Podcast Transcript:
ER+ metastatic breast cancer: Key insights on elacestrant from the latest EMERALD subgroup analyses

Brought to you by:
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Dr Virginia Kaklamani
Aditya, good morning. This is exciting for us to be talking about ER+ metastatic breast cancer and just, key insights on elacestrant, and the latest in the EMERALD subset analysis.

Dr Aditya Bardia
Absolutely. Looking forward to the discussion.

Dr Virginia Kaklamani
So, I guess I'll start with a few questions. So, first of all, let's start from the beginning. What is the standard of care in that 1st line therapy in ER+/HER2- metastatic breast cancer?

Dr Aditya Bardia
In general, I use endocrine therapy plus a CDK4/6 inhibitor as 1st line therapy for a patient with metastatic hormone receptor positive breast cancer. And that's based on multiple studies, including studies that have shown improvement in overall survival with this approach.
So that pretty much is my 1st line. And then after a patient has disease progression on 1st line therapy, in the 2nd line setting, I strongly recommend genotyping, plasma-based genotyping, because I find that actionable.

Dr Virginia Kaklamani

And that's exactly the point. So, one of the issues that we have after the patient's cancer is progressing on endocrine therapy is endocrine resistance. So, once t[1]hat cancer becomes endocrine resistant then what do we do, right? We have to, kind of, look at the mechanism behind endocrine resistance and one of the ways to do this is by doing genomic testing. Exactly.

Dr Aditya Bardia
Say you do genotyping and you find *ESR1* mutation, that's very actionable. In terms of potential therapies and also provides insight into potential mechanism of resistance. If a tumor has developed *ESR1* mutation, it would signal that it's likely dependent, still dependent on the ER pathway as opposed to some other alteration.

So, I find that very valuable. But the point I would make is that these are acquired mutations. So, it's important to do liquid biopsy or plasma-based genotyping if we profile the original, you know, primary breast cancer or even the biopsy that was done at the time of metastatic diagnosis, you can miss these mutations.

Dr Virginia Kaklamani
And that's an extremely important point that you made. These are sub clonal events, right? And so, if we do a solid tumor biopsy we have around a 20% or so chance of missing it because another site may have developed it. But all of these sites are going to shed their DNA into the blood and therefore captured with the liquid biopsy.
So, let's say a patient does have a tumor that has now developed an *ESR1* mutation. What is your go to strategy after that?

Dr Aditya Bardia
Well, we now have an FDA approved therapy. Elacestrant is approved for patients who have detectable *ESR1* mutations. In the clinical trial liquid biopsy was used for the detection of *ESR1* mutation.

So, this was based on the EMERALD study. The EMERALD study demonstrated elacestrant was superior to standard of care endocrine therapy for patients in the 2nd line plus setting. In the EMERALD trial, all patients had received prior CDK4/6 inhibitor, about 20% had received prior chemotherapy, 30% had received two prior lines of therapy. The primary endpoint of the trial was to look at progression-free survival between elacestrant versus standard of care. The study had two primary endpoints, one looking at the efficacy in the overall population, and a second primary endpoint of looking at elacestrant vs standard of care in patients with detectable *ESR1* mutations. And overall, the study met its primary endpoint in both these categories. Overall, there was improvement in progression-free survival with elacestrant versus standard of care in the total population. And if we look at patients with a detectable *ESR1* mutation, again, there was improvement in progression-free survival with elacestrant vs standard of care endocrine therapy that was clinically meaningful and statistically significant as well, with a hazard ratio of 0.55.

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And since a subset of patients had received prior chemotherapy, the team also looked at progression-free survival in patients who did not receive prior chemotherapy, and in that subgroup, you could see that the median progression-free survival with elacestrant was 5.3 months versus 1.9 months with standard chemotherapy.
So, in the 2nd line setting where elacestrant is often used, it's helpful to have these data, in terms of options.
And Virginia, you did some very nice, you know, subgroup analysis and presented at SABCS. What do you want to highlight in terms of what that represents and how the analysis was done and what it means?

Dr Virginia Kaklamani
Yeah, I think our point was exactly that there was a drop in the beginning with many patients probably having endocrine resistant disease that was not going to respond to any endocrine therapy. And so how do we tease out the patients that still have endocrine sensitive disease? And so, the way we looked at that is we looked at prior duration of a CDK4/6 inhibitor, and we found that, if the prior duration of the CDK4/6 inhibitor was at least 12 months, then the benefit from elacestrant was clinically meaningful with the median PFS at that point of 8.6 months.
Now interestingly, the standard of care arm, regardless of what median duration of the prior CDK4/6i we looked at, still was at around 1.9 to 2 months median PFS. So that, to me, tells me if a tumor has an *ESR1* mutation, and the patient has received already a CDK4/6 inhibitor, which is the majority of these patients, you don't want to give just standard of care endocrine therapy. The results are really not impressive. You want to do something different and elacestrant seems to be that.
Now, we also looked at a lot of other analyses because we were still trying to tease out patient populations that may not benefit as much from elacestrant or may benefit more, and so forth. So, we looked at patients that had bone metastases versus liver and lung metastases. It really didn't make any difference as long as the prior duration of the CDK4/6i was 12 months or more. We looked at commutations, *PIK3CA*, *TP53*, and again, it didn't really make a difference. Still, there was a nice, clinically significant benefit with elacestrant. We looked at HER2-low tumors or not. And we even looked at different *ESR1* mutations, and again, it didn't seem to matter. The important thing seemed to be the prior duration of the CDK4/6 inhibitor.

Dr Aditya Bardia
That's very helpful because now you have these different subgroups, *ESR1* plus *PIK3CA* mutant, which can be seen in clinic. And so, to see efficacy of elacestrant in that setting was very helpful. Plus, other subgroup analyses as well, lung liver mets, bone mets only.
So how do you incorporate this in clinical practice? Let's look at a scenario, Virginia. There's a patient, postmenopausal, say, a 60-year-old female who gets, AI plus CDK4/6 inhibitor in 1st line. That works for about two years or so, and the patient has disease progression. You get genotyping and it shows *ESR1* mutation, or it shows both *ESR1* and *PIK3CA*, these two scenarios. How would you incorporate that in terms of decision making?

Dr Virginia Kaklamani

So, I think that's where you have to look at efficacy but also toxicity. We have now three agents, two approved in the exact same setting that you just mentioned, capivasertib and alpelisib. But those are in combination with endocrine therapy. So, when you look at the toxicity of that regimen, the dual regimen of capivasertib plus endocrine therapy, or alpelisib plus endocrine therapy and you compare that to the toxicity profile of elacestrant, elacestrant has much fewer toxicities than the combination therapy.
So, if there is a co-mutation I'd likely give elacestrant first. I will reserve my capivasertib or alpelisib for the next line. Is that something that you do as well?

Dr Aditya Bardia
Yeah, I agree, I think it's good to have options. And we start with the therapy that has lower side effects. And then you can move on to therapy that has more side effects. So, I do consider elacestrant in this setting.
I do get scans closer to the two, two-and-a-half-month mark in this setting just to ensure if a patient is having disease progression, we pick that early and if that looks good, then we can space the scans out. But in this setting, just getting scans a bit early, I do find that helpful.

Dr Virginia Kaklamani
And if you're going to talk to your patients about elacestrant, what do you mention as far as adverse events?

Dr Aditya Bardia
That's a good point. So, when you're discussing elacestrant in this setting, the common side effects that I review include nausea, which is the number one side effect seen with elacestrant in the clinical trial, usually Grade 1, Grade 2. The incidences of Grade 3 for nausea in the clinical trials was 2.5%. So very low and generally don't need anti-nausea medications. There was no Grade 4 nausea, vomiting seen with elacestrant in the clinical trial. So that's the main thing I counsel patient about, generally taking elacestrant with food and that takes care of the nausea. With other combination drugs there are more side effects, and we can review that.

Dr Virginia Kaklamani
Now, we've had the data from EMERALD, which is really, a really pivotal clinical trial. But thankfully we also have real world data because we've been using elacestrant for a couple of years. Any conclusions from these trials that may not have really come out from EMERALD?

Dr Aditya Bardia
Yeah, we have real world analysis now close to, more than 1000 patients treated with elacestrant. And we see consistent results, that the median progression-free survival is in the 8-to-9-month range, which was seen with elacestrant in the EMERALD study in patients who had *ESR1* mutations and prior duration of CDK4/6 inhibitor for at least 12 months. So, we're seeing consistent results in the real world setting as well.

Dr Virginia Kaklamani
And that's interesting because typically, right, when we do real world analyses, we find worse outcomes than we find in our randomized clinical trials. But here both of these analyses pointed to better outcomes than what we've been used to in the EMERALD trial, which is actually pretty interesting.

Dr Aditya Bardia
Yeah, absolutely, absolutely. And it probably speaks to the drug being well tolerated. Sometimes in the real-world setting, we see slightly inferior outcomes as compared to randomized trials, because in randomized trials there are motivated patients there. AEs are very well managed. Here, you know, the drug is very well tolerated. And maybe that's why in the real-world setting, you see consistent results.

Dr Virginia Kaklamani
So, I guess I'll summarise a little bit what we've talked about. When we talk about patients that have previously received the CDK4/6 inhibitor, and now we're trying to make a decision as to what to give as our subsequent treatment, it's extremely important that we do genomic testing. It's extremely important that we understand what the makeup of the tumor is and how it's evolved over time. If the tumor has an *ESR1* mutation, and if we'd still consider the tumor endocrine sensitive and the way we, you know, I define it clinically is by the prior duration of a CDK4/6 inhibitor, that's where I will introduce elacestrant for my patients. I think with those scenarios there's a nice clinical benefit with giving elacestrant. Co-mutations are important, for me, for subsequent treatments since I've established my 2nd line therapy, but there are definitely patients that you might end up giving a CDK4/6 inhibitor as a 2nd line, or even a PI3 kinase inhibitor in that 2nd line as well. But the majority of my patients would be getting elacestrant.

Any other things to consider Aditya?

Dr Aditya Bardia
Now that's the key, do plasma genotyping in the 2nd line setting. And then based on that choose therapies. *ESR1* mutation elacestrant, *ESR1* plus *PIK3CA* mutation, again elacestrant is a consideration. And it's regardless of the type of *ESR1* mutation. Now there was some data with fulvestrant previously that Y537S, those *ESR1* mutations are resistant to fulvestrant, but we've not seen that with elacestrant per se. So, it's regardless of the type of *ESR1* mutation.
And also, in terms of safety. Safety analyses demonstrated that elacestrant has a manageable safety profile similar to endocrine therapies, without any of the toxicities that we see with PI3 kinase, AKT, mTOR or CDK4/6 inhibitors. So, comparatively, a very manageable safety profile.

Dr Virginia Kaklamani
And I think it's important to note a detail that the amount of antiemetic that was given on elacestrant was actually lower than in the patients that received an aromatase inhibitor in

EMERALD. And so around 8% of patients received an antiemetic if they were on elacestrant, 10% on an aromatase inhibitor, which I think is important for our practice.

Dr Aditya Bardia
Yeah, absolutely. Absolutely. This is great for Virginia. I very much enjoyed our discussion. It was good to review the different options and look forward to future discussions as well.

Dr Virginia Kaklamani
I do as well. Thank you.

Tonke (COR2ED)
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