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Advancing Care in ER+/HER2− *ESR1*m mBC: What EMERALD and Real-World Analyses Tell Us

Announcer:
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Dr. Wander is a paid consultant of Stemline Therapeutics, Inc.

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 take a closer look at elacestrant's demonstrated efficacy and safety in the EMERALD clinical trial and its effectiveness in real-world settings. We'll highlight outcomes in key patient subgroups that reflect the complexities of clinical practice in ER-positive, or hormone receptor-positive, HER2-negative, *ESR1*-mutated metastatic breast cancer.

Joining me today is Dr. Seth Wander, an Assistant Professor of Medicine at Harvard Medical School and a medical oncologist at Massachusetts General Hospital. Dr. Wander, thank you so much for being with us today.

Dr. Wander:
Thank you, I'm looking forward to it.

Dr. Caudle:
Before we begin our discussion, let's review the approved indications and usage for elacestrant.

Announcer:
INDICATIONS AND USAGE

Elacestrant is an estrogen receptor antagonist indicated for the treatment of postmenopausal women or adult men with ER+/HER2–, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

WARNINGS AND PRECAUTIONS

Elacestrant has warnings and precautions for dyslipidemia and embryo-fetal toxicity in the label.

Please stay tuned to the full program to hear Additional Safety and Highlights of the Prescribing Information.

Dr. Caudle:
So let's start with some background. Most patients with ER-positive, HER2-negative metastatic breast cancer receive endocrine therapy plus a CDK4/6 inhibitor as first-line treatment.[1-5] But once progression occurs, treatment decisions can become more complex.[1,6-10]

Now before we get into the EMERALD trial, Dr. Wander, could you walk us through what typically drives disease progression after first-line therapy, and what makes this setting challenging in clinical practice?

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Dr. Wander:
That's a great place to start. While this first-line treatment is initially effective, over time, most tumors eventually develop resistance to endocrine therapy, leading to disease progression.[11-16] At that point, treatment decisions become more challenging, as single-agent endocrine therapies such as aromatase inhibitors or fulvestrant tend to have limited durability.[1,6-10]

One of the main biological drivers of resistance in this setting is the development of *ESR1* mutations,[16,18] which often emerge under aromatase inhibitor pressure.[14-16,18,19] These mutations are reported in up to 40 to 50 percent of patients after first-line therapy,[16,20-24] and are associated with endocrine resistance, more aggressive disease features, and poorer outcomes.[25-29]

Importantly, however, tumors with *ESR1* mutations often remain dependent on estrogen receptor signaling. This provides a strong biological rationale for directly targeting or degrading the estrogen receptor after aromatase inhibitor progression.[30]

This brings us to elacestrant, an oral selective estrogen receptor degrader—or SERD—which demonstrated improved efficacy compared with standard-of-care endocrine therapy in the phase three EMERALD trial, particularly in patients with *ESR1*-mutated tumors.[17]

Dr. Caudle:
With that background in mind, let's talk more about EMERALD, which led to the approval of elacestrant. What did we learn from this trial?

Dr. Wander:
So EMERALD was a randomized, open-label, active controlled Phase three trial that enrolled men and postmenopausal women with estrogen receptor-positive, HER2-negative advanced or metastatic breast cancer who had progressed after endocrine therapy plus a CDK4/6 inhibitor. Patients were randomized to receive elacestrant or the investigator's choice of standard-of-care endocrine therapy, which included fulvestrant or an aromatase inhibitor. The primary endpoint was progression-free survival in the overall population and in a prespecified subgroup of patients with tumors harboring *ESR1* mutations.[10,17]

Looking at the EMERALD patient population, all enrolled patients had prior exposure to a CDK4/6 inhibitor, and approximately 70 percent had visceral metastases. This was a heavily pretreated patient population and about 24 percent had previously received fulvestrant and roughly 23 percent had received chemotherapy for metastatic disease. These baseline characteristics highlight that EMERALD evaluated elacestrant in a clinically challenging setting, reflecting real-world treatment complexity.[10,17]

So let's take a look at the key findings now. In the *ESR1*-mutated subgroup, median progression-free survival was longer with elacestrant compared with standard-of-care endocrine therapy, at 3.8 months versus 1.9 months, with a hazard ratio of 0.55 and a confidence interval of 0.39 to 0.77.[10,17]

When looking at the Kaplan–Meier curves from EMERALD, there is an early decline in progression-free survival observed in both treatment arms, followed by a separation of the curves over time. This likely reflects the heterogeneity of the study population, with some patients experiencing early progression and others deriving more sustained benefit.[10,17]

To better understand outcomes in patients with less prior treatment exposure, an exploratory subgroup analysis was conducted in 170 individuals with *ESR1*-mutated tumors who had not received prior chemotherapy. This subgroup represents a population with fewer lines of systemic therapy compared with the overall trial population.[31]

In this exploratory analysis, progression-free survival differed between treatment arms. Median progression-free survival was 5.3 months with elacestrant compared with 1.9 months with standard-of-care endocrine therapy, with a hazard ratio of 0.54 and a 95 percent confidence interval of 0.36 to 0.80.[31]

These findings are exploratory and should be interpreted with caution, but they provide additional context regarding outcomes in patients with less heavily pretreated disease.[31]

Dr. Caudle:
And could you tell us about the safety findings from EMERALD?

Dr. Wander:
Absolutely. So safety was evaluated in 467 patients, including 228 with *ESR1* mutations. The majority of adverse reactions were grade one or two.[17]

Among patients treated with elacestrant, nausea was the most frequently reported adverse event, occurring in 35 percent of patients,

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and was generally mild to moderate in severity.[17]

Treatment discontinuation due to adverse reactions occurred in six percent of patients; dose reductions were reported in three percent, and dose interruptions in 15 percent.[17]

Serious adverse reactions were reported in 12 percent of patients, with musculoskeletal pain in 1.7 percent and nausea in 1.3 percent. And fatal adverse events were reported in 1.7 percent of patients receiving elacestrant.[17]

Overall, the EMERALD trial showed that in these patients with *ESR1*-mutated metastatic breast cancer, elacestrant improved progression-free survival compared with standard of care endocrine therapy and was generally well-tolerated with a manageable safety profile.[32]

Dr. Caudle:
Now, the EMERALD trial also led to several post hoc exploratory analyses looking at clinically relevant patient subgroups. Can you take us through what these analyses set out to explore and some of the topline findings?

Dr. Wander:
Of course. For some background, the treatment duration on endocrine therapy plus CDK4/6 inhibitors is often considered as a clinical proxy for endocrine sensitivity.[32]

So a post hoc analysis was conducted to examine clinical outcomes among patients with *ESR1*-mutated tumors who appeared to retain endocrine sensitivity, among other clinically relevant subgroups.[32]

This analysis evaluated patients with *ESR1*-mutated tumors who had received at least 12 months of prior endocrine therapy plus a CDK4/6 inhibitor, a group often considered more endocrine-sensitive. In this subgroup, median progression-free survival was 8.6 months with single-agent elacestrant compared with 1.9 month with standard-of-care endocrine therapy. These findings were exploratory and should be interpreted in that context.[32]

An additional post-hoc analysis was performed to further examine the outcomes across clinically relevant subgroups within this endocrine-sensitive population. Improvements in median progression-free survival with elacestrant were observed across multiple clinical categories, including patients with bone metastases, those with liver or other visceral metastases, and patients with varying disease burden based on the number of metastatic sites.[32]

And when examining coexisting genomic and biologic characteristics, outcomes were evaluated in patients with tumors harboring *ESR1* and *PIK3CA* alterations, *TP53* mutations, and in those classified as HER2-low. In these exploratory analyses, median progression-free survival with elacestrant was 5.5 months in tumors with coexisting *ESR1* and *PIK3CA* alterations, 8.6 months in those with *TP53* mutations, and similar improvements were observed in the HER2-low subgroup. Elacestrant is not indicated based on *PIK3CA*, *TP53*, or HER2-low status; rather, these findings provide descriptive insight into clinical outcomes across molecular subgroups within this endocrine-sensitive population. As with other post hoc analyses, these results were exploratory and not adjusted for multiplicity, and therefore should be interpreted with caution.[32]

Dr. Caudle:
Thanks for that overview. And what about the safety findings from these post hoc subgroup analyses?

Dr. Wander:
Across post hoc subgroups, including patients with visceral disease, coexisting mutations, or more extensive prior treatment, the safety profile of elacestrant was consistent with what was observed in the overall EMERALD study population.[32]

Dr. Caudle:
For those of you 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. Seth Wander about both clinical trial and real-world data examining elacestrant for patients with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer.

So, Dr. Wander, now that we've covered the EMERALD trial and some of the post hoc subgroup findings, let's turn to elacestrant's use in clinical practice. Can you walk us through the real-world data?

Dr. Wander:
Absolutely. There are currently two published retrospective real-world evidence studies evaluating elacestrant use in U.S. clinical practice, which together include data from more than 1,000 patients treated across a range of oncology settings. One analysis used the

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GuardantINFORM database, which links circulating tumor DNA testing with longitudinal clinical outcomes. The second analysis was based on Komodo Health claims data, linked with Foundation Medicine genomic testing, which allowed for an integrated assessment of treatment patterns and outcomes in patients with *ESR1*-mutant metastatic breast cancer.[33,34]

Keep in mind, these analyses don't evaluate safety outcomes.

Both of the real-world evidence publications are available on *Clinical Cancer Research* and links are available within the related content section of this program.

It's important to note that because these studies are observational, they don't establish causality. Results may vary based on factors such as tumor burden, prior treatment, and follow-up duration.

Real-world analyses may also be subject to limitations related to the use of proxy endpoints, missing or incomplete data, variability in defining lines of therapy, and challenges associated with censoring and follow-up.

Additionally, findings from real-world analyses may differ from those observed in prospective clinical trials. And because both datasets are U.S.-based, generalizability to other regions may also be limited.

That said, these analyses offer descriptive insight into how elacestrant has been used in routine clinical practice, with outcomes reported in real-world patient populations.[33,34]

Dr. Caudle:
I'd love to dig a little deeper into both of these studies, starting with GuardantINFORM. What did that analysis show?

Dr. Wander:
This retrospective analysis included 756 patients in the U.S. with ER-positive, HER2-negative metastatic breast cancer who had an *ESR1* mutation detected by circulating tumor DNA testing within six months prior to starting elacestrant. Of these, 742 patients were evaluable for study outcomes. Clinical endpoints included time-to-next-treatment, or TTNT, time-to-treatment discontinuation, or TTD—both commonly used proxy measures for progression-free survival in retrospective real-world studies—overall survival was also measured.[33]

TTNT is defined as the interval from the start of one therapy to the initiation of the next, or death. While it may reflect aspects of disease control, tolerability, and patient adherence, TTNT doesn't account for progression in the same way as progression-free survival and may be influenced by nondisease-related factors.

This real-world cohort included patients with a high degree of disease burden and prior treatment exposure. More than half had visceral metastatic disease, and 73 percent had bone metastases. In terms of prior therapy, 52 percent had been treated with fulvestrant, 76 percent had progressed on a CDK4/6 inhibitor, and 79 percent had received an aromatase inhibitor. While most patients had received prior lines of metastatic therapy before elacestrant, including 38 percent who had four or more prior lines, nine percent were treated with elacestrant in the first-line metastatic setting.[33]

Dr. Caudle:
Now, if we take a closer look at how the real-world TTNT varied based on these key subgroups, what findings stood out?

Dr. Wander:
One finding was variation in TTNT based on prior treatment exposure. Patients who had received one or fewer prior lines of metastatic therapy had a longer median TTNT of approximately 8.8 months, compared with those who were more heavily pretreated. And in patients with two or more prior lines of therapy, median TTNT remained in the six-month range.[33]

Also, patients without prior fulvestrant had a median TTNT of 7.2 months compared with six months in those who had previously received fulvestrant.[33]

Dr. Caudle:
And did the analysis look at outcomes by molecular subgroups?

Dr. Wander:
Yes, the GuardantINFORM analysis also examined outcomes across several genomic subgroups, including co-occurring alterations often associated with more treatment-resistant biology. Tumors harboring PI3K-pathway alterations, such as *PIK3CA*, *AKT1*, or *PTEN* mutations, are associated with more aggressive biology. In this real-world analysis, patients with PI3K-altered disease had a median TTNT of 5.2 months. These results suggest that estrogen-receptor signaling may play a role in tumor biology in ER-positive, HER2-

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negative metastatic breast cancer with PI3K pathway activation.[33]

The study also assessed TTNT and TTD across *ESR1* profiles. Outcomes were similar in patients with a Y537S alteration compared with those without that variant. And when *ESR1* polyclonally was evaluated, patients with a higher burden—defined as four or more *ESR1* alterations—had shorter TTNT compared with patients with a single *ESR1* alteration.[33]

Dr. Caudle:
That's interesting. Now let's turn to the claims-based Komodo analysis. What can you tell us about this cohort?

Dr. Wander:
This retrospective analysis used U.S. claims data from the Komodo Research Dataset linked with data from the Foundation Medicine Clinical Genomic Database. This linkage enabled outcomes to be evaluated specifically in patients with genomically-confirmed *ESR1*-mutated metastatic breast cancer. The analysis included 306 patients with ER-positive, HER2-negative advanced or metastatic breast cancer treated with elacestrant in routine clinical practice. The primary outcome was also TTNT, including subgroup analyses based on prior treatments and disease characteristics.[34]

It's important to note that, as a claims-based dataset, the reasons for treatment discontinuation aren't captured and may reflect factors such as toxicity, access, or cost, rather than disease progression alone.

This cohort was predominantly endocrine-sensitive and the majority had extensive prior treatment. Nearly all patients, 94 percent, had received at least 12 months of prior endocrine therapy, with or without a CDK4/6 inhibitor, and more than half had received three or more prior lines of endocrine therapy in the metastatic setting. Close to 90 percent had exposure to a CDK4/6 inhibitor, around 70 percent had received fulvestrant, and about half had previously received chemotherapy.[34]

Patients also had substantial disease burden, as about 87 percent had visceral metastases, including 45 percent with liver involvement, and almost one in five patients had brain or spinal cord metastases.[34]

And while most patients had a single *ESR1* alteration, roughly 20 percent had two or more *ESR1* mutations detected. Co-occurring PI3K-pathway alterations were also observed in about 44 percent of patients.[34]

Dr. Caudle:
And with all of that in mind, what did this analysis show in terms of real-world outcomes?

Dr. Wander:
In the overall population, median TTNT was 7.9 months, with a 95 percent confidence interval of 7.1 to 9.8.[34]

Now when the cohort was stratified by prior endocrine therapy exposure, median TTNT was 10.8 months in patients with one prior line of endocrine therapy with or without a CDK4/6 inhibitor, 8.2 months in those with one to two prior lines, and 7.5 months in patients with three or more prior lines.[34]

TTNT also varied by disease burden. Median TTNT in patients with visceral metastases was 7.9 months and 7.2 months in those with liver metastases.[34]

Outcomes were further examined based on prior treatment exposure. Patients without prior fulvestrant exposure had a median TTNT of 12.9 months, and those without prior chemotherapy had a median TTNT of 8.4 months. Taken together, these findings describe how TTNT varied according to prior treatment exposure and other important disease characteristics.[34]

Dr. Caudle:
And what were the findings by genomic subgroups in the Komodo–Foundation analysis?

Dr. Wander:
The Komodo–Foundation analysis also evaluated TTNT across genomic subgroups, using linked Foundation Medicine data. Among patients with co-occurring *ESR1* mutations and PI3K-pathway alterations—such as *PIK3CA*, *AKT*, or *PTEN*—the median TTNT was 6.3 months.[34]

When outcomes were examined across common *ESR1* variants, median TTNT was 7.9 months in patients with variants of Y537S mutations and 8.0 months in those with D538G. And when patients were grouped by the number of *ESR1* mutations detected, median TTNT was 7.4 months in patients with a single mutation and 10.8 months in those with two or more *ESR1* mutations.[34]

Dr. Caudle:

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So when we step back and look at these real-world analyses, how should clinicians think about the findings in the broader context of the data we've discussed?

Dr. Wander:
I'm glad you asked. When we consider these findings in context, it's important to recognize that randomized clinical trials provide the most controlled assessment of efficacy and safety, while real-world analyses offer complementary insight into how treatments are used in routine clinical practice. It's important to note that these are separate retrospective real-world analyses and weren't designed for direct comparisons with each other or with randomized clinical trial data.[33,34]

With that in mind, when I look across the GuardantINFORM and Komodo–Foundation analyses, what stands out to me is that both datasets describe similar ranges of TTNT across a number of clinically relevant patient groups in U.S. clinical practice.[33,34]

In both analyses, TTNT tended to be longer in patients who have had fewer lines of prior endocrine therapy and shorter in those who were more heavily pretreated. When looking at patients with visceral disease, including those with liver metastases, TTNT estimates were within range of each other across both datasets, which helps frame how treatment duration looked in those settings.[33,34]

We also see in patients with co-occurring *ESR1* and PI3K-pathway alterations, TTNT estimates fell into a similar range in both real-world analyses. And when prior treatment exposure was considered, patients without prior fulvestrant exposure generally had longer TTNT compared with those who had received fulvestrant previously.[33,34]

Taken together, I see these real-world data as helping fill in how treatment duration with elacestrant has looked across different clinical and molecular subgroups in U.S. clinical practice. For clinicians, considering these findings alongside the clinical trial data we discussed earlier helps provide a more complete picture of the available evidence.[33,34]

Dr. Caudle:
Well that's a great point to close on. Before we go, let's hear the Highlights of the Prescribing Information for elacestrant.

Announcer:
The following content is the Highlights of Prescribing Information for elacestrant.

- These highlights do not include all the information needed to use elacestrant safely and effectively. See full prescribing information for elacestrant.

Indications and Usage

- Elacestrant is an estrogen receptor antagonist indicated for treatment of postmenopausal women or adult men, with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy.

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

- Strong and Moderate CYP3A4 Inducers. Avoid concomitant use with elacestrant. Strong and Moderate CYP3A4 Inhibitors. Avoid concomitant use with elacestrant.

Use in Specific Populations

Lactation

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- 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 with that safety message in mind, I want to thank my guest, Dr. Seth Wander, for helping us explore how real-world and clinical trial data come together to help inform treatment decisions in ER–positive, HER2-negative, *ESR1*-mutated metastatic breast cancer. Dr. Wander, it was great speaking with you today.

Dr. Wander:
Thanks for having me.

Announcer:
This medical industry feature was sponsored by Stemline Inc. US Medical Affairs.

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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