touch ONCOLOGY®

Improving outcomes in prostate cancer: What is the role of PARPi combination therapy?

Transcript from a touchTALKS activity

THE EXPERT

DR NEAL SHORE
Carolina Urologic Research Center, South Carolina, USA

This activity is funded by an independent medical education grant from Pfizer.

This activity is jointly provided by touchIME and USF Health.

Release date: 31 March 2021

INTRODUCTION

In this activity, Dr Shore will discuss the rationale and evidence for using PARP inhibitors in metastatic castration-resistant prostate cancer, using PARPis in clinical practice, and how PARPis in combination with androgen deprivation therapy are being assessed.

LEARNING OBJECTIVES

After watching this touchTALKS activity, you should be able to:

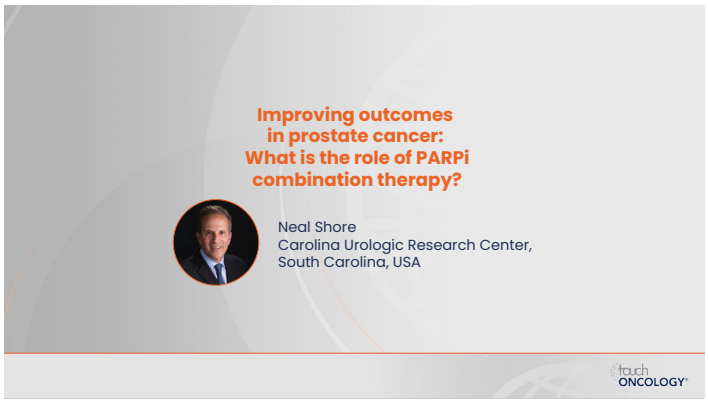
- Discuss the use of combination PARP inhibitor targeted therapy in the management of prostate cancer
- Evaluate how to select/identify patients for potential combination PARPi and androgen receptor targeted therapy for prostate cancer
- Review ongoing clinical trials exploring combination PARPi and androgen receptor targeted therapy for prostate cancer

TOPICS DISCUSSED

- PARP inhibitors for prostate cancer: A deep dive into the evidence
- Clinical strategies in patient selection for PARP inhibitor therapy
- New and emerging PARP inhibitor combinations for prostate cancer

PARP inhibitors for prostate cancer: A deep dive into the evidence

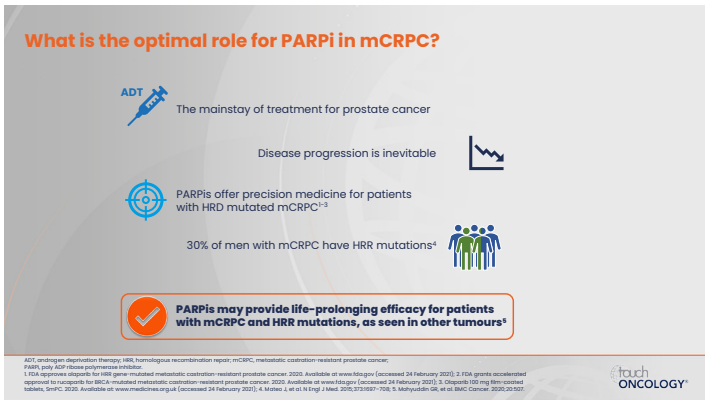
Hello, I'm Neal Shore. I'm the Medical Director of Carolina Urologic Research Centre. I'm a urologist and I'm very proud and happy to talk to you today about our title of our programming 'Improving outcomes in Prostate cancer: What is the role of PARP inhibitors combination therapy?' What a great year 2020 was for PARP inhibitor data reveal. I'm going to review that with you and the importance of testing and how PARP inhibitors work.



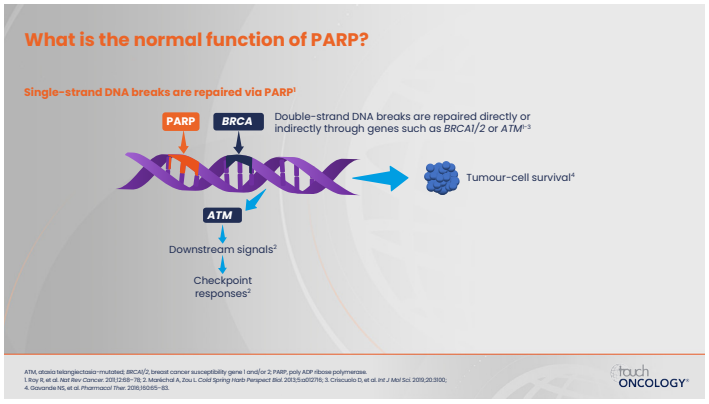
Let's take a dive into the evidence for PARP inhibitors. We have so many advances in mCRPC in the last decade and now we have another one regarding PARP inhibitors. PARP inhibitors will really create an opportunity now for you to think about genomic profiling and testing and also how to think about additional clinical trials that you may want to enrol patients in.

What is the optimal role for PARP inhibitors in mCRPC? Well, we have all these life-prolonging agents and some countries are fortunate enough to have up to eight or nine. But, at the end of the day, testosterone suppression is the mainstay of therapy. We see mutational aberrations and we see disease progression and still mCRPC is a lethal category. What can we do to enhance that and optimise patient survival, quality of life and avoidance of therapeutic complication? Well PARP inhibitors prevent DNA repair leading to cancer cell death. And they cause that apoptotic effect, and I will review that with you. They've now been approved. Two PARP inhibitors have been approved based upon trials, and I'll show you that. They selectively, notice, selectively, not for all patients but for selective patients, so you have to do the right testing - we'll talk more about that as well - and demonstrate homologous recombinant repair defects, sometimes these are called DNA damage repair mutations. And this has ushered in the era of precision medicine. Precision, more personalized or tailored therapy and not a one size fits all. I think this is an important construct.

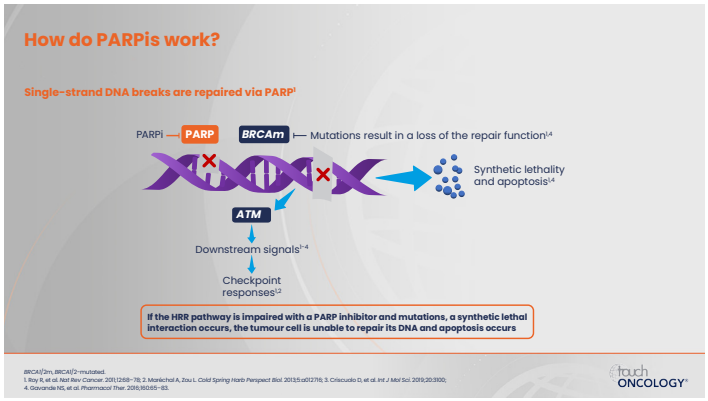
Up to 30% of men with mCRPC have mutations and homologous recombinant genes, up to 30% of our mCRPC patients, nearly 10% of our patients with metastatic castration sensitive prostate cancer. PARP inhibitors have demonstrated life prolonging efficacy in solid tumours with HRR mutations: breast, ovarian and pancreatic cancer. And now we have this opportunity to use them for our patients with mCRPC.



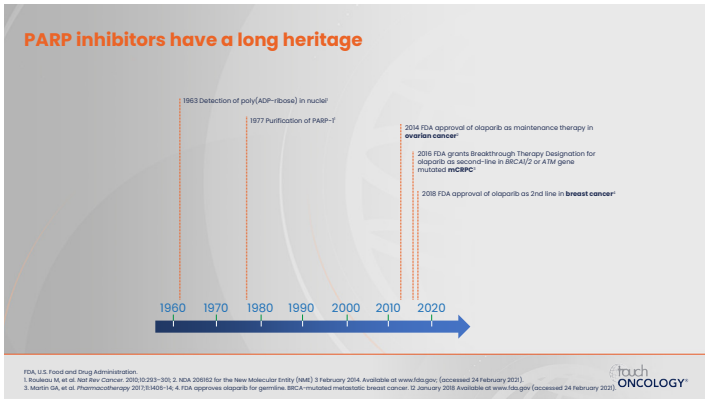
What's the normal function of PARP? Okay, so the normal function of PARP, or poly (ADP-ribose) polymerases, it's a lot easier to just say PARP. And what you see here is single stranded DNA breaks repaired via PARP enzyme and PARP protein. Double stranded DNA breaks are repaired directly or indirectly through genes known as *BRCA1/2* and ataxia telangiectasia mutation, *ATM*. And you see them on the alleles here of the DNA. And then ultimately if there is a defect, if there is a problem, then defective alterations will not be stopped and cellular proliferation will occur. There are also downstream signals and it's a bit of a complex mechanism of action and physiology and pathophysiology.



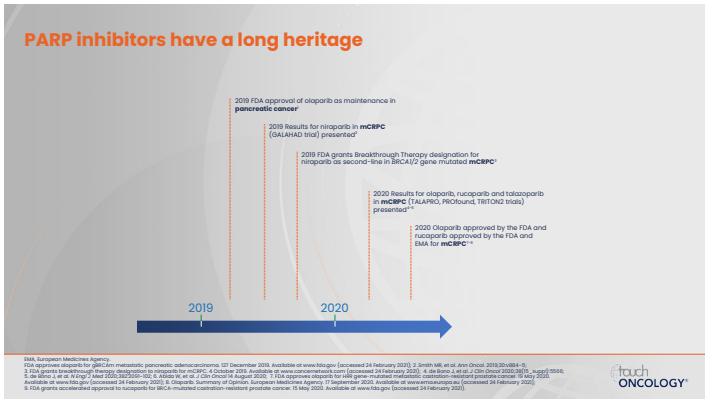
So, how do the PARP inhibitors work *per se*? Well, a PARP inhibitor, which we'll talk about, and there are four that are now being intensely investigated, two which have been approved, they block the PARP enzyme and they prevent PARP protein, and this ultimately results in a loss of the repair function and this can then ultimately lead to prevention of defective cellular proliferation, or what we ultimately call synthetically lethality, an apoptotic event. Now, there are some other downstream signals where you see *ATM*, and there are some other repair signals known as mismatch repair, and these also come into a really important role in preventing cellular proliferation. If the HRR pathway is impaired with a PARP inhibitor then you can develop the synthetic lethality or synthetic lethal interaction and the tumour cell is unable to repair. If you cannot block this then defective cells continue to move forward. Now this is only particularly true if you have an HRR mutation.



PARP inhibitors have a long heritage. One sees here in the historical timeline in the '60s the observation of PARP in nuclei, subsequent purification, the first approval for ovarian cancer in 2014, a breakthrough therapy designation of olaparib and subsequent approval of olaparib in 2018 in breast cancer.

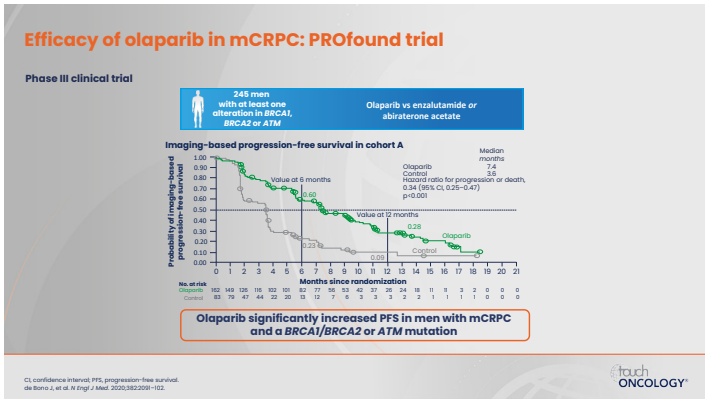


But then really fast forward in the last couple of years we've seen tremendous advancements, and that includes approvals for PARP inhibitors in pancreatic cancer in addition to breast and ovarian. We see breakthrough designations for additional PARP inhibitors such as niraparib, very important, and moving forward with other PARP inhibitors such as talazoparib and rucaparib. Rucaparib approved in prostate cancer and also in breast cancer; and talazoparib also, but still awaiting approval in prostate cancer.

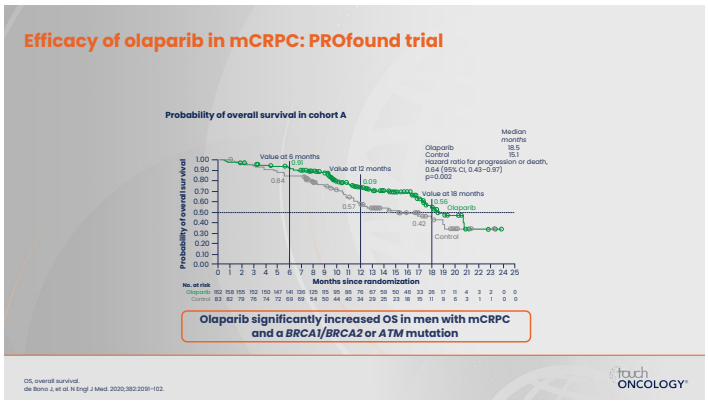


The first big study, phase III trial that has been completed is known as the PROfound study, 250 men globally accrued. Looking at cohort A, this was three particular HRR mutation genes: *BRCA1/2* and *ATM*. 12 other HRR mutation genes comprised cohort B. These were patients with mCRPC who had progressed on a novel hormonal agent, typically either abiraterone or enzalutamide. They were randomized in a 2:1 fashion to receive olaparib, at 300mg BID, versus sequencing to the other novel hormonal agent that they hadn't received, so abiraterone went to enzalutamide or enzalutamide went to abiraterone.

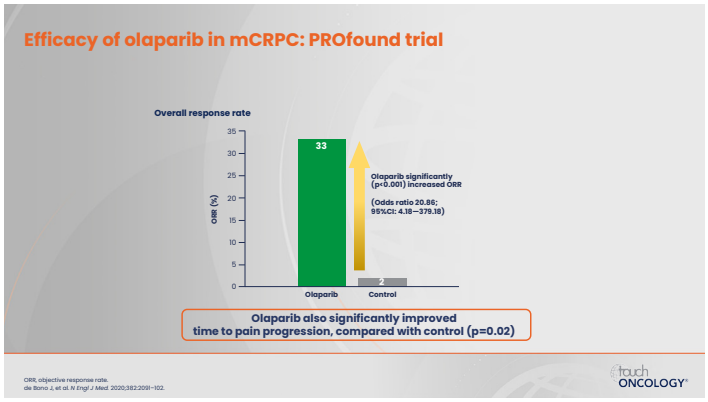
And here we see in cohort. A really rather dramatic, a more than doubling of the rPFS, a hazard ratio of 0.34. This led and met the primary endpoint and also led to the first New England Journal paper for the PROfound trial.



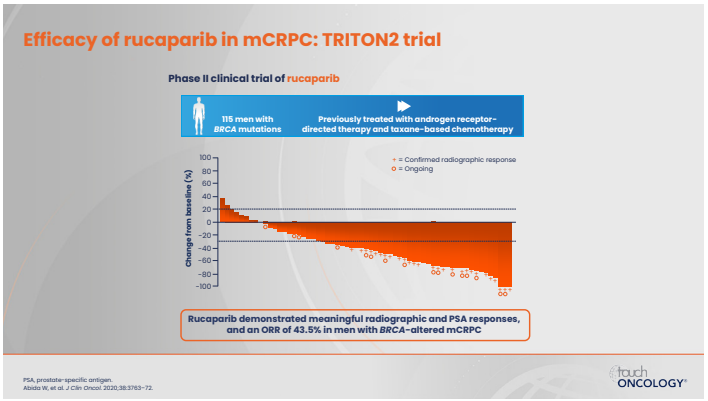
Subsequently, looking at the patients for overall survival as a secondary endpoint, clearly demonstrated again in cohort A, the *BRCA1/2 ATM* population, an improvement in their survival benefit. Again, these patients, two thirds had also received taxane therapy on top of progressing with a novel hormonal agent such as abiraterone or enzalutamide. And we see in this particular selected HRR mutation gene profile, an opportunity to improve survival by essentially over three months at the median, really, very impressive; a hazard ratio of 0.64. But it has to be for the selected patients. Why the importance of testing? Now, we'll talk more about that in the next segment.



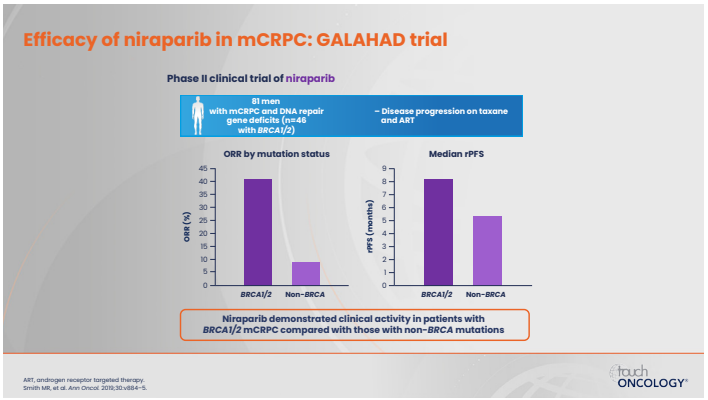
An objective response rate, another important secondary endpoint, one sees 33% objective response rate in the PROfound trial in cohort A versus a 2% in the sequencing physicians choice arm. And this was done with a blind and independent central radiologic review. It's important to also recognise that about two thirds of the patients in the physicians choice in the PROfound trial also went on to get olaparib, therefore potentially even muting a little bit of that overall survival benefit, yet it was still reached.



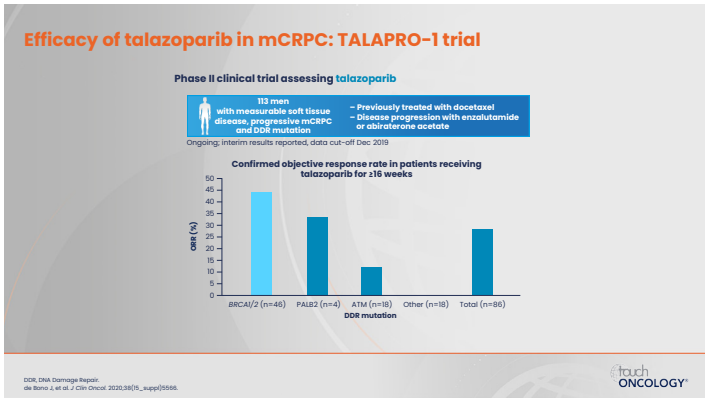
Here's rucaparib, a very nice phase II study, open-label, a single arm study demonstrating the benefit of rucaparib 600mg twice-a-day. It demonstrated meaningful radiographic and PSA responses and an objective response rate of 43.5% for patients with *BRCA1/2* gene alterations.



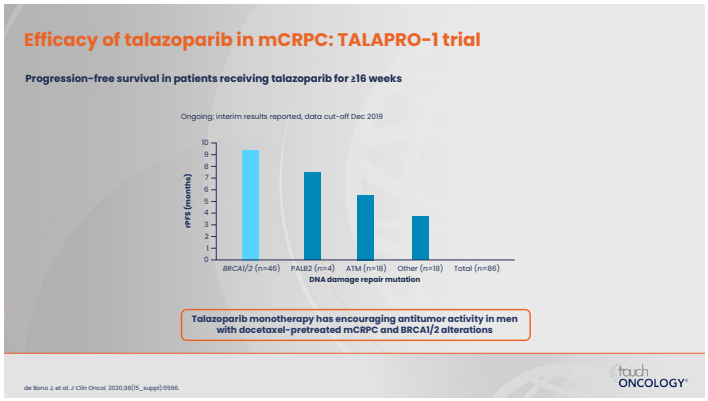
In addition we see niraparib. Niraparib, another phase II study, a little over 80 patients, again who had DNA repair gene defects. And one sees the difference in the left-hand side, of the objective response rate versus the radiographic progression-free survival, clearly again for patients who are selectively interrogated who benefit from the addition of a PARP inhibitor. And these are patients also who had progressed on a novel hormonal agent as well as taxane-based therapy.



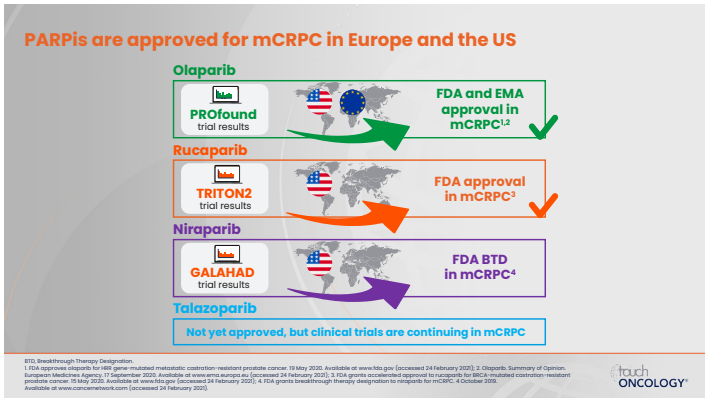
And now I bring your attention to talazoparib, a fourth PARP inhibitor now to very importantly enter the clinical trial landscape. Phase II study of 113 men, measurable disease, progressive mCRPC demonstrating DNA damage repair mutations, previous progression on taxane based therapy and a novel hormonal agent. And one can see looking at *BRCA1* and *2* and now *PALB2* also an important HRR mutation, smaller numbers though, only four in this particular study, *ATM* and seeing the confirmed objective response rates for patients who are on treatment for 4 months or longer.



The progression-free survival has also been now updated. We're seeing additional evidence now. We've had it presented at ASCO GU 2021. But here you're seeing in this graph the rPFS benefit in the same patient population just getting monotherapy talazoparib and so a really nice result.

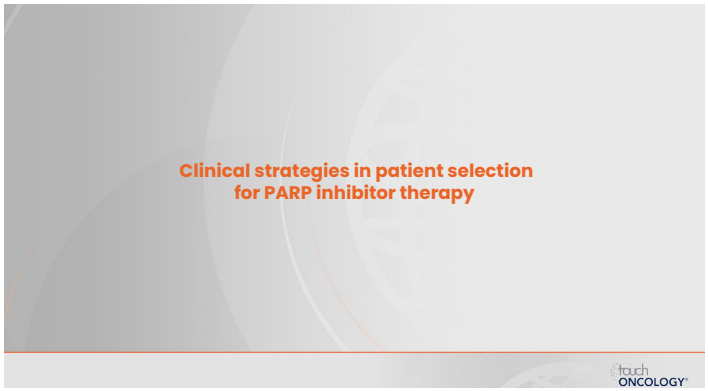


So, PARP inhibitors are approved for mCRPC in Europe and the United States. We see approvals for olaparib based upon the phase III PROfound trial, two New England Journal publications; rucaparib, published in JCO, FDA approved for mCRPC; we see that niraparib has breakthrough therapy designation by the FDA; and talazoparib has an ongoing phase III trial as well. I'm really proud that I was able to participate in all of these different studies. And it's very important for you to be thinking about, how can you really work this opportunity for your patients who have these selected HRR mutations, and also to consider placing them in clinical trials. This is a really exciting opportunity, I think, for selective precision tailored therapy and really offers our patients an additional advance. Thank you.



Clinical strategies in patient selection for PARP inhibitor therapy

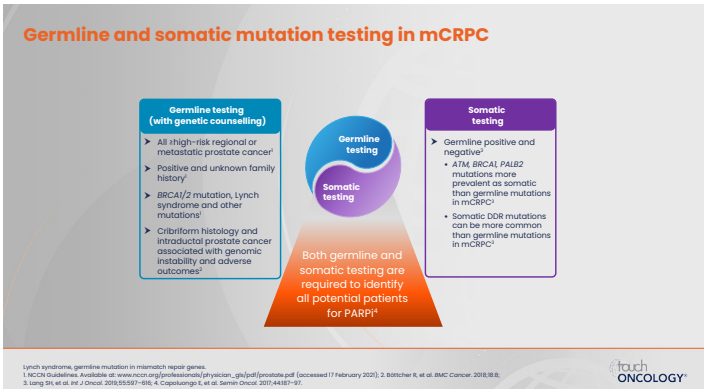
This segment, 'Clinical strategies in patient selection for PARP inhibitor therapy'. What is it, to make sure that we are optimising clinical selection?



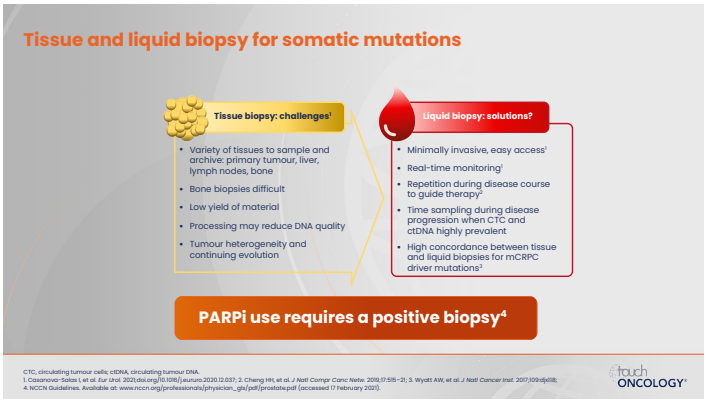
It's so important as we see in all aspects of our care for our patients with prostate cancer, and becoming even more important now. You must test, test, test. If you're not doing the testing you'll never know if a PARP inhibitor can help your patient. I can't over-emphasise this. So there are two forms of testing, and what we do know is that so many of our medical oncology and urology colleagues and radiation oncology colleagues, we're not testing enough. And part of that may be accessibility and it may be a cost issue, but hopefully that will be facilitated over time. Germline testing is testing the likelihood that you've inherited something from your mother and father. This is really familial ways of inheriting gene alterations that have significant impact, not just in prostate cancer but in many other forms of cancer.

So, the recent guidelines, they're not always completely in consensus, but if you look at something, for example NCCN, they recommend that all patients who have high risk regional or metastatic prostate cancer get a germline test, and this can be done with blood or through saliva. And anyone with a significant positive and even an unknown family history, so other relatives 60 years and younger with breast cancer, pancreatic cancer, male breast cancer, prostate cancer, melanoma, colorectal cancer. Very common alterations, you'll find *BRCA1/2*, Lynch syndrome which increases the risk of upper tract urothelial cancer; cribriform histology and intraductal prostate cancer has a lot of genomic instability and is associated with some of these germline alterations. If you have a germline alteration it's essentially in every cell of the body.

Now, 10% of men with mCSPC will have germline alterations consistent with HRR mutations. But that doesn't end right there because if it's negative you still would want to check for somatic, which is the gene alterations within the tumour tissue itself. And these can be also the classic ones that you have read about. We've talked about *ATM*, *BRCA1/2*, *PALB2*. There are others and they can come directly from the tumour tissue, up to 30% of mCRPC patients will have HRR mutations. So actually if you stop at germline you might miss up to 50% of patients who would have somatic mutations.

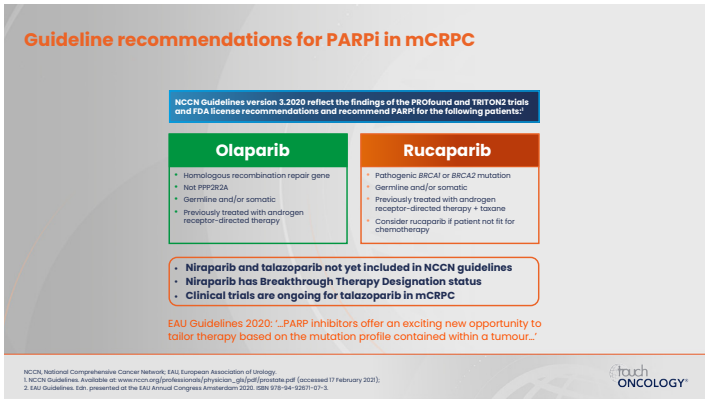


So, how do you test? Well, as I said, germline is easy. It's a saliva buccal smear or a blood test, but tissue comes from archival tissue, prostate biopsy, prostatectomy specimen, or you can do a metastases-directed biopsy. That's not always the easiest thing to do. Sometimes it can be. You need to develop a relationship with your interventional radiologist. Bone biopsies are achievable but there are some challenged nuances about doing it correctly and with the right technique. Sometimes the tumour tissue can be really old and may not be adequate to maintain tumour DNA for interrogation. It might not have been preserved adequately, there might not be enough for it to be looked at, and so liquid becomes an answer as well. There are multiple companies now that offer circulating tumour DNA simple blood tests and there's now about an 80% concordance. So, this is giving us additional opportunities. I really encourage you to read more deeply and more thoughtfully about the difference between germline and somatic alterations, how you test for them, and also the difference between tumour tissue testing for somatic and liquid-based testing. It gives us great flexibility and optionality to look for HRR mutations and the use and the role for a PARP inhibitor.

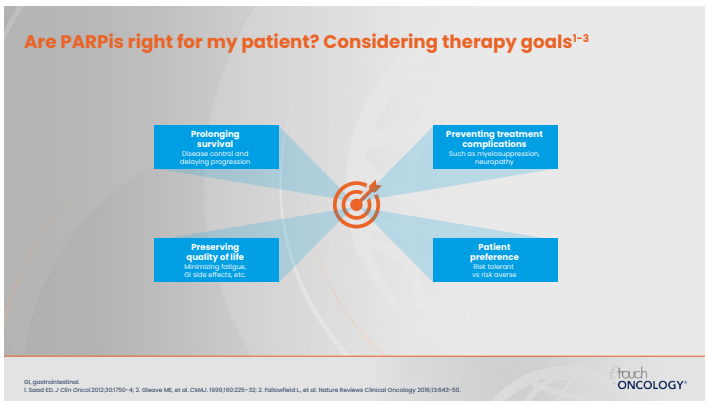


The guideline recommendations for PARP inhibitor and mCRPC, this is now updated in NCCN based upon PROfound and the TRITON2 trials, these, both olaparib and rucaparib, have approval in the US. Both can be approved now, based upon either use of a germline or a somatic-based testing. The difference between olaparib and rucaparib is that olaparib is approved in mCRPC for progression on a novel hormonal agent, abiraterone or enzalutamide. Rucaparib is approved based upon a progression with a novel hormonal agent and also a prior taxane therapy.

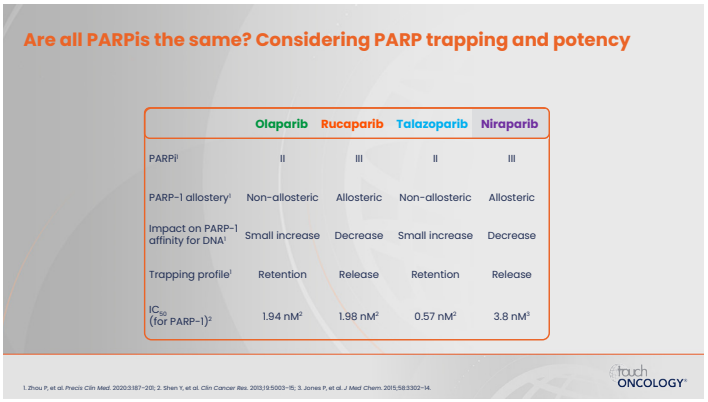
We now have niraparib and talazoparib. They're not yet in the NCCN guidelines. I say that based upon upcoming and additional trials and data we'll hopefully see them also be incorporated. Great to have multiple options of these oral PARP inhibitors to help enhance treatment decision making for our patients who have a lethal disease. There are mutational aberrations, resistance develops and if you have HRR mutation you can benefit from being on a PARP inhibitor.



Are the PARP inhibitors the right thing for my patients? Well, what are your goals for your patients? I think the goals should always be, I would describe it as four Ps: prolonging survival, preventing complication of therapy, and preserving quality of life, and knowing the patient's preference value: how risk averse or risk seeking are they for really any therapy?



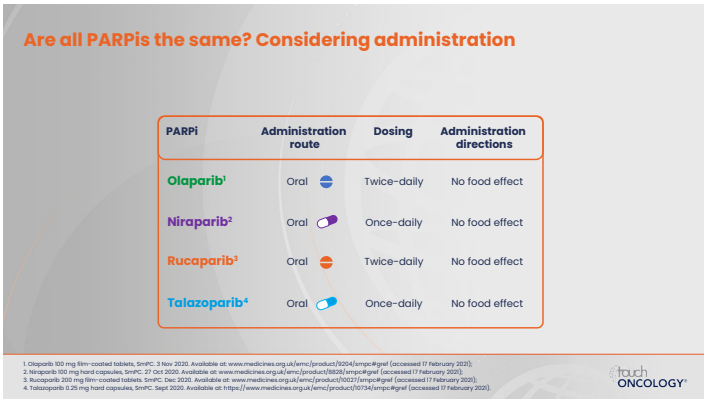
Now, we're going to see that the world of PARP inhibitors is really expanding and I think this is great. This is great for all of us as clinicians and it's great for us as patients. This is a very detailed slide which really goes into this table to tell you about the differences potentially in PARP inhibition potency of the enzyme. It also talks about their mechanism for how these work, whether it's directly effecting an effector response, what we sometimes call allosteric, versus non-allosteric; and the affinity for the PARP enzymes, the affinity for trapping or not and the inhibitory concentrations. Now, I wouldn't expect a busy clinician to really get into the weeds of this, but I like it because hopefully we'll see with future studies, well-conducted, direct comparator studies - all the PARP inhibitors, do they offer the same benefit to each patient? Will some be more efficacious and more potent than another? We don't know that yet, but one can see looking at the differences in how they trap the enzyme on a DNA and also on their inhibitory concentrations, there may be differences. Time will tell.



	Olaparib	Rucaparib	Talazoparib	Niraparib
PARPi[1]	II	III	II	III
PARP-1 allostery[1]	Non-allosteric	Allosteric	Non-allosteric	Allosteric
Impact on PARP-1 affinity for DNA[1]	Small increase	Decrease	Small increase	Decrease
Trapping profile[1]	Retention	Release	Retention	Release
IC_{50} (for PARP-1)[2]	1.94 nM[2]	1.98 nM[2]	0.57 nM[2]	3.8 nM[2]

1. Zhou P, et al. *Precis Clin Med.* 2020;3:187–201; 2. Shen Y, et al. *Clin Cancer Res.* 2013;19:5003–15; 3. Jones P, et al. *J Med Chem.* 2015;58:3302–14.

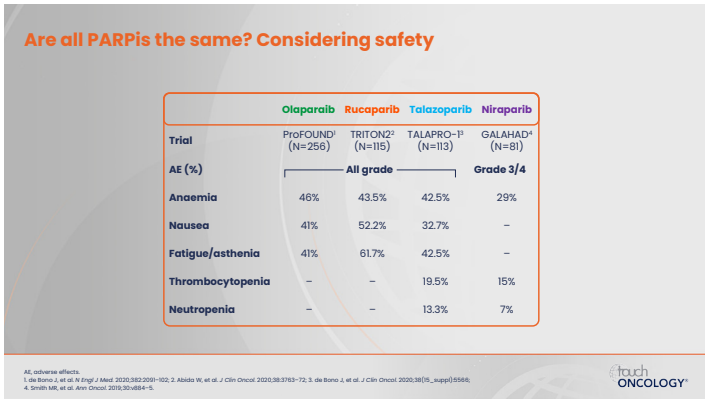
And again, they can be different in how they are given. Some are given in a BID dosing, some are given QD. Right now there are no food effects. Some of our other mCRPC therapies with PARP have a food effect requirement, so there is that nice luxury. None of these require concomitant use of a steroid.



PARPi	Administration route	Dosing	Administration directions
Olaparib[1]	Oral	Twice-daily	No food effect
Niraparib[2]	Oral	Once-daily	No food effect
Rucaparib[3]	Oral	Twice-daily	No food effect
Talazoparib[4]	Oral	Once-daily	No food effect

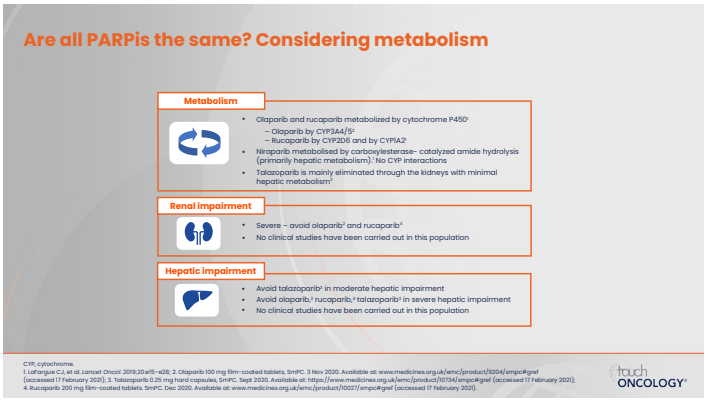
1. Olaparib 100 mg film-coated tablets, SmPC. 3 Nov 2020. Available at: www.medicines.org.uk/emc/product/9204/smpc#gref (accessed 17 February 2021);
2. Niraparib 100 mg hard capsules, SmPC. 27 Oct 2020. Available at: www.medicines.org.uk/emc/product/8828/smpc#gref (accessed 17 February 2021);
3. Rucaparib 200 mg film-coated tablets. SmPC. Dec 2020. Available at: www.medicines.org.uk/emc/product/10027/smpc#gref (accessed 17 February 2021);
4. Talazoparib 0.25 mg hard capsules, SmPC. Sept 2020. Available at: https://www.medicines.org.uk/emc/product/10734/smpc#gref (accessed 17 February 2021).

What are the side effects that we can expect to see? Well, none of these studies that I'm showing you here are direct comparator studies, so please understand that. Really, what I'm showing you here is what you've seen published or presented in educational forums. All grade, looking at anaemia, nausea, fatigue/asthenia and then grade 3/4 side effects really only listed here in niraparib, but I will tell you that they all run a consistent risk of myelosuppression, which seems to be a part of the AE profile. We see this in approvals for these PARP inhibitors, when appropriate, for breast, ovarian, pancreatic cancer. And typically all this requires is checking a CBC on a monthly basis. So, that's an important aspect. There will be combination therapies that are going to be looked at. We'll talk about that in the next module.

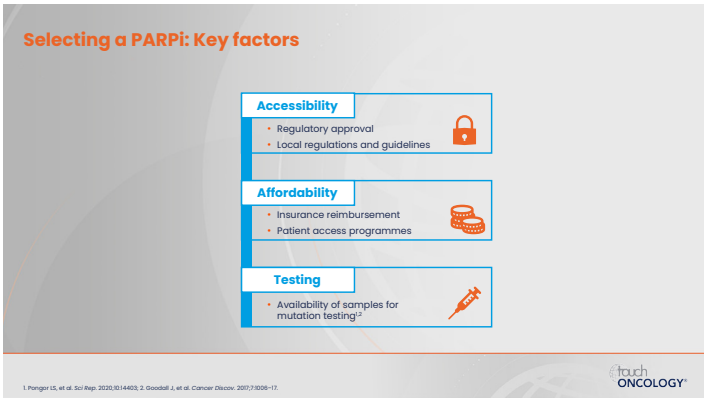


The metabolism is always important. Some have different metabolic profiles, whether they're using the CYP3A4/5, whether it's the CYP2D6, CYP1A2, niraparib is metabolized by carboxylesterase and catalyzed amide hydrolysis. No CYP interactions. This may have implications for choosing based upon drug-drug interaction. And so talazoparib is mainly eliminated through kidneys and has minimal hepatic metabolism. So, as we become more aware of other mCRCP therapies that have particular CYP interaction, drug-drug interaction, it's important to understand how this may play into PARP inhibitor drug selection. And then if there's renal impairment, really, we need to study a little bit more but I know that right now olaparib and rucaparib can be used in patients with clearances of 30cc and higher. And hepatic impairment, as I mentioned earlier here, it's important and we need to really understand.

Typically patients who have really severe Child-Pugh class C are often very hard to treat. Nonetheless, monitoring liver function tests periodically is always important in our advanced prostate cancer patients.

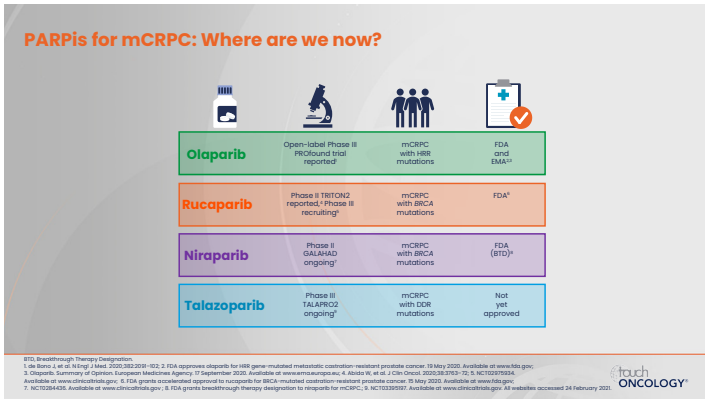


So, in addition to understanding different mechanisms of action, different adverse event profiles, different drug-drug interaction, what about just general accessibility? Well, this is not only on a global level but this can also be on a local regulatory level and one needs to be cognizant of this. All of these new therapies, all the oral oncolytics, they have a heavy price tag. I will say that I've been impressed that most of the companies really try to work with patients and healthcare providers in finding sampling programmes and compassionate use programmes and access programmes. So you have to do the best that you can. We have to continue to be champions for our patients. And then back to what I was saying earlier, you must test. You must think about getting germline testing in metastatic patients, patients newly diagnosed, non-metastatic who have significant family histories. If the germline testing is negative you have to think about going to somatic testing and getting a better understanding of whether you do archival tissue, metastasis-directed biopsies or even liquid-based testing. All of these will offer you opportunity to advance patient care.



And finally, where are we now? We see that we have olaparib and rucaparib approved by FDA, olaparib also approved by EMA; niraparib, which has got a breakthrough designation; talazoparib, also is working on additional studies, phase III trials. And I'm highly optimistic that in the foreseeable future we'll have four different PARP inhibitors that we can offer to our patients and we'll need additional studies to understand are there differences and benefits that we can provide to our patients.

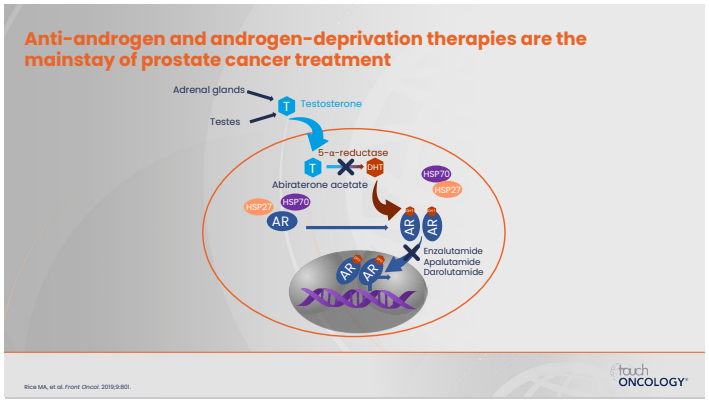
Thank you very much.



New and emerging PARP inhibitor combinations for prostate cancer

'New and emerging PARP inhibitor combinations for prostate cancer.' Really, one of the most interesting things, right, is how do we sequence our mCRPC therapies and at the end of the day how can we combine to get a more powerful effect in terms of slowing down the growth of prostate cancer and prolonging our patients' survival and maintaining quality of life, and, of course, doing it in a way that's accessible, affordable and doesn't increase adverse reactions.

So, the anti-androgen therapies and androgen suppression, these have really been the mainstay, the foundational aspect of prostate cancer.
You know, going back to the understanding the endocrine pathway of Huggins and Hodges surgical castration, LHRH agonist antagonist, and then recognising testosterone sources from the adrenal glands, testis and the tumour itself, ultimately slowing down testosterone, dihydrotestosterone impacting the androgen receptor and causing cellular proliferation of prostate cancer tissue.



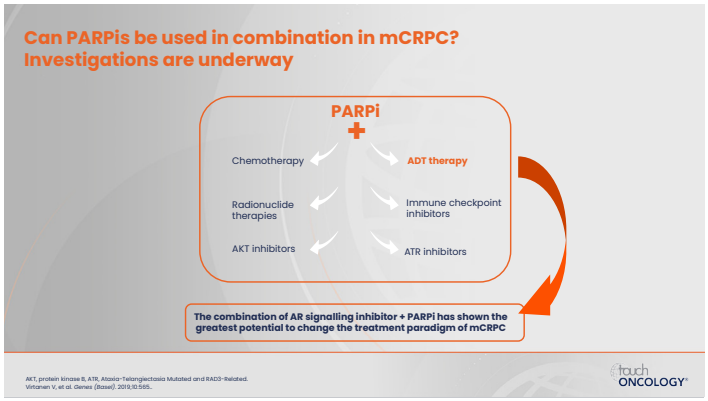
But, as we know, resistance is the bane of our therapies, isn't it? Mutational aberrations are ongoing, the canonical pathway of the AR can be disrupted and there are all of these great advances that have occurred to figure out ways to then go on to get second-line, third-line, fourth-line therapies. So, PARP inhibitors have now entered into the realm and the really exciting aspect is can we take these oral medications and combine them with other

oral medications, or even parenteral intravenous medications, and get an even better result?

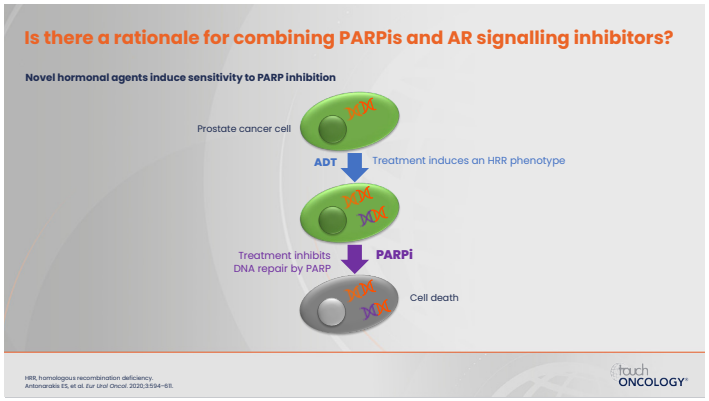
And that's really exciting, I think, for all of us who are doing clinical trials and take care of patients with advanced prostate cancer.

So, can PARP inhibitors be used in combination? Well, there are just so many investigations underway and so paying attention to ASCO GU, ASCO, AUA, ESMO, this is where you're going to hear about these therapies and so look at all the potential combinations that we can see. And this is not an exhaustive list, and thinking about where checkpoint inhibitors would come into play, ATR and the implication of *ATM* gene alterations; and, of course, with even traditional AR inhibitors, which I'm going to talk about, such as enzalutamide and abiraterone, radiopharmaceutical agents; a super exciting time. The PIK-AKT pathway, which is being trailed now for multiple drugs, particularly those who have *PTEN* genetic loss.

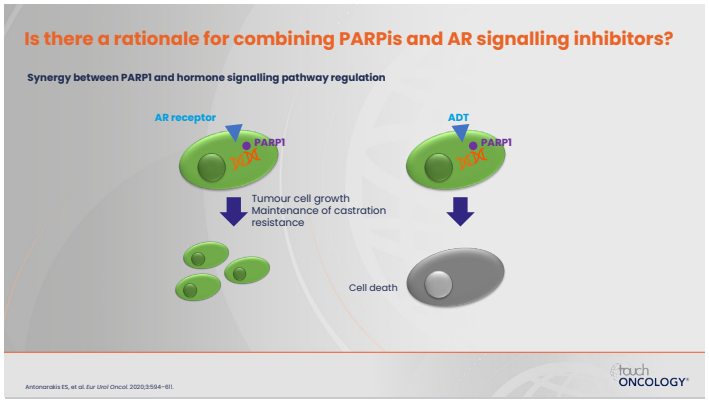
So, I'm going to focus on this segment really on combining PARP inhibitors with AR signalling pathway inhibitors.



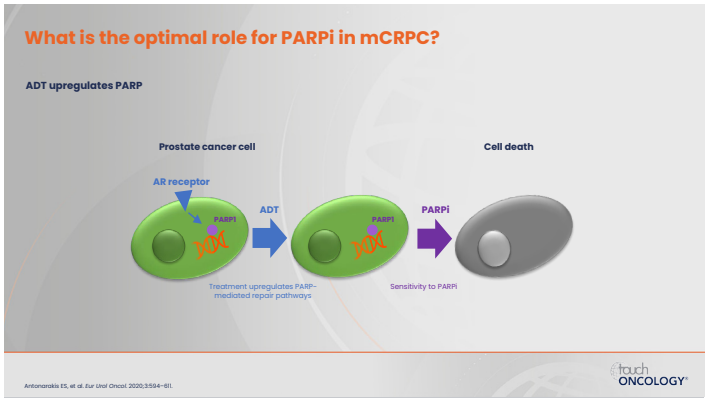
So, what's the rationale for doing this? Well, prostate cancer cells, as we know, when we provide testosterone suppression this can induce an HRR phenotype, that's been well established. And if you know that HRR phenotype, and particularly where there's a gene alteration, that's an area of susceptibility for taking advantage of that finding. So, treatment inhibiting a DNA repair by a PARP inhibitor that goes back to the concept of 1 +1 leading to a synthetic lethality. Testosterone suppression leads to an instability, there's a repair, there's a mutational event, and an AR inhibitor is added, now you add on a PARP inhibitor. So these are the sort of theoretical mechanisms of action to exploit a pathophysiologic benefit in advanced prostate cancer patients.



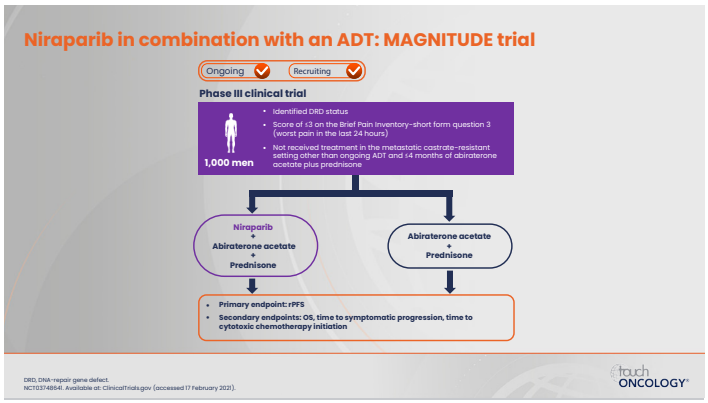
So that's the rationale for combining a PARP inhibitor and an AR signalling agent. There can be synergy between a PARP 1. There's also PARP 2, PARP 3, but PARP 1 is really where we have the most knowledge and the hormone signalling pathway regulation. And you can see here, if there is a translocation from cell receptor into the cytoplasm ultimately to the nucleus, we can see a tumour cell growth can be maintained by adding on a PARP inhibitor that can lead to an apoptotic, or cell death, event.



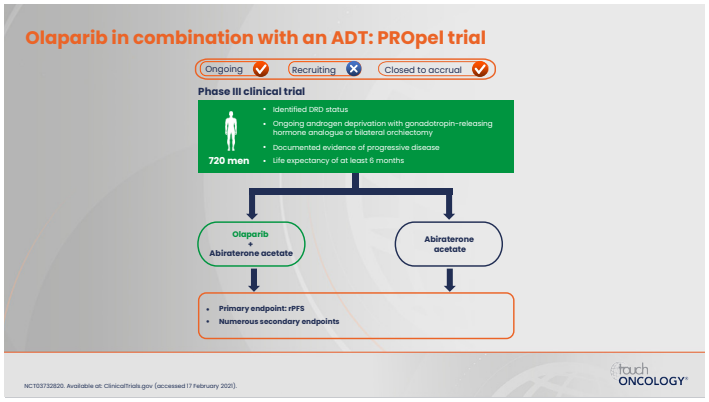
So, testosterone suppression, ADT, can lead to an upregulation in PARP mediated repair pathways, and so logically by putting in an inhibitor that can negate or obviate further cellular proliferation. So, based on the rationale that patients who potentially progress on androgen deprivation therapy develop mCRPC, how can we combine androgen receptor pathway inhibitors with a PARP inhibitor, particularly if they DNA damage repair defects, and do it in way that's both efficacious and safe and well-tolerated?



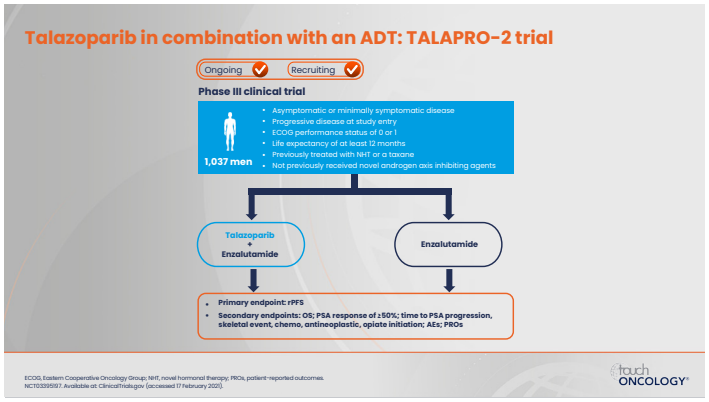
Well, let's look at niraparib in combination with androgen deprivation therapy. So, this is the MAGNITUDE trial. This is a phase III trial. Patients will have to be identified based upon their DNA repair damage status. This is pretty much a truism for all of these trials, which again goes back to the importance of you have to test to find these patients: germline testing, somatic-based testing. We will look at pain scores for these patients, but they've not really received treatment in the mCRPC setting, and so they'll get randomized to niraparib with abiraterone acetate and prednisone, an approved therapy for the first-line mCRPC versus abiraterone acetate and prednisone alone. So really, a very direct comparator prospective study: combination versus approved mCRPC ARP inhibitor. And this is a theme that I'm going to explain additionally here. The primary endpoint will be rPFS and then you see the usual secondary endpoints: the all important OS, time to progression, time to pain progression, and time to antineoplastic therapy.



Olaparib just is about to close accrual. I believe it has now closed accrual and this is the PROpel trial, based upon a prior large study, conducted by Noel Clarke and published in The Lancet Oncology, showing a benefit efficacy of combining olaparib with abiraterone acetate. So, again, primary endpoint rPFS and the typical secondary endpoints. You have to look at adding these together. We want to see efficacy but can we also demonstrate that it's safe and tolerable?

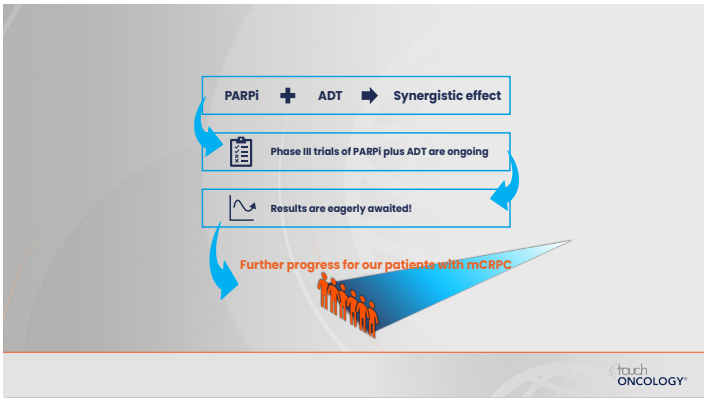


Talazoparib in combination with ADT, the TALAPRO-2 trial, a really important trial as well. We've talked about the potential benefit theoretically of its mechanism of action and possibly its metabolism and drug-drug interaction. But we need more trial data to really interrogate this. And here's an opportunity of combining talazoparib with enzalutamide, really a very powerful ARP inhibitor in the form of enzalutamide, which has been approved since 2012. And looking at these primary endpoints and the associated secondary endpoints, the concept being to make sure we have advancement in our armamentarium and treatment options for our patients.



So PARP inhibitors and androgen deprivation therapy, there's a synergistic effect. This has been well demonstrated in pre-clinical and basic science research and early phase studies, these combination trials, whether it be with abiraterone or with enzalutamide, are really important. We have a body of adverse reaction management that we understand how to do this with monotherapy PARP inhibitors, with the ARP pathway inhibitors. These results are important. You're going to hear more about them in all of our important congresses throughout 2021 and 2022.

Thank you very much.



The information provided by this CE activity is for continuing education purposes only and is not meant to substitute for the independent medical/clinical judgment of a healthcare provider relative to diagnostic and treatment options of a specific patient's medical condition.

USF is an Equal Opportunity / Affirmative Action / Equal Access Institution.

USF Health is accredited by the Accreditation Council for Continuing Medical Education, the American Nurses Credentialing Center and the Accreditation Council for Pharmacy Education to provide continuing education to healthcare professionals. As an accredited provider, USF Health is required to disclose personal information to relevant accredited bodies that certify CE to process credits/contact hours, comply with reporting requirements, and for internal recordkeeping and regulatory purposes. USF Health does not share or sell any individual's contact information or unique identifiers to any commercial supporter, advertiser, or third party without the specific permission of the individual.

Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions.

The presenting faculty have been advised by touchIME and USF Health to ensure that they disclose any such references made to unlabelled or unapproved use.

No endorsement by touchIME or USF Health of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in touchIME or USF Health activities.

touchIME and USF Health accept no responsibility for errors or omissions.

This content is intended for healthcare professionals.

Date of original release: 31 March 2021.
Date credits expire: 31 March 2022.

ABBREVIATIONS

ADT, androgen deprivation therapy; AE, adverse event; AR, androgen receptor; BID, twice-a-day; CBC, complete blood count; HRR, homologous recombinational repair; LHRH, luteinizing hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PARPi, poly (ADP-ribose) polymerases inhibitor; QD, once-a-day; rPFS, radiographic progression-free survival.