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Real-world Prevalence of *ESR1* Mutations Among Patients With ER+/HER2- Metastatic Breast Cancer After First-line Treatment With Endocrine Therapy and/or a CDK4/6 Inhibitor

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Objective

- To evaluate the real-world prevalence of estrogen receptor (ER) 1 gene mutations (*ESR1*m) and co-occurring mutations after first-line (1L) treatment with endocrine therapy (ET) and/or a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) among patients with ER+, human epidermal growth factor receptor (HER2)-metastatic breast cancer (MBC)

Key Findings

- Among 1,511 patients in the GuardantINFORM database considered evaluable for *ESR1*m, 45.4% had an *ESR1*m detected in circulating tumor DNA (ctDNA) at or before start of second-line (2L) therapy
- The majority of patients had received 1L treatment with an aromatase inhibitor (AI) or selective ER modulator (SERM) in combination with a CDK4/6i (33.1%) or as monotherapy (26.5%)
  - *ESR1m* were detected in a greater proportion of patients treated 1L with an AI/SERM + CDK4/6i (48.4%) vs AI/SERM monotherapy (38.3%)
- Patients who received 1L treatment for longer durations tended to have higher rates of *ESR1*m positivity, with the highest rates observed following 1L treatment of 12 to 24 months (54.9%)
- Most patients (67.9%) with *ESR1*m-positive ctDNA also tested positive for ≥1 other oncogenic gene alteration of interest (*PIK3CA*, *PTEN*, *AKT1 E17K*, *CCND1*, *ERBB2*, *FGFR1*, *KRAS*, *MYC*, *NF1*, and/or *RB1*)

Conclusions

- This real-world analysis showed frequent occurrence of *ESR1*m after 1L endocrine-based therapy across treatment types and durations, reflecting emerging resistance in a sizeable subgroup of patients with ER+/HER2- MBC that may benefit from more targeted forms of therapy
- The high rates of co-occurring oncogenic gene alterations underscore the need for comprehensive genomic testing to guide next-line treatment decisions

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Background

- Approximately 70% of patients with breast cancer have ER+/HER2- tumors[1]
- Combination therapy with ET and a CDK4/6i is standard 1L therapy for patients with ER+/HER2- MBC[2,3]
- While this approach is initially effective, treatment resistance develops in most patients, often due to the emergence of genetic alterations in tumor cells, including *ESR1*m[4,5]
- Reported *ESR1*m prevalence rates vary widely (~20% to 50%) after ≥1 line of treatment in the metastatic setting[6-9]
- The variability in reported rates is attributable to multiple factors, including heterogeneity among patient cohorts (eg, prior duration and setting of ET)
- To better understand the real-world prevalence of *ESR1*m and co-occurring gene alterations, we evaluated the prevalence of these mutations after receiving 1L ET and/or a CDK4/6i among patients with ER+/HER2- MBC in the GuardantINFORM database

Methods

- This noninterventional, retrospective analysis identified patients in the GuardantINFORM database in the United States who received ≥1 Guardant360 liquid biopsy test between January 1, 2014, and June 30, 2024
- Patients were included in the analysis population if they had received any of the following 1L treatments within 6 months of diagnosis of metastatic disease:
  - Endocrine monotherapy (AI, selective ER modulator [SERM], or SERD), or
  - CDK4/6i monotherapy, or
  - Combination treatment with ET (AI, SERM, and/or SERD) and a CDK4/6i
- Patients must have discontinued their 1L therapy and subsequently received 2L treatment
- The *ESR1*-evaluable population included patients with an *ESR1*-negative test result ≤90 days before initiating 2L therapy (to exclude patients who may have been tested preceding the potential development of resistance to 1L treatment) or a positive *ESR1*m result at any time before starting 2L therapy
- The *ESR1*-evaluable population included patients with ctDNA-positive and ctDNA-negative samples; 91.7% of the population tested were ctDNA-positive
  - A subgroup analysis of patients with only ctDNA-positive samples showed that trends were consistent with the overall population (data not shown)
- The proportion of *ESR1*-evaluable patients who were *ESR1*m positive (any missense mutation in codons 310–547 detected in ctDNA)[10] was analyzed in the overall *ESR1*-evaluable population and by the type and duration of 1L treatment
- Other oncogenic alterations linked to endocrine and/or CDK4/6i resistance were quantified, including *PIK3CA* mutations (R88Q, N345K, C420R, E542K, E545A, E545D, E545Q, E545K, E545G, Q546E, Q546K, Q546R, Q546P, M1043V, M1043I, H1047Y, H1047R, H1047L, G1049R), *PTEN*, *AKT1* E17K, *CCND1* alterations (including amplifications), *ERBB2, FGFR1* (including fusions and amplifications), *KRAS* (including amplifications), *MYC* (including amplifications), *NF1,* and *RB1*

Results

Study population

- A total of 8,335 adults in the GuardantINFORM database met initial screening criteria and initiated 1L ET and/or a CDK4/6i (**Table 1**)
- Of these, 1,511 patients had either a positive *ESR1*m test result anytime prior to starting 2L therapy or a negative *ESR1*m test result within 90-days of starting 2L therapy – these patients were considered to have *ESR1*m testing proximally to start of 2L therapy and were the primary cohort for these analyses

Table 1: Cohort attrition

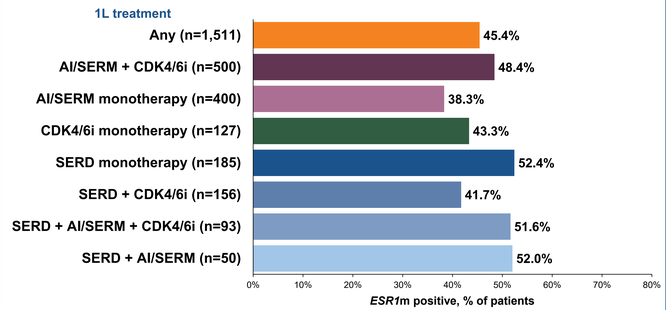
Step	Eligibility Criteria	No. of patients remaining	% of patients from previous step
1	CGP testing by a Guardant360 test on a sample with 2 distinct dates or encounters from Jan 1, 2014 to Jun 30, 2024 and MBC diagnosis code (ICD-9-CM and ICD-10-CM)	33,774	–
2	≥6 months of continuous medical and drug enrollment prior to date of MBC diagnosis	26,050	77.1%
3	Age ≥18 years and received 1L treatment with ET and/or a CDK4/6i within 6-months of the MBC diagnosis date (proxy for ER+ status), excluding other drug combinations	11,186	42.9%
4	Continuous medical and drug enrollment from date of MBC diagnosis to start of 1L therapy	11,146	99.6%
5	No other reasons for exclusion[a]	8,335	74.8%
6	*ESR1*-negative test result ≤90 days before initiating 2L therapy (to rule out false negatives from early testing preceding development of resistance) or a positive *ESR1*m test result any time before starting 2L therapy	1,511	18.1%

[a]Reasons for exclusion included (1) conflicting information between claim dates, test dates and death dates, (2) evidence (≥2 claims) of treatment for HER2+ disease (lapatinib, tucatinib, neratinib, trastuzumab, fam-trastuzumab deruxtecan-nxki, pertuzumab), (3) diagnosis of other primary cancers, other than non-melanoma skin cancer during the lookback period using ICD-9-CM and ICD-10-CM diagnosis codes, or (4) enrollment in a clinical trial during the study period, identified via ICD-9-CM and ICD-10-CM diagnosis codes.
1L=first-line; 2L=second-line; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CGP=comprehensive genomic profiling; ER=estrogen receptor; ET=endocrine therapy; *ESR1*m=ER 1 gene mutation; HER2=human epidermal growth factor receptor 2; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; MBC=metastatic breast cancer.

*ESR1*m positivity by type of 1L therapy

- Among all *ESR1*-evaluable patients, 45.4% had an *ESR1*m detected in ctDNA at or before start of 2L therapy (**Figure 1**)
- The majority of patients had received 1L therapy with an AI or SERM in combination with a CDK4/6i (33.1%; 500/1,511) or as monotherapy (26.5%; 400/1,511)
  - The *ESR1*m positivity rate was higher among patients treated with an AI/SERM plus a CDK4/6i (48.4%) vs AI/SERM monotherapy (38.3%; **Figure 1**)
- Approximately one third of patients had received a SERD as 1L therapy for MBC, either in combination with a CDK4/6i and/or an AI/SERM (19.8%; 299/1,511) or as monotherapy (12.2%; 185/1,511)
  - *ESR1*m were detected in 51.6% to 52.4% of patients who received a SERD as monotherapy or in combination with an AI/SERM ± CDK4/6i (**Figure 1**)

Figure 1: *ESR1*m positivity at or before start of 2L treatment[a] by type of 1L treatment received

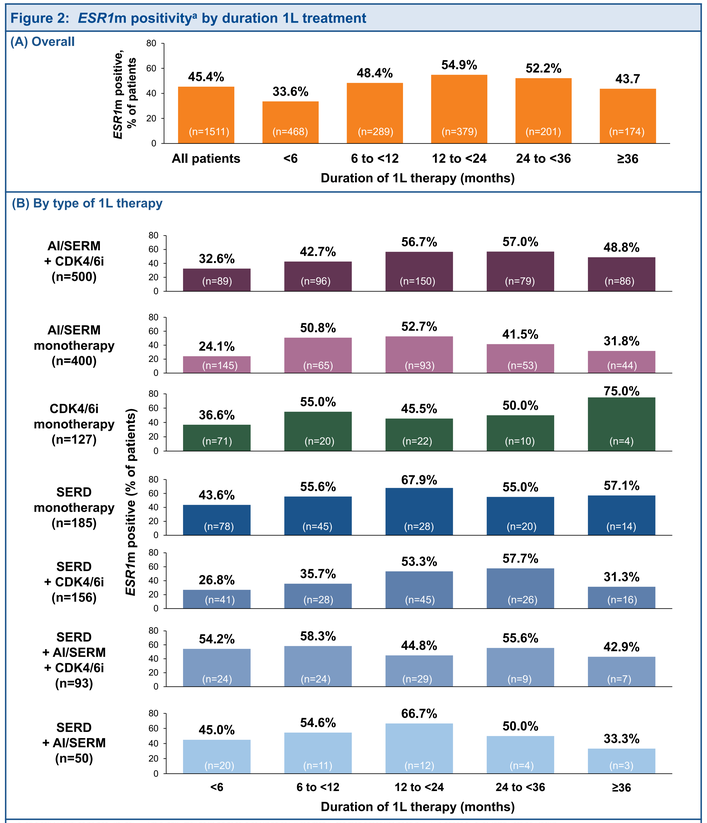


[a]Patients could have tested positive for *ESR1*m at any time, including prior to or during or 1L treatment. Treatments received prior to MBC diagnosis (ie, adjuvant) are not known.
1L=first-line; 2L=second-line; AI=aromatase inhibitor;CDK4/6i=cyclin dependent kinase 4/6 inhibitor; *ESR1*m=estrogen receptor 1 gene mutation; SERD=selective estrogen receptor degrader; SERM=selective estrogen receptor modulator.

*ESR1*m positivity by duration of 1L therapy

- Patients who had received 1L therapy for longer durations tended to have higher *ESR1*m rates, with the highest rates observed among patients treated 1L for 12 to <24 months (54.9%; **Figure 2A**)
- This trend was consistent across most 1L therapy types (**Figure 2B**)
  - *ESR1*m rates were lowest among those treated 1L with AI or SERM monotherapy for <6 months (24.1%) and highest among patients who received 1L SERD monotherapy for 12 to <24 months (67.9%)
  - Across most 1L therapy types, *ESR1*m rates were lower among patients treated for ≥36 months vs 12 to <24 months, possibly due to the small populations in these subgroups

Figure 2: *ESR1*m positivity[a] by duration 1L treatment

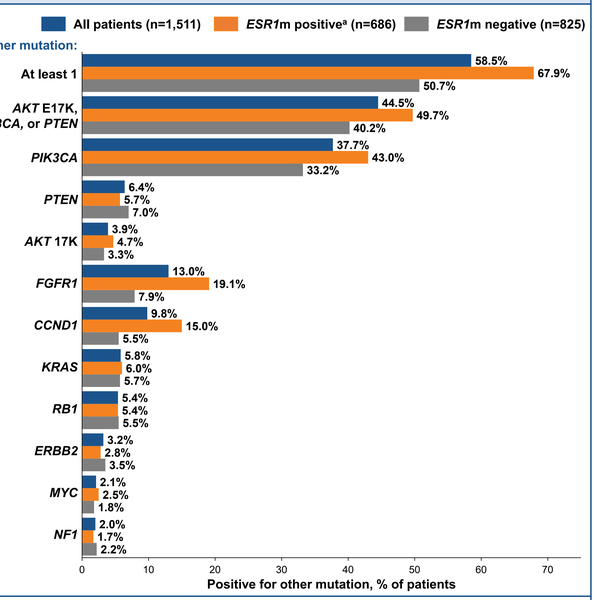


[a]Patients could have tested positive for *ESR1*m at any time, including prior to or during or 1L treatment. Treatments received prior to MBC diagnosis (ie, adjuvant) are not known.
1L=first-line;; AI=aromatase inhibitor;CDK4/6i=cyclin dependent kinase 4/6 inhibitor; *ESR1*m=estrogen receptor 1 gene mutation; SERD=selective estrogen receptor degrader; SERM=selective estrogen receptor modulator.

Co-occurring mutations

- Among all 1,511 *ESR1*-evaluable patients, 58.5% had ≥1 other oncogenic gene alteration detected in ctDNA (**Figure 3**)
- The proportion of patients with ≥1 other gene alteration was higher among patients with *ESR1*m-positive (67.9%) vs *ESR1*m-negative ctDNA (50.7%)
- *PIK3CA* mutations were the most common other alteration among patients with *ESR1*m-positive (43.0%) and *ESR1*m-negative ctDNA (33.2%)

Figure 3: Prevalence of other gene alterations of interest



[a]Patients could have tested positive for *ESR1*m at any time, including prior to or during or 1L treatment. Treatments received prior to MBC diagnosis (ie, adjuvant) are not known.
1L=first-line; *ESR1*m=estrogen receptor 1 gene mutation; WT=wild-type,

Limitations

- This analysis is subject to the limitations inherent to retrospective database analyses, including the potential for missing information and misclassification
- Potential misclassifications could include MBC status, ER and HER2 status, and timing of the start and end of 1L and 2L therapies
- There is a potential for selection bias, as only patients who underwent ≥1 Guardant360 liquid biopsy test were included; the analysis population may not represent the broader population of cancer patients, especially those who received other types of liquid biopsy or tumor tissue-based biopsy only
- Patients could have tested positive for *ESR1*m at any time, including prior to starting 1L therapy for MBC, and prior therapies received for non-metastatic disease (eg, neoadjuvant ET) are unknown; thus, the relatively high *ESR1*m rate among patients treated 1L with SERDs may be partially due to SERDs being prescribed for MBC that was *ESR1*m-positive at or before start of 1L therapy