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The Future of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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Dr. George:
Hi. I'm Dr. Dan George, medical oncologist and Professor of Medicine and Surgery at Duke University Medical Center, and I'm joined today with my colleague and good friend, Dr. Fred Saad. Fred, do you want to introduce yourself?

Dr. Saad:
Sure. So I am Professor and Chairman of Urology and Director of GU Oncology here in Montreal, at the University of Montreal.

Dr. George:
Fantastic, Fred. And happy to have you here with me, to talk about updates from GU ASCO. You know, this is hot off the press. We both just got back from the meeting, and a lot of exciting stuff. I think prostate cancer was really front and center again this year, with some really important updates in the field of metastatic castration resistant prostate cancer. Really, I think, 3, I think really important studies presented, around 3 different PARP inhibitors. Do you want to walk us through that data?

Dr. Saad:
Yeah, I think we could rename this session as the PARP session of GU ASCO. So really fascinating, because what was – and I think both you and I appreciated these confirmatory studies. You know, first with the rucaparib, that looked at patients, post novel hormonal therapy, and with mutations – BRCA and ATM – and confirmed what we saw in PROFOUND, where patients who are progressing after a novel hormonal therapy really benefit significantly from a PARP inhibitor, and rucaparib looks very similar to the efficacy of what we saw with olaparib. What this study added was they allowed physicians to choose a switch in novel hormonal or docetaxel. So, allowing us to get a sense for what is the appropriate sequence?

And clearly, patients didn't do any better if they went on to docetaxel before crossing over to rucaparib, or didn't do any better if they went on to docetaxel after having failed the novel hormonal therapy. So clearly, I think it points in the same direction as the olaparib study, that if you have a BRCA mutation especially, you should go as early as possible to a PARP inhibitor. So these patients really benefit from as early as possible PARP inhibition, if you harbor a BRCA mutation and are progressing on a novel hormonal.

Dr. George:
That's right. That's right, Fred. And just to be clear on that one, that when you say "early," that was still post AR pathway inhibitor. So, sort of a second line, if you will, in the castrate resistant space. But then we had two studies that really looked at combining a PARP inhibitor in the first line metastatic castrate resistant space, where patients hadn't yet really, you know, treated and failed on an AR pathway inhibitor. Walk us through those studies.

Dr. Saad:

Yeah. So, we had the updated results, in terms of overall survival from PROpel, which is looking at the combination of abiraterone and olaparib, in first line mCRPC patients who have not yet been treated for mCRPC. And then we had the results – the first results from TALAPRO-2, which is similar patient population, but combining enzalutamide with talazoparib, so another PARP inhibitor that's very potent. And so, both now, I think, confirm that patients that don't harbor detectable HRR mutations benefit from this combination in first line, with very significant improvement in radiographic, progression-free survival in those patients. So in terms of overall survival, the TALAPRO-2 study still is very immature. It's only about 30% of patients have died. The PROpel study is more mature, and so now we're getting some data that's becoming more and more convincing in terms of overall survival advantage, where there was 7.4-month improvement in overall survival in the intent to treat – the whole population, and we have to remember, this is against an active control. So the patients in the control arm are getting abiraterone and prednisone, which is one of the most commonly used therapies for first line mCRPC.

So, we're improving on a standard of care, so I think it really is an eye opener. Obviously, with only 800 patients, the p valued is still not clearly significant, but the confidence interval is really below – at exactly 1, so very borderline trend towards statistically significant improvement in overall survival, clearly driven, in part, by the BRCA-mutated patients, but clearly not exclusively by those patients. We're seeing patients that don't harbor BRCA mutations that look like they're benefiting clearly, in terms of RPFS, and probably even in terms of overall survival.

Dr. George:
It's really remarkable, when you think about, you know, this. And I think, you know, in some ways it's kind of, you know, sometimes maybe hard to get our head around. We've been commissioned, so to speak, to think that, you know, it's the BRCA genetic alteration that is making these tumors susceptible to PARP inhibition, and now suddenly that dogma is getting really redefined around an intention-to-treat population – everybody with metastatic castration resistance prostate cancer. Recognizing the heterogeneity that that pop – intention-to-treat population, you know, contains is benefiting from the combination of a novel hormonal agent and a PARP inhibitor, and just really speaks to the fact that we're still finding out today, after all these years, how hormonal therapy is working, and the many different ways it's working, in prostate cancer, in metastatic castration resistance prostate cancer, with these novel hormonal agents. It's destabilizing that DNA repair mechanism. It's creating a condition similar – maybe not as potent, but similar – to BRCA – an additive to BRCA, because the BRCA patients did exceedingly well in this setting. So this is maybe even a more dramatic and robust benefit than what we saw with the sequential use of novel hormonal therapies, followed by PARP inhibitors, in the BRCA patients. When we do them all together, up front, the results are really astonishing, and it's not exclusive to that population. As you said, we see this benefit in the, you know, in the broad population, and I think that's so important to keep in mind. Because yes, we'd like to say we test everybody, right? But the reality is nobody can say they test everybody, and you hate to miss a BRCA patient and the fact is, is there's biology we don't measure…

Dr. Saad:
Exactly.

Dr. George:
…in this intention-to-treat population that could be benefiting. So, so seeing this now over repeated studies, you know, in the TALAPRO-2, looks very similar, just maybe a little bit earlier, and we need to follow that out further. Now Fred, there was one other update in this story of PARP inhibition with novel hormonal agents – the MAGNITUDE study, with a second interim analysis. Do you want to update us on that one?

Dr. Saad:
Yeah, so the MAGNITUDE study is another combination, first-line study, using abiraterone plus niraparib, basically looking at the patients most needed, or most likely to respond – patients mainly with HRR mutations, and especially with BRCA mutations. And that study already reported very impressive RPFS benefit, with the combination of abiraterone and niraparib compared to abiraterone alone, with a hazard ratio of about 0.5 in those patients with BRCA mutations. And now, with this updated data, we're seeing the trend continue in favor of the combination, in terms of overall survival. So the data is still immature, but pointing in the right direction, that by intensification of treatment in patients that harbor these mutations, we clearly can change their survivals – their progression-free survivals at the very least – and these patients really need to be treated – found early and treated early, with the best possible therapeutic options that we have, which would include a PARP inhibitor, and I think niraparib is proving itself to be very effective in those patients.

Dr. George:
Fantastic. You know, it's in the – and again, sort of, you know, along the validation of this strategy, of really combining these agents together, and not using them in sequence, and whichever PARP inhibitor you choose here, we're seeing really robust signals in both the progression-free survival and the overall survival.

Fred, what about side effects? Because, I mean, a big issue here when you do combination therapy is added toxicities. What do we see for toxicities with these agents?

Dr. Saad:
Yeah, so, the toxicities are as we would have expected. So anemia is by far the most common adverse event that's reported. In PROPEL, we seem to see maybe a little bit less, because there was about 16% grade 3-4 anemia in the study, where it was about 46% grade 3-4 in anemia in the combination of talazoparib and enzalutamide, so that combination might be affecting the bone marrow a little bit more, but overall, these are manageable, but these patients need to be followed closely. So I don't think it's for physicians that are practicing in an office that don't have access to transfusion units, so this is something that going to have to be worked out, as how we introduce this. But regarding the efficacy, there are things we still need to understand. It clearly goes beyond BRCA, but if you look at the BRCA data, a hazard ratio of 0.29, in terms of improving overall survival over the standard of care of abiraterone, is absolutely outstanding and these patients with that combination of olaparib and abiraterone need to be treated as early as possible, to try to reduce the risk of early death in those patients. We clearly can't eliminate it, but we can significantly improve their survivals.

Dr. George:
Yeah, so genetic testing is not going away. We need to do genetic testing…

Dr. Saad:
Oh, yeah.

Dr. George:
…we need to find these patients, and make sure they get this combination at the start, because that's really the maximum benefit for that population, and it's a higher risk, a more aggressive disease biology. So, absolutely fantastic.

Well, Fred, thank you so much for that really exciting news from GU ASCO. Once again, always a pleasure to talk with you. Thank you.

Dr. Saad:
Yeah, and there was – there was one other study we might take 30 seconds to discuss. This whole issue of lutetium following radium. We have patients that are being treated with radium, that are sitting around, and now lutetium has just been approved in many countries around the world. And this idea that you have to wait at least 6 months was a criteria in the study, but what we're realizing with this data that's coming out, is that if the bone marrow is recovered, there's no reason to insist on waiting 6 months to introduce lutetium, and that's been our experience in our center. So, a nice paper – the RALU study, that I think is very reassuring that there's no reason to wait 6 months after radium, if lutetium is indicated.

Dr. George:
It's really – it's really a great study in the sense that, you know, we're not burning a bridge by using radium, and we're not delaying that next therapy by using radium. It's an opportunity, particularly for those patients that are, you know, really bone dominant disease, to target that disease 2 ways, right? One with radium and one with Pluvicto, and really encouraging to be able to see that good tolerance, long-term. I hope we can see some efficacy data, some randomized data in the future, but so far, this really gives us confidence in that treatment sequence. Thank you.

Dr. Saad:
Great. Thanks. Always fun.

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