Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/giredestrant-and-everolimus-in-hrher2-breast-cancer-insights-from-evera/36162/

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

Giredestrant and Everolimus in HR+/HER2- Breast Cancer: Insights from evERA

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 looking at the primary results of the phase 3 evERA Breast Cancer trial, which evaluated a combination of giredestrant and everolimus in patients with hormone receptor-positive, HER2-negative, advanced breast cancer who were previously treated with a CDK 4/6 inhibitor.

And joining me today in this discussion is Dr. Erica Mayer, who's a medical oncologist at the Dana-Farber Cancer Institute in Boston and the Director of Breast Cancer Clinical Research within the Dana-Farber Breast Oncology Program. She's also a co-author of the evERA Breast Cancer Study, which she presented at the 2025 ESMO Congress.

Dr. Mayer, welcome to the program.

Dr. Mayer:
Thank you so much for having me today. Thank you for the introduction.

Dr. Chalasani:
Now, I would like to start with some background, Dr. Mayer. What does the treatment landscape currently look like for hormone receptor-positive, HER2-negative advanced breast cancer patients following progression on a CDK 4/6 inhibitor, and what are some of the key challenges they face?

Dr. Mayer:
Yeah, so I think, as many people are aware, the most common subtype of breast cancer that we take care of is hormone receptor-positive, HER2-negative, so this is a large population of patients. For patients who develop metastatic disease, the global standard-of-care in the first-line setting is to offer endocrine therapy with a CDK 4/6 inhibitor. Fortunately, this is very effective and can provide disease control, often for a prolonged period of time. However, eventually, it is expected that the disease progresses, and why and how disease progresses can reflect a variety of different mechanisms, including development of resistance to one or both of the components.

Some of the mechanisms of resistance are reflected in the detection of mutations in the cancer itself, and this can include mutations in the estrogen receptor in the ESR1 mutation, or mutations in the PI3-kinase gene or pathway. And detecting mutations is very important to help consider what the subsequent lines of therapy are that should be considered for a patient.

In some ways, we're fortunate that there are many options post-CDK 4/6. However, it's important to understand the tumor biology and to also consider what the most effective treatment options post-CDK 4/6 inhibitor are. And so one of the greatest challenges we have is really trying to identify and optimize what the best treatment strategies are for patients that not only will provide excellent survival outcomes but also be well tolerated and maintain quality of life.

Dr. Chalasani:
With that background, let's turn to the evERA Breast Cancer trial. Can you tell us a little bit about this study, including the rationale for targeting both the estrogen receptor and the PI3K/AKT/mTOR pathways in this setting?

Dr. Mayer:
So evERA was designed specifically to help overcome resistance mechanisms post-CDK 4/6 inhibitor. As we know, both mutations in the estrogen receptor and mutations in the PI3-kinase/AKT pathway can be important in the post-CDK setting, so evERA was designed to try to target both of these resistance pathways.

evERA is a phase 3 randomized trial that enrolled patients who had all had prior CDK 4/6 inhibitor, had up to two prior lines of endocrine therapy for advanced disease, and no prior chemotherapy. Patients were randomized to receive a treatment arm using a medication called giredestrant, which is an oral SERD—that's selective estrogen receptor degrader—in combination with everolimus—an oral mTOR inhibitor—versus a standard-of-care arm, which was a provider-choice endocrine therapy and could be exemestane, fulvestrant, tamoxifen, plus the same everolimus.

So some important details of the study design: first of all, this is a combination versus a combination. Over the past few years, we've seen emerging data using oral SERDs in the post-CDK setting, and this has actually led to FDA approval of two oral SERDs: elacestrant, based on the EMERALD study, and imlunestrant, based on the EMBER-3 study. In both of these situations, these agents are targeted for patients whose cancers have developed an ESR1 mutation.

However, some of the most recent emerging data, including the combination arm of EMBER-3, has suggested that oral SERDs may provide their greatest benefit not as monotherapy, but when used as combination. So, very importantly, evERA is a combination of giredestrant with the mTOR inhibitor designed to target that PI3-kinase/AKT pathway.

So 373 patients were enrolled in evERA and randomized one-to-one to receive the oral SERD combination of giredestrant and everolimus or the standard-of-care option of endocrine therapy and everolimus, with co-primary endpoints looking at progression-free survival in the entire intention-to-treat population—the ITT population—and progression-free survival in the population of patients whose tumors were found to have an ESR1 mutation. And the trial was actually designed to enrich for this population of patients, with 55 percent of patients having ESR1 mutations. In general practice, we might consider that number to be more like 30 to 40 percent.

And what we demonstrated was that the patients who were randomized to receive giredestrant and everolimus had a statistically significant prolongation in progression-free survival with a median progression-free survival of almost 10 months. It was 9.99 months versus, in the comparator arm, 5.45 months. And this corresponded to a hazard ratio of 0.38, which was definitely statistically significant.

Importantly, these results were consistent whether a patient in the control arm was receiving exemestane and everolimus or fulvestrant and everolimus. This was in the ESR1-mutant population. In the ITT population, the co-primary endpoint, this was also a positive study with a prolongation to 8.77 months with giredestrant versus 5.49 months in the control arm with a hazard ratio 0.56.

So evERA was a positive study. The combination of the oral SERD, giredestrant, and everolimus was superior to standard-of-care endocrine therapy and everolimus in the ITT population in all patients and in the population of patients, 55 percent, whose tumors had an ESR1 mutation.

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 potential of giredestrant plus everolimus for treating hormone receptor-positive, HER2-negative advanced breast cancer post-CDK 4/6 inhibitor therapy.

Thank you for that clear, detailed review about the results, Dr. Mayer. With all that being said—with the review about efficacy—what's your take on the clinical significance of these results and the potential value of the combination for different patient groups, like patients with tumors which harbor the ESR1 mutations versus other biomarkers defined in the broader patient population?

Dr. Mayer:
Well, in a subgroup analysis that was presented at ESMO, the benefit of giredestrant was quite consistent across all of the key subgroups, and this included patients with visceral disease, patients with bone-only disease, patients who previously had fulvestrant, and also patients with and without PI3-kinase mutations in their cancer.

This year at San Antonio in December 2025, we will present an additional subgroup analysis looking at prior treatments and other clinically relevant subgroups in relationship to outcomes with giredestrant.

I should also add that giredestrant is very well tolerated. The major toxicities that were seen in the study reflect the individual study components, but primarily reflect everolimus, which is a drug that we know does have some risks of side effects. The most common side effects seen were stomatitis, diarrhea, nausea, and fatigue. These are all things we see with everolimus. Notably, the majority of

patients were using steroid mouthwash, which is strongly recommended when patients initiate everolimus based on the SWISH study. But there was no apparent contribution of adverse events from giredestrant over those seen with standard-of-care endocrine therapy. And rates of discontinuation of either giredestrant or endocrine therapy were quite low in both arms.

I will note there were a small number of cases of mild bradycardia—grade 1 bradycardia—which can be seen with some oral SERDs, and this was very mild. It did not cause any symptoms in patients. There were no subsequent complications, but it is something that is monitored for.

Another side effect of oral SERDs that is sometimes seen is something called photopsia, which can be flashing lights or after-images in low light conditions. This was not seen in evERA.

So, overall, I think these results are very exciting as we are definitely seeing a lot of activity from this combination. It is very well tolerated, particularly the oral SERD, and we're seeing activity not only in the ESR1-mutant population, but also in the ITT population. And so I'm hopeful that this may lead to a new treatment option that would be available for patients post-CDK 4/6 inhibitor.

Dr. Chalasani:
Taking all of this together, how do you think these results position the combination of giredestrant plus everolimus within the current treatment paradigm? And are there any further research questions which are posed by the evERA breast cancer study that are going to be explored further?

Dr. Mayer:
Yes. So, first of all, regarding further research questions, as I mentioned, we will be looking at subgroup analysis and additional key subgroups, including patients with dual mutations—both ESR1 mutation and PI3-kinase mutation—which is a small but very interesting category of patients. And also, we'll be looking at outcomes based on duration of prior treatments, for example, duration of prior CDK 4/6 inhibitor and treatment selection prior to study entry.

I should also add that overall survival data in evERA remains immature, however, it is trending in a very favorable way with hazard ratios that are very supportive of the agent. Again, this data is immature, but we need further follow-up on overall survival to see if there will eventually be an overall survival benefit from using the evERA regimen. So, there's a lot more to come from this study, in terms of further follow-up.

But I think a key point here, beyond evERA and just in general for breast cancer, is we really need to know whether people's cancers have these actionable mutations. And it is currently standard-of-care that when a patient is diagnosed with metastatic breast cancer that we obtain genomic sequencing, typically on tumor tissue if there's a biopsy, and/or by ctDNA. But moving forward, at times of disease progression, we should also be evaluating to see if there's emergence of an ESR1 mutation, as this is something that changes over time. And it needs to be looked for at times of progression when patients are receiving endocrine therapy. And this is best done through ctDNA. This is part of current ASCO guidance. And so being able to do that will really help identify, at a moment when patients are progressing, what the available treatment options are and what the best available treatment options are.

So, I would strongly encourage people to be really meticulous about making sure that their patients are having NGS testing done at the right time points and that that information is available when treatment decisions are being made.

Dr. Chalasani:
Before we wrap up our program, Dr. Mayer, do you have any final thoughts you'd like to share with our audience today?

Dr. Mayer:
I would just add that it's a really exciting time in the management of metastatic hormone receptor-positive breast cancer. I think that many of us feel like every few weeks we have a new drug approval or a new press release about a positive trial, and it kind of keeps your head spinning trying to figure out what the current treatments are. And so, on the one hand, it can feel a little bit confusing and overwhelming, but on the other hand, these are all treatment advances that hopefully will be benefiting our patients. So, ultimately, it's very exciting.

I do think, again, a big message from evERA which we will see carried forward in the future is the importance of combination treatments, and that, both in our clinical practice as well as in clinical trial design, we should no longer be offering endocrine monotherapy to our patients with metastatic disease, with rare exception, of course. But we consistently see that offering a combination of an endocrine agent and a targeted partner provides superior outcomes in terms of efficacy, and so when we're making these treatment decisions, we really need to prioritize combinations as our preferred treatment strategies.

Dr. Chalasani:
With those final comments towards the end of our program, I would like to thank my guest, Dr. Erica Mayer, for joining me to discuss

how the primary findings from evERA Breast Cancer can inform the management of hormone receptor positive, HER2-negative advanced breast cancer after CDK 4/6 inhibitor treatment.

Dr. Mayer, thanks for being here today.

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

Announcer:
You've been listening to *Project Oncology*, and this episode was brought to you in partnership with AstraZeneca and First Ascent Biomedical. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!