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EMERALD Trial: An Analysis of Key Biomarkers and Patient Subgroups

ReachMD Announcer:
You're listening to *Project Oncology* on ReachMD. This medical industry feature, titled "EMERALD Trial: An Analysis of Key Biomarkers and Patient Subgroups," is sponsored by Stemline, a Menarini Group company. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is *Project Oncology* on ReachMD, and I'm your host, Dr. Jennifer Caudle. Today, we'll be discussing the post hoc subgroup analysis of patients from the phase III EMERALD study with ER-positive/HER2-negative *ESR1*-mutated metastatic breast cancer. And joining me for this conversation is Dr. Joyce O'Shaughnessy, who's a medical oncologist specializing in breast cancer at Texas Oncology–Baylor Charles A. Sammons Cancer Center in Dallas and is a paid consultant for Stemline Therapeutics. Dr. O'Shaughnessy, welcome to the program.

Dr. O'Shaughnessy:
Thanks for having me.

Dr. Caudle:
Before we dive in, let's take a moment here to learn some Important Safety Information on ORSERDU®, or elacestrant.

ReachMD Announcer:
INDICATION
ORSERDU (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.

IMPORTANT SAFETY INFORMATION
Warnings and Precautions

- **Dyslipidemia:** Hypercholesterolemia and hypertriglyceridemia occurred in patients taking ORSERDU at an incidence of 30% and 27%, respectively. The incidence of Grade 3 and 4 hypercholesterolemia and hypertriglyceridemia were 0.9% and 2.2%, respectively. Monitor lipid profile prior to starting and periodically while taking ORSERDU.

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

Dr. Caudle:
Now that we've heard this Important Safety Information, let's get back to you, Dr. O'Shaughnessy. Before we explore the recent subgroup analysis, I'd like to revisit the EMERALD study. Can you provide some context on the study design and why it was pivotal in evaluating elacestrant's efficacy in this patient population?

Dr. O'Shaughnessy:
Surely. So as we know, endocrine therapy plus a CDK4/6 inhibitor is standard of care for the first-line treatment of ER-positive/HER2-negative metastatic breast cancer.[1,2]

However, tumors will eventually develop treatment resistance.[2-5] And *ESR1* mutations, in particular, can be a main driver of this and are

acquired in up to 40 percent of ER-positive/HER2-negative metastatic breast cancer patients after initial first-line treatment.[6-8]

Unfortunately, *ESR1* mutations are also associated with more aggressive disease progression and poorer outcomes.[9-12]

So after disease progression on first-line therapy, physicians and patients face a critical decision-making point to select the next best option.

Now if we zero in on the EMERALD trial, its results led to the approval of elacestrant as the first oral selective estrogen receptor degrader, or SERD, for treating ER-positive/HER2-negative metastatic breast cancer patients with an *ESR1* mutation after disease progression following at least one line of endocrine therapy.[13]

The study design included men and postmenopausal women who had ER-positive/HER2-negative advanced or metastatic breast cancer who had progression of disease on one or two prior lines of endocrine therapy, at least one of which must've been in combination with a CDK4/6 inhibitor. Patients could also have had up to one line of chemotherapy in the advanced metastatic disease setting.[13]

Patients were randomized one-to-one between study arms; 239 were assigned to receive single-agent elacestrant and another 239 patients received a single-agent endocrine therapy of the investigator's choice. The primary endpoint of the study was progression-free survival in patients whose tumors harbor an *ESR1*-mutation.[13]

Baseline characteristics in the EMERALD trial were well balanced across treatment arms and consistent with patients commonly seen in clinical practice. Among patients with *ESR1* mutations:[13,14]

- 100 percent of patients had prior CDK4/6 inhibitor exposure,
- Most patients, 71 percent, had visceral metastases,
- 39 percent had received two lines of endocrine therapy ,
- 24 percent of patients had prior fulvestrant, and
- 25 percent of patients had received prior chemotherapy.

And so the primary endpoint results from the EMERALD study showed a statistically significant prolonged median progression-free survival with elacestrant at 3.8 months versus 1.9 months for standard-of-care endocrine therapy in patients with ER-positive/HER2-negative *ESR1*-mutated metastatic breast cancer following progression on prior endocrine therapy and a CDK4/6 inhibitor. These results had a hazard ratio of 0.55 with a 95 percent confidence interval of 0.39 to 0.77.[13]

Now, let's turn to the safety results from EMERALD, which was evaluated in a total of 467 patients, including 228 patients with *ESR1*-mutations.[13]

Adverse reactions, or ARs, with elacestrant were manageable, with the majority being grade one or two, and no grade four ARs were reported.[13]

With elacestrant, ARs were related to a six percent discontinuation rate, three percent dose reduction rate, and 15 percent dose interruption rate.[13]

The most common ARs, reported in at least 10 percent of patients receiving elacestrant, included musculoskeletal pain, nausea, fatigue, vomiting, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia.[13]

Serious ARs occurred in 12 percent of patients who received elacestrant, and the serious ARs that occurred in at least one percent of patients in the elacestrant arm were musculoskeletal pain in 1.7 percent of patients and nausea in 1.3 percent of patients.[13]

Fatal ARs occurred in 1.7 percent of patients who received elacestrant versus 2.6 percent of patients who received standard-of-care endocrine therapy.[13,14]

Nausea was common in EMERALD, occurring at an incidence rate of 35 percent across all grades, with most cases being grade one or two. The discontinuation rate due to nausea was low at 1.3 percent.[13]

Dr. Caudle:
Thank you for this. And before we explore the 2023 subgroup analysis, let's revisit the post hoc analysis of EMERALD that was presented in 2022, which looked at CDK4/6 inhibitor duration. What were the results here?

Dr. O'Shaughnessy:
Well, we conducted a post hoc analysis of single-agent elacestrant versus standard-of-care endocrine therapy based on the prior duration of CDK4/6 inhibitor treatment in the metastatic setting.[15]

We should keep in mind that results of these post hoc analyses of median progression-free survival by duration of CDK4/6 inhibitors are observational in nature and should be interpreted with caution, as there was no prespecified statistical procedure controlling for type one error.

Patients with *ESR1* mutations who had at least 12 months of prior CDK4/6 inhibitor plus endocrine therapy achieved a median progression-free survival of 8.61 months with elacestrant versus 1.91 months with standard-of-care endocrine therapy, which was the investigator's choice of an aromatase inhibitor or fulvestrant.[15]

The results of the EMERALD trial suggest that elacestrant could become an important endocrine sequencing agent in second-line treatment.[15]

Turning to updated safety data from this analysis, most adverse events were grade one or two. Discontinuation rates in the elacestrant arm was 3.4 percent and 0.9 percent in the standard-of-care endocrine therapy arm. These were consistent with previously reported results.[15]

To help with nausea, an adverse reaction commonly reported in EMERALD, patients may be administered antiemetics according to the physician's clinical discretion. In this analysis, antiemetic use was low across treatment arms, at eight percent with elacestrant, 3.7 percent with fulvestrant, and 10.3 percent with aromatase inhibitors.[15] Taking elacestrant with food may help reduce risk of nausea.[13]

Finally, no deaths assessed as treatment-related were reported in either arm, no hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.[15]

The results from this analysis suggest that in these patients with *ESR1* mutations, a prior duration of CDK4/6 inhibitor treatment of at least one year may indicate that the tumor is still sensitive to endocrine therapies that may overcome resistance mechanisms in the estrogen receptor ligand, such as elacestrant.[15] Estrogen receptor alpha mutations result in ligand-independent estrogen receptor activation and constitutive estrogen receptor signaling.[7]

Dr. Caudle:
Thank you for providing us with all of that background, Dr. O'Shaughnessy. And with that in mind, let's now turn to the recent subgroup analysis that was presented in 2023. How do these prior studies impact the rationale for this new post hoc analysis?

Dr. O'Shaughnessy:
So as a result of these prior analyses, we've heard from clinicians who wanted to better understand the data for elacestrant in subgroups of patients with key clinical or biomarker characteristics.

For example, although bone is the most common site of metastatic disease in this subgroup of breast cancer,[16] many patients will develop metastatic disease in the liver and/or lung, which have a poorer prognosis than having only bone metastases.[17]

And as *ESR1* mutations are associated with visceral metastases, clinicians were interested in the data for elacestrant by metastatic site.[18-23]

Additionally, we wanted more data on other common mutations that may occur in patients with *ESR1* mutations, such as those in *PIK3CA* and *TP53*, which occur in approximately 30 to 40 percent of ER-positive breast cancers and confer poor prognosis and treatment resistance.[24-34]

Also of interest was the data for elacestrant in tumors with low expression of HER2. Although about 65 percent of patients with HR-positive disease will have low expression of HER2 in their tumor, recent data suggests that the tumor biology is mainly driven by the hormone receptor expression.[35-38]

And so the rationale for this latest post hoc analysis of elacestrant in these clinical and biomarker subgroups, which usually have a poorer prognosis, was to provide more data on the profile of elacestrant.

Dr. Caudle:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jennifer Caudle, and today I'm speaking with Dr. Joyce O'Shaughnessy about the 2023 post hoc subgroup analysis of the EMERALD study, which focused on elacestrant in metastatic

breast cancer.

So, Dr. O'Shaughnessy, let's now examine the data from this subgroup analysis. What were the key outcomes here?

Dr. O'Shaughnessy:
Well first, it's important to know that the population for the post-hoc subgroup analysis was made up of the 70 percent of patients in the EMERALD trial who had an *ESR1* mutation and who received at least one year of prior CDK4/6 inhibitor therapy.[39]

And let's remember that the results of these post hoc analyses of median progression-free survival by duration of CDK4/6 inhibitors are observational in nature and should be interpreted with caution. There was no prespecified statistical procedure controlling for type one error. And ORSERDU is not indicated to target *PIK3CA* or *TP53* mutations.

And so with that in mind, let's review each of these results, starting with the comparison of the anatomic site of metastatic disease.

Now I do want to point out that patients in the bone metastases group didn't necessarily have bone-only disease. Very few patients in the EMERALD trial had only one anatomic site of metastatic disease.[39] And as noted earlier, *ESR1* mutations are associated with visceral metastases.[18] In this subgroup of 86 percent of patients who had bone metastases, the median progression-free survival was 9.13 months in patients who received elacestrant versus 1.91 months in patients who received endocrine therapy.[39]

And for the 71 percent of patients who had liver and/or lung metastases, which confer a poorer prognosis than only bone metastases,[16] median progression-free survival was 7.26 months with elacestrant versus 1.87 months with endocrine therapy.[39]

The next subgroup analysis was in the 39 percent of patients with *ESR1* mutations who also happened to have *PIK3CA* mutations, which we know have a historically poor prognosis. The median progression-free survival was 5.45 months with elacestrant versus 1.94 months with standard-of-care endocrine therapy.

Among the 48 percent of patients in this subgroup with low expression of HER2, the median progression-free survival of those on elacestrant was 9.03 months versus 1.87 months for those on standard of care. And in patients with zero expression of HER2, the elacestrant arm had a median progression-free survival of 7.39 months compared to 3.29 months in the standard-of-care arm.[39]

Lastly, let's look at *TP53* mutations, which we know occur in about 30 percent of patients with breast cancer, confer a poor prognosis, and are difficult to treat due to resistance to endocrine therapy.[31]

And we see in the EMERALD subgroup analysis that 38 percent of patients had co-mutations in both *ESR1* and *TP53*. The median progression-free survival was 8.61 months with elacestrant versus 1.87 months with standard of care. And patients with *ESR1* mutations who didn't have a *TP53* mutation had a median progression-free survival of 7.39 months with elacestrant compared to 1.9 months on endocrine therapy.[39]

Now, I do want to mention that there were no new safety signals in this EMERALD subgroup analysis, and the safety data were consistent with what was previously reported for all patients in the study.[39]

Dr. Caudle:
Thank you for that. Now as we conclude our conversation, Dr. O'Shaughnessy, can you summarize what we covered today?

Dr. O'Shaughnessy:
Yes, so just to bring this all together, in patients with ER-positive/HER2-negative *ESR1*-mutated metastatic breast cancer upon progression on first-line CDK4/6 inhibitor plus endocrine therapy, we've seen the following results:[39]

- First: In the EMERALD trial, we saw nearly doubling of median progression-free survival of 3.8 months for elacestrant versus 1.9 months for standard-of-care endocrine therapy.
- Also, elacestrant demonstrated a manageable safety profile as the majority of adverse reactions were grade one and two.
- Next, in a post hoc analysis of patients with *ESR1* mutations treated with prior CDK4/6 inhibitor plus endocrine therapy for 12 months or more, elacestrant showed 8.6 months of median progression-free survival versus 1.91 months for those on standard-of-care endocrine therapy.
- And finally, a separate post hoc analysis was completed of patients with a confirmed *ESR1* mutation and 12 months or more on a prior CDK4/6 inhibitor and endocrine therapy included patients with bone metastases, liver and/or lung metastases, *PIK3CA* mutations, HER2- low expression, and *TP53* mutations. Patients who received elacestrant had longer median progression-free survival compared to standard-of-care endocrine therapy across all of these subgroups.
- But as I mentioned previously, these data from post hoc analyses should be interpreted with caution.

Please stay tuned for Important Safety Information.

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IMPORTANT SAFETY INFORMATION
Warnings and Precautions

- **Dyslipidemia:** Hypercholesterolemia and hypertriglyceridemia occurred in patients taking ORSERDU at an incidence of 30% and 27%, respectively. The incidence of Grade 3 and 4 hypercholesterolemia and hypertriglyceridemia were 0.9% and 2.2%, respectively. Monitor lipid profile prior to starting and periodically while taking ORSERDU.
- **Embryo-Fetal Toxicity:** Based on findings in animals and its mechanism of action, ORSERDU can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ORSERDU and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ORSERDU and for 1 week after the last dose.

Adverse Reactions

- **Serious adverse reactions** occurred in 12% of patients who received ORSERDU. Serious adverse reactions in >1% of patients who received ORSERDU were musculoskeletal pain (1.7%) and nausea (1.3%). Fatal adverse reactions occurred in 1.7% of patients who received ORSERDU, including cardiac arrest, septic shock, diverticulitis, and unknown cause (one patient each).
- **The most common adverse reactions** (≥10%), including laboratory abnormalities, of ORSERDU were musculoskeletal pain (41%), nausea (35%), increased cholesterol (30%), increased AST (29%), increased triglycerides (27%), fatigue (26%), decreased hemoglobin (26%), vomiting (19%), increased ALT (17%), decreased sodium (16%), increased creatinine (16%), decreased appetite (15%), diarrhea (13%), headache (12%), constipation (12%), abdominal pain (11%), hot flush (11%), and dyspepsia (10%).

Drug Reactions

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

Use in Specific Populations

- **Lactation:** Advise lactating women to not breastfeed during treatment with ORSERDU and for 1 week after the last dose.
- **Hepatic Impairment:** Avoid use of ORSERDU in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of ORSERDU in patients with moderate hepatic impairment (Child-Pugh B).

The safety and effectiveness of ORSERDU in pediatric patients have not been established.

ORSERDU is available as 345 mg tablets and 86 mg tablets.

To report SUSPECTED ADVERSE REACTIONS, contact Stemline Therapeutics, Inc. at 1-877-332-7961 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information, including Patient Information, at the link below: pi.orserduhcp.com

Dr. Caudle:
I'd like to thank my guest, Dr. Joyce O'Shaughnessy, for helping us better understand this analysis of elacestrant in a subgroup of EMERALD study patients with metastatic or advanced ER-positive/HER2-negative breast cancer. Dr. O'Shaughnessy, it was great speaking with you today.

Dr. O'Shaughnessy:
Thanks very much. It's been my pleasure.

ReachMD Announcer:
This medical industry feature was sponsored by Stemline, a Menarini Group company. 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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