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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Keeping Pace in GU Cancers: Clinical Considerations for Prostate Cancer – Global Perspectives

Announcer:
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Dr. de Bono:
Prostate cancer is the second most common cancer in incidence, and the fifth most frequent cause of cancer-related mortality in men worldwide. With the broader availability of PSA [prostate specific antigen] screening, the incidence of this disease has been increasing. Let's talk about the global perspectives and clinical considerations related to targeted therapy for metastatic castration-resistant prostate cancer, or mCRPC.

This is CME on ReachMD, and I'm Dr. Johann de Bono, Professor at The Institute of Cancer Research and Royal Marsden Hospital, in London, United Kingdom.

Dr. Morgans:
And I'm Dr. Alicia Morgans, GU medical oncologist and Medical Director of the Survivorship Program at Dana-Farber Cancer Institute in Boston in the US.

Dr. de Bono:
Thank you, Dr. Morgans. Can you talk about some of the advantages and limitations of our traditional prognostic measures related specifically to tumor biopsies and biomarkers in prostate cancer, and how do you see our GU medical community moving forward towards more predictive biomarkers for systemic therapy?

Dr. Morgans:
I think, of all people, you are quite the expert in this area, Dr. de Bono, and I think we as a community have seen a lot of advances in our understanding of biomarkers, and particularly in biomarkers that we may be able to target. I think about the DNA repair defect mutation, specifically when I mention that, things like BRCA1, BRCA2, and ATM, and some of the others. I would say that still despite having those biomarkers, we continue to have some barriers. The first barrier, for things like these DNA repair defect alterations, as well as others, is that we need to understand when to incorporate biomarker assessments into our clinical treatment algorithms, and we need to figure out which tests to use to do that. And then we need to make all of that happen in a way that's meaningful to patients as we actually hopefully use the data for treatment decisions related to them or for decisions related to their families as we're talking about DNA repair defect mutations in the germline. So I think we have faced some challenges. We have some advances.

And one of the things that I think that has been most meaningful to patients has been that guidelines, in the United States at least, have suggested that all men with metastatic prostate cancer should undergo germline genetic testing, so that we can identify biomarkers like these DNA repair defect alterations in their germline, to inform both them, for their future treatment, as well as for their family members. When it comes to somatic testing, there are definitely questions about whether we should be doing that testing in tumor tissue, from a

metastatic site, if we should be using circulating tumor DNA or cell-free DNA, and all of these approaches have their pros and their cons. And really, again, where I'm only really referencing these DNA repair defect mutations, there are other biomarkers that we can use, including thinking about things like MSI-high status, and tumor mutational burden. These kinds of alterations may give patients access to things like pembrolizumab. That's a very small proportion of patients with metastatic prostate cancer, but those tests, specifically thinking about MSI-high status, need to be done on somatic tissue testing, and when does that happen, how does that happen, and how does that happen in a way that's reliable and something that we can test the same patient over time, if we need to, and find that these answers are consistent, that the mutational burden is consistent or not consistent if the tumor is actually changing.

I would love to hear your thoughts on biomarkers because, as I said, you've really played a substantial role in this particular part of the field, among many others. But I know you have feelings and thoughts about testing tumor tissue versus testing metastatic sites versus testing liquid biomarkers. What are your thoughts?

Dr. de Bono:
Thank you, Dr. Morgans. I think what we have is increasing complexity, and maybe we have to simplify that. But first of all, I think I would argue that, if possible, we should try and get this genomic biomarker disease stratification as early as possible in a man with advanced disease. Ideally, we want to do a biopsy. I think there is increasing evidence that the tumor can change over time, and evolve – particularly true, next-generation hormonal agents – to develop resistance mechanisms that can also impart new, emerging DNA repair defects and genomic instability.

Detecting mutation is fairly easy, but detecting deletion can be particularly challenging, and in fact, the patients that benefit most from PARP inhibitors have homozygous deletions of genes like BRCA2. And I do think we are probably best able to get that data from tissue with the available assays today, although I am confident that in the not-too-distant future, using, for example, low-pass whole-genome sequencing, that we can get accurate copy number data from plasma DNA.

I do think that the mismatch repair population – probably about 3%-5% of all advanced prostate cancers – do need careful consideration. These are best detected by looking at a number of things: mutations in a mismatch repair genes, MSH2, MSH6, PMS2, MLH1, and other genes involved in mismatch repair, the POLE gene particularly, but also looking for tumor mutation burden. These tumors often have a very high tumor mutation burden, say, more than 15 or 20 mutations.

So shall we move on to the case discussion?

Dr. Morgans:
I appreciate you expanding on that.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Alicia Morgans, and here with me today is Dr. Johann de Bono. We're just about to discuss prostate cancer with an emphasis on metastatic castration-resistant disease.

So since we just talked about the pertinent prognostic and predictive mCRPC biomarkers, let's walk through a relevant patient case, as you suggest. We'll consider the appropriate sequencing of available therapeutic treatment options, with a special focus on targeted therapies in this setting. Dr. de Bono, what do you have for us?

Dr. de Bono:
So I'd like to discuss a mCRPC patient. A 67-year-old man with metastatic CRPC, his name is Robert, with symptomatic bone metastasis, and he's being followed up following ADT and enzalutamide for 18 months, and his molecular profiling of his initial tumor biopsy revealed a PALB2 mutation. So can you maybe tell us a bit more about how you would approach this patient, Dr. Morgans, please?

Dr. Morgans:
I'm happy to. I think always when we see patients with metastatic CRPC, we need to remember what the patient has had in the past, and that helps to really define how that patient can move forward in the future.

For this particular patient, we understand that the patient has had AR-targeted therapy with ADT and enzalutamide, and so we do have multiple options available for this patient, which include things like chemotherapy, as well as potentially things like radium, because this patient appears to have bone metastases, and they are symptomatic. But I think, because this patient underwent genetic testing, so we know that this patient has somatic testing demonstrating a PALB2 mutation, this really gives us another opportunity to potentially use a targeted therapy here, a PARP inhibitor. Now, because this patient has only had treatment with an ADT plus an AR-targeted agent, the options for PARP inhibitor treatments, in the US at least, would really come down to olaparib. And the other reason that that is the treatment that would be a potential option if we're thinking about a PARP inhibitor is that this patient has a PALB2 mutation, which is outside of the FDA approval for the other treatment that's available in the US. That's a PARP inhibitor, rucaparib, which is really only

approved at this point for BRCA1 and BRCA2. So if we wanted to pursue an oral agent that was a targeted approach for this patient, and I think that's a completely reasonable option, then olaparib would be an option for Robert, as he is seeking a treatment for his mCRPC.

What are the things that you think about given that you practice in the UK, and so perhaps indications are different? What would you think about for this patient?

Dr. de Bono:
Well, the first thing I would think about would be that this gentleman may have a significant risk of this being a germline mutation. In our experience that we published recently in *Cancer Discovery* by Carrera et al, the preponderance of the majority of patients with a PALB2 mutation had a germline alteration. So I would ask the gentleman to give me a family history, and that might require cascade testing and pursuit of trying to assist cancer prevention in the rest of his family – siblings and maybe children.

I hope that's helpful, Dr. Morgans.

Dr. Morgans:
I think that was a great comment, and I would really just emphasize to clinicians as they're thinking about using PARP inhibitors in their practice, just to think about the labels in addition to thinking about the nuances of the tests. We just need to remember that olaparib is available for patients in the US who have had progression on an AR-targeted agent plus their ADT. They don't need to have had prior exposure to chemotherapy, but rucaparib, one does need to have that prior exposure to chemotherapy. And rucaparib's only available for BRCA1, BRCA2, whereas olaparib is available for that whole string of mutations that we've talked about in the PROfound trial.

Dr. de Bono:
Thank you, Dr. Morgans. Let's move on now from that to maybe updates of ASCO and ESMO 2021. I am so pleased and proud to say that our GU oncology field for prostate cancer has really been moving so rapidly, so Dr. Morgans, these 2 conferences this year are behind us. We've had some pretty impressive data. What new data that new treatment options have really impressed you most from ASCO and ESMO '21, please?

Dr. Morgans:
I think that the big splash at ASCO 2021 was really the VISION trial, which was lutetium-PSMA-617, which is a radiopharmaceutical targeted at the PSMA protein on the surface of prostate cancer cells. And this trial focused in patients with metastatic CRPC who had already had exposure to an AR-targeted agent, as well as a taxane, and had progression. And really tried to identify patients who had had the extent of treatment that could have been helpful, including things like the second generation of taxane. In any event the lutetium plus standard of care versus the standard of care alone, which in many cases was either the alternate AR-targeted agent or a steroid or even pain medications, depending on how heavily pretreated the patient had been, demonstrated just about a 4-month advantage in overall survival to treat men with lutetium and best standard of care versus best standard of care alone. We did get subsequent information at ESMO that patients had a better quality of life on the lutetium treatment arm and fewer skeletal-related events. So I think in general, that difference was only 4 months, when we look at the median improvement in overall survival, may provide another option for our patients, and particularly, since we are looking at such an advanced and heavily pretreated population, may provide an option, when if used earlier, may give us maybe even a better disease control than we saw in the VISION trial.

What is your take on ASCO 2021 or ESMO 2021?

Dr. de Bono:
I think the main take for me is that men with advanced prostate cancer, or men with aggressive prostate cancer, now have better treatment options and will live longer and better than ever before. So I think we can be very proud that we've moved the field forward, but I think overall there's still a lot to do. You know, we do have some molecular stratification. These trials will, I think, change the standard of care, although we still await the FDA and European regulators' approval of lutetium-PSMA, although we're hopeful on that. Obviously, PARP inhibition is now approved in the US for BRCA2 and ATM and other disease mutations, alterations.

Dr. Morgans:
I think also importantly, there was a presentation on some updated analyses from the PROfound study. Johann, would you be able to share a little bit of what you and the team presented at GU ASCO 2021?

Dr. de Bono:
Yes, of course, Alicia. So one of the key questions that has really been raised is which genomic subsets of prostate cancer benefit most from PARP inhibition? At GU ASCO, we presented response rates for olaparib for the different genomic alterations in prostate cancer. And what we were able to clearly show is that the BRCA-altered tumors had the most benefit. But we also saw quite clear evidence of responses in ATM loss, prostate cancer, in the PROfound trial.

In our separate publication in *Cancer Discovery*, we were able to show that if we had evidence of biallelic loss of ATM, and particularly immunohistochemical loss of ATM at a protein level, those were the patients that had the longest RPFS [radiographic progression-free survival]. I should say that in the talazoparib trial, the TALAPRO-1 data that I also presented this year at these conferences, we have really replicated the PROfound data and proved, really, I think unequivocally, that PARP inhibition does have antitumor activity against ATM-loss prostate cancer, although it is not perhaps as impressive as what we see in the BRCA tumors.

I think there's so much happening in the field. Is there any final take-home messages you want to give Dr. Morgans?

Dr. Morgans:
Well, I think that comment that you just made, actually, sums it up quite well. There is so much happening in the field, which I think is exciting and provides new opportunities for patients in hope that there will be new things on the horizon that can continue to shift the survival curve and make people feel well as they're continuing to be treated. But it also leaves us, as clinical investigators, with so many questions that we still need to answer, so leaves us both hopeful and excited for the future, with a lot of work to do. What about you?

Dr. de Bono:
Yeah, I would agree. There's just so much exciting work going on, and this is a truly amazing time in prostate cancer research. So I'm excited to see what will happen next.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Morgans, for joining me and for sharing your very valuable insights. It's a real pleasure speaking with you again today.

Dr. Morgans:
Thank you so much, and thank you for your time today, too, Dr. de Bono.

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