Overcoming the Challenges in Getting Cancer Vaccines to Market

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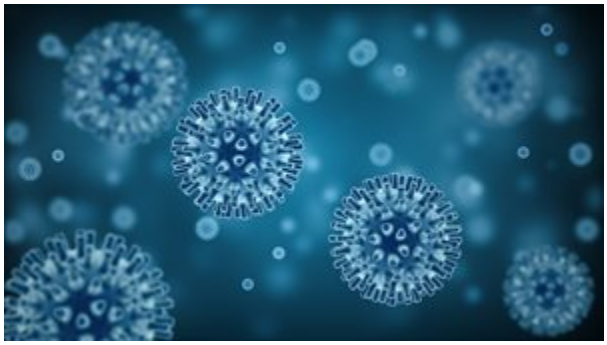
This article discusses advances in the development of "personalized" cancer vaccines and reviews the many challenges that need to be overcome to get new cancer vaccines approved and on the market. The authors highlight FDA's "Regenerative Medicine Advanced Therapy" (RMAT), a comprehensive policy framework aimed at providing oversight for cancer vaccines and regenerative medicine products, including novel cellular therapies.



Introduction

Cancer continues to be one of the leading causes of mortality worldwide and in 2015, responsible for 8.8 million deaths globally.[1] The American Cancer Society has estimated that in the US in 2018 there will be 1,735,350 new cancer cases diagnosed and 609,640 cancer deaths.[2] As the global burden of cancer continues to rise, therapeutic innovation based on improved understanding of disease biology and translational research has changed the paradigm of cancer treatment over the past two decades. Recent technical advances in the development of therapeutic vaccines—integrating immuno-oncology with precision medicine—are revolutionizing cancer therapy by implementing a strategy of utilizing the patients' immune system to treat cancer. Subsequently, recently approved cancer vaccines using this paradigm helped make 2017 a landmark year for approvals of new cancer vaccines.

An Emerging Modality

Cancer vaccines, designed to generate a targeted, immune-mediated antitumor response, offer a promising "precision" treatment strategy that stimulates the immune system to attack and kill malignant tumor cells.[3] Researchers at Stanford University, for example, have found that inactivated Induced Pluripotent Stem Cells (iPSCs) prevented or slowed the development of cancer in mice, suggesting promising clinical potential.[4] Another study at Stanford University demonstrated that directly injecting solid tumors in mice with minute amounts of two immune-stimulating agents could eliminate cancer, including distant, untreated metastases.[5] A recent pilot clinical trial demonstrated that a personalized, precision cancer vaccine is safe and improved survival rates in patients with ovarian cancer.[6] The global precision medicine market accounted for $43.59 billion in 2016 and is estimated to reach $141.70 billion

by 2026.[7] However, there is a need to both identify gaps and address challenges in therapeutic cancer vaccine development and translation as well as bolster further innovation in developing precision medicine approaches. **Figure 1** reviews current challenges and recommendations for facilitating clinical translation of personalized therapeutic cancer vaccines.

Figure 1. Current Challenges and Recommendations for Facilitating Clinical Translation of Personalized Therapeutic Cancer Vaccines

CHALLENGES	RECOMMENDATIONS
Hurdles in trial design and endpoint evaluation	• Select patients with low tumor burden • Employ tumor mutation burden (TMB) measurements to identify patients most likely to respond to specific cancer vaccines and to evaluate ongoing efficacy • Employ NGS-based companion diagnostic approaches to allow detection of early-stage cancers and longitudinal monitoring for resistance mechanisms • Validate surrogate biomarkers that correlate with clinical outcomes
Operational and commercialization challenges	• Standardization of protocols and personnel training to achieve operational consistency, robustness and sensitivity in diagnostic assays across multiple sites • Adopt a centralized approach to support a cost-efficient framework for NGS diagnostics • Consolidate oncology practices by integrated health networks that streamline oncology work flows, combine genomic information and, electronic medical records • Early evaluation of logistics underlying manufacturing and distribution to enable implementation of an economically feasible business model that meets regulatory standards
Regulatory and reimbursement hurdles	• Co-development of cancer vaccines and assays for targeted antigen and discussion with CBER and CDRH before IND and/or IDE submission • Early dialogue with FDA to seek consensus on surrogate endpoint that will qualify for accelerated approval and/or RMAT designation • Early dialogue with reimbursement authorities to determine coverage decisions • Consider diagnostic testing as an explicit and integral part of the value assessment of therapeutic cancer vaccines • Promote awareness and education about the use of value assessment frameworks in personalized therapeutic vaccine approach • Active collaboration between leaders in pharmaceuticals, diagnostics, health technology assessment organizations, regulatory authorities and, policy makers to promote patient access to innovative therapeutic vaccines

Clinical Translation of Therapeutic Cancer Vaccines: Challenges and Successes

Therapeutic cancer vaccines are a heterogeneous range of products “precision-targeted” toward a variety of tumors. However, some developers are advancing their products into clinical studies prior to establishing sufficient understanding about the underlying mechanism of action. A primary reason for this approach is the lack of sophisticated and predictive non-clinical models. The utility of non-clinical models varies depending on the cancer vaccine and the targeted tumor. Proof of concept and mechanism of action may be difficult or impossible to demonstrate in non-clinical models in some instances. An example may be found in autologous (patient self-donated) vaccines produced by isolating tumor cells from an individual, processing those cells into a vaccine formulation *in vitro*, then administering the vaccine to the individual from whom the tumor cells were originally isolated.

This landscape poses challenges for developers in terms of ensuring adequate evidence for safety and

efficacy from a non-clinical perspective.[8] As an alternative to animal models, *in vitro* testing of human tissues to examine the distribution of a candidate tumor associated antigen may be performed. However, there is difficulty in providing a standard, non-clinical program/regulatory guideline applicable to all therapeutic cancer vaccines.

Unlike prophylactic vaccines, such as hepatitis B virus and human papilloma virus vaccines which are aimed at preventing cancer occurrence in healthy individuals, the strategy behind therapeutic cancer vaccines is treating an existing cancer by strengthening the patient's immune response against tumor cells.[9] As far back as April 2010, FDA approved the first therapeutic cancer vaccine, Provenge® (Dendreon Corporation), for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer.[10] While Provenge® was a commercial failure for various reasons, its discovery highlighted the potential for immunological control of cancer and demonstrated the technical viability of this approach.

"Kymriah" (Novartis), the first Chimeric Antigen Receptor (CAR) T-cell therapy, was approved in 2017 for treating those patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia.[11] Also in 2017, "Yescarta" (Kite Pharma) became the second FDA-approved CAR-T therapy for treating adult patients with certain types of large B-cell lymphoma.[12] More recently, Kymriah was also approved by FDA for treating adult patients with relapsed large B-cell lymphoma non-Hodgkin lymphoma.[13]

Hurdles in Trial Design and Endpoint Evaluation

One of the major challenges in evaluating the effectiveness and efficacy of therapeutic cancer vaccines is patient selection, made difficult by the degree of immune suppression already experienced by patients with late-stage disease and large tumors, but who may benefit from the new therapy.[14] In addition, clinical trials of new oncology therapies are traditionally initially tested in patients with advanced cancers who have failed multiple treatment regimens.

Another challenge in trial design and evaluation is that the kinetics of tumor growth rate for vaccine therapy differs from those of traditional chemotherapy and radiotherapy.[15] As a result, positive responses to vaccine therapy may only begin months after treatment, as compared to cytotoxic therapies where treatment response occurs immediately following administration. More relevant immunologic endpoints are needed as the intermediate endpoint of progression-free survival based on the commonly used *Response Evaluation Criteria in Solid Tumors* or World Health Organization criteria may have limited value in evaluating vaccine therapies.

Regulatory, Commercialization and Reimbursement Challenges

Manufacturing therapeutic cancer vaccines is expensive and labor intensive and could benefit from adhering to a Good Manufacturing Practice (GMP) culture. Autologous cell-based vaccines are produced at a small-scale, in dedicated suites, with centralized manufacturing or localized manufacturing facilities close to the patient's point-of-care.[16] Treatment cost comprises of many components affecting overall manufacturing cost. These costs emerge from the logistics of obtaining, processing, manufacturing and returning autologous vaccine preparations for each individual patient while maintaining product sterility and stability. Getting the right product to the right patient is an important issue and control of the "cold chain" during procurement and distribution is critical. Because the logistics, chemistry, manufacturing and control for developing cancer vaccines is complex, it is imperative that manufacturers, regulators and

healthcare providers address the clinical, regulatory and reimbursement hurdles to facilitate successful clinical translation.

These difficulties translate into the need for firm regulatory oversight. Therapeutic cancer vaccines exhibiting promising potential to transform oncology treatment are regulated by CBER's Office of Tissues and Advanced Therapies (OTAT), CDER and CDRH and may be involved in product review.

FDA's accelerated approval regulations in 21 CFR Part 314, Subpart H (for drugs) and 21 CFR Part 601, Subpart E (for biologics) apply to new drug and biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses. FDA accepts tumor shrinkage as an appropriate surrogate endpoint in the setting of a population of cancer patients with advanced disease and tumors. However, cancer vaccines may not induce tumor shrinkage. As a result, accelerated approval regulations may need to accommodate therapeutic cancer vaccines where licensure can be based on immunological markers, ones reasonably likely to predict clinical benefit. There is also an urgent need to identify and validate biomarkers predicting efficacy and adverse events associated with therapeutic cancer vaccines.

Clinical Trial Design Optimization—Patient Selection and Validation of Immunological Biomarkers

Rigorous trial design at an early stage provides the ability to make clear go/no-go decisions and reduce failures at later stages of clinical development.[17] Review of past pivotal trial failures highlight the significance of appropriate patient profile identification. FDA guidance document for therapeutic cancer vaccine development provides recommendations for the design of clinical trials and recommends testing vaccines in patients with earlier-stage cancers or in patients with low tumor burden so as to allow sufficient survival time to administer multiple doses and elicit a detectable immune response.[18]

Another important trial design consideration is immunologic selection and response monitoring of patients. Measurement of baseline immune status should be considered early in the clinical program.[19] If a correlation is found in early phase studies between baseline immune status and response to vaccination, this information can be used to guide the design of future clinical trials.

Identification and validation of appropriate immunological biomarker is critical in development of therapeutic cancer vaccines. Pre-treatment markers help to determine which patients would most benefit from the vaccine. It is also important to identify and validate surrogate biomarkers correlating with clinical outcomes.

Tumor Mutational Burden (TMB), a measurement of the mutations carried by tumor cells, has emerged as a quantitative genomic biomarker for predicting potential responses to immunotherapies across different cancers, including melanoma, lung and bladder cancers.[20] TMB is consistently reproducible and can be used to better inform decisions pertaining to identification of patients most likely to respond to specific cancer vaccines, as well as to evaluate the ongoing efficacy of vaccine administration.

Next Generation Sequencing (NGS) Approaches

To realize the potential of precision medicine, healthcare providers need biomarkers predictive of a therapy's impact, as well as companion and comparative diagnostics to detect them. Gene expression signatures derived from NGS approaches provides information in terms of diagnosis, prognosis or

prediction of the therapeutic response to cancer vaccines.[21,22] NGS-based companion and comparative diagnostic approaches for therapeutic cancer vaccine development will open entire new avenues, including detection of early-stage cancers and longitudinal monitoring for resistance mechanisms, allowing patients to be matched with appropriate targeted therapies. Regulatory concerns to be addressed for efficient implementation of such approaches include: establishing and maintaining the clinical validity of NGS tests for approved biomarkers, identifying the level of evidence required for biomarkers that are rare in an indication and keeping pace with new discoveries and advancements in the rapidly growing field of oncology.

FDA has recently published guidance on the utilization of NGS-based approaches in the design, development and analytical validation of *in vitro* diagnostics, including those utilized as companion and comparative diagnostics.[23] Advances in NGS approaches will allow biologic information to be efficiently organized and interpreted for a maximum predictive value for individual patients.

Also, FDA recommends co-development of cancer vaccines and assays for targeted antigen encouraging discussion with relevant product review office, such as CBER and CDRH, early in the development process. A pre-Investigational New Drug (IND) meeting to discuss study design, Chemistry, Manufacturing and Controls (CMC) and nonclinical (toxicology) plans ideally before submission of an IND and/or IDE is strongly recommended to ensure that product development provides data to establish the safety and effectiveness of the therapeutic product and assay pair.[24]

FDA's RMAT and Other Guidances

In November 2017, FDA announced a comprehensive policy framework called *Regenerative Medicine Advanced Therapy* (RMAT) for the development and oversight of regenerative medicine products, including novel cellular therapies.[25] This regulatory framework is intended to foster further advances in regenerative medicine and allow innovators to bring new, effective therapies to patients as quickly and safely as possible. RMAT designation has caught the attention of sponsors of advanced therapies and could potentially impact the regulatory pathway for cancer vaccines. Under RMAT designation, the opportunity for early and more frequent interactions with FDA during critical development stages is very attractive as early interactions can address the unique CMC and clinical trial challenges associated with advanced therapy development. Although RMAT designation requires preliminary clinical evidence indicating the therapy has the potential to address unmet medical needs, RMAT does not require evidence indicating the drug may offer a substantial improvement over available therapies, as breakthrough designation requires. If an RMAT-designated product also receives an accelerated approval based on a surrogate endpoint, FDA could accept patient registries or other sources of real world evidence, such as electronic health records to satisfy post-approval requirements.

To be more informed about impending launches and the associated additional budget loads, reimbursement authorities appreciate early dialogues with sponsors. In response, companies are able to address their questions and create clarity regarding making the pipeline meet regulations and also attractive from a payer perspective. Along these lines, a recent FDA guidance was issued allowing drug makers to provide payers with certain information about unapproved drugs or unapproved uses of already cleared medicines that payers and drug makers may need to negotiate ahead of an approval decision and to appropriately craft a value-based payment scheme.[26] Extension of this guidance to advanced innovative medical products may be beneficial for determining coverage decisions and

accelerating patient access. Value assessment frameworks are intended to promote healthcare decision making. Existing healthcare technology assessments and value assessment frameworks lack established paradigms for assessing the value of advanced technologies and services within a full treatment regimen, such as diagnostic testing.[27]

Companion diagnostics play an important role in precision medicine. However, their value in terms of improving patient outcomes and effectiveness of the healthcare is not appropriately recognized by the reimbursement system.[28] Lack of reformed pricing and reimbursement policies and coverage for many diagnostic services, as well as uncertainty with respect to clinical evidence requirements, may disrupt the advancement of such precision medicine approaches. The use of diagnostic tests to help determine which therapeutic cancer vaccines will be most effective and safest to use in any given patient is a crucial element of the complete personalized treatment regimen. As a result, it is critical to consider diagnostic testing as an explicit and integral part of the value assessment of therapeutic cancer vaccines.[29] Finally, awareness and education about the use of value assessment frameworks in such precision medicine approaches will reduce the risk of inappropriate restriction of reimbursement and/or access to individualized care.

Conclusion

Recent advances in therapeutic cancer vaccine development offer the potential to transform oncology. However, it is imperative that sponsors engage in early dialogue with FDA's Oncology Center for Excellence to leverage the combined skills of regulatory scientists and reviewers with oncology clinical expertise to support an integrated approach to the advancement of cancer treatment. With novel technologies enabling newer concepts of personalized immune interventions, additional clinical and regulatory challenges have arisen. This demands a reformed regulatory, pricing and reimbursement framework. Overall, successful clinical translation and market penetration of therapeutic cancer vaccines will require close collaboration between leaders in pharmaceuticals, diagnostics, health technology assessment organizations, regulatory authorities and policy makers that will assist in making the right investments and build the right capabilities to materialize innovative approaches for cancer treatment.

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