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Elacestrant and Targeted Therapies in Breast Cancer: Preliminary Data From ELECTRA and ELEVATE

Announcer:
Welcome to *Project Oncology* on ReachMD. This episode is sponsored by Stemline Therapeutics. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is *Project Oncology* on ReachMD, and I'm your host, Dr. Jennifer Caudle. Today, I'm sitting down with Dr. Hope Rugo to discuss preliminary data from a pooled analysis of the ELECTRA and ELEVATE trials, which examined the use of elacestrant with PI3K, AKT, mTOR, or CDK4/6 inhibitors in patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer. Dr. Rugo is the Director of the Women's Cancer Program and Division Chief of Breast Medical Oncology at City of Hope Cancer Center in Duarte, California.

Dr. Rugo, thank you so much for being here today.

Dr. Rugo:
Thank you for having me.

Dr. Caudle:
Of course. So, if we start off with some background, Dr. Rugo, can you walk us through the available first-line treatment regimens for this population, the key clinical challenges associated with these therapies, and how these relate to the purpose of this pooled analysis?

Dr. Rugo:
Looking at first-line therapies, we have in patients with hormone receptor-positive, HER2-negative disease, and we are using CDK4/6 inhibitors and endocrine therapy, where at least one study has shown survival benefit. But clearly, there's tremendous progression-free survival benefit with generally quite tolerable toxicity from this combination. And these are patients who generally are receiving an aromatase inhibitor and a CDK4/6 inhibitor. We've been really happy with the responsiveness to first-line endocrine therapy and CDK4/6 inhibitors in this patient population.

And we also have learned from a variety of studies, including the EMERALD study that led to the approval of the oral SERD—elacestrant—that patients who stay on their first-line endocrine therapy with an AI and CDK4/6 inhibitor for at least six months, and then even more so for at least a year, it's like a surrogate marker of endocrine sensitivity. So those patients tend to do better and stay on second-line therapy as well.

But I think the key thing is that we get these patients who stay on therapy for a long time. There's a subset of patients whose cancers progress very rapidly. We know those patients are not going to have disease that's really sensitive to endocrine therapy. But in this larger population who stay on first-line therapy for a long time with very good disease control, we eventually see a resistance in all patients, and that's really frustrating. We want to understand the mechanisms of resistance and we want to understand the best treatment approaches for those patients, and in the long term, try and take those approaches into earlier lines of therapy so that we can prevent or delay the development of resistance.

So we've known for a long time that about 40 percent of breast cancers have activating mutations in PI3 kinase, and then an additional 5 percent each have AKT activating mutations and PTEN alterations all within this PI3 kinase/AKT/mTOR pathway. And we know that

that's been a driver of resistance—shorter time on endocrine therapy and targeted agents—and that these tumors are responding to PI3 kinase inhibitors. Again, this is a complicated area that's being studied including with triplets and adding in CDK4/6 inhibitors to the mix based on very robust preclinical data. And we already have an approved triplet combination in more resistant disease.

And then we have learned about a second, very important mechanism of resistance occurring in about 40 percent of patients who have been on endocrine therapy and then had progression of their disease, and about 40 percent of patients will have these acquired—not like PI3-kinase mutations that are clonal, that exist mostly in most patients from the beginning of diagnosis of breast cancer. The ESR1 mutations are acquired under the pressure of treatment with less than 5 percent of patients who haven't had pretreatment with endocrine therapy having a mutation. So we know that's been associated with resistance to aromatase inhibitors and the injectable SERD—fulvestrant—doesn't work as well as we'd like it to in that setting.

And we have data with elacestrant, and now emerging data with other oral selective estrogen receptor down-regulators, that these agents are superior to fulvestrant in the treatment of patients with these acquired ESR1 mutations. And that led to approval of the only oral SERD at present—elacestrant.

So the question that came up is, we like combination therapy and we like combination therapy in sequence, so what can we do with an oral SERD to try and better understand the safety and efficacy with combined targeted agents in patients who have ESR1 mutations and, potentially, in a larger population?

Dr. Caudle:
Thank you for that. And if we dive into the methodology behind the studies, could you explain the design and rationale?

Dr. Rugo:
Absolutely. We thought, well, elacestrant is approved, and we want to know if we can give it with targeted agents. And this whole thought started a long time ago, and subsequently, we've actually seen data with an experimental oral SERD—imlunestrant—and abemaciclib, even in some patients who'd had disease progression on a prior CDK4/6 inhibitor and saw that it was more effective than giving the single agent oral SERD alone in the EMBER-3 trial. So that data came way later. We were already on that idea that we wanted to give elacestrant in combination, so we started the ELEVATE trial, which is a phase 1b/2 open-label umbrella trial, trying to take all of the targeted agents that we use in the second- and greater-line settings in patients receiving endocrine therapy and see how they play in the sandbox with elacestrant.

So it's a standard phase 1b trial where you first escalate the elacestrant from one dose reduction to full dose, and then you have various levels of dose escalation of the targeted agents. And we studied the PI3-kinase inhibitor alpelisib. We're studying the AKT PI3 kinase PTEN inhibitor capivasertib now, and we are expanding the dosing on alpelisib. We have studied the mTOR inhibitor everolimus and CDK4/6 inhibitors palbociclib and ribociclib.

But we also wanted to know how elacestrant would combine with abemaciclib, which is less commonly given in the first-line setting because it causes diarrhea. But it's widely used in the high-risk, early-stage setting now, based on the data from monarchE with remarkable improvement in efficacy in high-risk patients.

So our goal was first to find the RP2D, or randomized Phase 2 dose, of the combinations, make sure it's safe, see some preliminary efficacy, and then do these phase 2 expansions. So, how to evaluate abemaciclib—it's the only CDK4/6 inhibitor which has a little bit of data about crossing the blood-brain barrier, with some limited data suggesting that, even as a single agent, it may have some efficacy against brain metastases in patients who have hormone receptor-positive, HER2-negative disease.

The ELECTRA study was designed to look at the efficacy of elacestrant and abemaciclib in a phase 2 study in patients who have brain metastases with this subtype of breast cancer. But of course, first they had to do a phase 1b approach—again, one dose-level lower with elacestrant, and then full dose, and the abemaciclib going from 100 milligrams BID to 150 milligrams BID. So then they had phase 1b for that.

Once they established the RP2D dose, we could do a dose expansion in patients who didn't have brain mets in the ELEVATE trial, which is where we were looking at all these combinations. So then it made sense to pool the data from both studies to try and get a preliminary idea about efficacy and safety data from a larger population. So we pooled the data and this was presented at ESMO—The European Society of Medical Oncology—in 2024, and hopefully we'll have updated data on the phase 2 parts of these studies in the next short while because the abemaciclib phase 2 in ELEVATE has completed accrual, and ELECTRA is continuing.

Dr. Caudle:
Thank you for that. And what can you tell us about the baseline characteristics of the cohort?

Dr. Rugo:

We'll look first at the patients who received abemaciclib. We had elacestrant again, so it went from 258 to 345 milligrams, and then abemaciclib 100 milligrams BID with a lower dose, 100 milligrams BID with the full dose, and then 150 BID. And in three different cohorts, we saw that most patients had visceral metastases. They had received prior endocrine therapy—up to two lines—but they couldn't have received prior chemotherapy for advanced disease. And they did not have to have an ESR1 mutation. And in the initial phase 1 dosing, you could have had some prior chemotherapy, but not in the phase 2 dose expansion. So some patients had prior chemotherapy—about 70 to 80 percent had prior fulvestrant. This is a really heavily pretreated group of patients where about 40 percent received two lines of prior endocrine therapy. And then primary endocrine resistance was seen in a cohort of patients throughout this—less than 50 percent, but up to 25 percent had primary endocrine resistance, and all patients had prior CDK4/6 inhibitors.

We also made preliminary efficacy data on the phase 1b cohorts, looking at everolimus, alpelisib, palbociclib and ribociclib. And these groups of patients were very similar. Again, in this cohort, we didn't allow prior chemotherapy in the metastatic setting, but 100 percent of people had to have CDK4/6 inhibitor. Overall, the visceral metastases were in about 70 percent, seven percent of the patients had primary endocrine resistance, and most patients had received two lines of prior therapy for advanced disease.

Dr. Caudle:
Thank you. And what were the key findings regarding efficacy?

Dr. Rugo:
When we look at the efficacy of these different groups, I think the first thing that's important to remember is almost half of these patients had received prior fulvestrant. And what we saw, interestingly, in the abemaciclib cohort, is that the response rates were very good, even though a lot of these patients had received prior fulvestrant—57 percent for the clinical benefit rate at 24 weeks, and then the overall response rate was in the 25 to 29 percent rate. And the responses were very durable. We saw very durable responses in this patient population.

So, in the ELEVATE trial, we had 26 patients who received elacestrant and abemaciclib, and they received the full dose—so 345 milligrams of elacestrant and 150 milligrams twice daily of abemaciclib. And in that group, we saw—and remember, they were a little less heavily pretreated than ELECTRA—an 85 percent clinical benefit rate. So an 84 percent pooled clinical benefit rate overall.

And if you looked at the overall response rate, the number of patients who have measurable disease who could be evaluated was small, so it was a little bit difficult to look at overall response rate. And in some of these patients, we still had very early follow-up. But when we looked at the durability in the ELEVATE portion of this trial, we saw that some patients stayed on for a very long period of time, and the overall progression-free survival of the ELECTRA phase 1b was 8.7 months. And a really encouraging—even with very high visceral metastases—high rate of prior fulvestrant, almost 70 percent of patients, etcetera. So I think that's really encouraging.

The other evaluations that we had from the ELEVATE trial were looking at ribociclib and everolimus. And we looked at these combinations as well and saw in the small numbers of patients—33 patients with ribociclib and 23 patients with everolimus—very nice data in terms of the responses and very durable progression-free survival—about 7.8 months for ribociclib in 33 patients, and over eight months for everolimus in 23 patients, with the everolimus dose in our final combination being 7.5 milligrams, which is better-tolerated. And again, these are patients with high visceral mets and large exposures to prior fulvestrant. And we did not base this on ESR1 mutation. So, it looked very nice and comparable to what we've seen in the randomized phase 3 EMBER-3 trial, where they looked at imlunestrant and abemaciclib.

In terms of safety, which was a primary outcome of the phase 1b, we saw no additional or new unexpected safety findings. So the adverse events were all as would be expected from the combinations with other endocrine therapy with abemaciclib, ribociclib, and everolimus. So very encouraging data, I think, for these combination studies.

Dr. Caudle:
For those of you who are just tuning in, this is *Project Oncology* on ReachMD. I'm Dr. Jennifer Caudle, and I'm speaking with Dr. Hope Rugo about the new data from the pooled analysis from the ELECTRA and ELEVATE trials on elacestrant with PI3K, AKT, mTOR, or CDK4/6 inhibitors in patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer.

So, based on these results, what is the significance of the pooled analysis findings?

Dr. Rugo:
Well, I think that we've really moved from studying single-agent endocrine therapy in sequence to using combination therapy. And certainly, that's been the standard of care now for some time in the first-line metastatic setting. But now, we really have seen that single-agent endocrine therapy, in studies where fulvestrant is the control, the PFS is really short—two and a half months in many situations, depending on how endocrine sensitive the population is, and in some settings, out to five months. We're not really sure why we see this

wide variation. But overall, I think we could agree that we're not ecstatic about these results, and we'd like something better for our patients to be able to stay on oral therapy for longer and to delay the onset of chemotherapy.

We've learned that ESR1 mutations are important, but from EMBER-3, the data suggests that if you combine a targeted agent—in that case, abemaciclib—with an oral SERD, you may see a benefit even though you don't have patients with ESR-1 mutations—that it will be true in the overall intent-to-treat population.

In the ELEVATE and ELECTRA trials, we've shown that combining elacestrant—right now, the only approved oral SERD—with a number of different targeted agents is safe. The safety findings that we saw were what we'd expect to see from the targeted agents combined with standard endocrine therapy.

But most importantly, in a heavily pretreated patient population where 70 to 80 percent had received prior fulvestrant and all had received prior CDK4/6 inhibitors, we've seen very nice, durable clinical benefits where progression-free survival is much longer than what we would have expected to have seen from single-agent endocrine therapy alone in patients who hadn't yet received fulvestrant. But it's remarkable to see that kind of durability in patients whose cancers have progressed on fulvestrant.

So I think that this is really important. We're seeing that these combination strategies are the preferred approach, and we've seen a way to try and improve the outcome for our patients. These are, of course, preliminary data, and we are waiting for the phase 2 expansion data with elacestrant and abemaciclib from the ELEVATE trial, as well as expanded data from the other combinations in the future, which will give us further information that we can bring to the clinic to treat our patients.

Dr. Caudle:
What's the significance of the other combinations with everolimus and ribociclib?

Dr. Rugo:
I think that this is also really important because there are parts of the world—less commonly in the US, where patients don't get CDK4/6 inhibitors in the first-line setting, and I think having the safety combination with ribociclib is important. There may also be patients who we are continuing a CDK4/6 inhibitor in the second-line setting. We saw that most recently in the SERENA-6 trial. And so understanding the combination with ribociclib is important, but also it may help us when we're treating patients who've developed a recurrence on adjuvant endocrine therapy and already have an ESR1 mutation up front. PI3-kinase mutation—elacestrant and ribociclib combinations may be important as well as other oral SERDs in combination.

Everolimus is still a drug that we use quite frequently in patients who don't have PI3-kinase mutations in the second-line setting—particularly, patients who might have received, say, abemaciclib in the first-line setting, or ribociclib, where we're not sure we want to keep going with a CDK4/6 inhibitor in the second-line setting. So having these combinations is really important for the variety of different case settings that we see in patients to really try and optimally treat each patient based on individual characteristics, response, disease, symptoms, etcetera.

And again, as I mentioned earlier, the everolimus dose in combination with 7.5 milligrams, that's not because it was terrible toxicity, but because, in clinical practice, 7.5 milligrams just tolerated better. And so it seemed as though because we were seeing responses in that group, we really didn't need to push the dose to 10 milligrams. And for ribociclib, we've seen equivalent efficacy with 400 milligrams versus 600 milligrams in the metastatic setting in patients who needed to dose-reduce, and it's the approved dose in the early-stage high-risk setting. So we used 400 milligrams to go forward in the phase 2 combination because we don't see as much neutropenia and fatigue, and patients just tolerate it much better.

And again, interestingly, probably because of the lack of significant cytopenia and certainly no impact on glucose rash like everolimus, or mouth sores, abemaciclib is dosed at full dose at 150 milligrams BID in our expansion cohorts. And there's also a portion of ELEVATE that's looking at patients who didn't receive a CDK4/6 inhibitor in the first-line setting just to see how that combination works as well.

So this will all help us not only in treating our patients who have metastatic disease, but also in understanding how we can combine this approach earlier in lines of therapy to further improve outcomes.

Dr. Caudle:
And what should we know about the safety findings?

Dr. Rugo:
Well, overall, it was really nice to see that in all three cohorts, we didn't see any new safety signals. The safety findings and adverse events were what we would expect and exactly what we've seen in other studies that have looked at AIs or fulvestrant in combination with these targeted agents. So that was really encouraging.

I mean, these are small populations—phase 1b, the pooled analysis for abemaciclib phase 1b, and a little bit of Phase 2 data. I think we don't really expect to see any differences. And other combination studies have not shown any interactions between oral SERDs and these targeted agents.

That's a little bit different from some other oral endocrine agents. Some of the oral endocrine agents do have drug-drug interactions—so-called DDIs—where you might have to dose-reduce one agent. The only reduction we made was with that small reduction in everolimus. But we didn't see any PK or PD alterations when the combinations were used. So I think that's really encouraging too.

Dr. Caudle:
As we approach the end of our program, Dr. Rugo, what are the anticipated next steps as we explore new therapeutic avenues for these patients?

Dr. Rugo:
I think that we want to move our effective drugs as early as possible in the treatment paradigm to try and improve outcomes. We are looking in the ELEGANT trial at elacestrant as a switching approach after patients have finished their CDK4/6 inhibitor or not, and they're not taking it at all, in the early-stage, high-risk setting. I expect most patients will receive a CDK4/6 inhibitor and they'll be randomized to switch to elacestrant versus continue their endocrine therapy for five years after two to three years, depending on when they get there. And there is another trial looking at imlunestrant in that setting—EMBER-4—that's also accruing. So I think that moving these drugs earlier plays a really big role.

There are trials that are looking at these combinations with oral SERDs in the first-line setting as well. That's important because we want to give targeted agents in that setting, and we want to be able to choose the best agent for the individual patient situation.

Dr. Caudle:
Excellent. And with those insights in mind, I'd like to thank my guest, Dr. Hope Rugo, for joining me to discuss the newest data from the ELECTRA and ELEVATE trials. Dr. Rugo, it was great having you on the program.

Dr. Rugo:
Thank you so much.

Announcer:
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