Oncology Central

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Prostate cancer: treatment milestones

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Panel discussion: how I treat non-metastatic castration-resistant prostate cancer

Gain an understanding of how oncologists are treating non-metastatic castration-resistant prostate cancer (CRPC) in our latest panel discussion, featuring experts insights from Catherine Marshall and Channing Paller (Johns Hopkins School of Medicine, MD, USA) and Judd Moul (Duke University Medical Center, NC, USA).

The panelists discuss the past, present and future of the treatment landscape for non-metastatic CRPC, and detail the treatments and sequencing used in their own practice. Marshall, Paller and Moul also present their own case studies and discuss how they would approach each other's cases.

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Question 1: What treatments and treatment sequencing do you currently use to treat non-metastatic CRPC?

Marshall: Before talking about non-metastatic CRPC, we first need to talk about non-metastatic prostate cancer. The treatment landscape in this space is still undefined. With new imaging techniques, the number of people we consider to have non-metastatic disease is shrinking. But we do not have great evidence to support when we should start continuous hormone therapy for these patients and many of these patients will still do quite well even without hormone therapy. The pivotal clinical trials – SPARTAN, PROSPER, and ARAMIS – that demonstrated overall survival (OS) benefit of Erleada® (apalutamide), Xtandi® (enzalutamide), and Nubeqa® (darolutamide), respectively, do not have information on when or why patients were started on continuous androgen deprivation therapy in the first place. So, all of that being said, I have not increased my use of androgen deprivation therapy in the non-metastatic space. But, if patients are on it, and progress to non-metastatic CRPC with a PSA doubling time of 10 months or less, I will start one of those approved agents.

Choosing which one to start with, for me, usually comes down to side effect profile, interactions with other medications, and which one is easiest for the patient to get and take every day. Cost and pill burden factor into the ease of taking. With all of this, darolutamide seems to be the option I most often use first. In terms of subsequent treatment, if patients have disease that is still non-metastatic, I will switch to one of the other oral anti-androgens approved for non-metastatic CRPC, recognizing that the benefit of a second agent in that space is unknown and a response to a second line anti-androgen for non-metastatic CRPC will likely be lower than the first. Clinical trials are always an option, and these patients should also undergo genetic testing to determine whether they would benefit from PARP inhibitors or other clinical trials in the future.

Moul: I am a urologist, but I work in a multidisciplinary clinic with genitourinary medical oncology. However, a lot of the patients with non-metastatic CRPC are in our urology practices. So, this is a topic that at least in the USA that urologists need to be very familiar with.

These patients are on hormone therapy for biochemical recurrence and then they have a rising PSA and are found to have non-metastatic CRPC. Up until 2018, we really did not have any novel treatments for the condition and the standard of care was just to monitor the patients until they developed metastasis.

Moul: Then in February of 2018, apalutamide was the first drug to get FDA approved in the USA for non-metastatic CRPC. So, that opened the door for this oral therapy, and it was initially based on an improvement in metastasis-free survival and the increase in survival was close to 2 years or over 2 years. This was a real clinically significant benefit where a once-a-day oral medication could actually improve metastasis-free survival by a really long-time, 2 years.

Then subsequently enzalutamide also received FDA approval in July 2018 and then roughly a year after that, darolutamide was the third oral agent approved in non-metastatic CRPC.

I guess the good news is we now have three oral agents that we can use in the United States to treat non-metastatic CRPC. They are all effective. One of the challenges we face is they are very similar, and so sometimes it is challenging to know which one of the three to prescribe.

Paller: We consider several variables when treating non-metastatic prostate cancer. We use conventional imaging studies (Technetium 99 Bone Scans and Cat Scans) to ensure there is no evidence of metastatic disease and that their disease is growing slowly (the prostate specific antigen doubling time is less than 10 months). If it is greater than 10 months, we often recommend continuing androgen deprivation therapy alone. Based on recent developments, many patients request more sensitive imaging with PSMA-based molecules that detect metastatic disease earlier than conventional imaging, but we do not know yet if detecting it earlier improves outcomes. Once we are sure the patient's disease is non-metastatic, we have three FDA approved treatments: apalutamide, darolutamide and enzalutamide. To choose the best treatment option, we consider the patient's comorbidities and other medications. For example, 24% of patients develop a rash with apalutamide, so I usually avoid apalutamide in patients with sensitive skin. Similarly, enzalutamide is contraindicated in patients with seizure disorder.

Further, both enzalutamide and apalutamide can induce cytochrome P450 (CYP) 3A4 enzymes that inhibit the activity of P-glycoprotein and could reduce the effectiveness of other medications. Darolutamide is generally well tolerated.

Question 2: What are the major challenges for CRPC treatment? How do you think they can be overcome?

Marshall: I think the major challenge for non-metastatic CRPC treatment is what to do about subsequent therapy. We have three options for first line treatment but no great information yet on what to do next. If patients have a slow subsequent PSA doubling time, you might not need to switch therapy right away. In the future, it will be important to get some real-world data on this, as clinical trials sequencing these agents are unlikely to be done. We do still also need more research on the best timing of initiating ADT for these patients. Finally, as we learn more about the genetics of prostate cancer and targeted treatment, more non-hormonal treatment strategies will likely be incorporated into the treatment paradigm.

Question 3: CRPC is often diagnosed at later stages. Could you give us a bit of a background to why this is?

Moul: I think it's multifactorial. I mean sometimes men who have prostate cancer sometimes they are not as proactive as females, for example. I think a lot of times females with breast cancer are more proactive.

A lot of guys with prostate cancer don't necessarily pay that much attention to their own disease, that must be one factor. They are on hormone therapy and they see their PSA rising but may not be as knowledgeable or do anything about it. The healthcare providers are busy. There is a shortage of urologist in the USA, and so sometimes the doctors are so busy that they overlook a rising PSA while the patient is on hormone therapy.

Then thirdly these medications are expensive and even though there is really pretty good insurance coverage in the USA these drugs are expensive and sometimes the patients just don't get put on the proper medications due to financial considerations.

Question 4: What are your hopes for how the treatment landscape of non-metastatic CRPC will evolve over the next 5 years?

Moul: We have these three oral agents that are now available and they all now show OS advantage. At ASCO in 2020 the trials came out that all three of these agents (apalutamide, enzalutamide and darolutamide) all showed an OS benefit.

So, in 2018, we knew that they extended the metastasis-free survival but now in 2020, we learnt that they extended OS. That was positive news, and for any of the doctors who were still on the fence as to whether they have used these agents, we now had survival advantage. Again, it took another barrier away from potentially doctors who may not believe that these drugs were beneficial.

We still face challenges with cost. They are expensive and you must go to a specialty pharmacy and work with the benefits manager to make sure the patient has coverage. Again, I can just speak for the situation in the USA - some patients can have as much as $10,000 per year in out-of-pocket expenses because of the way the system is structured as far as coverage and that is a challenge. As far as advancements through the future, I think eventually we will have other combination agents and potentially other mechanisms of action of drugs that may work but again, this has been a real advance having three effective agents approved in the space in a matter of essentially 1 year.

Paller: We have made extraordinary progress in treating prostate cancer during the past 5 years, with many new drugs and imaging techniques approved by the FDA that increase survival and quality of life for metastatic prostate cancer patients. I am very hopeful that we will continue to make advances in treatments in three ways: (1) moving the newly approved treatments earlier in the disease spectrum to delay metastasis. (2) combination therapies to delay resistance to treatments and improve quality of life, (3) and improved targeting of therapies using genetic biomarkers. Further we are just beginning to understand the clinical significance of finding cancer with more sensitive imaging (such as Pylarify®; (piflufolastat F18) approved by the FDA in May 2021 or 68Ga-PSMA approved December 2020) compared to conventional imaging. Thus, in the next 5 years we will better equipped to understand whether patients with detectable disease, with these next-generation imaging modalities, are better served. I hope this will lead to reducing toxicity and improving efficacy of therapeutic options for both metastatic and non-metastatic CRPC.

Marshall: I think with the recent approvals of Lynparza® (olaparib) and Rubraca® (rucaparib) for metastatic CRPC, genetic testing will be used more and more in practice. I also think that we will increasingly be using genomically targeted therapies in the treatment of men with CRPC.

Case studies

Case 1 (Marshall):

Let's say there is a patient with a PSA doubling time of greater than 3 months, PSA of 5ng/mL, no evidence of disease on imaging so this patient was started on continuous androgen deprivation therapy. After 6 months, with a suppressed testosterone, the patient again has a rising PSA with a PSA doubling time of 6 months and negative imaging and would be considered to have non-metastatic castration resistant prostate cancer. Let's say the patient has a mechanical heart valve so is on warfarin anticoagulation but no other medications or comorbidities. For this patient, I would choose darolutamide.

Some other considerations:

If the patient had a very long doubling time, let's say 15 months, I would not necessarily start any of these agents. The inclusion criteria for the trials was, with a PSADT <= 10 months, so the benefit to patients with a slower PSADT is unknown.

If a provider has more experience treating patients with one or two of the drugs over the others, I would go with the one that the provider has the most experience with using.

Paller comments: Daralutamide is better tolerated because it effectively does not cross the blood brain barrier and thus has less fatigue and no seizures. A Phase III study of patients with M0 castration resistant prostate cancer and a PSA doubling time of less than 10 months show that darolutamide at 600 mg twice daily improved the primary end point of metastases free survival over placebo (40.4 months versus 18.4 months). OS at 3 years was 83% compared to 77% of the placebo group. Adverse events that occurred more frequently with darolutamide included fatigue (12.1% versus 8.7%), pain in extremities (5.8 versus 3.2%), and rash 2.9 versus 0.9%. (PMID32905676)

That said there is recent data by Beer et al in a network meta-analysis suggesting that enzalutamide may be superior in terms of efficacy. In clinical practice one must also consider comorbidities and drug-drug interactions. Specifically, Xarelto (rivaroxaban) and Eliquis (apixaban) are contraindicated with enzalutamide because they are less effective in combination. With warfarin and enzalutamide, the international normalised ratio (INR) can fluctuate, if we still wanted to use enzalutamide, we would just monitor the INR more frequently.

Case studies

Moul comments: This is very reasonable to start darolutamide. The possible advantage of darolutamide would be less fatigue, less risk for falls and seizure due to its mechanism of action not crossing the blood-brain barrier. However, the dosing is twice daily versus enzalutamide and apalutamide once a day dosing. Based on the ARAMIS trial update from ASCO 2020:

- 31% reduction in the risk for death for darolutamide vs placebo.
- Median follow-up of 29.1 month
- 3-year OS rates were 83% and 77% for the darolutamide and placebo
- Darolutamide associated with significant delays in the time to pain progression, first cytotoxic chemotherapy, and first symptomatic skeletal event.

Case studies

Case 2 (Moul):

I can think specifically of one gentleman. He was about 70 years old. He was an executive in a very prominent grocery store chain in the USA. He had been the CEO of the major grocery chain, and he is now retired. I had met him several years earlier when he had localized prostate cancer and underwent a radical prostatectomy.

I had initially treated him for surgery and then about 2 years after the surgery, he had an initial rising PSA and received salvage radiation therapy to the prostate bed and the pelvis. That was effective for a period and then the PSA started to rise again. Eventually he went on androgen deprivation therapy with leuprolide acetate, and I believe even at that point in time he was on bicalutamide oral therapy with leuprolide acetate.

Then, that lasted a period and then his PSA actually started to rise on this hormone therapy. His PSA started to rise fairly slowly while he was still on the leuprolide acetate and once his PSA went above two, I was very concerned that he had non-metastatic castrate-resistant prostate cancer or well at that point, I wasn't sure if it was non-metastatic.

Once his PSA rose above two, I obtained a bone scan and a CAT scan to make sure he did not have metastatic disease and those were negative, and I also did a serum testosterone level and that was less than 50 indicating that he was castrate and he was compliant with his hormone therapy. Then I checked another PSA a month or so later and it had risen to approximately four.

Moul continues: Clearly this gentleman at this point, again, he has a rising PSA on traditional hormone therapy. He has a castrate testosterone less than 50 and he had negative bone scan and CAT scan indicating no obvious metastatic disease. This occurred in March 2018 and that was soon after apalutamide was FDA approved in USA and so he was a perfect patient, if you will on label, for the new oral agent. I wanted to get some experience in prescribing this and so he started on apalutamide and quite frankly, he is still doing fine. That was in spring of 2018, and we are now in the spring of 2021. So, he has been on that drug for 3 years and continues to do well.

Marshall comments: I agree with this approach. The patient had a PSA of 4ng/mL that doubled in about a month and had no evidence of disease on conventional images. Novel imaging using axumin or PSMA based imaging would be appropriate in this setting too. Either way, additional therapy is warranted and apalutamide is a fine choice. There may be long term complications of these medicines as patients are on them for longer periods of time but that remains to be seen.

Case studies

Paller comments: Apalutamide is a good option and this is a nice long response. A Phase III study of men with non-metastatic CRPC and PSADT <10 months assigned men placebo or apalutamide at 240 mg PO daily and the trial found improved metastases free survival over placebo at 40.5 months versus 16.2 months with the HR for metastasis or death being 0.28 95% CI 0.230.35, p<0.001. After median follow up at 52 months, final overall survival shows improvement in overall survival with apalutamide versus placebo being 73.9 months versus 59.9 months. Adverse events included rash (24% vs. 5.5%), fracture (11% vs. 6.5%), and hypothyroidism (8% vs 2%) PMID: 29420164. Like enzalutamide, it crosses the blood brain barrier thus has risks of fatigue and seizures, and can also cause similar side effects like hypertension, diarrhea, dizziness, and peripheral edema. In addition it has cyp3A4 interactions that makes it difficult to combine with blood thinners. Finally, unlike the other agent it has a serious risk of fractures as a listed side effect. Darolutamide has fewer side effects as it effectively does not cross the blood brain barrier.

Case studies

Case 3 (Paller):

A 71-year-old prostate cancer patient with atrial fibrillation on apixaban comes in for a second opinion. His general oncologist suggested he start enzalutamide for non-metastatic CRPC and wants to know what I think. I tell him I am concerned about drug-drug interactions and risk of bleeding and thus recommend he either switch his apixaban or switch the enzalutamide to darolutamide.

Marshall comments: I always want to think about whether or not starting or changing therapy is warranted in the first place. I would first want to know the absolute PSA for this patient and then I would want to see at least two or three PSA values over time to determine the PSA doubling time. If the absolute PSA is still very low, and the PSA doubling time is very long, I might wait on starting any treatment at all. Next I would also consider the time course for the concomitant medications, in this case the apixaban. If it were to be stopped soon, I might wait until after he is off of it to consider starting therapy for his prostate cancer. If he will be apixaban indefinitely, then would tailor my therapy to try and minimize drug-drug interactions. So, if he does need to start on therapy for his non-metastatic CRPC and has a PSA doubling time of 10 months or less, I would switch to darolutamide as well.

Moul comments: Prostate cancer and cardiac disease requiring anticoagulation is quite common in contemporary oncology practice. While all three FDA-approved 3rd generation nonsteroidal antiandrogens (apalutamide, daralutamide, enzalutamide) are associated with improved overall survival in M0 CRPC, the use of darolutamide in this clinical scenario is a prudent choice. It is important for clinicians managing advanced prostate cancer patients to be familiar with some of the subtle differences between these three oral agents.

Channing Paller

Channing Paller is Associate Professor Of Oncology And Urology at Johns Hopkins Kimmel Comprehensive Cancer Center (MD, USA) and Director For Oncology for Johns Hopkins Clinical Research Network (MD, USA). Her research focuses on translating basic scientific findings into treatments that extend lives and reduce toxicities for men with prostate cancer. She manages a growing portfolio of investigator-initiated clinical trials focused on providing precision medicine to cancer patients using biomarkers and targeted therapies. The largest of those is the PROMISE trial designed to screen 5000 prostate cancer patients to identify those who have rare germline mutations and follow their treatment and clinical progress over time. The goal is to develop new knowledge that will help us improve precision medicine.

Catherine Marshall

Catherine Marshall is an Assistant Professor of Oncology at the Johns Hopkins School of Medicine (MD, USA). She specializes in the treatment of patients with prostate cancer. Her research focuses on genetic alterations in prostate cancer and the overlap of cancer and cardiovascular disease.

Judd Moul

Judd Moul is a urologic-oncologist at Duke University Medical Center (NC, USA). He has been at his practice for approximately 17 years. Before that, he was an army doctor at Walter Reed Army Medical Center (WA, USA) and trained in the military. He has been working in the area of prostate cancer for over 25 years, and has been fortunate to have a career involved in clinical trials, basic science research in prostate cancer and clinical care.

Darolutamide and survival in nonmetastatic, castration-resistant prostate cancer: a patient perspective of the ARAMIS trial

The latest publication by the *Video Journal of Biomedicine* summarizes the ARAMIS (Androgen Receptor Antagonizing Agent for Metastasis-free Survival) trial, which was published in the New England Journal of Medicine in September 2020.

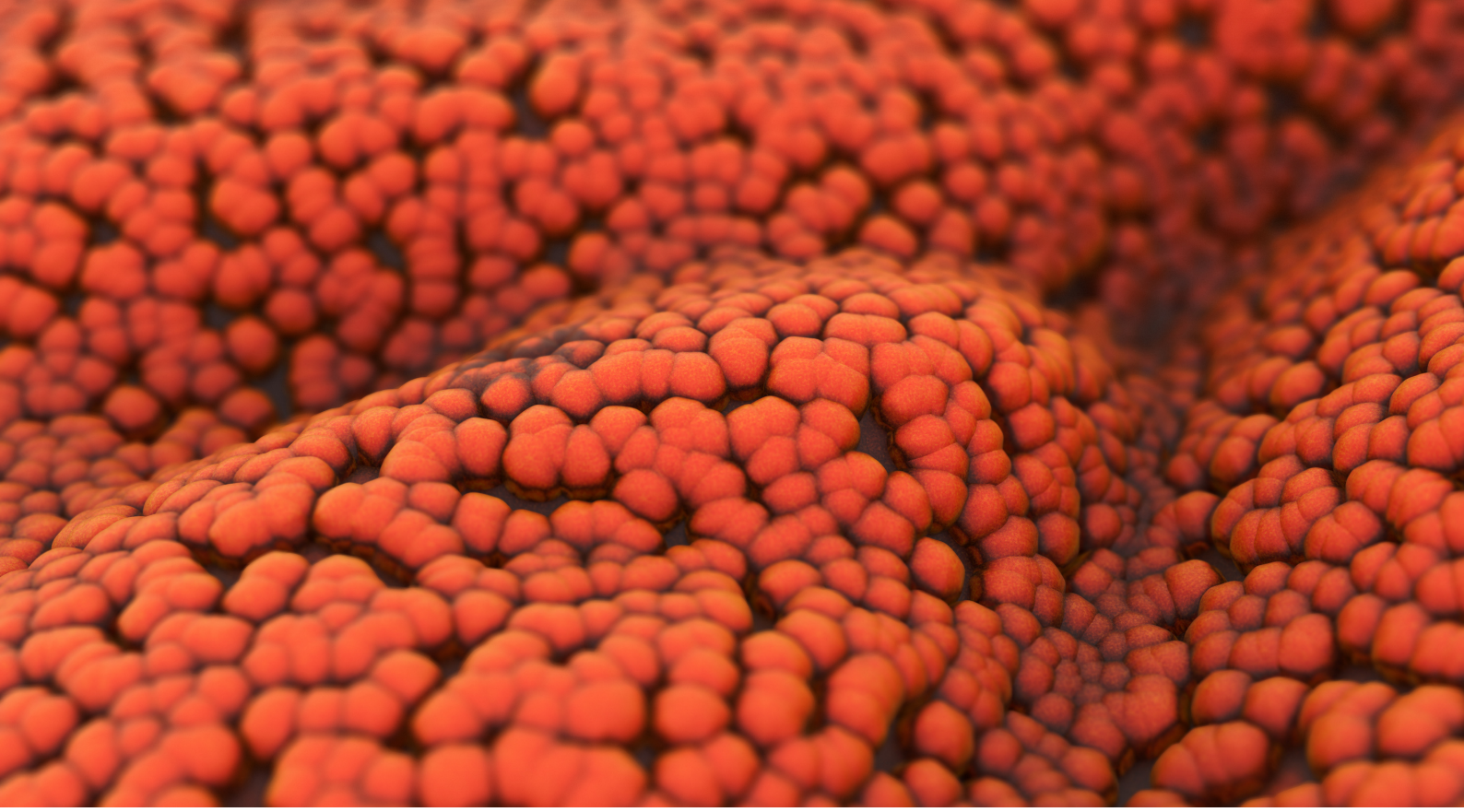
The trial was in adult participants with nonmetastatic, castration-resistant prostate cancer who received a trial treatment called darolutamide (brand name Nubeqa®). The summary also includes insights and perspectives from a participant who was in the ARAMIS trial and from a prostate cancer patient advocate.

Original publication:
Fizazi K, Blue I & Nowak JT. Darolutamide and survival in nonmetastatic, castration-resistant prostate cancer: a patient perspective of the ARAMIS trial. doi:10.2217/fon-2020-1291 *Future Oncol.* (2021).

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Oncology Central or Future Science Group.

Watch video on Oncology Central:

https://www.oncology-central.com/videos/darolutamide-and-survival-in-nonmetastatic-castration-resistant-prostate-cancer-a-patient-perspective-of-the-aramis-trial/



PSMA PET imaging in prostate cancer: an interview with Dr Jeremie Calais

Please could you introduce yourself, your research background and your current research interests?

My name is Jeremie Calais and I am a nuclear medicine physician. I was trained in France and I work now at UCLA (CA, USA). I am the Director of the Clinical Research Program of the Nuclear Medicine and Theragnostic Division at UCLA. My work focuses on improving the outcome of cancer patients by translating and applying novel diagnostic and therapeutic approaches. I use PET/CT imaging, for example, for cancer phenotyping, radiation therapy planning or therapy response assessments. Now, with the theragnostic era, which is a combination of a therapeutic and diagnostic agent targeting the same molecular target, the nuclear medicine field is booming with new targets and new targeted radioactive agents.

Prostate-specific membrane antigen (PSMA) has been the main focus of my research work in the past four years. It is overexpressed by prostate cancer cells in large amounts, which therefore makes it a very relevant target for prostate cancer imaging and therapy. There are other cancer specific targets as well, such as FAP and others.

What to you are the current challenges for prostate cancer in the USA? And how do you think this will continue to evolve?

Prostate cancer is the most common cancer in men, both in the USA and worldwide. It's a huge patient population and a big burden on the economy. One of the challenges is to stage the disease accurately and correctly before treatment. Of course, depending on where the disease is, patients will need to be treated differently.

You need accurate tests and imaging techniques to locate the disease and to be sure you are giving the correct treatment for each disease stage.

Staging is currently being done with conventional imaging, which includes computed tomography, bone scan or MRI. They can have limitations, especially to stage disease that has spread out outside of the prostate. Now, we have new imaging agents that target PSMA. PSMA PET imaging has higher sensitivity for extraprostatic metastatic staging and therefore can better select and classify patients for individualized therapy.

Could you tell us about the PSMAdRT Phase III randomized trial that you're currently involved in?

We have new imaging techniques, and we know that they perform better than the current standard-of-care imaging techniques. However, we don't know at the end if this really translates into improved outcome – if having better imaging techniques with higher sensitivity actually makes a difference in terms of therapy results and cancer patient outcomes. What we're doing here is a randomized trial to test this new imaging technique before definitive radiation therapy for prostate cancer.

We'll see if the patients who do not get the PSMA PET imaging technique before do better, equally or worse than patients who do get the PSMA PET imaging test before. It's a randomized trial comparing two groups. The standard group is definitive radiation therapy as initially planned, as currently done under the standard-of-care setting versus the intervention group, definitive radiation therapy after the PSMA PET imaging. Maybe the PSMA PET imaging will show some disease that wasn't seen by the conventional scans so the radiation oncologists can adapt their radiation fields or maybe PSMA PET imaging will show some disease already spread outside of the prostate that is not treatable using radiation therapy anymore.

The radiation oncologist will therefore not treat these patients with radiation therapy, which changes the therapy management.

How do you hope this trial will impact the field of prostate cancer, linking back to the challenges that you mentioned?

I am a nuclear medicine physician and theragnostic specialist, so I truly believe in molecular imaging and individualized approach. I hope that we can improve the results and the outcome of patients for each therapy. Usually, imaging trials are designed for showing improved diagnostic accuracy and improved sensitivity. However, they are rarely designed for improved patient outcomes because it's difficult to do. This is one of the rare trial designs for that and I hope it will succeed. I hope that the trial will be positive and pave the way to administer truly individualized therapy on a per patient basis. Ultimately, I hope that PSMA PET imaging will be available widely and that it will be integrated into clinical guidelines.

What are the next steps for this trial?

We need to recruit all the patients first and we have a limited time window to do it because to be able to do such a randomized trial you need specific conditions. One of which is to randomize patients to the control group. In the US, PSMA PET is not yet approved by the FDA so it's still a research procedure: it is not considered standard-of-care. This represents an opportunity because you can ethically randomize patients to the control group. As soon as PSMA PET gets approved, then it will be much more difficult to enroll patients because they will know that they have a 50–50 chance to go to the control group, whereas they could get the same scan outside of research in a standard-of-care setting. The main challenge is to be able to recruit enough patients to have enough statistical power before the PSMA PET agent gets approved and reimbursed in the US. As soon as one PSMA PET agent gets approved here, it will be

ethically very difficult to randomize patient to the control group.

The second challenge is to obtain proper follow up. You cannot request formally that the patients randomized to the control group do not try to get or get a PSMA PET scan at another institution. If a patient gets randomized to the control group, they may want to try to get the PSMA scan at another institution and then for us, it's a dropout so patient will be excluded from the study. By doing this interview, I hope to increase the visibility of the trial and I hope that many radiation oncologists can send us patients to increase the recruitment in this limited time window.

View online at Oncology Central:
PSMA PET imaging: an interview with Jeremie Calais (oncology-central.com)

The opinions expressed in this Interview are those of the author and do not necessarily reflect the views of Oncology Central or Future Science Group.

Drug Evaluation

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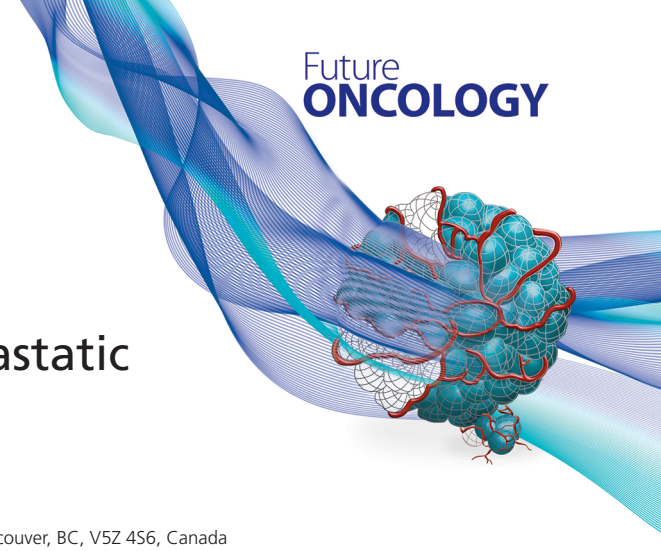

Olaparib for the treatment of metastatic prostate cancer

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Recent innovations in the treatment of metastatic prostate cancer have improved patient outcomes. Nonetheless, this disease remains fatal and additional treatment approaches are needed. Greater understanding of the molecular landscape of metastatic prostate cancer has revealed recurrent alterations in key pathways amenable to therapeutic targeting. One such pathway is DNA repair, particularly alterations in genes directly or indirectly associated with homologous recombination repair found in up to one-quarter of patients with metastatic castrate-resistant prostate cancer (mCRPC). Olaparib, an inhibitor of poly-ADP-ribose polymerase, has recently gained approval for the treatment of mCRPC harboring alterations in homologous recombination repair genes. This review will provide a summary of evidence regarding PARP inhibition in the treatment of mCRPC, with a specific focus on olaparib.

Lay abstract: The genetic material in cells, called DNA, is continually exposed to factors which can damage it. This damage must be corrected, which is done through specific DNA damage repair pathways. Mutations, which can be inheritable or arise just in the cancer itself, can occur in genes involved in DNA damage repair that impair the repair process. In 20–30% of prostate cancers, mutations are involved in genes associated with the homologous recombination repair pathway which can be taken advantage of for therapeutic effect by targeting an alternate repair pathway involving a protein called PARP. Olaparib, an inhibitor of PARP, was recently shown to improve outcomes in patients with advanced, metastatic prostate cancer harboring mutations in homologous recombination repair genes and subsequently gained approval for the treatment of such patients. This review will provide a summary of evidence regarding PARP inhibition in the treatment of prostate cancer, with a specific focus on olaparib.

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Keywords: ATM • *BRCA1/2* • *CDK12* • genomic alterations • homologous recombination repair • metastatic prostate cancer • olaparib • PARP inhibition

Prostate cancer is a leading cancer-related cause of death among men in the USA and Europe. An estimated 33,330 and 78,000 prostate cancer-related deaths are anticipated in the USA and Europe, respectively, in 2020 [1,2]. The role of androgens as drivers of disease progression in prostate cancer has long been established [3], and androgen ablation, either via chemical (gonadotropin-releasing hormone agonist or antagonist therapy) or surgical means, has become the mainstay of treatment of metastatic prostate cancer throughout the disease course [4]. However, despite castrate levels of androgen, progression is inevitable, a disease state termed metastatic castrate-resistant prostate cancer (mCRPC). Over the past two decades, several novel classes of agents were shown to provide survival benefit for patients with mCRPC and have been approved as standard of care for this indication. These include the androgen receptor pathway inhibitors (ARPIs); abiraterone acetate and prednisone (AAP) [5,6] enzalutamide [7,8], darolutamide [9] and apalutamide [10]), taxane chemotherapy (docetaxel [11] and cabazitaxel [12]) and the radiopharmaceutical radium 223 [13]. More recently, the treatment paradigm of metastatic prostate cancer has been further modified when ARPIs (AAP [14,15], enzalutamide [16,17] and apalutamide [18]) as well as docetaxel chemotherapy [19,20] were shown to provide a significant survival benefit when added to ADT in the earlier setting

Future Medicine

of the metastatic castrate sensitive disease state. Nonetheless, metastatic prostate cancer remains terminal and novel agents that provide further life prolongation in this disease setting are an unmet need.

Cancerous cells have characteristic traits that evolve throughout the process of neoplastic transformation and facilitate their malignant capabilities. These malignant traits can be genetic in origin, as a result of germline and/or somatic alterations [21]. Genomic studies of patient tumors have provided greater understanding of the molecular landscape of prostate cancer including the characteristic somatic mutations, copy number alterations and oncogenic structural DNA rearrangements that facilitate cancer initiation and progression [22] Robinson *et al.* [23] in their pivotal work subjecting metastatic lesions to whole-exome sequencing, defined the recurrent alteration landscape of mCRPC; the most frequently aberrant genes being *AR* (62.7%), *ETS* family members (56.7%), *TP53* (53.3%) and *PTEN* (40.7%). Nearly 90% of patients in this study harbored what the authors defined as 'clinically actionable aberrations', involving multiple pathways including the AR pathway, PI3K pathway, Wnt pathway, cell cycle pathways and DNA repair pathways. Of interest, 22.7% of subjects harbored an alteration in genes involved in DNA damage repair (DDR).

Some alterations in DDR genes, specifically aberrations in *BRCA1, BRCA2*, and others involved in homologous recombination repair (HRR), are associated with response to PARP inhibitor (PARPi), a novel class of drugs. Olaparib, the first PARPi to be approved for clinical use in any tumor type, has been shown to improve survival of patients with ovarian cancer harboring germline alterations in *BRCA1/2* (g*BRCA1/2*) when given as maintenance therapy, following platinum and taxane chemotherapy at first or second line of treatment [24–27]. Additionally, olaparib demonstrated single-agent activity in this population in later lines of treatment [28,29]. Furthermore, olaparib was shown to improved progression-free survival (PFS) among g*BRCA1/2* carriers with HER2 negative, metastatic breast cancer when given as single agent [30,31] and among g*BRCA1/2* pancreatic cancer patients when given as maintenance therapy following FOLFIRINOX chemotherapy [32]. Consequently, olaparib was approved for treatment of these indications.

The hypothesis that a subset of prostate cancer harboring HRR alterations may respond to PARPi prompted the investigation of the efficacy of olaparib in the treatment of such patients. The following review will discuss the characteristics of prostate cancer harboring DNA damage repair alterations and the biological and clinical evidence supporting the use of PARP inhibition and specifically olaparib for this indication.

HRR & prostate cancer

DNA damage occurs throughout the cell cycle and manifests as base modifications, single and double-strand breaks (DSBs) and intra- and interstrand cross links. The integrity of the genome is maintained by repair of this damage by enzymes of the DDR pathways. DSBs pose a particular repair challenge, as they lack complementary strands to provide a template for repair. Eukaryotic cells employ two distinct mechanisms to repair these breaks, nonhomologous end joining (NHEJ) and HRR. The former utilizes limited or no homology, and hence, has greater propensity for error giving rise to DNA sequence alterations and mutagenesis, whereas the latter pathway relies on sequence homology utilizing the sister chromatid as a template. Cancer cells harboring loss of function defects in HRR genes (e.g., biallelic *BRCA2* pathogenic mutation) deploy the alternative, NHEJ pathway and consequently accumulate DNA damage including potential driver mutations [33–35]. Studies into the molecular landscape of prostate cancer have revealed that 14–33% of mCRPC tumors harbor defects in genes with plausible links to HRR [23,36–40]. Robinson *et al.* in their aforementioned study, identified recurring DDR defects, the majority of which were in *BRCA2* (12.7%), however, alterations were also seen in *ATM, BRCA1, CDK12, FANCA, RAD51B* and *RAD51C.* Additional studies have described other, low prevalence DDR gene alterations in prostate cancer [36,41]. Somatic alterations in HRR-related genes *BRCA2*, *CDK12*, *ATM* and *PALB2* are suggested to occur early in prostate cancer tumorigenesis since they are typically found in the primary tumor of patients with metastatic disease [42,43]. Higher rates of patients with germline alterations in HRR, specifically, *BRCA2*, are seen among patients presenting with metastatic disease (3–6%) compared with those with strictly localized disease (1–3%) [44,45]. Furthermore, patients with g*BRCA1/2* alterations diagnosed initially with localized prostate cancer are more likely to develop metastatic disease and have worse cancer-specific survival when compared with a similar noncarrier population [46,47], indicative of the aggressive nature of g*BRCA1/2* altered prostate cancer. The impact of *BRCA1/2* alterations on response to treatment and survival among patients with mCRPC is controversial; several retrospective and prospective trials suggest that g*BRCA1/2* loss of function alterations convey poorer survival and lower duration and rates of response to ARPIs [36,43,45,48–50], whereas other studies contradicted these findings, suggesting similar outcomes among g*BRCA1/2* patients and the general mCRPC population [51,52].

CDK12 altered prostate cancer appears to have a more aggressive course with poorer survival outcome, based on retrospective data [53–55]. Other HRR-related gene alterations are infrequent and robust data on their effect on patient outcome is lacking. Ultimately, the effect of HRR alterations on mCRPC outcomes continues to be defined.

Both tumor tissue samples and plasma circulating cell-free DNA provide a source for analysis of tumor genomics. Fresh tumor tissue may be obtained via needle biopsy but may be deferred by physicians and patients to avoid secondary risks. Furthermore, metastatic prostate cancer has a predilection for bony dissemination which is more challenging to biopsy and obtain adequate cellularity for analyses. Archival tumor tissue is used as a substitute to fresh biopsy; however, for certain gene cohorts this may not be representative of the metastatic genotype and archival tissue may also be limited due to insufficient cellularity and poor quality DNA. These challenges were exemplified by both the aforementioned study by Robinson *et al.* [23] and the PROfound trial [56]. In the former study, of the 189 fresh biopsies obtained only 150 (79%) samples proved to have >20% tumor content required for full analysis and bone biopsies had a particularly poor yield: 43/76 samples (56%) had sufficient tumor content. In the PROfound trial, the majority of samples were archival (89.9%) and samples from only 69% of patients were successfully sequenced (in some cases requiring repeat testing [57]). Marginally higher sequencing success rates were achieved in newly collected samples than archival samples (63.9 vs 56.9%, respectively) [57]. Consequently, studies relying on tumor tissue genomic analysis of mCRPC patients may under-represent or misrepresent certain prostate cancer patient populations. Profiling circulating tumor DNA (ctDNA) from plasma provides a minimally invasive alternative to tumor tissue profiling but is also compromised in some patients due to low tumor content. Several studies have established the validity of ctDNA profiling for identification of DDR defects [58–60]. Wyatt *et al.* demonstrated high concordance of somatic mutations and copy number changes identified in matching tumor tissue samples and ctDNA [60], establishing ctDNA profiling as a valid alternative to tumor tissue profiling in patients with sufficient ctDNA in circulation. More recently, the US FDA approved the use of the Foundation Medicine ctDNA assay, FoundationOne liquid CDx [61], for the identification of mutations in *BRCA1/2* and ATM in mCRPC patients potentially eligible for olaparib and rucaparib, another PARPi which has limited approval for the treatment of *BRCA 1/2* altered mCRPC [62]. ctDNA levels are correlated with disease burden and approximately 25% of patients with mCRPC have very low levels of ctDNA [60] that can preclude somatic profiling, resulting in false negatives; this is a particular problem if evaluating for copy number changes rather than mutations. Prioritization of tissue selection for testing will need to incorporate considerations of tissue availability as well as patient and tumor burden considerations. Patients with progressive higher burden disease would likely have sufficient quantities of ctDNA in their blood for successful cell-free DNA testing, while those with minimal burden disease and slow progression may be better served through tissue profiling.

Olaparib drug information

The PARP superfamily of enzymes takes part in multiple cellular processes, including DNA damage repair. The most well-defined activity in this regard is that of PARP1 which takes part in multiple DNA damage repair pathways including single-strand breaks and both NHEJ and HRR double-strand break repair pathways [63]. Olaparib (AZD2281/KU-0059436) is a PARP inhibitor, exerting its inhibitory activity on PARP1, PARP2 and PARP3 by binding to the NAD+ binding site on PARP molecules, inhibiting PARP activity and trapping PARP-DNA complexes at sites of DNA damage. This inhibition is hypothesized to result in accumulation of DSBs. In tumors harboring HRR-related gene alterations, these DSB are met with a faulty HRR pathway resulting in DNA lesions that are incompatible with cell viability and subsequent cell stasis and death (Figure 1) [64–66]. This concept, by which simultaneous aberrations in two genes and their respective functions result in cell death, whereas an aberration in any of the two alone is compatible with cell viability is termed synthetic lethality [34,35]. *In vitro* and *in vivo*, *BRCA1*/2 deficient cells are up to a 1000-times more sensitive to PARPi when compared with heterozygous mutant or wild-type cells [64,67–69] demonstrating both the possible lethal effect of PARP inhibition on *BRCA1/2* deficient cells as well as the potential high therapeutic index of this approach which exploits a tumor-specific defect that is not found in healthy cells. A Phase I clinical trial established the maximal tolerated dose of olaparib in capsule formulation at 400 mg twice daily. At this dose maximal plasma concentration was achieved in 1–3 h post dose, terminal elimination half life was 11.9 h and the majority of drug excretion occurred via feces and urine [70,71]. Of note, in this Phase I trial, antitumor activity was observed solely in patients confirmed to be carriers of *BRCA1/2* alterations. One of these was a patient with g*BRCA2* mutated prostate cancer who had a >50% prostate-specific antigen (PSA) reduction and resolution of bone metastasis in response to treatment with olaparib, with a duration of response that exceeded 2 years [70]. A Phase II study examining the efficacy and safety of olaparib among cancer

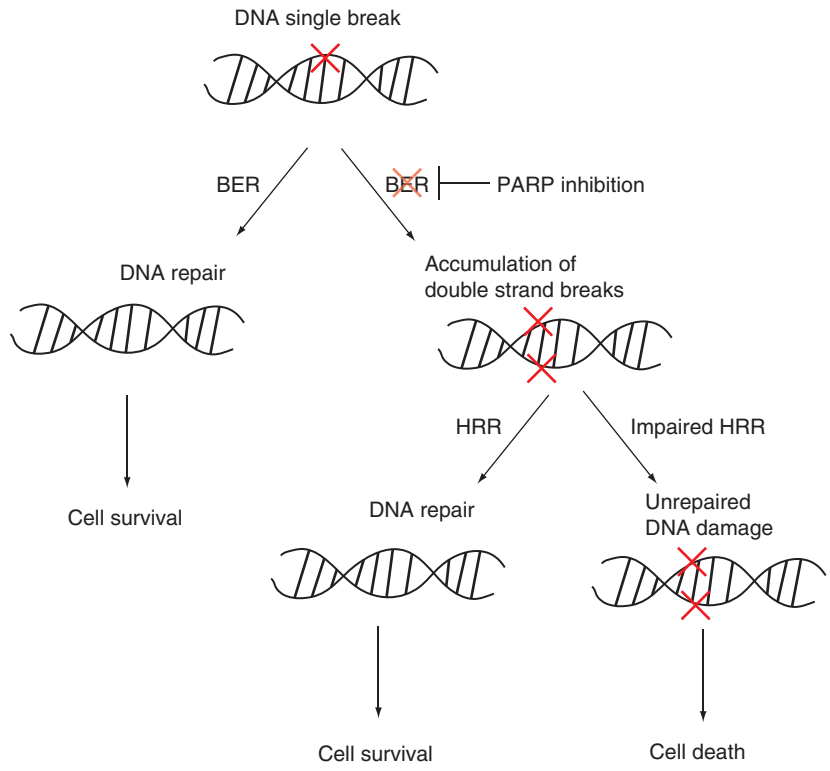

Figure 1. Poly-ADP-ribose polymerase inhibition mechanism of action.
BER: Base excision repair; HRR: Homologous recombination repair.

patients with g*BRCA1/2* mutations showed a 50% radiographic response among prostate cancer patients, further supporting the potential efficacy of olaparib in this sub-group of patients [28]. In 2016, an alternative formulation of olaparib at a dose of 300 mg in tablet form was shown to have similar or exceeding steady-state exposure to that of 400 mg in capsule formulation, simplifying drug administration [72]. Subsequent clinical trials of olaparib employed the 300 mg formulation twice daily.

Clinical trials of olaparib for mCRPC

Phase II trials of olaparib in patients with mCRPC

TOPARP A [73] was the first comprehensive study to explore the efficacy of olaparib in mCRPC. This Phase II, single-arm study, enrolled 50 molecularly unselected mCRPC patients who were heavily pretreated. The majority of patients had prior exposure to ARPIs; abiraterone (96%) and enzalutamide (28%) and taxane chemotherapy; docetaxel (100%) and cabazitaxel (58%). The response rate, defined as a composite of radiographic response, PSA response >50% and/or circulating tumor cells (CTC) conversion rate (decline from baseline to <5 cells per 7.5 ml of blood), was 33% (95% CI: 20–48%). Whole-exome sequencing of tumor tissue demonstrated that 16 patients (33%) harbored apparently deleterious alterations in genes linked to HRR, of which 14 (88%) had response to olaparib, compared with a 2/33 (6%) among patients without detected HRR defects, indicating that HRR gene alterations may serve as positive predictive biomarkers (sensitivity: 88%; specificity: 94%). Seven of the responders had *BRCA2* alteration(s), four had deleterious mutations in *ATM* and the remaining three had a somatic homozygous deletion of both *BRCA1* and *FANCA*, biallelic *PALB2* aberrations, and biallelic somatic aberrations in *HDAC2*. Interestingly, one of the two 'biomarker negative' patients who responded had monoallelic deletions of both *BRCA2* and *PALB2*. 'Biomarker positive' patients had significantly longer radiographic-PFS (rPFS) (median: 9.8 vs 2.7 months; $p < 0.001$) and overall survival (OS) (median: 13.8 vs 7.5 months; $p = 0.05$) when compared with the biomarker negative patients. Toxicity profile was in keeping with previous olaparib data, the most common olaparib-related grade 3–4 adverse events were anemia (20%) and fatigue (12%). A subsequent follow-up trial, TOPARP B [41] attempted to further define the role of alterations in genes related to HRR as predictive biomarkers for response to treatment with olaparib among mCRPC patients, as well as determine the optimal dosing of olaparib

Table 1. PROfound major outcomes.

Primary outcomes				
Cohort A – *BRCA1/2, ATM*	**Olaparib arm**	**Control arm**	**HR or OR (95% CI)**	**p-value**
rPFS	7.4 months	3.6 months	HR: 0.34 (0.25–0.47)	<0.001
Secondary outcomes				
Cohort A – *BRCA1/2, ATM*				
OS	19.1 months	14.7 months	HR: 0.69 (0.5–0.97)	0.02
ORR	33%	2%	OR: 20.86 (4.18–379.18)	<0.001
Time to second progression	15.5 months	10.6 months	HR: 0.64 (0.45–0.93)	NA
PSA50 RR	43%	8%	NA	NA
CTC conversion	30%	11%	NA	NA
Cohort B – *BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L*				
OS	14.1 months	11.5 months	HR: 0.96 (0.63–1.49)	NA
Time to second progression	9.9 months	7.9 months	HR: 0.77 (0.5–1.21)	NA
Entire population – cohort A and B				
rPFS	5.8 months	3.5 months	HR: 0.49 (0.38–0.63)	<0.001
OS	17.3 months	14.0 months	HR: 0.79 (0.61–1.03)	NA
ORR	22%	4%	OR: 5.93 (2.01–25.40)	NA
Time to second progression	13.4 months	9.7 months	HR: 0.68 (0.51–0.9)	NA
PSA50 RR	30%	10%	NA	NA
CTC conversion	27%	10%	NA	NA

CTC: Circulating tumor cell; HR: Hazard ratio; NA: Not applicable; OR: Odds ratio; ORR: Objective response rate; OS: Overall survival; PSA50 RR: PSA50 response rate (the proportion of patients with a decrease of greater than 50% in PSA from baseline); rPFS: Radiographic progression-free survival.
Data taken from [56,74].

for this indication. mCRPC patients with alterations in HRR-related genes that could be associated with sensitivity to PARPi were preselected. Eligible patients were randomized to receive either 300 mg or 400 mg twice daily in tablet formulation. The primary end point was response rate as defined in TOPARP-A. Ninety-eight patients with mCRPC harboring HRR alterations were randomized. The most common HRR-related alteration was in *BRCA2* (7%), followed by *ATM* (7%) and *CDK12* (6%). Distribution of HRR alterations was similar across cohorts with the exception of *CDK12* which had greater representation in the 300 mg dose cohort. There was no statistically significant difference between the dose cohorts with respect to the composite response rate of 54.3% and 39.1% ($p = 0.14$) in the 400 and 300 mg, respectively, with only the 400 mg cohort meeting the prespecified criteria for efficacy of >50% composite response rate. Response rates varied across the different gene alterations with the greatest response rate seen in the *BRCA1/2* subgroup (83.3%). Eleven patients pursued permitted dose escalation from 300 to 400 mg at time of progression, none of which achieved response to escalation. Safety profile was in line with previous reports, the most common drug-related adverse event, grade 3–4, was anemia (31 and 34% in the 300 and 400 mg, respectively); however, significantly more patients required dose modification in the 400 mg cohort compared with the 300 mg cohort primarily due to anemia (37 vs 12%). This study provided further support of the efficacy of olaparib in the treatment of HRR-altered mCRPC patients. While the results of this trial indicate that the 400 mg regimen may have superior efficacy, there were several confounding factors including the higher presentation of *CDK12* patients in the 300 mg dose regimen. This subgroup fared poorly regardless of dose cohort, and together with the high rate of dose reduction in the 400 mg dose cohort (37 vs 13%), suggests that the 300 mg dose regimen may be sufficient.

PROfound: Phase III trial of olaparib for the treatment of mCRPC

The efficacy of olaparib in the treatment of men with alterations in genes related to HRR mCRPC was further studied in the Phase III prospective, randomized, open label PROfound study (Table 1) [56]. In this trial, men with mCRPC were screened for prespecified somatic or germline alterations in genes directly or indirectly involved in HRR. Men in cohort A had at least one alteration in *BRCA1, BRCA2* or *ATM*, whereas men harboring alteration in at least one of 12 additional genes that were judged to be directly or indirectly involved in HRR (*BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L*) were enrolled in cohort B. Prior treatment with either enzalutamide or AAP for mCSPC, mCRPC or non-mCRPC

was a prerequisite for trial enrollment, prior taxane chemotherapy for metastatic disease in all castration states was permitted. Men in both cohorts were randomized in a 2:1 ratio to treatment with olaparib at a dose of 300 mg tablet formulation twice daily or physician's choice of enzalutamide or AAP. Crossover to olaparib at progression was allowed. The primary end point of the trial was rPFS in cohort A according to a blinded independent central review. Secondary end points were tested in a hierarchical manner: objective response rate (ORR) (cohort A), rPFS (overall population), time to pain progression (cohort A), OS (cohort A), PSA50 response rate (defined as decrease of PSA >50% from baseline) and CTC conversion rate. Of patients with evaluable biopsy samples, 778 (28%) harbored alterations in one or more of the 15 prespecified HRR-related genes and 387 patients met all eligibility criteria and were randomized to cohort A (245 patients) or cohort B (142 patients) based on their specific alterations. Approximately 20% of randomized patients received prior treatment with both enzalutamide and AAP and 65% received either 1 (45%) or 2 (20%) lines of taxane chemotherapy. Sixty-six percent of patients in the control group crossed over to olaparib following progression [74]. rPFS in cohort A was significantly longer in the olaparib arm (7.4 vs 3.6 months, hazard ratio [HR]: 0.34; 95% CI: 0.25–0.47; $p < 0.001$). ORR (33 vs 2%; odds ratio for objective response rate 20.86; 95% CI: 4.18–379.18; $p < 0.001$) and median time to pain progression (HR: 0.44; 95% CI: 0.22–0.91; $p = 0.02$) in cohort A were all superior in the olaparib arm compared with control. Additionally, PSA50 response rate (43 vs 8%) and CTC conversion rate (30 vs 11%) were numerically greater, albeit not statistically tested due to failure of interim survival analysis in cohort A to meet prespecified 0.01 two-sided alpha level. In a final analysis [74], OS in cohort A was superior in the olaparib arm compared with control (19.1 vs 14.7 months; HR: 0.69; 95% CI: 0.50–0.97; $p = 0.02$) and this was accentuated when adjusting for crossover in this cohort (HR: 0.42; 95% CI: 0.19–0.91). Time to second progression was also superior in the olaparib arm of cohort A (15.5 vs 10.6 months; HR: 0.64; 95% CI: 0.45–0.93). In the overall population of the trial (arm A + B), median rPFS was significantly longer in the olaparib arm compared with control (5.8 vs 3.5 months; HR: 0.49; 95% CI: 0.38–0.63; $p < 0.001$) [56]. Furthermore, ORR, time to pain progression, PSA50 response rate and CTC conversion rates were all numerically greater in the olaparib arm of the overall population, albeit to a lesser extent than in cohort A. A trend toward improved OS in the olaparib arm was demonstrated in the overall population (HR: 0.79; 95% CI: 0.61–1.03) and in cohort B (HR: 0.96; 95% CI: 0.63–1.49) with further support if this trend after adjusting for cross-over. Of note, in a survival analysis of patients with *PPP2R2A* alterations a detrimental effect was demonstrated in the olaparib arm compared with the control (HR for death 5.11; 95% CI: 1.10–35.73), subsequently, a *post-hoc* sensitivity analysis for OS excluding patients with *PPP2R2A* alterations, demonstrated a trend favoring the olaparib arm over the control arm in the overall population (HR: 0.76; 95% CI: 0.58–1.00) and in cohort B (HR: 0.79; 95% CI: 0.51–1.25) [74]. In keeping with previous reports of olaparib the most common adverse event among patients receiving olaparib was anemia (50%) followed by nausea (43%) and fatigue and asthenia (42%) both of which were primarily of grade 1–2. Anemia was also the most common grade 3–4 adverse event (23%) resulting in olaparib discontinuation in 7% of patients [74]. Health-related quality of life was better maintained in the olaparib arm than the control arm in both cohort A and the entire population and time to deterioration was numerically favorable in the olaparib arm of both cohorts as well [75], providing further support of the efficacy of this treatment.

Translating trials to practice: clinical considerations for olaparib use in mCRPC

Patient selection: do all HRR-related genes associate equally with response to PARP inhibition?

There are over 100 known genes that are directly or indirectly involved in HRR [76]. Different sets of HRR-related genes were eligibility requirements in the aforementioned Phase II and III trials [41,56,73]. The most commonly altered HRR gene in mCRPC is *BRCA2* with a prevalence of 7–14% in patients with evaluable tissue samples, whereas alterations in *BRCA1* are much less prevalent (~1%) [41,56,73]. All trials to date were under-powered to assess outcome by individual gene alterations, nonetheless, in all reported trials the *BRCA1/2* sub-group appears to fare better than other subgroups. In the PROfound trial a sub-group analysis of patients harboring *BRCA1/2* alterations (9.7% of evaluable population) suggested a significantly longer rPFS compared with the control arm (9.8 vs 3 months, HR: 0.22; 95% CI: 0.15–0.32) [56]. In a survival analysis of the *BRCA1/2* cohort, OS in the olaparib arm was 19.1 versus 15.1 months in the control arm [56]. Single gene sub-analysis revealed HR for death in the *BRCA2* cohort of 0.59 (95% CI: 0.37–0.95) whereas, for *BRCA1*, findings were similar in direction but with wide confidence intervals (HR: 0.42; 95% CI: 0.12–1.53) due to the much smaller cohort (13 patients) [74]. In contrast, the HR for death in the non-BRCA cohort (olaparib vs control) puts in question the efficacy of olaparib in this

cohort as a whole (HR: 0.95; 95% CI: 0.68–1.34) [74]. These findings suggest that olaparib treatment effects may vary per specific HRR gene alteration with the greatest benefit among patients harboring *BRCA1/2* alterations.

The efficacy of olaparib in the treatment of patients harboring alterations in *ATM* and *CDK12*, the next most frequently altered DNA repair genes in mCRPC, has been raised into question. ATM is a member of the phosphatidylinositol-3 kinase-like family of serine/threonine protein kinases, it plays a role in DNA damage response by phosphorylation of a multitude of downstream target proteins active in DDR, however, its role in HRR pathways is unclear. Cells with deficient *ATM* appear to have increased sensitivity to DNA damaging agents in preclinical studies [77]. In mCRPC, *ATM* alterations are present in approximately 5% of patients. A preclinical study aimed to investigate the impact of *ATM* loss or dysfunction on DDR and cell sensitivity to PARP inhibition [78]. In this study, *ATM* loss was shown to alter DDR, however, this did not occur via the HRR pathway which remained functionally intact. Furthermore, *ATM* loss in prostate cancer cells resulted in significant sensitivity to ionizing radiation, however, no significant difference in sensitivity was seen between *ATM* deficient and *ATM* proficient prostate cancer cells treated with carboplatin and PARP inhibition. Clinical trials have also questioned the efficacy of PARPi in the sub-group of patients harboring an *ATM* alteration. In the initial TOPARP-A trial 4/5 (80%) of patients with *ATM* alterations had composite response rate, however, the subsequent TOPARP-B demonstrated much lower composite response rate (36.8%; 16.3–61.6), the majority of which manifested as CTC conversion alone with only 2/19 of these patients having radiographic and/or PSA response (10.5%; 1.3–33.1). A retrospective study evaluating the response to olaparib among men with *BRCA1/2/ATM* altered mCRPC reported 0% PSA responses among men with *ATM* alterations [79]. In the *ATM* cohort of the PROfound trial (5.9% of the evaluable population) rPFS and OS did not differ between the olaparib and control arms (5.4 vs 4.7 months, HR: 1.04; 95% CI: 0.61–1.87) and (17.3 vs 17.9, HR: 0.82; 95% CI: 0.39–1.88), respectively [56]. The findings in this cohort are supported by preclinical data indicating that PARP inhibition induces reversible G2 arrest in ATM deficient cancer cells, resulting in reversible cell cycle arrest rather than cell death [77].

CDK12 alterations are found in 3–7% of mCRPC patients. *CDK12* is involved in multiple cell processes including regulating expression of genes involved in HRR; *BRCA1, ATR, FANCL* and *FANCD2*. In preclinical models absence of CDK12 and its associated cyclin kinase K resulted in transcription defects to *BRCA1* and *FANCL* and subsequent increased sensitivity to DNA damage [80,81]. In the PROfound trial, 89 patients (6.3%) with evaluable samples had aberrations in *CDK12*. In an exploratory analysis of this subgroup median rPFS was 5.1 and 2.2 months in the the olaparib and control group, respectively (HR: 0.74; 95% CI: 0.44–1.31) and OS was 14.2 and 11.5 months, respectively (HR: 0.69; 95% CI: 0.53–1.25) [56]. These findings are notable for this cohort's poorer outcome irrespective of arm of treatment when compared with the entire cohort and other subgroups, in keeping with previous reports of *CDK12* altered mCRPC outcome [53–55]. In the TOPARP-B trial, the overall response in the *CDK12* cohort was 25% (95% CI: 8.7–49.1%) all of which were limited to CTC conversion. Other case series show similarly low response rates; in a retrospective, multicenter trial 11/60 mCRPC patients harboring *CDK12* alterations were treated with PARPi and none had a PSA response. In contrast, patients with CDK12 defects treated with PD1 inhibitors (9/60) had a 33.3% PSA response rate [54]. Wu *et al.* analyzed mCRPC samples harboring alterations in *CDK12* [82] and demonstrated that these tumors are associated with higher neoantigen levels compared with other mCRPC tumors and increased tumor T-cell infiltration/clonal expansion, suggestive of potential response to immunotherapy, this hypothesis is being explored in clinical trials [83,84].

Over time, *bona fide* defects in DNA damage repair result in an accumulation of genomic aberrations and a distinct genomic scar depending on the affected DNA repair pathway. Whole-genome and exome sequencing of prostate cancers have shown that deleterious defects in mismatch repair genes, HRR genes and *CDK12* associate with mutually exclusive genomic phenotypes (signatures). The most distinctive feature of *BRCA2*-defective genomes is microhomology at chromosomal breakpoints whereas *CDK12* altered cancers exhibit focal tandem duplications [82]. *ATM* alterations are not linked to genomic signatures of defective HRR and show minimal if any distinctive phenotype [82,85,86]. A combined score of genomic scars linked to *BRCA1/2* deficiency has been termed a homologous recombination deficiency (HRD) phenotype. This HRD phenotype is linked to response to platinum-based chemotherapy and PARPi among *BRCA1/2* wild-type ovarian and triple-negative breast cancer patients [87–89]. Prostate cancer with *BRCA1/2* alterations also show evidence of HRD by genome or exome sequencing. Interestingly, in one such study, a few tumors without detected HRR-related gene alterations (12/286) exhibited evidence of HRD [90]. There is some suggestion that detection of the HRD phenotype may offer an alternative to standard HRR gene testing as a predictive biomarker for PARPi response, but prospective trials are needed.

The representation of the 11 additional genes in the PROfound trial was limited by their low prevalence. Of these, *RAD51* and *PALB2* function are closely related to that of *BRCA1/2* and, therefore, may be more likely to benefit from PARPi [91,92]. This is unlike patients with alterations in *PPP2R2A* treated with olaparib in the PROfound trial (six patients), who had a particularly poor survival compared with those in the control arm (four patients) (HR: 5.11; 95% CI: 1.1–35.73) [74].

Subsequent to the results of the PROfound trial, olaparib gained approval for the treatment of mCRPC who progressed on prior ARPI by key agencies. However, the approvals vary in the specific genes approved. While the US FDA granted approval to all HRR gene mutations examined in the PROfound trial, with the exception of *PPP2R2A*, the Canadian agency limited the approval to gene alterations represented in cohort A (i.e., BRCA1/2 and ATM) and the European Medicines Evaluation Agency specified the approval for those harboring alterations in *BRCA1/2*. Indeed, the results of the PROfound trial support the incorporation of olaparib into the treatment paradigm of mCRPC harboring *BRCA1/2* alterations, however, the data with regards to *ATM* and *CDK12* as well as other, low prevalence genes is not as evident. Single gene analyses in the PROfound trial are limited by their exploratory design and the small size of cohorts restricting their application in the general population. Further study into single gene cohorts, while desired, may prove impractical for accrual, and require large population-based analysis, potentially, meta-analysis across all PARPi trials or real-world evidence designs.

Timing: before or after docetaxel?

The PROfound trial was designed to enroll mCRPC patients as early as the first line of therapy for mCRPC or at later lines of therapy dictating ARPI treatment as the only mandatory prior line of therapy. Based on these criteria, approval was granted for the post ARPI state. However, the majority of patients were heavily pretreated. Interestingly, in cohort A, analysis of OS according to prior taxane exposure revealed greater benefit to olaparib in the population that was previously exposed to taxane (HR: 0.56; 95% CI: 0.38–0.84) compared with those who had no prior exposure (HR: 1.03; 95% CI: 0.53–1.92) [74]. These findings are in contrast to an exploratory analysis of patients in the *BRCA1/2* cohort in which patients who did not receive prior taxane therapy experienced greater survival benefit compared with the control group (OS not reached vs 18.8 months, HR: 0.3; 95% CI: 0.1–0.78) than those who had prior taxane therapy (OS: 17.4 vs 12.6 months, HR: 0.64; 95% CI: 0.39–1.08) [93]. These findings are suggestive of a potential greater benefit for olaparib at earlier lines of therapy in the *BRCA1/2* cohort, but possibly not in the *ATM* cohort that may have driven the OS results in the entire cohort A. Administration of olaparib at earlier lines of treatment is further supported by a shorter duration on olaparib observed in the control group that crossed over to olaparib compared with those initially randomized to olaparib (4.8 vs 7.6 months). Future studies (Table 3) will need to address the potential benefit of PARPi at earlier stages of disease, specifically in the *BRCA1/2* cohort, and evaluate the efficacy of olaparib compared with taxane chemotherapy [94,95], which has superior efficacy compared with second-line ARPI which was used as treatment in the control arm of the PROfound study.

Mechanisms of resistance

All patients who initially respond to PARPi eventually progress and response rates, even among the most responsive *BRCA1/2* cohort, are in the range of 40–50% [56,96,97] indicative of primary and secondary resistance. Four distinct mechanisms have been hypothesized to cause resistance to PARP inhibition, namely; increased drug efflux, decreased PARP trapping, restoration of the HRR pathway and stabilization stalled replication forks [98,99]. The only resistance mechanism that is clearly demonstrated in the clinical setting is restoration of the HRR pathway via reversion mutations in *BRCA2*. These reversion mutations are secondary mutations in *BRCA2* that restore the open reading frame of the gene, enabling translation of (at least partially) functional BRCA2 protein and subsequently, negating PARPi synthetic lethality effect. Multi-clonal *BRCA2* reversion mutations have been described as a mechanism of secondary resistance to PARPi among patients harboring g/s*BRCA2* and s*PALB2* alterations [58,100]. The prevalence of these mutations among HRR-deficient mCRPC patients and their effect on primary and secondary resistance to PARPi is yet to be determined in larger cohorts. There is limited data on the efficacy of available systemic therapies post PARPi to guide recommendations, although case series have described responses with platinum and taxane-based therapy in patients with mCRPC [101].

Table 2. Ongoing clinical trials.

Single agent								
Trial	**NCT**	**Indication**	**Investigational arms**	**Control arm**	**Primary end points**	**Status**	**Anticipated results**	**Ref.**
TRITON3	NCT02975934	mCRPC harboring BRCA1/2, ATM alterations post ARPIs	Rucaparib	Physician choice – enzalutamide – AAP – Docetaxel	rPFS	Recruiting	2022	[102]
PARP inhibition + ARPI								
Trial	**NCT**	**Indication**	**Investigational arms**	**Control arm**	**Primary end points**	**Status**	**Anticipated results**	
PROpel	NCT03732820	Molecularly unselected, first-line mCRPC	AAP and olaparib	AAP and placebo	rPFS	Active, completed accrual	2021	[103]
TALAPRO-2	NCT03395197	Molecularly unselected, first-line mCRPC	Enzalutamide and talazoparib	Enzalutamide and placebo	Confirm dose of talazoparib rPFS	Recruiting	2021	[104]
CASPAR	NCT04455750	Molecularly unselected, first-line mCRPC	Enzalutamide and rucaparib	Enzalutamide and placebo	rPFS OS	Not yet recruiting	2023	[105]
MAGNITUDE	NCT03748641	Cohort 1: first-line mCRPC, harboring HRR-related gene alterations	AAP and niraparib	AAP and placebo	rPFS in cohorts 1 and 3	Recruiting	2022	[106]
		Cohort 2: first-line mCRPC, not harboring HRR-related gene alterations	AAP and niraparib	AAP and placebo				
		Cohort 3: open label-molecularly unselected mCRPC	New formulation of niraparib 200 mg and AA 1000 mg tablets and prednisone	NA				
AMPLITUDE	NCT04497844	mCSPS harboring HRR-related gene alterations	AAP and niraparib	AAP and placebo	rPFS	Recruiting	2024	[107]
PARP inhibition and IO								
Trial	**NCT**	**Indication**	**Investigational arms**	**Control arm**	**Primary end points**	**Status**	**Anticipated results**	
KEYLYNK-010	NCT03834519	Molecularly unselected mCRPC post one line of ARPI and docetaxel	Olaparib and pembrolizumab	Enzalutamide or AAP	OS rPFS	Recruiting	2022	[108]

AA: Abiraterone acetate; AAP: Abiraterone acetate and prednisone; ARPI: Androgen receptor pathway inhibitor; HRR: Homologous recombination repair; IO: Immuno-oncology; mCRPC: Metastatic castrate-resistant prostate cancer; mCSPC: Metastatic castrate sensitive prostate cancer; OS: Overall survival; rPFS: Radiographic progression-free survival.

Ongoing clinical trials with olaparib in the treatment of metastatic prostate cancer

There are multiple early and advanced stage clinical trials exploring olaparib in different prostate cancer disease states with different drug combinations. Several such combinations are currently being studied in Phase III trials (Table 2).

The concomitant inhibition of AR pathway and PARP has raised interest in the treatment of prostate cancer. AR has a direct role in regulation of HRR pathway. Expression of *RAD51*, a key factor in HRR pathway, is upregulated in high AR expressing prostate cancer cells. AR signaling blockade has been shown to reduce HRR activity and induce PARP signaling, similar to the upregulation in *BRCA* defective cells [109]. PARP1, specifically, has also been shown to take part in modulation of AR function acting as a transcriptional factor [110]. Subsequently, it was hypothesized that dual PARP and AR pathway inhibition may have a synergistic effect in the treatment of prostate cancer. A Phase II randomized, placebo-controlled clinical trial compared treatment with abiraterone and olaparib to abiraterone and placebo in men with mCRPC irrespective of HRR status [111]. One hundred and forty two patients who received up to two prior lines of chemotherapy and no previous ARPIs were enrolled. rPFS, the primary outcome of the study, was superior for the combination arm compared with the control arm (13.8 vs 8.2 months, HR: 0.65; 95% CI: 0.44–0.97; p = 0.034). At initial analysis (predatabase lock) 15% of patients had alterations in HRR-related genes, 25% of patients had confirmed wild-type HRR, whereas the remaining 61% had incomplete HRR profile characterization (germline, plasma tumor DNA and tumor tissue profiling). At final analysis (postdatabase lock), 16% had alterations in HRR-related genes, 51% of patients had confirmed wild-type

Table 3. Other poly-ADP-ribose polymerase inhibitors in development for prostate cancer.

Drug name/drug information	Niraparib	Rucaparib	Talazoparib	Ref.
Dosage	300 mg QD	600 mg BID	1 mg QD†	
T1/2	36.4 h (range: 32.8–46.0)	Range: 15.3–79.2 h	52.9 h (SD 13.4)	
Trial mCRPC	Phase II, open label, single-arm GALAHAD	Phase II, open label, single-arm TRITON2	Phase II, open label, single-arm TALPRO-1	[96,97,119–121]
HRR-related gene alterations	*BRCA1, BRCA2, ATM, FANCA, PALB2, CHEK2, BRIP1, HDAC2*	*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*	*BRCA1, BRCA2, ATM, ATR,CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*	
Eligibility criteria of interest	≥1 prior ARPI and ≥1 taxane chemotherapy treatment Biallelic alteration in at least one HRR-related gene of interest	≥1 prior ARPI and 1 taxane chemotherapy treatment Monoallelic or biallelic alteration in at least one HRR-related gene of interest	≥1 prior ARPI and ≥1 taxane chemotherapy treatment Biallelic alteration in at least one HRR-related gene of interest Measurable soft tissue disease per RECIST 1.1	
Primary outcome	ORR in the *BRCA1/2* cohort	ORR PSA50 RR	ORR	
Significant reported outcomes (95% CI)	ORR in BRCA1/2 cohort: 41.4%	ORR in the *BRCA1/2* cohort: 43.5%(31.0–56.7%) PSA50 RR in the *BRCA1/2* cohort: 54.8% (45.2–64.1%) ORR: *ATM*: 10.5%; *CDK12*: 0%; *CHEK2*: 11.1% PSA50 RR: *ATM:* 4.1%; *CDK12*: 6.7%; *CHEK2*: 16.7%	ORR: 25.6% (13.5–41.2) ORR *BRCA1/2*: 50.0% (27.2–72.8); *ATM*: 7.1% (0.2–33.9)	
US FDA approval	Breakthrough therapy designation for *BRCA1/2* alterations	Accelerated approval for *BRCA1/2* alterations	NA	

†Adjustment required for renal impairment.
ARPI: Androgen receptor pathway inhibitor; BID: Twice daily; HRR: Homologous recombination repair; mCRPC: Metastatic castrate-resistant prostate cancer; ref: reference; NA: Not applicable; ORR: Objective response rate; PSA50 RR: PSA50 response rate (the proportion of patients with a decrease of greater than 50% in PSA from baseline); QD: Once daily; $T_{1/2}$: Elimination half time.

HRR and the remaining 32% had partial HRR profile characterization [112]. In a preplanned subgroup analysis, rPFS was longer in the combination arm compared with the control arm irrespective of HRR status, though all did not meet significance, possibly due to small sample size. The PROpel trial [103] is a Phase III, randomized, placebo-controlled clinical trial designed to compare treatment with abiraterone and olaparib to abiraterone and placebo in a population of molecularly unselected mCRPC patients at first-line setting. The trial has completed accrual and preliminary results are anticipated in 2021.

An additional combination of interest is olaparib and anti PD1 immunotherapy. In preclinical *in vitro* and *in vivo* models, concomitant PARP and PD1/PDL1 inhibition demonstrated a synergistic effect in both wild-type and mutated *BRCA1/2* ovarian and prostate cancer cells [113,114]. A Phase Ib/II, multi-arm trial, reported in abstract form, evaluated the combination of olaparib and pembrolizumab in molecularly unselected men with mCRPC in an advanced line setting. Limited response was seen in this study with 9% (7/82) PSA50 response rate and an ORR of 8% (2/24) [115]. More significant PSA50 responses (47%) were seen among molecularly unselected mCRPC patients in a Phase II, single-arm trial examining the efficacy of a combination of durvalumab (PD-L1 inhibitor) and olaparib [116]. A regimen of olaparib in combination with pembrolizumab is currently being studied in a Phase III open label, randomized, KEYLYNK-010 trial comparing olaparib and pembrolizumab to enzalutamide or abiraterone in a molecularly unselected mCRPC patient population post docetaxel and one prior line of ARPI [108].

Additional PARP inhibitors in clinical development for prostate cancer

In addition to olaparib, there are three other PARPi that have been approved by the FDA for the treatment of several cancer types; niraparib, rucaparib and talazoparib (Table 3). All agents target multiple enzymes of the PARP family inhibiting PARP activity and trapping PARP complexes at sites of DNA damage, however their selectivity and potency vary and each has a unique range of off-target kinase activity. Niraparib was shown to have the greatest selectivity to PARP 1 and 2 and talazoparib has the greatest trapping potency [65,117,118]. Rucaparib was assessed in a Phase II, open label, single-arm, TRITON2 trial (Table 2) [96]. In this trial, 115 patients with *BRCA1/2* as well additional HRR-related alterations, who have progressed on ARPI and taxane chemotherapy, were enrolled to

receive rucaparib at a dose of 600 mg twice daily. ORR per independent review in the *BRCA1/2* cohort, the primary end point of the trial, was 43.5% (95% CI: 31–56.7%). Of note, In a report of patients with non-*BRCA* alteration in TRITON2 trial [119] minimal radiographic and PSA responses were seen among patients with *ATM*, *CDK12* and *CHEK2*, while greater proportion of responses were seen among patients with alterations in lower prevalence genes; *FANCA, PALB2, BRIP1* and *RAD51b*, albeit at very small numbers. Enrollment in TRITON2 trial was not restricted to biallelic alterations and either biallelic or monoallelic alterations were permitted. Patients with biallelic *BRCA2* alterations had the greatest proportion of responses, however, responses were also reported among patients with monoallelic alterations [96]. Subsequently, rucaparib gained accelerated approval by the FDA for the treatment of mCRPC harboring BRCA1/2 alterations post ARPI and taxane chemotherapy. Rucaparib is currently being evaluated in a Phase III, randomized controlled trial compared with physician choice of enzalutamide, abiraterone or docetaxel in men with mCRPC harboring alterations in *BRCA1/2* or *ATM*, who have progressed on one line of ARPI (Table 3) [102]. Niraparib was granted breakthrough drug designation for the treatment of men with mCRPC harboring *BRCA1/2* alterations following initial results of the Phase II, open label, single-arm GALAHAD trial [120]. The study population was similar to that of the TRITON2 trial, albeit with somewhat different HRR alterations (Table 3). Niraparib was administered once daily at a dose of 300 mg. The ORR in the BRCA1/2 population of the trial was 41.4%. Talazoparib is currently being evaluated for the treatment of mCRPC harboring HRR-related gene alterations in a Phase II, open label, single-arm TALAPRO1 trial [121]. Patient population in this trial differs from the other trials with regards to non-*BRCA1/2* HRR alterations and disease dissemination, limiting enrollment to patients with measurable, soft tissue disease (Table 3). Preliminary results demonstrated an ORR of 25.6% (95% CI: 13.5–41.2%) in the entire cohort and 50% (95% CI: 27.2–72.8%) in the *BRCA1/2* cohort. Results of trials evaluating PARPis consistently demonstrated the efficacy of PARP inhibition among mCRPC patients with *BRCA1/2* alterations. There are ongoing Phase III clinical trials evaluating the efficacy of the different PARPis in combination with additional agents in different disease states (Table 2) [104–107]. An additional question of interest is whether drug properties of the different PARPi agents may convey differential outcomes. Head to head trials are needed to determine whether such differences have clinical impact.

Conclusion & future perspective

Biomarker directed therapy is considered the holy grail of cancer therapy, providing personalized, patient tailored treatment with the aim of achieving maximal treatment response while steering away from potential detrimental side effects of futile treatments. The PROfound trial demonstrated improved OS and rPFS in the investigational arm, establishing the superiority of olaparib over physician's choice of ARPI in an HRR altered biomarker positive population of mCRPC patients. This marks significant progress in the treatment of mCRPC patients, as olaparib becomes the first molecularly targeted therapy in this setting, as well as underlines the importance of molecular screening. The most substantial and consistent evidence supports the incorporation of olaparib into the treatment algorithm of *BRCA1/2* altered mCRPC tumors, whereas patients harboring alterations in *ATM*, *CDK12* may benefit from alternative treatments and patients with *PPP2R2A* alterations experience detrimental effect with olaparib. Evidence of olaparib for other HRR-related gene alterations is limited. Single gene trials are impractical due to their low prevalence and further research is required to understand the benefit of PARP inhibition in these cohorts. a search for alternative predictive tools in this setting may be more feasible. Additionally, future trials will need to address the timing of PARPi within the mCRPC treatment paradigm, the efficacy of PARPi combination treatments and whether any of the PARPi may be superior to other agents in this class with regards to disease outcomes, safety profile or patient experience.

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In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

Executive summary

Introduction

- Recent advances in treatment of metastatic prostate cancer (mPC) have improved patients' outcome.
- Prostate cancer remains the second leading cause of cancer-related death among men.
- Up to 90% of patients with metastatic castrate-resistant prostate cancer (mCRPC) harbor potentially targetable gene alterations.
- The most frequently aberrant genes in mCRPC are *AR*, *ETS* family, *TP53* and *PTEN*.

Homologous recombination repair & prostate cancer

- Up to 25% of patients with mCRPC harbor alterations in genes directly or indirectly involved in homologous recombination repair (HRR).
- Tumors harboring loss of function alteration in HRR are dependent on the more error prone nonhomologous end joining pathway and are more inclined to genomic instability.
- Both tissue samples and plasma circulating tumor DNA (ctDNA) are amenable to genomic analysis.
- Tissue samples are limited by accessibility and quality of sample.
- Plasma ctDNA limited to samples with adequate ctDNA quantity.

Olaparib drug information

- Olaparib is an inhibitor of poly-ADP-ribose polymerase, resulting in accumulation of double-strand breaks.
- PARP inhibition, via olaparib, in patients with alterations in BRCA1/2 and possibly other HRR-related genes results in synthetic lethality and cell death.

Clinical trials of olaparib for mCRPC

- Two Phase II trials, TOPARP-a and TOPARP-B demonstrated significant response rate among mCRPC patients harboring alteration in HRR-related genes, treated with olaparib.
- PROfound, Phase III, randomized, open label trial demonstrated superior radiographic progression-free survival (PFS) and overall survival (OS) among BRCA1/2, ATM altered mCRPC patients when compared with physicians' choice of androgen receptor pathway inhibitors.

Translating trials to practice: clinical considerations for olaparib use in mCRPC

- Results of the PROfound trial are inconclusive regarding the efficacy of olaparib in non-BRCA HRR-related altered genes, specifically, CDK12 and ATM.
- Results of the PROfound trial do not provide data as to the optimal timing of olaparib within the treatment algorithm of HRR-altered mCRPC.

Ongoing clinical trials with olaparib in the treatment of metastatic prostate cancer

- Ongoing Phase III clinical trials are evaluating the combination of olaparib and abiraterone acetate and prednisone in the treatment of mCRPC.
- Ongoing Phase III clinical trial is evaluating the combination of olaparib and pembrolizumab in the treatment of mCRPC.

Additional PARP inhibitors in clinical development for prostate cancer

- Niraparib, rucaparib and talozaparib are additional agents in the class of poly-ADP-ribose polymerase inhibitor.
- The additional three agents are at different stages of evaluation and approval for the treatment of mCRPC patients harboring alterations in HRR-related genes.

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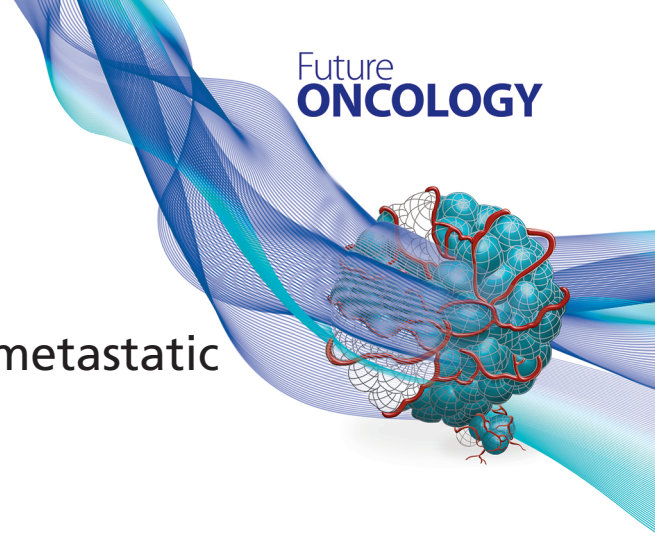
Drug Evaluation

Future ONCOLOGY



Apalutamide for the treatment of metastatic castration-sensitive prostate cancer

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Prostate cancer is the fifth leading cause of cancer-related death among men with the majority of deaths linked to metastatic disease. Accumulating clinical data have confirmed the substantial survival benefit of the addition of docetaxel or androgen signaling inhibitors to androgen deprivation therapy for the treatment of metastatic castration-sensitive prostate cancer (mCSPC). Apalutamide, a next-generation androgen receptor inhibitor, has recently been shown to provide an added survival benefit in the treatment of mCSPC and consequently approved for this indication. This review summarizes the body of evidence with regards to the preclinical activity and clinical efficacy of apalutamide with a specific focus on its efficacy in the treatment of mCSPC.

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Keywords: additional indications • apalutamide • castrate sensitive • efficacy • future trials • mechanism of action • metastatic • prostate cancer • TITAN trial • toxicity

Prostate cancer is the second most frequent cause of cancer and the fifth leading cause of death among men [1]. In the USA, it is estimated that 4% of men age <75 years and 12% of men aged ≥75 diagnosed with prostate cancer will present with metastatic disease at diagnosis [2]. Historical data indicate that an additional 18%, diagnosed with localized disease will eventually develop metastatic disease [3]. Whereas a more recent report suggests lower rates of metastatic recurrence, ranging between 2.4 and 5.6% at 10 years follow-up [4]. Globally, the incidence rate of metastatic disease varies with a large part of the world having higher rates of metastatic disease than that seen in the USA. This is suggested by higher rates of prostate cancer-related mortality, the vast majority of which are linked to metastatic disease. According to GLOBOCAN, in 2018 the global age standardized prostate cancer-related death rate was 7.6 per 100,000; ranging from as high as 26.8 per 100,000 in southern Africa to as low as 3.3 per 100,000 in south-central Asia [5].

Disease dissemination occurs in two potential pathways; via hematogenous spread, most commonly involving the bones of the axial skeleton, and lymphatic spread, involving the pelvic or retroperitoneal nodes with no consistent sentinel landing zone. The high burden of skeletal disease at diagnosis has been shown to be prognostic [6]. High burden disease was defined in the CHAARTED trial as the presence of visceral metastases and/or 4 or more bone metastases, with at least one of which involves the extra axial skeleton [7]. High burden disease bears a much worse survival outcome than that of low volume disease (HR for death 1.9–2.48; 95% CI: 1.31–3.36) [8]. It should be noted that, visceral involvement carries a particularly poor prognosis [9,10]. Regardless of initial characteristics of metastatic prostate cancer, the disease is, in the vast majority of cases, fatal (5-year relative survival of 30.1%; 95% CI: 29.5–30.7) [11]. The rates of metastatic disease as well as its consequential fatality rates are indicative of a need for more effective interventions in the treatment of this disease state.

The mainstay of treatment for mCSPC is androgen deprivation therapy (ADT) in the form of medical or surgical castration [12,13]. The majority of patients will respond to initial treatment with ADT. however, patients will inevitably develop castration resistance, which is defined as progressive disease despite castrate levels of testosterone [14]. The median time to progression to castrate-resistant disease, following initiation of ADT is 1–2 year [8,15]. Once disease has entered the castration-resistant state, the addition of androgen signaling inhibitors, taxane chemotherapy, immunotherapy or bone-targeted radiopharmaceutical agents results in modestly improved survival [16].

Future Medicine

The concept of initial castration of patients diagnosed with metastatic prostate cancer, followed by an addition of active agents at time of castration resistance has been the standard of care for nearly 80 years. Since 2015, the treatment paradigm of mCSPC has been redefined. The publication of several Phase III, randomized, clinical trials that demonstrated a substantial survival benefit to the addition of docetaxel or one of several androgen signaling inhibitors to ADT in the mCSPC setting [7,17–25] established this approach as the new standard of care.

Apalutamide is a next-generation androgen receptor (AR) inhibitor, which has been approved for the treatment of nonmetastatic castrate-resistant prostate cancer (nmCRPC) and mCSPC. The following review summarizes the published preclinical and clinical data on apalutamide with a focus on the treatment with apalutamide in the mCSPC setting.

Prostate cancer, androgen & the AR

Prostate cancer is an androgen responsive disease. Since 1941, when Huggins and Hodges first demonstrated that testosterone ablation promotes prostate cancer disease regression, ADT via surgical or chemical castration has become the mainstay of treatment for metastatic prostate cancer [12].

Androgen production

The main source of androgen is testosterone, which is synthesized in the testes. In addition, the adrenal gland serves as a minor source of androgen in the form of androstenedione and dehydroepiandrosterone (DHEA). In the prostate, testosterone is reduced by 5α-reductase to 5α-dihydrotestosterone (DHT), a more potent AR agonist [26]. Testosterone production in the testis and the adrenal are regulated via different pathways. In the testis, it is regulated by secretion of gonadotropin-releasing hormone from the hypothalamus, which stimulates release of luteinizing hormone. Luteinizing hormone in turn stimulates production of testosterone by Leydig cells. In contrast, androgen production in the adrenal is driven by secretion of adrenocorticotropin hormone from the anterior pituitary. This secretion is regulated by corticotropin-releasing hormone secreted from the hypothalamous [27].

Surgical castration (via orchiectomy) or chemical castration (via gonadotropin-releasing hormone agonists and antagonist) results in cessation of production of testosterone in the testes and castrate levels of testosterone in the serum. Such castration only partially affects the testosterone and DHT in prostatic cancer tissue. An analysis of human prostatic tissue [28] demonstrated that, following castration, DHT levels remained at approximately 25% of the amount measured before androgen deprivation therapy. Moreover, testosterone levels in castrate-resistant prostate cancer (CRPC) tissue were shown to be similar to those of noncastrated healthy prostate tissue [29,30]. The persistent levels of tumor androgen are suggested to be due to residual adrenal production of androgens which are converted into DHT in the prostate [28,31] as well as prostate cancer cells' autonomic intracrine stereogenesis [32].

AR

AR is a 110 kD nuclear receptor activated by two ligands, testosterone and DHT [33]. The AR, like other members of the steroid receptor superfamily, contains four functional domains; a conserved DNA binding domain, a hinge region, a ligand-binding domain and a less conserved amino-terminal domain [34,35]. Binding of testosterone and DHT, to the ligand-binding domain of the AR in the cytoplasm of prostate cells promotes dissociation of the AR from heat shock proteins, followed by phosphorylation and dimerization of the AR into its active form. Activated, ligand bound AR is then translocated to the nucleus where it binds to androgen responsive elements in the promoter regions of target genes to induce proliferative, apoptotic and angiogenic events [36].

In the normal prostate tissue, androgen-bound AR functions as a transcription factor to regulate genes involved in an array of physiological processes, most notably male sexual differentiation and maturation, and the maintenance of spermatogenesis [37]. In prostate cancer, AR is expressed in the cancerous cells throughout cancer progression, both in the castration-sensitive and -resistant states [36]. Activation of the AR results in enhanced proliferation, primarily by inducing increase of cyclin-dependent kinase activity and stimulation of cells to enter S Phase of the cell cycle, as well as down regulation of the cell cycle inhibitor p16 [38]. In addition, activation of the AR induces an anti-apoptotic effect via up-regulation of p21 (an anti-apoptotic factor), and via inhibition of caspase activation in both extrinsic and intrinsic cell death pathways [39,40].

One of the main mechanisms of escape from castration, resulting in the CRPC state, is restoration of competent AR signaling [41] which is attributed to result from multiple mechanisms including persistent extra-gonadal androgen production via adrenal or intratumoral production, AR alterations resulting in enhanced ligand-dependent or nonligand-dependent activation and activation and cross talk with other signal transduction pathways [42].

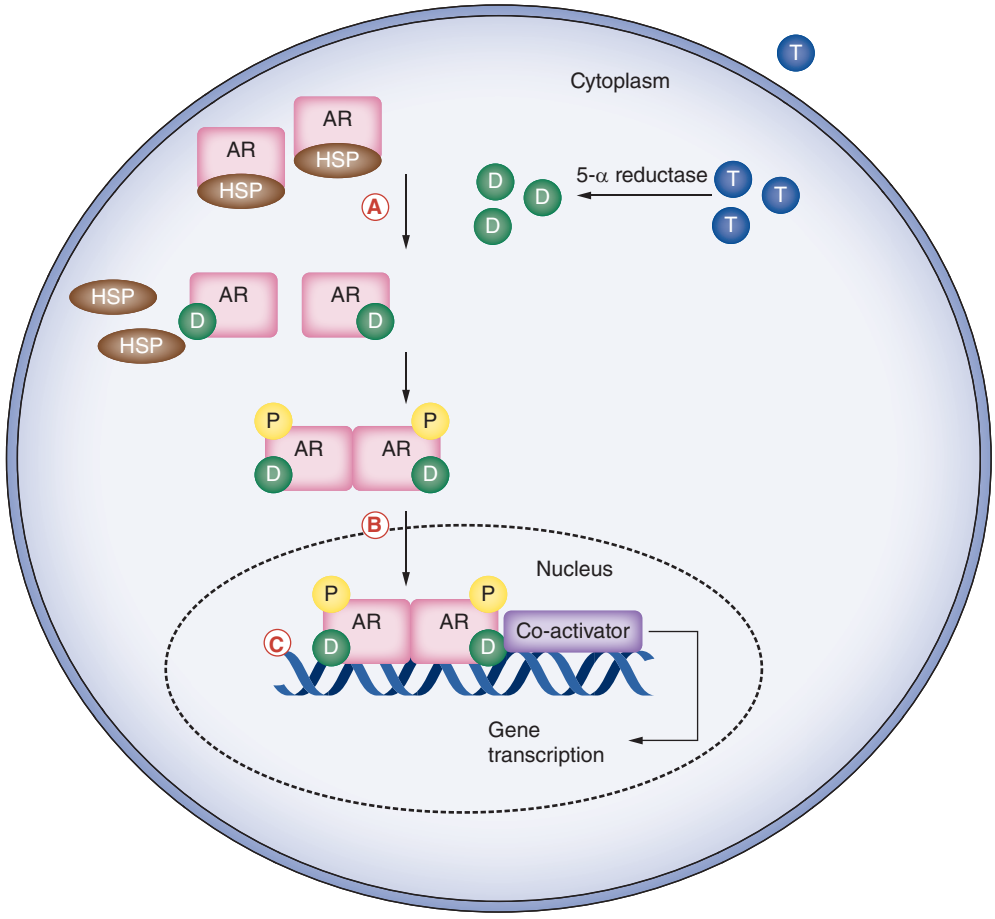

Figure 1. Apalutamide mechanism of action in prostate cancer. (A) Apalutamide binds to the ligand-binding domain of AR, preventing the attachment of androgens to their binding domain, rendering the AR inactive. **(B)** Apalutamide inhibits translocation of AR from cytoplasm to nucleus **(C)** Apalutamide inhibits nuclear AR recruitment to promoters of target genes in prostate cancer-cells.
AR: Androgen receptor; D-5α: Dihydrotestosterone; HSP: Heat shock protein; P: Phosphorus; T: Testosterone.

Apalutamide: drug information

Apalutamide is an orally administered compound that is a next-generation antiandrogen selective AR inhibitor. Based on a Phase I clinical trial, the recommended initial treatment dose is 240 mg daily. At this dose, the mean steady-state C_{max} and $AUC_{0–24\ hours}$ were 7.6 and 127 μgh/ml, respectively. The mean half-life values at steady-state were 3–4 days [43].

Compared with the earlier generation AR inhibitor bicalutamide, apalutamide binds to the ligand-binding domain of the AR with a 7–10-fold greater affinity and has no significant AR agonist activity [44]. Furthermore, apalutamide has been shown to decrease translocation of AR from cytoplasm to nucleus, an essential step in AR-mediated gene-regulation. In addition, it has been shown to inhibit nuclear AR recruitment to promoters of target genes in prostate cancer cells with potential to modulate transcription. Both are indicative of apalutamide's activity in transcription inhibition [44] (Figure 1). In a clinical trial, administration of [^{18}F]fluoro-α-dihydrotestosterone (FDHT), following treatment with apalutamide at a dose of ≥120 mg QD resulted in a decline of ≥90% in uptake of FDHT suggesting that treatment with apalutamide results in a decrease of ≥90% of androgen binding to AR [43].

Apalutamide: clinical data

Apalutamide: prior clinical trials

Metastatic castration-resistant prostate cancer

The activity of apalutamide in patients with and without prior abiraterone acetate plus prednisone (AAP) treatment was evaluated in a Phase II, open-label, single-arm clinical trial [45]. Forty-six patients were enrolled in the AAP-naive (n = 25) and post-AAP (n = 21) cohorts. The median duration of apalutamide treatment was 21 months (range: 2.6–37.5) for AAP-naive and 4.9 months (range: 1.3–23.2) for post-AAP cohorts. A 50% or greater decline in PSA from baseline at 12 weeks was observed in 88% (95% CI: 69–97%) of AAP-naive patients and 22% (95% CI: 6–48%) of post-AAP patients. The proportion of patients with PSA decline from baseline of ≥50% at any time was 92% for AAP-naive patients and 28% for post-AAP patients. The median time to PSA progression was 18.2 months (95% CI: 8.3 months–not reached) for the AAP-naive cohort and 3.7 months (95% CI: 2.8–5.6 months) for the post-AAP cohort. The most common treatment-related adverse events were fatigue, nausea, abdominal pain and diarrhea. This preliminary data demonstrated the clinical activity of apalutamide in the treatment of mCRPC. A Phase III randomized, placebo-controlled double-blind study of apalutamide in combination with AAP versus AAP alone in men with mCRPC (the ACIS study) has completed accrual and results are awaited on the primary end point of radiographic progression-free survival [46] (ClincialTrials.gov; NCT02257736).

Nonmetastatic (M0) castration-resistant prostate cancer

The efficacy of apalutamide added to continuous ADT in the treatment of nonmetastatic (M0) castration-resistant prostate cancer (nmCRPC) was evaluated in a double-blind, placebo-controlled, Phase III trial (SPARTAN trial) [47]. In this trial, 1207 men were enrolled with nmCRPC who were at high risk for the development of metastasis, defined as a PSA doubling time of 10 months or less during continuous ADT. The participants underwent a 2:1 randomization to apalutamide or placebo, plus ADT, respectively. The primary end point of this trial, median metastasis-free survival, was significantly improved with apalutamide versus placebo: 40.5 months in the apalutamide arm versus 16.2 months in the placebo arm (HR: 0.28; 95% CI: 0.23–0.35; $p < 0.001$). Second-progression-free survival (defined from the time of randomization to investigator determined disease progression with first subsequent therapy or death) was also significantly longer in the apalutamide arm (HR: 0.49; 95% CI: 0.36 –0.66). A final survival report was issued with a follow-up of 52 months and occurrences of 428 of 427 required OS events. The addition of apalutamide demonstrated a significant survival benefit (mOS 73.9 vs 59.9 months in the apalutamide and placebo arms respectfully; HR: 0.784; $p = 0.0161$) [48]. The health-related quality of life in the apalutamide arm did not differ substantially from that of the placebo arm [49]. Apalutamide treatment was well tolerated and drug-related adverse events in the apalutamide arm vs placebo arm that were considered of interest were fatigue (30.4 vs 21.1%), rash (23.8 vs 5.5%), falls (15.6 vs 9.0%), fractures (11.7 vs 6.5%), hypothyroidism (8.1 vs 2.0%) and seizures (0.2 vs 0%). The SPARTAN trial established the superiority of apalutamide over placebo in the treatment of high-risk nmCRPC. Subsequently, apalutamide was the first drug approved for the treatment of high-risk nmCRPC both in North America and Europe.

Apalutamide in the treatment of castration-sensitive metastatic prostate cancer

Rational

A key factor in progression to the castration-resistant state is dependent upon restoration of AR signaling and enhanced AR transcription activity [31]. As previously described, AR activity in prostate cancer cells is maintained following castration. Deeper AR signaling inhibition at the hormone-sensitive state of disease, prior to development of resistance pathways, is postulated to yield greater clinical benefit. This hypothesis is supported by preclinical data showing that the addition of flutamide, a first-generation AR blocker, acted to suppress the binding of the residual DHT to AR in prostate cancer tissue [28]. Clinical trials have demonstrated that the addition of first-generation AR blockers bicalutamide, nilutamide and flutamide, to standard androgen suppression for the treatment of mCSPC improved 5-year survival by 2–3% [50]. The increased potency and efficacy of next-generation AR inhibitor over earlier-generation AR inhibitors in the treatment of mCRPC [51,52] offers an indication that they may have an added benefit in the mCSPC setting.

Table 1. TITAN trial, major outcomes.

Outcomes	Apalutamide arm	Placebo arm	Hazard ratio (95% CI)	p-value
Primary outcomes				
Median radiographic progression free survival months (95% CI)	NE	22.1 (18.5–32.9)	–	–
Patients with radiographic progression free survival at24 months, % (95% CI)	68.2 (62.9–72.9)	47.5 (42.1–52.8)	0.48 (0.39–0.60)	$p < 0.001$
Median overall survival months (95% CI)	NE	NE	–	–
Patients with overall survival at 24 months, % (95% CI)	82.4 (78.4–85.8)	73.5 (68.7–77.8)	0.67 (0.51–0.89)	$p = 0.005$
Secondary outcomes				
Median time to cytotoxic chemotherapy	NE	NE	0.39 (0.27–0.56)	$p < 0.001$
Median time to pain progression	NE	NE	0.83 (0.65–1.05)	$p = 0.12$
Additional clinically relevant outcomes				
Median time to symptomatic local progression	NE	NE	1.20 (0.71–2.02)	–
Median time to PSA progression	NE	12.9	0.26 (0.21–0.32)	–
Median second progression-free survival	NE	NE	0.66 (0.50–0.87)	–

Created using data from [17].
NE: Could not be estimated; PSA: Prostate specific antigen.

Efficacy

The TITAN trial [17] was a randomized, double-blind, placebo-controlled, multinational trial designed to determine whether apalutamide, at a dose of 240 mg daily, would result in longer radiographic progression-free survival (rPFS) and overall survival (OS) with an acceptable safety profile and health-related quality of life among patients with mCSPC receiving concomitant ADT. The study was conducted at 260 sites in 23 countries. A broad patient population was accrued with key eligibility criteria including histology of prostatic adenocarcinoma, presence of castration-sensitive disease that was metastatic (defined by at least one lesion on bone scan, with or without visceral or lymph-node involvement). Prior docetaxel treatment for mCSPC was acceptable and a maximum of 6 months of ADT for mCSPC was permitted prior to randomization. A total of 1052 patients were enrolled: 525 patients were randomized to the apalutamide arm and 527 were randomized to the placebo arm. At baseline, the majority of patients had high volume disease (63%) and no or mild pain only (76%); 11% had received prior docetaxel.

At the time of the study's first analysis, which was the final analysis for rPFS and the first interim analysis for OS, the dual primary end points of the study were achieved meeting the preset criteria for statistical significance (Table 1). rPFS, defined as the time from randomization to first progression of disease per imaging or death, was improved in favor of apalutamide with a 52% lower risk of radiographic progression or death (HR: 0.48; 95% CI: 0.39–0.60; $p < 0.001$). Overall survival, defined as time from randomization to date of death of any cause was also in favor of apalutamide with a 33% lower risk of death (HR: 0.67; 95% CI: 0.51–0.89; $p = 0.005$).

The efficacy of the addition of apalutamide to ADT on rPFS and OS was maintained across a variety of patient subgroups with no evidence for heterogeneity of effect. In a protocol-defined analysis, the effect of apalutamide on rPFS was consistently favorable, regardless of volume of disease (high volume HR: 0.53 95% CI: 0.41–0.67; low volume HR: 0.36; 95% CI: 0.22–0.57). This was also maintained for OS, with no significant difference in the effect of apalutamide according to disease volume (high volume disease HR: 0.68; 95% CI: 0.50–0.92, low volume HR: 0.67; 95% CI: 0.34–1.32). An additional question of clinical interest related to the benefit of adding apalutamide to ADT following treatment with docetaxel for mCSPC. The benefit of apalutamide in terms of rPFS was maintained (HR: 0.47; 95% CI: 0.22–1.01) among the 11% of patients who had received docetaxel therapy in the protocol-defined subgroup analysis. However, this benefit was not demonstrated for OS (HR: 1.27; 95% CI: 0.52–3.09), although the small sample size and relatively few events limits any conclusions that can be drawn from this subgroup. In an attempt to improve clinical outcomes, there may be a biological rational to combining different treatment modalities each having proven benefit in the mCSPC setting, but, further follow-up of the TITAN and other studies and larger cohorts are required in order to determine whether such an approach will realize a survival advantage.

Secondary end points of the TITAN study were time to cytotoxic chemotherapy, time to pain progression (assessed by the Brief Pain Inventory – Short Form), time to chronic opioids use and to first skeletal-related events (Table 1). The time to cytotoxic chemotherapy was significantly longer with apalutamide than with placebo (HR:

0.39; 95% CI: 0.27–0.56; p < 0.001). The other secondary end points were in favor of apalutamide, however as the time to pain progression did not reach statistical significance, no formal testing for further secondary end points was conducted as per the prespecified hierarchical testing sequence.

Exploratory end points included time to prostate-specific antigen (PSA) progression, time to symptomatic local progression and the time to second progression-free survival defined as time from randomization to investigator determined progression on subsequent therapy or death (Table 1). The median time to PSA progression was substantially greater for apalutamide than with placebo (median not reached vs 12.9 months, respectively (HR: 0.26; 95% CI: 0.21–0.32)). The median second progression-free survival was longer with apalutamide than with placebo (HR: 0.66; 95% CI: 0.50–0.87), emphasizing the benefits of earlier treatment with apalutamide as opposed to waiting until CRPC to start additional therapy. There were few events of symptomatic local progression and no substantial difference between the two arms.

Safety

In the TITAN study, the rates of any adverse event (apalutamide 96.8% vs placebo 96.6%), grade 3–4 adverse events (42.2 vs 40.8%) and serious adverse events (19.8 vs 20.3%), regardless of attribution, were similar in both arms. Adverse events resulting in treatment discontinuation occurred in 8.0 and 5.3% of patients in the apalutamide and placebo arms, respectively [17]. Whereas death as a result of adverse events favored apalutamide (1.9 vs 3% for placebo) [17].

Rash was the most common apalutamide-related adverse event (any grade in 27.1 vs 8.5%, grade 3–4 in 6.3 vs 0.6%, for apalutamide vs placebo), with 2.3% of patients discontinuing apalutamide because of rash (vs 0.2% for placebo). While apalutamide has been shown to cause increased rates of fatigue in previous studies [45,47], this was not as apparent in the TITAN trial with the rates of fatigue in both arms being largely similar (any grade fatigue was 19.7 vs 16.7%; and grade 3–4 fatigue 1.5 vs 1.1% in the apalutamide and placebo arms, respectively).

Several other adverse events of special interest were reported in the trial. Hypothyroidism of any grade AE was more common among patients in the apalutamide arm, however, none of these events exceeded grade 2 (6.5 vs 1.1% in the apalutamide and placebo arm). Ischemic heart disease was numerically more common in the apalutamide arm (4.4 vs 1.5% in the apalutamide and placebo arms), with two cases in each arm resulting in death. There was a similar rate of falls in both the apalutamide and placebo arms 7.0–7.4%, however, there was a greater proportion of fractures in the apalutamide versus placebo arms (any grade adverse event 6.3 vs 4.6%; grade 3–4 adverse events 1.3 vs 0.8%).

In the TITAN trial seizure occurred in 0.6 and 0.4% of patients in the apalutamide and placebo arms, respectively. One event in the apalutamide arm was of grade 3 or above.

Patient reported outcomes & health-related quality of life

At baseline, the majority of patients accrued to TITAN were in good general health as reflected by absence or limited pain and a good performance status (ECOG performance status was 0–1 in 100% of patients). In such a study, aimed at prolonging survival and maintaining disease control in the future, it is of importance that the investigational agent does not impair patients' quality of life. In this study, patient-reported outcomes of pain, fatigue, prostate cancer symptoms and overall health-related quality of life (HRQOL) were predefined exploratory end points and were reported in a separate publication [53]. The data were collected per treatment cycle utilizing the Brief Pain Inventory – Short Form (BPI-SF), Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy – Prostate (FACT-P; version 4) and the EuroQoL five dimensions, five-levels questionnaire (EQ-5D-5L). Time to pain, fatigue and HRQOL deterioration were defined as the time from patient's randomization to the first clinically meaningful threshold change in score on a patient-reported outcome scale.

Compliance with questionnaires was similar in both cohorts. Median time to worst pain intensity progression was numerically longer for the apalutamide arm (19.09 vs 11.99 months), however, no statistically significant difference was found (HR: 0.89; 95% CI: 0.75–1.06; p = 0.20). All measures of pain, including pain progression, pain intensity, pain interference and average pain favored apalutamide over placebo, although were not statistically significant. Among patients with severe pain at baseline, a greater proportion had significant improvement (2 points or more) in pain severity in the apalutamide arm compared with the placebo arm. This improvement was witnessed from cycle 5 to the end of study [53]. Worst fatigue intensity and fatigue interference mean were similar between arms. Furthermore, there were no differences in the time to HRQOL deterioration between the treatment arms as

Table 2. Ongoing clinical trials: apalutamide in the treatment of hormone-sensitive prostate cancer.

Trial	NCT	indication	Investigational arms	Comparative arm	Primary end points	Status	Ref.
ATLAS	NCT02531516	High-risk localized/locally advanced PC	Apalutamide + ADT + RT	ADT + RT	Metastasis-free survival	Enrollment completed	[54]
EORTC-1531-ROG	NCT03488810	Intermediate/limited high-risk PC	Apalutamide + ADT + RT	ADT + RT	Disease-free survival	Not yet recruiting	[55]
PROTEUS	NCT03767244	High-risk localized/locally advanced PC	Apalutamide + ADT + RP	ADT + RP	1. Proportion of pathological complete response 2. Metastasis-free survival	Enrolling	[56]
NGC	NCT04134260	Pathological node positive PC following RP	Adj. apalutamide + ADT + RT	Adj. ADT + RT	Metastasis-free survival	Enrolling	[57]
D'Amico *et al.*	NCT03777982	Patients with PC and residual detectable PSA following ADT + RT	Apalutamide + AAP + ADT	ADT	Metastasis-free survival	Enrolling	[58]
Alliance	NCT03009981	Hormone-sensitive, high-risk biochemical failure	Apalutamide + ADT Apalutamide + AAP + ADT	ADT	1. PSA progression-free survival 2. Progression-free survival	Enrolling	[59]

AAP: Abiraterone acetate plus prednisone; ADT: Androgen deprivation therapy; PC: Prostate cancer; PSA: Prostate-specific antigen; RP: Radical prostatectomy; RT: Radiation.

determined by FACT-P and EQ-5D-5L scores. Overall, the addition of apalutamide did not compromise patients' health-related quality of life in comparison to the placebo arm.

Ongoing clinical trials: apalutamide in the treatment of castration-sensitive prostate cancer

There are several ongoing Phase III clinical trials examining the utility of apalutamide in earlier prostate cancer disease states (Table 2).

The ATLAS trial [54] is a Phase III, randomized, placebo controlled clinical trial designed to determine the efficacy of the addition of apalutamide to standard of care ADT with radiation for the treatment of patients with high-risk localized or locally advanced prostate cancer. Both arms were to be treated with ADT for the duration of 30 months and radiation at a dose of 74–80 gray at 8 weeks after randomization. Treatment with apalutamide is intended to be administered for the duration of 30 months in combination with a bicalutamide placebo for 4 months, while the comparison arm is intended to receive 4 months of bicalutamide at a dose of 50 mg with placebo for 30 months. The primary end point of this study is metastasis-free survival. The study has completed accrual and is anticipated to report preliminary results in 2023. A similar study, EORTC 1531-ROG [55], is designed to examine the utility of the addition of apalutimide to ADT and radiation in patients with intermediate and limited high-risk localized prostate cancer. In this Phase III, randomized, open-label study, eligible patients will receive 6 months of ADT with or without apalutaimde in a 1:1 randomization scheme in addition to standard fractionated radiation. The primary end point of the study is disease-free survival as determined by treating physician. The study is anticipated to complete recruitment in 2026.

The PROTEUS [56] trial aims to determine the efficacy of the addition of apalutamide and ADT for the treatment of high-risk, localized or locally advanced hormone-sensitive prostate cancer. However, in this study the intended definitive treatment is radical surgical prostatectomy. Patients in this study are intended to receive continuous treatment with ADT and apalutamide/placebo for a one-year duration. Following 6 months of systemic treatment the patients are to undergo radical prostatectomy. The primary end points of this study are the proportion of patients with a pathological complete response and metastasis-free survival. The study is currently recruiting and is estimated to report initial results by the end of 2024.

A Phase III study [57] comparing ADT and radiation to ADT, apalutamide and radiation as adjuvant treatment following radical prostatectomy for patients with pathological node positive disease was recently initiated (NRG-GU008). The study is designed to continue systemic treatment for 24 months with a primary end point of metastasis-free survival.

A well-accepted treatment protocol for patients with hig-risk, localized prostate cancer is radiation in combination with ADT for the duration of 18–35 months [16]. In this treatment protocol, both pre-radiation and post radiation residual serum PSA have been shown to correlate with higher rates of biochemical failure and prostate cancer-specific mortality and lower rates of metastasis-free survival [60,61]. D'Amico and colleagues [58] are examining the utility of the addition of apalutamide and AAP to ongoing ADT in patients with high-risk localized prostate cancer and a residual detectable PSA following radiation and 6–8 months of standard ADT treatment. Patients in the investigational arm are intended to receive investigational agents until completion of ADT. ADT in both arms is intended be administered for 12–36 months according to physician discretion. The primary end point of the study is metastasis-free survival. This study is estimated to report first results in 2026.

Finally, the Alliance foundation trials is carrying out a Phase III [59], open-label, randomized trial in men with high-risk biochemical failure, defined as PSA doubling time of ≤9 months, after primary or salvage radiation. The study has three comparative arms of ADT versus ADT and apalutamide versus ADT, apalutamide and AAP. Treatment is intended to continue for a 52-week duration followed by observation. The primary outcome is defined as PSA progression-free survival and progression-free survival. Enrollment is ongoing and preliminary results are expected in 2023.

Summary

Apalutamide is a next-generation AR inhibitor. It inhibits AR activity by irreversibly binding to its ligand-binding domain and decreasing AR translocation and inhibiting promoter recruitment to target genes. Clinical data indicate that apalutamide is well tolerated and provides additional clinical benefit in the treatment of prostate cancer. The recent TITAN trial, which accrued a broad spectrum of patients with mCSPC, including those with low- and high-volume disease and patients who had received prior docetaxel chemotherapy, has elucidated the role of the addition of apalutamide to ADT in the treatment of mCSPC, demonstrating the superiority of apalutamide over placebo with regards to overall survival and radiographic progression-free survival while maintaining patients' health-related quality of life and a tolerable toxicity profile. Based on these results, health authorities in North America and Europe have expanded the indication for treatment with apalutamide to include patients with mCSPC. The TITAN trial has placed apalutamide as part of an increasing armature of treatments with a proven substantial survival benefit in the treatment of mCSPC. Several unanswered questions remain with regards to the optimal treatment of mCSPC which will be addressed in part with further follow-up and analysis of the TITAN trial and other studies in this space. On-going clinical trials have the potential to further expand the treatment indications of apalutamide in the treatment of prostate cancer in earlier disease states.

Executive summary

Introduction: prostate cancer

- Metastatic prostate cancer is the sixth leading cause of death among men with a 5-year relative survival of 30.1%.
- The rates of metastatic disease as well as its consequential fatality are indicative of a need for more effective interventions in the treatment of this disease state.
- In recent years, the addition of docetaxel or one of several androgen signaling drugs to androgen deprivation therapy, in the metastatic castration-sensitive prostate cancer (mCSPC) setting, have all been shown to add substantial survival benefit and have become the new standard of care.

Prostate cancer, androgen & the androgen receptor

- Prostate cancer is an androgen-responsive disease, ablation of androgens through castration therapy promotes prostate cancer disease regression.
- Binding of androgens to the androgen receptor (AR) in the prostate cancer cells, induces gene transcription and enhanced proliferation.
- Following castration, there are residual androgen levels in the tumor which are suggested to be due to residual adrenal production of androgens, as well as prostate cancer cells' autonomic intracrine stereogenesis.
- One of the main mechanisms of escape from castration is restoration of competent AR signaling.

Apalutamide: drug information

- Apalutamide is an orally administered next-generation AR inhibitor.
- Apalutamide binds to cytoplasmic AR, inhibiting androgen attachment to AR, decreasing translocation of AR from the cytoplasm to the nucleus and inhibiting nuclear AR recruitment to promoters of target genes in prostate cancer cells.

Apalutamide: clinical data

- In the SPARTAN trial, the addition of apalutamide to androgen deprivation therapy (ADT) in the nonmetastatic castrate-resistant prostate cancer setting has been shown to significantly improve metastasis-free survival, making this the first drug to be approved for the treatment of nonmetastatic castrate-resistant prostate cancer.
- The TITAN trial was a randomized, double-blind, placebo-controlled, multinational trial designed to determine whether apalutamide and concomitant ADT would result in longer radiographic progression-free survival (rPFS) and overall survival (OS) among patients with mCSPC.
- The TITAN study met its primary end points: the addition of apalutamide to ADT significantly improved both OS and rPFS.
- The efficacy of the addition of apalutamide to ADT on rPFS and OS was maintained across a variety of patient subgroups with no evidence for heterogeneity of effect.
- Apalutamide was well tolerated and health-related quality of life was maintained among patients in the TITAN trial.
- Subsequent to the results of the TITAN trial, apalutamide was approved for the treatment of mCSPC.
- There are several ongoing clinical trials examining the utility of apalutamide for the treatment of different prostate cancer disease states.

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In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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Review

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Oligometastatic prostate cancer treatment

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Oligometastatic prostate cancer is an intermediate state between localized disease and widespread metastasis. Its biological and clinical peculiarities are still to be elucidated. New imaging techniques contribute to the detection of patients with oligometastatic disease. PET/CT scanning with prostate-specific membrane antigen can improve the selection of men with true early, low-volume oligometastatic disease, who are candidates for metastasis-directed therapy. Clinical studies demonstrated that androgen deprivation therapy can be delayed in oligometastatic patients with a low tumor burden, although no survival benefit has been demonstrated at present. This article presents available evidence on the treatment strategies for oligometastatic prostate cancer.

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In 1995, it was proposed that a subgroup of patients with prostate cancer may exhibit an intermediate state between localized disease and widespread metastasis, referred to as oligometastatic disease [1]. In these patients, cancer is confined to a limited number of sites and could potentially be curable with metastasis-directed treatments [1]. At present, the concept of a subset of subjects with a distinct prognostic and therapeutic profile has not been linked to a complete understanding of the biology of oligometastatic prostate cancer (OMPC). This prevents a wide consensus on the definition of the condition, along with clinical criteria for diagnosis, treatment and prognosis [1,2].

Typically, OMPC has been defined based on the number of metastases and involved sites, but several other variables could be relevant for treatment decisions: the distinction of synchronous (*de novo* or within 3 months of primary diagnosis) versus metachronous (or recurrent) metastases, whether the patient is castration-naive or castration-resistant and the imaging method used to define oligometastatic disease [3,4].

Current evidence suggests that metastasis-directed treatment of OMPC may improve survival and that the management of patients with a limited number of metastases (typically $\leq$5) should be based on the integration of local therapies. Nevertheless, a wide range of OMPCs seems to exist, with peculiar sensibilities to treatment [5]. An emerging challenge for the management of OMPC is the identification of imaging modalities sufficient to detect the oligometastatic state, define the tumor burden and support treatment planning. In addition, specific treatments for oligorecurrent cancer and primary cancer in patients with oligometastases are to be stated.

To explore these issues, we reviewed available evidence about imaging modalities and currently recommended treatment in patients with oligometastatic prostate cancer.

Patients & methods

For this narrative review of the literature, a non-systematic search was performed in PubMed using the following keywords: 'prostate cancer', 'oligometastatic', 'oligorecurrent', 'treatment' and 'imaging'. Articles in English or with English abstracts were retrieved. Out of 358 articles, all clinical trials were read and reviewed by at least two authors (22 articles), while guidelines, reviews and preclinical evidence were chosen based on the authors' evaluation of

relevance. The search was concluded in September 2020 and included all articles present in PubMed, without temporal limits.

Imaging modalities for metachronous oligometastatic prostate cancer

The detection of metastases is highly dependent on the imaging technique used [6]. Newer imaging techniques will detect more metastases in many patients classified as 'oligometastatic' by conventional imaging (CT scanning and bone scintigraphy), while patients considered to have no metastases on conventional imaging may turn out to have oligometastatic disease, as shown by retrospective studies [4,7,8]. Actually, current evidence suggests that imaging by CT and bone scintigraphy is not sufficient to define the oligometastatic state and for treatment planning [4]. In the last years, functional, or molecular, imaging has given a significant contribution to clinical decision-making in biochemically relapsed prostate cancer, allowing early diagnosis of metastatic disease [9,10]. New-generation imaging for prostate cancer, which has allowed better detection of oligometastatic lesions, is based on PET/CT or MRI with PSMA, choline or fluciclovine tracers, and/or whole-body morphological and diffusion-weighted MRI [11–13]. Recently, in 25 patients with prostate cancer recurrence after primary surgery, ^{68}Ga-PSMA ligand PET/CT was used in addition to conventional imaging techniques such as CT and/or MRI for restaging. The additional information from PSMA ligand PET provided the identification of a higher number of metastases and allowed for smaller target volumes [14].

Finally, it is to be mentioned here that criteria for the definition of oligometastases are not shared, and the concept of oligovisible polymetastases challenges researchers to find a consensus as diagnostic techniques are quickly evolving [15].

Stereotactic radiotherapy & the role of PET

Conventional treatment for men with metastatic prostate cancer is systemic therapy, either hormonal or chemotherapy; however, some authors found that stereotactic ablative radiotherapy (SABR) in the oligometastatic setting may achieve sufficient PSA control [16–18]. Such results were also shown by several retrospective studies and two prospective trials, in which disease was diagnosed on the detection of metastases by fluorodeoxyglucose, choline or sodium fluoride PET scans or PSMA-PET/CT [19–22]. The potential for ^{18}F-fluciclovine PET/CT to guide targeted treatment of oligometastases was supported by results of the LOCATE trial, where 79% of men with oligometastatic disease had a change to the management plan following the scan [23].

PSMA-PET/CT can improve the selection of men with true early, low-volume oligometastatic disease who are candidates for SABR, and is useful for the correct target delineation during the contouring phase by fusion with the simulation planning CT [22]. The results from the ORIOLE study showed that PET may contribute to the correct detection of oligometastases, which is necessary to identify eligible subjects for SABR [24,32].

In the future, it is possible that PSMA-PET/CT could also be used during the delivery of radiation treatment for intrafraction tumor tracking, attenuating the effect of the internal target motion on treatment uncertainty [25].

The use of PSMA-PET/CT has probably improved our selection of men with true early, low-volume oligometastatic disease. This is evident in the much lower pre-SABR PSA levels and lower proportion of men who had bone metastases in our cohort, compared with earlier studies based on non-PSMA-PET/CT staging.

Imaging techniques are involved in the effort to identify reliable criteria for patients' eligibility for SABR. The role of ^{18}F-methylcholine PET/CT in the selection of patients with prostate cancer suitable for SABR was evaluated in a prospective study. Patients with biochemical recurrence and a maximum of three lesions revealed by ^{18}F-methylcholine PET/CT were enrolled (n = 46, with 67 lesions) and treated with SABR on all active lesions, resulting in a median systemic therapy-free survival of 39.1 months (95% CI: 6.5–68.6) [26].

For therapy decisions, clinicians need simple tools to evaluate prognostic risk following the use of metastasis-directed therapy (MDT). A classification was proposed to predict biochemical relapse-free survival (bRFS) after PSMA-PET-guided MDT in patients who had undergone prostatectomy. Patients in risk class I, with PSA $<$0.8 ng/ml and local relapse only, had the most promising mean bRFS (36.3 months; 95% CI: 32.4–40.1); patients in class II, with PSA $\geq$0.8 ng/ml without bone or visceral metastases, had a mean bRFS of 25.8 months (95% CI: 22.5–29.1); in class III, patients with bone metastases independent of the PSA level, mean bRFS was 16.0 months (95% CI: 12.4–19.6); and in patients in class IV, with PSA $\geq$0.8 ng/ml and visceral metastases but without bone metastases, bRFS was 5.7 months (95% CI: 2.7–8.7). According to this score, MDT can still be considered beneficial in class III, while it should be discussed individually in patients with visceral metastases [27].

Table 1. Clinical studies on metastasis-directed therapy for oligometastatic prostate cancer.

Design	Definition of OMPC	Intervention	n	Follow-up (median)	Outcomes	Ref.
Observational	≤3 synchronous active lesions detected with [^{18}F]-MCH PET/CT		29 patients 45 lesions	11.5 months	20 patients in the study	[15]
Randomized, Phase II	PSA relapse, ≤3 extracranial metastases on choline PET-CT	Surveillance vs MDT (metastasectomy or SBRT)	62 patients	3 years	Median ADT-free survival: 13 months for the surveillance group and 21 months for the MDT group	[19]
Prospective	1–3 oligometastases on CT, bone scan, sodium fluoride PET	SABR	33 patients 50 metastases		2-year LPFS: 93%; 2-year DPFS: 39%	[20]
Retrospective	≤7 metastases, no local recurrence	SBRT	30 patients	29.4 months	At 24 months: local relapse-free survival 50.7%, PFS 14.9%; OS 62.5%	[29]
Randomized, Phase II	Recurrent hormone-sensitive prostate cancer and 1–3 metastases detectable by conventional imaging who had not received ADT	SABR vs observation	54 patients		Progression at 6 months: 19% SABR, 61% observation PFS not reached vs 5.8 months Risk of new lesions at 6 months: 16% vs 63%	[32]

ADT: Androgen deprivation therapy; DPFS: Distant progression-free survival; LPFS: Local progression-free survival; MCH: Methylcholine; MDT: Metastasis-directed therapy; OMPC: Oligometastatic prostate cancer; OS: Overall survival; PFS: Progression-free survival; SABR: Stereotactic ablative radiotherapy; SBRT: Stereotactic body radiotherapy.

Although MDT is appealing as a possible strategy to delay disease progression without the adverse events of systemic therapy, the data remain too immature to recommend MDT on a large scale; thus MDT should be administered only within a clinical trial [28].

Recommended treatment for patients with oligorecurrent (metachronous) OMPC

The best treatment for men with metachronous metastases after local treatment of the primary prostate tumor is currently debated (Table 1); the use of associated systemic therapy plus local treatment of all lesions was suggested by the 2019 edition of the Advanced Prostate Cancer Consensus Conference, where a 75% consensus was reached on this issue [11]. The available data are difficult to interpret and compare, mainly due to the absence of a shared definition of oligometastases, as evident in Table 1; in addition, relevant outcomes for clinical research in this setting are still to be identified.

The use of MDT alone, consisting of surgery or SABR, for oligorecurrent (metachronous) oligometastatic prostate cancer has been proposed by some authors [29]. Specifically, PSA decrease was obtained with metastasectomy in 16/17 (94%) patients. In addition, 16 (94.1%) patients developed metastatic recurrence, of which 11 (64.7%) were again oligometastatic and amenable for repeated MDT [30]. Increased androgen deprivation therapy (ADT)-free survival was obtained with MDT compared with surveillance in a Phase II prospective randomized trial on 62 patients (median 13 months [80% CI: 12–17 months] for the surveillance group vs 21 months [80% CI: 14–29 months] for the MDT group; hazard ratio: 0.60 [80% CI: 0.40–0.90]; log-rank p = 0.11); it may be added that this result may be underestimated as the surveillance group had more Gleason 6, low T-stage, pN0 cases in comparison with the MDT group. MDT was well tolerated and did not impact on quality of life [20]. Specifically, while only men from the surveillance group initiated ADT because of local or symptomatic progression, an almost equal number of men from each group received ADT because of polymetastatic progression. This observation suggests that two distinct subpopulations were present in the oligorecurrent cohort of the study: one subgroup had oligometastatic disease and their future metastatic colonization was influenced by MDT, and one subgroup had polymetastatic disease, which could not be detected (oligovisible polymetastatic disease) and was beyond the possibility to benefit from MDT alone. This concept stresses the importance of considering the sensitivity and specificity of detection methods in this setting [15].

Accordingly, another prospective trial, which was not randomized but consecutively enrolled patients with one to three lesions, found that about one-third of subjects remained ADT-free 2 years after receiving SABR [20]. Finally, reirradiation of oligometastatic pelvic cancer was also found to be safe and effective by a retrospective study on 30 patients (30.8% with prostate cancer) [31].

Although MDT is promising to delay systemic therapy, progression of distant metastases seems not to be controlled by this approach [32]. In a case series of 24 patients receiving SABR, the mean PSA decreased from 4.58 ng/ml (range: 0.05–50.25) before SABR to 1.19 ng/ml (range: 0.01–8.85) after completion of SABR,

and the mean biochemical progression-free survival was 17.6 months (range: 0.7–85.0). Notwithstanding, in 17 patients, distant metastasis progression was diagnosed by imaging after a mean of 16.2 months (range: 1.6–40.6) [32].

No survival benefit was detected, but improvement of recurrence-free survival was found, in an observational study comparing outcomes of ADT with those of radiological or surgical MDT [33].

The Phase II randomized ORIOLE study found that treatment with SABR induced a systemic immune response and improved outcomes in terms of PFS (not reached for SABR vs 5.8 months for observation only; hazard ratio: 0.30; 95% CI: 0.11–0.81; p = 0.002) and frequency of progression at 6 months (19% for SABR vs 61% for observation; p = 0.005) [24]. These results support the use of SABR in oligometastatic subjects to delay ADT.

Real-world evidence from a prospective, registry-based, single-arm, observational, evaluation study on patients with solid cancer (prostate cancer was the most common type) and oligometastases complemented the results of the Phase II trial [34].

In conclusion, promising experiences are published but it must be remembered that no randomized Phase III trials with a primary end point of OS have yet been published, and the overall clinical utility of SABR remains undemonstrated. Finally, the best treatment regimen for MDT would deserve attention, but no criteria are available. A recent Dutch panel reported that although there was a consensus that targeted treatment of all metastases in OMPC will delay further dissemination of the disease, opinions on specific treatment regimens were divided [35].

In addition, definition of clinically significant outcomes is necessary for future studies; a survey carried out within the Canadian Society of Urologic Oncology found that a minimum cure rate of 11% and an ADT-free survival at 1 year could be considered clinically significant [36].

Management of the primary tumor in the metastatic setting

Local prostate irradiation of newly diagnosed prostate cancer with distant metastases was not recommended before 2018; however, although definitive evidence is still lacking, prostate treatment in the oligometastatic setting is currently considered to improve outcomes on the basis of some promising studies [37]. In a cohort of 210 patients assessed by ^{18}F-choline PET/CT, the outcomes of 12 patients found to be oligometastatic suggested that intended curative treatment of the primary tumor could have been beneficial [37]. Data collected in 2018 by two trials, STAMPEDE and HORRAD, were aggregated for meta-analysis, comparing the effects of prostate radiotherapy associated with ADT versus ADT alone [38–40]. Although no overall improvement in survival was found with radiotherapy, the effect of prostate radiotherapy varied by metastatic burden, and there was a 7% improvement in 3-year survival in men with fewer than five bone metastases. It should be noted, for a correct understanding of results, that metastatic burden at randomization was assessed by conventional imaging, such as whole-body scintigraphy and CT or MRI [38,39]. Based on the evidence available in 2019, radiotherapy was considered the preferred local treatment for the majority of patients with newly diagnosed, low-volume/burden metastatic (M1) hormone-sensitive prostate cancer by 84% of panelists of the 2019 Advanced Prostate Cancer Consensus Conference, while prostatectomy was preferred by 16% of panelists [11,38–40].

Observational data supported the synchronous irradiation of primary tumor and bone metastases, with promising survival results and limited toxicity; after a median follow-up of 46.5 months, 19/39 patients were still in ADT and had undetectable PSA levels, while five patients who discontinued ADT after a median of 34 months (range: 5.8–41) were free from biochemical relapse [41]. Finally, untreated primary prostate cancer was found to be a negative predictor for OS in a retrospective study of 176 prostate cancer patients with 353 lesions receiving MDT [42]. In the opinion of the authors, further study is needed to understand whether primary tumor treatment in the metastatic setting has a survival benefit, and whether this is impacted by molecular imaging.

Conclusion

Although the concept of oligometastatic prostate cancer is not fully understood in its biological characteristics and is widely debated in its relevance to treatment and prognosis, current evidence suggests that patients with three to five metastases may have a distinct prognostic and therapeutic profile [1,11]. As a consequence of such an incomplete understanding of the phenomenon, shared criteria for the diagnosis of oligometastases are not available, making difficult the comparison of results from clinical trials. Notwithstanding these limitations, local treatment (either surgery or SABR) of both primary tumor and metastases seems to be effective to reduce PSA values and provides a recurrence-free survival benefit with reduced toxicity in comparison with systemic therapy [43]. On the contrary, systemic treatment could be delayed in this setting with no detrimental effect. Although MDT provided a longer

time to radiological recurrence, to second-line systemic therapy and to castration-resistant prostate cancer in comparison with ADT, a survival benefit of MDT is still to be demonstrated [24,33,34,36].

Future perspective

Current clinical research is trying to identify shared diagnostic tools and parameters, as classic imaging techniques are considered insufficient to identify low-volume metastases. In addition, new technique imaging is necessary to guide SABR, which has been found to increase survival [11–14,19–21].

Definition of criteria for the diagnosis of oligometastases will facilitate the design of clinical trials and the acquisition of relevant evidence. Currently, evidence about primary tumor treatment in this setting is scant and needs further investigation; data from STAMPEDE and HORRAD suggest that radiotherapy of the primary tumor may have a survival benefit for patients with reduced tumor burden [38–40]. It is necessary to demonstrate that patients with a low metastatic burden will benefit from localized treatment better than from systemic therapy, with good efficacy and reduced toxicity. As the results from STOMP suggested the existence of different subpopulations in this setting, deeper insight will be necessary to identify patients eligible for MDT.

Executive summary

- The term oligometastatic disease describes patients in whom cancer is confined to a limited number of sites and who could potentially be curable with metastasis-directed treatments.

Imaging modalities for metachronous oligometastatic prostate cancer

- The detection of metastases is highly dependent on the imaging technique used. In the last years, new-generation imaging for prostate cancer, based on PET/CT/MRI scanning with prostate-specific membrane antigen, choline or fluciclovine tracers, and/or whole-body morphological and diffusion-weighted MRI, has allowed better detection of oligometastatic lesions.

Stereotactic radiotherapy & the role of PET

- Some authors found that radiotherapy in the oligometastatic setting may achieve sufficient PSA control, although the data remain too immature to recommend metastasis-directed therapy on a large scale. Imaging techniques are involved in the effort to identify reliable criteria for eligibility to SABR.

Recommended treatment for patients with oligorecurrent (metachronous) oligometastatic prostate cancer

- The Phase II randomized ORIOLE study found that treatment with SABR induced a systemic immune response and improved outcomes, and delayed initiation of androgen deprivation therapy was obtained in patients receiving metastasis-directed therapy in the STOMP trial. Therefore metastasis-directed therapy is promising to delay systemic therapy, but no randomized Phase III trials with a primary end point of overall survival have yet been published.

Management of the primary tumor in the metastatic setting

- Prostate treatment in the oligometastatic setting is currently considered to improve outcomes based on some promising studies, and a reduced tumor burden was found to be associated with better results in the STAMPEDE and HORRAD trials. Based on the evidence available in 2019, radiotherapy was considered the preferred local treatment for the majority of patients with newly diagnosed, low-volume/burden metastatic (M1) hormone-sensitive prostate cancer.

Author contributions

S Rossetti: conceptualization; funding acquisition; investigation; supervision; validation; writing. S Pignata: conceptualization; supervision; validation. M Di Napoli, C Pisano, S Cecere, R Tambaro, J Ventriglia, A Passarelli, G Iovane, F Feroce, S Lastoria, F Di Gennaro, P Muto, V Borzillo, R Di Franco, S Perdonà, G Quarto: visualization.

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• **A clinical study with relevant results.**

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