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Recent Progress in Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC)

Announcer:
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Dr. Saad:
Hello. I am Fred Saad, Professor and Chairman of Urology and Director of GU Oncology in Montreal, Canada, and it's a pleasure to be discussing today with my friend and colleague, Professor Dan George, on the topic of nonmetastatic CRPC. We haven't heard much new. We've had 3 pivotal trials that have shown significant improvements in delaying metastases, and in terms of improving overall survival. So, Dan led an important data analysis of patients on the 3 drugs that are now approved, and maybe you can share some thoughts and some results from that study.

Dr. George:
Happy to do, Fred. Yeah, so, you know, as you said, we've had 3 really large pivotal trials that have demonstrated the metastasis-free survival and overall survival benefits associated with either darolutamide or enzalutamide or apalutamide in this space, and really become kind of a standard of care. But the trials are also handled a little bit differently in terms of follow-up. They were all placebo-controlled, but, you know, cross-trial comparisons are, you know, a little bit difficult because of those differences, and whatnot. So, you know, we're kind of left with having to make treatment decisions on which drug to use without really, kind of clear, comparative data. So sometimes we'll turn to real-world evidence, to help fill this gap, and granted, real world is not a, you know, head-to-head, randomized clinical trial, but it does give us some insights into, 1 – you know, how patients are managed, and, 2 – how patients are tolerating therapy, in practice. And so, we did an analysis looking in a large urology practice group, across the country. This was – this was over 100 urology practices, and really an extensive electronic medical record review of prescript – prescribing information as well as their management, and clinical outcomes. And this was done over a 3-year period – 2019, 20 and 21 – looking at, sort of the use of darolutamide, enzalutamide and apalutamide.

Had a, you know, roughly 700 patients, and it worked out to be about the same for darolutamide, enzalutamide – apalutamide was less used. Enzalutamide a little more early, and darolutamide a little more late. So to take all that into consideration, and when we look across, what was really interesting – we looked at a composite endpoint of both time to discontinuation of therapy, and also time to progression. Remember, these 3 pivotal trials had, you know, median times to metastasis, so abruptly, you know, 36-40 months. So we're expecting something along those lines, and we didn't see that. We saw, you know, the time to treatment discontinuation for either metastasis or progression to metastasis, or unacceptable toxicity to be closer to around 24 months for enzalutamide and apalutamide. For darolutamide, it wasn't reached, with the lower limit confidence interval of 30 months, so we'll see where that one actually ends. And it's interesting, it does appear across the population that darolutamide had a longer time to discontinuation or progression/death. So, we dug into that a little bit. We could see that it was kind of broken out with both. We saw, kind of equal rates of about 50% less discontinuation because of AE's, and about 50% less discontinuation because of progression metastasis for darolutamide compared to enzalutamide or apalutamide. So again, this is real-world data. Right, this is – there may be some differences in patient selection, or in

management or whatnot. But the reality is, is this was an older population – median age of 80, and so it's possible that, you know, drugs like darolutamide, that don't cross the blood-brain barrier, have a little bit of a different tolerance pattern in these patients that aren't necessarily represented in the pivotal trials. So, I think we need more data, but it's worth looking in real-world data to understand these things, and to really understand how trial data applies into our practice.

Dr. Saad:
Well, that's really fascinating. I mean, it was – I enjoyed reading that abstract, and it actually was quite surprising, and we need that kind of data because individually, when we treat a few patients, we don't really get a sense for these kind of differences, so thanks for sharing that.

And there was another study, looking at the ARAMIS results, in terms of the long-term safety data in – with patients treated in the ARAMIS study. Any thoughts around that?

Dr. George:
Yeah, you know, this was led by some of our colleagues, Neal Shore and others, and it was a rollover study. This was for patients that had really, you know, completed the, you know, the ARAMIS darolutamide study and still were going on, so rather than sort of just roll them over to standard of care, we rolled them over the standard of care with sort of a registry, if you will, for follow-up. And, you know, over – almost half the patients, about 450 patients or so, that rolled over, and what was really interesting was that overall, the toxicity profile was very similar. There was a slight increase, as you can imagine, a little bit of cumulative toxicity will occur, but it was all the expected side effects we'd seen earlier, so no new signals of safety issues, and really kind of minimal, you know, increases in those rates, and largely low-grade. But over half of the patients in that rollover study were out to 4+ years, without progression. So now, we're starting to see – you know, we saw the median, 40-month median, metastasis-free survival. Now we're seeing that, you know, really extend further, and – and it really suggests there is a group of patients that can get very long-term disease control, and acceptable tolerance, you know, on darolutamide in this setting.

Dr. Saad:
Yeah, no, no, fascinating, and I think that's what reflects the real world, and in our practice, that if you're going to get adverse events, they're usually pretty much in the first few months of starting therapy, so have to get patients through that first hurdle. So I think that's very informative, and it actually is going to probably lead to other studies into these really long-term survivors or responders. You know, who are they, how can we predict who they are, and should we start thinking of de-intensification in some patients? That's for another time. Hopefully, we will be able to discuss some of that stuff later, because I think we're all conscious of long-term exposure to patients who might not actually need it. So, very, very interesting.

So thanks, and maybe just to finish, present yourself, because I think we didn't present you formally when we started this session.

Dr. George:
Oh, thanks, Fred. Yes, hi, I'm Dan George. I'm a medical oncologist at Duke University and Professor of Medicine Surgery. I'm happy to speak to you today. Thanks so much for the opportunity.

Dr. Saad:
Yeah, and anybody who doesn't know Dan shouldn't be working in prostate cancer. Take care, Dan. Thanks a lot.

Dr. George:
Thank you.

Announcer:
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