Poster PS2-02-04

Real-World Treatment Patterns and Clinical Outcomes in Patients With Emerging Estrogen Receptor 1 (*ESR1*)-Mutated ER+ Metastatic Breast Cancer in the U.S., 2018-2024

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Objective

- This study aimed to characterize treatment patterns of patients with metastatic breast cancer (mBC) whose tumors were tested for estrogen receptor 1 (*ESR1)* mutations during first-line (1L) therapy and assess the impact of *ESR1* mutations on clinical outcomes, including real-world overall survival (rwOS) and real-world progression-free survival (rwPFS)

Conclusions

- Patients with mBC whose tumors harbor an *ESR1* mutation during 1L had worse clinical outcomes than those who did not have an *ESR1* mutation detected
- These findings highlight the potential real-world clinical benefit of surveillance for *ESR1* mutation during 1L therapy, and the potential unmet need for treatment options that delay progression and improve survival for patients with emerging *ESR1*-mutated, estrogen receptor-positive (ER+) breast cancer

Plain language summary

Why did we perform this research?
Mutations in the *ESR1* gene can lead to resistance to certain types of endocrine therapy (ET), the standard of care treatment for patients with mBC whose tumors express the estrogen receptor, resulting in shorter survival. This real-world study aimed to assess the impact of *ESR1* mutations on real-world treatment patterns and patient outcomes

How did we perform this research?
We analyzed data from adults diagnosed with HR+/HER2- mBC from January 2018 to April 2024 using data from electronic health records during routine clinical care

What were the findings of this research?
Among the 7772 patients included in the study who received 1L treatment, most patients were not tested for *ESR1* during 1L therapy. For those tested for *ESR1* in 1L, treatment patterns were similar in 1L regardless of *ESR1* mutation status, with a CDK4/6 inhibitor plus an aromatase inhibitor (AI) being the most common regimen. In the second-line (2L) setting, patients with a known *ESR1* mutation were more likely to receive targeted therapies like elacestrant or a CDK4/6 inhibitor plus fulvestrant. Patients who had an *ESR1* mutation detected during 1L therapy had significantly worse clinical outcomes

What are the implications of this research?
There is an unmet need for therapies to treat emergent *ESR1*-mutated breast cancer before progression on 1L therapy. 1L combinations with novel selective estrogen receptor degraders hold promise for addressing these mutations

Poster | Plain language summary

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Acknowledgements

The authors would like to thank Hashem Meriesh, PhD, from Flatiron Health for medical writing support, and Teresa Tung and Moumita Chaki.

This study was funded by AstraZeneca.

Poster presented at the San Antionio Breast Cancer Symposium, December 9-12, 2025, San Antonio, TX.

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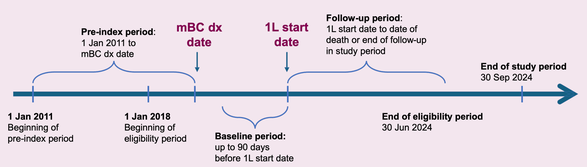
Introduction

- Activating mutations in the *ESR1* gene are a significant mechanism of resistance to endocrine therapy (ET) in ER+ mBC, and are associated with shorter progression-free and overall survival[1,2]
- The clinical relevance of monitoring for *ESR1* mutation emergence during 1L was highlighted by the clinical studies PADA-1 and SERENA 6,[3,4] where improved outcomes were observed when therapy was changed upon detection of an *ESR1* mutation
- However, less is known about the real-world practice for patients with *ESR1* mutations detected during 1L therapy and before progression, as well as their outcomes

Methods

- This retrospective, observational cohort study used the US-based, deidentified Flatiron Health Research Database[5]
- Adult patients with a confirmed diagnosis of ER+/HER2- mBC from 1/1/2018 to 6/30/2024 were included in the study (**Figure 1**)
- Treatment patterns were descriptively analyzed
- rwOS and rwPFS were estimated for patients with an *ESR1* mutation detected at first *ESR1* test during 1L (time zero) prior to progression using the Kaplan-Meier methodology and compared to those without an *ESR1* mutation detected at first *ESR1* test using 1:1 propensity score matching on key covariates (time from 1L start to first *ESR1* test result, ER expression level, presence of liver metastases, age, duration of prior AI therapy, menopausal status)

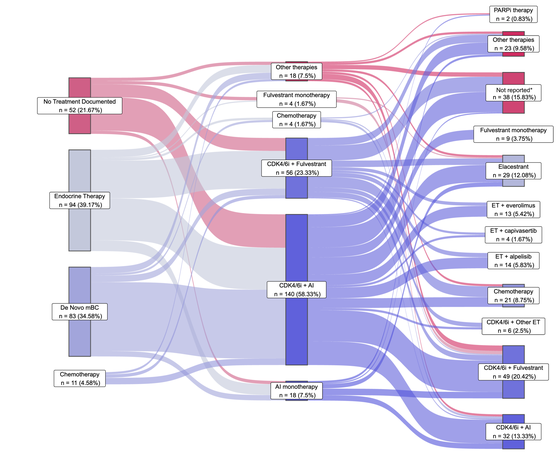
Figure 1. Study Design Diagram



Results and interpretation

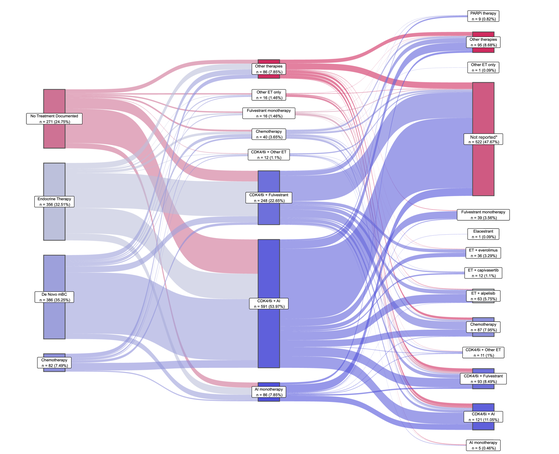
- This study included 8581 eligible patients, of whom 7772 (91%) initiated 1L therapy; *ESR1* mutation status was evaluated for 1335 patients (17%) in 1L, 1086 were eligible for rwOS and rwPFS analyses
- Median (IQR) time from 1L start to positive *ESR1* test result during 1L therapy was 18 (4-33) months
- Median time from detection of an *ESR1* mutation during 1L therapy to progression was 5.9 months
- Treatment patterns in 1L were comparable between patients with (n=240; **Figure 2**) and without (n=1095; **Figure 3**) an *ESR1* mutation detected during 1L therapy
- Patients with an *ESR1* mutation detected during 1L therapy were more likely to receive CDK4/6i + fulvestrant or elacestrant as a second-line (2L) therapy (**Figure 2**)
- A greater proportion of patients with an *ESR1*-mutant tumor detected in 1L switched to 2L therapy before clinician-documented progression compared to patients without an *ESR1* mutation detected (35/152 [23%] vs 83/918 [9%]; data not shown)
- Patients with an *ESR1* mutation detected on their earliest test during 1L therapy had shorter median rwPFS and median rwOS compared with those without an *ESR1* mutation detected (**Table 1**; **Figure 4**)
- After propensity score matching, both median rwPFS (hazard ratio [HR] 0.68 [95% CI: 0.48-0.96]) and median rwOS (HR: 0.58 [95% CI: 0.36-0.95]) were shorter in patients with an *ESR1* mutation detected during 1L therapy (**Table 1; Figure 5**)

Figure 2. Sankey Diagram of Treatment Patterns Among Patients With mBC With an *ESR1* Mutation Detected During 1L Therapy



*at time of analysis

Figure 3. Sankey Diagram of Treatment Patterns Among Patients With mBC Without an *ESR1* Mutation Detected During 1L Therapy



*at time of analysis

Table 1. Real-World Survival Outcomes

Characteristic	N	Events	Median (95% CI)
rwPFS			
ESR1 mutation detected	104	72	7.7 (5.7-11.4)
ESR1 mutation not detected	961	546	15.3 (14.0-16.8)
rwOS			
ESR1 mutation detected	105	38	32.2 (21.2-NA)
ESR1 mutation not detected	981	289	45.6 (41.7-53.9)
rwPFS (matched)			
ESR1 mutation detected	104	72	7.7 (5.7-11.4)
ESR1 mutation not detected	102	63	13.6 (9.9-16.5)
rwOS (matched)			
ESR1 mutation detected	105	38	32.2 (21.2-NA)
ESR1 mutation not detected	105	28	NA (35.4-NA)

Figure 4. A) rwPFS and B) rwOS of Patients From First Test During 1L of Therapy, Based on Earliest *ESR1* Test Result

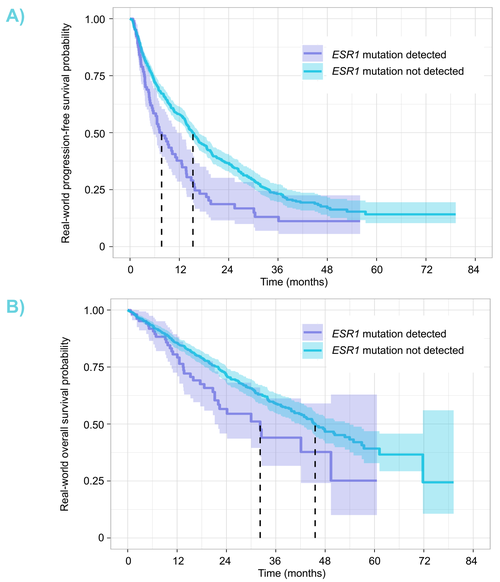
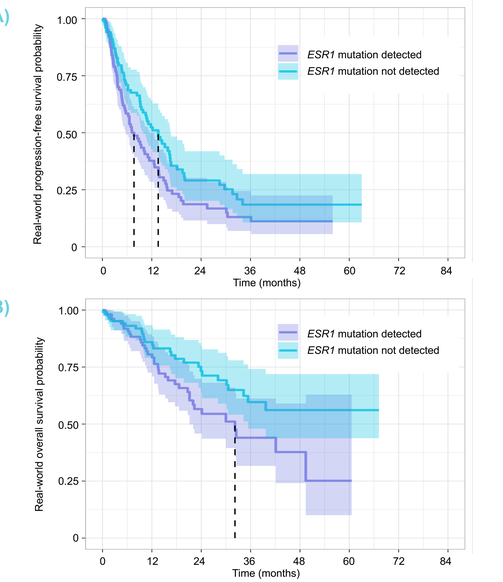


Figure 5. A) rwPFS and B) rwOS of Patients From First Test During 1L of Therapy, Based on Earliest *ESR1* Test Result (matched)



References 1. Hanker AB, et al. *Cancer Cell.* 2020;37(4):496-513. 2. Pejerrey SM, et al. *Horm Cancer.* 2018;9(4):215-228. 3. Bidard FC, et al. *Lancet Oncol.* 2022;23(11):1367–77. 4. Bidard FC, et al. *NEJM.* 2025; 93(6):569-580. 5. Flatiron Health. https://flatiron.com/database-characterization.