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Treating ER+/HER2− *ESR1*m mBC: EMERALD Subgroup Analyses in Clinical Cancer Research

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Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is *Project Oncology* on ReachMD, and I'm your host, Dr. Jennifer Caudle. And today, we'll be discussing a recent publication in *Clinical Cancer Research* featuring post hoc analyses from the EMERALD trial. The article is titled, "*Elacestrant in ER+, HER2− Metastatic Breast Cancer with ESR1-Mutated Tumors: Subgroup Analyses from the Phase III EMERALD Trial by Prior Duration of Endocrine Therapy plus CDK4/6 Inhibitor and in Clinical Subgroups*." Joining me in this conversation is Dr. Komal Jhaveri.

She's a breast medical oncologist and early drug development specialist at Memorial Sloan Kettering Cancer Center in New York. Dr. Jhaveri is a consultant for Stemline Therapeutics, Inc.

Dr. Jhaveri, welcome to the program.

Dr. Jhaveri:
It's great to be here today.

Dr. Caudle:
Before we jump into our discussion, let's review the approved indication for elacestrant.

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INDICATION

Elacestrant is indicated for the treatment of postmenopausal women or adult men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

Please stay tuned to the whole program to hear Important Safety Information.

Dr. Caudle:
Let's start with some background. Dr. Jhaveri, what are some key challenges in managing patients who progress during first-line therapy for ER-positive/HER2-negative metastatic breast cancer?

Dr. Jhaveri:
Thank you. Such an important question and a really good place to start. For patients with ER-positive/HER2-negative metastatic breast

cancer, first-line treatment with endocrine therapy and a CDK4/6 inhibitor is initially highly effective.[1–5]

However, tumors can then develop resistance to standard-of-care endocrine therapy and patients develop progression of their disease.[6–11]

And as a result, these tumors can be challenging to treat with standard-of-care options with monotherapy drugs like aromatase inhibitors or fulvestrant.[1,12–16] The median progression-free survival with fulvestrant monotherapy after progression on a CDK4/6 inhibitor therapy with endocrine therapy is about two to three months.[16,17]

One of the main drivers of resistance in this setting are *ESR1* mutations.[11,18] Unlike intrinsic mutations such as *PIK3CA*, *ESR1* mutations are acquired and may develop during treatment for metastatic disease under the selective pressure of endocrine therapy, namely aromatase inhibitors, which is why they're rarely detected in early-stage breast cancer.[9–11,18,19] *ESR1* mutations increase with each disease progression and are found in up to 50 percent of patients after first-line therapy.[11,20–24]

They are not only associated with endocrine therapy resistance and disease progression, but also with visceral metastases and a worse prognosis.[25-29]

And this is why managing patients after progression on first-line treatment requires a more targeted approach. This is where therapies like elacestrant have made a difference. Elacestrant is the first oral selective estrogen receptor degrader, or SERD, to show improved efficacy over endocrine monotherapy in the randomized Phase III EMERALD trial, particularly in patients harboring *ESR1* mutations.[16]

Now because these *ESR1* mutations predominantly arise in the metastatic disease setting during first-line therapy, and there's now an approved *ESR1*-targeting therapeutic, multiple clinical guidelines recommend testing for the emergence of these *ESR1* mutations at *every* disease progression after first-line therapy in the metastatic setting. Recommendations in *ESR1* mutation testing are included in guidelines such as The National Comprehensive Cancer Network®, or NCCN, American Society of Clinical Oncology, or ASCO guidelines, and European Society of Medical Oncology, or ESMO guidelines.[18,19,30–32]

The preferred testing method uses circulating tumor DNA, or what you would call a ctDNA, which is minimally invasive and more sensitive in detecting these *ESR1* mutations than a tissue biopsy.[19,30–32] Primary archived breast cancer tissue isn't reliable for detecting *ESR1* mutations because these mutations are acquired during endocrine therapy treatment and may not be present in primary tissue samples.[30]

Dr. Caudle:
With that background in mind, Dr. Jhaveri, let's turn to the EMERALD trial, which led to the approval of elacestrant. Can you walk us through its design and the key findings on efficacy and safety?

Dr. Jhaveri:
Of course. The phase III EMERALD trial included men and postmenopausal women with ER-positive/HER2-negative advanced or metastatic breast cancer. All participants had previously progressed on the standard-of-care first-line treatment with a CDK4/6 inhibitor plus endocrine therapy.[17]

Now these patients were randomized to receive either single-agent elacestrant or a standard-of-care endocrine therapy of the investigator's choice, which included an aromatase inhibitor or fulvestrant. The primary endpoint was progression-free survival, including in patients whose tumors harbored *ESR1* mutations.[17]

In terms of efficacy, for patients with *ESR1*-mutated tumors, the median progression-free survival was 3.8 months with elacestrant compared to 1.9 months with standard-of-care endocrine therapy. This was statistically significant and represented a hazard ratio of 0.55 with a 95 percent confidence interval of 0.39 to 0.77, demonstrating a 45 percent reduction in the risk of disease progression or death with elacestrant monotherapy.[17]

In the intention-to-treat population, there was also a statistically significant improvement in progression-free survival; however, these results were primarily attributable to patients in the *ESR1*-mutated subgroup.[16]

Most adverse reactions experienced by patients in EMERALD were grade one or two in severity.[17]

Now looking at the safety of elacestrant, serious adverse reactions occurred in 12 percent of patients who received elacestrant, with musculoskeletal pain reported in 1.7 percent and nausea in 1.3 percent. Fatal adverse events occurred in 1.7 percent of patients in the elacestrant group.[17] These most common adverse reactions, seen in at least 10 percent of patients, did include musculoskeletal pain,

nausea, fatigue, vomiting, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia.

Nausea occurred in 35 percent of patients who received elacestrant across all grades, but most cases were mild to moderate.[17] Nausea was observed in 19 percent of patients in the standard-of-care arm. Vomiting was 19 percent in the elacestrant arm versus nine percent in the standard-of-care arm. There were no reports of grade four nausea or vomiting on elacestrant.[33]

Antiemetic use was low across treatment arms: eight percent with elacestrant, and 3.7 percent with fulvestrant, and 10.3 percent with aromatase inhibitors. Taking elacestrant with food may further help reduce nausea, and antiemetics can be used as needed.[33]

Treatment discontinuations due to adverse reactions were six percent, with dose reductions at three percent and dose interruptions at 15 percent. And the discontinuation rate specifically due to nausea was low at 1.3 percent. The discontinuation rate for musculoskeletal pain was 1.7 percent.[17]

And so overall, the EMERALD trial showed that elacestrant demonstrated a statistically significant and clinically meaningful improvement in progression-free survival in patients with *ESR1*-mutated metastatic breast cancer compared to standard-of-care endocrine therapy, but was also generally well-tolerated with manageable safety profile.[33]

Dr. Caudle:
Now, the EMERALD trial generated a lot of follow-up research. So what questions did these post hoc exploratory analyses aim to answer?

Dr. Jhaveri:
So the post hoc analyses sought to better define treatment selection in subgroups of patients with *ESR1*-mutated tumors. By evaluating factors like prior treatment duration with endocrine therapy plus a CDK4/6 inhibitor, tumor metastatic sites, and common coexisting mutations or molecular expressions, the analyses explored how these variables may influence elacestrant efficacy. These subgroup analyses aimed to help identify *ESR1*-mutated tumors that may remain endocrine-sensitive despite acquired resistance to prior endocrine therapy, offering insights that can help inform treatment decisions.[33]

However, keep in mind that the results of these post hoc analyses were observational in nature and should be interpreted with caution, as there was no prespecified statistical procedure controlling for type one error.[33]

Now, the first subgroup analysis looked at progression-free survival in patients with tumors harboring detectable *ESR1* mutations based on the duration of prior endocrine therapy plus CDK4/6 inhibitors in the advanced or metastatic setting. Patients were grouped by whether they'd had greater than or equal to six months, 12 months, or 18 months of prior therapy. This helped illustrate how the duration of prior treatment with an endocrine therapy, which is often linked to an increased risk of resistance and *ESR1* mutations, could impact progression-free survival outcomes with elacestrant compared to standard-of-care endocrine therapy.[33]

The results showed that a longer duration of prior endocrine therapy plus a CDK4/6 inhibitor was associated with an improvement in progression-free survival with elacestrant compared to standard-of-care endocrine therapy in patients with tumors harboring detectable *ESR1* mutations. Patients who'd had at least 12 months of prior endocrine therapy plus a CDK4/6 inhibitor represented about 70 percent of the trial population. And in this population, the median progression-free survival was 8.6 months with elacestrant compared to 1.9 months with standard-of-care endocrine therapy.[33]

These exploratory findings suggested that in patients with *ESR1*-mutated tumors, a longer duration of endocrine therapy with CDK4/6 inhibitor treatment may indicate that tumors remain sensitive to some forms of endocrine therapy, such as elacestrant, despite progression on standard-of-care endocrine treatment.[33]

Dr. Caudle:
And were there any other subgroup analyses we should be aware of?

Dr. Jhaveri:
Yes. So as I mentioned earlier, another post hoc analysis of the EMERALD trial examined subgroups with clinically relevant tumor characteristics, such as metastatic sites and additional mutations. This analysis was conducted in patients with *ESR1*-mutated tumors who had received at least 12 months of prior endocrine therapy plus a CDK4/6 inhibitor.[33]

As with other post hoc analyses, these findings were observational and should be interpreted cautiously, as no prespecified statistical procedure controlled for type one error.

This analysis focused on clinically-relevant subgroups, including patients with[33]:

- Bone metastases,
- Liver and/or lung metastases,
- Three or more metastatic sites versus fewer than three,
- Co-occurring *PIK3CA* or *TP53* mutations,
- HER2-low tumor expression,

And *ESR1* mutation variants, including D538G and Y537S/N mutations.

The findings showed that patients with *ESR1*-mutated tumors who received at least one year of prior endocrine therapy plus CDK4/6 inhibitor had a longer progression-free survival with elacestrant compared to those patients who received standard-of-care endocrine therapy across all clinically relevant subgroups, regardless of metastatic site location or number, coexisting *PIK3CA* or *TP53* gene mutations, HER2-low expression, or *ESR1* mutation variant.[33]

Among patients with bone metastases, the median progression-free survival was 9.1 months with elacestrant compared to 1.9 months with standard-of-care endocrine treatment. Similarly, patients with liver and/or lung metastases had a median progression-free survival of 7.3 months with elacestrant compared to 1.9 months with standard-of-care endocrine therapy.[33]

When comparing the number of metastatic sites, patients with fewer than three had a median progression-free survival of nine months with elacestrant compared to 1.9 months with standard-of-care, while those with three or more had an even longer median progression-free survival of 10.8 months, compared to just 1.8 months with standard-of-care endocrine therapy.[33]

The subgroup analyses suggest that elacestrant may be an option for patients with *ESR1*-mutated, endocrine-sensitive tumors regardless of metastatic site location or number. Even among patients with coexisting mutations, including *PIK3CA* and *TP53*, elacestrant demonstrated prolonged median progression-free survival compared to standard-of-care therapy. Patients with coexisting *PIK3CA* and *ESR1* mutations had a median progression-free survival of 5.5 months compared to 1.9 months with standard-of-care endocrine therapy.[33]

Patients with coexisting *TP53* and *ESR1* mutations had a median progression free survival of 8.6 months compared to 1.9 months with standard-of-care endocrine therapy.[33]

However, it should be noted that elacestrant is not indicated for mutations like *PIK3CA* or *TP53*.[17]

These results highlight a potential benefit with elacestrant in patients with tumors harboring coexisting *ESR1* and *PIK3CA* mutations, suggesting that in this subgroup, disease progression after endocrine therapy plus a CDK4/6 inhibitor may still be driven by estrogen receptors.[33]

And finally, prolonged median progression-free survival results also extended to HER2-low expression and different *ESR1* mutations. The benefit observed with elacestrant compared to standard-of-care endocrine therapy wasn't impacted by the presence of these commonly occurring mutations or molecular expressions.[33]

While these analyses were exploratory and hypothesis-generating, they suggested that certain tumors with poor prognostic factors may retain endocrine sensitivity to elacestrant. So identifying these characteristics could help guide our selection of patients who are most likely to benefit from elacestrant as a next-line option.[33]

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and Dr. Komal Jhaveri and I are discussing a subgroup analysis from the EMERALD trial, published in *Clinical Cancer Research*. The trial examined elacestrant for ER-positive/HER2-negative *ESR1*-mutated metastatic breast cancer after progression on endocrine therapy plus CDK4/6 inhibitor.

So Dr. Jhaveri, as we keep exploring the latest data on elacestrant, can you share the updated safety findings from the EMERALD trial?

Dr. Jhaveri:
The analysis showed that safety data for patients with *ESR1*-mutated tumors by prior endocrine therapy plus CDK4/6 inhibitor duration or clinical and biomarker subgroups were consistent with the safety profile in the overall population. [33]

Dr. Caudle:
And as we near the end of our program, Dr. Jhaveri, how could these results help inform treatment strategies moving forward?

Dr. Jhaveri:
Well, clinicians often face uncertainty about the right second-line treatment sequencing after progression on first-line CDK4/6 inhibitors and endocrine therapy. Ideally, in the absence of visceral crisis, we aim to exhaust all endocrine therapy options per clinical guidelines.[16,33]

In the EMERALD trial, we saw that elacestrant nearly doubled median progression-free survival compared to standard-of-care endocrine therapy—3.8 months compared to 1.9 months—with a manageable safety profile.[16] In a post hoc analysis of patients with *ESR1* mutations and at least 12 months of prior endocrine therapy plus CDK4/6 inhibitors, elacestrant showed a median progression-free survival of 8.6 months versus 1.91 months.[33]

These findings suggest that for patients with *ESR1*-mutated tumors that remain endocrine sensitive, elacestrant may support sequencing in the second-line setting before other targeted therapies or drug combinations and may delay chemotherapy, including antibody-drug conjugates. It's also important to note that these exploratory analyses in patients with *ESR1*-mutated tumors who received at least one year of prior endocrine therapy with CDK4/6 inhibitor in the metastatic setting showed consistent benefit with elacestrant compared with standard-of-care endocrine therapy across all clinically relevant subgroups of patients with poor prognostic factors, such as co-mutations or visceral metastases. For example, patients with liver and/or lung metastases saw consistent efficacy with elacestrant.[33]

Lastly, these results support current guidelines recommending routine testing for *ESR1* mutations using ctDNA at each progression to guide treatment decisions.[33] I'm looking forward to more data on tailored treatment strategies to optimize care for these patients.

Dr. Caudle:
Well, given those potential impacts, let's hear some Important Safety Information on elacestrant.

ReachMD Announcer:
IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Dyslipidemia:** Elacestrant may cause hypercholesterolemia and hypertriglyceridemia. Monitor lipid profile prior to starting treatment and periodically thereafter.
- **Embryo-Fetal Toxicity:** Elacestrant can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception.

Adverse Reactions

- **The most common (≥10%) adverse reactions**, including laboratory abnormalities, of elacestrant were musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia.

Drug Interactions

- **Concomitant use with strong and moderate CYP3A4 inducers and/or inhibitors:** Avoid concomitant use with elacestrant.

Use in Specific Populations

- **Lactation:** Advise not to breastfeed.
- **Hepatic Impairment:** Avoid use in patients with severe hepatic impairment (Child-Pugh C). Reduce the dosage for patients with moderate hepatic impairment (Child-Pugh B).

Dr. Caudle:
And as that brings us to the end of our program, I'd like to thank my guest, Dr. Komal Jhaveri, for helping us better understand these analyses of elacestrant in patients with metastatic or advanced ER-positive/HER2-negative breast cancer. Dr. Jhaveri, it was great speaking with you today.

Dr. Jhaveri:
Thank you so much for having me, it was a pleasure.

Announcer Close

If you missed any part of this discussion or to find others in this series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge.

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