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Poster Pearl: Treating ER+/HER2- mBC with Elacestrant and Endocrine Therapy

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

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Today, I'm joined by Dr. Hope Rugo to discuss the preliminary findings from the ELEVATE study, which is currently evaluating the efficacy and safety of elacestrant in combination with endocrine therapy for ER+/HER2- locally advanced or metastatic breast cancer. In addition to being the lead study author, Dr. Rugo is a Professor of Medicine and the Winterhoff Distinguished Professor of Breast Oncology at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center. She's also the Director of Breast Oncology and Clinical Trials Education there. Dr. Rugo, welcome to the program.

Dr. Rugo:
Thank you so much.

Dr. Turck:
Well, to start us off, what's the background and rationale behind the ELEVATE study?

Dr. Rugo:
Well, I think that as we have all seen, when we're looking at novel endocrine therapies now as opposed to the recent past, the question is not so much can we find one better endocrine therapy than another, although this is a very important area of research and an important advance for our patients. But it's how do these agents play in the sandbox? In other words, how can we combine our novel agents with the targeted therapies that we now are using in sequential lines of treatment for patients with metastatic ER+/HER2- breast cancer?

Dr. Turck:
And what can you tell us about how the ELEVATE study was designed?

Dr. Rugo:
The goal of the ELEVATE trial was to understand the safety and efficacy of elacestrant in combination with various targeted agents in patients with metastatic breast cancer. So we didn't require that patients have ESR1 mutations. We did want to know that patients had received the prior standard-of-care endocrine therapy and CDK 4/6 inhibitors in the first-line setting. And because we're evaluating response, we also wanted patients to have either a measurable lesion or a mainly lytic bone lesion that we could assess for response. And then the goal of this trial was to first evaluate in a phase 1B design how we could combine elacestrant with a variety of targeted therapies, including everolimus, palbociclib, ribociclib, and alpelisib.

Dr. Turck:
For those who tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking to Dr. Hope Rugo about the preliminary data from ELEVATE, which is a phase 1b/2 open-label study.

So, Dr. Rugo, now that we know how the study was designed, let's shift over to some of the key findings you've seen so far. What could you tell us about the efficacy of elacestrant being combined with other forms of targeted therapy?

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Dr. Rugo:
We looked at elacestrant and everolimus, and we had a total of 18 evaluable patients in phase 1B. There, we saw an overall response rate of 22 percent, all of which were patients who had previously been treated with endocrine therapy and two lines of prior treatment, and we saw a clinical benefit rate at 24 weeks of 72 percent in the 18 evaluable patients. We also, of course, looked at these patients in terms of the toxicity, as I mentioned, as our primary goal, and what we saw was no difference in the toxicity that we would have expected in these patients if you were to give everolimus, for example, in standard combination with exemestane or fulvestrant that's been studied in phase 2 trials. We ended up using a dose at our RP2D, a randomized phase 2 dose, of 345 milligrams of elacestrant and 7.5 milligrams of everolimus.

And then I mentioned that we also looked at ribociclib in combination. There, we had four different cohorts. Again, we're looking at escalating doses in these patients. And we looked at the responses as well. This data is still quite early, but we have toxicity data in these patients with ribociclib. The combination is very well tolerated. And we're still looking at whether or not we want to increase the dose of elacestrant or decrease the dose of ribociclib in order to make this most tolerable for the pretreated patients. So our last cohort was elacestrant at 172 milligrams and ribociclib had 600 milligrams. But of course, as we are going forward, we've been able to increase the elacestrant dose. And I think that it's interesting now that we have the NATALIE data, most patients even in the metastatic setting are receiving ribociclib at 400 milligrams rather than 600 when they're not getting it in the first-line setting.

We also looked at elacestrant and alpelisib. Now this was complicated by the toxicity that we see with alpelisib anyway. So at the time, we looked at just two cohorts. The last cohort was alpelisib at 200 milligrams at dose reduction and elacestrant at 258 milligrams. And again, we saw the primary issues of hyperglycemia and rash in 2 out of the 6 patients that we looked at. So there's ongoing conversations about looking at elacestrant and alpelisib at different dose levels.

And then, of course, palbociclib was studied in addition, and in our last cohort, we were able to look at elacestrant 345 milligrams and full-dose palbociclib 125 milligrams. In that group, the combination is also very well tolerated, which was really encouraging. And, of course, as we looked at the combinations in terms of the efficacy, we have efficacy primarily in the alpelisib and everolimus cohort. I mentioned the efficacy in the everolimus cohort already, and in the alpelisib cohort, we also saw nice responses, but the number of patients is very small.

Dr. Turck:
And are there any other key safety findings that you observed in the ELEVATE study so far?

Dr. Rugo:
I think when we look at safety, we really have only seen safety issues at higher grades that you would see associated with the targeted agent. So, for example, with palbociclib, we saw neutropenia, and with ribociclib, we saw neutropenia. These are small numbers in phase 1B, so we haven't seen other toxicities like liver enzyme elevations. With alpelisib, we saw rash and hyperglycemia, and then with the everolimus group, we saw stomatitis. But again, some of the patients don't use the steroid mouthwash we piloted up front, which really prevents any grade 3 stomatitis. And then one patient had mild pneumonitis. But these were all attributed to the targeted agent.

Interestingly, the elacestrant, even when you give it in combination, was very well tolerated. These patients did very well. And if you look at all the cohorts, you just aren't seeing much in the way of toxicity from elacestrant other than what you would expect as a single agent—low grade nausea, a little bit of diarrhea—again, the other toxicities primarily associated with the targeted agent.

Dr. Turck:
Now I know it's still just a little bit early, but how might this research help to begin to address patients' unmet needs?

Dr. Rugo:
I think it's a really critical area of research. We've definitely spoken with our feet that we don't want to use single-agent endocrine therapy in the second- and greater-line setting. And the standard of care in international guidelines is to use CDK 4/6 inhibitors, preferably in the first-line setting, although certainly in some patients, second line is appropriate. I generally always give a CDK 4/6 inhibitor in the first-line setting, so if there aren't competing morbidities or issues associated with using a CDK 4/6 inhibitor, that's what we are doing at present.

So when we get to the second-line and third-line setting, current randomized trials, with a few exceptions, have suggested that the overall response, but importantly, progression-free survival, with single-agent fulvestrant is very short, in the range of a couple of months. Again, there are some notable exceptions—a couple of trials that showed better PFS with fulvestrant—and I think if you select a group of patients who have exquisitely endocrine-sensitive disease and have minimal visceral metastases, you might be able to increase that PFS to more like 4 months. But it's still really short for our patient population.

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So when we use our endocrine therapies in combination with targeted agents, we're seeing more like a 7-8-month progression-free survival, and in some situations even longer. So we definitely want to be using our best therapies for our patients to prolong the duration of exposure to endocrine therapy and delay the start of chemotherapy.

Dr. Turck:
And to close out our program, Dr. Rugo, what are the next steps for the ELEVATE study?

Dr. Rugo:
So now we moved on in the arms where we identified an RP2D dose—in other words, a treatment dose that we could give safely with some early efficacy—and moved on to the phase 2 combination. And so that's been very nice to have with elacestrant and everolimus where we identified that dose. In elacestrant and alpelisib, we're really trying to figure out where alpelisib is sitting right now and evaluating additional dose combinations to see how to manage it and also to tell the treating physicians upfront how to manage the expected toxicities of alpelisib, which I think for all of us is a challenge.

And then, the combination with palbociclib should be evaluated very soon, as well as ribociclib. And I think that in the phase 2 expansion, one of the other areas of great interest is moving on to the first-line setting where we can give everolimus in patients with early relapse from the early-stage setting who have a higher rate of ESR-1 mutations, a shorter progression-free survival, and lower response rates in the first-line metastatic setting to see how those patients respond. And of course, I expect that most of those patients won't have mutations in PI3-kinase, given the recent approval of the inavolisib triplet combination in those patients. But I think we're always balancing toxicity and efficacy in our patients, so doublet therapy is still very important. And as we move these combinations earlier in the metastatic setting, I think we'll be having additional treatment options for our patients that are important.

Dr. Turck:
Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. Hope Rugo, for joining me to discuss the preliminary findings from the ELEVATE study. Dr. Rugo, it was great having you on the program.

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

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