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Practice Changing Studies in Metastatic Hormone-Sensitive Prostate Cancer

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Dr. Petrylak:
Morning, my name is Dr. Dan Petrylak, from the Smilow Cancer Center at Yale University, and I'm joined by my colleague, Dr. Matthew Smith, from Massachusetts General Hospital in Boston, and we're here today to discuss some of the exciting findings at the ASCO GU Meeting. We'd like to focus this morning on the treatment of Hormone-Sensitive Disease. And Matt, what are some of the exciting abstracts that were presented at this year's ASCO GU Meeting in Hormone-Sensitive Prostate Cancer?

Dr. Smith:
Yeah. Thanks for the opportunity to comment. Yeah, the big presentation at ASCO GU is ARASENS. So, ARASENS is a global, randomized phase-three trial of darolutamide in combination with ADT and docetaxel in patients with metastatic hormone-sensitive prostate cancer. The key thing about that study is it was designed soon after the positive results of STAMPEDE and CHAARTED, showing an improvement no less with the addition of docetaxel to ADT. And accordingly, the control arm for ARASENS was ADT and docetaxel. It's began enrolling patients in 2016, and as you know, that was before the first report that any AR pathway inhibitor improved outcomes in MHSSPC. So, big undertaking, 286 centers in 23 countries, more than 1,300 patients. Within 12 weeks of starting standard ADT, patients are randomized to darolutamide or placebo, and then within six weeks of randomization, patients in both groups were treated with docetaxel for six cycles. The primary endpoint was overall survival, and then there was, as you'd expect, a number of key secondary endpoints. Clearly positive trial with the large improvement in overall survival, darolutamide reduced the risk of death by 32.5% compared to the placebo group. The median overall survival was 48 months in the control group, and not yet reached in the darolutamide group. And the four-year overall survival rate was 50.4% with the placebo, and 62% in the darolutamide group. So, really quite a large treatment effect, hazard ratio is 0.68, so the magnitude of the benefit was as great as what was seen by any individual agent in prior studies in MHSPC.

Dr. Petrylak:
I think it's interesting you point that out, because when you look at the STAMPEDE DATA, abiraterone plus, predminisol, prednisone, excuse me, versus placebo in hormone naive prostate cancer. At four years, the survival is 65%. So, it seems to be in line with some of the other data that's been presented. So, it really asks the question whether we really do need docetaxel in the treatment regimen.

Dr. Smith:
It is an intriguing sort of, of course the study wasn't designed to ask that, you know, our results are consistent with the docetaxel subgroup of piece one, which showed the addition of abiraterone to ADT, docetaxel improved survival. There, the hazard ratio's about 0.75 in that control group, but sort of unexpectedly, the big question that's raised is, you know, do we really need docetaxel? And I think that it is an open question, and there was some interesting data presented at ASCO GU, it's exploratory for sure. But I think the key takeaways from ARASENS, and the same extent from the docetaxel subgroup of piece one, if you're gonna treat a patient with ADT

docetaxel, it's very clear you should be adding a third drug, an AR pathway inhibitor, in this case, either abi or darolutamide. The more challenging question though, is for patients, particularly with poor prognosis, is, do you need a doublet of ADT and an AR pathway inhibitor, or the triplet with the addition of docetaxel? Now, candidly, the way the study was designed, both studies were designed in sort of ARASENS, is you began with ADT and darolutamide, and then added docetaxel later. So I could envision in the clinic as you're getting started, particularly patients with de novo metastatic disease, you're gonna do, you know, ADT AR pathway inhibitor, and then as you get to know the patient in the weeks or few months that follow, make the decision about whether they're an appropriate candidate for docetaxel.

Dr. Petrylak:
It's certainly making the discussion with the patient at the initiation of hormone therapy much, much more complex. In fact, what I actually do is I introduce the concepts right at the beginning when we first undergo androgen deprivation therapy, review the different side effects and toxicity profiles of each of the individual anti-androgens, also discuss chemotherapy in the piece one trial. So, that generally takes several visits, and I think the way these trials were designed, where they administer these treatments within the first three months of therapy, not necessarily right off the bat, allows the clinician now to have that chance to discuss with patients exactly which treatment they're going to undergo, and it is a complex discussion.

Dr. Smith:
I agree. And I think that I like the way you described that, because I think the way we need to approach this with patients is they don't need to know all the prior history, right, they don't need to know decades of history, right? You know, in the old days, we used to give ADT alone, and then now we're gonna have this conversation, like, should we intensify therapy? I mean, the data is so consistent and clear for the addition of an AR pathway inhibitor, what I've adopted is much like you have, which is introducing that early in the conversation to say, "Here is your foundational treatment. You're gonna start with this injection that's gonna lower your testosterone, and we're gonna add this other drug, that's the foundation of your treatment." And then, you know, based on the results of these newer trials, the question will become, particularly for de novo high volume patients is should we also add docetaxel?

Dr. Petrylak:
And you know, I also try to design the treatment regimen for the patient based upon the side effect pattern in each individual drug. And the unfortunate part about ARASENS is the fact that you're wedding darolutamide to docetaxel in this trial. So, are there any other trials that are out there right now that are looking at the question of darolutamide alone in this situation?

Dr. Smith:
There are a couple of ongoing trials looking at that with, you know, there are other ongoing randomized trials that are looking at the comparison of ADT, ADT-darolutamide. Those won't read out for a couple years, so we will have that information. But I take this, I realize the control arm is ADT-docetaxel, So I really just take this as additional evidence for the importance of an AR pathway inhibitor. And my takeaway, my personal takeaway, is I have no concern at all about using darolutamide in combination with ADT in appropriate patients.

Dr. Petrylak:
Neither do I, and there's certainly advantages to darolutamide, particularly the fact that it does not cross the blood-brain barrier to the same degree as the other anti-androgens.

Dr. Smith:
And we really saw that in the safety data from ARASENS, it was really quite striking. You know, there was really no difference in adverse events between placebo and darolutamide for, you know, any emerging adverse events, serious adverse events, adverse events leading to discontinuation. And then if you even looked at the AEs of special interest, once you control for exposure, there's really no difference between darolutamide and placebo. So, very, very consistent with the favorable safety profile that had then previously reported in ARAMIS in non-metastatic CRPC.

Dr. Petrylak:
Terrific, Matt. Any closing thoughts on Hormone-Sensitive Disease at the ASCO GU Meeting?

Dr. Smith:
Yeah, I think this just adds to the continued drum beat and consistent data about the favorable impact of AR pathway inhibition in Metastatic Hormone-Sensitive Disease. We really need to get away from ADT alone, most patients with MHSBC should not be treated with ADT alone. And then it also raises this important issue about the potential role of triplet therapy, particularly in those patients with a poor prognosis disease.

Dr. Petrylak:

So, one of the interesting abstracts that I found important to the overall health of patients with castration resistant, castration sensitive prostate cancer, is a presentation by Dr. Rubode about bone marrow density in men with de novo metastatic prostate cancer. And what they found in this is that abiraterone did not seem to have the effect on bone that we would've thought, and there wasn't any big difference in the loss of bone and of density of abiraterone versus just simply androgen deprivation therapy. I know you're really one of the world's experts on bone disease, bone effects of prostate cancer, what did you think about that abstract?

Dr. Smith:
I think that the concept that they're attempting to address is important. It's technically challenging, so my answer will be a little mundane, in that it's very difficult to reliably measure bone density in patients with bone metastases, because bone metastases from prostate cancer are osteoblastic, they're dense, and so if you're measuring BMD, particularly total BMD, in patients with metastatic prostate cancer, your measurements may not reflect the impact of treatment on normal bone, but also on bone metastases, so, it's a little bit difficult to interpret for that reason.

Dr. Petrylak:
It's almost a chicken and egg argument, because if you actually took the normal bone and measured the density there, is that reflective of what's going on in the cancer itself?

Dr. Smith:
Right, exactly. Yeah.

Dr. Petrylak:
Yeah, we really don't have a good way to measure bone density in those patients who have documented metastatic disease, and although I do routinely measure bone density in those patients who are on antigen deprivation therapy for non-metastatic disease, 'cause I think it's important to measure that, and then, of course, act if they do have significant osteopenia or osteoporosis.

Dr. Smith:
And in a way, the issues that you raise are totally okay, because patients with bone metastases, it's disease related skeletal complications that dominate the clinical picture, in patients without bone metastases, it's treatment related osteoporosis and fractures that dominate the clinical picture. So, the therapeutic intention is the same, it's to reduce skeletal morbidity, but you're dealing with sort of two parallel problems.

Dr. Petrylak:
Well Matt, great as always talking with you, and thank you for your really insightful analysis of these particular trials.

Dr. Smith:
Thank you. Great to speak with you.

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