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Updates on Breast Cancer Treatment: Exploring CDK4/6 Inhibitors & Endocrine Therapy

Dr. Chalasani:
CDK4/6 inhibitors have made significant impact in the treatment of hormone receptor-positive/HER2-negative metastatic breast cancer. However, when there is disease progression on CDK4/6 inhibitor, there's always a question: Should we continue that or change to endocrine therapy backbone? Will that help MAINTAIN a response? While there were some observational individual institutional experiences and reports, we do not have any prospective clinical trial data to suggest what might be the next step. Today we are going to talk with—Sorry. Today we are going to talk with the lead investigator of the MAINTAIN trial to answer that question.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani. And joining me today to talk about the MAINTAIN trial is Dr. Kevin Kalinsky, Director of the Glenn Family Breast Center at the Winship Cancer Institute at Emory University.

Dr. Kalinsky, thanks for joining me today.

Dr. Kalinsky:
Thank you, Dr. Chalasani. It's nice to see you.

Dr. Chalasani:
So, to start us off, Dr. Kalinsky, can you just give us the background on what encouraged you and your study team members to evaluate or investigate continuation of CDK4/6 inhibitors?

Dr. Kalinsky:
Yeah. You know, I think we have seen that CDK4/6 inhibitors with endocrine therapy have really led to significant improvement for our patients with metastatic hormone receptor-positive/HER2-negative disease, and with ribociclib now, we've seen three large phase III randomized trials demonstrating an OS benefit with the combination of ribo plus endocrine therapy compared to endocrine therapy alone. And there had been preclinical and clinical data that had demonstrated that when, CDK4/6 inhibition is removed, there'll be less tumor proliferation so—and there have been some observational data demonstrating that this could potentially be a means of treating patients, meaning continuing a CDK4/6 inhibitor and switching the endocrine therapy at the time of CDK4/6 inhibitor progression. However, up to this point, there have been no randomized trials that had been reported that had shown whether this was a beneficial approach or not.

Dr. Chalasani:
Great. So, what were some of the primary objectives of the MAINTAIN trial?

Dr. Kalinsky:
The primary objective of the MAINTAIN trial was for patients who had had metastatic hormone receptor-positive/HER2-negative breast cancer that had a tumor that progressed on any CDK4/6 inhibitor and any endocrine therapy, measurable disease or not, that they were randomized in a one to one fashion to ribociclib plus fulvestrant versus ribociclib plus placebo, and the primary objective was to see if there was an improvement in progression-free survival favoring those who were randomized to the combination.

Dr. Chalasani:
Okay. Great. So, can you give us an overview on, the patients who were enrolled and some of the key results?

Dr. Kalinsky:
So, of the patients who were randomized in evaluable in the MAINTAIN trial, which was 119 participants, the patients were well

balanced between the arms. The only statistically significant difference is that there was a higher rate of patients who had visceral metastasis at diagnosis in the placebo arm compared to the ribociclib arm, but 2/3 of patients had visceral metastasis. Only nine percent of patients had prior chemotherapy. And, the vast majority of patients had received prior palbociclib as their CDK4/6 inhibitor. About 12 percent of patients received prior ribociclib, and there were only two patients who received prior abemaciclib, both of those in the ribociclib arm.

I will say that the population primarily represented an endocrine-sensitive population in that 2/3 of patients had been on their prior CDK4/6 inhibitor for more than 12 months, and all the patients received their prior CDK4/6 inhibitor in the metastatic setting. There were none who received it in the operable setting.

Dr. Chalasani:
Were there any patients who were treated with fulvestrant, anything prior to this study?

Dr. Kalinsky:
So the study was originally designed for fulvestrant-naive patients, and patients originally were randomized to fulvestrant plus ribociclib versus fulvestrant plus placebo, but in 2018, MAINTAIN accrued patients over 5.5 years, and for accrual purposes and also to reflect real world practice, we amended the protocol such that if you had had prior fulvestrant, that you could receive exemestane as the endocrine therapy backbone. However, you know, the 119 randomized and evaluable patients, 99 of those, so the vast majority of patients, received fulvestrant as their endocrine therapy backbone in MAINTAIN.

Dr. Chalasani:
All right. So, can you just comment on the key findings on the study?

Dr. Kalinsky:
So the, the MAINTAIN trial was a positive study. We saw that for the patients who were randomized to ribociclib plus fulvestrant, that there was an improvement in progression-free survival with a hazard ratio really that's similar to what we've seen in the CDK4/6 inhibitor-naive population of about 0.57 or so with the confidence interval that did not cross one and a statistically significant P value. We also looked at the PFS rate at six months and 12 months and saw that, and this was an exploratory analysis—but we saw the rate at six months in terms of not having had progression was about twice as high in the ribociclib arm compared to the placebo arm. When you look at 12 months, it was nearly triple.

Dr. Chalasani:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking with Dr. Kevin Kalinsky about hormone receptor-positive/HER2-negative metastatic breast cancer patients on the MAINTAIN trial.
So, I know the protocols are amended, and there's always concerns for accrual, but, you know, you did amend to make sure it reflects the real world practice, but can you comment on some of the limitations of the study?

Dr. Kalinsky:
Yeah. You know, we did do an exploratory analysis where we looked at those fulvestrant-alone patients because it was the majority of patients, about 86 percent of the patients, and the data looked exactly the same. Right? One of the limitations is that the exemestane-alone arm is a small population. I think other limitations, you know, this is a randomized phase II trial. This was not designed as a registration trial. This was really designed as a proof of principle study. I think a major limitation of the study is, despite our best efforts to enrich for patients who had prior ribociclib, the majority of patients had prior palbociclib, and, you know, there remains this question within the field of is—are the CDK4/6 inhibitors really all the same or not, so it's hard to know if the benefit that we're seeing was a post-palbo effect or just a post-CDK4/6 inhibitor effect.

I will say, when we look at the hazard ratio for those who had prior palbo or prior ribo, the hazard ratio looks exactly the same, but also, the confidence interval for the prior ribo is really quite wide, so just 14 patients. So I think that, you know, a major limitation is that this remains an unanswered question. However, there are other studies that we are waiting, like PACE and like the PARSIFAL study, which will really be palbo post palbo, and that will really help inform whether this is a CDK4/6 inhibitor effect or a ribo post-palbo sort of thing.

Dr. Chalasani:
Oh, absolutely. And if you focus on the clinical application for a moment, how do you see, you know—granted we are still waiting for some results—like how these study results could be applied in our clinical practice?

Dr. Kalinsky:
Well, what I will say, the safety profile for ribociclib plus endocrine therapy in this post-CDK4/6 inhibitor setting was the same really as what we saw in the CDK4/6 inhibitor-naive population. There were no surprises. I think, you know, this is the first randomized trial that has demonstrated a benefit of CDK4/6 inhibitor after a CDK4/6 inhibitor progression. I think that there are some individuals who were

already doing this in their practice, and I think for those individuals it justifies that use, also understanding that this study will not lead to a change in the label. I think that there are a number of ongoing questions, including like What's the best sequencing? Would it be CDK4/6 inhibitor after CDK4/6 inhibitor? What's the role? Like, what's the sequencing in terms of exemestane?
So I think that there are a number of outstanding questions, but I will also say that it is really quite nice to see that what we saw in preclinical findings and also in observational data turned out to be true in this randomized, placebo-controlled trial.

Dr. Chalasani:
Absolutely. So, before we close, Dr. Kalinsky, do you have any final thoughts or takeaways you would like to share with our audience?

Dr. Kalinsky:
I think that these data reflect that there is clinical activity of a CDK4/6 inhibitor after a CDK4/6 inhibitor and that this is a tolerable combination. I do think that we should await additional randomized phase II trials, the ones that I had mentioned, including the PARSIFAL trial and the PACE trial. And I will also say that there is an ongoing phase III randomized trial, the post-MONARCH study, that is looking at fulvestrant with or without abemaciclib for patients who have had tumors that have progressed in the metastatic setting but also if patients had received their CDK4/6 inhibitor in the adjuvant setting. So I think that that study will help in terms of being a definitive understanding of whether there's a role of CDK4/6 inhibitor post CDK4/6 inhibitor.

Dr. Chalasani:
Great.

Thanks for sharing those takeaways with us. As we close, I'd like to thank my guest, Dr. Kevin Kalinsky, for sharing his insights on the MAINTAIN trial. Dr. Kalinsky, it was great speaking with you.

Dr. Kalinsky:
Always a pleasure. Thank you.

Dr. Chalasani:
I'm Dr. Pavani Chalasani. To access this and other episodes in our series, visit reachmd.com/project-oncology where you can be Part of the Knowledge. Thanks for listening.