

Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: <https://reachmd.com/programs/medical-industry-feature/emerald-trial-an-analysis-of-key-biomarkers-and-patient-subgroups/16040/>

ReachMD

www.reachmd.com
info@reachmd.com
(866) 423-7849

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.

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.
- **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** ($\geq 10\%$), 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.

References:

1. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol.* 2021;32(12):1475-1495. doi:10.1016/j.annonc.2021.09.019
2. Burstein HJ, Somerfield MR, Barton DL, et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update. *J Clin Oncol.* 2021;39(35):3959-3977. doi:10.1200/JCO.21.01392
3. Zhao M, Hanson KA, Zhang Y, Zhou A, Cha-Silva AS. Place in therapy of cyclin-dependent kinase 4/6 inhibitors in breast cancer: a targeted literature review. *Target Oncol.* 2023;18(3):327-358. doi:10.1007/s11523-023-00957-7
4. Burstein HJ. Systemic therapy for estrogen receptor-positive, HER2-negative breast cancer. *N Engl J Med.* 2020;383(26):2557-2570. doi:10.1056/NEJMra1307118
5. Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. *Annu Rev Med.* 2011;62:233-247. doi:10.1146/annurev-med-070909-182917
6. Bidard FC, Hardy-Bessard AC, Dalenc F, et al. Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2022;23(11):1367-1377. doi:10.1016/S1470-2045(22)00555-1
7. Brett JO, Spring LM, Bardia A, Wander SA. ESR1 Mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Res.* 2021;23(1):85. Published 2021 Aug 15. doi:10.1186/s13058-021-01462-3
8. Santiago Novello RG, Lobo M, Silveira Vilbert M, Sanches SM, Cesca MG. Abstract 220P - Oral selective estrogen receptor degraders for metastatic hormone receptor-positive, HER2 negative breast cancer according to ESR1 mutation: a systematic review and meta-analysis of randomized control trials. *ESMO Open.* 2023; 8(1 Suppl 4):25. doi:10.1016/j.esmoop.2023.101409
9. Clatot F, Perdrix A, Beaussire L, et al. Risk of early progression according to circulating ESR1 mutation, CA-15.3 and cfDNA increases under first-line anti-aromatase treatment in metastatic breast cancer. *Breast Cancer Res.* 2020;22(1):56. Published 2020 May 28. doi:10.1186/s13058-020-01290-x
10. Turner NC, Swift C, Kilburn L, et al. ESR1 Mutations and overall survival on fulvestrant versus exemestane in advanced hormone receptor-positive breast cancer: a combined analysis of the phase III SoFEA and EFECT trials. *Clin Cancer Res.* 2020;26(19):5172-5177. doi:10.1158/1078-0432.CCR-20-0224
11. Chandarlapaty S, Chen D, He W, et al. Prevalence of ESR1 mutations in cell-free DNA and outcomes in metastatic breast cancer: a secondary analysis of the BOLERO-2 clinical trial. *JAMA Oncol.* 2016;2(10):1310-1315. doi:10.1001/jamaoncol.2016.1279
12. Zundeleovich A, Dadiani M, Kahana-Edwin S, et al. ESR1 mutations are frequent in newly diagnosed metastatic and loco-regional recurrence of endocrine-treated breast cancer and carry worse prognosis. *Breast Cancer Res.* 2020;22(1):16. Published 2020 Feb 3. doi:10.1186/s13058-020-1246-5
13. ORSERDU [prescribing information]. New York, NY: Stemline Therapeutics, Inc., a Menarini Group Company; 2023.
14. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol.* 2022;40(28):3246-3256. doi:10.1200/JCO.22.00338
15. Bardia A, Bidard FC, Neven P, et al. Abstract GS3-01: EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: updated results by duration of prior CDK4/6i in metastatic setting. Presented at: San Antonio Breast Cancer Symposium; December 6-10, 2022; San Antonio, TX.
16. Grote I, Poppe A, Lehmann U, Christgen M, Kreipe H, Bartels S. Frequency of genetic alterations differs in advanced breast cancer between metastatic sites. *Genes Chromosomes Cancer.* 2024;63(1):e23199. Published online September 6, 2023. doi:10.1002/gcc.23199
17. Gerratana L, Fanotto V, Bonotto M, et al. Pattern of metastasis and outcome in patients with breast cancer. *Clin Exp Metastasis.* 2015;32(2):125-133. doi:10.1007/s10585-015-9697-2
18. Reinert T, Coelho GP, Mandelli J, et al. Association of ESR1 mutations and visceral metastasis in patients with estrogen receptor-positive advanced breast cancer from Brazil. *J Oncol.* 2019;2019:1947215. Published 2019 Aug 14. doi:10.1155/2019/1947215
19. Fribbens C, O'Leary B, Kilburn L, et al. Plasma ESR1 mutations and the treatment of estrogen receptor-positive advanced breast cancer. *J Clin Oncol.* 2016;34(25):2961-2968. doi:10.1200/JCO.2016.67.3061
20. Kuang Y, Siddiqui B, Hu J, et al. Unraveling the clinicopathological features driving the emergence of ESR1 mutations in

- metastatic breast cancer. *NPJ Breast Cancer*. 2018;4:22. Published 2018 Aug 2. doi:10.1038/s41523-018-0075-5
21. Corné J, Quillien V, Callens C, et al. Development of sensitive and robust multiplex digital PCR assays for the detection of ESR1 mutations in the plasma of metastatic breast cancer patients. *Clin Chim Acta*. 2023;545:117366. doi:10.1016/j.cca.2023.117366
 22. Bertucci F, Ng CKY, Patsouris A, et al. Genomic characterization of metastatic breast cancers. *Nature*. 2019;569(7757):560-564. doi:10.1038/s41586-019-1056-z
 23. Jeselsohn R, Bergholz JS, Pun M, et al. Allele-specific chromatin recruitment and therapeutic vulnerabilities of ESR1 activating mutations. *Cancer Cell*. 2018;33(2):173-186.e5. doi:10.1016/j.ccell.2018.01.004
 24. Chen JW, Murugesan K, Newberg JY, et al. Comparison of PIK3CA mutation prevalence in breast cancer across predicted ancestry populations. *JCO Precis Oncol*. 2022;6:e2200341. doi:10.1200/PO.22.00341
 25. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490(7418):61-70. doi:10.1038/nature11412
 26. Sobhani N, Roviello G, Corona SP, et al. The prognostic value of PI3K mutational status in breast cancer: a meta-analysis. *J Cell Biochem*. 2018;119(6):4287-4292. doi:10.1002/jcb.26687
 27. Fillbrunn M, Signorovitch J, André F, et al. PIK3CA mutation status, progression and survival in advanced HR + /HER2- breast cancer: a meta-analysis of published clinical trials. *BMC Cancer*. 2022;22(1):1002. Published 2022 Sep 21. doi:10.1186/s12885-022-10078-5
 28. Rao X, Chen Y, Beyrer J, et al. Clinical and genomic characteristics of patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer following progression on cyclin-dependent kinase 4 and 6 inhibitors. *Clin Cancer Res*. 2023;29(17):3372-3383. doi:10.1158/1078-0432.CCR-22-3843
 29. Davis AA, Luo J, Zheng T, et al. Genomic complexity predicts resistance to endocrine therapy and CDK4/6 inhibition in hormone receptor-positive (HR+)/HER2-negative metastatic breast cancer. *Clin Cancer Res*. 2023;29(9):1719-1729. doi:10.1158/1078-0432.CCR-22-2177
 30. Meric-Bernstam F, Zheng X, Shariati M, et al. Survival outcomes by TP53 mutation status in metastatic breast cancer. *JCO Precis Oncol*. 2018;2018:PO.17.00245. doi:10.1200/PO.17.00245
 31. Ungerleider NA, Rao SG, Shahbandi A, et al. Breast cancer survival predicted by TP53 mutation status differs markedly depending on treatment. *Breast Cancer Res*. 2018;20(1):115. Published 2018 Oct 1. doi:10.1186/s13058-018-1044-5
 32. Silwal-Pandit L, Vollan HK, Chin SF, et al. TP53 mutation spectrum in breast cancer is subtype specific and has distinct prognostic relevance. *Clin Cancer Res*. 2014;20(13):3569-3580. doi:10.1158/1078-0432.CCR-13-2943
 33. Muendlein A, Geiger K, Gaenger S, et al. Significant impact of circulating tumour DNA mutations on survival in metastatic breast cancer patients. *Sci Rep*. 2021;11(1):6761. Published 2021 Mar 24. doi:10.1038/s41598-021-86238-7
 34. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol*. 2018;29(7):1541-1547. doi:10.1093/annonc/mdy155
 35. Miglietta F, Griguolo G, Bottosso M, et al. HER2-low-positive breast cancer: evolution from primary tumor to residual disease after neoadjuvant treatment. *NPJ Breast Cancer*. 2022;8(1):66. Published 2022 May 20. doi:10.1038/s41523-022-00434-w
 36. Schettini F, Chic N, Brasó-Maristany F, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer*. 2021;7(1):1. Published 2021 Jan 4. doi:10.1038/s41523-020-00208-2
 37. Gampenrieder SP, Rinnerthaler G, Tinchon C, et al. Landscape of HER2-low metastatic breast cancer (MBC): results from the Austrian AGMT_MBC-Registry. *Breast Cancer Res*. 2021;23(1):112. Published 2021 Dec 14. doi:10.1186/s13058-021-01492-x
 38. Tarantino P, Viale G, Press MF, et al. ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer. *Ann Oncol*. 2023;34(8):645-659. doi:10.1016/j.annonc.2023.05.008
 39. Bardia A, Bidard FC, Neven P, et al. Abstract PS17-02: Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with ESR1 mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial. Presented at the 2023 San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, TX.

MAT-US-ELA-00142/Copyright 2024- Stemline Therapeutics, Inc. All rights reserved. May 2024.