**Clinical Updates from San Antonio: HR+/HER2- Breast Cancer – CDK4/6 Inhibitors**

Rahul Gosain, MD: Good morning, everyone. I am Rahul Gosain.

Rohit Gosain, MD: And I am Rohit Gosain.

Rahul Gosain, MD: And we are oncology brothers. Today we're joined by Dr. Sara Tolaney, a world-renowned Medical Oncologist from the Dana-Farber Cancer Institute. In our discussion with her, we're hoping to focus on three important studies: updates on monarchE and MONARCH 2 and then the PACE study that were presented at the SABCS 2022, and how these studies should shape our current practice.

Let us welcome Dr. Sara Tolaney.

Sara Tolaney, MD, MPH: Oh thank you so much for having me.

Rohit Gosain, MD: Thank you for joining us, Dr. Tolaney. Let us begin our first study discussion, update on monarchE data. Dr. Tolaney, can you please walk us through the study design and inclusion criteria as we still continue to scratch our heads on who should receive abemaciclib adjuvant settings, especially when Ki-67 can be so subjective?

Sara Tolaney, MD, MPH: Yeah, it's an excellent question. So monarchE looked at the use of adjuvant abemaciclib and, specifically, it enrolled patients who have what we call high-risk hormone receptor positive breast cancer. So that meant they enrolled people into two different cohorts. Cohort 1 focused on patients who had four or more positive lymph nodes, or they could have one to three positive nodes; but if they had one to three positive nodes, they also had to have a large tumor, so tumor over 5 centimeters or it had to be high grade.

They had a second cohort that was specifically for those patients who had one to three positive nodes but didn't meet the tumor size or high-grade criteria of cohort 1, but rather had what we

call high Ki-67 defined as being greater than or equal to 20%. And so those patients then got randomized to get their adjuvant endocrine therapy with or without abemaciclib, with the abemaciclib being given for the first two years of that endocrine therapy. And so I can understand how the design can be a little confusing for what determines high risk.

But they did show that the use of adjuvant abemaciclib did significantly reduce recurrence, which was really important. And, in fact, at San Antonio this year, we actually, finally, have now seen data that looks at invasive disease-free survival at a timepoint when everyone has actually already completed their abemaciclib, which I think is really important because the prior cut points were when people were still on therapy and there was some concern about what's going to happen when people finish their treatment. But what we're seeing is that, in fact, the use of adjuvant abemaciclib reduces rates of recurrence by about a third, which I think is really very clinically meaningful and it translates into an absolute difference of about 6%. So really, really nice to see these data.

Rahul Gosain, MD: Thank you for going over that, Dr. Tolaney. Dr. Tolaney, we have a few agents approved in adjuvant settings – olaparib, capecitabine though not that often used in this patient population, and abemaciclib. In a patient with residual disease or a BRCA-positive patient with a hormone receptor-positive breast cancer, would you combine any of these drugs or consider them in a sequential use?

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Sara Tolaney, MD, MPH: So, one, I would not combine any of these drugs. There's not good safety data to do that, and so I would highly encourage people not to do that. What I would say, though, is if you do have a high-risk hormone receptor-positive patient who, let's say, has a

germline BRCA mutation, but also would meet high-risk eligibility for monarchE, I think the question comes up is what do you do? Are you going to give them olaparib or are you going to give them abemaciclib?

And, you know, I think with the OlympiAD data, we did see that use of a year of adjuvant olaparib did, in fact, improve not just invasive disease-free survival but actually, also had an overall survival benefit. And so knowing that, I do think the preference currently for a germline BRCA patient is to give one year of olaparib.

That being said, what if you had a patient who had like 10 positive lymph nodes or 15 positive nodes and was super, super high-risk? You know, I think the question is would you ever think about sequencing them? Would you give, for example, a year of olaparib and then, upon completion of that, would you then give two years of abemaciclib?

And I would say, in an extreme case like that with just incredibly high risk, certainly you could consider it. We do not have any data on this, but I think it's something one could consider doing.

Rahul Gosain, MD: Thank you for that. Coming back to monarchE data, the presenter stated 43% of the patients required dose reduction with abemaciclib. But despite the lower dose, patients still had ongoing benefit. In your clinical practice, how do you manage abemaciclib dosing and its side effects?

Sara Tolaney, MD, MPH: Yeah. I think that's a great question. So abemaciclib we start off dosing at 150 milligrams twice a day. And you do see the median onset to time of diarrhea is about eight days. So it is early, and it does mean it's really important to counsel your patients about potential GI toxicity, to instruct them how to use loperamide as needed, which I think works

quite well. But if they do run into issues with persistent grade 2 diarrhea, I do dose modify, and I do go from that 150 dose to 100; and I find that that dose modification actually makes a big difference in terms of tolerability.

So really important to monitor your patients closely. You will be seeing them every two weeks for the first two months anyway to be checking laboratory counts per the guidance. But I think, again, if you're running into issues with persistent grade 2 diarrhea, do think about dose modification.

Rohit Gosain, MD: Just to reiterate, quality of life in the scenario is extremely important when we are talking about adjuvant settings. And now to also explore best lowest dose versus highest tolerated dose, as we've also seen with babytam, low-dose tamoxifen. Now let us dive into our second study, same agent in discussion, abemaciclib, but in metastatic setting. Can you please walk us through the study design and updates from MONARCH 2?

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Sara Tolaney, MD, MPH: Yes. So MONARCH 2 was a study for patients who had metastatic hormone receptor-positive breast cancer. They were randomized to get fulvestrant with or without abemaciclib. These were patients who were all AI (aromatase inhibitor) refractory, so they had to have relapsed on or within a year of adjuvant AI or had to progress on an AI in the metastatic setting. And we had already seen data for both progression-free and overall survival from this study, which had shown what I think has been very consistent across the CDK4/6 inhibitors is that the progression-free survival is, in fact, about doubled. The hazard ratio is a little over .5 there, so I think that's been remarkable to see.

And I think this updated analysis was really interesting because now with five years of follow-up, you can see a little over 20% of patients are actually progression free. That's really intriguing to see that there are patients on this long, particularly in an AI refractory population. So I think I was very excited to see those data. And then they did update their overall survival data, which we already knew was statistically significant, and the findings in the hazard ratio are fairly consistent with what we had previously seen, so I think just solidifying the fact that use of abemaciclib with fulvestrant does, in fact, not just improve progression-free survival but does improve overall survival.

Rahul Gosain, MD: And as you've mentioned, we've seen a PFS (progression-free survival) benefit from all these CDK4/6 inhibitors. In your clinic in metastatic settings, how do you decide one agent over the other when you're talking to your patients?

Sara Tolaney, MD, MPH: Yeah. This is becoming a really challenging topic and conversation because the data have evolved a bit over time. You know, palbociclib was our first FDA approved CDK4/6 inhibitor. I think, truthfully, people just got really used to using it. It was first approved; it's very well tolerated. Usually the major side effect is neutropenia. We got used to managing it and that's what most people had been prescribing in the first-line setting given data from PALOMA-2.

We've now seen updated analyses across all of these CDK4/6 inhibitor trials and, unfortunately, we have yet to see a significant survival benefit with palbociclib in the metastatic setting. We've seen data from PALOMA-2 with regards to OS (overall survival) with no significant difference. We've also seen in PALOMA-3, the more pretreated population, that there was also no survival difference. And this stands in contrast to what we've now seen with regards to ribociclib and

abemaciclib in the metastatic setting where, in fact, all of the ribociclib metastatic trials have had an OS benefit, whether it's first line or second line. And with abemaciclib, we've seen survival benefit, as we just discussed, in the MONARCH 2 study in the fulvestrant arm. We have seen data also from MONARCH 3 in combination with an AI, which also suggests a trend towards OS; didn't quite meet statistical significance, but it was a very robust difference. So I think with the final analysis next year, I think we're likely to see statistically significant OS.

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And so I think these conflicting data have made us a little bit cautious about palbociclib thinking maybe there are some differences, in fact, between these CDK4/6 inhibitors. We don't know that for sure. There are definitely challenges with cross-trial comparisons and differences in patient populations, so I don't want to say this is definitive. But when you're seeing a patient in a clinic and they're sitting before you, and you're trying to make a decision about what to use in the first-line setting, currently the only agent we technically have a significant OS benefit for in the first line is ribociclib. So I think many people have started prescribing ribociclib when starting an AI for first-line patients.

Rohit Gosain, MD: So when utilizing ribociclib, managing the QTc interval prolongation, how do you go about scheduling the EKGs and do you space them out as they follow on from the therapy initiation?

Sara Tolaney, MD, MPH: Yeah. It's a good point. It is a unique toxicity relative to palbociclib and abemaciclib where we have seen QTc prolongation. And as you note, it is important to monitor for this, so it is recommended to get a QTc prior to starting the ribociclib at day 15, so 2 weeks

after starting your ribociclib and then at cycle 2, day 1. So in essence, every 2 weeks for the first month.

So, you know, we're oncologists. We're not used to checking EKGs regularly. It does put a new twist in our practice, so it is really important.

I would say the other thing that's very important is to make sure you look at their concomitant medications because there are agents that can prolong QTc. There are some drug/drug interactions because of that with prolongation, so you do need to think about that very carefully and make sure that if there's something you can tailor that they're also on to diminish issues with QTc prolongation to be cognizant of that.

Rohit Gosain, MD: Thank you. It's interesting how oncologists continue to wear more hats.

Sara Tolaney, MD, MPH: Exactly.

Rohit Gosain, MD: This is perfect transition to our last study, Phase II PACE study. Is there a benefit in continuing CDK4/6 inhibitor after progression? Dr. Tolaney, your thoughts on this study.

Sara Tolaney, MD, MPH: Yeah. And this is a really interesting question. You know, in other subtypes of breast cancer, we do continue a drug beyond progression. Like think about HER2-positive disease, right, you stop your chemo/trastuzumab and you move onto a different chemotherapy and trastuzumab. And so it does beg this question, should we think about when someone progresses on an AI and CDK, should we just switch out the endocrine backbone and continue the CDK4/6 inhibitor?

And we'd seen some data with regards to this question from the MAINTAIN trial when presented at ASCO earlier this year. And in that particular study they switched people, in

essence, from endocrine therapy palbociclib going to a different endocrine agent with ribociclib. And in that study, we did see that that switch resulted in an improvement in progression-free survival from a little over two months to a little over five months. So I think that was really intriguing. It was a randomized Phase II but did seem to suggest that if you switched endocrine backbone and switched the CDK to ribo, you would see benefit.

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But then at San Antonio this year, we saw data from the PACE study, actually run by my colleague Erica Mayer, and that trial was a little different because it was looking, in essence, at the question of continuation of palbociclib beyond palbociclib because everyone in the first-line setting, in essence, got an AI in palbociclib, then went on to fulvestrant with or without palbociclib. And, unfortunately, in this trial, there was no benefit to continuing palbo beyond palbo with just a switch in the endocrine backbone.

They did have a really interesting third arm, which was more just hypothesis generating, which looked at fulvestrant-palbociclib-avelumab, so adding, in fact, a PD-L1 inhibitor to the therapy. And there you did see the PFS was actually a lot longer. It was, in fact, double with what we saw with either fulvestrant or fulvestrant-palbo. So I think an interesting signal that we'll need further validation. But I do think PACE tells us we should not be continuing palbo beyond palbo at least at this time.

There are other studies ongoing we will get data from. PALMIRA is looking at this continuation of palbo question as well, so we're awaiting those data. And then there are lots of actually studies looking at abemaciclib post-CDK, post-MONARCH, EMBER trial, and these are Phase III trials so we will get more definitive data in the future. But, for now, I'd say there's a hint that

we could consider ribociclib post-palbociclib in select patients if you change out the endocrine backbone. I would say it's not definitive, but, in truth, I think, many of us do do this in practice if we see someone who's been on an upfront endocrine therapy and CDK4/6 for a really long time and they have a tiny bit of progression, and they don't have a ton of visceral disease, you're like, "Well I'll just switch out the endocrine backbone and, you know, give them another CDK4/6 inhibitor." So I think in those select patients, we can think about doing that.

Rahul Gosain, MD: Again, I think it comes back to the same thing that you mentioned, and we also saw a debate, are these all CDK4/6 inhibitors the same? Is switching better? Is it going to be continuing with the same thing? So exciting times and more to come on this story.

Rohit Gosain, MD: Dr. Tolaney, thank you so much for taking the time to discuss these practice-changing updates from San Antonio Breast Cancer Symposium with us today.

To recap, abemaciclib still remains the standard of care in high-risk adjuvant hormone-receptor positive breast cancer patients, and it is also approved in metastatic settings with an updated OS benefit.

Thanks so much Dr. Tolaney.

Sara Tolaney, MD, MPH: Oh, thank you so much.