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Novel Hormonal Therapy Advances in Metastatic Hormone-Sensitive Prostate Cancer

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Dr. Saad:
Hello, I'm Fred Saad, urological oncologist from the University of Montreal, and I'm joined today by Rana McKay, medical oncologist in San Diego. And we're here to talk about some of the highlights at ASCO regarding prostate cancer, and we'll focus on hormone-sensitive metastatic prostate cancer, where there was quite a bit of results that were reported.

So if I just start off, clearly, we've been hearing a lot about triplet therapy with the results from piece one, some of the results from ENZAMET that were reported a couple of years ago. But really the first trial that was really aimed at answering the question of whether intensification over standard of care with a angio receptor inhibitor like darolutamide over ADT plus docetaxel leads to better outcome than ADT and docetaxel. So the ARASENS trial was clearly a very positive study. We clearly improved time to castration resistance, time to PSA progression, time to symptom progression, but importantly, very powerfully improvement in overall survival with a 32.5% reduction in death in patients getting ADT docetaxel plus darolutamide compared to ADT and docetaxel. What we looked at ASCO was looking at PSA response in patients getting the triplet versus the double approach. And there's been a lot of data saying that PSA response can correlate to outcome, but very little in terms of how the combination of ADT docetaxel and an AR inhibitor like darolutamide would result. And so clearly we went from about a 25, 20 8% PSA undetectable rate with ADT docetaxel alone. And that went up to 67% with the addition of darolutamide. And when we looked at the darolutamide combination, if you achieved a PSA below 0.2 compared to not achieving 0.2, the results were very very different with over 60% reduction in the risk of death in patients that received that were able to go below 0.2 compared to patients who didn't achieve getting to below 0.2.

So clearly this is reinforcing this objective or this early surrogate for outcome of trying to achieve a 0.2 reduction or less with whatever we're going to do. And here this study shows the triplet of ADT docetaxel and darolutamide achieve that at a much higher rate and leads to a much better outcome. What we need to do for patients who don't get to 0.2 further intensification are going to be other questions for the future. And so clearly in that sense I think this is an addition to what we know. So Rana, I think people are looking forward to seeing what can darolutamide might do without docetaxel and maybe your thoughts on some of the trials?

Dr. McKay:
Yeah, absolutely. I mean, I think when the ARASENS trial was designed the field had changed with the introduction of the docetaxel for metastatic hormone sensitive disease based on the charted data. And so prior to the trial launching it was sort of mandated that all patients received docetaxel to align with the new evolving standard of care. And so really what ARASENS hoped to answer was what does darolutamide add to the then standard of care which was ADT plus docetaxel.

Since the presentation of the charted data, we've seen multiple other studies report out with NHT escalation in the metastatic hormone-sensitive space. And we don't really know what is the role of darolutamide without docetaxel, just ADT plus darolutamide for those not receiving docetaxel. And there are a series of studies that are seeking to actually answer that question. So ARANOTE is currently

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ongoing. It's an XUX study which is looking at ADT plus minus darolutamide for patients with metastatic hormone-sensitive disease. And also the ARASENS study is also going to be looking at answering this question. This is a U.S based study. It's an open label study with darolutamide plus ADT and it's being compared to a matched control set of patients that were enrolled and charted. So hopefully between ARANOTE and ARASENS will have data around what is the role of darolutamide in the metastatic hormone-sensitive setting.

Dr. Saad:
Great. So I think we look forward and I think we can expect that darolatamide given what we know in the non-metastatic CRPC setting and now in the metastatic hormone-sensitive setting in docetaxel that I think we can expect to be both effective and hopefully show that we can get even more tolerability because these patients are going to be on therapy for a long time. So clearly looking forward to those results. There has been data at ASCO that was presented on enzalutamide. So we know the arches results that showed that we improve RPFs and overall survival. And so the analysis that was presented was looking at patients below and above 75 years of age. And what it showed was that it was as effective in patients older and younger than 75, but also well-tolerated in the older patients. So this is I think important information when trying to decide on intensification in the older patient where clearly these metastatic patients, except for the very few exceptionally frail patients probably all need to be intensified.

Dr. McKay:
Yeah. And yeah, piggybacking on the ARCHES data, looking at those less than 75 and greater than or equal to 75 years of age was the updated overall survival data from ENZAMET. Which again, just continued to confirm that escalation with enzalutamide compared to ADT alone results in statistically significant improvement in overall survival for patients with metastatic hormone-sensitive disease. What was presented was various subset analyses based on receipt of docetaxel, which was not mandated, but was allowed for investigator discretion and also sort of a breakdown by volume of disease and whether patients had synchronous or metachronous disease.

And I really think we can get lost in the weeds with all these subset analyses and really the take-home message is that enzalutamide, in addition to ADT, improves overall survival compared to enza alone, I think the subsets are it's really hard to sort of define, there's no benefit in the docetaxel treated patients, or I think to kind of break up the study like that, it was not really powered for all these subset analyses. So I think the take-home message really is escalate, escalate, escalate on ADT plus X. Whatever that X may be is the new standard of care. There are lots of options to select from and for those patients receiving docetaxel we now have two studies between piece one and also ARESENS that demonstrate that the addition of NHT to patients receiving docetaxel improves outcome. So I think there are options for patients with a metastatic hormone-sensitive disease.

Dr. Saad:
Absolutely. And I think what's striking even going against what my own beliefs several years ago was that even in the very lowest risk or lowest volume metastatic hormone sensor disease patients, they benefit maybe even the most. So it goes against what preconceived notions. So really don't under treat those patients. They're likely to be the ones that benefit the most. And I think there was some data that was presented that the patients, at least with enzalutamide combination that might benefit the least, are the very low risk low volume patients getting docetaxel over enzalutamide.

So in terms of looking forward in hormone sensitive disease, we're trying to integrate biomarkers. And so TelePro three is still a trial in progress but looking at hormone sensitive, newly diagnosed, mainly newly diagnosed patients that are metastatic and looking for a DNA repair defect mutations and then randomizing them to get upfront talazoparib versus the standard of ADT plus enzalutamide. So looking at earlier settings of introducing PARP inhibitors in patients that are metastatic hormone sensitive.

Dr. McKay:
Yeah, no, I think that's going to be a very important study. That's biomarker-driven for those patients that really have HRD gene alterations. And we know that various data has demonstrated that such patients actually have worse outcomes. How can we escalate therapy for them with a targeted agent in the hormone-sensitive setting? So that's going to be a very important trial. I think there's a lot of questions about these patients can do well for a long time in the metastatic hormone-sensitive setting and sort of what's the gain added with a PARP inhibitor. So very exciting data that hopefully will come out from that trial.

Dr. Saad:
Right. So, I think overall nothing earth-shattering was presented, but I think it helps us to start further integrating biomarkers, as simple as PSA and response like we saw in ARESENS and trying to integrate looking for mutations that might be actionable earlier in the disease spectrum. So a lot of really good data and looking forward to more data on darolutamide in the metastatic hormone-sensitive setting without docetaxel. I think a lot of people are looking forward to that. So thanks, Rana. Thanks for sitting in and listening to this and hope you found this informative.

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