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## Real-World CDK4/6 Inhibitor Patterns in HR+/HER2– Metastatic Breast Cancer

### Announcer:

You're listening to *Project Oncology* on ReachMD. This episode is brought to you in partnership with AstraZeneca and First Ascent Biomedical. Here's your host, Dr. Pavani Chalasani.

### Dr. Chalasani:

This is *Project Oncology* on ReachMD, and I'm Dr. Pavani Chalasani. Today, we'll be discussing a real-world study that looked at patient characteristics and treatment patterns with first-line palbociclib, ribociclib, and abemaciclib plus an aromatase inhibitor for hormone receptor-positive, HER2-negative metastatic breast cancer.

Joining me to share his insights is Dr. Adam Brufsky, who is a Professor of Medicine and the Associate Division Chief for the Division of Hematology and Oncology at the University of Pittsburgh School of Medicine in Pennsylvania. He's also a co-author of the study we'll be discussing today, which he presented at the 2025 ESMO Congress. Dr. Brufsky, welcome to the program.

### Dr. Brufsky:

Thank you, Dr. Chalasani. Thank you very much. Thanks for having me.

### Dr. Chalasani:

So to set the stage for our discussion, could you walk us through the current gaps in real-world research going on for metastatic breast cancer treatment?

### Dr. Brufsky:

Yeah, I think there's a bunch of different reasons. For a lot of the trials, we have the randomized clinical trials, but randomized trials are very controlled experiments. Usually, they're for label of a drug or label expansion of a drug, and so they have to be very, very controlled. And they don't really reflect the real world that we have, which is very messy, and we have people who, say, have a lot of comorbidity, especially women who are older. There's very little data in the randomized clinical trials of CDK4/6 inhibitors in women over 70, for example.

And so we need data from the real world to help inform us. The problem with real-world data, though, is that it can be biased. And so it's really hard to figure that out. There's a lot of missing data that we have when we try to evaluate real-world data and a lot of selection bias, so we have to figure out how to do that.

And I think there's a lot of really interesting statistical techniques that we use now to almost do a pseudo-clinical trial. And it's not a real randomized trial, but what we try to do is make the groups as close as possible to each other in terms of their baseline characteristics. And they often differ from the clinical trials. I mean, they tend to be older and they tend to have a lot more comorbidities than we ordinarily would see in a clinical trial.

In CDK4/6 inhibitors in particular, I think that we're very interested in trying to figure out if they all truly do behave the same way in the real world, because there were some differences in the clinical trials between them. And I think the efforts that we had been making initially were really to try to figure out, how do the three CDK4/6 inhibitors that we currently have available to us behave in the real world? And are there really any differences that we can find between them?

So that was the genesis of a lot of our research in this area.

### Dr. Chalasani:

Oh, yes, that is so correctly put, especially with the clinical trial data which has been presented versus real-world.

So with that in mind, how did your teams do the trial setup, and how did everything come together to address these gaps for the study that you presented?

**Dr. Brufsky:**

So what we did is an analysis called P-VERIFY—it was actually published in *ESMO Open* earlier this year—where we looked at about 9,000 women who had been receiving one of the three CDK4/6 inhibitors plus endocrine therapy—an aromatase inhibitor—as first-line therapy for ER-positive metastatic breast cancer. And the primary output of that trial was initially to look at the overall survival of all the patients, because, again, there had been differences that were postulated from the clinical trials data. And what we found in that initial analysis is that there was no overall survival difference with any of the three CDK4/6 inhibitors. There was about, probably, a little over 6,000 women who received palbociclib, about 1,500 who received ribociclib, and about 1,000 who received abemaciclib.

And the reason why there was a difference is that palbociclib was approved in the US in 2015, where I think ribo was approved in 2017 and abema in 2018. So there's going to be less follow-up with the other two CDK4/6 inhibitors, because they just haven't been around as long.

If you look at the publication and some of the presentations we did—I think we presented this at San Antonio last year also—is that the three groups were as balanced as we possibly could make them. They were a little more balanced because of their age, menopausal status, discontinuation rates, and use of subsequent therapy. And I think that we really tried to balance the patients as much as we could. And again, what we found is that the overall survival was the same in all three.

So what we did at ESMO actually extended that a little bit further. And what we did is we actually now looked at over 11,000 patients in the P-VERIFY analysis. And what we were doing in that case is that we were looking at the treatment duration—how long they were on all of the CDK4/6 inhibitors. And what we also did was look at the subsequent therapies that were given. And I think when you look at this trial, you can see the patients were very well balanced, I think, in all three arms. And this is now 11,000 patients. It's 8,000 patients who had palbociclib, about 2,000 that had ribo, and about 1,500 that had abema.

And so this is the beauty of big data and real-world data—that we're really getting really, really large groups. Very, very big groups. And when you start to really get big groups, I think you can really start to mitigate some claims here. I think, statistically, if you're going to have a trial maybe of a couple hundred per arm, in a real-world analysis, it gets a little tough with bias. But when you're talking now about 8,000, 2,000, and 1,500, I think you're really starting to get some really good data here.

I think the important thing we looked at were two things. Number one, we looked at time to discontinuation, which is kind of a surrogate treatment duration, a surrogate for progression-free survival. I mean, it includes changing for toxicity, for example, so it's not quite PFS. And then we looked at what people got afterwards, which was kind of helpful, because we had some really interesting kind of things that happened in the study.

So yeah, it was a really interesting trial, and I think it was a really interesting analysis that we did.

**Dr. Chalasani:**

Yeah, and I think there is strength in such numbers, especially when you're looking at that, because we do not get that in large, randomized trials. So it's really interesting that we are able to leverage some real-world data.

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking with Dr. Adam Brufsky about real-world patterns in hormone receptor-positive, HER2-negative metastatic breast cancer treatment.

So Dr. Brufsky, let's turn our attention now to the findings on your study. In terms of the duration, there was a difference in various CDK4/6 inhibitors. How would you interpret this data? And what factors do you think might be contributing to these differences?

**Dr. Brufsky:**

Yeah, I think what's really interesting is that the palbo seemed to be a little bit longer treatment duration, almost 21 months, versus like 18 with ribo and 17 with abema. And how could that be? Why is that? And then again, you look at the subsequent therapy, and more people who got palbo basically got chemo in another treatment, versus about 30 percent of the ribo and 40 percent in the abema.

But I think the interesting thing here is that, what do you think is happening? And I think that, basically, it has to do with the toxicity of the drugs. Again, when you look at treatment duration, you're not only looking at clinical progression, where you change treatment, but actually changes in the treatment for toxicity. And I think that in the real world, people are changing ribo and changing abema a little bit more than palbo.

And we talk to people. You probably see this in your own practice, and most oncologists probably see this too, but of the three, palbo's probably the best tolerated. We can give it to older women. We can give it to women with comorbidities, whereas with ribo, you got to be careful with QT prolongation, even though it's not really clinically significant. But you do have to be careful with drug-drug interaction with ribociclib and LFT abnormalities. With abema, you have to be careful with the GI toxicity. People tend to get diarrhea with abema. And so there are reasons why we're switching ribo and abema to palbo, which is what was happening here.

And I think we see this in many patients in the real world, and again, it's the real world—it's not a very controlled clinical trial where you couldn't switch to another CDK4/6. In some of the first-line trials, like MONALEESA, MONARCH, and even PALOMA, you couldn't switch. If you wanted to switch, you had to come off study. And so in the real world, you can switch. And I think that's what we're seeing.

**Dr. Chalasani:**

Now, another key finding was the difference in the use of subsequent therapy. What do you think stood out among those downstream treatment patterns and also explains those findings?

**Dr. Brufsky:**

Basically, when you look at ribo and abema, more patients switch to a different CDK4/6 in ribo and abema than with palbo. So that's, for example, 43 percent of the patients who are on first-line palbo and AI, for their subsequent therapy, got another CDK4/6. And a lot of that probably could have been abema. We had the data from post MONARCH, for example, that came out kind of during this trial, that had people switch to a different CDK. Some people thought, actually, during the time, they switched to ribo because the survival data from MONALEESA came out that found that maybe ribo had a potential survival advantage. So people switched to ribo. So that's probably the people from palbo who switched.

But I think that 54 percent of the ribociclib patients switched to something else, and I suspect it was the palbociclib because of, probably, LFT abnormalities. We don't have that in the data. We have that in the database, but we haven't looked at it with that much granularity. And same thing with the abema: they probably switched to a different CDK, either ribo or palbo, because they had diarrhea. And that's about 55 percent of the patients switched.

So you're talking about another 10 to 15 percent of the patients with the other two CDKs, other than palbo, who switched to a different CDK. And a lot of that probably was due to toxicity and tolerability. And I think that in future analyses, I think we do have the granularity in Flatiron to look at that, we just didn't look at it in this particular analysis.

**Dr. Chalasani:**

Yep, that's right. I mean, we do see that kind of following in the real world in all our practices, too.

With that, I just wanted to pivot to just a few other variables that you mentioned and evaluated in the study, which is age and premenopausal status. The study found that the median age of the palbociclib group was about two to three years greater than that of ribociclib and abemaciclib group and was similar to the premenopausal status, which was different. With that being said, how do you think this puts in together with what we see, what we practice, or the clinical data?

**Dr. Brufsky:**

Yeah, well, when you talk to a lot of oncologists, and again, I've talked about CDK4/6 inhibitors around the world, it's pretty much the same wherever you go. I think that most people feel that palbociclib is much better tolerated, and it's a lot easier to give to older patients. Again, the major side effect of palbo is basically neutropenia, and that's adjustable by dose reduction. And I think that a lot of women, for example, have comorbidities, like pre-existing cardiovascular disease, and so a lot of people don't like to use ribo then. And a lot of older women don't like having diarrhea, so we don't tend to use abema.

So I think that we see this anyway. It's kind of what's confirming what we all see in our practice, that a lot of us tend to use palbo in the women that are a little bit older. We actually have data. We have randomized data, for example, for ribociclib in premenopausal women, which we don't really have for abema or palbo. So that's a reason to give the ribociclib and aromatase inhibitor to younger women, because we have that randomized data from MONALEESA-7.

So it's kind of interesting just to see how this is happening. But this is kind of just reflective of US practice, where I think the feeling is that palbociclib is probably better tolerated than the other two, and we tend to give it to older women.

**Dr. Chalasani:**

Yeah, and again, I think the strength is also in the numbers with the real world that you're able to generate too.

With that, before we wrap up our program, Dr. Brufsky, just looking ahead, where do you see the greatest need for additional investigation in the metastatic breast cancer treatments? And where do you see the strength in this real-world data basis?

**Dr. Brufsky:**

Yeah, well, I think that what the real-world data right now has done for me is that—again, I may be a little bit different than a lot of my colleagues—at least in the metastatic setting, there is not a lot of difference between the three CDK4/6 inhibitors in terms of efficacy. And I think the decision really should be made for toxicity. I think that what we're going to see going forward, though, is what happens afterwards in the second line. And as we all know, based on ASCO and now ESMO and probably San Antonio this year, there's a lot of talk about practice-changing trials and what you do after CDK4/6 progression. And we're probably going to need real-world data to help us sort this out, because we're not going to get randomized head-to-head comparisons. And I think that, at least in metastatic breast cancer, that's where the next big push is going to be, is for us to try to understand what happens after.

I mean, this first thing, if you look at this poster, we do that kind of a little bit, but we don't really talk about in granular detail what the patients are getting, what their PFS is in the next line of therapy, how they do, or what the toxicities of those therapies are. I think that's going to be the next big push in the real world. And the beauty of Flatiron is in the numbers, and in the fact that we can now use AI to quickly figure this out, almost in real time—believe it or not. And I think it's going to be really interesting to see where this goes in the future.

**Dr. Chalasani:**

With those final insights in mind, I want to thank my guest, Dr. Adam Brufsky, for joining me to discuss how real-world treatment patterns vary across CDK4/6 inhibitors for hormone receptor-positive, HER2-negative metastatic breast cancer. Dr. Brufsky, it was great having you on the program.

**Dr. Brufsky:**

Thank you very much for having me.

**Announcer:**

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