Real world data (RWD) outcome analysis of *ESR1* mutation emergence in HR+/HER2- metastatic breast cancer through the continuum of standard of care hormonal therapy

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INTRODUCTION

Molecular surveillance adoption in hormone receptor-positive, HER2-negative metastatic breast cancer (HR+/HER2- mBC) patients (pts) treated with aromatase inhibitor (AI) plus CDK4/6 inhibitor (CDK4/6i) therapy has the potential to inform critical treatment decisions with detected *ESR1* mutations (*ESR1m*). *ESR1m* patterns remain poorly characterized in real-world practice. We characterize *ESR1m* emergence and clinical impact in a large RWD cohort of HR+/HER2- mBC pts monitored with longitudinal testing.

METHODS

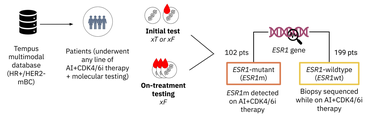
Cohort definition:
Study cohort included pts in Tempus AI's RWD, multimodal database with HR+/HER2- mBC diagnosis prior to January 2023 who:

- received AI+CDK4/6i therapy (all lines)
- had an initial Tempus xT (tissue biopsy) or xF (liquid biopsy) test within 24 months of starting AI+CDK4/6i therapy (study entry)
- Had ≥1 on-treatment xF tests (longitudinal monitoring)

Pts were stratified by *ESR1m* and ESR1-wildtype (ESR1wt) status during AI+CDK4/6i.

Outcomes analysis:

- Follow-up was measured from AI+CDK4/6i therapy initiation to death or last known activity
- Kaplan-Meier estimates of rwOS are reported. Risk set adjustment was used to account for delayed study entry, due to first biopsy sequencing occurring after therapy initiation
- Pts were censored at 60 mos after AI+CDK4/6i initiation or at last known followup. Pts who switched to elacestrant, *ESR1m* targeted therapy, were censored at its initiation
- Survival differences between ESR1m and wt groups were assessed with a log-rank test.



SUMMARY

- This analysis of a large multimodal RWD cohort from longitudinal molecular surveillance testing in HR+/HER2- mBC pts treated with AI+CDK4/6i sheds light on the continuum of *ESR1*m emergence and survival outcomes from 1L and beyond outside of clinical trial data.
- *ESR1*m is associated with reduced survival compared to *ESR1*wt regardless of line of therapy.
- Molecular surveillance indicates the complexity of *ESR1*m driven resistance including multiple mutations or co-mutations with *PIK3CA* and occurrence of rare *ESR1*m variants.

RESULTS

Table 1. Characteristics of patients in study cohort

Characteristic	*ESR1*m (n = 102)	*ESR1*wt (n = 199)
Median age (range) – yr	64 (35 - 87)	63 (29 - 86)
Female sex – no. (%)	101 (99.0%)	198 (99.5%)
Race – no. (%)		
White	56 (54.9%)	114 (57.3%)
Asian	4 (3.9%)	8 (4.0%)
Black	7 (6.9%)	13 (6.5%)
Other	13 (12.8%)	21 (10.5%)
Unknown	22 (21.6%)	43 (21.6%)
Ethnicity – no. (%)		
Hispanic	12 (11.8%)	16 (8.0%)
Non-Hispanic	61 (59.8%)	118 (59.3%)
Unknown	29 (28.4%)	65 (32.7%)
Practice type		
Non-academic	63 (61.8%)	111 (55.8%)
Academic	25 (24.5%)	65 (32.7%)
Academic & Non-academic	14 (13.7%)	23 (11.5%)
PIK3CA co-mutations – no. (%)	43 (42.2%)	65 (32.7%)
AI+CDK4/6i Line of Treatment		
1 (n=203)	69 (34.0%)	134 (66.0%)
2L+ (n=98)	33 (33.7%)	65 (66.3%)
Median number of xF tests per patient (range)	2 (1 - 7)	2 (1 - 16)
Median time from initiation of AI+CDK4/6i to *ESR1*m detection (range) — mo	19.1 (0.20 - 72.1)	--
1	21.0 (0.39 - 72.1)	--
2L+	12.3 (0.20 - 36.4)	--

Figure 1. *ESR1m* status was associated with reduced survival

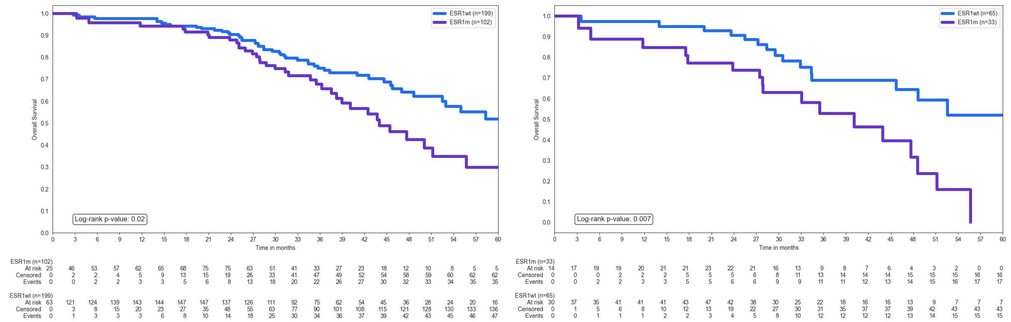


Figure 1. Kaplan Meier curves showing survival between *ESR1*m and *ESR1*wt groups. Left: Across lines of therapy (median rwOS 44.0 mo vs. not reached for *ESR1*wt; log-rank test p=0.02). Right: 2L+ (median rwOS 40.1 mo vs not reached for *ESR1*wt; log-rank test p=0.007).

Figure 2. Therapy switch patterns after *ESR1*m detection

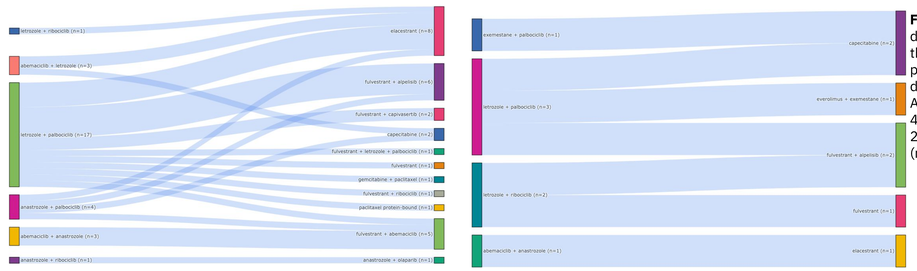


Figure 2. Sankey diagram showing therapy switch patterns after *ESR1*m detection. Left: 1L AI+CDK4/6i (n=29, 42% of 1L). Right: 2L+ AI+CDK4/6i (n=7, 21% of 2L+).

Figure 3. Top point mutation combinations at *ESR1*m detection

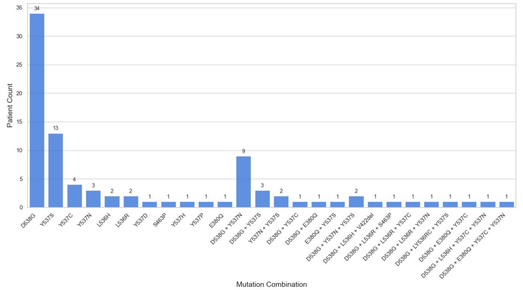


Figure 3. The most frequent *ESR1* point mutation combinations identified in the cohort at the time of *ESR1*m detection. Frequencies for each combination are shown

Table 2. Top *ESR1* mutations were comparable to those reported in SERENA-06

Top ESR1 mutations at *ESR1m* detection – no.(%)		SERENA-6 (n=158)
D538G	58 (64.4%)	82 (51.9%)
Y537S	22 (24.4%)	60 (38.0%)
Y537N	19 (21.1%)	25 (15.8%)
Y537C	9 (10.0%)	–
E380Q	5 (5.6%)	–

Death rates among patients with most common single point mutations, and among those with single vs. triple mutations:

- D538G: 41.2% (14/34)
- Y537S: 38.5% (5/13)
- Single: 49.2% (31/63)
- Triple: 75.0% (6/8)

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