Transcript Details

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Guideline recommendations for first-line treatment intensification with PARP inhibitor combinations in patients with metastatic castration-resistant prostate cancer

Announcer:
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Dr. Xu:
Hello. This is CME on ReachMD, and I'm Dr. Vincent Xu.

Dr. Srinivas:
Hi, I'm Sandy Srinivas.

Dr. Xu:
Dr. Srinivas, what data support our guideline recommendations for treatment intensification with PARP inhibitor combinations in patients with metastatic castration-resistant prostate cancer, CRPC, who have not received novel hormone therapies or docetaxel?

Dr. Srinivas:
Well, the concept of co-targeting androgen receptors, along with the pathway that inhibits the homologous recombinant repair pathway, really came about with a small trial that showed that there was a benefit to combining novel hormonal therapies such as abiraterone and enzalutamide to PARP inhibitors.

I want to highlight three trials that explored the combination of PARP inhibitors with novel hormonal therapy. I want to talk about the PROpel trial which combined olaparib with abiraterone, the MAGNITUDE trial that looked at niraparib plus abiraterone, and finally TALAPRO-2 which looked at enzalutamide plus talazoparib.

All three trials showed an improvement in rPFS. The group that had the highest benefit in all of these trials were those who had BRCA mutations. The next group that derived the maximum benefit were those who had the HRR mutation. These trials all had different FDA labels. PROpel with olaparib and abiraterone and niraparib plus abiraterone have it specifically for the BRCA mutated population, while TALAPRO-2 has a broader approval for all of HRR. We just heard recently that TALAPRO-2 met its endpoint of achieving overall survival. So really excited to see that data in an upcoming meeting.

But I just wanted to point out a few things in all of these three studies, that this was for first-line CRPC, patients having prior NHT were very small. So in the PROpel trial it was less than 1%, in the MAGNITUDE it was 3%, and in TALAPRO-2 it was 8%. There were a fraction who had prior docetaxel, so in all of these trials about 1/4 of patients had prior doce. My overall take from these three trials is that the group who's BRCA positive has the highest benefit. That's where we see the best hazard ratio. The next group is those who are HRR positive. And the last one is allcomers.

Dr. Xu:

Great. Thank you so much, Dr. Srinivas. And now let's take a look at how those trials that you just described are going to influence our NCCN guidelines.

When you look at the NCCN guidelines for CRPC, they really break down depending on whether the patient that you're seeing has received prior docetaxel, and even more importantly, whether they've received prior ARSi, such as abiraterone or enzalutamide. For patients who have not received prior docetaxel or ARSi, these are the patients that you might imagine might benefit the most from combination therapies, and those patients could be a candidate for niraparib plus abiraterone or olaparib plus abiraterone, or talazoparib plus enzalutamide, especially with that recent exciting overall survival data.

Similarly, patients who've had prior docetaxel but not prior ARSi might benefit also from combination therapies, same combos: niraparib/abiraterone, olaparib/abiraterone, or talazoparib and enzalutamide. I think one thing to point out is that if you look at the FDA labels, talazoparib plus enzalutamide is approved in HRR mutations, whereas the other combos are approved for BRCA mutations 1 or 2.

It's a little bit different in patients who have had prior ARSi. As you mentioned, Dr. Srinivas, even though patients with prior ARSi were included in these combination trials, the numbers were very small and it's very hard to draw any definitive conclusions from those combinations. And so for those patients who've progressed after prior ARSi, single-agent olaparib or rucaparib are good options for patients with BRCA mutations. It's not really known whether these combination therapies with niraparib plus abiraterone or talazoparib plus enzalutamide add much in this particular setting.

And one final thing to point out is that olaparib is approved for the homologous recombinant mutations in the prior docetaxel and prior ARSi setting.

So one problem that I encounter in my clinical practice is that you only know how to target these mutations if you know the mutations are there. So Dr. Srinivas, I'm curious, what is your approach to somatic testing in patients with CRPC? When do you test? How do you do your test? And do you repeat testing in these patients?

Dr. Srinivas:
I think that's such an important point for our viewers that till you test, you won't know whether they harbor this. So given that we have therapeutic options, it's really a plea that we should be doing somatic testing for all our patients with CRPC. I tend to do it now more earlier just because you have options in the CRPC setting. And I do repeat it at least one more time, given that there are issues with the tissue viability.

Dr. Xu:
Well, this has been a brief but great discussion. I hope we gave you something to think about, and thanks for tuning in.

Announcer:
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