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A Look at the Therapeutic Landscape for Metastatic Breast Cancer

Dr. Chalasani:
While the treatment landscape for metastatic breast cancer has seen many clinical breakthroughs over the years, there is still a need for more effective endocrine treatment options for patients with hormone receptor-positive HER2- metastatic breast tumors. Emerging research may shed some light on a promising new treatment option for these patients.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani. And joining me today to discuss the EMERALD trial and talk about an oral selective estrogen receptor degrader, or SERD for short, in metastatic breast cancer patients is Dr. Aditya Bardia, an associate professor at Harvard Medical School and a medical oncologist and Director of Breast Cancer Research at Massachusetts General Hospital.

Dr. Bardia, thanks for joining me today.

Dr. Bardia:
Yes, absolutely.

Dr. Chalasani:
Let's start with some background on the EMERALD trial, Dr. Bardia. What were your objectives in evaluating this oral SERD? And can you share some of your key findings with us?

Dr. Bardia:
Yeah, absolutely. So, endocrine therapy is the mainstay of management of hormone receptor-positive breast cancer, and currently, endocrine therapy plus a CDK4/6 inhibitor is the recommended first-line treatment for ER+ metastatic breast cancer. When patients have disease progression and in the second- and third-line setting, we tend to use fulvestrant or switch the, aromatase inhibitor, but the clinical benefit, the median progression-free survival, is quite short with these kind of endocrine options, so there's a need for better endocrine therapies. Also, fulvestrant is given as an intramuscular shot so from a patient perspective can be inconvenient. So we were interested in developing a better endocrine option for patients with ER+ breast cancer.

In a phase I/phase II trial, elacestrant had demonstrated promising clinical activity. So the EMERALD trial was essentially designed to look at this new agent. Elacestrant was the standard of care endocrine therapy with fulvestrant or AI in the second/third-line ER+ metastatic breast cancer setting in patients who had received prior CDK4/6 inhibitor. The trial had co-primary endpoints of progression-free survival in the full population and also progression-free survival in patients who had mutations in the estrogen receptor, the so-called ESR1 mutations.

In terms of the study results, the trial was positive. It showed that patients who received EMERALD did better as compared to standard of care endocrine therapy in terms of progression-free survival in the overall population as well as patients who had ESR1 mutations. The hazard ratio was about 0.7 in the overall population and was 0.55 in patients with ESR1 mutations. In that group you could particularly see almost doubling of progression-free survival. And there was also a trend in terms of improvement in overall survival in the overall population, and patients who had ESR1 mutations. So bottom line and conclusion was that elacestrant demonstrated superior activity as compared to standard of care endocrine therapy, and in the future, we need to develop, this agent and other oral SERDs as well, in the first-line in adjuvant setting and also look at combination therapy.

Dr. Chalasani:
So, given these results, when do you recommend testing for the ESR1 mutation? Is it prior to, you think, using the oral SERD, or is it any time point during the treatment decision that you do?

Dr. Bardia:
Yeah, good question about testing of ESR1 mutations. ESR1 mutations are acquired mutations, so if you test the primary tumor, you're likely going to miss ESR1 mutations. Our routine clinical practice at this time is once a patient has disease progression on first-line therapy, we tend to do tumor genotyping, usually plasma-based genotyping, to look at, say, PIK3CA because alpelisib is FDA approved for PIK3CA-mutant ER+ metastatic breast cancer. And often we do panel testing, and as long as ESR1 is part of that panel, you can look at both ESR1 and PIK3CA and other genes, so that would be my recommendation, testing for ESR1 after first-line therapy with endocrine plus CDK4/6 inhibitor.

Dr. Chalasani:
Yeah. So given the current EMERALD results and the benefit of elacestrant even after fulvestrant, how do you see sequencing of fulvestrant versus elacestrant in clinical practice?

Dr. Bardia:
Yeah. I view elacestrant as an oral and stronger or better version of fulvestrant. So, wherever fulvestrant is used currently, one could potentially consider elacestrant. Based on the study as well as other planned studies, that's the concept. That's the vision. So I would consider elacestrant in the second-line setting instead of fulvestrant.

Dr. Chalasani:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking to Dr. Aditya Bardia about sacituzumab as a treatment option for metastatic triple-negative breast cancer patients.

You know, let's just dig a little deeper into this oral SERD. What are some of the most common adverse events with this treatment option? And how do you go about managing them?

Dr. Bardia:
Yeah, elacestrant is oral, and the number one side effect we see is nausea. With this agent, incidents of any grade nausea being about 30%. Most patients don't need any anti-nausea medications, but if a patient has severe nausea, you could certainly use an anti-nausea medication such as ondansetron or prochlorperazine. Outside of that, the side effects are pretty much similar to what you would expect with other endocrine therapy: some hot flashes, and other menopausal-related side effects. Because it's oral, it does not cause any problems like fulvestrant with the intramuscular shot. So that's with elacestrant.

There are other oral SERDs in development, such as amcenestrant, giredestrant, imlunestrant, camizestrant, a lot of oral SERDs in clinical development, but you have a slightly different, side effect profile. Some of the other oral SERDs can cause vision disturbances, dizziness. One of them is also known to decrease the heart rate or cause bradycardia. So we'll have to be careful in terms of the side effects because there might be drug-specific side effects besides class-specific side effects.

Dr. Chalasani:
Great. Thank you. I know you briefly commented on which clinical scenario or where you would incorporate, but at this time the trial focused on the use of elacestrant as a single agent. So, if this oral SERD is approved, what kind of patient population would you routinely use it in clinic? For patients, what kind of disease burden would you see yourself using or recommending this treatment?

Dr. Bardia:
Yeah, good question. So I would use this agent in the study population similar to EMERALD, so, in the second-line or third-line post CDK4/6 setting, that is where I would use this agent. The EMERALD trial did include patients who had visceral metastases and would even receive one line of prior chemo, so I would feel comfortable using this agent in that setting. There are landmark studies looking at elacestrant with other target therapies, and if we have safety data and some evidence of efficacy, I would also feel comfortable using combination therapy as long as we have some data. Obviously, outside of data I would only use it as a single agent.

Dr. Chalasani:
And before we close, Dr. Bardia, let's look towards the future. How do you think the development of this oral SERD will impact the treatment landscape and, you know, overall outcomes for patients with hormone receptor-positive HER2-negative metastatic breast cancer?

Dr. Bardia:
Endocrine therapy is the mainstay of management of ER+ breast cancer. Currently, we use aromatase inhibitors and sometimes tamoxifen and fulvestrant, so if this oral SERD or other oral SERDs get approved, that would be great news for patients because we'll have another endocrine therapy option that can be used. And if they get developed in the first-line setting, in the adjuvant setting, they could potentially replace aromatase inhibitors as the preferred endocrine option. So there's a lot of interest and excitement about developing better endocrine options for our patients with ER+ disease.

Dr. Chalasani:
And with those forward-facing insights, I want to thank my guest, Dr. Aditya Bardia, for joining me today and sharing his research and his insights from EMERALD trial and the oral selective estrogen receptor degrader. Dr. Bardia, it was great having you on the program today.

Dr. Bardia:
Yeah. Thank you so much for having me.

Dr. Chalasani:
I'm Dr. Pavani Chalasani. To access this and other episodes in our series, visit reachmd.com/projectoncology, where you can Be a Part of the Knowledge. Thanks for listening.