Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/practice-changing-studies-in-the-frontline-treatment-of-metastatic-castration-resistant-prostate-cancer/14021/

Released: 06/24/2022
Valid until: 06/24/2023
Time needed to complete: 1h 00m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Practice Changing Studies in the Frontline Treatment of Metastatic Castration-Resistant Prostate Cancer

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.
Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Petrylak:
Hello. My name is Dr. Daniel Petrylak, Professor of Medicine and Urology at the Smilow Cancer Center, Yale University. I'm joined by my good friend and colleague, Dr. Matthew Smith, Professor of Medicine at Harvard University and Director of Genitourinary Oncology at the Massachusetts General Hospital. And we're going to discuss some of the exciting findings at ASCO GU regarding castration resistant prostate cancer. So, Matt, what are some of the really exciting abstracts that you found at this meeting this year?

Dr. Smith:
It's great to be with you today, Dan, and, you know, it was really perfect in the oral abstract session. There was a propel primary study results followed by magnitude. So these are two trials looking at abiraterone plus or minus the addition of a PARP inhibitor. In the case of PROpel its Olaparib. In case of magnitude it's Niraparib. And it was just a perfect to have them back to back because while there are some similar conclusions there are also some striking differences. And I think there was a lot of interest in what might may explain those differences. First, the similarities, both studies reported that in the basically biomarker positive patients HR positive patients, the addition of a PARP inhibitor to abiraterone, acetate and prednisone improved radiographic progression free survival. In the magnitude study, most of the benefit being derived in the BRCA 1 and 2 patients. The difference though came in the interpretation of biomarker negative patients where, so in PROpel, they reported a positive effect in the overall population and a modest, but positive effect in the biomarker negative patients. Magnitude was designed in a different way, and the patients were screened by study entry and assigned to different cohorts according to their biomarker status. And the biomarker negative group was studied, that part of the study was discontinued early for futility. So reaching the conclusion that the combination is not effective in biomarker negative patients. So magnitude. All the patients were screened before study entry and then assigned to the cohort according to their biomarker status.

Dr. Petrylak:
I see.

Dr. Smith
In PROpel, they sort of enrolled all comers and then did the analysis by the biomarker that was done after study enrollment or at the time of study enrollment. So, there was no assignment of group.

Dr. Petrylak:
There was no assignment.

Dr. Smith
Yeah.

Dr. Petrylak:
So how do you explain the difference? This has been, there's a theoretical reason why you can combine these is that the PARP inhibitor is it's the sequencing of how they administered the drugs. Is there's something that was unique about each trial that may have led to a difference in the, in the outcomes.

Dr. Smith:
So, first I would say, I don't believe it's due to the differences in the PARP inhibitor. So I don't think, I don't think is that, one drug is better than the other because best available data says they're far more similar than different

Dr. Petrylak:
Exactly.

Dr. Smith:
Both in prostate cancer and other cancer. So I don't think that explains I think it's simply the study design. And while in some ways the magnitude study design might be deemed more complicated. The interpretation is more straightforward because by having the biomarker negative cohort it was more precisely designed to determine whether there was activity in that group. And I'd also say, I guess what difference are we distinguishing between because the so-called positive result in the biomarker negative patients in PROpel, in my opinion, was quite modest. So for this intermediate endpoint of rPFS, the hazard ratio 0.74 corresponding to about a five-month improvement in rPFS. And candidly, that magnitude of improvement in every other study has never translated into an OS benefit. So I think it's a small effect and it's quite possible again, in my opinion, that that may overestimate the true effect in that patient population for two reasons. First, the imaging interval I believe was every three months. So it's kind of somewhere between one and two imaging interval improvements. So the true effect could be smaller. And then second, and this was very feisty conversation in the discussion section as to whether or not there could have been contamination in the biomarker negative group with false negative patients. So in other words, some of the observed treatment effect could have been from contamination of the biomarker negative group with patients who had homologous recombination repair deficiency

Dr. Petrylak:
Right? And also the other thing too is how the patients do? What type of assay used to get put these patients on trial? I don't recall what the assays were and at what point they sampled the particular markers but obviously you can take it at any point during the continuum of hormone-sensitive and castrate-resistant disease. And we've actually seen some situations where we've had the development of somatic mutations in patients when they've been germline negative. And that potentially could be another reason why these patients could have had contamination. Although I do believe they did liquid biopsies right before these patients.

Dr. Smith:
Yeah, that's my understanding. This is the point that came up in the conversation, very provocative discussion. From those presentations was that PROpel used ctDNA. And the concern is if you were ctDNA basically null or uninformative, you'd be assigned, I believe you were assigned to the biomarker negative group. So you could have had, it’s plausible that you could have had some patients in that group with false negatives.

Dr. Petrylak:
Right. We've seen just simply the HRD positive patients in PROpel, but we've not seen if there's been a difference between the BRCA 1, BRCA 2s and the remaining DNA repair mutations. And I think that's a really a big question because this may be driven predominantly by the BRCA 2s. We've seen this in other trials where there have been combinations between immune checkpoint inhibitors between anti angiogenesis agents and the rPFS turns out to be positive. But when you do the subanalysis based upon the individual components, it turns out that most of this is being driven by BRCA 1 and BRCA 2.

Dr. Smith:
And that point is exactly what was seen in the magnitude trial, where the biomark positive patients are positive, but it's really being as expected to your point, driven by BRCA 1 and 2 mutants.

Dr. Petrylak:
Exactly. The other issue here is the general applicability in 2022 of the trial results. Because as we're seeing more patients being treated with next generation, anti androgens in the castration-sensitive state, this population is going to actually decline significantly because you're not going to have these de Novo patients right after either just simply angio deprivation therapy or Docetaxel, and you're not going to have those patients to treat in this fashion. So I think one interesting idea would be to do a trial perhaps in just the BRCA 2s to determine whether a patient should continue on abiraterone and then receive a PARP inhibitor versus just simply the PARP inhibitor. And I think that's going to be more relevant to the future population.

Dr. Smith:
A great point. The other, the other thing I considered looking at this is the question for clinicians, right for us in the clinic is if you have BRCA, say BRCA 2 germline patient it's clear you're going prioritize giving that patient a PARP inhibitor. But what we don't know from either trial is whether you should do that in combination or sequentially and so of course neither trial formally addressed the sequential question. And so we're going to be left wondering whether the combination is truly better than sequential therapy with Abbi followed by a PARP inhibitor.

Dr. Petrylak:
Exactly. So, I mean, exciting results, I think we need further follow up. We need to see the OS data. Clearly.

Dr. Smith:
I agree.

Dr. Petrylak:
In these studies. I think that's going to be key because again the question is, does rPFS correlate with OS and is the hazard ratio sufficient to see that particular change later on. We've seen that in other trials where particularly the Apalutamide abiraterone study compared to abiraterone alone where there was a great rPFS initially, and then last year I think, or the year before they reported no difference in survival. So it's still, I think something we need to follow up and see.

Dr. Smith:
Agreed.

Dr. Petrylak:
Terrific. So other really interesting targets. PSMA although there weren't really any major presentations at this year's meeting, but certainly this is something that's on the horizon for the treatment of castrate resistant, prostate cancer. What are your thoughts on PSMA, PSMA imaging and how we're going to incorporate that into our clinical armamentarium?

Dr. Smith:
PSMA is going to have a huge impact in the field in two ways. Imaging, so PSMA PET/CT or PET/MRI will change the landscape dramatically. We're going to be reclassifying patients. We're going to be the logical impact of that is going to be greater therapy, more therapy earlier and intensification of therapy due to reclassification of patients. There's going to be a lot of metastasis directed therapy as a consequence of that better imaging. And we have a lot too, we're going to have a lot to learn because the technology is now in front of us. The other really exciting part of course is PSMA targeted therapeutics. We believe PSMA lutetium is coming soon. That's going to be a really important tool in our toolbox for patients who have few other treatment options. And then there are a number of novel PSMA targeted therapies in development, PSMA BiTEs, PSMA TriTEs, PSMA CAR Ts. So all these are very exciting and we hope to see a lot more from that space in coming years.

Dr. Petrylak:
It's been, I think really satisfying to see this because after all the years of pursuing PSMA imaging remember the Prostascint scan years ago,

Dr. Smith:
Yeah.

Dr. Petrylak:
which really, unfortunately never really met its promise. And then of course, all the PSMA ADCs that were developed that really did never really bore fruit. Now we're seeing, after all of this research the really the great PET imaging and also now the therapeutic tissue, which I think is really a major advance. I think the real question is going to be how are we going to use these PSMA scans, as you say for intensifying therapy earlier. And are we starting? Are we going to do too much? Because certainly antigen deprivation therapy has long term side effects as you've very well described over the years with bone and with muscle and with other metabolic issues but the question's going to be, how do we integrate this? How do we design trials with the patients knowing this information and saying, "Hey I've got something on my scans. I don't want to be randomized. I want to be treated now, or I don't want to be treated because I don't want to undergo the side effects." So there's going to be a lot of challenges in designing clinical trials and using some of our novel agents earlier.

Dr. Smith:
Very well said, but you know once that door is open, it's very hard to close it and pretend

Dr. Petrylak:

Exactly.

Dr. Smith:
you didn't look in there. So this is how, you know, the technology of PSMA PET imaging is going to is, is already in front of us. And we're going to have to catch up as quickly as we can.

Dr. Petrylak:
Terrific. Matt, any closing thoughts?

Dr. Smith:
No, thank you very much. Great to speak with you today.

Dr. Petrylak:
As always. And thank you all for joining us with this really exciting review of ASCO GU.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.
To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.