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Exploring Combination Treatment in ER+/HER2- Breast Cancer

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

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and today I'm joined by Dr. Wassim McHayleh, who serves as the Medical Director of Breast Oncology at AdventHealth Cancer Institute and an Associate Professor of Medicine at the University of Central Florida. Together, we'll review new findings from ELEVATE, an ongoing phase 1b and 2 open-label umbrella study evaluating elacestrant-based combination approaches in patients with ER-positive, HER2-negative advanced breast cancer. Specifically, we'll focus on the results of elacestrant in combination with capivasertib, which were presented at the 2026 American Society of Clinical Oncology Annual Meeting.

Dr. McHayleh, thanks for being here today.

Dr. McHayleh:
Thank you for having me.

Dr. Turck:
Well, Dr. McHayleh, let's start with some context. For patients with ER-positive, HER2-negative advanced breast cancer who have progressed on endocrine therapy and CDK4/6 inhibition, what are the key resistance mechanisms at play? And what was the scientific rationale for evaluating elacestrant in combination with capivasertib?

Dr. McHayleh:
I think this is a very important question because if we start from the first line, patients do very well on our current standard aromatase inhibitor plus CDK4/6 inhibitor with a median PFS ranging anywhere from 24 to 28 months. But then, at the time of the progression, we try to determine the driver of the progression. Where is the resistance happening?

One of the mechanisms of resistance is the development of an *ESR1* mutation in about 40 to 50 percent of the patients. Another mechanism of resistance would be an alteration of the PI3 kinase pathway, or what we call the PAM pathway, including the *AKT* and *PTEN* alterations. And this pathway could be a mutation existing at the time of the diagnosis, while the *ESR1* mutation could be an acquired mutation.

As clinicians, whenever progression happens, we are faced with a big dilemma, especially in the presence of more than one mutation: what's driving the resistance, and what is the smartest way to treat this patient? What should we target?

Dr. Turck:
Now, with that in mind, would you briefly walk us through the ELEVATE study design and the patient population included in the capivasertib cohort?

Dr. McHayleh:
So ELEVATE is a Phase 1b trial. It's a multi-cohort trial testing the combinations of elacestrant with multiple targeted therapies, including everolimus, ribociclib, and capivasertib. And our focus in the ASCO meeting in 2026 was to present this particular cohort. The goal of this trial is to discuss the safety as well as the observed efficacy in this trial, and then recommend the safe phase 2 dose for the phase 2 clinical trial.

Dr. Turck:
Turning now to the efficacy data, the investigators reported a median progression-free survival of 11.3 months with elacestrant and capivasertib at the recommended phase two dose. How do you interpret that finding, especially given the characteristics of patients in this cohort?

Dr. McHayleh:
That's an impressive initial number, even though we're looking at a small number of patients. And when we look at targeting each of the mutations separately, we see that the combination is very effective and the numbers are impressive and exceed each one of them separately. We're not trying to cross-compare trials, but as an initial impression, an 11.3 months median PFS, in my opinion, is a very impressive number in this setting.

Dr. Turck:
Now, beyond progression-free survival, the data showed a disease control rate of 88.9 percent and a clinical benefit rate of 66.7 percent at 24 weeks follow-up. When you consider those findings together, what do they tell us about overall disease control and durability of benefit with this regimen?

Dr. McHayleh:
Yeah, even though when we look at the efficacy, we didn't see any complete responses, in the setting of an HR-positive breast cancer, I consider stable disease a valid endpoint, especially when the patients have minimal disease burden or they're asymptomatic with no organ compromise. So when you add the stable disease and the partial responses, the numbers are impressive, and those are durable responses.

And I think it supports the use of this combination in the appropriate patients.

Having said that, I think we need to wait for additional efficacy data that will be presented in the phase 2 trial. This is a larger number of patients—60 patients. The trial completed accrual, and we're anticipating the results in the near future.

Dr. Turck:
Well, Dr. McHayleh, what can you tell us that was notable about the patient baseline characteristics in this study?

Dr. McHayleh:
In this particular cohort, we included 31 patients. The patients should have a *PIK3CA* alteration—or an alteration in this pathway, *PIK3CA* mutation being the most common—but we allowed *AKT* and *PTEN* alterations. So 100 percent of the patients had one of those. 55 percent of the patients had co-mutations, meaning an *ESR1* plus a *PIK3CA* alteration.

All patients were females. Most patients had been exposed to a CDK4/6 inhibitor, and over 40 percent of the patients had previous exposure to fulvestrant. Now, when we look at the previous CDK4/6 exposure, ribociclib was the most commonly used, palbociclib being the second most commonly used CDK4/6 inhibitor in the previous setting.

Dr. Turck:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Wassim McHayleh about new findings from the ELEVATE trial involving elacestrant and capivasertib in ER-positive, HER2-negative advanced breast cancer.

So, Dr. McHayleh, taking a closer look at the response data, researchers observed an objective response rate of 33.3 percent with all objective responses occurring in patients whose tumors harbored both *ESR1* and *PIK3CA* mutations. What does that tell us about the crosstalk between endocrine and PI3K/AKT signaling, and why might the simultaneous targeting of multiple nodes along these pathways matter, even in wild-type tumors?

Dr. McHayleh:
When we look at the responses, we see that most objective responses happened in patients harboring both mutations. We also saw that some of the stable diseases were seen in patients carrying one of the mutations—so the *PIK3CA* mutation and the *ESR1* wild-type patients—and those were also durable responses.

So at this point, I don't think I'm ready to draw a conclusion that we must target both mutations. But I think the conclusion from this study is, number one, this is a safe combination. It helped us determine the right dose to combine those two agents and confirm that this is a safe combination to utilize in patients, to be determined in the future based on subsequent trials, phase two and beyond, the efficacy compared to other combinations and what would be the best approach. But based on this study, I believe that we established that the combination of capivasertib with elacestrant is a safe combination. We determined the right dosing. We learned that the PKs are

appropriate when those drugs are combined.

Dr. Turck:
Now, the safety and tolerability profile at the recommended phase 2 dose is an important part of these findings. Would you walk us through what that safety data looked like and what the findings tell us about managing this regimen, particularly when it comes to capivasertib dosing?

Dr. McHayleh:
Well, one of the objectives of this trial was to determine the appropriate dose combination. So there were three cohorts in this study. One cohort included elacestrant at the dose of 258 milligrams and capivasertib 320 milligrams. The second cohort included elacestrant at the dose of 345 milligrams and capivasertib at 320 milligrams. And then the third cohort included elacestrant at 345 milligrams and capivasertib at 400 milligrams.

And what we found that in cohort three, there was actually increased skin and increased hyperglycemia grade three toxicities. So we saw, actually, 27 percent grade three and four rash in this particular cohort. We saw also saw 20 percent grade three and four hyperglycemia. So this was not actually a recommended dose.

What we learned is the safest combination was actually cohort two, where elacestrant was given at the dose of 345 milligrams and capivasertib at 320 twice a day, four days on, three days off. And in this particular cohort, there were no grade three or four skin toxicities or hyperglycemia. There was only one case of grade three and four diarrhea and one case of grade three or four fatigue, and this was determined to be the recommended phase two dose.

Dr. Turck:
And finally, Dr. McHayleh, pharmacokinetic analyses found no meaningful interaction between elacestrant and capivasertib. So when you consider those findings alongside everything we've discussed—the efficacy outcomes, the durability of response, the biomarker findings, and the safety and tolerability profile—what are the key takeaways from ELEVATE, and what questions remain to be answered?

Dr. McHayleh:
The pharmacokinetic assessment was actually one of the secondary objectives here, and the study confirmed that when we used the combination, the co-administration had no significant impact on the elacestrant or capivasertib exposure. So they both reached the appropriate therapeutic levels, and that was a very important finding.

So the conclusion of this study is that when we have coexisting *ESR1* and *PIK3CA* mutations, combining elacestrant with capivasertib may provide an all-oral treatment option that can simultaneously target dual genomic drivers as a novel treatment option. It helped us determine the appropriate dosing for this combination and establish the combination as a safe option awaiting additional data to be presented in future meetings. I always encourage my colleagues to enroll patients in clinical trials when available, and more to come. It's an exciting time for our patients.

Dr. Turck:
Great insights for us to think on as we come to the end of today's program. And I want to thank my guest, Dr. Wassim McHayleh, for joining me to discuss these new findings on combination treatment with elacestrant and capivasertib in ER-positive, HER2-negative advanced breast cancer.

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

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

Announcer:
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