemosensitivity and outcomes similar to those of ES, and reports from several case series support the use of ES-based chemotherapy in *BCOR*-rearranged sarcoma.[95-97] In the GRACefUI cohort, the rate of OR in localized *BCOR-CCNB3*–rearranged sarcoma treated with an ES-based regimen was 70%, although there were no responses observed in the two patients with metastatic disease after ES-based therapy. Three-year OS was 92.2% in patients with *BCOR-CCNB3* rearrangements.[90]

Emerging Strategies in Osteosarcoma and ES

Osteosarcoma and ES have effective initial therapies that often lead to symptom reduction and necrosis of primary tumor. In combination with local control, these therapies have demonstrated substantial improvements in survival when compared with local control measures alone in patients with localized disease.[98,99] Because of the rapid natural history of resected-only osteosarcoma, usually with development of numerous pulmonary metastases in under 6 months, we can conclude that chemotherapy is able to eliminate subclinical osteosarcoma cells outside the surgical field in about half of patients.[100-104] As detailed above, EFS in patients with localized ES has also markedly improved with chemotherapy.[105] However, there has been little change in the agents used and outcomes for patients with metastatic bone sarcoma and for patients with recurrent disease. A series of phase II studies of single-agent cytotoxic chemotherapy have been conducted and lack sufficient efficacy to further evaluate. These negative studies have served as the null hypothesis for current phase II studies in measurable disease.[106,107] Similarly, historical relapse rates for lung-only metastatic disease serve as the null hypothesis for adjuvant osteosarcoma trials.[107] The rEECur trial detailed above adds important data to our understanding of combination therapy in relapsed ES.

Why have recent attempts to improve survival through the addition of active cytotoxic or novel agents to frontline therapy in high-risk populations failed?[59,108-113] At present, we identify agent activity only through responses or delayed EFS, metrics for a dominant cancer cell population without focusing on agents with the potential to eliminate the residual population persisting during temporary complete responses. Increasingly, there are insights into these populations, and a translational path for agents that can affect the small populations resistant to VDC/IE or MAP (methotrexate, doxorubicin and cisplatin) chemotherapy is needed.[114-118,183,184]

ES. ES, defined here as including the characteristic *FET-ETS* translocations, has a clear target: the novel fusion oncoprotein. Although the normal functions of the fusion proteins are in mRNA stabilization (*FLI1*) and DNA binding (*EWSR*), the fusion globally changes transcription. When combined with a limited set of second hits, such as aneuploidy of particular arms or loss of function of *TP53* or *STAG2*, ES occurs.[119-126] Thus, targeting this central driver is rational, although challenging, as the fusion couples an intrinsically disordered protein to a transcription factor.[127] Trabectedin, mithramycin, TK216, and LSD1 inhibitors can affect *EWSR-FLI1* epigenetic reprogramming.[127-133] Table 4 compiles selected trials with a focus on ES or osteosarcoma. RNA interference, protein degraders, and immunotherapy directed to the novel epitope are also potential strategies to target the oncoprotein.

RNA transcription, processing, and translation involve CDK9, CDK12, and CDK13, among many other proteins. This class has shown preclinical promise both alone and in combinations with oncoprotein or growth factor targeting with trials underway.[134-136] The similarly named but differently functioning cell cycle proteins CDK4 and CDK6 have also been identified in several screens as potential targets unrelated to the fusion oncoprotein. CDK4 and CDK6 inhibitor trials are ongoing, many in combination with relapsed ES chemotherapy regimens.[137,138]

ES is more sensitive to DNA-damaging agents, with poly (ADP-ribose) polymerase (PARP) inhibition being seen as a possible therapeutic strategy. However, single-agent trials did not demonstrate efficacy, and incorporation of combination therapies to maximize DNA damage is associated with dose-limiting toxicity.[139-143] Further insights may provide a pathway for this initially very encouraging preclinical signal of activity.[144-147] ATR (Ataxia-Telangiectasia mutated and Rad3-related kinase) inhibitors and other agents that target DNA damage remain potential strategies.

As mentioned above, MTKIs have a clinical signal of activity in recurrent ES.[68,69] Along with oral administration and a manageable side effect profile, MTKIs are an appealing

TABLE 4. Selected Ongoing Trials Investigating Novel Targets in Ewing Sarcoma and Osteosarcoma

Pathway/Target/Agent	Trial (NCT No.)
Ewing sarcoma	
Fusion oncoprotein Trabectedin	NCT04067115: SARC037: A Phase I/II Study to Evaluate the Safety of Trabectedin in Combination With Irinotecan in Ewing Sarcoma Patients
LSD1 inhibition	NCT03600649: Clinical Trial of SP-2577 (Seclidemstat) in Patients With Relapsed or Refractory Ewing or Ewing-related Sarcomas
TK216	NCT02657005: TK216 in Patients With Relapsed or Refractory Ewing Sarcoma
CDK9	NCT03604783: First-in-Human Study of Oral TP-1287 in Patients with Advanced Solid Tumors
CDK4/6	NCT03709680: Study of Palbociclib Combined With Chemotherapy in Pediatric Patients With Recurrent/Refractory Solid Tumors
PARP	NCT04901702: Study of Onivyde With Talazoparib or Temozolomide in Children With Recurrent Solid Tumors and Ewing Sarcoma
PARP	NCT02813135: European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (ESMART): Arm D: Olaparib + irinotecan, Arm H: Olaparib and ATR inhibitor
MTKI	NCT05093322: A Study of Surufatinib in Combination With Gemcitabine in Pediatric, Adolescent, and Young Adult Patients With Recurrent or Refractory Solid Tumors
Osteosarcoma	
MTKI	NCT05691478: A Study to Test the Addition of the Drug Cabozantinib to Chemotherapy in Patients With Newly Diagnosed Osteosarcoma
Surfaceome—HER2	NCT04616560: Trastuzumab Deruxtecan for the Treatment of HER2+ Newly Diagnosed or Recurrent Osteosarcoma
Surfaceome—GD2	NCT02502786: A Phase II Study of Humanized Monoclonal Antibody 3F8 (Hu3F8) With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) in the Treatment of Recurrent Osteosarcoma
Immunostimulatory	NCT04974008: Osteosarcoma Maintenance Therapy With OST31-164 (OST-164-01)
Cell cycle	NCT04833582: A Study of ZN-c3 in Combination With Gemcitabine in Subjects With Osteosarcoma NCT04040205: Abemaciclib for Bone and Soft Tissue Sarcoma With Cyclin-Dependent Kinase (CDK) Pathway Alteration NCT03242382: Trial of Palbociclib in Second Line of Advanced Sarcomas With CDK4 Overexpression (PalboSarc)
DNA damage	NCT04417062: Phase II Trial of Olaparib in Combination With Ceralasertib in Patients With Recurrent Osteosarcoma
PD-1 + PARP	NCT04544995: Dose Escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Pediatric Participants with Solid Tumors
PD-1 + TKI	NCT04803877: SARC038: Phase 2 Study of Regorafenib and Nivolumab in Osteosarcoma NCT05019703: Atezolizumab and Cabozantinib for the Treatment of Adolescents and Young Adults With Recurrent or Metastatic Osteosarcoma, TACOS Study NCT05182164: Combination of Pembrolizumab and Cabozantinib in Patients With Advanced Sarcomas (PEMBROCABOSARC)
PD-1 + epigenetic	NCT03628209: Nivolumab or Nivolumab and Azacitidine in Patients With Recurrent, Resectable Osteosarcoma

Abbreviations: ATR, Ataxia-Telangiectasia mutated and Rad3-related kinase; HER2, human epidermal growth factor receptor 2; MTKI, multitargeted tyrosine kinase inhibitor; PARP, poly (ADP-ribose) polymerase; TKI, tyrosine kinase inhibitor.

choice for further investigation in clinical trials either as single-agent maintenance or in combination with chemotherapy. The surfaceome proteins expressed uniquely on ES cells, and thus good immunotherapy targets, remain an interesting strategy as well.[148]

Promising agents for ES were recently reviewed, and a framework was proposed to improve translation into clinical benefit.[149] We are increasingly appreciating the heterogeneity and dynamism of solid tumors through analyses of resistant populations and peripheral blood biomarkers, such as ctDNA.[116,117,150-152] Strategies that anticipate the minor resistant clones are needed to change PRs and delayed progression to durable remissions.

Osteosarcoma. Unlike ES, the targets for osteosarcoma are less clear, and next-generation sequencing has not clarified a therapeutic strategy. Fundamentally, osteosarcoma has

recurrent tumor suppressor loss with nearly all cases having loss of *TP53* activity that is currently not amenable to pharmacologic intervention.[153,154] Finding actionable targets has been difficult because of the complexity of the genome, tumor cell heterogeneity, and the variation in osteosarcoma tumor microenvironments. Explorations into targets on both the cell surface and the kinome, evaluating the altered cell cycle that is present in nearly all osteosarcoma, investigating DNA damage responses with the rearranged genome, and surveying the immune landscape are current strategies in osteosarcoma therapy.[153,155-159]

MTKIs show potential for the treatment of osteosarcoma. Although these agents inhibit several pathways concurrently, inhibition of angiogenesis by hindering VEGF receptor seems to be a shared mechanism. Several clinical trials exploring a MTKI as a single agent have demonstrated activity in excess of the PFS duration specified as having activity when compared with historical relapsed trials.[21,69,107,160,161] Further trials with a MTKI in combination with chemotherapy and as maintenance therapy are underway and planned.

Agents targeting surface proteins in osteosarcoma, such as B7H3 GD2, EGFR, and human epidermal growth factor receptor 2 (HER2), either as antibody-drug conjugates or using chimeric antigen receptor (CAR) T cells is another approach being explored, and considerations for the target, linker, and chemotherapy payload should be considered when evaluating the efficacy data.[156,162-170]

Both *RB1* loss and CDK4 amplification have been observed in osteosarcoma cell lines, patient-derived xenograph models, and patient samples.[158,171,172] Preclinical trials have shown inhibition of osteosarcoma cell lines and efficacy in patient-derived xenograph models with a CDK4 inhibitor supporting trials that include osteosarcoma.[171,173] WEE1 inhibitors have a track record of preclinical activity and are being combined with second-line chemotherapy.[175] Inhibiting DNA damage repair mechanisms may reduce chemoresistance and is being evaluated in a study combining PARP and ATR inhibitors.[175,176]

To our knowledge, to date, the role for immunotherapy remains undefined in osteosarcoma. Unfortunately, there is not a signal of activity with single-agent immune checkpoint inhibitors; several combination studies with MTKIs will provide efficacy data for this combination.[33] Innovative studies attempting to stimulate tumor-associated macrophages, collecting tumor-infiltrating lymphocytes from a patient's tumor and then reinfusing them back into the patient, the use of CAR T cells, and natural killer cell therapies are all being explored.[177-182]

In summary, the optimal therapy of metastatic and recurrent ES and osteosarcoma remains elusive. Ongoing preclinical and clinical research may identify agents with activity against these bone sarcomas. Heterogeneity and a focus on agents with activity in the selected resistant clones after primary therapy must be addressed to improve outcomes for these patients.

CONCLUSION

Over the past several decades, preclinical and translational research has positively transformed our understanding of tumor biology and therapeutic vulnerabilities of sarcomas. However, many questions and controversies remain in the optimal management of patients with these aggressive bone sarcomas, and clinical translation of novel targets into patient benefit has been challenging.

This argues for novel approaches to clinical trial design, the importance of correlative biomarker analysis, and greater international collaboration across scientific and pediatric and adult oncology communities in the mission to improve outcomes for these patients.

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Current Therapeutic Targets in Cancer Cachexia: A Pathophysiologic Approach

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overview

Significant progress in our understanding of cancer cachexia has occurred in recent years. Despite these advances, no pharmacologic agent has achieved US Food and Drug Administration approval for this common and highly morbid syndrome. Fortunately, improved understanding of the molecular basis of cancer cachexia has led to novel targeted approaches that are in varying stages of drug development. This article reviews two major thematic areas that are driving these pharmacologic strategies, including those targeting signal mediators at the level of the CNS and skeletal muscle. Additionally, pharmacologic strategies are being tested in combination with targeted nutrients, nutrition therapy, and exercise to treat cancer cachexia. To this end, we highlight recently published and ongoing trials evaluating cancer cachexia therapies in these specific areas.

INTRODUCTION

Cancer cachexia remains a prevalent complication in the late stages of most cancers and can develop early in the course of others (eg, pancreatic, gastroesophageal, lung).[1] Cachexia is a hypercatabolic state characterized by anorexia and progressive wasting of adipose and skeletal muscle tissue. These complications cause reductions in physical functioning, health-related quality of life, poor tolerance to anticancer therapies, and decreased survival. Despite some randomized trials, no pharmacologic agent has yet achieved US Food and Drug Administration (FDA) approval, highlighting the urgent need for effective therapies.[2]

The incidence of cancer cachexia varies significantly by cancer site and stage.[3] Patients with upper GI and thoracic cancers often present with features of cachexia at diagnosis whereas other common malignancies such as breast and prostate typically develop cachexia during advanced stages of the disease. Notably, there can be significant interpatient variation independent of cancer site and stage, and new diagnostic tools continue to be explored to enhance early identification and understanding of individual cachexia susceptibility.[4,5]

Although diagnostic criteria continue to be updated and revised, they are based on the presence and extent of weight loss in clinical practice.[2,6,7] Cachexia is often overlooked and underestimated.[8] Certain elements of cachexia are amenable to clinical management, including control of pain and symptoms such as nausea, which severely impair dietary intake. Nutritional deficits may be substantial, and while cachexia is not entirely reversible by diet alone, nutrition therapy can be partially effective. Unfortunately, cachexia often progresses unabated, culminating in a state of extreme depletion, at which late point interventions cannot reverse the wasting process. As such, accurately identifying cachexia early has significant therapeutic implications. Cancer imaging can be exploited to detect muscle depletion; however, there are currently no laboratory tests with established clinical utility that confirms the diagnosis of cachexia although progress related to potential biomarkers continues.[9-11]

It is now clear that there is significant tumor-organ and interorgan crosstalk involved with the development and progression of cancer cachexia (Fig 1); this is a roadmap for understanding the therapeutic strategies in current clinical trials (Table 1).

In this study, we provide a concise review of the major thematic areas driving current cachexia treatment strategies. These include pharmacologic agents targeting signal mediators within CNS controls of appetite/satiety as well as drugs designed to interrupt catabolic signaling in skeletal muscle. Drugs may be delivered alone or in combination with exercise and nutrition therapy to restore anabolic growth factor–signaling, nutrient-signaling, and contractile-signaling pathways in muscle.

Currently, investigational new therapies for cachexia are focused on the regulation of appetite/satiety and on the regulation of skeletal muscle mass (Table 1). Regulatory authorities in the United States, Europe, and other countries do not have an international standard for approval of the current generation of cachexia therapies. Regulators require that the agent reverse or slow cachexia, as demonstrated by blunting of weight loss and/or of radiologically define skeletal muscle and fat mass. Regulators additionally require a

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PRACTICAL APPLICATIONS

- Cancer cachexia is a highly morbid condition that negatively affects quality of life, reduces tolerance to anticancer therapy, and confers poor survival. Despite this, there is no current US Food and Drug Administration–approved pharmacological agent for cachexia.
- Improved understanding of the complex interactions among tumor byproducts and their effect on multiple organs provide rationale for targeted therapeutic strategies currently in development.
- The CNS is integral in the pathogenesis of cancer cachexia through varied mechanisms including hypothalamic and neuroendocrine alterations that promote and accelerate anorexia and peripheral tissue catabolism.
- Skeletal muscle wasting, a hallmark of cachexia, involves dysregulation at the level of the skeletal muscle cell induced by specific tumor-derived and inflammation-derived factors, anticancer therapies, and deficits of nutrients and contractile activity.
- The complex pathophysiology of cachexia indicates that a multifaceted approach involving reversal of anorexia, inhibition of catabolic changes, as well as nutrition and rehabilitation will be vital for effective therapies.

demonstrable clinical benefit (coprimary end point), and it is this category of end points that have engendered the most debate. This accounts for the fact that cachexia trials in phase I/II typically have multiple secondary outcomes to better define the potential clinical benefit(s).

THE CNS AND CANCER CACHEXIA

The neurobiology of cancer is an area of investigation that explores the bidirectional nature of cancer on the nervous system which receives and paradoxically amplifies the effect of cytokines via multiple aberrant pathways.[12] Increasing evidence highlights the role of the CNS in the pathophysiology of cancer cachexia including hypothalamic inflammation, neuroendocrine perturbations, and increased sympathetic nervous system tone, all of which are potential and ongoing targets for drug development (Fig 2).[13,14]

Therapeutic Target: Anorexia, Satiety, and Hypothalamic Inflammation

The hypothalamus is a critical brain structure responsible for maintaining homeostasis and regulates food intake and systemic energy balance via inputs from a broad variety of stimuli. In cancer, hypothalamic neurons contribute to peripheral wasting by two major mechanisms. First, tumor-derived inflammatory cytokines (eg, interleukin-6 [IL-6]) influence specific endocrine hormones (eg, leptin and ghrelin) which alter food intake by downregulation of orexigenic/prophagic and upregulation of anorexigenic responses.[13] Second, the hypothalamus aberrantly responds to peripheral inflammation by central production of other proinflammatory mediators (eg, interleukin-1 beta [IL-1β] and leukemia inhibitory factor [LIF]) which activates the hypothalamic-pituitary-adrenal axis (HPA) and contributes directly to loss of muscle and adipose tissue.[14] This combination of reduced appetite along with stimulation of tissue catabolism represents the pathologic result of hypothalamic inflammation.

Melanocortin Type 4 Receptor Antagonists

The melanocortin-4 receptor (MC4R) is a G-protein coupled receptor that is regulated by endogenous MC4R agonists in response to the nutritional/energy state. When activated, pro-opiomelanocortin neurons release the endogenous MC4R agonist, α-melanocyte–stimulating hormone (α-MSH), which binds to MC4R and activates signaling to reduce appetite and food intake.[15] The agouti-related peptide is a competitive antagonist of α-MSH produced in the hypothalamus during an energy deficit, leading to increased appetite via suppression of MC4R signaling. As such, inhibitors of MC4R signaling (ie, melanocortin antagonists) are putative mechanisms to reduce anorexia. Early clinical studies of melanocortin antagonists in animals showed anticachexia properties relatively consistent but were limited by their requirement for intracerebroventricular administration to achieve efficacy.[16,17]

TCMCB07. A novel MC4R antagonist, TCMCB07 is a synthetic peptide that has blood-brain barrier transport properties. An initial study involving rat cachexia models confirmed that peripheral routes of administration stimulated food intake, reduced weight loss, and preserved fat and lean mass.[18] These data have led to an ongoing phase I study of TCMCB07 given as a subcutaneous injection in healthy volunteers to assess the safety, tolerability, and pharmacokinetics.

PF-07258669. An orally bioavailable small-molecule MC4R antagonist, PF-07258669, has been evaluated in animal models and increased food consumption and weight gain.[19] Two phase I studies in healthy volunteers have been conducted with this agent. The initial study of 29 patients completed accrual in 2021, and the results are yet to be published.

Therapeutic Target: Neuroendocrine Changes and Cachexia

Central endocrine organ regulation is largely mediated by the HPA and hypothalamic-pituitary-gonadal axes (Fig 2). Cachexia-inducing factors such as tumor-derived cytokines (eg, tumor necrosis factor-α [TNF-α] and IL-6) as well as centrally produced proinflammatory mediators (eg, IL-1β) activate both pathways. Stimulation of the HPA axis leads to excessive production of cortisol which increases peripheral skeletal

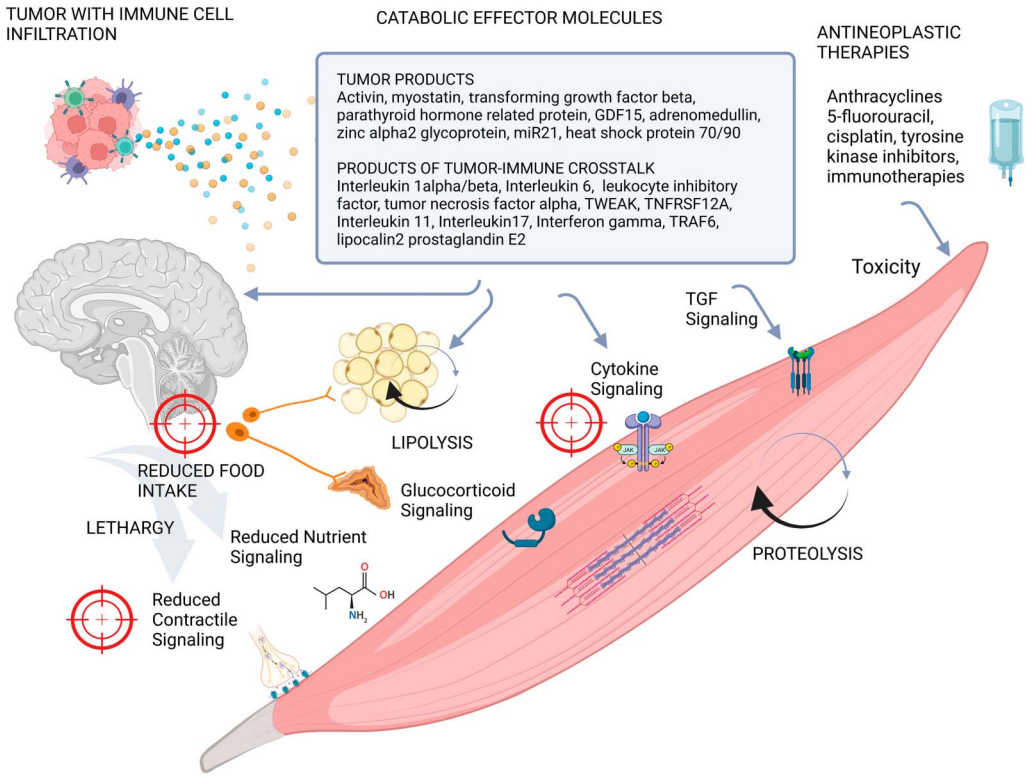

FIG 1. Interorgan relationships in cancer cachexia: Where do the therapeutic targets reside? Cachexia is initiated by a complex mixture of tumor-derived catabolic factors and proinflammatory molecules generated through tumor crosstalk with associated stromal cells and the immune system. Some of these factors act directly on muscles and adipose tissues to elicit excess catabolism (eg, lipolysis inducers adrenomedullin, zinc α2 glycoprotein). Skeletal muscle catabolism is induced by proinflammatory cytokines, eicosanoids, and transforming growth factor-β (TGFβ) family effectors (eg, activin A, myostatin). Alteration of CNS functions further induces catabolism. Altered CNS outputs are neural (eg, activation of sympathetic output to adipocytes) and neuroendocrine (activation of adrenal with increased catabolic glucocorticoid signaling to muscle). Behavioral changes associated with malignant disease include reduced food intake and lethargy, reducing anabolic growth factor, nutrient, and contractile activity signaling. Systemic therapy–associated wasting is a powerful impetus to the overall loss of skeletal muscle, via specific toxic actions at the cellular level. GDF15, growth differentiation factor 15; miR, microRNA; TNF, tumor necrosis factor; TNFRSF12A, TNF receptor superfamily member 12A; TRAF6, TNF receptor–associated factor 6; TWEAK, TNF-related weak inducer of apoptosis.

muscle wasting via complex changes in the regulation of genes involved with muscle catabolism (eg, *Foxo1*, *Slc39a14*, *Cebpd*) as well as inactivation of key regulators of muscle anabolism, such as the mammalian target of rapamycin (mTOR).[20,21] Important central mediators involved with failure of food intake are putative therapeutic targets, including growth differentiation factor 15 (GDF15) and ghrelin receptor agonists.

GDF15 Antibodies

The cytokine, GDF15, directly contributes to anorexia by binding to glial cell-derived neurotrophic factor family receptor α-like (GFRAL) within the feeding center of the brainstem.[22,23] The mechanisms by which the GDF15-GFRAL axis contributes to cachexia includes an anorexia-mediating effect suggested by the presence of GFRAL receptors in the vomiting center of the brain (area postrema) leading to nausea as well as the direct influence of GDF15 on peripheral fat metabolism via autonomic outflow to the liver.[24,25] GDF15 is higher in patients with evidence of cachexia than noncachectic patients, and platinum therapies further increase the expression of GDF15.[26-28] Recombinant GDF15 reduces food intake and promotes weight loss via anorexia and promotion of lipolysis; subsequent blockade of GFRAL signaling reverses these changes.[28,29] As such, inhibition of the GDF15-GFRAL axis is an area of active investigation.

PF-06946860. This anti-GDF15 humanized monoclonal antibody binds to GDF15, inhibiting its interaction with the GFRAL receptor. Subcutaneous administration at varying doses in healthy participants observed no serious treatment-emergent adverse effects although the results have not been formally published. A phase IB 12-week study of PF-06946860 in patients with non–small-cell lung cancer

TABLE 1. Targeted Therapeutic Trials in Cancer Cachexia

Therapeutic Target Area and Mechanism of Action	Compound/Route of Administration	Phase and Design	N	Population	Primary/Secondary Outcomes[a]	Study Start and Completion Dates[b]	Results	Clinical Trial No.
CNS—appetite/satiety/hypothalamic inflammation								
Melanocortin type 4 receptor antagonists	TCMCB07, SQ	I, randomized, double-blind, placebo-controlled	97	US, healthy volunteers	Safety/pharmacokinetics	July 12, 2022-January 2023	Recruiting	NCT05529849
Melanocortin type 4 receptor antagonists	PF-07258669, oral	I, randomized, double-blind, placebo-controlled	29	US, healthy volunteers	Safety/pharmacokinetics	March 16, 2021-August 25, 2021	Completed and results awaited	NCT04628793
Anti-GDF15	Ponsegromab (PF-06946860), SQ	II, randomized, double-blind, placebo-controlled	168	US, advanced cancers (NSCLC, pancreatic, CRC) with elevated GDF15 levels	Change in body weight/physical activity	November 21, 2022-May 15, 2025	Recruiting	NCT05546476
Anti-GDF15	Ponsegromab (PF-06946860), SQ	I, randomized, double-blind, placebo-controlled	63	US, healthy volunteers	Safety/pharmacokinetics	July 30, 2018-September 18, 2019	Completed and results awaited	NCT03599063
Anti-GDF15	Ponsegromab (PF-06946860), SQ	Pilot, randomized, double-blind, placebo-controlled	18	US and Canada, advanced cancers (NSCLC, pancreatic, CRC, prostate, breast, or ovarian)	Change in Cancer-Related Cachexia Symptom Assessment-Appetite score/fatigue and safety	May 11, 2021-August 9, 2022	Completed and results awaited	NCT04803305
Anti-GDF15	Ponsegromab (PF-06946860), SQ	IB, nonrandomized	11	US, advanced cancers (NSCLC, pancreatic, CRC)	Safety/pharmacokinetics	November 17, 2020-March 30, 2022	Completed and results awaited	NCT04299048
Anti-GDF15	Ponsegromab (PF-06946860), SQ	I, randomized, double-blind, placebo-controlled	8	Japanese, healthy volunteers	Safety/pharmacokinetics	July 8, 2019-January 10, 2020	Completed and results awaited	NCT03974776
Anti-GDF15	NGM120, SQ	I, randomized, double-blind, placebo-controlled	92	Australia, healthy volunteers	Safety	January 29, 2018-March 11, 2019	Completed and results awaited	NCT03392116
Anti-GDF15	NGM120, SQ	I/II, randomized, double-blind, placebo-controlled	75	US, advanced solid cancers	Safety/Bodyweight and Skeletal muscle index change	October 16, 2019-January 2025	Recruiting	NCT04068896
Anti-GDF15	AV380, IV and SQ	I, randomized, double-blind, placebo-controlled	56	US, healthy volunteers	Safety/pharmacokinetics and GDF15 levels by dose and serum level of AV380	February 22, 2021-January 2022	Active, not recruiting	NCT04815551
Anti-GDF15	CTL002, IV	I/II, nonrandomized	155	Europe, advanced cancers after progression on one previous anti-PD-1/PD-L1 treatment	Safety/change in appetite via questionnaire, BMI, and skeletal muscle index	December 9, 2020-May 31, 2025	Recruiting	NCT04725474
Ghrelin receptor agonist	Anamorelin, oral	III, randomized, double-blind, placebo-controlled	318	US and international, unresectable stage III or stage IV NSCLC	Weight change and 5-item Anorexia Symptom Subscale	December 18, 2018-Janaury 31, 2023	Active, not recruiting	NCT03743064
Ghrelin receptor agonist	Anamorelin, oral	III, randomized, double-blind, placebo-controlled	316	US and international, unresectable stage III or stage IV NSCLC	Weight change and 5-item Anorexia Symptom Subscale	December 18, 2018-February 2023	Active, not recruiting	NCT03743051

(Continued on following page)

TABLE 1. Targeted Therapeutic Trials in Cancer Cachexia (Continued)

Therapeutic Target Area and Mechanism of Action	Compound/Route of Administration	Phase and Design	N	Population	Primary/Secondary Outcomes[a]	Study Start and Completion Dates[b]	Results	Clinical Trial No.
Ghrelin receptor agonist	Anamorelin, oral	II, randomized, double-blind, placebo-controlled	100	US, locally advanced or metastatic pancreatic cancer	Weight change/5-item Anorexia Symptom Subscale, survival, and Fatigue Subscale	September 30, 2022-December 31, 2023	Recruiting	NCT04844970
Dopamine and serotonin receptor antagonist	Olanzapine, oral	III, randomized, open-label *v* megestrol	360	US, advanced solid or hematologic cancers	Change in appetite	October 15, 2021-December 2024	Recruiting	NCT04939090
Skeletal muscle								
JAK2/STAT inhibitor	Ruloxitinib, oral	Pilot, nonrandomized	20	US, stage IV NSCLC	Safety/change in QOL and anorexia via questionnaire	February 23, 2022-February 2024	Recruiting	NCT04906746
Multimodality approach								
MENAC: anti-inflammatory, nutrient signaling, contractile work	Ibuprofen + ONS with EPA + nutritional counseling + exercise prescription	III, randomized, open-label *v* standard palliative care	240	US and international, advanced NSCLC or pancreas	Weight change	April 2015-September 2022	Active, not recruiting	NCT02330926
Nutrient signaling, anti-inflammatory	Arginine + omega-3 fatty acids	III, randomized, double-blind, placebo-controlled	200	US, bladder cancer	Postoperative complications/changes in body composition	February 21, 2019-May 1, 2026	Recruiting	NCT03757949
MIRACLE: anti-inflammatory, nutrient signaling, contractile work	Ibuprofen + omega-3 fatty acids + ONS + Bojungikki-tang + nutritional counseling + exercise prescription	II, randomized, open-label *v* standard palliative care	112	Korea, advanced NSCLC or GI cancers	Weight change and handgrip strength	January 31, 2020-June 30, 2022	Recruiting	NCT04907864
NEXTAC-III: ghrelin receptor agonist, nutrient signaling, contractile work	Anamorelin + nutritional counseling + home-based resistance training	II, randomized, open-label *v* SOC	90	Japan, advanced NSCLC or pancreas	Change in 6-minute walking distance	September 01, 2021-NP	Recruiting	jRCTs041210053

Abbreviations: BMI, body mass index; CRC, colorectal cancer; EPA, eicosapentaenoic acid; GDF, growth differentiation factor; IV, intravenous; JAK/STAT, Janus kinase-signal transducer and activator of transcription pathway; NP, not provided; NSCLC, non–small-cell lung cancer; ONS, oral nutritional supplement; QOL, quality of life; SOC, standard of care; SQ, subcutaneous.

[a]For phase I and II trials, select secondary outcomes focused on cachexia-related end points provided as available.

[b]For trials not completed, estimated study completion dates per ClinicalTrials.gov provided.

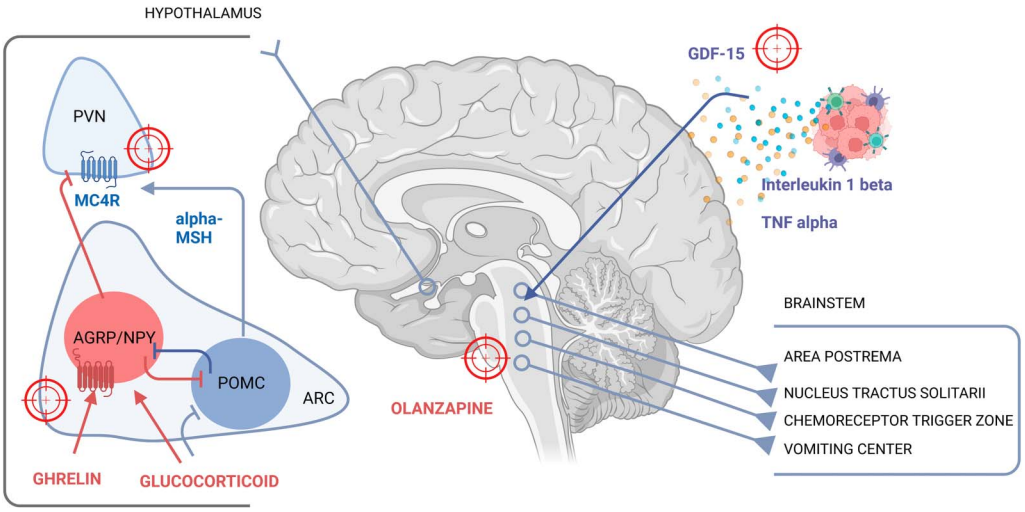

FIG 2. CNS-mediated mechanisms of cancer cachexia. Anorexia and excessive peripheral catabolism originate in part by tumor-induced and inflammatory changes in specific regions of the hypothalamus and brainstem. Cytokines (eg, IL1, TNFα) exert a profound inflammatory effect on the hypothalamus resulting in activation of anorexigenic neurons (ie, POMC) and inhibition of orexigenic neurons (ie, NPY). NPY neurons stimulate food intake in response to a variety of mediators including ghrelin. Ghrelin is a multifaceted gut hormone which activates the growth hormone secretagogue receptor (GHS-R). Ghrelin's hallmark functions are its stimulatory effects on food intake, fat deposition, and growth hormone release. POMC neurons inhibit food intake by the production of α-MSH, a neuropeptide of the melanocortin family, which acts via type 4 melanocortin receptors (MC4R) in the paraventricular nucleus (PVN). Small molecular weight, orally active agonists of GHS-R, and antagonists of MC4R have been developed for the indication of anorexia/cancer cachexia. Growth differentiation factor (GDF15) is overexpressed by some cancers and inhibits food intake by activating the GFRAL-RET signaling pathway in the brainstem area postrema and nucleus tractus solitarii. Advanced stage cancers may be associated with persistent non–chemotherapy-related nausea, and clinical management of these symptoms with antiemetic regimens is recommended to enable food intake. High-dose corticosteroids activate NPY neurons and inhibit POMC neurons; however, this is limited as a therapeutic approach because of secondary toxicity including muscle atrophy, poor glycemic control, and thrombosis. AGRP, agouti-related peptide; GDF15, growth differentiation factor 15; IL1, interleukin-1; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; TNFα, tumor necrosis factor-α; α-MSH, α-melanocyte–stimulating hormone.

(NSCLC), pancreatic, and colorectal cancer and a 6-week, randomized, double-blind study of 18 patients with advanced cancer, anorexia, and elevated circulating GDF15 levels have completed accrual, and results are awaited.

Three other anti-GDF15 agents are under investigation in phase I trials (*NGM120, AV380, CTL-002*) and include cachexia-related end points (Table 1).

Ghrelin Receptor Agonists

Ghrelin, produced primarily in the stomach, is a peptide hormone and an endogenous ligand for the growth hormone secretagogue receptor (GHS-R) in the hypothalamus.[30] Ghrelin activates NPY neurons (ie, orexigenic action) and promotes GI motility. It has pleiotropic effects on bodyweight and fat mass as well as food intake. GHS-R activity increases growth hormone secretion from the pituitary which stimulates insulin-like grow factor from the liver contributing to muscle mass anabolism and stimulation of lipogenic pathways.[31] The overall effect is stimulation of energy intake and inhibition of expenditure. As such, ghrelin receptor agonists continue to be studied to reduce the burden of cancer cachexia.

Anamorelin. Anamorelin hydrochloride is a selective ghrelin receptor agonist. ROMANA 1 and ROMANA 2 were randomized, double-blind, placebo-controlled phase 3 trials in patients with advanced NSCLC that evaluated anamorelin at 100 mg daily and observed benefit (Table 2). Both studies detected statistically significant and clinically modest increases in lean body mass (as measured by dual-energy x-ray absorptiometry [DXA]). In addition, statistically significant improvements in bodyweight and patient-reported anorexia-cachexia were found as measured by the Functional Assessment of Cancer Therapy anorexia-cachexia scale over a 12-week period. However, both studies failed to meet the coprimary end point of improved handgrip strength.[32] ROMANA 3, an extension of these studies, included 513 patients with preserved functional status after completing 12 weeks of therapy and found that anamorelin continued to be well tolerated with improvements in bodyweight and

maintenance of anorexia-cachexia scores through 24 weeks although no difference in handgrip strength was observed.[33]

In December 2020, anamorelin (ONO-7643) was approved in Japan for cancer cachexia, specifically in NSCLC, gastric cancer, pancreatic cancer, and colorectal cancer on the basis of the results from two Japanese prospective studies. The largest was a randomized, double-blind, placebo-controlled trial of 174 patients with stage III/IV NSCLC and showed improvement in the primary end point of lean body mass over a 12-week period but no difference in handgrip strength or 6-minute walk test.[34] The other study was a nonrandomized study involving 50 patients with advanced stage GI cancers and showed similar improvement in lean body mass assessed by DXA.[35] Multiple other studies evaluating anamorelin are ongoing (Table 1).

Macimorelin. A phase II randomized study of oral macimorelin, a ghrelin receptor agonist, in advanced cancers was closed early because of poor accrual and study relocation. The investigators observed a modest numerical difference in bodyweight and quality of life with macimorelin (n = 15) compared with placebo (n = 10) over a 1-week period.[36]

SKELETAL MUSCLE AND CANCER CACHEXIA

Tumor and Cancer Therapy Act to Cause Muscle Wasting

Disease-related and treatment-related factors seem to simultaneously drive catabolism in muscle (Fig 1).

This is in part mediated by the CNS, via suppression of dietary intake and HPA activation. Tumor and inflammation-derived products also have panoply of direct, receptor-mediated effects on muscle. On top of the tumor effects, systemic therapy–associated skeletal muscle wasting is emerging as a powerful impetus to the overall loss of skeletal muscle experienced by patients with cancer. Clinical findings are based on precise, specific measures of muscle loss over the duration of chemotherapy, targeted therapy, and immunotherapy. Nearly all therapeutic classes of anticancer agents induce quantitatively important muscle loss, independent of tumor response. Parallel experimental studies provide understanding of the specific molecular basis of wasting, which can include inhibition of protein synthesis, proliferation and differentiation, and activation of inflammation, reactive oxygen species, autophagy, mitophagy, apoptosis, necroptosis, protein catabolism, fibrosis, and steatosis in muscle.

Anabolic-Catabolic Regulation in Muscle

Mechanisms underlying skeletal muscle growth, maintenance, and atrophy are well-characterized. A network of signaling pathways coordinates muscle protein balance (Fig 3). This network includes an anabolic arm, reliant on growth factors, contractile activity and nutrient signaling via a pathway involving phosphatidylinositol-3 kinase (PI3K), serine/threonine protein kinase (Akt), and the mTOR, which leads to muscle protein synthesis. The catabolic arm is characterized by multiple signaling cascades, connected ultimately to transcriptional control of genes involved in autophagy and to ubiquitin-mediated proteasomal degradation of myofibrils.

Cytokine mediators of muscle wasting include IL-6, which is a key regulator of skeletal muscle, IL-1, TNF, IFNγ, LIF, and TNF-related weak inducer of apoptosis (TWEAK; Fig 3). These factors signal through their respective cell surface receptors and activate selective transcription factors, which in turn promote the transcription of ubiquitin-proteasome and autophagy components (Fig 3). In addition to inflammatory cytokines, the TGF-β family ligands myostatin, GDF11, and activins are negative regulators of skeletal muscle mass, which primarily signal via type 2 activin receptors (ACV2R) to induce muscle wasting. Activin-A is produced by both tumor and immune cells. In models of cancer cachexia, inhibiting ACV2R reverse muscle wasting and prolongs survival, even with continued tumor growth.[37]

Endemic Muscle Loss During Systemic Cancer Therapy

With the advent of diagnostic imaging-based methods, it has become possible to precisely characterize muscle loss during treatment. The precision of these measures of tissue change over time is excellent when performed by trained experts, with precision values in the range of approximately 1.3 cm^2 for a determination of muscle cross-sectional area and a least significant change value of approximately 2.9 cm^2 (ie, the smallest change detectable above measurement error).[38]

Two meta-analyses describe muscle loss during cancer treatment.[39,40] Wang et al[39] reviewed 25 studies (N = 2,706 participants) of neoadjuvant chemoradiotherapy for gastroesophageal cancers, finding a pooled loss of skeletal muscle index (SMI, cm^2/m^2) of –2.47 cm^2/m^2 (ie, losses of approximately 10%). Jang et al[40] reviewed 15 studies (N = 2,662 participants) with diverse cancers (lung, GI, head and neck, gynecological) and treatment regimens. The mean difference in SMI was –2.72 cm^2/m^2. The highest mean losses were up to 11% over the treatment plan (approximately 3 months), seen among patients with pancreatic cancers on leucovorin, fluorouracil, irinotecan, and oxaliplatin and in patients receiving neoadjuvant chemoradiation for head and neck or esophageal cancers. Rinninella et al[43] reviewed 11 studies of muscle loss during tyrosine kinase inhibitor (TKI) therapy but did not conduct a meta-analysis owing to a lack of consistency in the measures of muscle loss. Studies to date include muscle changes during treatment with sorafenib, regorafenib, sunitinib, lenvatinib, pazopanib, axitinib, and vandetanib. These investigations were generally consistent in finding loss of skeletal muscle, although the authors speculated that effect sizes might vary according to differences in the specificities of TKI for different tyrosine kinases in the growth factor receptor signaling pathways.

TABLE 2. Results From Phase III Randomized Trials of Anamorelin

Trial Name	Phase and Design	Population	Primary Outcomes	Primary Results (95% CI) or (SE)	Key Secondary Outcomes	Secondary Results (95% CI) or (SE)	Study Start and Completion Dates	Clinical Trial No.
ROMANA 1 (N = 484)	III, randomized, double-blind, placebo-controlled	US and international, unresectable stage III or stage IV NSCLC	Coprimary end point: change in LBM (kg) and HGS (kg)	LBM: anamorelin 0.99 (0.61 to 1.36) *v* placebo –0.47 (–1.00 to 0.21), $P < .0001$; HGS: –1.10 (–1.69 to –0.40) *v* –1.58 (–2.99 to –1.14), $P = .15$	Change in bodyweight (kg), symptoms of anorexia-cachexia and fatigue[a], and overall survival[b]	Mean bodyweight: anamorelin 2.2 (0.33) *v* placebo 0.14 (0.36), $P < .0001$; anorexia: 4.12 (0.75) *v* 1.92 (0.81), $P = .0004$; fatigue: 0.26 (0.89) *v* -1.91 (0.93), $P = .054$; survival: 8.9 (8.3 to 9.8) *v* 9.17 months (7.9 to 11.0), $P = .47$	July 8, 2011-January 28, 2014	NCT01387269
ROMANA 2 (N = 495)	III, randomized, double-blind, placebo-controlled	US and international, unresectable stage III or stage IV NSCLC	Coprimary end point: change in LBM (kg) and HGS (kg)	LBM: anamorelin 0.65 (0.38 to 0.91) *v* placebo –0.98 (–1.49 to –0.41), $P < .0001$; HGS: -1.49 (–2.06 to –0.58) *v* –0.95 (–1.56 to 0.04), $P = .65$	Change in bodyweight (kg), symptoms of anorexia-cachexia and fatigue[a], and overall survival	Mean bodyweight: anamorelin 0.95 (0.39) *v* placebo –0.57 (0.44), $P < .0001$; anorexia: 3.48 (0.94) *v* 1.34 (1.03), $P = .0016$; fatigue: 1.37 (1.17) *v* 1.23 (1.29), $P = .86$; survival: 8.9 (8.3-9.8) *v* 9.17 months (7.9-11.0), $P = .47$	July 14, 2011-October 31, 2013	NCT01387282
Katakami et al (N = 174)	III, randomized, double-blind, placebo-controlled	Japan, unresectable stage III or stage IV NSCLC	Change in LBM (kg)	LBM: anamorelin 1.38 (0.18) *v* placebo –0.17 (0.17), $P < .0001$	Change in bodyweight (kg), symptoms of appetite[c] and fatigue[d], 6MWT (meters)	Mean bodyweight: anamorelin 1.06 (0.2) *v* placebo –0.5 (0.19), $P < .0001$; appetite: 0.7 (0.1) *v* 0.3 (0.1), $P = .005$; fatigue: 1.7 (0.7) *v* 1.4 (0.7), $P = .717$; 6MWT: 11.7 (7.8) *v* 11.7 (7.2), $P = .998$	May 2014-January 2015	JapicCTI-142451

Abbreviations: 6MWT, 6-minute walk test; HGS, handgrip strength; IV, intravenous; LBM, lean body mass; NSCLC, non–small-cell lung cancer.

[a]12-item anorexia-cachexia scale of the Functional Assessment of Anorexia/Cachexia Therapy has scores ranging from 0 to 48, and higher scores suggest lower levels of anorexia-cachexia.

[b]3-item fatigue scale of the Functional Assessment of Chronic Illness Therapy-Fatigue has scores ranging from 0 to 52, and higher scores suggest less fatigue.

[c]Appetite was a self-rated single item on a 1-5 scale, with a lower score indicating worse appetite.

[d]Cancer Fatigue Scale is a self-rated fatigue scale and has 15 items scored on a 1-5 scale for a maximum score of 60, with higher scores indicating more severe fatigue.

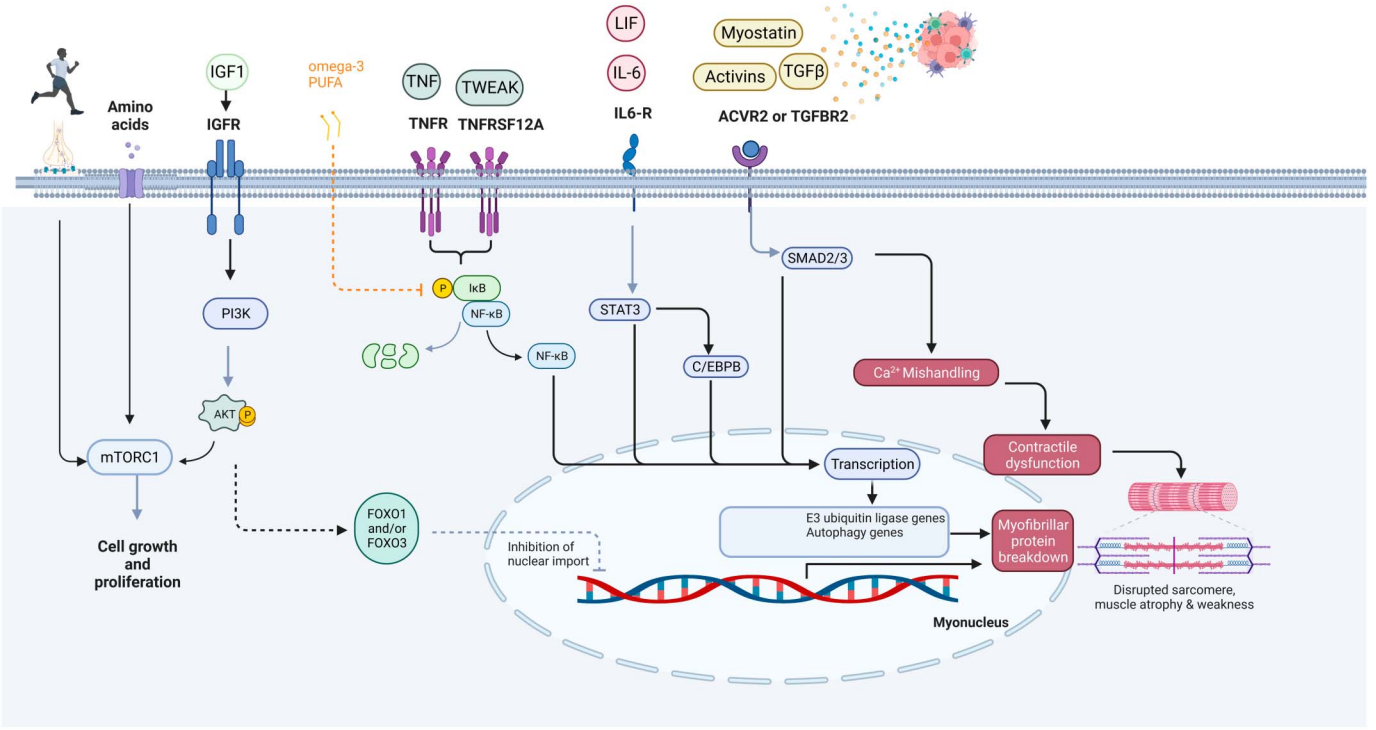

FIG 3. Signaling pathways involved in tumor-induced skeletal muscle atrophy. Signaling pathways involved in the control of muscle anabolism and catabolism. Protein synthesis, cell growth, and proliferation are normally maintained by growth factors, nutrients, and contractile activity. Anabolism is activated by downstream pathways that converge at the mTOR complex 1, a multicomplex protein able to activate transcription of hypertrophy genes. Phosphorylated AKT also blunts catabolic signaling via inhibition of *FoxO* and its downstream signaling to transcription of atrophy genes. Omega-3 PUFA suppress the dissociation of NF-κB/IκB and decrease the translation of atrophy genes in the nucleus induced by NF-κB. Protein breakdown is regulated by transcriptional regulation of atrophy genes, mediated by NF-kB, *STAT3*, *C/EBPβ*, and SMAD2/3 transcription factors. Tumor products and products of activated host immune cells induce atrophy, TNF-α, and TWEAK acting via downstream signaling that induces a dissociation of NF-κB/IκB complex and NF-κB translocation to the nucleus. IL-6 and LIF induce STAT3 and C/EBPβ signaling pathways, and TGF-β superfamily members (eg, myostatin, activin-A) activate SMAD2/SMAD3. ACVR2, activin receptor type 2; AKT, serine/threonine protein kinase; C/EBPβ, CCAAT/enhancer-binding protein-β; FoxO, forkhead box protein O complex; IκB, inhibitory subunit of NF-κB; IGF1, insulin-like growth factor-1; IGFR, IGF receptor; IL-6, interleukin-6; IL-6R, IL-6 receptor; LIF, leukocyte inhibitory factor, mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; PI3K, phosphatidylinositol-3 kinase; PUFA, polyunsaturated fatty acid; STAT3, signal transducer and activator of transcription 3; TGFBR2, TGF-β receptor type 2; TNF, tumor necrosis factor; TNFR, TNF receptor; TNFRSF12A, TNF receptor superfamily member 12A; TWEAK, TNF-related weak inducer of apoptosis.

In Figure 4, we present a summary of recent reports on loss of skeletal muscle during cancer treatment. Most regimens associated with muscle loss (range, 0% to –13.7%/100 days), except for neoadjuvant chemotherapy for breast cancer (regimens including anthracycline, cyclophosphamide, and taxane) in three studies which were negative or showed a low rate of muscle loss.[41,44,45] This is perhaps expected since weight gain and not weight loss is common in breast cancer. By contrast, studies in advanced stage pancreatic cancer showed high intensity of loss –11.1% to –13.7%/100 days.[42,46]

A 10% muscle loss over approximately 100 days on a cancer therapy is a relatively intense rate of catabolism. By contrast, age-related muscle loss of 10% would be expected to take approximately 20 years in men and approximately 25 years in women.[56] Thus, muscle losses consequent to 100 days of cancer therapy are of similar magnitude to approximately 2 decades of age-related muscle depletion. Another point of reference is in critical care, where the mean overall rate of muscle loss of 1.75%/day (12%/week) was reported in a meta-analysis.[57]

Therapeutic Targets: Molecular Pathways of Treatment-Related Muscle Loss and JAK/STAT Inhibition

Off-target effects of systemic cancer therapies add to skeletal muscle loss experienced by patients with cancer, by a broad range of mechanisms related to their specific modes of action (Fig 5). Targeted therapies are a diverse class of inhibitors of intracellular signal transduction pathways involved in growth factor–mediated cell proliferation, such as PI3K, Akt, and mTOR. Members of the TKI class are

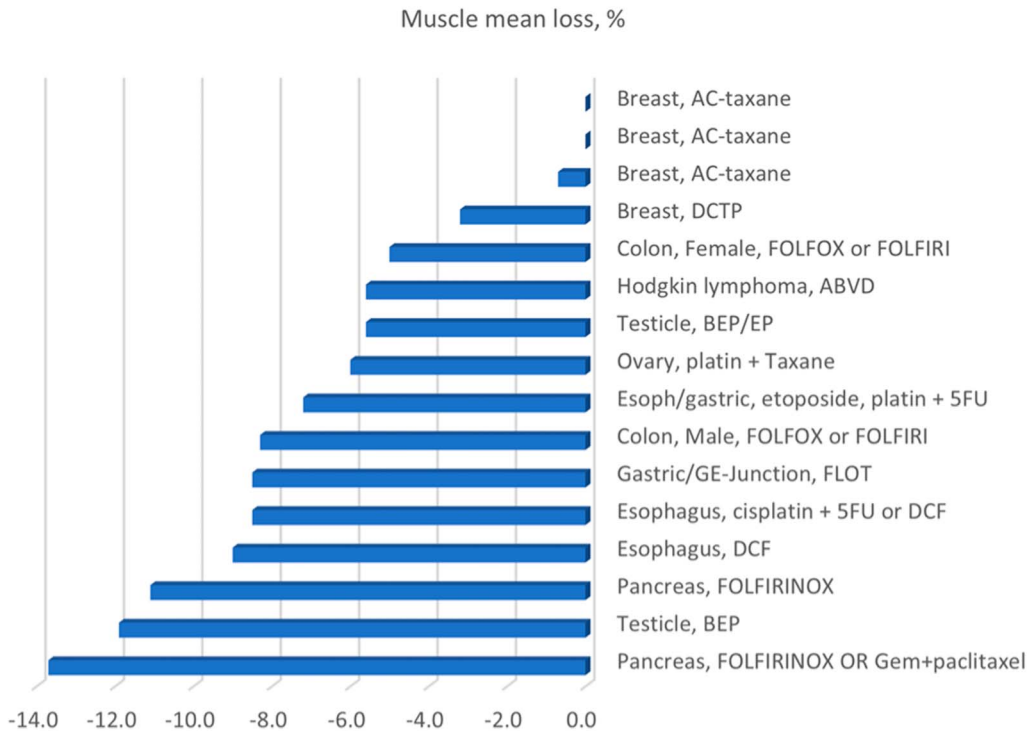

FIG 4. A summary of recent reports of muscle loss rates during systemic cancer therapies. Data are for muscle loss reported during standard regimens. Because of variations in scan interval, for purposes of comparison, author-reported mean muscle loss was converted to % lost per 100 days on treatment. Data are from existing studies.[41,42,44-55] ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AC, anthracycline and cyclophosphamide; BEP, bleomycin, etoposide, platinum; BEV, bevacizumab; DCF, docetaxel, cisplatin, fluorouracil; DCTP, docetaxel, carboplatin, trastuzumab, and pertuzumab; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; FOLFIRINOX, leucovorin, fluorouracil, irinotecan, oxaliplatin; FOLFOX, leucovorin, fluorouracil, oxaliplatin; FU, fluorouracil; GE, gastroesophageal; Gem, gemcitabine.

predictably deleterious to muscle because the PI3K-Akt-mTOR pathway plays a key role in muscle protein synthesis. Cytotoxic antineoplastic agents induce a wide variety of cellular perturbations in protein turnover, proliferation, differentiation, and mitochondrial function. There is also evidence for fibrosis, loss of motor units, inflammatory cell infiltration, and fatty infiltration of muscle. Cisplatin remains the most intensively studied individual compound.[58,59] Cisplatin suppresses protein synthesis via an Akt protein kinase B (Akt)–dependent mechanism, which leads to p70S6k1 dephosphorylation. Cisplatin modifies mTORC1 and forkhead box O (FoxO)–dependent signaling cascades, enhances the transcription of atrophy genes, and synergistically activates the ubiquitin proteasome system and autophagy, resulting in myofibrillar degradation. Cisplatin also induces several changes contributing to atrophy and contractile dysfunction, H_2O_2 production, oxidative stress, increased/compromised Ca2+ dynamics, and desensitized excitability of action potentials, which seem likely to explain reduced force production and weakness.

Ruloxitinib. Among the pathways indicated in Figure 5, the JAK/STAT pathway, which is involved in signal transduction downstream of interleukin-6 and LIF, causes loss of muscle mass and function. There are a variety of FDA-approved inhibitors of JAK1/2 in trials related to myeloproliferative neoplasms as well as inflammatory diseases such as GVHD, rheumatoid arthritis, and critical illness myopathy.[60,61] Exercise, may in part, exert its anti-inflammatory action on muscle via the JAK-STAT pathway.[62] The JAK1/2 inhibitor ruxolitinib was created as an oral agent with the capacity to antagonize JAK/STAT signaling across cell types. In a phase I trial (Table 1), ruxolitinib will be evaluated in an open-label approach to antagonize JAK/STAT signaling as a means of curtailing cachexia progression in patients with stage IV NSCLC. This study will ensure an acceptable toxicity profile when ruxolitinib is used in patients with cancer cachexia. The use of ruxolitinib dose escalation in the study with frequent tissue and serum collections will permit us to better understand how important JAK/STAT signaling is to cancer cachexia.

NUTRIENT SIGNALING AND MULTIMODALITY APPROACHES FOR CANCER CACHEXIA

Reduction in food intake is strongly associated with weight loss, and this is not surprising given that total energy expenditure of patients with cancer is approximately 30 kcal/kg bodyweight/day with many patients showing moderately reduced and severely reduced food intake of the order of 22.2 ± 7.7 and 13.3 ± 7.7 kcal/kg/day, respectively. Attempts to correct anorexia and excess satiety in the CNS are underway (see Section, The CNS and Cancer Cachexia). However, the dietary intake of many patients with cancer has the potential to be optimized by engaging oncology-specific nutritionists and physical therapists who focus on raising intake of specific anabolic nutrients and timely clinical management of pain, and nutrition affect symptoms such as nausea and enable muscle anabolism through concurrent exercise.

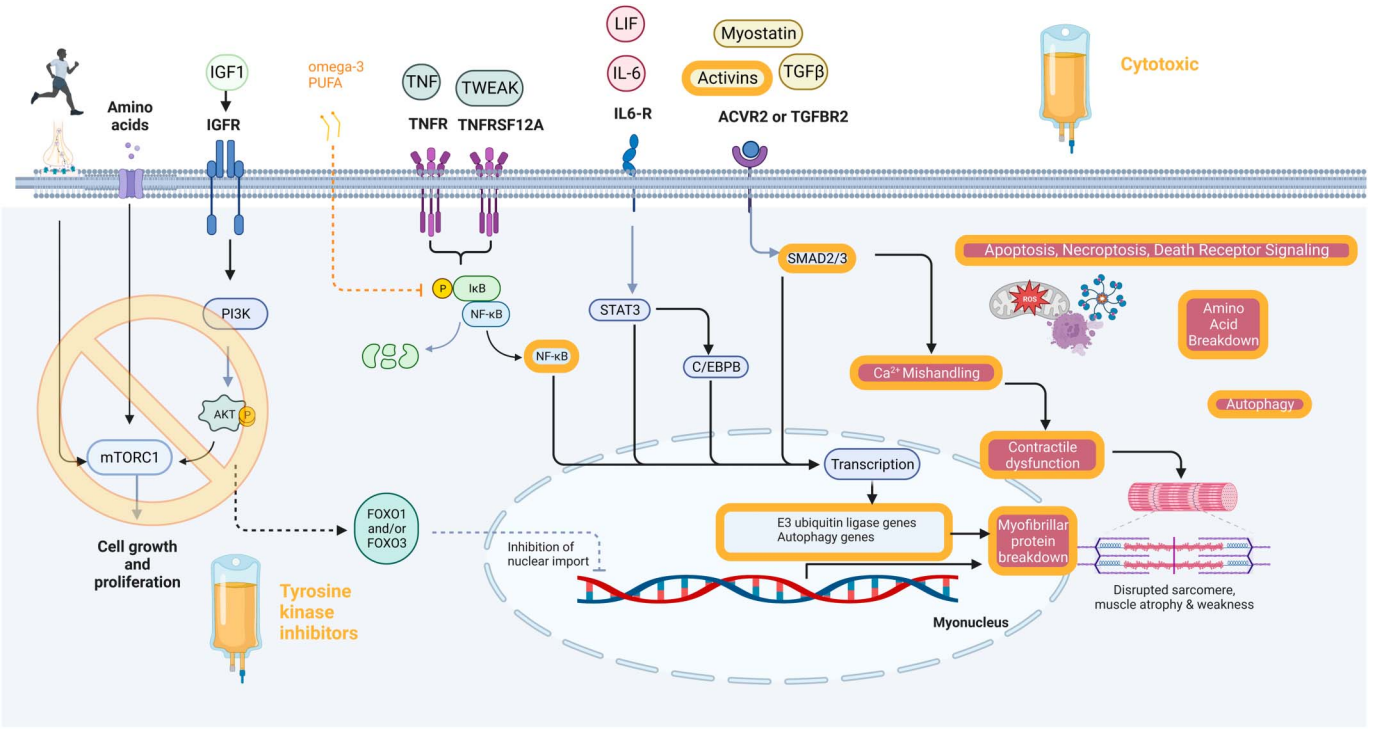

FIG 5. Signaling pathways involved in antineoplastic therapy–induced skeletal muscle atrophy. Cytotoxic cancer therapies induce transcriptional activation of pathways of myofibrillar destruction by the ubiquitin proteasome system, autophagy, and catabolism of amino acids. Apoptosis, necroptosis, and death receptor signaling are also activated, along with mitochondrial dysfunction and overproduction of reactive oxygen species. ACVR2, activin receptor type 2; AKT, serine/threonine protein kinase; C/EBPβ, CCAAT/enhancer-binding protein-β; FoxO, forkhead box protein O complex; IκB, inhibitory subunit of NF-κB; IGF1, insulin-like growth factor-1; IGFR, IGF receptor; IL-6, interleukin-6; IL-6R, IL-6 receptor; LIF, leukocyte inhibitory factor; mTORC1, mammalian target of rapamycin complex 1; PI3K, phosphatidylinositol-3 kinase; PUFA, polyunsaturated fatty acid; STAT3, signal transducer and activator of transcription 3; TGFBR2, TGF-β receptor type 2; TNF, tumor necrosis factor; TNFR, TNF receptor; TNFRSF12A, TNF receptor superfamily member 12A; TWEAK, TNF-related weak inducer of apoptosis.

Therapeutic Targets: Nutrient Signaling

For nutrients and their metabolites that are rate-limiting in key metabolic pathways, preventing any deficiencies may help preserve or restore metabolic homeostasis.

Omega-3 fatty acids. Omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are naturally occurring in fish oil and are known to reduce inflammation. Several signaling pathways of omega-3 fatty acids action have been proposed as targeted nutrient signaling that could facilitate a mechanistic effect by elevating the resolution of inflammation while producing anti-inflammatory mediators, decreasing proinflammatory factors, reducing the activation of proteolytic pathways, and increasing appetite.[63]

The evidence for a therapeutic effect of supplementation with omega-3 fatty acids on cancer cachexia is inconclusive.[64] The effects of omega-3 fatty acids are likely dependent on timing, dose, and duration; therefore, meta-analyses cannot account for this variability across studies with the current evidence available. The timing of omega-3 fatty acids could be an important consideration with more recent studies showing potential benefits when the interventions are earlier in the progression of cancer cachexia or given before a catabolic trigger such as surgery.[65,66] Moreover, dose ranges vary greatly with an intake of >2 g/d (EPA + DHA) which is the amount needed to have an anti-inflammatory effect.[67] The most practical implications for dietary interventions in this population are to use strategies to increase adherence and to measure fatty acid biomarkers to account for variability expected in supplementation adherence. It is also noteworthy that many of the positive studies gave omega-3 fatty acids as part of an oral nutrition formulation, and 2020 ASCO Cancer Cachexia Guidelines suggest use of omega-3 fatty acids within foods as tolerated.[2]

Proteins/Amino Acids

Muscle depletion and catabolism are key physical features of cachexia. Tissue demands for amino acids become critical in times of stress, cancer, or traumatic injury (eg, surgery). Muscle protein is the main reservoir to replace blood amino acids when they are taken up by other tissues and will be catabolized to export amino acids to meet this need. Proteolysis in patients with cachexia can worsen with cancer

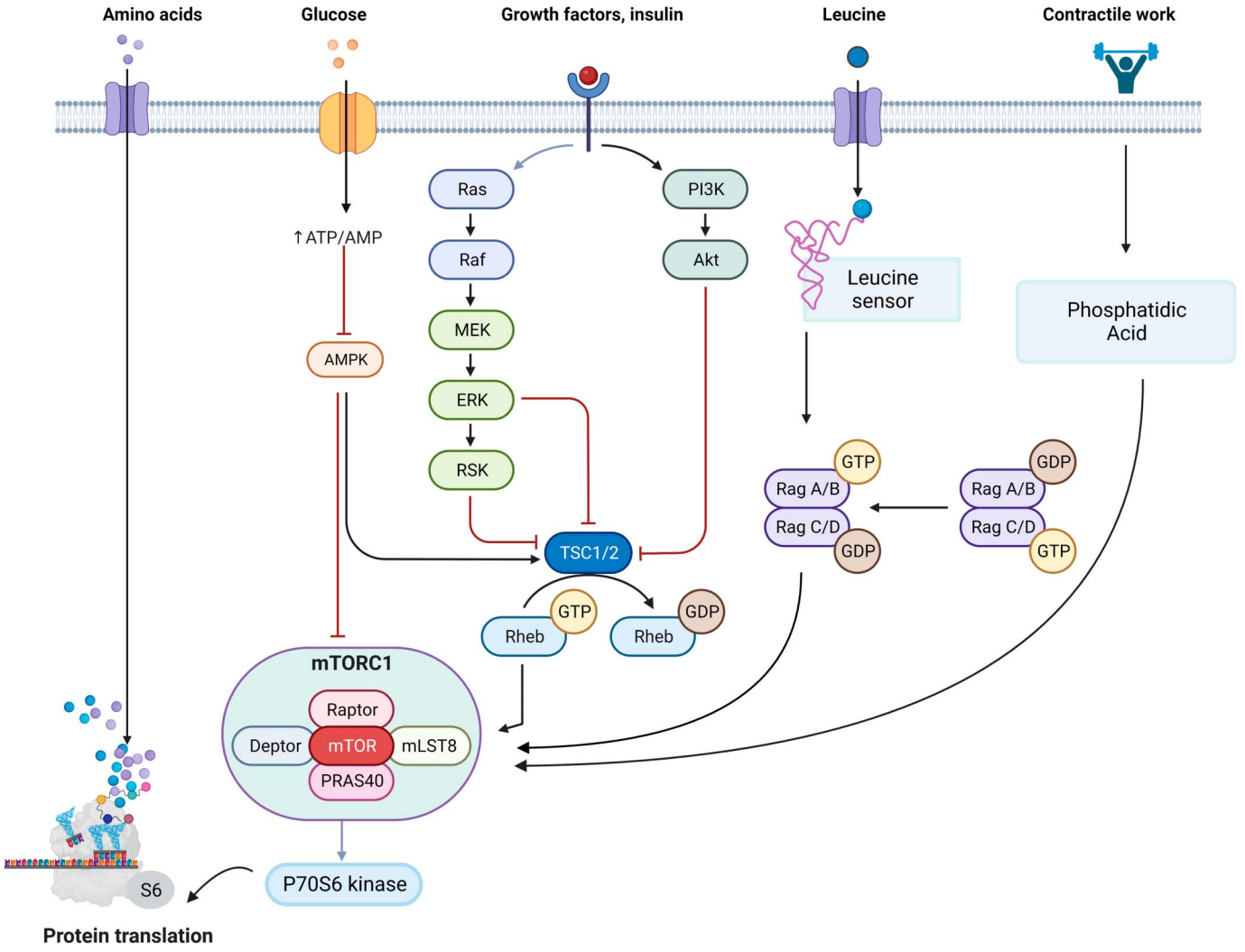

FIG 6. Pathways of nutrient-related, growth factor–related, and contraction-related signaling activate muscle protein synthesis. The growth factor–sensitive and nutrient-sensitive mammalian/mechanistic target of rapamycin complex 1 (mTORC1) is a master regulator anabolism in muscle cells. Signaling pathways activated by nutrients, growth factors, and contractile work are convergent to mTORC1, and activation of the complex requires both nutrients and growth factors to be present. Muscle protein biosynthesis requires availability of 20 amino acids, which are the substrate for the formation of protein. However, the branched chain amino acids, particularly leucine, also have a signaling action. Leucine sensing proteins, such as leucyl t-RNA synthetase, participate in the activation of mTORC1 via the activation of RagB/RagD. Contractile activity that is either high load (resistance training) or high torque (eccentric contraction) signals mTORC1 activation via formation of phosphatidic acid, the ζ isoform of diacylglycerol kinase is necessary for the mechanically induced increase in phosphatidic acid. On activation, mTORC1 will phosphorylate P70S6 kinase, which goes on to phosphorylate ribosomal protein S6 and initiate RNA translation. Akt, serine/threonine protein kinase; AMPK, AMP-dependent protein kinase; ATP/AMP, adenosine triphosphate/adenosine monophosphate; ERK, extracellular signal–regulated kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; MEK, mitogen-activated protein kinase; mLST8, mammalian lethal with SEC13 protein 8; mTORC1, mammalian target of rapamycin complex 1; PI3K, phosphatidylinositol-3 kinase; PRAS40, proline-rich Akt substrate of 40 kDa; Raf, rapidly accelerated fibrosarcoma; Rag, recombination-activating genes; Ras, rat sarcoma; Rheb, RAS homolog enriched in brain; RSK, ribosomal S6 kinase; TSC1/2, tuberous sclerosis complex.

treatments depleting both essential and nonessential amino acids, which then become conditionally essential. Proteins are made from chains of essential and nonessential amino acids. When any single amino acid is deficient due to inadequate intake or a higher metabolic demand, then growth or nitrogen balance is compromised. Adequate supply of dietary protein is a prerequisite to maintain or gain skeletal muscle mass. Patients with cancer can have an anabolic response to eating protein. Higher dietary protein intake can increase protein synthesis by increasing systemic amino acid availability. Branched-chain amino acids (BCAA) are essential amino acids that are important for muscle, and arginine is an amino acid that becomes depleted in surgery (Fig 6).

BCAA/Leucine. Metabolic changes contributing to cancer cachexia are characterized by a net protein breakdown and an increased oxidation of BCAAs in the skeletal muscle to support gluconeogenesis and to supply amino acids for acute-phase protein synthesis in the liver.[68] A 2023 meta-analysis by Sideris et al[69] concluded that BCAA supplementation in patients with liver cancer during treatment led to higher albumin concentrations, but there were insufficient data to draw conclusions on improvement in lean mass. Leucine is more potent than isoleucine and valine in stimulating muscle protein synthesis, while it also decreases muscle protein degradation.[70]

Arginine. Arginine is a semiessential amino acid important for immune function. Normally, we obtain a small proportion of arginine from food and synthesize the remaining 70%-75% from citrulline or protein turnover. During cachexia or other catabolic and inflammatory conditions, arginine concentrations are depleted.[71] In patients with cancer, arginine supplementation demonstrated immunomodulating properties together with improvement in survival and malnutrition.[72] In a perioperative, randomized, controlled trial of patients with bladder cancer, 66% of patients had insufficient arginine before their radical cystectomy. Supplementing arginine in an oral nutritional supplement (ONS) product before and after this catabolic surgery prevented the arginine and ornithine depletion, in contrast to the control ONS group, and showed a trend toward preservation of muscle mass and led to favorable immunomodulation and lower postoperative infection rates.[66,73] A large retrospective study also reported lower postoperative infections with the same supplementation.[74] A phase III trial is currently underway to test the effects of this regimen which provides arginine and omega-3 fatty acids in an ONS versus a control ONS in a patient population at high risk for cachexia by evaluating 30-day postoperative complications, immune and nutrient biomarkers, and lean mass.

Physical activity. Exercise improves muscle mass and physical function in adults with cancer who are at risk of developing cachexia. The current evidence base is less clear for patients with cancer cachexia. A 2021 Cochrane review of four studies found no clear evidence that an exercise program alone or as a component of a multimodal intervention improved outcomes in patients with cancer cachexia.[75] By contrast, a 2022 review by Mavropalias et al[76] summarized the evidence from exercise training trials involving patients with cancer cachexia and noted several studies reporting improved outcomes of maintaining bodyweight and lean mass. Anabolic deficit may be partly addressed by maintaining physical activity. It is noteworthy that exercise improves the effectiveness of nutritional therapy and helps stimulate appetite in cachexia because of other advanced chronic illnesses such as chronic obstructive pulmonary disease. Acute exercise training affects molecular signaling pathways that support building muscle mass, and regular exercise training can lead to beneficial metabolic adaptations.[77] It is unlikely that physical activity without other supportive care can overcome cancer cachexia; however, data suggest that giving patients support to facilitate exercise training safely throughout the treatment spectrum is helpful.

Multimodality. Multimodal strategies, if pragmatic, are a logical approach to address the varied mechanisms driving cachexia. Nutrition and exercise training can help combat muscle loss if implemented earlier and might complement conventional care to help prevent cachexia. Evidence is not conclusive, and yet, it is clear that maintenance or building of muscle mass requires adequate energy, correction of nutrient deficiencies, and physical activity. A prehabilitation program using a multimodal approach that included exercise, nutrition counseling, and psychosocial support showed significant improvements in quality of life in a retrospective study.[78] A feasibility study with an exercise and nutrition intervention during first-line chemotherapy in patients with advanced pancreatic and lung cancer demonstrated safety and adherence.[79] These data have led to the phase II trial, called NEXTAC-III, currently in progress in Japan, which adds anamorelin to a multimodal strategy. Another multimodal phase II trial, called MIRACLE, is in progress in Korea using ibuprofen, omega-3 fatty acids, ONS, Bojungikki-tang (which mediates immune modulation), nutrition counseling, and an exercise intervention compared with conventional palliative care.[80] MENAC, a phase III multimodal trial, was conducted in Europe and the United States, and results are pending. In this trial, patients with lung or pancreatic cancers either received standard treatment for their cancer or standard treatment plus a home-based exercise regimen, ONS-containing EPA, and dietary guidance, along with daily ibuprofen. Accrual targets were met for this study in 2022, and results are expected in 2023. More well-designed multimodal trials focused on end points evaluating changes in body composition, nutrition and nutrient status, energy balance, and physical function are needed.[81]

CONCLUSION

The etiology of cachexia is multifactorial, with various procachectic abnormalities spanning the skeletal muscles, adipose tissues, immune, neural, endocrine, cardiac, respiratory, and GI systems. While much remains to be understood, investigational new therapies are directed at perturbations of appetite and satiety and at the relentless catabolism of skeletal muscle. Participation in clinical research of cachexia therapies will provide patients with access to the leading treatments currently in phase I, phase II, and phase III studies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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How to Make Evidence-Based Integrative Medicine a Part of Everyday Oncology Practice

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overview

Integrativety oncology (IO) is a "patient-centered, evidence-informed field of comprehensive cancer care that utilizes mind-body practices, natural products, and lifestyle modifications from different traditions alongside conventional cancer treatments." There is an urgent need to educate oncology health care providers on the fundamentals of evidence-based IO to meet the needs of people with cancer. In this chapter, we aim to provide oncology professionals with actionable guidance on the basis of the Society for Integrative Oncology (SIO)-American Society of Clinical Oncology (ASCO) guidelines on integrative medicine use during oncology visits to help alleviate symptoms and side effects in people with cancer during and after treatment.

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INTRODUCTION

The term integrative oncology (IO) is defined by the Society for Integrative Oncology (SIO) as "a patient-centered, evidence-informed field of comprehensive cancer care that utilizes mind-body practices, natural products, and lifestyle modifications from different traditions alongside conventional cancer treatments."[1] Use of integrative therapies such as these by people with cancer has grown significantly over the past 50 years, from approximately 20% in the 1970s to the 80% range in 2017.[2] Concurrently, IO services at National Cancer Institute (NCI)-Designated Comprehensive Cancer Centers have increased from about 50% in 2009 to 80% in 2016.[3] This growth corresponds to a significant rise in integrative medicine research, expanding our understanding of the role of IO as part of evidence-informed, high-quality, personalized cancer care.

With high utilization of integrative therapies in populations with cancer, frequent requests from people with cancer, and the growing body of evidence for specific therapies, there is a need to enhance IO training opportunities for oncology professionals. Currently, oncology professionals are poorly equipped to guide people with cancer on evidence-based integrative medicine usage during and after anticancer treatments.[4] Moreover, the successful delivery of high-quality care will require providers to acknowledge the values and preferences of people with cancer to enable shared decision making. Thus, there is an urgent need to educate oncology health care providers on the fundamentals of evidence-based IO to meet the needs of people with cancer.

In this chapter, we aim to address this gap and provide oncology professionals with actionable guidance on the basis of the SIO-American Society of Clinical Oncology (ASCO) guidelines on integrative medicine use during oncology visits to help alleviate symptoms and side effects in people with cancer during and after treatment.

HOW TO INCORPORATE IO INTO PATIENT CARE

People with cancer and their families and/or caregivers may have questions about the role of IO approaches to support their cancer journey. Gaps in communication can occur when oncology providers do not ask their patients about integrative therapies and patients do not feel comfortable enough to initiate these kinds of conversations on their own.[5] Although clinicians may have experience with integrative approaches on the basis of their own health goals, it is important for oncology professionals to go beyond their personal experience in making recommendations for their patients. Knowledge regarding an evidence-informed framework can help oncology professionals guide people with cancer in making thoughtful decisions about integrative approaches. Such a framework ideally considers the aspects of safety and an understanding of the latest evidence and clinical practice guidelines.

People with cancer often struggle with multiple cancer- or treatment-related symptoms and side effects. People with cancer often turn first to their oncology health care team for guidance in managing these symptoms. They often prefer IO approaches because of their desire for nonpharmacologic and holistic health approaches which may align better with their personal health belief system.[6] More natural and holistic approaches are often perceived as less likely to cause harm or additional side effects. By discussing and recommending evidence-based integrative approaches as a first line of action

PRACTICAL APPLICATIONS

- This chapter provides oncology professionals with actionable guidance on the basis of the Society for Integrative Oncology (SIO)-American Society of Clinical Oncology (ASCO) guidelines on integrative medicine use during oncology visits to help alleviate symptoms and side effects in people with cancer during and after treatment.
- It provides guidance for oncology professions on structured approaches to advise and manage the safe and appropriate use of dietary supplements.
- It offers a summary of mind-body therapies to support people with cancer, which can be readily used in oncology practice.
- It offers a blueprint on how integrative oncology could become part of standard cancer care soon.

for addressing many symptoms, this approach meets the needs of people with cancer, gains their trust, and subsequently improves the quality of the professional relationship and the quality of life of people with cancer.

Questions about IO approaches may fall into any of the following categories: (1) managing symptoms, (2) supporting health and well-being, and (3) treating cancer. An awareness of these categories and the motivation of any given person seeking care can be helpful in guiding choices that support their interests. Effectively engaging people in discussions about their IO questions is an important way to strengthen and maintain the therapeutic alliance. It is important to acknowledge and respect a person's values and interests and recognize the medical team's own limitations of time or expertise to fully address their needs in a specific health area. Having resources and materials on hand for referrals to evidence-based IO information and care can support these efforts.

IO as a specialty area of oncology practice draws from many disciplines and health traditions, some of which may be rooted in the specific cultural traditions of people with cancer. Listening to peoples' questions about their healing traditions demonstrates cultural sensitivity that can also strengthen the therapeutic alliance. Although oncology team treatment discussions are rooted in western biomedicine, peoples' questions about integrative medicine may be rooted in cultural traditions. A useful perspective from medical anthropology speaks to the importance of recognizing the difference between having a disease (eg, cancer) and experiencing illness (the full experience of having a disease).[7] Most often, the interest of people with cancer in integrative medicine is about supporting well-being, not treating the disease.

Managing Symptoms

Symptom assessment using tools measuring patient-reported outcomes is the foundation of successful symptom management.[8] Understanding a person's symptoms can lead to thoughtful, evidence-based discussions regarding pharmacologic and nonpharmacologic therapeutic interventions. According to the recent ASCO guidelines regarding diet, exercise, and weight management, the Expert Panel identified the highest level of evidence for exercise, recommending oncology providers prescribe aerobic and resistance exercise during active treatment with curative intent to mitigate side effects of cancer treatment, such as fatigue, anxiety, and depression.[9]

Supporting Well-being

Supporting well-being in people with cancer during cancer treatment through lifestyle medicine is a fundamental aspect of IO. It addresses lifestyle factors such as diet/nutrition, exercise, stress reduction and mental health, social support, and sleep quality in the context of comorbidities and treatment phase in the cancer journey.[6] Health behavior strategies may include exercise counseling to reduce cancer-related fatigue, cognitive behavior therapy for insomnia to address sleep disturbances, or participation in mind-body practices (eg, mindfulness-based interventions, yoga therapy) to reduce anxiety. Partnering with mental health professions such as psychology, social work, or psychiatry can help patients with management of anxiety and/or mood disorders, whether preexisting or instigated by their cancer experience. Keep in mind that a history of mental health problems is a significant risk factor for recurrence of mood and anxiety disorders during cancer.

Treating Cancer

People with cancer, caregivers, and their families may have unrealistic expectations regarding the role of non–evidence-based therapies in the context of their cancer treatment. Pursuit of alternative, non–evidence-based therapies to treat cancer may cause harm, including but not limited to drug-herb interactions, direct organ toxicity, and financial toxicity.[10] Concerns regarding the use of alternative or non–evidence-based therapies include delays in access to conventional therapies that do offer opportunities for cure, potential for drug-herb interactions and/or organ toxicity (hepatotoxicity, nephrotoxicity, and bleeding risk), and financial toxicity.[10] Providing people with cancer and their families access to IO counseling can support evidence-based decision making regarding their cancer care, helping them preserve the therapeutic alliance with their oncology team and opportunities to improve treatment outcomes.

Evidence-based clinical practice guidelines for oncology care. One of the main questions oncology professionals may encounter is how to manage cancer and cancer

treatment–related symptoms, such as nausea, fatigue, pain, arthralgias, hot flashes, dry mouth, insomnia, depression, and anxiety. With awareness of the evidence supporting or not supporting certain IO approaches, oncology professionals can more competently lead discussions about managing common cancer-related symptoms. In addition to National Comprehensive Cancer Network guidelines, SIO and ASCO have developed several guidelines to help support clinicians working with people diagnosed with cancer. The oncology team should be familiar with two of the most recent SIO-ASCO guidelines and important clinical trials supporting them.

The first is the 2017 guideline on the use of integrative therapies during and after breast cancer treatment published by Greenlee et al,[11] which was subsequently endorsed by ASCO and published by Lyman et al[12] in 2018. This guideline summarizes the existing evidence and provides guidance on the use of integrative therapies for the management of symptoms and adverse effects, such as anxiety and stress, mood disorders, fatigue, pain, and sleep disturbance.[12] This guideline made the recommendation on the basis of the US Preventive Services Task Force (USPSTF) evidence grade definition, which defines grade A as "the USPSTF recommends the service as there is high certainty that the net benefit is substantial; grade B as USPSTF recommends the service as there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial; and grade C as the USPSTF recommends selectively offering or providing this service to individual patients based on professional judgement and patient preferences. There is at least moderate certainty that the net benefit is small."[13]

The key recommendations of this guideline include the use of music therapy, meditation, stress management, massage, and yoga for anxiety/stress reduction and depression/mood disorders, and acupressure and acupuncture for reducing chemotherapy-induced nausea and vomiting.[12] Although this guideline pertained only to women with breast cancer, with whom most of the research has been conducted to date, a growing volume of studies with people suffering from other types of cancer are consistently corroborating these recommendations. New joint SIO-ASCO guidelines on the use of integrative therapies for anxiety and depression across cancer types are in development and on track to be published in 2023.

The 2022 SIO-ASCO guideline on integrative medicine for pain management in oncology was developed by a group of international multidisciplinary experts and includes evidence-based recommendations for cancer pain management.[14] The following are the key recommendations (Table 1):

TABLE 1. Recommendations for the Use of Integrative Therapies During and After Breast Cancer Treatment

Symptom	Integrative Medicine Recommendations
Anxiety	Grade A: Meditation Grade B: Music, yoga, stress management
Depression and mood disorders	Grade A: MBSR meditation, relaxation Grade B: Music therapy
Fatigue	Grade C: Hypnosis
Quality of life	Grade A: Meditation Grade B: Yoga
Sleep disturbance	Grade C: Yoga

NOTE. Grade A: recommendation with high certainty; grade B: recommendation with moderate certainty; grade C: recommend selective offering. Adapted from the Integrative Medicine Breast Cancer guidelines.[11,12]
Abbreviation: MBSR, mindful based stress reduction.

1. Acupuncture should be offered to breast cancer survivors suffering from aromatase inhibitor–induced joint muscle pain.
2. Acupuncture may also be offered for general cancer pain or musculoskeletal pain.
3. Massage therapy may be offered to patients experiencing pain during palliative or hospice care.[14]

These recommendations stem from several large randomized controlled trials (RCTs). A phase III RCT randomly assigned 226 people with cancer suffering from aromatase inhibitor–induced joint muscle pain to three groups (acupuncture, sham acupuncture, and waitlist control); a greater proportion of people in the acupuncture group had clinically significant improvement in joint muscle pain compared with sham and control arms with minimal toxicities.[15] Durable treatment effects were reported at 6 months after random assignment.[16] Another large RCT with 360 people with cancer compared electroacupuncture with auricular (ear) acupuncture and usual care. It showed that electroacupuncture significantly reduced musculoskeletal pain by 1.9 points on a 0-10 numeric rating scale, auricular acupuncture reduced pain by 1.6 points, and usual care showed no significant improvement.[17] In another multicenter RCT, a total of 380 people with advanced cancer experiencing moderate-to-severe pain (90% were enrolled in hospice) were randomly assigned to massage or simple touch sessions (six 30-minute sessions over 2 weeks); massage was found to have immediate beneficial effect on pain reduction (mean difference, 0.90; $P = .001$) with no side effects.[18]

Tables 1 and 2 highlight the main evidence-based integrative medicine symptom management recommendations for people with cancer on the basis of the two above-mentioned guidelines.[11]

TABLE 2. Integrative Medicine Recommendations for Cancer-Related Pain Management

Symptom	Integrative Medicine Recommendations
Aromatase inhibitor–related join pain	Acupuncture (moderate strength)
	Yoga (weak strength)
General cancer pain or musculoskeletal pain	Acupuncture (moderate)
	Reflexology (moderate)
	Massage (moderate)
	Yoga (weak)
	Guided imagery with progressive muscle relaxation (weak)
Chemotherapy-induced peripheral neuropathy	Acupuncture (weak)
	Reflexology (weak)
Procedural pain	Hypnosis (moderate)
Surgical pain	Acupuncture (weak)
	Music (weak)
Pain during palliative care	Massage (moderate)

NOTE. Adapted from the Integrative Cancer Pain guidelines.[14]

TABLE 3. Questions to Ask About Each Dietary Supplement

Question	Rationale
What is the name of the supplement?	To identify the supplement
What brand is it?	To determine manufacturing quality of supplement
What dose are you taking?	To understand exposure and assess the effect
What is the duration of use?	To understand exposure and assess the effect
What are your goals of use?	To understand patient goals, beliefs, and priorities
Where did you get information about this supplement?	To understand if self-initiated vs. recommended by a health care professional

APPROPRIATE USE OF DIETARY SUPPLEMENTS DURING AND AFTER CANCER TREATMENT

People with cancer commonly use or are curious about using dietary supplements during and after cancer treatment: By some estimates, 64%-81% use vitamins and minerals; 26%-77% use multivitamins, and 24% use herbal and nonvitamin supplements.[19,20] In a 2014 ASCO Education Book, Harvie[21] reviewed phase II and phase III trials of nutrition supplements in cancer documenting potential benefits and proven harms. With few phase III trials, definitive data on the effects of dietary supplements are limited. Many trials investigating the effects of dietary supplements in patients on active cancer treatment are phase I and II trials. These gaps in knowledge make it challenging for providers to decide how best to counsel patients on the safe and appropriate use of dietary supplements.

SIO guidelines have also reviewed dietary supplements in published guidelines, and there are currently no strong recommendations to use dietary supplements for benefit. SIO guidelines have also recommended avoiding the use of some supplements for lack of benefit or possible harm. For example, acetyl-L-carnitine and guarana are not recommended for breast cancer treatment–related fatigue, and acetyl-L-carnitine is not recommended for prevention of chemotherapy-induced peripheral neuropathy because of potential harm.[11] Associations between any antioxidant use before and during chemotherapy treatment with cyclophosphamide, doxorubicin, and paclitaxel for breast cancer and increased hazard of recurrence also warrant caution.[22] Of note, high use of dietary supplements at the time of diagnosis has been associated with a decrease in treatment initiation.[23] Here, we provide our recommendations for best practices on dietary supplement use in oncology care.

Understand Goals of Dietary Supplement Use

It is important to understand a person's reasons for wanting to use a dietary supplement so that an appropriate conversation and informed decision-making process can follow. This is a conversation to have with people with cancer at multiple points during their care as they may change their dietary supplement use throughout their cancer treatment journey. It is useful to conduct a screening interview with people to determine detailed information on current or planned supplement use and to accurately document use in the medical record (eg, medication list). Table 3 lists specific information to ask about for each supplement.

Check for Interactions

Next, if possible, check the list of supplements for drug-supplement and supplement-supplement interactions for all supplements and drugs, not only oncology drugs. It is important to consider these interactions when initiating a new drug or clinically indicated supplement. Supplements should also be checked for potential harm as acetyl-L-carnitine may worsen chemotherapy-induced peripheral neuropathy.[24] Supplements may also have unwanted effects on disease states such as stimulation of hormone-sensitive cancers by products adulterated with testosterone or herbs that possess estrogenic properties.[25-28] It is important to again review for interactions when any new supplements are being considered or recommended. Table 4 shows a list of databases that can be useful when checking for interactions.

Efficacy

Once safety concerns are reviewed, it is important to understand why the person is interested in taking a supplement, review the evidence, and partner in making an

TABLE 4. Resources to Screen for Drug-Supplement and Supplement-Supplement Interactions

Name	Cost	URL
Memorial Sloan Kettering Cancer Center's About Herbs	No cost	https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs
National Cancer Institute PDQ Cancer Information Summary: Integrative, Alternative, and Complementary Therapies	No cost	https://www.cancer.gov/publications/pdq/information-summaries/cam
National Institutes of Health Office of Dietary Supplements	No cost	https://ods.od.nih.gov
Natural Medicines	Access fee, some institutions have licenses	https://naturalmedicines.therapeuticresearch.com
UpToDate	Access fee, many institutions have licenses	https://www.uptodate.com
Consumer Labs	Access fee	https://www.consumerlab.com

NOTE. Ideally, clinicians can partner with their clinical pharmacy team who can screen for interactions, advise clinicians of potential concerns regarding the level of interaction (eg, none, minor, moderate, or major), and recommend a course of action. A small but growing number of oncology pharmacy groups have pharmacists identified who can do this work.

informed clinical recommendation regarding its use or discontinuation. Searching for peer-reviewed content using resources such as PubMed is a reliable approach to obtain information on the efficacy of specific supplements. Aggregate sources such as those listed in Table 4 can provide useful information more efficiently.

People with cancer may have an interest in supplements to help prevent or treat cancer treatment–related symptoms. As part of a therapeutic alliance, understanding these interests can help clinicians guide patients to consider other pharmacologic or nonpharmacologic evidence-based interventions for symptom relief.

Exploring patient goals in connection supplement use can include a discussion about nondietary supplement conventional or integrative medicine interventions that may benefit them.

Counseling People With Cancer About Safety and Efficacy

After gathering the necessary safety and efficacy information and understanding the person's values, goals, and beliefs, clinicians can use the pharmacists' recommendations, the available literature, and their clinical experience to counsel people on a recommended course of action. Follow-up dietary supplement counseling can be conducted through an additional appointment, phone call, electronic health record messages, or patient education documents. Documenting counseling recommendations in the medical record can be a helpful way to alert the health care team about these discussions and can also serve as a reminder for patients' future reference. Providers can build trust by sharing information about knowledge gaps and the levels of evidence (eg, preclinical, observational, human clinical trial, phase I, etc) that exist for specific dietary supplements (in a way that is accessible and easy to understand). In our clinical experience, people with cancer appreciate the process of making informed decisions about their dietary supplement use and are generally receptive to the information and recommendations provided to them.

Summary and Future Directions

Oncology patients frequently use dietary supplements at all points along the cancer care continuum. Patients may benefit from structured approaches to advising and managing the safe and appropriate use of dietary supplements. Further research is needed to fill in the large knowledge gaps in the areas of dietary supplement safety and efficacy.

MIND-BODY THERAPIES TO SUPPORT PEOPLE WITH CANCER

The definition of mind-body therapies (MBTs) is not clear-cut. The NCI defines a mind-body practice as "a health practice that combines mental focus, controlled breathing, and body movements to help relax the body and mind"[29] while the National Center for Complimentary and Integrative Health (NCCIH) describes MBTs as "a large and diverse group of procedures or techniques that are administered or taught by a trained practitioner or teacher."[30] There is agreement that practices including meditation, yoga, relaxation, hypnosis, and creative therapies are MBTs, but sometimes practices such as acupuncture, Reiki, and tai chi/qigong are also included. We will use an inclusive definition here. MBTs have been documented to improve emotional and psychological well-being in people with cancer and effectively address a variety of cancer-related symptoms, such as pain, fatigue, vasomotor symptoms, anxiety, depression, quality of life, and sleep. Brief summaries of the evidence for these symptoms are presented in the following sections.

Pain

Pain is a common and often persistent symptom after a cancer diagnosis.[31] MBTs have demonstrated efficacy in

different types of cancer-related pain. Meditation has been demonstrated to mediate pain via endogenous opioid pathways, which can be inhibited with naloxone.[32] Acupuncture has been recommended for joint pain related to aromatase inhibitor use, general cancer-related pain, and musculoskeletal pain.[14] Hypnosis was recommended for procedural pain.[14] As we have more fully entered the digital world with the COVID-19 global pandemic, mind-body therapies are being studied in virtual formats. Virtual-guided imagery is currently being studied as a pain treatment modality in the home setting.[33] Healing touch and music therapy received a USPSTF grade C, indicating that the evidence was equivocal.[13]

Fatigue

Individuals affected by cancer may experience fatigue at any point throughout their cancer journey. Although initially related to the disease, the side effects of therapy (eg, anemia) or to other factors (eg, poor sleep, deconditioning, or psychosocial stress) may also contribute to fatigue. Chronic persistent fatigue is present in about a third of persons with a history of breast cancer.[34] People describe fatigue as a weariness not relieved by rest and severely affecting one's quality of life.[35] In the 2017 guideline on the use of integrative therapies during and after breast cancer treatment, hypnosis and acupuncture received a grade C recommendation.[36,37] A more recent literature review recommended cognitive behavioral therapy plus hypnosis as recommendations for fatigue during active therapy and acupressure, mindfulness-based cognitive therapy, and qigong/Tai Chi Easy for post-treatment fatigue.[38]

Vasomotor Symptoms

Vasomotor symptoms or hot flashes may be a significant postcancer diagnosis symptom that is associated with changes in estrogens and androgens in the respective biological sex. These symptoms may be related to any treatment that affects hormonal function, which may include surgery, radiation, chemotherapy, and hormonal blockade therapy. The severity of the experience and the duration of the symptoms vary widely. Some people report vasomotor symptoms even years after the last menses.[39] Hot flashes are unpredictable and may be associated with palpitations, anxiety, poor sleep, and overall decreased quality of life. The 2017 breast cancer guideline gave a C grade to acupuncture on the basis of a large trial with electroacupuncture that demonstrated significant hot flash reduction in the electroacupuncture group compared with the sham and control groups.[40] One nonrandomized study in persons undergoing breast cancer surgery assessed hypnosis plus analgesic drugs compared with a single anesthesia treatment. Improvements in multiple postoperative factors including reduction of hot flashes were demonstrated.[41] A multinational study is currently investigating the role of acupuncture for hot flashes in persons with hormone receptor–positive breast cancer.[42]

Anxiety and Depression

Two of the most common and often inter-related symptoms that people with cancer experience, which are amenable to treatment with mind-body practices, are anxiety and depression. A systematic review of 210 studies reported a mean prevalence of clinical depression of 21.2% across cancer types,[43] and in 24 studies of people with advanced cancers, the rate of depressive disorder diagnoses was 24.6%.[44] Cross-culturally, a meta-analysis of 40 studies in 15 low- and middle-income countries reported a prevalence of 21% for major depression.[45] Within anxiety, a meta-analysis of 44 studies of over 50,000 cancer survivors reported a 17.9% prevalence of elevated anxiety symptoms.[46] Rates of anxiety and depression tend to be even higher around the time of diagnosis as the initial shock and implications of the disease are still being processed.[47]

The published 2017 SIO clinical practice guidelines on treating anxiety and depression in women with breast cancer include mindfulness meditation as a grade A recommendation for both symptoms.[20] Relaxation therapies also receive a grade A for relieving symptoms of depression and mood disturbance. Grade B therapies include yoga and music therapy for both anxiety and depression and massage for depression. Weaker recommendations for acupuncture and healing touch were made for anxiety and depression, respectively. These are summarized in Table 2, which also describes the key features of each of these mind-body therapies. Although this guideline pertained only to women with breast cancer, with whom most of the research has been conducted to date, a growing volume of studies with people suffering from other types of cancer are consistently corroborating these recommendations. New updated joint SIO-ASCO guidelines on integrative therapies for anxiety and depression across cancer types will be published later in 2023.

Quality of Life

Overall quality of life has been assessed as an outcome in many mind-body therapy studies. Tools used typically assess emotional, physical, functional, and social quality of life, as well as overall total quality of life across these domains. In this realm, mindfulness mediation again received a grade A recommendation, followed by yoga at grade B, and acupuncture, qigong, reflexology, and stress management as grade C therapies, like anxiety and depression.

Sleep

Sleep disturbance is another very common and burdensome symptom many people with cancer experience, with a prevalence of insomnia reported at nearly three times that of the general population, at 30%-50% of all people with cancer.[48] The research on integrative therapies for treating sleep disturbances and insomnia is less extensive than for the other symptoms covered, with only gentle yoga currently

being recommended in the breast cancer guidelines for improving sleep.[11] However, the gold standard treatment for insomnia is cognitive behavioral therapy for insomnia (CBT-I),[49] which is an adaptation of CBT specifically designed to address insomnia symptoms using behavioral methods, such as sleep monitoring, sleep restriction, relaxation training, and stimulus control, along with basic sleep hygiene. A noninferiority randomized controlled trial comparing a mindfulness-based intervention with CBT-I in people with cancer who were post-treatment diagnosed with full-blown insomnia showed quicker benefit for CBT-I immediately after treatment, but in a 3-month follow-up, the MBI was noninferior for improving both subjective and objective measures of sleep, as well as anxiety and depression.[50]

Choosing an MBT

Many different MBTs can be effective in treating the same symptom, as noted above. They have rarely been compared with one another in research studies, so making specific recommendations can be difficult. In general, whichever MBT a person is drawn to and feels they could participate in on a regular basis is likely to be beneficial. Typically, during treatment, less effortful therapies such as hypnosis, relaxation, and imagery can help alleviate symptoms; going into long-term survivorship, therapies that require more individual self-management and effort such as mediation and yoga may be preferred.

How to Find an Integrative Clinician

NCI-Designated Cancer Centers increasingly include IO care.[3] Reaching out to a nearby cancer center may provide you with potential contacts and referrals for your patients and for additional CME opportunities. The SIO offers a public directory on its website (https://integrativeonc.org/public-directory). The University of Arizona offers a directory of clinicians who have completed the fellowship in integrative medicine (https://integrativemedicine.arizona.edu/alumni.html). The American Board of Physician Specialties provides a search function on their website to identify physicians boarded in integrative medicine (https://www.abpsus.org/for-patients/).

CONCLUSION

IO incorporates evidence-based integrative therapies into cancer care using a person-centered approach and can effectively manage some cancer symptoms and cancer treatment–related side effects. Oncology health care professionals should be aware of the importance of this growing field, be well-versed in the evidence behind it, and willing to discuss integrative therapy options to help improve the quality of life of people with cancer and develop and maintain trust and rapport. Future research is needed to continue to expand the field to understand the mechanisms, efficacy, effectiveness, and implement ability of IO approaches to reduce cancer symptom and side effects.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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