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PARP Inhibitors in Prostate Cancer: Improving Patient Outcomes Through Precision Therapy

Announcer Open:
Welcome to CME on ReachMD. This activity, titled "An Update on Biomarkers in Non-Small Cell Lung Cancer Clinical Management," is provided by Partners for Advancing Clinical Education – PACE – and supported by an educational grant from Merck Sharp & Dohme, LLC and Novartis Pharmaceuticals Corporation. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Sims:
Welcome to our next session, which is focusing on topic that I am interested in, particularly because of my practice, which is PARP Inhibitors in Prostate Cancer: Improving Patient Outcomes through precision therapy. And we have a very experienced speaker today, Frank dela Rama, who works now as a CNS and clinical nurse specialist with oncology and genomics in Palo Alto Medical Foundation and Sutter Health in Palo Alto, California. And I think he will bring a lot to this discussion today. Welcome, Frank. And here are his disclosures, and I'll just remind you of the session learning objectives, which is to review the mechanism of action and clinical rationale for the use of PARP inhibitors in metastatic, castrate-resistant prostate cancer; apply recommended strategies to ameliorate a ease associated with PARP inhibitors; and to develop advised treatment strategies for use of PARP inhibitors in patients with MCRC, based on molecular testing, guideline recommendations, and clinical trial evidence. So now, please let me welcome Frank dela Rama. Frank, it's all yours.

Mr. dela Rama:
I am a prostate cancer navigator by training, and so I've been working with prostate cancer for over 20 years. But I also do genetics and genomics since I got my Master's in that, so my practice is half cancer navigation and half genetic testing and counselling, and I'm happy to be here again today. Today, we're looking at the PARPs, which are a new tool that we use in advanced prostate cancer. We're going to start with an – a little bit about that. You know, advanced prostate cancer is the most frequently diagnosed cancer, second leading cause of cancer death among U.S. men, first being lung. Unfortunately, the median overall survival, as you see there: bone is about 21 months, lung a little over 19, liver 13 months. We don't like to see that, but definitely if you came – if you saw those numbers in 2004 or earlier, we didn't have a lot of these tools that we have today.

And so, it's really encouraging that we can kind of help men with first, second and third line therapies when it comes to metastatic, castrate-resistant prostate cancer. We don't really understand why these treatments stop working. Usually with metastatic or biochemical recurrence, we'll start people on ADT – you know, hormone deprivation therapy – and we'll keep giving it until it doesn't work. And so, often once a cancer becomes castrate-resistant, you know, we have already tried ADT. We think that the androgen receptor probably has something to do with driving these cancers, even though this testosterone is basically castrate… So there's a lot of different pathways that are involved, these days.

And another thing I know I'm hearing in the Silicon Valley. I got a lot of engineer patients, and you know, they'll look up these papers with median survival. You know, median survival just means, I'll explain to them that, you know, 50% of the men at 21.3 months with bone mets, are still surviving. It doesn't mean that if you multiply that times 2, that doesn't mean we double that and try to figure out, you know are they all going to be gone at 42 months. And so, it could be longer, could be shorter. I'll kind of point those out on some survival curves later today.

But first, kind of key terms in prostate cancer, if you don't work with it every day, definitely biochemical recurrence. You know, the measure of success after surgery or radiation for localized treatment is measuring the PSA. We want it to be steady – either

undetectable after surgery or we want it to be lower and not go up after radiation, but if it starts to rise, we need to do something else. That's what biochemical recurrence is. HSPC is hormone sensitive prostate cancer, so cancer that's still responsive to ADT and those type of medications. CRPC is castrate-resistant prostate cancer. You know, we're going to focus on that quite a bit, so cancer that has become too smart, and you know, it's kind of growing beyond the hormonal treatments. High volume metastatic prostate cancer, UCB a criteria there. High risk prostate cancer, you know, high risk features are a Gleason score of 8 or higher, or more bone mets. You know, we can really – we can actually have answers that are either/or, or both. You know, high volume and high risk. Once in a while will find de novo out of the blue metastatic cancer upon these patients.

So, this is what normally happens in prostate cancer in the blue box. You know, best case scenario, we catch these cancers very early. It's localized. You have a definitive therapy, either with surgery, medication, and hopefully we stay there. If the PSA starts to rise, you know, that's biochemical recurrence. Then we're kind of back in there, looking at what needs to be done. If the scans show no, kind of, frank metastasis, then we're going to go up to the gray box there. You know, metastatic, hormone sensitive prostate cancer, so we're going to give that some hormones, and hopefully we'll keep giving that until it doesn't work anymore.

If the PSA is rising, and let's say we start some hormone therapy and we go – we still don't see anything on the imaging but the prostate cancer seems to be resistant to the hormone therapy, that's still non-metastatic, castrate-resistant prostate cancer, there in the green. Now, once these cancers progress one step further, you know, rising PSAs despite, you know, ADT, if we have metastasis, that's where we're in this category that we're talking about today – metastatic castrate-resistant prostate cancer.

Today, we're talking about PARP. So why talk about PARP? You know, PARP is enzyme, basically, that helps DNA repair. The reason we want to use something like a PARP inhibitor is that we want to encourage these cancer cells to die. And so, what you see here, on the screen in the left corner, there are just these risk factors related to how is DNA damage caused? This isn't just environmental. Could be UV, could be radiation. Is it just normal physiology? You know, in the process of cell division, there is a mistake that can happen. You know, chemotherapy and radiotherapy can cause these types of mistake in the cells, and so, for example, with single strand breaks, let's say a cell has one of those – the cell will, you know, recruit PARP as a protein to help repair that. If there's double strand breaks, you know, BRCA1 and 2 are the genes that make those proteins that help repair those types of breaks by homologous recombination. And the PARP is also the and, you know, fixing replication lesions or these other types of DNA damage.

And so, really, in our own cells, we all have PARP every day, but the normal cells, we want these PARP proteins, we want these BRCA proteins to work as it's going to keep the cells intact. What we're doing with PARP inhibitors, we're giving – we're stopping the mechanics in the prostate cancer cells, so hopefully that will lead to a lot more cell death, when it comes to prostate cancer cells.

So now genetic testing, you know, genetic testing, why are we talking about this? You know, perhaps we're going to reveal a genetic or genomic finding that'll allow us to, you know, use PARP inhibitors. One of the criteria behind it, so again, when I was seeing prostate cancer patients in the early 2000s, we didn't really talk much about genetics, but today, you know, a lot of prostate cancer patients were curious about their germline or the genetics that has a BRCA1, 2, or all these other genes. We're curious about, you know, if we have some tissue from a metastatic prostate cancer, can we do a genetic analysis of that, to kind of find out what's going on? So really, you know, in genetics, BRCA1 and 2, and other, kind of, these at the germline mutations are associated with increased risk for prostate cancer. About 11.8% of men, there in the yellow – in the orange box, will have – possibly have a germline mutation. So now, today's criteria for BRCA testing for prostate cancer have met that, so we're testing quite a few people, if not all of the metastatic and advanced prostate cancer cases.

Somatic mutations are mutations not so much in the germline, but in the tissue. We find it in the tissue. Maybe it's been there at birth. Maybe it's something that developed over time, but when it comes to metastatic prostate cancer, you know, almost 20% are going to have some type of clinically actionable mutation, so really the bottom line is, you know, definitely, and then with metastatic prostate cancer or advanced cancer, should be doing genetic testing, either of the germline with a blood or saliva sample, or – and/or the tissue because we want to, you know, we could uncover other, you know, treatment possibilities for them. You know, throwing in there as a side, even and some of the localized cancers, if it's intermediate or high risk, or if they have family history of breast, ovarian or pancreatic cancer, it kind of fits within the criteria of germline testing for BRCA1 and 2 in prostate cancer.

One of the most common genes we find that is mutated in prostate cancer is the BRCA2. If you were to look at – even though there's plenty of these other genes that are related to metastatic prostate cancer, BRCA2 is one of the most – is one of the most frequently mutations – you know, 5.3 in metastatic prostate cancers. You know, when that is there, we think the cancers are going to be a little bit more aggressive. You know, they're going to be genomically unstable. The DNA is kind of a little bit more fragile, a little bit more unorganized, so the cells are a little bit more worrisome. Increased frequency of single nucleotide polymorphism, so that's something that's related to the genomics of cancer, only to respect the aggressiveness.

If a man has a germline, basically inherited cancer mutation, you know, there – it's associated with a higher risk for prostate cancer. We

usually see either young cancers in people who have a germline test. We may not see it. We may see it with family history, so definitely germline mutations are going to be associated with some risk for prostate cancer patients, but germline mutations, you know, we have a chance of sharing that with our kids, with our brothers and sisters, so if I were to pass that mutation on to my daughter, you know, we're not going to watch her for prostate cancer, of course, but it is related to a risk for breast and ovarian cancer. So BRCA2 is really another thing that pops up a lot in metastatic cancer.

I think we'll do a little case study here, Taren, on the next…

Dr. Sims:
This was Michael, a 63-year-old, diagnosed with metastatic, castrate-resistant prostate cancer, who presents with radiographic, symptomatic progression, on enzalutamide. His prior therapy included docetaxel until progression, and enzalutamide following the docetaxel. In his mutation analysis, we see somatic BRCA2 mutation.

Mr. dela Rama:
Okay. So PARP inhibitors, olaparib and rucaparib are kind of the main, you know, the ones we use day-to-day, that have been incorporated into the NCCN guidelines in metastatic, castrate-resistant prostate cancer. They are both PARP inhibitors. You'll notice here the difference between the two is olaparib, we give it for patients with a deleterious or suspected germline or somatic HRR gene, mutated. So what that means is, HRR genes – homologous recombination repair genes – include BRCA1 and 2, but they include other genes, such as ATM and a handful of other genes, so olaparib is a little bit more broader, in, where we can apply that based upon genetics. There is a genetic test that we would do prior, or let's say we find a HRR mutation on a somatic test, then we'll – we may look into giving olaparib.

Rucaparib is more specific to the BRCA 1 and 2 only. So, it's only shown to improve survival in a BRCA1 and 2 specific. It is the same mechanism, but it's mainly given for those men who have a germline or somatic mutation in BRCA. And just kind of a trick to remember which is which, I mean, if you do google and look at what B – brand name of rucaparib is, it literally just spells out R-U-BRACA. So, put a question mark at the end, so that's a good way to remember that. So, rucaparib – BRCA only, olaparib, you know, we can use other HRR genes that we find.

So we're going to kind of step into some clinical trials here. The phase 3 PROFOUND study – the question here was, does olaparib improve outcomes? Does it improve radiographic progression-free survival? So, really, as compared to physician's choice – you know, back then. So this was that study, kind of, is olaparib going to? So these are men with metastatic, castrate-resistant prostate cancer with disease progression, and they've had abiraterone or enzalutamide. And then, they were tested and they have some type of HRR gene. There is 2 cohorts here. So, Cohort A is just BRCA1, BRCA2 or ATM. Cohort B is other HRR mutations, and they were both – they were all randomized to olaparib or just physician's choice. And whenever you see these survival curves kind of split up, in favor of the intervention arm, you know, there is a little bit of benefit there. Specifically in the Cohort A, or the BRCA 1 and 2, the – that reduced the risk of death by 31%, that reduced the risk of imaging-based progression, or death, by 66%. So, we don't see a lot of mets on imaging, at that point. So, none of the overall benefit in Cohort B, but it still is something, olaparib we could use, and those men that have HRR type of mutation.

The next trial is the TRITON3. So it's kind of the same question. You know, is rucaparib going to improve survival – image-based survival, so RPFS. Again, this study is with metastatic, castrate-resistant prostate cancer who have had disease progression. They've had an AR inhibitor, and they do have a mutation in BRCA1 or BRCA2 or ATM.

So they were randomized to either get rucaparib, or to get the physician's choice of docetaxel, abiraterone and enzalutamide. And again, we see the separation of the curves. You know, there seems to be a significantly reduced risk of progression and death, in the whole intent-to-treat population – a reduction by 39%. If you just look at the BRCA group, you know, even more favorable – looks like a 50% reduction in progression or death there.

That curve is – this is one of those things where it's kind of interesting to look at a curve, so rucaparib, the median survival is 10.2 months, and so you look at the graph at 10 months, and then you look at the graph at 20 months. There's still quite a few people living – 30, 39, 42, 45 – so there's still people, you know, living well beyond double. That'll last, and so that's something that hopefully can be encouraging to patients that you see – your engineer patients.

So how do we give it – I mean, basically it's oral. Dosing is a little bit different between olaparib and rucaparib, as you can see on the slide. If we need to reduce the dose for some reason, there's some guidelines there for those of you who prescribe that day to day. The difference is again, with what to look out for. With olaparib, if there is a moderate renal impairment, perhaps we'll dose-reduce there a little bit, based upon their labs. We want to make sure they're not on prone to moderate cyp inhibitors, because that's going to mess around with the level of the drug in the system. You know, so work with your pharmacist or your NP to kind of, you know, make sure

there's no drug-drug interactions. But those are kind of the differences between the two, and you can try to select those for your patients, or if you're not selecting, if your patients kind of know what to look out for.

So what are the common adverse events? Again, they're pretty similar across, so I'll just kind of point out the differences. I mean, they're both related to fatigue, GI, and anemias, thrombocytopenia, blood cells – I mean, the other term you're going to see come up is cytopenia. Kind of captures all that. We're worried about low blood counts in general, when it comes to these types of medications. When – with olaparib, there's a little bit more assessment that we worry about. A little bit of cough and a little bit of dyspnea, so do some good lung assessments for sure. On this side, there is some rare side effects with olaparib. You know, thrombotic events – so those are the things we'll monitor for. When it comes to rucaparib, the things that stand out here are the, you know, watching the liver enzymes, and possible rash. And so, there's overall the main AEs, kind of grouped are fatigue, GI and cytopenias. But there's some subtle differences between the two that we'll keep an eye on, depending upon what your patient is taking.

So kind of an overview of all these AE - adverse events with PARP inhibitors. You know, what do we suggest for management with fatigue? Of course we know we tell our patients, just like home. Definitely exercise is going to be a good thing to help combat the fatigue. There's other things that we would suggest – massage, cognitive behavioral therapy, you know, looking at the blood counts as well. Maybe it's related to anemia. There are GI toxicity AEs, and so we're going to work with getting some prophylactic antiemetics in there. If they need some loperamide for diarrhea, that's something that we can kind of keep an eye out. And definitely, watching the blood counts – you know, cytopenia is kind of what that is – anemia, thrombocytopenia, neutropenia. And so, we want to look at the blood counts for sure. The other things on the radar are definitely creatinine - you know, renal function, liver enzymes and rareties on the list there. So really, take home is that with these PARP inhibitors, the top 3 – fatigue, GI and cytopenias are going to be what we're going to be looking out for.

If we want to dig into GI toxicity a little bit more, being and the quality of life is why we're doing all this. And so, if we can help them avoid any kind of impact on their quality of life, even, nausea and vomiting, we want to address that. We want to make sure they take their antiemetics, you know, half an hour to an hour prior. Taking each PARP inhibitor dose, it may happen twice daily. Avoid aprepitant. You know, aprepitant is one of those interactions-related to CYP3A4, and so that's something we want to avoid, when it comes to PARP inhibitors. Taking it after meals, you know, food diarrhea, all good things to remember, you know, for sure if they vomit after taking that PARP inhibitor, do not take an additional dose, so we're just kind of watching them, pretty closely, and, I'm going into a little case study here, Taren. I'll throw it back to you.

Dr. Sims:
So, here's Michael, our case continues. He started olaparib 300, p.o, twice daily, four weeks ago. He now reports fatigue, dizziness with standing, shortness of breath and a headache. He's diagnosed with grade 3 anemia.

Mr. dela Rama:
Perfect. Yeah. It looks like most GRE, no? Coming in here again, the toxicity targets here, like I said earlier, the top 3 - you know, the top of the list here is anemia, so part of that cytopenia group. We're definitely looking at that in our patients who are on PARP inhibitors. Nausea, as you can see, is second. Fatigue or ischemia, either being tired or not want – feeling weak, is kind of the top 3, when it comes there.

So when it comes to the anemia that we're talking about in the case study, as you recall, his hemoglobin went from 9.4 down to 6.8, so he does have a less than 8.0, and a grade 3 anemia, is kind of what he's dealing with there.

And the guideline there, for anemia management, is we'll definitely hold the PARP inhibitor, as 60% of you guys already knew, for grade 3. We may consider it for grade 2, but we will, kind of, plan to transfuse and pack red blood cells. We will wait for that hemoglobin to get – improve. To let the symptoms resolve, and then we'll restart it at a reduced dose. And here – below here are some guidelines on what the next – you know, the reduced dose is going to be. And so, and keeping an eye on the blood counts, is going to be key.

So let's go over – some other things to consider. Definitely, when our patients are on PARP, you know, a lot of times, even though with my patients on ADP, how long am I going to be on this? You know. Basically, we're going to keep giving it until it – the disease progresses, it becomes too smart, goes beyond that type of treatment, or if the toxicity is unacceptable as well. Most of the time, our patients who are getting PARP inhibitors for metastatic, castrate-resistant prostate cancer are receiving, at the same time, a GnRH inhibitor or have gone on some depth of hormone deprivation intervention.

Even though we talked about anemia, transfusions for thrombocytopenia are pretty rare, but if your – if their patient's platelets are below, uh, 10,000, you know, maybe that's something they will reconsider. Now, outside of the top 3, you know, fatigue, GI and anemias and cytopenias, other things to look out for – I mean, if we're all doing a good nursing assessment, or we're – a full, kind of, clinical assessment, we're always going to do the head-to-toe, but headache, insomnia, dizziness, cough, especially on olaparib. You know,

skin reactions, more with the rucaparib, and so we're basically going to keep a close eye on these patients. We're probably already watching them pretty closely, but it's important to kind of watch them. When it comes to the skin reactions, you know, we're going to counsel them, you know, we want to give the power to our patients, to take care of themselves and give them all the tools they need. So definitely tell them to use sunscreen, you know, stay out of the sun as much as they can, use moisturizers because it can make the skin dry sometimes. If we have some rashes, which can come up with the rucaparib, you know, hydrocortisone, the topical, is going to be a good thing to have, right? They have hand-foot syndrome, maybe that's going to be helpful as well.

So really, I think the best thing to do with our patients is because we've been through this, you know, possibly hundreds of times, or we know our colleagues or our doctors are going to help these patients through. I think that patients and caregivers benefit most from kind of knowing, a heads up. As a navigator, in my day-to-day practice, I want to give them a heads up, you know, what to look out for, if I need to teach that again and again and again. So these are the things, you know, what – especially the PARP inhibitors, we kind of help them, you know, manage expectations.

You know, we want them to be on the lookout for these side effects. We don't want them to be too scared of it, but at least they know if there's any changes in their level of energy, if there's any changes in how they feel, you know, my stomach feels kind of weird after, you know, let us know. And so, at least they have the power to go – all these patients are basically outpatient, right, so it's not like they're here, ready for us to assess in front of us all the time.

You know, when to contact us. You know, definitely provide – if you're not the navigator, if you're not the one prescribing the medication, and you happen to see this patient in another part of the clinic, at least you know who to contact if you think it might be related to their PARP inhibitors. Now there are plenty of things that we can do, as in the previous slide. You know, we can try to prevent or reduce the side effects of fatigue and nausea, with some of these premedications or other interventions. At home, taking pills – again, we're trying to promote adherence, and educating them to kind of, you know, handle these medications versus when we're giving chemo, we know exactly when to give it and how much. We want to teach our patients that – have that power within themselves to do that.

And clinical trials are always something that – and we're going to go over some a little bit later, so believe it or not, maybe your patient will be eligible for a clinical trial, so they'll have access to some of these newer medications out here on the horizon. So it's definitely something to keep an eye on for our patients.

You know, in day-to-day practice, some patients are good about sharing their symptoms, sharing what they – their concerns, or give some type of electronic messaging portal – you know, that – those are great ways to kind of get information. Some patients are less likely to tell everything. They don't want to disappoint our doctor, or the nurse. You know, they want to tell them to encourage them to share their – share how they're feeling. Definitely symptom questionnaires can be helpful in the case. I know at our clinic, we have some questionnaires specific to some of these things, so we can kind of administer that, either in person or have a nurse go over it with them in the clinic, or you can maybe electronically. It's a team effort, so metastatic prostate cancer definitely – you may identify, you know, in your assessment of their physical being. You know, they may need help with emotional or mental health, and so definitely your – your social worker, your – definitely palliative care is a wonderful resource, that hopefully these metastatic prostate cancer patients already are connected with. And there's plenty of support groups, either in person or virtual, that I think are helpful because it's kind of nice to be, you know, someone else – to hear from someone else who's going through the same thing, and so that – the first person perspective is always going to be helpful. You know, again, any type of clergy or religious – that kind of support – so just treating the whole patient, you know, spiritual, emotional.

When it comes to these treatments affecting hormone levels, you know, sexual dysfunction is something that, uh, in my world, they're a little bit more open to kind of sharing that information. You know, definitely, ADT and some of these effects on the hormones, you know, are going to affect sexual function or libido. You know, it's important to point out that the loss of libido and erectile dysfunction are – are common, unfortunately, with these – with this cancer journey with these medications, but they're – one doesn't fix the other. So, you know, you can give an ED drug to affect – to fix – or fix the loss of libido. So, if you do have people who need specific help related to this, you know, urology can be a start. If you have a specialist in sexual health, that could be useful at your facility.

And you know, when it comes to the patient experience and they're beginning to feel weak, they feel like they've – or they feel like they've lost some muscle tone. There are some body changes. Again, we don't want them just to lay around. We want – exercise is the best intervention when it comes to combating fatigue. If you have physical therapy sources nearby, that's going to be very helpful, for especially some of your older patients. I know locally here, we have a Live Strong, Live Well. So cancer patients have access to the YMCA, and – and a specific exercise program. But again, giving the power to the patient – managing their nutrition, managing their exercise. They're going to feel less helpless in the middle of all this, so they feel as if they're contributing to fighting this cancer, for sure.

As with – especially in metastatic prostate cancer, we hope to prevent the bone-related events, so you may be having this patient on denosumab or zoledronic acid. You know, if there's some bone metastasis, you know, hopefully they'll be compliant with these

medications and the team. But yeah, again, it's about communication, so we want to have open lines of communications between the patient, the caregiver and the advanced practice provider, and you know, you're working closely with the oncology team – all of you who are involved. I don't care what type of cancer you're working in, it's a team effort, so including the nurse and patient navigators as well. So if we can have these frank discussions about what to expect, hopefully you won't get all these side effects, but at least they kind of know what to keep an eye on, just in case.

Well, the next – on the horizon, PARP inhibitors are now something we're beginning to use in metastatic cancer, and you know, maybe it's coming up to where it's first line, second line, and so what you're going to see on these next few slides are some of the clinical trials related to what kind of combinations of therapies can they give. Is that going to help? The first one here, PROpel, is a trial, phase 3, so we're looking at first line. What happens if we add olaparib to abiraterone and prednisone? So, the question here is, you know, these are first line metastatic patients. They haven't had any prior treatment for metastatic cancer. They could have, you know, docetaxel. Maybe they have AP – they have had ADT.

They should not have had a prior abiraterone, be in relatively good shape. There was no screening for the HRR mutations required, but then in this study, they did kind of collect data and we kind of split that. They were randomized to 2 groups. You know, just placebo with abiraterone, or olaparib with abiraterone. And then, you know, we really want to see how it's going to be affecting radiographic progression-free survival.

So again, when the curves split up, you know, we're seeing some benefit of adding olaparib here. The median overall survivor is improved. As you can see, the blue line is creeping up, and then when we drill down to those cancers that have a mutation in one of those HRR genes, we see some aim or benefit there. So, as a results of this study, perhaps first-line olaparib with abiraterone is going to be helpful in these patients, in prolonging their radiographic progression-free survival.

So the next trial here – same question. Now we're looking at niraparib. So it's another PARP inhibitor that's on the – on the radar. Again, it's pretty similar. You know, these are patients who have metastatic, castrate-resistant prostate cancer. They haven't had any prior treatment for – no prior systemic treatment for this type of cancer. No prior PARP inhibitor. If they've had a abiraterone prior to the enrollment in the study for 4 months, which basically gave the opportunity for those men to kind of get their biomarker testing, because the groups that we split them up into, or that the study did, is those with HRR mutations or top gray square, versus those without. And then, those cohorts were further randomized to receive niraparib plus abiraterone or placebo plus abiraterone. Again, the endpoint here is, we want to see, is it going to affect their radiographic progression-free survival? We'll go to the survival curve here. So again, the curves start to separate, so there appears to be some benefit. The left-hand side is, you know, all HRR mutations. That's at the cohort, so there's a little bit of an improvement. Median survival goes from 13 up to 16.5 months. When it comes radiographic events, there is a little bit more benefit there, when we just look at the BRCA1 and 2 patients. And so, what's going on now is that's currently under review. Maybe that's going to be something that's going to be helpful, specifically for BRCA1 and 2 patients, personally.

So yet another IB, and so this research question here is: you know, the first one was olaparib; niraparib; now talazoparib is this other one here. So the question here is again, what if we add talazoparib to enzalutamide? You know, again, these are patients with no prior treatment, so this is first-line therapy for metastatic, castrate-resistant in this case, or non-metastatic castrate-resistant prostate cancer. And then they were assessed for their HRR gene status. They were randomized again to receiving talazoparib plus enzalutamide, or placebo plus enzalutamide.

And we're looking at radio – as a primary endpoint – radiographic progression-free survival. And you can see here, again, the separation of the curves, which seem to show some benefit to – in the left-hand graph, the green is the enzalutamide plus talazoparib, and you'll see the median progression-free survival radiographically is improved. On the right is those that didn't have any HRR mutations. So, the take-home message here, in the clinical trial world, is the first-line enzalutamide plus talazoparib improved radiographic progression-free survival regardless of HRR status. So, with the other, hopefully the FDA will approve that. It'll, you know, capture a little bit more patients, given again, talazoparib plus enzalutamide might be able to be used regardless of HRR.

And yet another, kind of, looking at another combination, instead of previous slide, talazoparib, we're just looking here now at rucaparib. So, what's going to happen if we can give enzalutamide plus rucaparib first-line, for patients that have no prior treatment for metastatic, castrate-resistant prostate cancer. Again, they are going to be randomized to either having rucaparib or not, in addition to enzalutamide, and looking at radiographic progression-free survival again. So really, that's a trial that's ongoing. As you can see, these combinations seem to be on the horizon. Niraparib and rucaparib, meaning more related to just BRCA. Olaparib and talazoparib, you know, regardless of HRR, might be something to use within early clinical practice. Like in our case studies, it's olaparib and rucaparib. So a lot of if's, but a lot of – a lot more combinations so these are really more options that are going to be more and more available to our patients in the tool box, for dealing with metastatic, castrate-resistant prostate cancers.

So, what do we want to do now? Definitely learning all this today, you know, what do we do for our patients who we happen to encounter

with metastatic, castrate-resistant prostate cancer? You now know, germline and somatic mutation, or blood, saliva and tissue testing for these mutations is going to be important for all patients with metastatic prostate cancer, so basically, that's the question – did you get genetic counseling and germline testing, or did they test your tissue?

Which PARP inhibitors have FDA-approved indications, like, olaparib and rucaparib, and the differences between their indications? And the top 3 adverse events we're looking out for in the – as a nurse or as a provider – fatigue, GI, cytopenias are kind of what we're looking at here. And then, you know, we can't – we may need to implement the dose modification, so that's kind of our action plan, as a clinician.

Dr. Sims:
Could you clarify or define the younger prostate cancer diagnosis? What ages are we talking about in younger diagnosis?

Mr. dela Rama:
Right.

Dr. Sims:
… and the survival rate decrease that you talked about?

Mr. dela Rama:
Yeah, yeah. So definitely, younger - you know, I would say the median age of prostate cancer is probably somewhere around 65. There's not a look, a concrete NCCN guideline. We know early breast cancer is 50, but I would say anything under 65 is probably, you know, what we would call younger. You know, younger than average is kind of what that is. But if we do get the opportunity, again the quest – the slide there, I think, was originally a PC – a younger prostate cancer patient. You know, maybe ask those questions about family history. You know, perhaps he can pursue some type of somatic testing and so if we do gather the germline or the somatic information, you know, if we do identify it, we're more likely to identify BRCA2 or other, kind of, HRR mutations in the younger types of prostate cancer. That's probably where that, kind of, comes up there. But I would say younger is, you know, less than 65.

Dr. Sims:
Can we do somatic testing on the initial biopsy prostate tissue, if it was done years ago?

Mr. dela Rama:
Yes, and that's kind of a dilemma. You know, definitely it depends upon the lab you're working with, how, you know, I've seen some somatic tissue done, a year or two afterwards. If it's been quite a while, the question is maybe if we have a metastatic site to get a biopsy, or there's some, you know, circulating tumor cell-type of testing, where we can get somatic information from a blood test. And so, of course, the first option would be try to pursue, you know, the tissue from the biopsy. You know, that cancer could have changed between the biopsy and whatever you're dealing with now, so if the patient doesn't need another biopsy of the metastatic region, maybe consider the, you know, the circulating tumor cell blood test, a way of getting that somatic same type of testing done.

Dr. Sims:
She's saved many patients who have been treated with prostate cancer. Post proctectomy or treated with either radiation or chemotherapy. Do you know why one would do better than the other, or we should just choose – how do you choose one over the other?

Mr. dela Rama:
Yeah, I think, most of us see these patients, you know, localized so intermediate risk, or low risk. You know, they're often at surgery or radiation. High risk, you know, we're high in the – higher intermediate risk. We're giving hormones plus radiation, sometimes adding docetaxel. You know, we – I think, Tarren, we're probably on the same page, you know, we usually do chemo for the higher risk patients. There's probably not – I mean, we're really trying to treat the cancers and seeing what the outcome is, so there are some somatic testing that kind of gives us an eye how effective certain chemotherapies would be, but I think, you know, leading up to the higher risk, localized – we're using chemotherapy, I'm not sure if one works better than the other. When we get into the very risk – very high risk category, a lot of times we're using radiation plus hormones plus chemotherapy. So I think, based upon risk stratification, we're going to throw everything at it that we can, keeping in mind that the – that the patient can tolerate it, so we don't want to - you know, the goal there is not to overtreat to where the side effects are irreparable, and so I'm not sure if one is better than the other, but chemo is only appropriate for certain patients in the spectrum.

Dr. Sims:
Thanks. And I also – I'll just add to that, that sometimes the patient has recurrence, and they're castrate-resistant. They have a solitary bone met, for example. Radiation for the treatment of pain at that bone that might be effective, but ultimately, either chemo in the high risk group or appropriate further adjuvant treatment is really where you're going. Radiation is not appropriate for all – for multiple metastatic sites, but perhaps for metastatic sites, post-treatment we might see that.

Do you use the PSMA scan to look for metastatic disease in your patient population?

Mr. dela Rama:
Yeah, it's a newer technology, that is more readily available now. We do use PSMA. PSMA is a prostate-specific membrane antigen, so when we do a PSMA scan, opposed to a standard CT/PET, the images are a lot clearer, the areas that light up are specific to the prostate, with a PSMA antigen are on the – on the prostate cancer cells, so we do use that, you know, for the higher risk patients, to evaluate if there is mets there. And then, we do use it for those metastatic patients who we want to evaluate how it changes over time. The main barrier is sometimes insurance, now, unfortunately. It's relatively expensive but some plans are covering it, but a lot of times we will do our best to get things covered, because it's a great tool. You know, when you see those images, they're a lot more precise and, you know, kind of speaking to, like, the next generation of – if we can know where the – if we can target the PSMA membrane antigen on a diagnostic, the next question is going to be, can we have some targeted therapies?

So there is some things around the bend, where they can, you know, attach a medication and infuse it then, so PSMA kind of helps the medication go directly to the tumor. So I would say today, we're hope – we do strive to use PSMA as best we can, but, you know, cost is sometimes an issue. I don't know if that – if that comes up in your clinic as well, Tarren?

Dr. Sims:
And what do you think to be the biggest barrier to patients getting genetic testing? In your experience?

Mr. dela Rama:
You know, sometimes it's just not knowing. You know, even providers who deal with it, or even, you know, the way we have it set up here in my facility is we've trained, even primary care to kind of keep an eye out for, you know, if they have family history, or personal history of breast, prostate, when they were cancerous. So, it's key to have a genetics professional in, who's accessible. It used to be a lot of doctors and providers would order this independently, and that's another workload. And so, awareness with providers, to let them know who is your local genetics professional. I'm a navigator, so I refer to myself first, but if you're a nurse navigator and know who your genetic counselor is. If you're a patient or if you're, you know, counseling a patient, inform them to ask those questions, because some doctors may be less likely to bring it up versus not, because they are covering so many other things. So I think it's – knowledge is probably the barrier, but the reality is, most of the time it's available and covered by insurance, and it's information that going to be helpful for the patient, and his treatment, and potentially, you know, future generations for prevention of other cancers as well.

Dr. Sims:
Okay. Thank you. Well, I want to thank you, Frank, for great presentation today. I've learned a lot about PARP inhibitors, and I know the audience joins me in thanking you for this great talk today.

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