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EMERALD Expert Views: Managing ER+/HER2-, ESR1m mBC Disease Progression Post ET+CDK4/6i

Announcer:
You're listening to *Project Oncology* on ReachMD. This medical industry feature, titled "EMERALD Expert Views: Managing ER+/HER2-, ESR1m mBC Disease Progression Post ET+CDK4/6i" 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. And today, we'll be examining the clinical impact of second-line therapy, treatment sequencing, and timely biomarker testing in the management of ER-positive/HER2-negative metastatic breast cancer, with a special focus on insights from the EMERALD trial and subgroup analysis. And joining me in our discussion is Dr. Virginia Kaklamani and Dr. Anne O'Dea.

Dr. Kaklamani is a Professor of Medicine in the Division of Hematology and Medical Oncology at the UT Health Sciences Center in San Antonio. She's also the leader of the breast cancer program at the Mays Cancer Center, which is home to UT Health San Antonio MD Anderson and is a paid consultant for Stemline Therapeutics.

Dr. Kaklamani, welcome to the program.

Dr. Kaklamani:
Thank you, it's great to be here today.

Dr. Caudle:
And Dr. O'Dea is a breast medical oncologist at the University of Kansas Comprehensive Cancer Center. She's also an Associate Professor of Medicine at the University of Kansas School of Medicine. Dr. O'Dea is a paid consultant for Stemline Therapeutics.

It's great to have you with us as well.

Dr. O'Dea:
Thank you for having me.

Dr. Caudle:
Now, let's take a moment to learn some Important Safety Information on ORSERDU®, or elacestrant.

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 the Important Safety message, let's start our discussion with you, Dr. Kaklamani. Could you tell us about the clinical challenges and complexities when determining the sequencing of second-line treatment options?

Dr. Kaklamani:
Of course. So for our patients with ER-positive/HER2-negative metastatic or advanced breast cancer, the first-line standard-of-care treatment is endocrine therapy with a CDK4/6 inhibitor.[1,2] But we still face clinical challenges on how to manage patients who have disease progression after CDK4/6 inhibitor and treatment sequencing of second-line options.

Those second-line treatment options after CDK4/6 inhibitor plus endocrine therapy include endocrine monotherapy or combinations of endocrine therapy with PI3-kinase, AKT, and mTOR pathway inhibitors. And this is because we'd prefer to exhaust available endocrine treatments before using chemotherapy.[1] Now, although patients may have derived benefit with first-line standard-of-care treatment tumors can develop treatment resistance to standard-of-care endocrine therapy.[2-5]

As a result, these tumors become very difficult to treat with standard-of-care endocrine therapies, and median progression-free survival with fulvestrant monotherapy after progression on a CDK4/6 inhibitor plus endocrine therapy is about two months.[2-7] So the rise of treatment-resistant mechanisms requires a targeted treatment approach. And one of the most common drivers of endocrine therapy resistance is an acquired mutation of *ESR1*, which is an estrogen receptor gene.[8-10]

Dr. Caudle:
And as a quick follow-up, how do these mutations impact tumor behavior and patient outcomes?

Dr. Kaklamani:
ESR1 mutations are rarely seen in primary tumors before first-line treatment with endocrine therapy in the metastatic disease setting. And that's because these mutations often develop under the selective pressure of endocrine therapy and can occur in up to 40 percent of ER-positive/HER2-negative metastatic breast cancer patients and after first-line therapy.[8-10] *ESR1* mutations are not only associated with disease progression, but also with poorer prognosis.[11-14]

We also see mutations in *PIK3CA* and *TP53,* which occur in approximately 30 to 40 percent of ER-positive breast cancers. These mutations are correlated with a worse outcome for patients, regardless of when they're detected. So there's a great deal of interest in data for second-line options beyond the standard-of-care therapy for tumors based on mutational status.[15-25]

Dr. Caudle:
Now let's turn to you, Dr. O'Dea. What can you share about the considerations that go into second-line treatment decisions after CDK4/6 inhibition and endocrine therapy?

Dr. O'Dea:
Well, as Dr. Kaklamani just described, there's uncertainty on the optimal second-line sequencing of treatments after disease progression on first-line CDK4/6 inhibition and endocrine therapy, and several factors go into second-line treatment selection.

Also, when treating relevant clinical subgroups with worsened prognosis in this population, such as those having co-mutations or visceral metastases, clinicians face unique treatment challenges that require tailored approaches.

So, let's take a look at some of the considerations in selecting a second-line therapy from the current treatment landscape. Of course, the efficacy of treatment in the second line setting following a CDK4/6 inhibitor with endocrine therapy, in addition to its tolerability and safety, clearly factor into treatment selection. But we must also consider the efficacy in second-line treatment for the patient's unique tumor biology. And as Dr. Kaklamani described, this includes its endocrine sensitivity or resistance, as well as the presence of mutations such as *ESR1* or *PIK3CA*.[26]

We're also thinking about monotherapy versus combination therapy, the progression-free survival offered, the potential for further treatment resistance, and toxicity—which could lead to treatment interruption or discontinuation.[1,26] And now, based on the results of the EMERALD trial, we have elacestrant approved for the treatment of patients with ER-positive/HER2-negative *ESR1*-mutated metastatic breast cancer after disease progression on endocrine therapy.[27]

Dr. Cadule:
And with all of these considerations in mind, let's come back to you, Dr. Kaklamani, and discuss the EMERALD trial. What were the significant outcomes, and how do they contribute to our understanding of second-line treatment options?

Dr. Kaklamani:
So the phase three EMERALD study included men and postmenopausal women with ER-positive/HER2-negative advanced or metastatic breast cancer. And let me just note here that all patients on EMERALD had progressed on prior treatment with CDK4/6 inhibitor plus endocrine therapy.[27] Randomized patients were assigned to receive either single-agent elacestrant or a single-agent standard-of-care endocrine therapy, which was the investigator's choice of aromatase inhibitor or fulvestrant. The primary endpoint of the study was progression-free survival in patients whose tumors harbor an *ESR1*-mutation.[27]

The results from EMERALD showed a statistically significant prolonged median progression-free survival with elacestrant of 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 CDK4/6 inhibitor. These results had a hazard ratio of 0.55 with a 95 percent confidence interval of 0.39 to 0.77.[7,27]

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.[27] The majority of adverse reactions with elacestrant were grade one or two, with no grade four events reported.[27] And these were related to a six percent discontinuation rate, three percent dose reduction rate, and 15 percent dose interruption rate with elacestrant.[27]

The most common adverse reactions, 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.[27] Serious adverse reactions occurred in 12 percent of patients who received elacestrant. Serious events occurring 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.[27] Fatal adverse reactions occurred in 1.7 percent of patients who received elacestrant versus 2.6 percent of patients who received standard-of-care endocrine therapy.[7,27] 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.[27]

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 today I'm speaking with Dr. Virginia Kaklamani and Dr. Anne O'Dea about how findings from the EMERALD trial and subgroup analyses may impact the challenges in managing ER-positive/HER2-negative *ESR1*-mutated metastatic breast cancer post-CDK4/6 inhibition.

Now that we've reviewed the primary EMERALD results, I'd like to get back to you, Dr. O'Dea. Can you tell us about the findings from the first post hoc analysis on EMERALD, presented in 2022?

Dr. O'Dea:
Yes, a follow-up post hoc analysis of EMERALD was performed which looked at the results based on prior treatment duration of CDK4/6 inhibition. I do want to note here 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.

Now, the patients with *ESR1* mutations who had at least one year of prior CDK4/6 inhibitor treatment had a statistically significant median progression-free survival of 8.6 months with elacestrant monotherapy compared to 1.9 months with standard-of-care endocrine therapy.[28] These results 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.[28] Estrogen receptor alpha mutations result in ligand-independent estrogen receptor activation and constitutive estrogen receptor signaling.[9]

Turning to updated safety data from this post-hoc 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.[28]

To help with nausea, an adverse reaction commonly reported in EMERALD, patients may be administered antiemetics according to the physician's clinical discretion.[27] 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.[28] Taking elacestrant with food may help reduce risk of nausea.[27]

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.[28]

So, it's interesting that even after disease progression on CDK4/6 inhibitor plus endocrine therapy, a significant portion of the patient population continue to be endocrine sensitive. These patients initially and durably responded to single agent endocrine therapy and CDK4/6 inhibition, and so selecting an endocrine therapy for the next-line option would be reasonable.[28]

Dr. Caudle:
And now to follow up on the 2022 EMERALD subgroup analysis, a new subgroup analysis was recently presented in 2023. So, Dr. Kaklamani, what can you tell us about the rationale behind this analysis and the findings?

Dr. Kaklamani:
Yes, so because the EMERALD trial demonstrated elacestrant's efficacy in patients with *ESR1* mutations and the 2022 subgroup analysis found that at least one year of prior CDK4/6 inhibitor plus endocrine therapy was related to progression-free survival, we've heard from clinicians interested in the further exploration of elacestrant's data in clinically relevant subgroups of patients with *ESR1* mutations.

In particular, clinicians expressed interest in the data for elacestrant in populations with key clinical and biomarker characteristics that confer a poor prognosis, such as patients with additional mutations or visceral metastasis to the liver and/or lung.[24,29] And so we presented a recent post hoc subgroup analysis of the 70 percent of patients in the EMERALD study who had an *ESR1* mutation and received at least one year of prior CDK4/6 inhibitor plus endocrine therapy.[30]

Now before we dive into the results, let's remember again that these post hoc analyses are observational and should be interpreted with caution, and there wasn't a prespecified statistical procedure controlling for a type one error. Also, keep in mind that elacestrant isn't indicated to target *PIK3CA* or *TP53* mutations.

Now the subgroup analysis results show consistent median progression-free survival results with elacestrant versus standard of care across all clinically relevant subgroups studied, which included patients with *PIK3CA* or *TP53* mutations, liver and/or lung metastasis, or low expression of HER2.[30]

And so these findings provide new evidence to consider in the selection of next-line treatment sequencing after disease progression. For example, this subgroup analysis of patients with *ESR1* mutated tumors who received at least one year of endocrine therapy with CDK4/6 inhibitor looked at patients with bone-dominant metastatic disease and patients with visceral metastatic disease to the liver and/or lungs, and the results show that both patient groups appear to benefit from elacestrant.[30]

Additionally, the results included patients with mutations of *ESR1* who also had mutations in *PIK3CA* and/or *TP53*, which confer poorer prognosis and treatment resistance. In patients with *ESR1* mutations who also had *PIK3CA* mutations, the median PFS was 5.45 months with elacestrant versus 1.94 months with the standard-of-care endocrine therapy. And for patients with 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.[30]

In treatment sequencing for an individual patient, this shared decision-making will also need to factor in the safety profiles of the available treatment options, as well as the patient's goals of therapy.[26] And I'm personally looking forward to more data in the future on the potential for tailored treatment using elacestrant in the second-line setting.

Dr. Caudle:
And so, Dr. O'Dea, now that we've examined the EMERALD data and subgroup analyses results, how do you recommend clinicians assess whether their patients would benefit from elacestrant in the second-line setting?

Dr. O'Dea:
Well, the first point I'd like to emphasize is the need to test for *ESR1* mutations in the blood at every disease progression after first-line therapy in the metastatic disease setting to guide treatment sequencing, especially because *ESR1* mutations are rarely present in early breast cancer. These mutations develop under the pressure of endocrine therapy in the metastatic disease setting, and they increase in frequency at each disease progression.[9,31]

Unlike other mutations that are primarily stable and can be detected at the time of metastatic breast cancer diagnosis, *ESR1* mutations almost always develop as a direct result of selective pressure from prior endocrine therapy.[10] So testing for *ESR1* mutations at each time of disease progression is key to help inform your next treatment decision by including the therapeutic option of elacestrant.[31]

Circulating tumor DNA, or ctDNA for short, is the preferred and more sensitive method for detecting *ESR1* mutations, and it's minimally invasive compared to testing with tissue specimens.[27,32,33]

The National Comprehensive Cancer Network®(NCCN®) recommends evaluating *ESR1* mutational status using next-generation

sequencing or by assessing tumor tissue or the ctDNA in the blood using PCR.[34] Because *ESR1* mutations are acquired during treatment, primary archived breast cancer tissue should not be used as a source of tumor tissue for *ESR1* mutation testing. And keep in mind that tissue biopsies are heterogeneous and may not contain tumor cells with *ESR1* mutations.[35,36]

American Society of Clinical Oncology guidelines recommend routine testing for the emergence of *ESR1* mutations using liquid biopsies due to their greater sensitivity.[31] The overall turnaround time from ordering the test to seeing the patient's results is about two weeks.[37]

Dr. Caudle:
Now we've certainly covered a lot of ground today, so just to bring this all together, Dr. O'Dea, can you provide us with a quick recap of the key takeaways from our discussion?

Dr. O'Dea:
I'd be happy to. So just to summarize, clinicians face many challenges associated with the management of ER-positive/HER2-negative metastatic breast cancer after progression on first-line endocrine therapy.

And so far, we've seen the following data from the EMERALD trial:[30]

- Studied patients with ER-positive/HER2-negative *ESR1*-mutated metastatic breast cancer upon progression on first-line CDK4/6 inhibitor plus endocrine therapy. And in this trial, we saw median progression-free survival of 3.8 months versus 1.9 months for elacestrant standard-of-care endocrine therapy, respectively.
- In the EMERALD trial, the majority of adverse reactions with elacestrant were grade one or two, with no grade four events reported.
- Then, in a post hoc analysis of patients treated with prior CDK4/6 inhibitor plus endocrine therapy for 12 months or more, patients on elacestrant had a median progression-free survival of 8.6 months versus 1.91 months for those on standard-of-care endocrine therapy.
- Most recently, patients from the EMERALD trial with a confirmed *ESR1* mutation and 12 months or more on a prior CDK4/6 inhibitor and endocrine therapy were part of a separate post hoc analysis for further data on elacestrant in 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 mentioned previously, these data from post hoc analyses should be interpreted with caution. And it's important to note here that elacestrant is indicated for patients with *ESR1* mutations *only*, it's not approved to target *PIK3CA* or *TP53* mutations.[27]

Stay tuned for Important Safety Information.

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.
- **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:
And as that brings us to the end of our program, I'd like to thank my guests, Dr. Virginia Kaklamani and Dr. Anne O'Dea, for joining me to talk about how data from the EMERALD trial and subsequent post-hoc subgroup analysis may help direct the treatment of ER-positive, HER2-negative ESR1-mutated metastatic breast cancer in the second-line setting. Dr. Kaklamani and Dr. O'Dea, it was great speaking with you both.

Dr. Kaklamani:
Thanks for having us.

Dr. O'Dea:
It's been a pleasure.

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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Presented at: San Antonio Breast Cancer Symposium; December 6-10, 2022; San Antonio, TX.
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