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Exploring Elacestrant Combinations for ER+/HER2- mBC: Early Data from ELEVATE

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Stemline Therapeutics. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and today I'm joined by Dr. Virginia Kaklamani to discuss updated safety and preliminary efficacy data for various elacestrant combinations from the ongoing ELEVATE study, which was recently presented at ASCO 2025. Dr. Kaklamani is a Professor of Medicine in the Division of Hematology and Oncology at the University of Texas Health Science Center at San Antonio.

Dr. Kaklamani, welcome to the program.

Dr. Kaklamani:
Thank you for having me.

Dr. Turck:
Well, let's start with the rationale behind the ELEVATE study. What unmet needs does this trial aim to address in patients with advanced ER-positive HER2-negative breast cancer—particularly in those with metastatic disease?

Dr. Kaklamani:
So patients with metastatic HR-positive breast cancer are usually given a CDK4/6 inhibitor as primary therapy for their breast cancer. But we know that within a couple of years, these cancers become resistant to the endocrine therapy, and the mechanisms of resistance are very complex. They can include the development of ESR1 mutations, which are mutations in the estrogen receptor. They can include upregulation of the PI3 kinase pathway, which includes PI3 kinase, AKT, mTOR, and so forth.

And so we are able to address each one of these pathways by themselves. For example, elacestrant, which is an oral selective estrogen receptor degrader, has been approved for tumors that have developed these ESR1 mutations and is a good treatment for these tumors. We know that medications such as alpelisib, capivasertib, and everolimus have also been developed to address tumors that are becoming estrogen resistant because of mutations in the AKT pathway, the mTOR pathway, the PI3 kinase pathway, and so forth.

But we also know that these mechanisms coexist, and so trying to address one pathway doesn't necessarily give us as good efficacy as if we try to target two or three pathways at the same time. So instead of using monotherapies, it would be nice to use combination therapies, and that's why the ELEVATE trial is looking at combining elacestrant with several other drugs that we use to treat metastatic breast cancer, such as CDK4/6 inhibitors, everolimus, alpelisib, capivasertib, and so forth.

So the power of ELEVATE is finding the right combination dose but also giving us some preliminary efficacy of these combinations so that we know which ones can then move on to larger phase 3 clinical trials.

Dr. Turck:
And building on that, would you explain why some of the specific combinations of agents the ELEVATE study examined could be useful in this patient population?

Dr. Kaklamani:

Absolutely. So let's take, for example, the CDK4/6 inhibitors. CDK4/6 inhibitors are used in the first line, but we also know that we can sequence them. If patients have received one CDK4/6 inhibitor in the first line, they could receive a second one in the second line.

So by combining elacestrant with that CDK4/6 inhibitor, we could get initial efficacy in what we would expect the first-line combination to look like, but also be able to find out if we sequence a CDK4/6 inhibitor and give it in that second line, and we just change our endocrine therapy to elacestrant, what that is efficacy going to look like. And again, toxicity is very important as well. When we look at tumors that are co-mutated with ESR1 and have a mutation in the AKT pathway and we combine capivasertib with elacestrant, targeting both pathways at the same time, how much better can the efficacy be?

So those are good questions that we need small studies to answer before we go into larger phase 3 trials that are going to take time to accrue and quite some time to get results.

Dr. Turck:
Now, what can you tell us about the design objectives and key eligibility criteria for the ELEVATE study?

Dr. Kaklamani:
The ELEVATE study is a phase 1b/2 clinical trial. So that means we have the phase 1b component, which is a dose-finding component, and we are combining elacestrant with, again, CDK4/6 inhibitors, alpelisib, everolimus, and capivasertib, and we're establishing what the next phase dose would be. And then the phase 2 dose-expansion study is where we are including more patients in the key cohorts that we think are worth pursuing in a larger patient population.

Now, when we look at the inclusion criteria, a lot of times, they depend on which phase we are under. But the main inclusion criteria are women or men that are over the age of 18 who have metastatic ER-positive, HER2-negative breast cancer. They must have had measurable lesions, good performance status, and then have received a prior CDK4/6 inhibitor in many cases, but not all cases. Patients that are going to be on the capivasertib arm should also have AKT alterations, and so forth.

So these criteria changed depending on what cohort the patients were on, but the main criteria are patients who have metastatic HR-positive, HER2-negative breast cancer who are eligible for treatment with elacestrant.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Virginia Kaklamani about early data from the ELEVATE study, which examined elacestrant-based combination regimens used after endocrine therapy and CDK4/6 inhibitors in patients with ER-positive, HER2-negative advanced or metastatic breast cancer.

So Dr. Kaklamani, let's dive into the findings from the study. What are the latest updates on efficacy from the phase 1b portion?

Dr. Kaklamani:
So the latest update in efficacy has to do with two of the combinations. One is the combination of elacestrant and everolimus. And here we can see that the median progression-free survival was 8.3 months, which is pretty impressive, especially because on this arm, patients had previously received the CDK4/6 inhibitor. Also, when we're looking at response rate, it's pretty solid at 25 percent, which, again, is something that we would expect with this combination in patients who have HR-positive, HER2-negative metastatic breast cancer.

The second update comes from the combination of elacestrant and ribociclib. The ribociclib dose that we are going to be looking at for further evaluation is going to be the 400 milligram dose. The median progression-free survival was 7.8 months, which is more than what we've seen with some of the clinical trials where we're sequencing CDK4/6 inhibitors and giving one CDK4/6 inhibitor in the first line and then a second one in the second line.

So these were pretty solid, encouraging data. I think it's telling us that we should pursue these combinations in a larger cohort of patients and then see how we can design larger phase 3 trials with at least one of these combinations that will change our standard-of-care therapy.

Dr. Turck:
And what can you tell us about the latest safety data?

Dr. Kaklamani:
So the other important thing as far as safety is the fact that the combinations did not really provide us with any toxicities that were a surprise to us. There were some minor toxicities with elacestrant. Elacestrant typically can have some GI toxicity, but relatively mild—usually grade 1 and maybe grade 2.

The CDK4/6 inhibitors and everolimus can have their own toxicities, but they were not accentuated with the addition of elacestrant. The dose for everolimus that should be pursued in a larger trial would be the 7.5 milligram daily dose instead of the 10 milligram dose. So that is something also important for us to recognize, and it's unclear why, but several of the trials in other tumor types, as well as breast cancer, have looked at different doses of everolimus, including 5 milligram daily doses.

Dr. Turck:
So given these findings, Dr. Kaklamani, what are the key takeaways? And what should we be on the lookout for as the ELEVATE study continues?

Dr. Kaklamani:
So the key takeaway is that combining elacestrant with several of these targeted agents is producing a very solid toxicity profile, but also a very solid efficacy profile, with median progression-free survivals that are surpassing seven and a half months. And so this is extremely encouraging for this trial, but also for future trials.

I think that in the future, when we're starting to look at how we're going to be giving endocrine therapy post-CDK4/6 inhibitors, combination approaches seem to be gaining momentum. And again, the reason for that is because we're addressing more than one pathway of resistance at the same time.

So we are going to need larger trials that are going to help show us that these combination therapies are better than single-agent or older combination therapies. But the use of elacestrant in combination with these targeted agents is providing very solid results as far as both efficacy and toxicity.

Dr. Turck:
Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. Virginia Kaklamani, for joining me to discuss early data from the ELEVATE study.

Dr. Kaklamani, it was great having you on the program.

Dr. Kaklamani:
Thank you so much.

Announcer:
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