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SERENA-6: Assessing Camizestrant's Impact in HR+/HER2- 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:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and today, we'll be looking at patient-reported outcomes from the SERENA-6 trial, which examined camizestrant in combination with a CDK 4/6 inhibitor for patients with hormone receptor-positive, HER2-negative advanced breast cancer whose tumors have developed ESR1 mutation while on first-line endocrine therapy. And joining me to share these findings is one of the study's co-authors, Dr. Erica Mayer. Not only is she a Breast Medical Oncologist at the Dana-Farber Cancer Institute in Boston, she's also the Director of Breast Cancer Clinical Research within the Dana-Farber Breast Oncology Program. She also presented this study at the 2025 ESMO Congress.

Dr. Mayer, it's great to have you with us.

Dr. Mayer:
Thank you so much for having me.

Dr. Chalasani:
Well, to provide some context for our discussion today, Dr. Mayer, can you give us an overview of the SERENA-6 trial and what was found with the combination of camizestrant and a CDK 4/6 inhibitor?

Dr. Mayer:
Yes. So, SERENA-6 is one of the most interesting and novel clinical trials that we've had in the breast cancer space over the past several years. This is a trial that was designated for metastatic hormone receptor-positive, HER2-negative breast cancer. We know that over time, when patients are receiving first-line therapy with aromatase inhibitor and CDK 4/6 inhibitor, cancers can develop resistance. And this eventually can lead to disease progression, meaning that a patient will need to leave their first-line therapy and move to second-line or subsequent lines of treatment.

One of the major mechanisms of resistance that can develop is a mutation in the estrogen receptor, called an ESR1 mutation. These mutations are very infrequently found when a cancer is initially diagnosed as metastatic, but they develop over time under pressure while being treated with an aromatase inhibitor. We also know that tumors that develop an ESR1 mutation may no longer be sensitive to treatment with an aromatase inhibitor and may be better suited to treatment with other types of endocrine therapies, for example, a SERD—a selective estrogen receptor degrader.

So, first of all, SERENA-6 had two steps: step one and step two. Eligible patients for step one had initiated first-line therapy for metastatic hormone receptor positive, HER2-negative breast cancer using an aromatase inhibitor and a CDK 4/6 inhibitor, and they had been stable on their therapy for at least six months. Then, they could enter step one. Step one was the screening step. So patients in step one had ctDNA drawn to look for ESR1 mutation, and this was done at times of restaging, so approximately four times a year. If the patient was found to have no ESR1 mutation, they just continued having the screening. If the patient was found to have an ESR1 mutation, then it was determined whether they had clinical progression or not based on their regular staging study. If that special opportunity was identified, where the mutation was found, but disease was clinically stable on scans, then they could enter step two of SERENA-6.

In step two, those patients were then randomized to switch their therapy from aromatase inhibitor to an oral SERD, a drug called camizestrant, and continue their CDK 4/6 inhibitor, and they had a placebo added—it was a placebo-controlled study. That would be the treatment arm, versus the control arm, where they stayed on their aromatase inhibitor, they continued their CDK 4/6 inhibitor, and they had a placebo added.

315 patients moved from step one to step two and were randomized to one of those two arms. Results from SERENA-6 were presented in a plenary session in ASCO 2025 and demonstrated that the patients who switched from aromatase inhibitor to the oral SERD camizestrant at the time of emergence of an ESR1 mutation but in the absence of clinical progression had a significant improvement in progression-free survival at 16 months versus nine months for those who remained on aromatase inhibitor and did not make the switch. And this had a hazard ratio of 0.44. So this was a positive finding and suggested that this could be a beneficial strategy for patients to make this switch at the time of emergence of a resistance mutation.

An important finding that was also presented at ASCO 2025 and supports the SERENA-6 approach was looking at global quality of health. And it demonstrated that the patients who made the switch had a substantial delay in clinically meaningful deterioration in Global Health Score Quality of Life. The patients who made the switch had almost a year and a half delay until deterioration in quality of life compared to patients who remained on aromatase inhibitor. And so this was a very important finding that supported the progression-free survival data that was presented at ASCO.

Dr. Chalasani:
With that segue, can you comment on the need to examine patient-reported outcomes in general and also for this study, and which outcomes were you specifically looking at?

Dr. Mayer:
Yes, so this year at ESMO 2025, we were able to present a much more detailed analysis of quality of life in the patients who had been enrolled in SERENA-6. There were two quality-of-life instruments used. One of them was the EORTC-QLQ-C30, which is an oncology-specific instrument, and then the EORTC-QLQ-BR23, which is a breast cancer-specific instrument. And there were key quality of life endpoints that were focused on, and this included time to deterioration in pain, in arm and breast symptoms, and in physical functioning.

So what was demonstrated and what we presented at ESMO this year was that the patients who made the switch to camizestrant when the ESR1 mutation was detected had a delayed time to deterioration in many of the facets of quality of life. This included patient-reported cancer symptoms, including pain, fatigue, and shortness of breath.

Additionally, we looked at patient functioning, and this included physical functioning, which includes things like being able to walk around, do errands, carry groceries, as well as other functioning skills, including role functioning—the ability to work and do daily activities—and emotional functioning—whether a patient felt anxious, depressed, or irritable. And across all of these key domains as well, patients who made the switch to camizestrant had a delayed deterioration. So, again, this suggests that from a patient's point of view, they are able to do more and they are feeling better when they make this early switch to camizestrant.

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. Erica Mayer about the SERENA-6 trial and its patient-reported outcome findings on camizestrant and a CDK 4/6 inhibitor in hormone receptor-positive, HER2-negative advanced breast cancer.

All right. So, continuing our discussion by talking about safety, which was assessed according to the Patient Global Impression of Treatment Tolerability Scale, the data show that at week two, 14 percent of the patients receiving camizestrant plus a CDK 4/6 inhibitor versus 18 percent receiving the aromatase inhibitor with this combination, with the CDK 4/6 inhibitor, reported being somewhat, quite a bit, or very much bothered by side effects.

From your perspective, what do these findings suggest about the response to camizestrant or the patient's perspective?

Dr. Mayer:
So I think these findings are important in that these numbers are very low, and it's basically our patients telling us that when they're receiving endocrine therapy, whether it's an aromatase inhibitor or a CDK 4/6 inhibitor, overall, these agents are not causing too many side effects, and the vast majority of patients are not very bothered by side effects from endocrine therapy. And I think that this is not surprising because we often consider endocrine therapies to be among our very well-tolerated medicines and the whole spectrum of different agents that we offer for breast cancer. It is interesting, though, that the numbers are slightly lower for camizestrant for being bothered by symptoms compared to aromatase inhibitor. And this is a signal that has been seen across the board for oral SERDs.

These are well-tolerated drugs, and in particular, they may cause less arthralgias compared to aromatase inhibitors.

Now, we do see some special side effects with oral SERDs that we note, but in general, tend to be very mild. Some oral SERDs can cause bradycardia, but this is not something that interferes with function. It doesn't interfere with patients' ability to exercise or do their activities. It's just something that could get picked up when patients come in and have vital signs done.

So, overall, this is a really very well-tolerated category of drugs.

Dr. Chalasani:
With these results in mind, I would like to talk about the practical applications of these results in the clinic. How do you see these outcomes influencing conversations between oncologists and patients, especially when it comes to making treatment decisions or a sequencing decision?

Dr. Mayer:
Well, I think one of the important aspects of SERENA-6 is the step one concept of the serial ctDNA screening. This is quite different than what we do in practice. Per ASCO guidance, we get NGS testing at time of diagnosis of metastatic disease, and then we are encouraged to repeat it at times of disease progression as mutations like ESR1 are kinetic—they change over time and they increase over time. And so we have to check for them at times of disease progression to see if an ESR1 mutation has emerged and we can consider an oral SERD.

What SERENA-6 is suggesting, however, is that we should be doing ctDNA testing for ESR1 much more frequently, not at times of progression, but at times of disease stability. And this is quite different than our usual paradigm. And so there certainly are implications if this paradigm is adopted in terms of how our clinics function and financial considerations. And so this really needs to be thought out.

However, I will add, as an investigator on SERENA-6 and having treated many patients in both step one and step two, I do think that our patients want this information. My patients in SERENA-6 were excited to have ctDNA done and to learn more about their cancer.

So, I think that partnering with patients and really talking about why this type of testing is important and how it could lead to offering medicines that are well tolerated and can make a difference for them, I would hope, could lead this to be broadly accepted by patients and providers. But it is definitely a new paradigm for us to consider in clinic and operationalizing it, and thinking about how this gets incorporated would be the next challenge for us.

Dr. Chalasani:
In addition to the testing, would you also, do you think, integrate the data from the patient-reported outcomes to review with them in clinic?

Dr. Mayer:
I think that's a great idea. And certainly when we talk about offering new therapies to patients, if I was presenting the SERENA-6 approach to a patient, I think it would be very appropriate to not only discuss that making these switches improves progression-free survival, but also to show patients that this improves quality of life, or, shall we say, prevents deterioration in quality of life in a very clinically meaningful way. And our goals when we're taking care of patients with metastatic breast cancer are to prolong survival and maintain quality of life. And I think the data from SERENA-6 is really touching on both of those goals. And so, that certainly should be shared with patients.

Dr. Chalasani:
As we come to the end of our program, Dr. Mayer, what key takeaway would you like our audience to remember from our discussion today?

Dr. Mayer:
I think that what we learned from SERENA-6 really reflects where we are right now in the breast cancer space, where we have really moved beyond an era where we just offered serial endocrine monotherapy and now we are offering combinations. And with the emergence of oral SERDs, I think it's very exciting to increasingly see data supporting combining oral SERDs with targeted agents, as that's where we are seeing our greatest benefits.

I also think that genomic testing—which, once upon a time, was really more of a research endeavor and seemed somewhat exotic—is now very much a standard-of-care approach globally for many of our patients. And so bringing these two things together, being able to learn more in real time about what's going on inside a cancer, understanding the resistance mechanisms, and then applying that data into treatment decisions and picking best possible treatments is really a very contemporary way to address metastatic breast cancer and really is our paradigm moving forward.

Dr. Chalasani:
With those final insights in mind, I want to thank my guest, Dr. Erica Mayer, for joining me to talk about how patient-reported outcomes from the SERENA-6 trial can help us understand the impact of hormone receptor-positive, HER2-negative advanced breast cancer treatment.

Dr. Mayer, it was great speaking with you today.

Dr. Mayer:
Thank you so much for having me.

Announcer:
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