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Global Perspectives on PARP inhibitor Combinations in mCRPC Match Play: European vs. US Integration in Practice

**Annoucner Open:**
Welcome to CME on ReachMD. This 7-part activity, titled Global Perspectives on PARP Inhibitor Combinations in Metastatic Castration-Resistant Prostate Cancer Match Play: European vs. US Integration in Practice is developed by AXIS Medical Education and is supported by an educational grant from Pfizer. Before starting this activity, please be sure to review the disclosure statements as well as the Learning Objectives.

Here is Dr. Neeraj Agarwal

**Dr. Agarwal:**
Three PARP inhibitor combinations were approved by the FDA in 2023 as frontline treatment of metastatic castration-resistant prostate cancer, and two combinations are approved in Europe. How, why, and in what patient populations should we use them? This is CME on ReachMD, and today we're looking at some very important questions surrounding the use of PARP [poly(ADP-ribose) polymerase] inhibitor combination therapies.

My name is Dr. Neeraj Agarwal. I'm a GU [genitourinary] Medical Oncologist and Professor of Medicine at the Huntsman Cancer Institute at the University of Utah in Salt Lake City in the United States.

Today's activity, which is inspired by the Ryder Cup, our expert medical oncologist and urologist faculty will answer questions pertaining to the use of PARP inhibitor combinations in metastatic castrate-resistant prostate cancer in a "Match Play" style discussion, evaluating both the U.S. and European perspectives on recent developments in the field.

**FIRST TOPIC: MECHANISM OF ACTION**

**Dr. Agarwal:**
So, first, let's set the stage for the Match Play discussion by briefly reviewing the mechanism of action and rationale for PARP inhibitor combinations in metastatic castrate-resistant prostate cancer.

So Elena, I'd like to start with you. If you could tell us the mechanism of action of AR targeted therapies, and then I can discuss the mechanism of action of PARP inhibitors, and the rationale for combining them.

**Dr. Castro:**
Yes, we currently have androgen receptor signaling inhibitors with two mechanisms of action. One is abiraterone acetate that inhibits the biosynthesis of androgen by inhibiting one of the cytochromes involved in its production, and we also have androgen receptor direct inhibitors, that is enzalutamide, apalutamide, darolutamide. And what they do is they compete with the ligand of the androgen receptor, and also affects the internalization of the androgen receptor to the nucleus and interrupt also the transcription of some AR [androgen receptor]-regulated genes.

**Dr. Agarwal:**
Great. So, regarding the PARP inhibitors, we know these are already approved in mCRPC [metastatic castration-resistant prostate cancer] space, in the form of olaparib and rucaparib, and now we have three more combinations approved in the first-line mCRPC


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setting. Poly (ADP-ribose) polymerase enzyme is a key enzyme which is required for repairing the single-strand DNA repair mutations. Now, if PARP falters, befell the DNA single-strand break, turns into double-strand break, and when that happens these prostate cancer cells are quickly repaired by the homologous recombination repair mutations. Now, if there is a problem with homologous recombination repair mutations, either in the form of a mutation such as BRCA1/BRCA2 mutation, or many other mutations, or we induce some kind of vulnerability in the cells by adding another synergistic drug, or another drug which cooperates with PARP inhibitors. In allowing that, a single-strand break, not to be repaired, after it becomes double-strand break, we call it synthetic lethality, meaning if PARP is inhibited in those circumstances where a double-strand break has already happened or is not allowed to be repaired, then it basically means that cells repaired their DNA by an inefficient mechanism, known as non-homologous end joining, which leads to basically a defective DNA, which is not compatible with survival of the cells. In this case, prostate cancer cells. Now there are some PARP inhibitors which can also trap the PARP at the replication form, and then can further accentuate the overall DNA repair defects, or the accumulation of DNA repair defects.

So, why do we combine them? Preclinical data have shown that when prostate cancer cells are targeted by AR inhibitors, the PARP gets upregulated. In simple way to explain that, as PARP gets upregulated to basically save the cells from dying after being hit by AR inhibitors. So AR inhibition leads to upregulation of PARP. And when we inhibit PARP, that leads to down-regulation of androgen receptor. So when you combine them, that basically leads to the cooperative inhibition of both AR and PARP, which leads to basically inefficient DNA repair, which leads to accumulation of DNA breaks in the cells, which can interfere with survival of the cells.

So I think the bottom line for the audience is that AR inhibition and PARP inhibition can come together to increase the vulnerability in the prostate cancer cells, to attack by the androgen receptor inhibitors.

Alright, let's get started with our Match Play. In Match 1, let's talk biomarkers.

**MATCH PLAY 1: BIOMARKERS**

**Dr. Shore:**

Our first question is, how can we personalize therapy with PARP inhibitor combinations with the use of biomarkers? I'll start with the U.S. perspective.

Testing is important. And I think that many of us, myself and my friend, Dr. Merseburger, we have been promoting early testing by urologists. Right now, we know that the overwhelming majority of urologists, especially in community, are not testing. And if they test, they typically just get one test, it's often just a germline. Rarely the somatic, but sometimes they'll just get a somatic and not the germline. And that's important because germline testing has implications for family members. There are some challenges in getting access to tissue. A germline is easy. It's a simple blood test or a buccal smear. The somatic or the tumor tissue, I usually like to get it early when there's metastatic disease sensitive, I don't wait for it to be resistant, because I want to use the archival prostate biopsy tissue with a prostatectomy specimen to make sure that that tissue is viable, hasn't been degraded. And I can get a genetic alteration evaluation if I can't, and I can't get a metastasis-directed biopsy with my interventional radiology colleagues, I'll do liquid-based testing, the ctDNA.

I work collaboratively with all of my uro-oncology partners, and my medical oncology partners. And we always offer genetic education. It doesn't always have to be a certified genetic counselor. If you have one, I think that that's great. Dr. Merseburger, can you please review any differences in European practices on the points that I stated?

**Dr. Merseburger:**

Dr. Shore, yes, I sure can.

And fully agree that biomarkers play a crucial role in personalizing therapy with those PARP inhibitors and the combinations, especially in this context of mCRPC treatment. And I think there are several ways in which biomarkers can be applied in to personalized therapy in those PARP combinations. We have precisely focused on the DNA repair deficiencies, the BRCA gene, and also other genes. So, we can also perform comprehensive genomic profiling beyond BRCA mutations. We have the HRD, the homologous recombination deficiency testing, and also looking towards patient stratification, monitoring treatment response with biomarkers in the future, and looking at treatment resistant mechanism combination therapy selection, possibly in the future. So, this is very exciting.

**Dr. Shore:**

Regarding the question of tissue versus liquid-based testing. So first, to be very clear, for the germline or the hereditary risk, it's a very simple blood test, extremely accurate with a validated sponsor panel. Or one can get a buccal smear, a saliva test as it's often called, you don't need a tumor tissue. And it's an important test because it has implications for the patient's family and the patient's siblings, and that patient's sibling's children. And it's come down in cost dramatically over the last decade.

As it relates to the somatic, you know, people will oftentimes say tissue is the issue. I think we like to be able to have enough tumor tissue, tumor cells with adequate number of nuclei, to interrogate DNA and RNA depending upon the type of test that you're doing. But


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at the end of the day, tissue is great, whether it's archival prostate biopsy, or from the prostatectomy specimen, or from metastasis-directed biopsies of soft tissue, liver lesions, and even occasionally bone lesions. And you can go back 5 years, even sometimes upwards of 10 years, and the tissue is still viable. Depends on how much was there, the tumor tissue, and how it was preserved.

But in those cases where it's not adequately accessible, not adequately preserved, you can't go forward with a metastasis-directed biopsy, then liquid, a simple blood draw is good. And there's about, most people would agree about an 80% concordance with tissue; it's not 100%, it's about 80%. And there are some issues regarding false positives and false negatives. But overall, it's certainly the next best thing if you can't access the tissue itself.

**Dr. Merseburger:**
So probably 90% of the countries worldwide, when it comes to metastatic disease, the urologist refers to the medical oncologists, except Japan, Germany, and some parts of Austria and Switzerland where the urologist is trained and also able and allowed to treat up till the death. So, an mCRPC second and third line with the exception of radioligand therapy, which is done by a nuclear medicine expert. So the rest, like systemic therapy, docetaxel, cabazitaxel, is and can be within the hands of the urologist in Germany, Japan, and some parts of Switzerland and Austria.

**Dr. Shore:**
Yeah, I think it's a really interesting evolution. In the United States, we do have advanced prostate cancer clinics, or what we sometimes call center of excellence. As Axel was talking about, following the German, the Japanese, the Austrian, Swiss example, and no longer just thinking of the urologist, uro-oncologist, as a surgical oncologist, some might say a proceduralist strictly doing surgery, but getting an expertise and a commitment to systemic therapies. So that would include doublet, triplet therapy for mHSPC [metastatic hormone-resistant prostate cancer] and then of course, first and second and third line, arguably even fourth line, for mCRPC. From my perspective, it's just making sure the patient gets all of the right discussion and gets all the right opportunity to have that very important patient-physician shared decision-making.

**Dr. Merseburger:**
I can only echo and maybe add a short sentence. I think, very, very wise and good comments. And when the field is moving forward towards treatment intensification in perioperative setting, we need the urologist on board, and that's why I think it's an excellent approach of Dr. Shore to getting experience within the hands of the urologist of novel hormone treatment and beyond in order to also deal with the side effects, shared decision-making with a patient and the carer. So, I think this is very important when it comes to neoadjuvant, adjuvant, and early salvage treatment like we've just learned from trials treating with NHT and biochemical recurrence.

So dear colleagues, I think it is very important as we've learned in this module, that urologists and medical oncologists really work together and have a very well-informed patient and carers in order to provide best adherence and best results, clinical results, and in the future hopefully a prolong the overall survival benefit with PARP inhibitor combination and NHT. I think this triplet therapy in mCRPC is the future and especially a must for men with HRR [homologous recombination repair] alterations like BRCA 1 and BRCA 2.

That's it for our first match. Stay tuned for Match 2 to learn which patient populations are appropriate for PARP inhibitor combination therapy.

## MATCH PLAY 2: PATIENT POPULATIONS

**Dr. Agarwal:**
Our question for this match is: In which patient population are PARP inhibitors combinations ready for consideration in metastatic castrate-resistant prostate cancer?

I will answer first question from a U.S. point of view, as we have had three combinations of FDA approval in 2023.

So according to the PROpel trial data, olaparib plus abiraterone combination is approved for patients with mCRPC who are BRCA1 and BRCA2 mutation, either detected by germline or somatic mutations. And despite the fact that benefit was present, regardless of HRR mutation, and with the caveat that benefit was more pronounced in patients with HRR mutation.

Now the second combination, which is talazoparib plus enzalutamide, was approved for patients with mCRPC with all homologous recombination repair mutations, whether germline and/or somatic. And this combination was approved based on the results of the TALAPRO-2 trial in June 2023. And, just for your recollection, the combination showed benefit irrespective of homologous recombination repair mutation status. When it was prospectively assessed in this patient population, again with the caveat that the benefit is more pronounced in patients with homologous recombination repair mutations.

Now the third combination is approved based on the MAGNITUDE trial results, and this is a combination of abiraterone plus the


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niraparib combination, which is approved for patients with mCRPC who harbor BRCA1 and BRCA2 mutations, either in germline or somatic genes. And this combination is approved in August 2023.

But bottom line is, how to decide which patients should get these combinations and which combinations should be offered to our patients.

Let's hear the European perspective, from a very renowned oncologist, Dr. Elena Castro.

**Dr. Castro:**
Currently in Europe, we have an approval of the combination of abiraterone plus olaparib as first line of treatment for mCRPC patients regardless of HRR or a BRCA status. And we also have approval for niraparib in combination with abiraterone based on the data from the MAGNITUDE trial for patients with alterations in BRCA1 and BRCA2. So, although the approvals are not limited for patients who have or have not received an androgen receptor signaling inhibitor prior to reaching first-line mCRPC and the data we have from these studies include only a minimal number of patients who have received these agents prior to entering the trial. So we cannot really get conclusions on whether what is the efficacy of these combinations for patients who have been exposed to an androgen receptor signaling inhibitor. In Europe, at present, we still don't have approval for talazoparib in combination with enzalutamide, but it is expected by the end of the year or the first quarter of 2024.

**Dr. Agarwal:**
This is great discussion. Let me use this opportunity to ask you. Abiraterone/olaparib combination is approved for all-comers in mCRPC setting. Abiraterone plus the niraparib combination is approved for BRCA1 and BRCA2 positive patients in mCRPC setting. And assuming TALAPRO-2 approval goes through, we'll have talazoparib plus enzalutamide in EU for, say, all-comer population for the sake of discussion. And if you have a patient, say many of those patients who have received ADT [androgen deprivation therapy] monotherapy for biochemical recurrence in last 3, 4, 5, 6 years and they are slowly moving to the mCRPC state, would you consider the combination therapy for all patients? Or are you only considering for HRR positive patients in the EU?

**Dr. Castro:**
The combination, with the data we have at present, I will consider it only for patients with HRR or BRCA or other HRR alterations, because I think that it is clear that adding a PARP inhibitor to a hormonal agent results in increased toxicity, and we know that the benefit of the treatment is different if the patient has a BRCA alteration or another HRR alteration, or if we do not detect these alterations. So for me is a matter of finding the balance between the toxicity that we know is the same for the different groups, and the benefit that we know is different for these groups.

**Dr. Agarwal:**
And for us in the U.S., it's decision-making is relatively straightforward. All these combinations are approved in homologous recombination repair mutation-positive patients, for enzalutamide plus talazoparib, and the abiraterone-based combinations are only approved for patients with BRCA1 and BRCA2 mutation in the mCRPC setting. However, we do see patients who have received limited duration say abiraterone. It becomes very challenging to treat them with chemotherapy. So for me, my practice is quite straightforward, as far as use of combination therapy is concerned. I look at whether they are candidates for abiraterone or enzalutamide, and if they have respective mutations. So if I have a patient who is going to be a candidate for enzalutamide, and if they have HRR mutation, for me, I use talazoparib plus enzalutamide.

**Dr. Castro:**
I totally agree. If it's a patient with a HRR alteration or a BRCA alteration that has already received abi or enza, and they embark a scenario or we are going to see more and more of these patients. And, if a patient with one of these HRR or BRCA alterations, that has been demonstrated that are clearly associated with poor clinical outcomes, and the only thing that actually improves their outcomes is a PARP inhibitor I would be very happy to give it to them in combination, I wouldn't feel very happy by starting a hormonal agent again and waiting until they progress to a second one. So, I will be very happy in those patients to start the combination up front, because the PARP inhibitor I don't know if the synergy will really add something to these patients. We still don't have that information, but I know the PARP will. So, because this is the approval I have, I will be very happy to give them this in combination.

**Dr. Agarwal:**
To clarify to the viewers, we are talking about those patients who have been exposed but not progressed on the first AR inhibitor, or AR pathway inhibitor. And of course, we have a large patient population in the U.S. with biochemical recurrence after localized therapy, who are being treated with androgen deprivation therapy currently, and they have castrate level of testosterone, and they are slowly progressing to mCRPC, they remain eligible. And in addition, patients who receive docetaxel chemotherapy in the hormone-sensitive setting, and now they are progressing to mCRPC setting, in my practice, I do offer them a combination of PARP inhibitors if they have HRR mutations or BRCA1 or BRCA2 mutations.


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One more situation I think is quite common in our clinics, when a patient cannot really get enzalutamide, or abiraterone because of drug-drug interaction, or, they don't want to be corticosteroids for a long time, or just for the sake of discussion, they have liver toxicity because of, say, abiraterone and you have to switch to enzalutamide. So, in most of the cases – and of course, in the U.S. we also worry about the co-pay. So, in my practice, I mostly look at what androgen receptor pathway inhibitor I'm going to use. That's the first decision-making I have to do, for BRCA1 and BRCA2 mutation patients. Then I just add a PARP inhibitor, which is compatible with that ARPI. For non-BRCA1/BRCA2 mutations, I am basically limited to using enzalutamide plus talazoparib.

I think with that we can we think this is how we are seeing these patients in the U.S. and the EU, and how these combinations are approved, and how we are thinking about using these combinations for these patients.

So this is the wrap on this match. But please join us for the next match on the adverse events.

**MATCH PLAY 3: ADVERSE EVENTS**

**Dr. Agarwal**:
Dr. Castro, I'll ask you, what are the adverse events seen for PARP inhibitor combinations? And how can we best coordinate care? So I'd like to get the European perspective from you.

**Dr. Castro:**
Yes, what we have consistently seen in the three trials that have already reported their results in the combination of PARP inhibitors and hormonal agents, the toxicity we see is in line with the toxicity associated with PARP inhibitors also in monotherapy and in other tumor types as a class effect toxicity, which is mostly hematological toxicity, fatigue or asthenia, and gastrointestinal toxicity. So, for the hematological toxicity, it is mostly anemia, depending on the agent, it has been reported in over 50% of patients, and grade 3 anemia in about 20%, and with talazoparib, it's slightly higher. It seems to be related to the ability of trapping PARP1, and also or perhaps mostly PARP2.

So, the fact that many patients present with grade 3 anemia means that a significant proportion of these patients will require a blood transfusion. And this is something we need to be careful about. We need to remember that patients who are treated with PARP inhibitors need to be monitored closely. Sometimes when we treat patients with NHTs [neoadjuvant hormonal therapies] alone, we may see them every month or every 2 months or even but for these patients, we need to be aware of the hematologic toxicity and we need to check their blood counts regularly. Neutropenia is also frequent, mostly grade 1, grade 2 particularly once again the rate was higher with talazoparib, but grade 3 was noted 15% of patients or less. And then the third frequent side effect is thrombopenia with niraparib and talazoparib, was reported in about 20% of patients also, mostly grade 1 and grade 2.

So these toxicities can be managed by stopping the treatment and with transfusion support in the case of anemia, sometimes just by stopping the treatment and waiting a week or so, repeating the blood test. And in most cases, the blood counts will go up. If that [occurs] a second time, we may consider decreasing the PARP inhibitor dose and this is very well established how to decrease treatment for these patients. Fatigue and asthenia that are associated with PARP inhibitors are also somehow related with the anemia. And we cannot forget that also, the hormonal agents are associated themselves with some degree of fatigue. So this is also something to take into consideration.

And for the gastrointestinal toxicity most of the side effects are grade 1 side effects. Now there could also be grade 2, but in most cases it is grade 1, and can be managed by administering the PARP inhibitor with some food. Some patients may also present with vomit, but it's not very frequent. Constipation or diarrhea has also been reported in about 20% of patients mostly, mostly grade 1.

So because of the hematological toxicity some patients had to discontinue the PARP inhibitor and the discontinuation rate was slightly higher in the combination of talazoparib and enzalutamide, followed by olaparib and abiraterone, and then niraparib. And so, I think it is very important that we recognize that there are some side effects associated with PARP inhibitors that can be managed, tightly managed, it's just, I would say, a question of practice, and informing the patient that this is something that can happen, that we may need to stop treatment at some point, patients may require a transfusion, and then we may have to reduce the dose as well. So I believe communication with the patients is key with these treatments. And we may also need multidisciplinary collaboration in case of exactly that, we need to transfuse the patient or bring the patient to the clinic more often, have one of the nurses or one of the colleagues contacting the patients to see how is the fatigue going, if the nausea has already been resolved, etc., etc. So just be aware of the side effects and be confident that we can really manage them relatively easily.

**Dr. Agarwal:**
Thanks for such a comprehensive review of side effects and management from the European perspective. I'll just talk about the U.S. perspective, which is not going to be very different. I'd like to talk about three side effects which are common class effects, GI side effects, hematologic side effects, and fatigue. And, of course, there are some PARP inhibitors which have unique side effects such as


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hypertension, in the case of niraparib. But if we look at all these three major categories you already discussed about fatigue, Elena, I'm not going to repeat that. But you talked about GI side effects. I agree with you, we send all our patients with anti-nausea medications when we send them out on a PARP inhibitor prescription. And with that, nausea and vomiting has largely been controlled very well as long as we are proactive.

Now coming to the hematologic side effects, if you look at the number of patients in the TALAPRO-2 HRR mutation-positive cohort, 55% patients had grade 1 or 2 anemia, even before entering the trial. And this high proportion of patients with grade 1 or 2 anemia basically reflect how aggressive the disease is. Now, I agree that 40% patients develop grade 3 or 4 anemia. Fortunately, that happened – median time to answer a grade 3/4 anemia was 3.4 months. So, we know that patients were going to develop grade 3/4 anemia, they develop it quite early on during the course of treatment with talazoparib. And they were dose-reduced or received blood transfusion and then, after that, most of the patients were able to continue PARP inhibitors, especially if you're talking about talazoparib, so I like to highlight that. Most patients were able to continue treatment with talazoparib while gaining survival advantages, and alternate dose discontinuation rates were only 4%.

So, the lesson I learned from this experience of TALAPRO-2 trial is, yes, anemia is common – because baseline anemia is so common in this patient population, that get worse, and the moment it gets worse, because there's so many grade 1 or 2 anemia, it gets worse. Our patients that develop grade 3/4 anemia but fortunately, they're easily manageable with tiny reduction in the dose of the drug and transfusion as needed. And once they get to the dose reduction level, my experience has been that they are able to continue that dose of PARP inhibitor for a long time without discontinuation. Very small number of patients have to actually discontinue PARP inhibitors.

But bottom line is, as you said, Elena, first 3, 4, 5 months are crucial, more close follow-up. I usually do local labs. I don't feel compelled to get them to the clinic. Local labs, frequent monitoring, hemoglobin goes below 8, I stop the drug, reduce the drug. If they are symptomatic, give them transfusion. And like most other drugs we are using in our clinic, we are able to continue them on PARP inhibitors for long time, for most of these patients who continue to respond. I think this is very important that we work collaboratively with the primary care doctors and their respective family physician as far as management of side effects are concerned.

Well, thank you again Elena for such a fantastic discussion on the safety data, how to manage toxicities in the real world.

And with that, I'd like to get ready for our next match, discussing quality of life.

**Dr. Agarwal:**
For those just tuning in, you're listening to the CME on ReachMD. I'm Dr. Neeraj Agarwal, and here with me today are the expert oncologists and urologists from the United States and from the European Union. Together, we are exploring PARP inhibitor combination therapy as first-line treatment of metastatic castrate-resistant prostate cancer.

**MATCH PLAY 4: PATIENT-REPORTED OUTCOMES**
**Dr. Mersberger:**
So dear colleagues, for this match our question is: What are the shared decision-making implications of patient-reported outcomes for PARP inhibitor combination trials?

So let me start with that. The patient-reported outcomes, or PROs, play a crucial role in understanding the impact of medical interventions, including the PARP inhibitors and PARP combination trials on patients' lives. We know how PARP inhibitors work and that they work in certain cancers and also prostate cancer, in particular those associated with DNA repair defects. And some shared decision-making implications related to patient outcome from PARP inhibitor combination trials I would like to summarize. Also, symptom burden and side effects of the treatment and treatment combination. We want to find out about treatment preferences. This is also a big topic from patients but also carers, how they see their relatives and spouses and patients. So, the long-term impact is important and also communication and education in this situation.

So, we have learned from the combination trials, the PROpel trial for example, which combined olaparib and abiraterone that helps related quality of life, as determined by the FACT-P assessment did not affect or was not affected by the combination therapy. Same accounts for the TALAPRO-2 trial where talazoparib plus enzalutamide significantly prolonged the time to definitive clinical meaningful deterioration of the health and quality of life.

So, I think it is important in this stabilization of mCRPC that patients are seen by urologists but also by medical oncologists in a multidisciplinary shared decision-making approach and to learn from the patient, also learn from this MDT approach and possibly have the best patient adherence with that.

So, Dr. Shore, what are your thoughts on this topic?

**Dr. Shore:**


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Well, thank you very much. I think you, summarized that very well. You know, in these two very important prospective global phase 3 trials, TALAPRO-2 and PROpel, validated questionnaires looking at the various subscale domains of FACT-P, and some other questionnaires were used. And as you had stated, there wasn't any significant deterioration or change or delta between the combination versus the control arm, whether it was enza or abi with a placebo. And so, I think that's very important in terms of establishing quality of life not being adversely impacted.

Now, of course, we do know that the androgen receptor pathway inhibitor drugs, whether they're direct inhibitor of the AR pathway, drugs like enzalutamide versus abiraterone, a androgen biosynthesis inhibitor, they do have different adverse events of interest. Those have been well documented and described. And we saw those differences in these, in TALAPRO-2 and PROpel.

Likewise, the class of drugs known as the PARP inhibitors, where we don't have any direct head-to-head comparator trials, we do know that there are certain class effects, side effects of PARP inhibition. And it can, as a class, there's myelosuppression, you know, anemia, thrombocytopenia, occasionally leukopenia, neutropenia, and then GI side effects, diarrhea, nausea, of course, fatigue. And these side effects are very manageable. I think our medical oncology colleagues have been working with PARP inhibitors much longer than uro-oncologists because there have been approvals for PARP inhibitors in breast and ovarian and pancreatic cancer. Of course, those are different tumor types and different demographics potentially.

And so, we're learning a lot regarding how to think about monotherapy PARP inhibition for prostate cancer patients and now the opportunity for combination. You know, in particularly, as we've seen, the patients with BCRA have rather dramatic, all capital letters dramatic, responses, delaying their progression and clearly enhancing their overall survival.

So, I think that the opportunity for urologists and medical oncologists, whether you're in the U.S. or Europe or any part of the world, is to have that comfort to say, okay, I can manage these combinations, recognizing there are some increase adverse events I need to be familiar with, which is a good thing. But then similarly, understanding, is a patient risk averse? Or are they risk seeking? How aggressive do they want to be in trying to combat their cancer? And in first line mCRPC, patients' performance statuses are usually pretty strong as opposed to second and third, fourth line, if they even get that far.

So, I think the notion around shared decision-making, we can never take that lightly. We have to be very good communicators, regardless of your specialty, to give patients the opportunity to demonstrate their preference value.

So, the next match we'll discuss key abstracts and data from the 2023 European Society for Medical Oncology, ESMO, meeting.

**MATCH PLAY 5: KEY ESMO 2023 ABSTRACTS**

**Dr. Agarwal:**

Elena, we were both in European Society of Medical Oncology meeting in Madrid just a few weeks ago. And fantastic meeting as usual. Would you like to tell us any new data on the combination of AR inhibitor and PARP inhibitors in the ESMO meeting?

**Dr. Castro:**

Yeah, while most of the survival data have already been presented this year at ASCO and ASCO-GU, at ESMO, we learned the final survival analysis for the MAGNITUDE trial in a multivariate analysis it was demonstrated that the combination of niraparib plus abiraterone was superior to abiraterone alone for patients with BRCA alterations and thus just is consistent and adds very nicely to the data we have from TALAPRO-2 and PROpel.

And there were also some abstracts that presented data on patients with germline and somatic alterations and showing that both benefited from the combination of talazoparib and enzalutamide. There was also another abstract that proved that a greater exposure to this combination, talazoparib and enzalutamide, was associated with better RPFS responses. And treatment with this combination also resulted in more prolonged time to clinical deterioration, particularly in patients with HRR and BRCA alterations. And I think this is very important because, as you mentioned earlier, these patients have very poor outcomes. And the disease progressed very rapidly when conventionally treated with taxanes or hormonal agents or radium-223 with the available therapies for mCRPC.

**Dr. Agarwal:**

That's such a nice summary of all ESMO abstracts in a few minutes. It's so great to do these discussions with you. Even I learn so much from your experience, always. And thank you.

So let's move on to some case discussions. When and how to intensify early treatment. So this is Match Play 6.

**Match Play 6: CASE DISCUSSION**

**Dr. Agarwal:**

So, let's start with the case study. And I'll present this case to Dr. Castro and see how she would manage in Madrid in Spain. And I'll discuss how we would like to manage here in the U.S. I think this is going to be very similar, but for the sake of discussion. So let's start


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with this case, 68-year-old man who was diagnosed with a localized prostate cancer 5 years ago, was treated with surgery and had PSA recurrence in2019, and was treated with androgen deprivation therapy alone. So he was treated with the intermittent androgen deprivation therapy initially, and then was slowly transition to continuous ADT. And as we discussed, this a large number of patient population we are seeing in our clinic who are now developing mCRPC. So localized prostate cancer, the most common wait for prostate cancer to present, had surgery. PSA recurrence, treated with intermittent then continuous ADT. Now PSA is arising, and you do a PSMA [prostate-specific membrane antigen] scan or CT [computed tomography] scan, conventional scan, and patient is found to have bone metastasis. The biomarker analysis revealed that patient had a HRR mutation. And for the sake of discussion, let's call it CDK12 mutation. How would you manage this patient in Europe? Elena?

**Dr. Castro:**
Well, this is very, very interesting, particularly because of the alteration that was identified. We know that patients with HRR alterations have poor outcomes. And this is also true for patients with biallelic CDK12 defects. And this has been shown by several groups, that these patients, when conventionally treated do very poorly. There were high expectations that these patients may benefit from checkpoint inhibitors, that some trials, it's still ongoing suggest otherwise. So PARP inhibitors in monotherapy do not seem to be very beneficial for patients with CDK12 alterations. Nonetheless, in the TALAPRO-2 study, we have seen that the combination of talazoparib plus enzalutamide could be quite effective for these patients with CDK12 alterations.

So in this case, at present, we don't have approval for this combination which as I mentioned earlier, it is expected for in the near future in the months to come. If I were in a situation where I wouldn't be able to use talazoparib plus enzalutamide, perhaps I will try olaparib plus abiraterone, although we have not seen, because it has not been reported, whether these patients may or may not benefit from this combination.

**Dr. Agarwal:**
So I think the abiraterone/olaparib combination is a very reasonable combination, if enzalutamide/talazoparib combination is not available. And as you said, the hazard ratio for radiographic PFS showed that there was a 50% reduction in risk of progression or death even though the trials were not powered for individual subset analysis, the data in CDK12 was quite compelling, I agree with you. But I guess – as you mentioned, if that is not available, I think it's fine to use abiraterone plus olaparib combination. And just for the sake of discussion, if this was any other mutation, let's for the sake of discussion, BRCA1/BRCA2 mutation, what would use?

**Dr. Castro:**
Yes I was going to say that just in the case that the patient had another mutation that was not CDK12 once again the drugs that have demonstrated to improve the outcomes of these patients, the only one so far are PARP inhibitors. So we need to make sure that we identify all our patients with BRCA alterations and offer them a PARP inhibitor. I will say that the earlier the better. But I agree that we don't have that data yet. But because their outcomes are so poor I'm very tempted to offer them a PARP inhibitor as soon as possible. And in this situation, a patient who had only received ADT, the patient would be a perfect candidate for a PARP inhibitor in combination. So the approvals may be different from one region to another. The reimbursement may be different in Europe from one country to another, or even from one region to another. There may be centers that have access to one combination, but not to another, just use one PARP inhibitor and but make sure that these patients receive one, and as I said, perhaps as soon as possible.

**Dr. Agarwal:**
That was great, thank you. So, for the sake of discussion, in the U.S. we have approval for these patients, so we have enzalutamide plus talazoparib, abiraterone plus niraparib or olaparib approved for patients who have BRCA1/BRCA2 mutations, and this new diagnosis of mCRPC. And for all other HRR mutations, we have enzalutamide plus talazoparib approved. As Dr. Castro mentioned, in Madrid and in European Union, we have abiraterone plus olaparib approved for all HRR mutations, it looks like, and abiraterone plus niraparib combination is approved for BRCA1 and BRCA2 mutations, at least for patients like this, who are progressing on single-agent ADT after biochemical recurrence and now developing mCRPC.

**KEY TAKEAWAYS**
**Dr. Agarwal:**
Well, this has been a fascinating conversation. Before we wrap up, let's each provide a practical take-home message with our audience. Dr. Castro, I will start with you.

**Dr. Castro:**
Well, PARP inhibitors are the first targeted therapy available for patients with advanced prostate cancer. And we have the opportunity to treat patients with BRCA and other HRR alterations with these new therapies that have demonstrated to really improve the outcomes of these patients. We know that when conventionally treated, these patients have very poor outcomes. And we should really make an effort to identify who these patients are and offer them treatment with a PARP inhibitor as soon as we can. And it may mean in


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combination with a hormonal agent, if they have not received it earlier, but we need to make sure to find these patients and offer them a PARP inhibitor.

**Dr. Agarwal:**
Thank you. And you're right, these PARP inhibitors may move to even newly diagnosed metastatic prostate cancer patients in the near future. So very valid point.

My take on this is testing. It is unfortunate to see so many patients are not being offered tumor tissue testing or genomic testing of the tumor. So germline testing. Every single guideline worth any name has recommended, all the panels have recommended genomic testing of the tumor tissue. If tumor tissue is not available, somatic testing can be done through ctDNA, or we call it liquid biopsies, and of course, germline testing, because patients with metastatic prostate cancer, a significant number of patients, clinically important number of patients, are carrying germline mutations in their families, and they have implications on their own diagnosis and own treatments. So I think there is no denying that we have to improve the rates of testing, which is not adequately being performed at the moment.

And given that, so many patients don't see a subsequent line of therapy, and the fact that the disease course is so aggressive in patients with HRR mutations on conventional therapies, I'm trying my best to use PARP inhibitors as early as possible, and as early as PARP inhibitors are available for my clinic. So testing and early use of PARP inhibitors are the messages from me.

**Dr. Merseburger**:
Dear colleagues, friends, and guests, it was a great pleasure. And as always, I've learned a lot from my colleagues here in this group, and especially here with Dr. Shore. And I always learn a lot and I think it was - it wasn't a match, I think it was a collaboration, and I think this is what we should do all together for our patients for the fight against the disease of metastatic castration-resistant prostate cancer, discover novel modes of actions, discover novel combinations in the future, to best stabilize, and hopefully in the future, maybe somehow cure or stop this disease from growing. Thanks a lot.

**Dr. Shore:**
Testing germline somatic is essential. It's no longer a question of if you're going to do it, but when you're going to do it and in a routine and regular manner. And additionally, we have wonderful studies, TALAPRO-2 and PROpel, which have demonstrated that there is a clear unabashed synergy of combining a PARP inhibitor with an androgen receptor pathway drug that will help not only patients with BRCA, but patients with other HRR mutations, as well as patients in the all comer non HRR and the wild type. There's differences in the benefits, there are clearly similarities across the populations regarding the AE profiles. But really understanding how you can have that shared decision-making conversation with your patient to offer the most effective therapies. And I think it's important that we move away from being, you know, historically very paternalistic, whether it's government agencies or just physician agencies, but making sure that patients have an opportunity to make decisions for themselves along with their caregivers.

So I think the notion regarding both multidisciplinary teams, and importantly shared decision-making, giving patients the opportunity to think about options to optimize novel mechanisms of action, the PARP inhibition action, they are pathway inhibition, in a combination way, even if you are not HRR mutated positive, should certainly be something that should be offered, depending upon the country that you live in, and what regulatory approvals have established.

**Dr. Agarwal:**
We hope you enjoyed this fun Match Play format. I want to thank our audience for listening in, and offer a special thank you to our expert panel for sharing all of your valuable insights and expertise. It was great exploring this topic with you. Thank you very much again.

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