Informed Prostate Cancer Support Group Inc.
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Saturday, January 15, 2022

JANUARY 2022 NEWSLETTER

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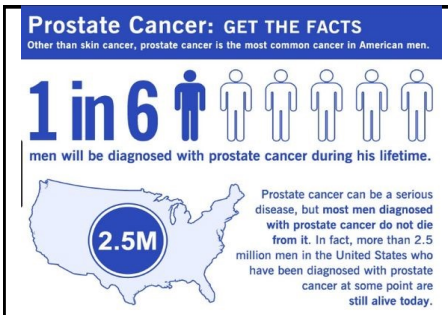
Volume 15 Issue 01

- **Next Meeting Saturday, JAN 15, 2022 IPCSG - Live-Stream Event, 10:00am PT**.
- Speaker Dr. Arno J. Mundt, MD—UCSD Radiology. Dr. Mundt and his colleagues will present the latest updates in the field of Radiation Oncology.
  - **Arno J Mundt MD FASTRO FACRO**—Professor and Chair UCSD Dept. of Radiation Medicine & Applied Sciences
  - **John Einck MD FACRO**—Professor UCSD Dept. of Radiation Medicine & Applied Sciences California Proton Therapy Center
  - **Carl Rossi MD** Professor UCSD Dept. of Radiation Medicine & Applied Sciences California Proton Therapy Center
  - **Brent Rose MD** Assistant Professor UCSD Dept. of Radiation Medicine & Applied Sciences UCSD Department of Urology
- February Meeting Speaker Dr. Richard Lam, MD—Prostate Oncology Specialists
- March Meeting—members will share their experiences
- Due to COVID-19, no in-person meetings at the Sanford Burnham Prebys Medical Discovery Institute

- No Meeting in December—see last newsletter for November summary



Organization

a 501c3 non-profit organization - all positions are performed gratis

IPCSG

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Stephen Pendergast ..... Editor

NEWSLETTER

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PROSTATE CANCER—*2 WORDS, NOT A SENTENCE*

What We Are About

Our Group offers the complete spectrum of information on prevention and treatment. We provide a forum where you can get all your questions answered in one place by men that have lived through the experience. Prostate cancer is very personal. Our goal is to make you more aware of your options before you begin a treatment that has serious side effects that were not properly explained. Impotence, incontinence, and a high rate of recurrence are very common side effects and may be for life. Men who are newly diagnosed with PCa are often overwhelmed by the frightening magnitude of their condition. Networking with our members will help identify what options are best suited for your life style.

Meeting Video DVD's

DVD's of our meetings are available for purchase on our website at https://ipcsg.org/purchase-dvds and are generally available by the next meeting date.

Join the IPCSG TEAM

If you consider the IPCSG to be valuable in your cancer journey, realize that we need people to step up and HELP. Call **President** Bill Lewis @ (619) 591-8670 ; or **Director** Gene Van Vleet @ 619-890-8447.

From the Editor

Due to COVID-19, no in-person meetings will be held until further notice. We will continue to post and distribute the newsletter in the interim. Our speaker this month will be broadcast via the IPCSG website at https://ipcsg.org/live-stream and can be watched by scrolling down and clicking on the "WATCH THE PRESENTATION" button. The broadcast will begin approximately 10 minutes before to the listed start time.

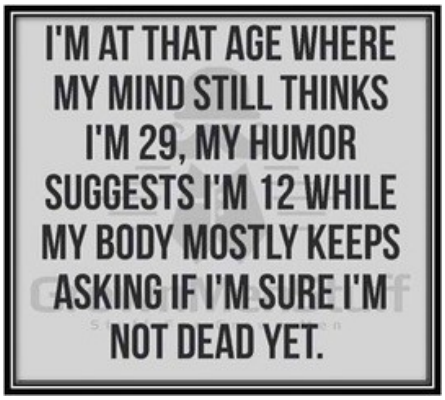
In this issue:

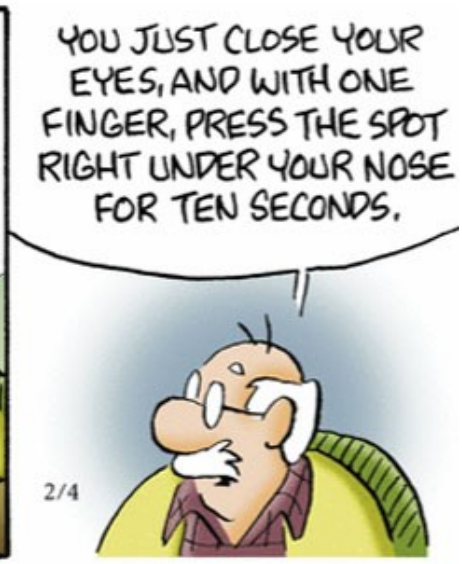
Bill Lewis produced a short summary of the last stream video on HIFU which was shared in the December newsletter. This issue focuses on summaries of last years achievements, estimates of coming attractions, and other news.

Articles of Interest:

- PCF Scientific Retreat 2021:
    1. Top Stories for Patients —living with prostate cancer
    2. Top Stories for Patients—new treatments
- The future of prostate cancer research in the next decade
- Targeted drugs that are kinder to patients
- 3D imaging for better pathology
- Inherited links for Prostate Cancer
- New Strategy Against treatment resistant PCa
- Comprehensive approaches to delaying resistance to ADT

On the Lighter Side





Articles of Interest

pcf.org

PCF Scientific Retreat 2021: Top Stories For Patients

The PCF 28th Annual Scientific Retreat was held virtually over 4 days in October and November. Once again, researchers, industry partners, clinicians, patient advocates, and others were able to join from anywhere in the world to discuss the latest findings in prostate cancer research, treatment, and survivorship. PCF's Dr. Andrea Miyahira has identified the top stories for patients.

PCF funds research to help men not only survive through prostate cancer, but to thrive. Three key presentations focused on lifestyle changes that can help men live better, and even reduce the chance of fatal prostate cancer in men at high genetic risk.

For Prostate Cancer Survivors, Exercise is Medicine

Christina Dieli-Conwright, PhD, MPH

Harvard: Dana-Farber Cancer Institute

What this means for patients: Dr. Dieli-Conwright has shown that exercise significantly benefits patients with prostate cancer, including improving fitness and quality of life, reducing obesity and other metabolic problems, and reducing muscle wasting. Exercise is a key "prescription" for better outcomes.

The use of exercise to enhance the lives of people diagnosed with cancer dates back 100 years, when doctors noticed an inverse relationship between cancer mortality and "muscular work." The field of exercise oncology has gained ground, especially in the last 10 years, as studies verified the many health benefits linked to consistent exercise. Much like diet, exercise is known to improve physical and mental quality of life for everyone, with very probable additional benefits to patients with prostate cancer. Today, exercise guidelines have been established for cancer survivorship, and include both aerobic and resistance exercise.

Dr. Dieli-Conwright reported on several clinical trials of exercise in patients with prostate cancer, especially among those undergoing ADT. Exercise interventions had multiple health benefits, including reduced waist circumference, greater lean mass, and improved fitness. Patients on active surveillance participating in high-intensity interval training had lower PSA levels and slower rise in PSA. Obese men saw improvements, such as a lower chance of developing type 2 diabetes. Overall, exercise should be considered paramount for patients seeking to optimize their health and quality of life during and after treatment. Future studies will help identify the most effective exercise "prescriptions" for prostate cancer survivors.

Wake Up! It's Time to Address Sleep Issues in Prostate Cancer

Stacy Loeb, MD, MSc, PhD (Hon)

New York University; Manhattan Veterans Affairs Hospital

What this means to patients: Sleep is important to physical and mental health. Sleep disturbances are experienced by the large majority of prostate cancer patients and caregivers. More studies into the links between sleep and prostate cancer, as well as interventional studies to improve sleep in patients are needed to improve patient outcomes and quality of life.

(Continued on page 5)

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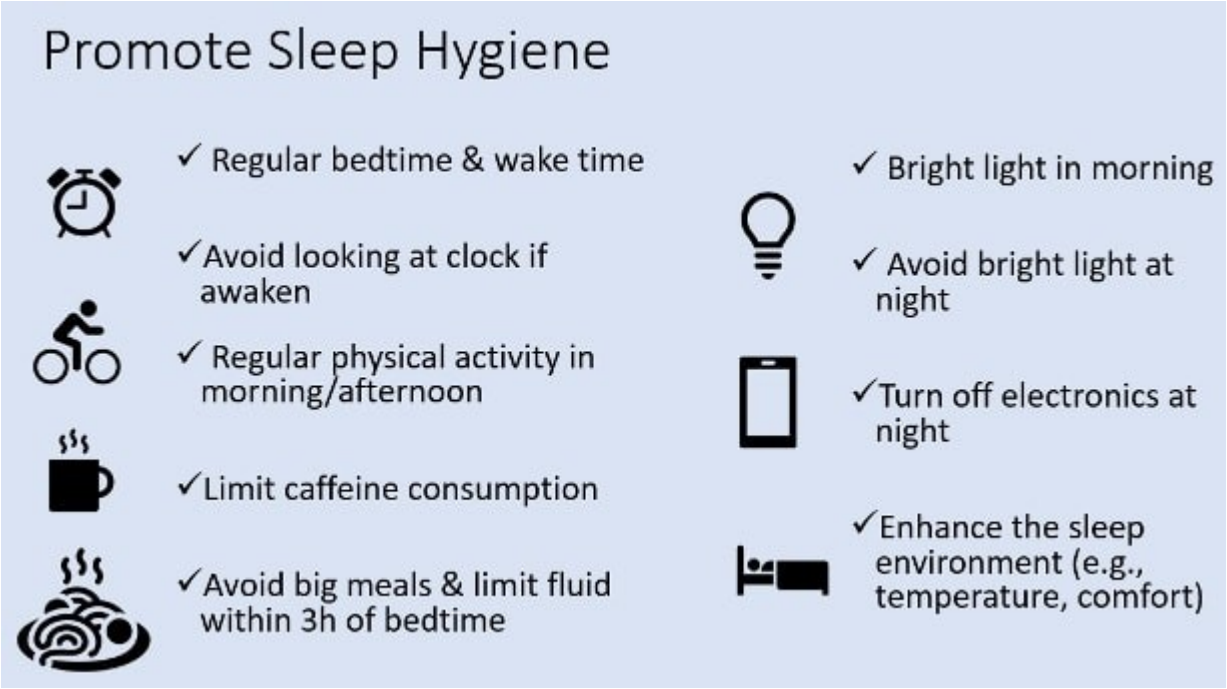
Sleep disturbances—such as insomnia and obstructive sleep apnea—are common and are known to have both mental and physical health consequences. Several studies have investigated the relationship between sleep or circadian rhythm disturbances with prostate cancer risk, and many, but not all, suggest an association.

Dr. Loeb and team used a number of methods to study the links between sleep/circadian disruptions and prostate cancer. These include "social listening," a method that evaluates posts on online prostate cancer communities, surveys of patients and caregivers, and reviewing scientific studies.

Social listening studies found that sleep was a common concern among prostate cancer patients. Surveys found that sleep disturbances are very common among patients and caregivers, with 67% of patients and 88% of caregivers meeting cutoffs for poor sleep quality. However, a survey of urologists found that sleep is rarely discussed with patients and sleep quality is rarely measured.

The team recently initiated a trial that will test a 3-month digital sleep intervention in prostate cancer patients. Dr. Loeb's practical suggestions for improving sleep hygiene include:



Healthy Lifestyle Can Offset a High Genetic Risk of Prostate Cancer

Anna Plym, PhD

Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health

What this means for patients: People can't change their genes, but they can change their lifestyle by increasing exercise, maintaining a healthy weight, quitting smoking (or not starting), and choosing healthy foods such as tomatoes and fatty fish. This study shows that for men at high genetic risk of prostate cancer, lifestyle changes may be key to lowering their risk of dying from the disease.

Prostate cancer is highly heritable, with over 50% of cases being linked to inherited factors. The recently developed Smith test can identify men at highest genetic risk for prostate cancer. Studies by Dr.

(Continued on page 6)

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Plym and colleagues have validated the Smith test and now show that having a healthy lifestyle can reduce the chance of lethal prostate cancer by about 45% in men with highest genetic risk. This suggests that exercise, not smoking, and a healthy diet are essential tools to offset prostate cancer risk in this population.

pcf.org

PCF Scientific Retreat 2021: Top Stories For Patients (part 2)

PCF held the 28th Annual Scientific Retreat virtually over 4 days in October and November. Once again, researchers, industry partners, clinicians, patient advocates, and others were able to join from anywhere in the world to discuss the latest findings in prostate cancer research, treatment, and survivorship. PCF's Dr. Andrea Miyahira has identified the top stories for patients.

PRINCE Trial Shows Promise For Combination of LuPSMA + Pembrolizumab

Shahneen Sandhu, MBBS

Peter MacCallum Cancer Centre, Australia

What this means for patients: LuPSMA is an emerging treatment for advanced prostate cancer that is anticipated to gain FDA approval in the next few months. The results of a recent clinical trial combining LuPSMA with pembrolizumab showed significant promise, with 73% of patients experiencing at least a 50% decline in PSA, and some patients having ongoing complete responses.

^{177}Lu-PSMA-617 (LuPSMA) is a groundbreaking new "seek and destroy" therapy that delivers a radioactive molecule to prostate cancer cells. It significantly improves overall survival in patients with metastatic castration-resistant prostate cancer (mCRPC). However, patients treated with LuPSMA eventually progress, and further optimization is needed. Radiation therapies are thought to cause cancer cells to die in a way that alerts the immune system, and thus may synergize with immunotherapy.

Dr. Sandhu and team led the PRINCE trial to test the combination of LuPSMA with the immunotherapy drug pembrolizumab in 37 patients with mCRPC. Results were encouraging, with 73% of patients seeing their PSA drop by at least 50%. At 24 weeks, 65% of patients had radiographic progression-free survival (rPFS; no worsening of disease on scans). Some patients have had deep and durable responses: For instance, one case was presented in which an 81-year old man experienced a complete response lasting over 60 weeks. Side effects were consistent with those observed for LuPSMA and pembrolizumab alone.

Further studies are needed to define the impact of adding pembrolizumab to LuPSMA on rPFS and overall survival.

Harnessing Immune Cells to Kill Prostate Cancer

Oliver Sartor, MD

Tulane University

What this means for patients: Bi-specific antibodies are a promising experimental class of treatments for advanced prostate cancer that leverage the body's immune system to kill tumor cells. Early-phase clinical trials show efficacy for several different bi-specific antibodies. Future studies will test new agents and address mechanisms of resistance.

(Continued on page 7)

There is a crucial need for effective treatments for metastatic castration-resistant prostate cancer (mCRPC). One option involves immunotherapy, helping the body's T cells to recognize, bind to, and kill cancer cells. Bi-specific antibodies are specially-designed proteins that have two (hence the "bi") parts and can bind to T-cells and tumor cells simultaneously. When these treatments are infused into the patient, they find their way to the tumor, bringing the T cells with them.

As one example, AMG 160 is a bi-specific antibody that binds to prostate-specific membrane antigen (PSMA) with one of its "arms" and T-cells with the other. In a phase 1 study, nearly 70% of patients had a reduction in PSA. Certain precautions are taken to lessen side effects associated with stimulating the immune system. AMG 160 is being tested in combination with other medicines, and a number of other therapies in this class are in early-stage clinical development for the treatment of prostate cancer.

Using VA Prostate Cancer Data to Improve Clinical Trials

Tito Fojo, MD, PhD

Columbia University and the James J. Peters VAMC

What this means for patients: Dr. Fojo and colleagues have developed a new method called "g" to calculate tumor growth rate. g strongly predicts overall survival, the current "gold standard" outcome in clinical trials. g may eventually be used in several ways to accelerate trials and the development of new treatments.

Currently, the criteria for measuring disease response versus progression in prostate cancer is based on changes in tumors on scans. PSA responses are also used, but are not considered valid by the FDA to determine the efficacy of new treatments. Dr. Fojo and colleagues have developed a novel method to calculate tumor regression and growth that is more accurate and informative than standard methods.

This new approach, called "*g*," is calculated from PSA levels over time. The research team found that g strongly predicts overall survival, and thus may act as a "surrogate biomarker" for making treatment decisions and evaluating the efficacy of a new treatment. (In other words, *g* may provide information earlier about how well a treatment works, rather than waiting many years for survival data.) They also evaluated the use of *g* as a marker in a large study of Veterans who were switched from abiraterone to enzalutamide or vice versa. How to identify which patients should remain on a therapy vs. switch to another is an important question.

Using existing data, *g* can be used to reduce the size of or even eliminate control arms. *g* could also be used to inform decisions about new treatments under development, and make decisions with small numbers of patients, including those with rare cancers or rare mutations. The FDA has requested further studies to evaluate *g* for use in clinical trials.

Prostate Cancer Disparities: What We Know, and What We Can Do

Brandon Mahal, MD

University of Miami

What this means for patients: Prostate cancer disparities result in large part from unequal access to care. Additional research on biology and genetic factors remains to be done. Solutions must be multi-pronged, including: increasing access to insurance and clinical trials, and actively engaging diverse communities.

African Americans are over 75% more likely than Caucasians to be diagnosed with prostate cancer, and more than twice as likely to die from it. We know that genetics plays some role, but the impact of social and economic inequalities is better defined. One such factor is medical insurance: Mahal and col-

leagues have reported that among uninsured men with prostate cancer, Black men were much more likely to go untreated (28%) vs. Caucasian men (16%). Knowing about gene mutations in a tumor can help save lives, but research studies include relatively fewer people of non-European ancestry. Moreover, Black men tend to get this type of tumor testing later in their treatment course.

Solutions to disparities requires research in diverse populations, and outreach programs to bring care delivery and cutting-edge science to diverse communities. Patients and communities must be engaged as research partners rather than subjects. These approaches should incorporate transparency, education, acknowledgment of the history of racism, and a diverse oncology workforce.

icr.ac.uk

The future of prostate cancer research: what could the next decade bring?

About 1 in 8 men will get prostate cancer at some point in their life. This makes prostate cancer the most common cancer in men, and the second most common cancer overall in the UK. Over 50,000 men are diagnosed with prostate cancer in the UK every year – that's more than 100 each day.

Ongoing prostate cancer research is looking at new treatment and early detection approaches, such as genetic screening, PSMA-targeting drugs and new targeted therapies, including precision medicines like PARP inhibitors and immunotherapies.

The ICR's scientists, including Professor Ros Eeles, Professor Johann de Bono and Professor Nick James, are advancing our understanding of prostate cancer and how to treat it – so that many more men can live longer, better lives in the next decade.

Targeted screening based on individuals' genetic profiles

As our understanding of the genetics behind prostate cancer expands, it's possible that simple tests could reveal someone's risk of prostate cancer, meaning those at highest risk could benefit from more frequent screening.

Professor Ros Eeles has been studying prostate cancer genetics at the ICR for more than 25 years. She has led research identifying more than two thirds of the currently known genetic variants that increase prostate cancer risk – and could identify many more in the next decade.

"One of the main research areas undergoing a revolution in cancer research is the use of genetic discoveries to group and separate populations into different levels of risk, so that we can target early detection to those men that need it the most," she said.

At the ICR, Professor Eeles is leading studies like GENPROS, an international study following men with changes in genes such as BRCA1, BRCA2, MMR or HOXB13, and following their prostate cancer diagnosis and treatment. The aim is to better understand how well treatments work in these men at higher risk.

Prostate cancers can often grow too slowly to threaten a man's life. For this reason, many men who have early disease and do not carry a mutation linked to cancer would normally just be watched closely by clinicians, as the disease is unlikely to progress further.

What Professor Eeles and her team are trying to figure out as part of GENPROS is: should we use the same 'active surveillance approach' with men who carry certain mutations, such as BRCA2, for example?

Along with GENPROS, Professor Eeles is also leading PROFILE and IMPACT, two other studies investigating the most appropriate screening and management of prostate cancer in different groups of men at higher risk.

Improving diagnosis through liquid biopsies

"Once we know who is more likely to benefit from screening, we can work to achieve early diagnosis. This is where a second revolutionary area of research becomes important: developing and using new types of diagnostic techniques. For example, liquid biopsies – simple blood tests aiming to identify changes specific to the tumour which can direct the clinician as to where they should try new targeted treatments," says Professor Eeles.

Liquid biopsies could transform clinical practice in the future, as they enable a new, more personalised approach to cancer treatment. Instead of using conventional tissue biopsies, which involve surgically removing a piece of the tumour and are invasive and painful, to analyse tumour DNA, researchers can use blood tests that pick up tumour DNA circulating in the bloodstream.

Last year, Professor Johann de Bono and his team used liquid biopsies to predict how well men with advanced prostate cancer responded to treatment with abiraterone with or without ipatasertib. Their research suggested these simple blood tests could replace some of the existing methods used to characterise and track the disease in the clinic.

When they analysed cancer DNA from the blood tests, researchers found specific genetic changes associated with drug resistance – which indicate that men are at risk of early relapse.

"These simple blood tests could help us track how cancer changes and stops responding to treatment. We are already using them as part of clinical trials and they are likely to eventually become part of routine care. Liquid biopsies are minimally invasive, cost-effective and can be performed often and with ease. Tracking prostate cancer with a blood test instead of a painful surgical biopsy could significantly improve patients' quality of life," said Professor Johann de Bono.

Help us continue to find new ways to defeat prostate cancer – and improve the chance of survival for men with this disease. Please make a donation today.

Delivering a radioactive payload directly to cancer cells

Professor Johann De Bono has also been working on research involving a new 'search-and-destroy' medicine known as PSMA therapy. The treatment acts like a guided missile, consisting of a radioactive particle that can be delivered directly to cancer cells.

The treatment, sometimes known as Lutetium-177 PSMA, uses a 'homing device' to seek out cancers by detecting the presence of a target molecule called prostate-specific membrane antigen (PSMA) on the surface of cancer cells. Once in contact, it delivers a radioactive payload to kill them.

Professor De Bono's team found that the treatment's PSMA target is present at higher levels on the surface of cancer cells in some patients than others, making it possible that a genetic test could pick out men who are most likely to benefit from the therapy.

This year a phase III trial called VISION, involving Professor Johann De Bono, showed for the first time that the therapy is effective and can keep patients with advanced prostate cancer alive and healthy for longer.

Around a third to a half of the 10,000 men a year diagnosed with advanced prostate cancer have tumours with high levels of PSMA and could therefore benefit from the treatment. For this reason, PSMA therapy, which was approved by the U.S. Food and Drug Administration (FDA) earlier this year, could be a game-changer in years to come.

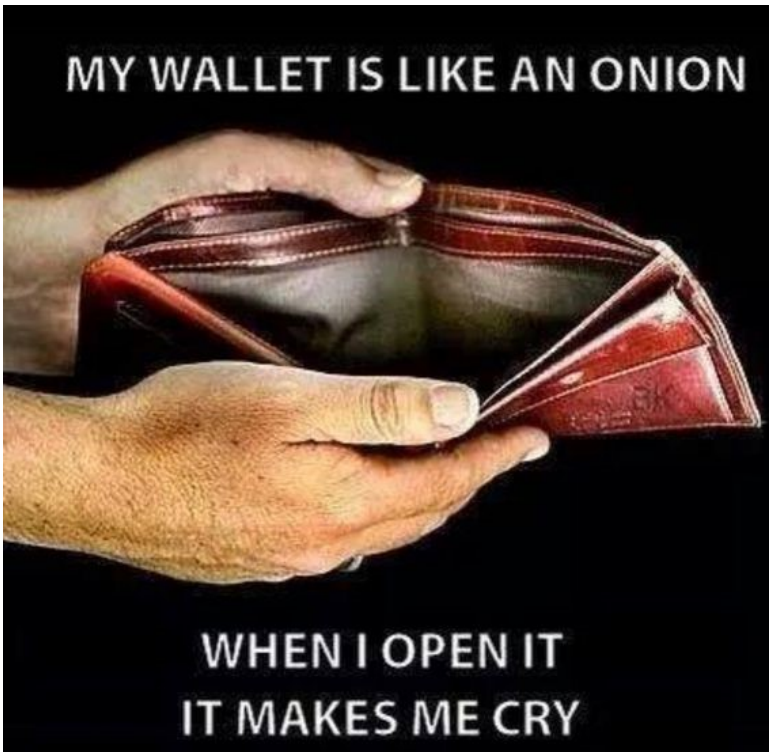
NETWORKING

Please help us in our outreach efforts. Our speakers bureau consisting of Gene Van Vleet is available to speak to organizations of which you might be a member. Contact Gene 619-890-8447 or gene@ipcsg.org to coordinate.

Member John Tassi is the webmaster of our website and welcomes any suggestions to make our website simple and easy to navigate. Check out the Personal Experiences page and send us your story. Go to: https://ipcsg.org/personal-experience

Our brochure provides the group philosophy and explains our goals. Copies may be obtained by mail or email on request. Please pass them along to friends and contacts.

FINANCES



We want to thank those of you who have made special donations to IPCSG. Remember that your gifts are tax deductible because we are a 501(c)(3) non-profit organization.

We again are reminding our members and friends to consider giving a large financial contribution to the IPCSG. This can include estate giving as well as giving in memory of a loved one. You can also have a distribution from your IRA made to our account. We need your support. We will, in turn, make contributions from our group to Prostate Cancer researchers and other groups as appropriate for a non-profit organization. Our group ID number is 54-2141691. Corporate donors are welcome!

While our monthly meetings are suspended, we still have continuing needs, but no monthly collection. If you have the internet you can contribute easily by going to our website, http://ipcsg.org and clicking on "Donate" Follow the instructions on that page. OR just mail a check to: IPCSG, P. O. Box 420142, San Diego CA 92142

Targeted drugs that are kinder to patients

Increasingly, we are moving away from a 'one-size-fits-all' approach to cancer care and we are getting better at tailoring treatment to individuals.

The benefit of targeted treatments is that they involve fewer side effects and can help prostate cancer patients live longer but also with a better quality of life.

In the next decade, we are hoping to increase access to targeted treatments that already exist, bringing them to more patients, and we are also hoping to discover and develop new ones.

Abiraterone, a targeted hormone therapy discovered at the ICR and developed in partnership with our partner hospital The Royal Marsden has already given hundreds of thousands of men around the world extra years of life without the side effects of other treatments.

Another precision drug, olaparib, is known for its use in breast and ovarian cancer, but Professor Johann de Bono has led trials showing that olaparib can be effective in men with prostate cancer who have tumours with mutations in specific genes involved in DNA damage repair, such as BRCA1 and BRCA2. It is now available in Scotland as a treatment for some men with prostate cancer.

Better clinical trials with adaptive, smarter designs

It is thanks to well-conducted clinical trials that new cutting edge drugs eventually become available to patients.

STAMPEDE, led by Professor Nick James, is an innovative multi-arm multi-stage (MAMS) trial which also helped change the standard of care for men with advanced prostate cancer. Three of the treatments tested have shown substantially improved survival: abiraterone, docetaxel chemotherapy and prostate radiotherapy in men with disease that has spread at diagnosis.

"When we started the STAMPEDE trial back in 2005, the survival of advanced prostate cancer that had spread to other parts of the body was around three and a half years, on average. Now, it's around seven to ten years – and abiraterone and the other advances from the STAMPEDE trial can claim a lot of the credit for that," said Professor James

STAMPEDE is an adaptive clinical trial – meaning researchers can add in new treatments to the trial and drop ineffective treatments early. In other words, MAMS trials help us answer multiple research questions simultaneously and compare more than one treatment under a single trial protocol – saving money, time and resources, while also generating evidence more quickly and accelerating the delivery of the next game-changing treatments for patients.

The MAMS approach has famously been used to trial potential COVID-19 treatments in the RECOVERY trial, the world's largest clinical trial into treatments for COVID-19, involving more than 40,000 participants across 185 trial sites in the UK.

"Rather than waiting to set up a new trial to test a new treatment, you can just add a new treatment arm to a trial that is already ongoing. Additionally, recruitment to a trial takes a long time to build up, but by adding a new arm to an existing trial, recruitment becomes less of an issue as the set up process has already happened," said Professor James.

"As STAMPEDE progresses, we've been adding new comparisons to the trial, which should help us answer even more questions, allowing us to figure out what the best way of treating men with newly diagnosed advanced prostate cancer is, faster. So far, STAMPEDE has tested ten different treatment combinations, with three more new ones in set up."

Training the immune system to fight cancer

The immune system is able to kills cells that are harming the body, including cancer cells. However, cancer can often turn off the body's natural 'anti-cancer immune responses'. One way in which our scientists are trying to defeat cancer is by reawakening the immune system, encouraging immune cells to attack cancer cells.

Immunotherapy is a type of treatment that has been very effective in other cancers, including skin cancer, but we are just beginning to make it work for men with prostate cancer.

However, investigating the immune response in prostate cancer is already starting to show promise. Professor Johann de Bono has been working to understand and target a protein known as CD38, displayed on the surface of immune cells. He will soon be leading a clinical trial in this area, which is a first in prostate cancer – looking at drugs which target CD38, which could hold promise against prostate cancer by reawakening the anti-cancer immune response and fighting cancer's 'cloaking' strategy, which allows it to hide from the immune system.

Another trial looking at an immunotherapy showed that some men with advanced prostate cancer with mutations in genes involved in DNA repair, like the BRCA genes, and who had exhausted all other treatment options could live for two years or more on the immunotherapy pembrolizumab.

Manipulating 'gut bugs'

More and more evidence is showing that the microbiome – the community of microorganisms living in and on us, which are essential to our development and immunity – plays a role in many diseases, including prostate cancer.

Recently, Professor de Bono and his team found that common gut bacteria can become 'hormone factories' and sustain prostate cancer's growth, progression and resistance to hormone therapy – opening up a whole new research avenue.

In future we might see bacterial 'fingerprints' used in the clinic to pick out patients at high risk of developing resistance to treatment. These patients could then benefit from strategies to manipulate their microbiome – for example, men could undergo faecal transplants to alter their intestinal microbiota, reducing the number of certain potentially harmful bacterial strains.

Ultimately, researchers hope to come up with a yoghurt drink enriched with bacteria that could also switch the microbiome to a more favourable profile and avoid or delay resistance to hormone treatments.

Cutting edge radiotherapy

There have also been many advances in the field of radiotherapy, including new courses of radiotherapy, known as 'hypofractionated radiotherapy', delivering higher doses of radiotherapy in fewer sessions. This supports a shorter treatment plan that allows men to finish treatment sooner – reducing the number of trips to hospital without negatively affecting men's quality of life in the long term.

Another recent advance is the MR Linac, which combines two technologies — an MRI scanner and a linear accelerator. This technology, which is currently being trialled by researchers at the ICR and The Royal Marsden, allows radiographers and clinicians to precisely locate tumours, tailor the shape of X-ray beams in real time, and accurately deliver doses of radiation even to moving tumours. This is particularly important for cancers that can move during radiotherapy, or between scanning and treatment, including prostate cancer.

Innovation still to come

Professor de Bono shared his thoughts on the future:

"The last decade has been historic for prostate cancer research, many advances have been made – we have started to use genetic information to personalise treatment, reduced side effects thanks to targeted therapies and we are just beginning to train the immune system to combat prostate cancer.

"But we're already looking ahead, and there is no doubt that the most innovative years in prostate cancer research history are yet to come."

zerocancer.org

3D imaging method may help doctors better determine prostate cancer aggressiveness | University of Washington Medicine | ZERO - The End of Prostate Cancer

Prostate cancer is the most common cancer for men and, for men in the United States, it's the second leading cause of death.

Some prostate cancers might be slow-growing and can be monitored over time whereas others need to be treated right away. To determine how aggressive someone's cancer is, doctors look for abnormalities in slices of biopsied tissue on a slide. But this 2D method makes it hard to properly diagnose borderline cases.

Now a team led by the University of Washington has developed a new, non-destructive method that images entire 3D biopsies instead of just a slice. In a proof-of-principle experiment, the researchers imaged 300 3D biopsies taken from 50 patients — six biopsies per patient — and had a computer use 3D and 2D results to predict the likelihood that a patient had aggressive cancer. The 3D features made it easier for the computer to identify the cases that were more likely to recur within five years.

Read the full article here.

zerocancer.org

Inherited mutation linked to aggressive prostate cancer | University of Washington Medicine | ZERO - The End of Prostate Cancer

Men who inherit mutations in a gene called TP53 have a high risk of developing aggressive prostate cancer, a multicenter research team in the United States has found. The findings were reported in the journal European Urology. Researchers from more than a dozen institutions across the United States collaborated on the study. Dr. Kara N. Maxwell, assistant professor of medicine at the Perelman School of Medicine at the University of Pennsylvania is the paper's lead author. The TP53 gene instructs cells to make tumor protein 53. This protein detects damaged DNA and determines if the DNA can be repaired. If it can, the protein initiates the DNA-repair process. If it cannot, the protein triggers a process that causes the cell to self-destruct, preventing it from replicating with damaged–and potentially cancer-causing–DNA.

Read the full article here.

source: *Leila Gray - University of Washington Medicine*

zerocancer.org

Prostate cancer organoids pave way towards precision oncology | Drug Target Review | ZERO - The End of Prostate Cancer

Scientists develop organoid models of neuroendocrine prostate cancer to study EZH2 inhibitors and reveal a potential new target.

Researchers at the Georgia Institute of Technology, US, have developed research tools that shed new light on a currently untreatable form of prostate cancer, opening a pathway that may lead to novel therapeutics.

Read the full article here.

source: *Anne Begley - Drug Target Review*

zerocancer.org

New strategy against treatment-resistant prostate cancer identified | Washington University School of Medicine in St. Louis | ZERO - The End of Prostate Cancer

A study from Washington University School of Medicine in St. Louis has identified an RNA molecule that suppresses prostate tumors. According to the research — conducted in mice implanted with human prostate tumor samples — restoring this so-called long noncoding RNA could be a new strategy to treat prostate cancer that has developed resistance to hormonal therapies.

Read the full article here.

source: *Julia Evangelous Strait - Washington University School of Medicine in St. Louis*

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Androgen receptor signaling inhibitors: post-chemotherapy, pre-chemotherapy and now in castration-sensitive prostate cancer

Abstract

Based on pioneering work by Huggins, Hodges and others, hormonal therapies have been established as an effective approach for advanced prostate cancer (PC) for the past eight decades. However, it quickly became evident that androgen deprivation therapy (ADT) via surgical or medical castration accomplishes inadequate inhibition of the androgen receptor (AR) axis, with clinical resistance inevitably emerging due to adrenal and intratumoral sources of androgens and other mechanisms. Early efforts to augment ADT by adding adrenal-targeting agents (aminoglutethimide, ketoconazole) or AR antagonists (flutamide, bicalutamide, nilutamide, cyproterone) failed to achieve overall survival (OS) benefits, although they did exhibit some evidence of limited clinical activity. More recently, four new androgen receptor signaling inhibitors (ARSIs) successfully entered clinical practice. Specifically, the CYP17 inhibitor abiraterone acetate and the second generation AR antagonists (enzalutamide, apalutamide and darolutamide) achieved OS benefits for PC patients, confirmed the importance of reactivated AR signaling in castration-resistant PC and validated important concepts that had been proposed in the field several decades ago but had remained so far unproven, including adrenal-targeted therapy and combined androgen blockade. The past decade has seen steady advances toward more comprehensive AR axis targeting. Now the question is raised whether we have accomplished the maximum AR axis inhibition possible or there is still room for improvement. This review, marking the 80-year anniversary of ADT and 10-year anniversary of successful ARSIs, examines their current clinical use and discusses future directions, in particular combination regimens, to maximize their efficacy, delay emergence of resistance and improve patient outcomes.

Introductory concepts and historical perspective

The pioneering work of Huggins & Hodges (1941), that we are celebrating in this issue of ERC (Zoubeidi & Ghosh 2021), not only set the framework for the hormonal treatment of advanced prostate cancer

(PC), but also was one of the first successful 'targeted' therapies for cancer in general. While most patients with advanced PC benefited from castration (androgen deprivation therapy (ADT)), resistance emerged quickly in most cases (within 1–3 years, in general). This led to a series of important questions:

- What are the mechanisms of resistance to first-line ADT?
- Can a more comprehensive approach targeting all sources of androgenic stimulation delay emergence of resistance to ADT?
- What is the best timing of the treatment intensification? Is earlier use of intensified ADT more effective? How early is early enough?
- If deeper AR axis inhibition can accomplish better clinical outcomes, then how deep AR inhibition is enough to maximize the clinical benefit?
- What are the mechanisms of resistance to the newer androgen receptor signaling inhibitors (ARSIs) and what is the next step in their use for improving outcomes for our patients?

Historically, the term ADT has been and still is used to refer only to suppression of production of testosterone by the testicular Leydig cells via surgical castration (bilateral orchiectomy) or medical castration (targeting the hypothalamic-testicular axis with GnRH analogs) (Mitsiades *et al.* 2011, Mitsiades 2013, Relugolix FDA Package Insert 2020). For the purposes of this article, we will refer to this regimen as 'standard ADT' (sADT). In PC patients receiving sADT, a circulating (peripheral) testosterone (circT) level of <50 ng/dL has been and still is considered adequate testosterone suppression (Mitsiades *et al.* 2011, Relugolix FDA Package Insert 2020). When clinical progression would, inevitably, occur while maintaining circT <50 ng/dL, it would be and still is defined as castration-resistant PC (CRPC).

However, several studies have reported that accomplishing stricter (lower) circT thresholds (<30 ng/dL, <25 ng/dL, or even <20 ng/dL) was associated with even better clinical outcomes (Bertaglia *et al.* 2013, Wang *et al.* 2017, Ozyigit *et al.* 2019). The same was shown when circT was analyzed as a continuous variable (Perachino *et al.* 2010). Collectively, these results suggest that our ideal therapeutic goal should be to lower androgenic stimulation to as low as safely achievable. In further support, several mechanisms of PC cell resistance to ADT involve hypersensitization of the PC cells to (low levels of residual) androgens, for example, due to overexpression of AR mRNA and protein, frequently due to amplification at the AR gene locus (Visakorpi *et al.* 1995, Mitsiades *et al.* 2011, 2012, Mitsiades 2013, Quigley *et al.* 2018, Takeda *et al.* 2018, Viswanathan *et al.* 2018). Therefore, it is important to simultaneously suppress testosterone levels to the lowest level achievable and that goal requires comprehensive targeting of all sources of androgenic stimulation: gonadal, adrenal and intratumoral steroidogenesis (Mitsiades 2013).

In healthy adult men, >95% of circT is of gonadal origin. The rest is synthesized either in the adrenals or in other, peripheral tissues (including the prostate gland and PC tissues). In situ ('intracrine') steroidogenesis can be de novo (with all enzymatic steps from cholesterol to testosterone and DHT happening in some PC tissues) or by conversion of weaker androgen precursors of adrenal origin: DHEA and androstenedione. DHEA, in the form of DHEA-sulfate, is the steroid with the highest circulating concentration in humans and thus, is an abundantly available precursor. Upon initiation of ADT, these extra-gonadal sources of androgens become very important for residual AR activation that allows for the survival of the PC cells, until other mechanisms of resistance make the cells completely resistant.

The importance of intratumoral steroid metabolism is highlighted by strong evidence that even well suppressed circT levels do not guarantee complete depletion of intratumoral androgens (Montgomery *et al.* 2008). In fact, intratumoral androgens and AR-dependent gene expression drop by a much lower degree compared to the degree of suppression of serum androgens after ADT (Mostaghel *et al.* 2007). Several steroidogenic enzymes are expressed in the prostate gland and in PC tissue (Montgomery *et al.* 2008) and

can even be upregulated by androgen withdrawal (Mitsiades *et al.* 2012). For example, the mRNA levels of AKR1C3, an enzyme that can convert androstenedione to testosterone, are upregulated in PC cells within a few hours of androgen withdrawal (Mitsiades *et al.* 2012). Therefore, androgen deprivation triggers an acute adaptation feedback loop that enhances the ability of the PC cell to metabolize adrenal precursors into testosterone and DHT, thus sustaining tissue androgen levels and AR stimulation.

In essence, the term ADT has been used historically to describe, under the form of sADT, a now outdated hormonal therapy regimen that was inadequate androgen deprivation at the cellular level within the PC microenvironment, as intratumoral androgens actually persisted under these conditions (Montgomery *et al.* 2008). The PC field has since moved significantly forward with the addition of ARSIs to the ADT backbone. For the purposes of this review, we will focus our discussion on the newer, more effective ARSIs: specifically, the CYP17 inhibitor abiraterone and the second generation AR ligand-binding domain (LBD) antagonists (antiandrogens) enzalutamide, apalutamide and darolutamide, as these are the agents that have entered the market in recent years. Several names have been used to describe these regimens such as 'Intense Androgen Deprivation', 'intensified ADT', 'Comprehensive AR axis Targeting', 'augmented ADT', etc. The clinical successes of these combination regimens have led to substantial clinical benefits for PC patients, while validating the old hypotheses in the field about concurrently targeting all sources of androgenic stimulation, and redefining the use of ADT.

Can a more comprehensive approach targeting all sources of androgenic stimulation delay emergence of resistance to ADT?

Historical review of older efforts

Earlier efforts to target the androgenic contribution of extra-gonadal sources in CRPC go back several decades, with some clinical successes (some well-documented response rates and PFS benefits), but never established a definitive prolongation of overall survival (OS) via Phase III randomized controlled trials (RCTs) in the pre-abiraterone/enzalutamide era. As a result, while intriguing and sometimes widely used, these early approaches failed to gain level 1 evidence in their support.

Earlier adrenal-targeted approaches

Suppression of adrenal steroid production via surgical adrenalectomy or use of exogenous glucocorticoids in the past yielded some clinical successes (Storlie *et al.* 1995, Sartor *et al.* 1998, Kantoff *et al.* 1999, Nishimura *et al.* 2000, Fossa *et al.* 2001, Koutsilieris *et al.* 2001, Saika *et al.* 2001, Berry *et al.* 2002, Morioka *et al.* 2002, Tannock *et al.* 2004, Mitsiades *et al.* 2011) that have historical significance as proof-of-principle for the role of adrenal steroids in CRPC. Similarly, chemical adrenalectomy via the anticonvulsant aminoglutethimide or the antifungal ketoconazole (both are also non-specific inhibitors of several cytochrome P450 enzymes, including those involved in steroidogenesis) accomplished PSA responses in some patients (Small *et al.* 1997, Kruit *et al.* 2004, Peer *et al.* 2014) but the lack of an OS benefit in Phase III RCTs together with their significant toxicity (nausea, fatigue, edema, hepatotoxicity, neurotoxicity, rash, anorexia) and multiple interactions with other P450 substrate drugs prevented their formal FDA approval for this indication (Abratt *et al.* 2004, Small *et al.* 2004, Mitsiades *et al.* 2011). However ketoconazole was widely used (off label) in CRPC and did serve as a forerunner of CYP17 inhibitors such as abiraterone.

Earlier anti-androgens and 'combined androgen blockade'

Another approach to target residual AR activation in ADT-treated patients is to directly displace the androgenic ligand from the AR, via a competitive ligand-binding domain (LBD) inhibitor (also called an anti-

androgen). The first generation of such agents included flutamide, bicalutamide, nilutamide and cyproterone acetate (Chen *et al.* 2009, Mitsiades *et al.* 2011), which achieved PSA responses in some CRPC patients and gained popularity in this setting, but never definitively established an OS benefit for CRPC patients (Mitsiades *et al.* 2011). Moreover, they were extensively tested in the metastatic castration-sensitive PC (mCSPC) setting in combination with sADT under the concept of 'maximal' or 'combined androgen blockade' (Labrie *et al.* 1985), with a miniscule, at best, survival benefit (Klotz 2008, Mitsiades *et al.* 2011). One possible explanation for that overall failure was that these agents were not adequately potent AR antagonists, but rather partial agonists, and also prone to 'antagonist-to-agonist' conversion (Culig *et al.* 1999), an intellectually interesting (yet clinically detrimental) clinical phenomenon where the very hormonal treatment used was actually fueling the growth of the PC cells. This was first noticed due to clinical responses encountered in a subset of anti-androgen-treated CRPC patients (15–30%) after withdrawal of the anti-androgen (Kelly & Scher 1993, Leone *et al.* 2018) and was attributed to dysregulation of the AR complex via various types of somatically-acquired events, including:

- AR LBD gain-of-function mutations such as T878A, W742C/L, H875Y and L702H (originally reported as T877A, W741C/L, H874Y and L701H, respectively) and others (Taplin *et al.* 1995, Marcelli *et al.* 2000, Hara *et al.* 2003, Yoshida *et al.* 2005, Chen *et al.* 2009, Gottlieb *et al.* 2012, Leone *et al.* 2018). (Note: A change in the current reference sequence of the androgen receptor cDNA (Gottlieb *et al.* 2012, McEwan & Brinkmann 2016) led to a +2 shift in amino acid numbering between residues 78 and 449 and to a +1 shift between residues 472 and 919 compared with the previously used, original reference sequence (M20132.1)).
- AR mRNA and protein overexpression, attributed to numerous mechanisms such as copy number gains of the *AR* coding sequence and/or of an upstream enhancer, as well as changes in epigenetic and microRNA regulatory loops (Visakorpi *et al.* 1995, Chen *et al.* 2004, Mitsiades *et al.* 2012, Mitsiades 2013, He *et al.* 2014, Coarfa *et al.* 2016, Quigley *et al.* 2018, Takeda *et al.* 2018, Viswanathan *et al.* 2018).
- Altered expression and recruitment of AR coactivators. for example, the p160 steroid receptor coactivators (SRCs) SRC-1, SRC-2 and SRC-3, also known as Nuclear Coactivators NCoA1, NCoA2 and NCoA3, are found to be overexpressed in advanced PC and, in particular, CRPC (Gregory *et al.* 2001, Agoulnik *et al.* 2005, 2006, Zhou *et al.* 2005, Taylor *et al.* 2010).

Overall, the first generation anti-androgens had suboptimal clinical performance with inadequate AR inhibitory activity and, while FDA-approved for use in PC, never achieved documented OS benefits in CRPC or as 'combined androgen blockade' in CSPC.

Better drugs validate old concepts

So were the concepts of adrenal-targeted therapy, anti-androgen use and combined androgen blockade flawed? No – they were just impeded by the availability of only suboptimal first generation agents with clear PD deficiencies. The field has significantly advanced due to emergence of:

More selective enzymatic inhibitors of androgen synthesis that are better-tolerated and more effective. Specifically, the CYP17 inhibitor abiraterone (CB7598) is a potent inhibitor of androgen biosynthesis. CYP17 (steroid 17-alpha-hydroxylase/17,20 lyase; gene name CYP17A1) has two enzymatic activities: 17-hydroxylase (necessary for the synthesis of both androgens and glucocorticoids) and 17,20 lyase (necessary for the synthesis of androgens only). Abiraterone inhibits both activities. Consequently, in the absence of glucocorticoid supplementation, abiraterone raises serum ACTH levels and increases adrenal conversion of cholesterol to pregnenolone, progesterone and mineralocorticoids (which do not require CYP17). The mineralocorticoid excess can cause

fluid retention, edema, hypertension and hypokalemia, while progesterone can function as a non-canonical AR agonist (especially in the case of LBD-mutant AR) and as a canonical PR agonist, both of which can drive resistance to abiraterone (Cai *et al.* 2011, Chen *et al.* 2015*a*). For that reason, abiraterone-treated patients are also given replacement doses of prednisone or prednisolone (P), in order to decrease the risk of mineralocorticoid side-effects and to enhance anticancer activity (Danila *et al.* 2010, Bedoya & Mitsiades 2013).

Because abiraterone has poor oral absorption and is susceptible to hydrolysis by esterases, abiraterone acetate (AA, CB7630) was developed as an orally bioavailable, esterase-resistant prodrug (Ryan & Cheng 2013). Abiraterone is at least 10-times more potent as an inhibitor of CYP17 than ketoconazole (Haidar *et al.* 2003) and more selective, hence better tolerated. Not surprisingly, several studies have shown that AA+P is more effective than ketoconazole (Peer *et al.* 2014) and still somewhat effective even in ketoconazole-resistant CRPC (Danila *et al.* 2010, Kim *et al.* 2014). It deserves to be noted that there are additional proposed mechanisms of action for the anticancer activity of abiraterone, including direct antagonism of AR (Richards *et al.* 2012, Norris *et al.* 2017).

Second generation orally bioavailable anti-androgens (enzalutamide, apalutamide and darolutamide) with improved PD properties: As mentioned above, flutamide, bicalutamide, nilutamide and cyproterone are prone to 'antagonist-to-agonist' conversion in PC cells due to overexpression of AR or its coactivators, somatic AR mutations, or other mechanisms (Mitsiades *et al.* 2011). For that reason, a library of nonsteroidal anti-androgens were rationally optimized for inhibition of AR transcriptional activity based on the AR crystal structure and were screened to select for lack of agonistic activity (Tran *et al.* 2009). The lead compound MDV3100 (enzalutamide) and the related ARN-509 (apalutamide) were reported to bind AR with higher affinity than bicalutamide, prevent its nuclear translocation and DNA binding, and have anticancer activity in preclinical *in vitro* and *in vivo* models without incurring agonistic activity (Tran *et al.* 2009, Scher *et al.* 2010, Clegg *et al.* 2012, Rathkopf & Scher 2013). The phase 1–2 study of enzalutamide documented antitumor effects at all doses used (Scher *et al.* 2010) and set the stage for its rapid entry into Phase III testing and FDA approval. In agreement with its higher inhibitory activity and lower propensity for 'antagonist-to-agonist' conversion, anti-androgen withdrawal responses after discontinuing enzalutamide, although possible, are significantly less common and less durable than what was encountered with first generation anti-androgens (Phillips 2014, Schrader *et al.* 2014, von Klot *et al.* 2014*a*, von Klot *et al.* 2014*b*, Rodriguez-Vida *et al.* 2015, Poole *et al.* 2017, Leone *et al.* 2018). Still, the AR F877L (previously F876L) mutation has been reported to confer an antagonist-to-agonist switch to enzalutamide and apalutamide that drives resistance (Balbas *et al.* 2013, Joseph *et al.* 2013, Korpal *et al.* 2013).

More recently, darolutamide (ODM-201, BAY-1841788), an AR antagonist with a distinct chemical structure, was introduced to the clinic and approved for the treatment of patients with non-metastatic castration-resistant PC (nmCRPC) (Fizazi *et al.* 2019, 2020). Some preclinical experiments indicate that darolutamide is active against LBD-mutant ARs that confer resistance to enzalutamide and apalutamide such as AR F877L (previously F876L) and W742C/L (previously W741C/L), but that remains to be confirmed in the clinic (Sugawara *et al.* 2019). Darolutamide is reported to exhibit negligible blood-brain barrier (BRB) penetration, which may explain why, contrary to enzalutamide, its trials show that it does not significantly increase the risk of seizures, falls, or fractures (Moilanen *et al.* 2015, Shore 2017, Sugawara *et al.* 2019).

Novel ARSIs find their place in PC treatment

Early phase II studies of abiraterone (Danila *et al.* 2010, Reid *et al.* 2010) and enzalutamide (Scher *et al.* 2010) provided proof of principle that these are active agents in CRPC and established that the term 'androgen-independent' PC, in the way that it had been used until those studies, was actually a misnomer. The same Phase II studies provided evidence that abiraterone and enzalutamide are active even in CRPC patients previously treated with older agents such as ketoconazole or bicalutamide, although in some cases with somewhat lower response rate (Danila *et al.* 2010). As a result, subsequent studies generally excluded patients with prior exposure to any ARSI of any generation in order to avoid cross-resistance. In these Phase III studies, both abiraterone and enzalutamide had substantial OS benefits and PSA response rates in mCRPC patients, both in the post-chemotherapy and pre-chemotherapy settings (Table 1), and that led to their approval, first for chemotherapy-refractory mCRPC and, soon afterwards, for chemotherapy-naïve mCRPC. Subsequent results from Phase III studies established the efficacy of abiraterone and enzalutamide in earlier disease states, namely non-metastatic (M0) CRPC and mCSPC. Apalutamide and darolutamide, which entered clinical development a few years after abiraterone and enzalutamide, were examined directly in these earlier disease states, as their administration to CRPC patients who had already received enzalutamide (or even abiraterone) would likely mask their clinical efficacy. Based on these clinical trials (timeline presented in Table 1), the current status of regulatory approval at the time of this writing (February 2021) is:

Table 1 Timeline of major clinical trials that have led to the approval of ARSIs.

Arsi	Metastatic CRPC (chemotherapy-refractory)	Metastatic CRPC (chemotherapy-naïve)	Non-metastatic (M0) CRPC	Metastatic CSPC	N1M0 and High-risk N0M0 CSPC
Abiraterone	COU-AA-301 (de Bono et al. 2011) OS benefit 3.9 months over the control arm. PSA RR 29%.	COU-AA-302 (Ryan *et al.* 2013, 2015) OS benefit 4.4 months over the control arm. PSA RR 62%.	No Phase III trial data reported yet and no FDA approval in this clinical space, but a phase II single-arm trial showed ≥50% PSA reduction in 86.9% of patients and a ≥90% PSA reduction in 59.8% of patients (Ryan *et al.* 2018).	- LATITUDE[a] (Fizazi *et al.* 2017, 2019) OS benefit was 16.8 months over the control arm. 3-year OS was 66% (vs 49% in the control arm). HR for death was 0.66.	STAMPEDE (arm G)[b] (James *et al.* 2017)

[remainder of table 1 not shown]

- AA+P is approved for the treatment of patients with metastatic castration-resistant PC (mCRPC) and metastatic high-risk castration-sensitive PC (CSPC).
- - Enzalutamide is approved for the treatment of patients with CRPC (irrespective of metastatic or not status) and metastatic CSPC (mCSPC), irrespective of risk stratification.
- - Apalutamide is approved for the treatment of patients with mCSPC, irrespective of risk stratification, and non-metastatic CRPC (nmCRPC).
- - Darolutamide is approved for the treatment of patients with nmCRPC.

Ongoing clinical trials are examining the role of ARSIs in earlier disease states such as enhancing neoadjuvant sADT prior to prostatectomy (e.g. https://clinicaltrials.gov/ct2/show/NCT03080116, https://clinicaltrials.gov/ct2/show/NCT03767244).

Conclusions from the ARSI clinical trials and thoughts on augmenting frontline ADT

- Deeper AR axis inhibition accomplished better outcomes: It is clear that the concepts of adrenal-targeted therapy, anti-androgen use, and combined androgen blockade were correct but were previously impeded by the lack of good pharmacological agents. These newer ARSIs have validated the old concepts because they have superior PD and PK properties. In addition to the overall success of the newer ARSIs (which far eclipses any efficacy the older agents such as first generation anti-androgens and ketoconazole had ever shown), head-to-head comparison trials (TERRAIN (Shore *et al.* 2016), STRIVE (Penson *et al.* 2016)) have also confirmed that enzalutamide is clearly superior to bicalutamide and, consequently, has almost completely replaced it in the clinic (although still included as an option in the National Comprehensive Cancer Network guidelines). Similarly, the use of ketoconazole in PC has essentially been completely replaced by AA+P (although still included as an option in the National Comprehensive Cancer Network guidelines).

- Direct comparison of the absolute clinical benefit between these studies is hindered by the differences between study populations and trial designs, and can only be considered hypothesis-generating. With those caveats in mind, one could notice that *all four ARSIs are biologically active* and no particular pattern of superiority emerges from the results of the studies in Table 1. PSA response rates tend to be slightly numerically higher with enzalutamide than with AA+P, but this does not appear to translate into longer survival benefits. As of February 2021, enzalutamide has the broadest approval for use in all states of CRPC (irrespective of metastatic status and prior chemotherapy use) and metastatic CSPC. The current approval for AA+P covers only metastatic CRPC and metastatic high-risk (as defined by the LATITUDE criteria (Fizazi *et al.* 2017)) CSPC. However, arm G of the STAMPEDE trial (AA+P) also enrolled patients with low-risk metastatic CSPC or lymph-node positive PC or non-metastatic PC receiving ADT. From this heterogeneous study arm, in our clinical practice (N M) we frequently extrapolate and extend, off label, the use of AA+P to intensify ADT used in the low-risk M1 or N1M0 or N0M0 CSPS settings.

- More significantly, it is our opinion that the differences in the approved indications between the four ARSIs in Table 1 simply reflect strategic decisions of the respective manufacturers to prioritize positioning of each drug in certain clinical spaces, rather than actual differences in clinical activity. The approved indications for all ARSIs are very likely to continue expanding in the near future, based on emerging data from ongoing and future clinical trials. For example, AA+P does not (yet) have FDA approval for use in non-metastatic (M0) CRPC, but this is only due to lack of reported Phase III clinical trial data, and it has

actually shown promising Phase II data (Ryan *et al.* 2018). Similarly, apalutamide and darolutamide would be expected to be active in an ARSI-naïve, chemotherapy-refractory metastatic CRPC patient, but such patients should be uncommon now that four ARSIs carry approved indications for much earlier disease states and, therefore, such a clinical trial would be both very difficult to accrue and practically irrelevant for real-world clinical care. Thus, lack of data supporting activity in that clinical space does not mean lack of activity in that space.

Timing of the intensification

The use of ARSIs in pre-chemotherapy mCRPC is not substantially more effective than their use in post-chemotherapy mCRPC (the PSA response rates are numerically higher in the pre-chemotherapy setting, but the OS benefits are not). However, the use of ARSIs in mCSPC or nmCRPC is substantially more effective than use in the mCRPC state. For example, the improvement in median OS upon addition of AA+P to sADT in mCRPC patients is about 4 months (irrespective of prior chemotherapy use), but four times as much in mCSPC patients. Similarly, the improvement in median OS with the addition of enzalutamide to sADT is far more substantial in nmCRPC than in mCRPC patients. That suggests that initiating an ARSI earlier (before establishment of metastatic CRPC or before emergence of clinical metastasis) is associated with substantially better clinical outcomes. Data from the addition of an ARSI to sADT in the nmCSPC state is not yet available, but it would be very interesting to know if the clinical benefits will be even higher in that even earlier disease state.

Why does the combination of an(y) ARSI with sADT work better if started earlier? One possible explanation is that, because several mechanisms of resistance overlap between sADT and ARSIs, implementing more comprehensive AR axis inhibition earlier prevents the emergence of resistant clones (Mitsiades 2013). Several studies examining the significance of the PSA nadir on ADT support this hypothesis. The SWOG Trial 9346 (INT-0162) showed that the absolute PSA value after ADT is a strong independent predictor of survival in mPC (Hussain *et al.* 2006). Specifically, median survival was 13 months for patients with a PSA of more than 4 ng/mL after 7 months of ADT, 44 months for patients with PSA of more than 0.2–4 ng/mL after seven months of ADT, and 75 months for patients with PSA of 0.2 ng/mL or less after seven months of ADT. In a subsequent SWOG study, metastatic PC patients with a suboptimal response to ADT (PSA > 4.0 ng/mL after 6–12 months of ADT) had their hormonal regimen augmented with AA+P. However, only five of 40 participants (13%) patients achieved a PSA level of ≤0.2 ng/mL, while 13 (33%) additional patients achieved a reduction in the PSA level to <4.0 ng/mL but >0.2 ng/mL (Flaig *et al.* 2017). A cumulative PSA response rate of 45% in this small study may not be statistically different from what was seen in COU-AA-302 (Ryan *et al.* 2013, 2015), but overall, this study failed to reach its predefined endpoint, and was considered as evidence that ADT intensification after castration-resistance has emerged in metastatic PC may be too late for optimal efficacy.

Optimal ARSI sequencing and cross-resistance

All major clinical trials that led to the clinical development, registration, and FDA approval of each ARSI (Table 1) excluded patients who had been significantly exposed to any other ARSI (including older generation agents such as ketoconazole, aminoglutethimide, etc.) in order to avoid contamination by cross-resistance. As a result, all ARSIs entered the market based only on data from 'ideal cases' of patients who were naïve to all other ARSIs and without any studies directly comparing ('head-to-head') the activity of different ARSIs or examining cross-resistance between them. As pointed out in the previous section, the informal numerical comparison of the response rates and OS benefits seen in these registration trials (interpreted with caution, as the use of different study populations and trial designs prohibits a formal comparison), do not highlight any particular ARSI as substantially superior to the others (enzalutamide

tends to give numerically higher PSA response rates than abiraterone, but this does not appear to translate into longer survival benefits). Moreover, a prospective study that randomized mCRPC patients to first-line abiraterone (+P) or enzalutamide for a head-to-head comparison found no significant difference between the two ARSIs in time to PSA progression, even though PSA responses were more common in the enzalutamide cohort (Khalaf *et al.* 2019).

After FDA approval of these agents and general use in real-world practice, it became a common experience that the clinical responses to either abiraterone (+P) or enzalutamide as second-line ARSIs after progression on the other agent are, at best, modest (PSA response rates in the range of 2–36%) and not durable (Loriot *et al.* 2013, Noonan *et al.* 2013, Bianchini *et al.* 2014, Azad *et al.* 2015*a*, Attard *et al.* 2018, de Bono *et al.* 2018, Khalaf *et al.* 2019). This cross-resistance between these two classes of ARSIs is not surprising, as several mechanisms can provide resistance to both CYP17 inhibitors and 2nd generation anti-androgens. Such mechanisms include constitutively active AR variants (including ARv7), and treatment-associated NEPC transdifferentiation (see section on 'Mechanisms of resistance to ARSIs'). Nevertheless, crossover from one ARSI to another is used frequently in the clinic, especially as it is more appealing to use another hormonal agent instead of cytotoxic chemotherapy.

In that scenario, the question arises regarding the optimal sequencing of the ARSIs: The same study of mCRPC patients by Khalaf *et al.* found that the abiraterone (+P) → enzalutamide sequence may be associated with longer time to second PSA progression and higher PSA response rates on second-line ARSI therapy compared to the inverse sequence (Khalaf *et al.* 2019). A systematic review and meta-analysis of 10 crossover studies confirmed that the abiraterone (+P) → enzalutamide sequence was significantly associated with better PFS than with the opposite treatment sequence, but the OS barely missed statistical significance (pooled HR: 0.77, 95% CI: 0.59–1.01, $P = 0.055$) (Mori *et al.* 2020). Thus, it is possible that using abiraterone acetate followed by enzalutamide may provide the maximum possible benefit, at least as far as PFS. Other factors that may affect clinical decision making in selecting which ARSI to use first are the adverse event profile of each agent (Table 2) and cost (abiraterone is already generic in the US, while the three second generation anti-androgens are not). The use of biomarkers in this setting remains to be explored. For example, it is plausible but remains to be established whether ARv7-negative status after progression to the first ARSI agent would accurately predict sensitivity to a second ARSI agent.

Table 2—Reported Adverse Events of ARSIs, from Abiraterone FDA Package Insert (2020), Apalutamide FDA Package Insert (2020), Enzalutamide FDA Package Insert (2020), Darolutamide FDA Package Insert (2021).

Abiraterone	Enzalutamide	Apalutamide	Darolutamide
Hypertension, hypokalemia, edema, due to mineralocorticoid excess.	Risk of seizure (0.5% across all patients and 2.2% in those with predisposing factors).	Risk of seizure (0.4% across all patients).	Reportedly not crossing the blood-brain barrier, so it does not significantly increase risk of seizures or falls.
Liver toxicity, fatigue. Need for glucocorticoid replacement (concern for diabetics, etc.).	Posterior reversible encephalopathy syndrome (PRES) Asthenia, musculoskeletal pain and arthralgias. Falls and fractures.	Musculoskeletal pain and arthralgias, decreased neutrophil count. Falls and fractures. Hyperglycemia and hypertriglyceridemia.	Fatigue, decreased neutrophil count, transaminitis, hyperbilirubinemia.
	No need for glucocorticoid replacement (actually, discouraged as it may drive resistance).	No need for glucocorticoid replacement (actually, discouraged as it may drive resistance).	No need for glucocorticoid replacement (actually, discouraged as it may drive resistance).

Again, it should be noted that irrespective of the sequencing of these ARSIs, the response to whichever agent is used as a second-line ARSI is short-lived. In our own clinical practice (N M), after progression on an ARSI, we stratify patients based on severity of symptoms and urgency of the need for a clinical response at that point. We offer the option of a second ARSI agent in sequence after progression on the first ARSI agent only for those CRPC patients who are generally asymptomatic and are not at imminent risk of harm from delaying active therapy. In metastatic CRPC patients who, after progression on the first ARSI agent, are symptomatic or at high risk for a skeletal event, visceral crisis or other major complication, we strongly recommend cytotoxic chemotherapy (taxane). This is supported by the results of the CARD trial, where patients who had progressed on abiraterone or enzalutamide received the other ARSI or cabazitaxel, with cabazitaxel showing superior progression-free survival and overall survival (de Wit *et al.* 2019).

Depth of AR axis inhibition: how much is optimal?

With the (long overdue) success of combining two hormonal agents (sADT+ one ARSI), have we reached the maximum potential benefit or is there room for further improvement in our hormonal regimens for PC? If the addition of an ARSI to sADT improves clinical outcomes (two hormonal agents in combination work better than one), then one could hypothesize that the combination of three hormonal agents (sADT to suppress testicular androgen production + CYP17 inhibitor to suppress adrenal steroidogenesis + anti-androgen to block binding of any escaping/residual androgen to the AR) might target that AR axis more comprehensively, overcoming more putative mechanisms of resistance and might yield even better clinical results. Unfortunately, this has not been the case so far:

Adding the second ARSI after progression to the first ARSI in CRPC patients: The randomized PLATO study examined whether, in the setting of enzalutamide resistance in mCRPC, the addition of AA+P to continuous

enzalutamide use would be superior to switching to AA+P (plus placebo). Unfortunately, there was no difference in PFS between the groups, and the PSA response rates were very low (1% for the combination group that received the two ARSIs concurrently and 2% for the sequential treatment group that switched from enzalutamide to AA+P (Attard *et al.* 2018)).
Combining two ARSIs with ADT in ARSI-naïve CRPC: The phase III trial Alliance A031201 (NCT01949337) examined whether the addition of AA+P to enzalutamide would be superior to enzalutamide monotherapy in men with ARSI-naïve mCRPC. Unfortunately, the study showed no advantage for the combination of the 2 ARSIs over enzalutamide alone. Grade 3–5 adverse events occurred in 55.6% and 68.8% of patients taking enzalutamide and enzalutamide/abiraterone/prednisone, respectively. Treatment discontinuation (12% vs 5%) and patient withdrawal rates (13% vs 5%) were higher in the combination group due to adverse events. Another trial (ACIS) examined a similar concept, using apalutamide instead of enzalutamide. Again, the combination of apalutamide + abiraterone/prednisone did not improve OS compared to abiraterone/prednisone in mCRPC (Rathkopf *et al.* 2021). The combination of enzalutamide with abiraterone and sADT has also been undergoing testing since July 2014 as arm J of the STAMPEDE trial (NCT00268476) (Attard *et al.* 2014).

Using two ARSIs+ADT in the neoadjuvant setting: The neoadjuvant setting allows to rapidly assess the anticancer activity of a systemic therapy, examine possible biomarkers of response, and dissect mechanistic hypotheses. Neoadjuvant systemic therapy is now commonly used in early breast cancer and the achievement of pathologic complete response (pCR) has been proposed as a surrogate endpoint for OS. On the contrary, despite significant efforts, neoadjuvant systemic therapy (including hormonal therapy) is still not considered a standard-of-care approach for localized/locally advanced PCs prior to prostatectomy and was never able to improve disease-free survival (DFS) and overall survival (OS). It is possible that sADT cannot adequately suppress the AR axis inside the PC cells in order to achieve pCR. Indeed, in a randomized phase II trial, the addition of AA+P to ADT resulted in more effective suppression of intraprostatic androgens than ADT alone (Taplin *et al.* 2014). Still, in the same study, even after 24 weeks of neoadjuvant hormonal therapy with ADT+AA+P, the pCR rate was only 10%. For that reason, a follow-up study examined whether the combination of neoadjuvant ADT + enzalutamide + AA+P would be more effective than ADT + enzalutamide for 6 months before radical prostatectomy in men with locally advanced PC (McKay *et al.* 2019). Unfortunately, the pCR rate was only 10 and 8% in the two groups, respectively. In addition, more intense hormonal therapy was not associated with better outcomes as far as surgical margin positivity, extracapsular extension, or seminal vesicle invasion, although it showed a non-statistically significant trend for more minimal residual disease (less than 5 mm). In agreement, in another phase II neoadjuvant study of six months ADT+apalutamide with or without abiraterone in localized high-risk PC, dual ARSI treatment did not result in better outcomes at the time of prostatectomy (Efstathiou *et al.* 2020).

In summary, so far the clinical evidence suggests that combining more than one ARSI with ADT is not beneficial. This may sound counterintuitive at first, and a mechanism to explain it has not been established. It is possible that the combination of ADT with one ARSI (either AA+P or second generation antiandrogen) may have already brought AR axis activation to its nadir, and there is no more additional benefit from the third agent. Another point to consider is that AA must be administered together with glucocorticoids (albeit at replacement doses) and glucocorticoids are known to drive resistance to second generation anti-androgens via GR (see section on 'Mechanisms of resistance to ARSIs'); therefore, perhaps this combination is flawed at its inception. Finally, a more complex hypothesis comes from an interesting study that suggests that, while originally considered a pure AR antagonist, enzalutamide may function as a partial agonist that reprograms AR binding from canonical AREs to a distinct DNA motif and to a differ-

ent set of genes that promote CRPC growth (Chen *et al.* 2015*b*). The pioneer transcription factor GATA2 may play a role in this switch (Yuan *et al.* 2019) and both androgen deprivation and enzalutamide are known to increase the levels of GATA2 in PC cells (He *et al.* 2014). Thus, one can propose that in patients treated with ADT alone (testicular androgen suppression only), adrenal and intratumoral steroidogenesis results in substantial tissue DHT levels that drive AR signaling and can be antagonized by enzalutamide (hence explaining the significant clinical benefit of adding enzalulamide to sADT in CSPC and CRPC), while in patients receiving ADT+AA+P the intratumoral androgen levels have already been suppressed so low that now the dominant effect of enzalutamide is its GATA2-mediated agonistic effect on AR. Certainly, this hypothesis remains to be proven in the clinic, and the development of a GATA2 inhibitory approach would be one way to examine whether it can overcome the agonistic activity of enzalutamide (as a quadruple therapy of ADT+2 ARSIs + GATA2 inhibitor).

Mechanisms of resistance to ARSIs

Several mechanisms of resistance to ARSIs have been proposed (Vlachostergios *et al.* 2017), including:

1. Reactivation of the AR transcriptional program via alterations in AR itself such as

- AR mRNA and protein overexpression. AR represses its own mRNA expression, and profound AR inhibition leads to adaptive derepression of its expression. Additionally, amplification events in the *AR* gene locus (involving the gene body and/or upstream enhancer sequences) are common in CRPC, in particular ARSI-resistant CRPC (Visakorpi *et al.* 1995, Waltering *et al.* 2009, Grasso *et al.* 2012, Mitsiades *et al.* 2012, He *et al.* 2014, Azad *et al.* 2015*b*, Romanel *et al.* 2015, Foley & Mitsiades 2016, Quigley *et al.* 2018, Takeda *et al.* 2018, Viswanathan *et al.* 2018).

- AR LBD mutations that restore AR activity in the presence of ARSI (Balk 2002, Steinkamp *et al.* 2009, Gottlieb *et al.* 2012, Azad *et al.* 2015*b*, Wyatt *et al.* 2016, Steinestel *et al.* 2019). The AR F877L (previously F876L) mutation has been reported to confer an antagonist-to-agonist switch to enzalutamide and apalutamide that drives resistance (Balbas *et al.* 2013, Joseph *et al.* 2013, Korpal *et al.* 2013). It needs to be examined clinically whether darolutamide can overcome that resistance, as has been proposed based on *in vitro* studies (Sugawara *et al.* 2019).

- Constitutively active, truncated AR splice variants that lack part of or the entire LBD and function in a ligand-independent manner (Hu *et al.* 2009, Dehm & Tindall 2011, Hornberg *et al.* 2011, Lu & Luo 2013, Antonarakis *et al.* 2014, Djusberg *et al.* 2017, Jernberg *et al.* 2017, Prekovic *et al.* 2018).

Reactivation of the AR transcriptional program via an alternate steroid receptor. Four steroid receptors (AR, progesterone receptor (PR), glucocorticoid receptor (GR) and mineralocorticoid receptor (MR)) can recognize and bind to the same DNA motif, allowing for overlap in their transcriptional output and functional compensation (Isikbay *et al.* 2014). Active AR suppresses not only its own expression, but also the expression of GR. Consequently, inhibition of the AR axis results in derepressed expression of both AR and GR, and GR activity can bypass the AR blockade from ARSIs (Arora *et al.* 2013, Xie *et al.* 2015, Puhr *et al.* 2018).

o AR-program-independent mechanisms of resistance such as:

- Increased activation of kinase pathways, for example, PI3K/AKT (Carver *et al.* 2011, Liu & Dong 2014, Adelaiye-Ogala *et al.* 2020) and receptor tyrosine kinases (RTKs) (Drake *et al.* 2012, 2013, 2014, 2016, Faltermeier *et al.* 2016, VanDeusen*et al.* 2020).

- Cell lineage plasticity and transdifferentiation from a luminal epithelial phenotype to other AR-indifferent

phenotypes, including neuroendocrine (NEPC), small cell, as well as the double-negative PC (DNPC) that is both AR-negative and neuroendocrine-negative and is driven by the FGF and MAPK pathways (Bluemn *et al.* 2017, Abida *et al.* 2019, Handle *et al.* 2019, Yamada & Beltran 2021). An aberrant CRPC type with a gastrointestinal-lineage transcriptome has also been described (Shukla *et al.* 2017). Such transdifferentiation is frequently driven by transcription factors (ONECUT2, HNF4G, HNF1A, SOX2, ASCL1, BRN2, MYCN), epigenetic changes in DNA methylation, histone modifications, chromatin integrity and accessibility, and EZH2 activity (Beltran *et al.* 2011, Shukla *et al.* 2017, Abida *et al.* 2019, Yamada & Beltran 2021). Ku *et al.* reported that EZH2 inhibition is able to reverse the lineage switch and restore the sensitivity to AR-targeted therapy (Ku *et al.* 2017). Interestingly, several of the transcription factors driving this transdifferentiation are suppressed by AR under hormone-replete conditions; thus deep AR axis inhibition results in their derepressed expression. In other words, the emergence of these NEPC and other AR-indifferent CRPC phenotypes is not via random, stochastic events, but is based on pre-determined transcriptional programs that were repressed by androgen, and thus represent an inescapable consequence of deep AR inhibition (Kaochar & Mitsiades 2019). In agreement, these AR-indifferent PC phenotypes are very rarely seen *de novo* in hormone-naïve PC patients, become more frequent in CRPC after sADT, and even more common after the use of ARSIs for deeper AR inhibition. In parallel, the related process of epithelial–mesenchymal transition (EMT) (Dicken *et al.* 2019), which is involved in cancer cell invasion and metastasis (Kahn *et al.* 2014), has been shown to be regulated by the androgen-AR signaling axis. Complex and frequently opposing effects of AR signaling on EMT have been reported (Zhu & Kyprianou 2010, Matuszak & Kyprianou 2011, Jacob *et al.* 2014, Nakazawa & Kyprianou 2017, Lin *et al.* 2018).

Future directions

This year marks not only the 80-year anniversary of ADT, but also the 10-year anniversary of the introduction of the first successful ARSI to the market (abiraterone 2011). In the past decade, ARSIs have prolonged survival and improved quality of life for many PC patients, but resistance eventually emerges in the clinic and requires innovative approaches to address it.

In the case of ARSI-resistance driven by full-length AR, there is room for additional inhibition, for example, via degradation by proteolysis targeting chimeras (PROTACs) (Han *et al.* 2019, Neklesa *et al.* 2019, Kregel *et al.* 2020, Petrylak *et al.* 2020), an approach that can target both ligand-dependent and ligand-independent functions of full-length AR. A PROTAC consists of a protein-ligand domain (that recruits the target protein), a linker region, and a ligase ligand domain (that binds a specific E3 ubiquitin ligase, which will ubiquitinate the protein of interest and promote its degradation). One advantage of PROTACs is their activity at very low concentrations, because they promote the degradation of their target proteins, essentially functioning in a catalytic manner and not as competitive antagonists. The protein-ligand domain is obviously critical in determining which forms of the target protein will be degraded. The presence of a LBD on full-length AR makes it an obvious choice for PROTAC design but also limits PROTAC activity accordingly. For example, ARCC-4, a prototypic PROTAC that was designed by linking enzalutamide to a VHL E3 ligase ligand, promotes the degradation of full-length AR, including of the F877L mutant that is functionally activated by the parent LBD ligand (enzalutamide). Thus, the switch from a competitive antagonism mechanism to a degradation-promoting mechanism of action can broaden the spectrum of activity of a LBD ligand. However, as expected, ARCC-4 cannot promote degradation of the LBD-lacking ARv7 (Salami *et al.* 2018). Similarly, ARV-110, a related PROTAC that is already in clinical trials, targets for degradation WT full-length AR and many of its variants (T878A, H875Y, F877L, M895V), but not L702H or ARv7 (Neklesa 2019, Petrylak 2020).

As a result, for ARSI-resistant CRPCs driven by AR variants that lack the LBD, a different approach is

needed. The N-terminal domain (NTD) of AR (which is present in all AR variants, including LBD-mutants and LBD-lacking splice variants), has been proposed as druggable, and clinical results from this promising approach are eagerly awaited (Andersen *et al.* 2010, Myung *et al.* 2013, Banuelos *et al.* 2016, Sadar 2020).

Our prediction is that further targeting of AR, either at the LBD or at the NTD, may benefit select patients with specific mechanisms of resistance such as ligand-dependent (e.g. LBD-mutant AR) and ligand-independent (e.g. LBD-lacking splice variants) CRPC, thus having a clinical value in a biomarker-driven manner. However, at the same time, they would be expected to drive even more CRPCs, as an adaptive pre-determined mechanism, toward AR-indifferent biology and, in particular, treatment-associated NEPC and related phenotypes. This will further increase the urgent need for developing targeted therapies to address this lethal transition (Beltran & Demichelis 2021).
Another direction is to combine ARSIs with other pathway inhibitors in a biomarker-guided approach. For example, the addition of the Akt inhibitor ipatasertib to the CYP17 inhibitor abiraterone in patients with mCRPC showed superior antitumor activity to abiraterone alone in a phase Ib/II study, especially in patients with PTEN loss (de Bono *et al.* 2019). In the subsequent phase III, randomized, double-blind IPATential150 study, adding ipatasertib to abiraterone in asymptomatic or mildly symptomatic patients previously untreated for mCRPC, improved PFS in patients who had PTEN loss (de Bono *et al.* 2020). Other combinations of ARSIs with PARP inhibitors (Rao *et al.* 2021) or chemotherapy (Smith *et al.* 2018*a*) are currently being investigated as well.

However, combination regimens need to be approached carefully and in a manner driven by rationale, mechanism and evidence. Not all combinations benefit patients, as described above regarding combinations involving AA+P plus a second generation anti-androgen. Furthermore, in ERA-223, a randomized, double-blind, placebo-controlled, phase 3 trial in chemotherapy-naïve CRPC with bone metastases, the addition of radium-223 to AA+P did not improve symptomatic skeletal event-free survival, and was associated with an increased frequency of bone fractures compared with placebo. In fact, the study was unblinded prematurely, after more fractures and deaths were noted in the radium-223 group than in the placebo group (Smith *et al.* 2019). Similarly, the addition of enzalutamide to radium-223 did not improve OS (Ahmed *et al.* 2021). Consequently, these combinations are not recommended at this point.

General thoughts/reflections on the state of the field

The last decade has seen dramatic progress in the treatment of advanced PC. The four approved ARSIs have improved outcomes for patients and also have validated older concepts about hormonal treatment, thus cementing our understanding of PC biology. Reflecting on these advances, we would like to give some personal opinions:
Is there still a role/indication for using standard ADT as monotherapy without ARSI (thus targeting testicular androgen production only) in any setting in PC?

Technically, in the case of men with high-risk N0M0 or N1M0 (regional lymphadenopathy) CSPC who initiate treatment with ADT±radiation, there is no FDA approval for adding an ARSI to the ADT. As mentioned above, in our clinical practice (N M), we frequently extrapolate based on the STAMPEDE data (James *et al.* 2017, Hoyle *et al.* 2019) and add AA+P, off-label, to the ADT regimen in such patients. Strictly speaking, though, as of February 2021, AA+P is not FDA-approved even for metastatic CSPC that falls in the low-risk M1 stratification (as defined by LATITUDE (Fizazi *et al.* 2017)), a clinical state for which enzalutamide and apalutamide are approved. Again, our clinical practice (N M) is to consider AA+P, enzalutamide and apalutamide as equally accepta-

ble options for all metastatic CSPC patients who start ADT, irrespective of risk stratification. Finally, for patients who initiate ADT for biochemical recurrence (non-metastatic or M0 disease) after prior prostatectomy or prostate irradiation, there is again no FDA approval for adding any ARSI.

Our personal opinion is that these subtleties (as well as those detailed in Table 1) most likely represent the way clinical trials for each ARSI were designed and prioritized, and do not suggest any actual differences in clinical activity. We anticipate that future evidence will expand the upfront incorporation of ARSIs across the entire space of ADT use. Hence we propose that if a patient is to initiate ADT, he should be offered the best AR axis suppression possible (which, as of February 2021, is ADT+ any one of the four ARSIs that are on the market), unless comorbidities, life expectancy, adverse effects and patient preference would favor otherwise. We believe that failure to add an ARSI allows residual adrenal and intratumoral androgens to persistently activate the AR axis, which increases the opportunities for PC cells to survive, adapt and evolve into CRPC.

How to deal with outdated (and incorrect) terminology?

The term 'androgen deprivation therapy', as used historically (without ARSI), is a misnomer, because intratumoral androgens actually persist (Montgomery *et al.* 2008). Similarly, the term 'hormone-independent' PC was a misnomer at the time before ARSIs.

Nowadays, however, ARSIs are approaching the goal of achieving true 'androgen deprivation therapy' at the cellular level, and the resistant PC cells are frequently truly 'hormone-independent' PC at the cellular level (although not always). For example, NEPC could be called a truly hormone-independent PC. So could the term 'androgen-independent' PC make a clinical comeback, this time to describe post-ARSI CRPC that is driven by ligand-independent mechanisms?

Technically, this time the term may be correct at a cellular level for many ARSI-refractory CRPCs and it could be used accurately in select cases after molecular studies have carefully dissected and confirmed such mechanisms of resistance on an individual level, but it would probably be too confusing to bring it back in the clinic to describe ARSI-refractory CRPC. To avoid confusion, use of a different term such as 'androgen-indifferent' or similar term, is preferred.

For the same reason, while the current use of second generation anti-androgens together with front-line ADT in metastatic CSPC is essentially a combined androgen blockade (CAB), that term is (unfortunately) linked to the previously tried use of first generation anti-androgens in that setting, so perhaps it would be best to leave that term in the past as well, to avoid confusion.

3. Better (deeper, earlier, more comprehensive) AR axis targeting will benefit patients, but will also make 'androgen-indifferent' variants more common in an inevitable, deterministic way that is driven by our own hormonal therapies. Metastatic prostate adenocarcinoma patients will receive endocrine therapies for significant periods of time, but the disease phenotype that will be most lethal in the future will resemble small cell cancer of the lung (and perhaps will be treated borrowing principles and advances from that field).

Despite the widespread use of AR targeting as first-line choice for treating advanced PC, it is remarkable that the decision to start hormonal therapy and the choice of the specific hormonal regimen has essentially never been driven by a genetic/genomic biomarker. At a time in Precision Oncology where targeted therapies are chosen for each patient based on matching to activating mutations in their targets, the use of hormonal therapies in advanced PC remains remarkably not biomarker-driven. Review of any genomic dataset from treatment-naïve PC reveals little (if any) evidence to nominate AR as a major therapeutic target. In fact, AR overexpression, gene amplification, mutations, expression of splice variants, etc., happen in meaningful frequencies only after the hormonal equilibrium of the PC cell has been perturbed by

ADT, when depressed feedback loops and escape mechanisms try to re-equilibrate the cell's intracellular signaling balance. In the clinic, we utilize ADT as first-line therapy irrespective of the patient's baseline serum testosterone levels, AR mutation status, or even whether the tumor expresses AR or not. In fact, we do not even test for AR expression in regular clinical practice, although one could point out that the production of PSA by the tumor is evidence of AR activity (but also greatly affected by tumor burden and thus not a quantitatively accurate measure of AR activity). In other words, the clinical algorithm for making decisions regarding when to start hormonal therapy and which agents to use does not incorporate any assessment of the specific degree of AR dependence or any predictive biomarker of responsiveness of each patient's PC to hormonal therapy.

An explanation for this paradox is that ADT does not treat only PC – it treats the entire prostate epithelial lineage as a whole, and we (the physicians) have accepted that normal prostate function will be sacrificed in the process, just as we (the physicians) consider hot flashes, erectile dysfunction, loss of bone density, etc., as unavoidable consequences of ADT. But all these adverse effects add significant morbidity for our patients, which is also becoming more prolonged as their life expectancy increases due to more active therapy. More emphasis on survivorship for ADT-treated patients is needed, and we need clinical trials that will try to mitigate these adverse events such as via intermittent use of ADT±ARSI or more refined patient selection. This may at first sound contrary to the point we made above in (a) ('if you initiate ADT, offer the best AR axis suppression possible by adding an ARSI'), but it is actually not. Standard ADT is an incomplete therapy that practically guarantees emergence of CRPC, while the patients still have to suffer the adverse events of androgen deprivation. As an alternative approach, more comprehensive AR axis targeting with ADT+ARSI for shorter periods of time may allow for more definitive control of the cancer that then can be followed by careful withdrawal of hormonal therapy in select cases and under close monitoring. This is similar to the concept of 'intermittent ADT', which in recent years has been less popular, after Hussain *et al.* (2013) gave us reasons for concern that intermittent ADT may not be adequate therapy. It is possible, though, that, just like the ARSIs validated several other old concepts in the last decade, they could also resurrect the concept of cycling between periods of intense therapy and de-intensification. Again, the theme is to look back at older paradigms that possibly had value but previously failed in the clinic due to lack of appropriate pharmacological agents, and examine them again in well-designed, biomarker-driven clinical trials that incorporate ARSIs.

And finally, we close our article honoring the pioneering work of Huggins & Hodges (1941) by mentioning the Holy Grail of AR targeting in PC: to separate the growth-promoting effects of AR signaling on PC cells from the normal functions of androgens and AR in the rest of the body, so that we can, someday, selectively target PC cells while sparing healthy cells in the body, thus minimizing the adverse events of ADT for our patients. The work continues!

Declaration of interest

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