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Systematic literature review on the prevalence and burden of estrogen receptor 1 (ESR1) gene mutations in advanced breast cancer

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ADMINISTRATIVE INFORMATION

Support - Arvinas.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - Kimberly Ruiz is an employee of Cencora. Cencora provides consulting and other research services to pharmaceutical and related organizations.

INPLASY registration number: INPLASY202590112

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 September 2025 and was last updated on 27 September 2025.

INTRODUCTION

Review question / Objective 1. What is the ESR1 testing rate and what are the ESR1 testing guidelines in key markets including but not limited to United States (US), United Kingdom (UK), France, Germany, Italy, and Spain?
2. What is the reported prevalence of ESR1 mutations and the proportion of patients who harbor select actionable co-mutations (eg, PIK3CA, AKT, PTEN) in aBC in the identified markets?
3. What are the patient characteristics, treatment patterns, clinical, economic, or societal outcomes among patients with ESR1-mutated aBC in the identified markets?
4. How does timing of testing in treatment journey, previous treatments and other factors impact the findings of objectives 1-3?

Rationale Breast cancer is a complex and heterogeneous disease, and the therapeutic approach and prognosis are greatly influenced by the status of certain molecular markers, including hormone receptors (ie, estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor 2 (HER2). Patients diagnosed with ER+/HER2- advanced or metastatic breast cancer (aBC) are often treated with endocrine combination therapy in the first-line setting. Current National Comprehensive Cancer Network (NCCN) guidelines recommend aromatase inhibitors in combination with a cyclin-dependent kinase 4/6 inhibitor. However, most patients will eventually develop endocrine resistance to current treatments, leading to disease progression. A common cause of endocrine resistance for patients with ER+ locally advanced or metastatic breast cancer is the presence of mutations in the estrogen receptor 1 (ESR1) gene after specific types of endocrine therapy (ET). ESR1 mutations are almost exclusively seen in patients with ER+/HER2- advanced or metastatic breast cancer who have previously received ET, occurring in

approximately 40% of these patients. Thus, ESR1 mutations limit treatment options for subsequent therapy. Historically, development of an ESR1 mutation after first-line treatment for ER+/HER2- metastatic breast cancer was associated with significantly lower median overall survival (OS) vs patients without an ESR1 mutation, although prognostic significance is less clear in the current treatment era. This systematic literature review (SLR) will examine the prevalence of ESR1 gene mutations, testing patterns, as well as the clinical, economic, and societal burden of ESR1 mutations in the context of ER+/HER2- aBC.

Condition being studied ESR1 mutations in ER+/HER2- advanced or metastatic breast cancer (aBC).

METHODS

Search strategy

exp breast cancer/
exp Breast Neoplasms/
((breast or mammary) adj3 (cancer* or neoplasm* or malignan* or tumor* or tumour*)).mp.
or/1-3
(metasta* or stage IV or stage 4 or stage 3 or stage III or advance*).mp.
4 and 5
((HR or ER or hormone or estrogen) adj3 (positive or pos or overexpress* or amplifi* or receptor-positive or receptor-pos)).mp.
hormone receptor positive breast cancer/
exp estrogen receptor positive breast cancer/
hormone receptor-positive, HER2-negative breast cancer/
or/7-10
estrogen receptor alpha/
("estrogen receptor 1" or "oestrogen receptor 1" or "estrogen receptor alpha" or "oestrogen receptor alpha" or ESR1 or "ESR 1" or ESR-1).mp.
or/12-13
6 and 11 and 14
exp animal/ not exp human/
(rat or rats or mouse or mice or murine).ti. or (nonhuman or in vitro study or in vivo study).hw.
case report/ or case study/ or (case* adj2 (report* or series)).mp.
(note or letter or editorial or comment or study guide or protocol).pt.
exp animals/ not exp humans/
letter/ or news/ or editorial/ or comment/ or note/ or study guide/
(letter or editorial or comment or study guide).pt.
review.pt. not (systematic adj2 review).pt,ti,ab.
or/16-23
15 not 24
conference$.pt,st.
limit 26 to yr="1974 – 2022"
25 not 27
remove duplicates from 28
limit 29 to english language.

Participant or population Population for epidemiology research questions:
Patients with ER+/HER2- aBC
• Studies of HR+/HER2- disease will be included during title/abstract screening since ER+ is a subtype of HR+ disease
• aBC will include populations described as stage III and IV
• aBC will include populations described as locally advanced
Studies where ESR1m are not discussed in the abstract and studies with sample size <30 patients will be excluded.
Population for clinical, economic, and societal burden research questions:
Patients with ER+/HER2- aBC with ESR1 mutation
• Studies of HR+/HER2- disease will be included during title/abstract screening since ER+ is a subtype of HR+ disease
• aBC will include populations described as stage III and IV
• aBC will include populations described as locally advanced
Studies where ESR1m are not discussed in the abstract will be excluded and studies where the number of patients with ESR1 <10 will be excluded.

Intervention No restrictions on interventions or comparators.

Comparator No restrictions on interventions or comparators.

Study designs to be included Observational studies and guidelines.

Eligibility criteria Studies only reporting outcomes for ESR1 co-occurring with mutations other than AKT/PTEN/PIK3CA will be excluded.
Studies on ESR1 expression rather than ESR1 mutations will be excluded.
ESR1 testing validation studies will be excluded.

Information sources

MEDLINE and Embase (via Ovid.com)
• Manual check of bibliography lists of any relevant SLRs/MAs
• Manual check of references used for elacestrant model inputs
• Elacestrant NICE submission
• NCCN, ASCO, ACS, and ESMO websites

• Relevant conferences listed below. Any conferences that are not indexed in Embase will be hand searched.
- ISPOR
- ISPOR EU
- ASCO
- ESMO
- ESMO BC
- SABCS
- AACR
- MBCC.

Main outcome(s)
For studies reporting epidemiology evidence, inclusion was limited to the following outcomes:
ESR1 testing rates
Method of ESR1 test (liquid or tumor)
ESR1m prevalence (including co-occurring mutations)
Point prevalence
Prevalence trends over time
Studies only reporting outcomes for ESR1 co-occurring with mutations other than AKT/PTEN/PIK3CA will be excluded.
Studies on ESR1 expression rather than ESR1 mutations will be excluded.
For studies reporting clinical, economic, or societal burden evidence, inclusion was limited to the following outcomes:
Treatment patterns:
Number of prior treatments
Type of prior treatments
Current treatments
Clinical burden:
Overall survival
Progression-free survival/Time to next treatment/Time to treatment discontinuation
Response (OR, DoR)
Clinical benefit rate
Rates of treatment resistance
Mortality
Patient reported outcomes
Economic burden:
Direct costs
Indirect costs
Healthcare resource use
Societal burden:
Health-related quality of life
Productivity loss
Absenteeism/presenteeism
Social impact of disease.

Data management Citations retrieved by the literature searches will be downloaded into reference management software (EndNote X20 [Clarivate Analytics; Philadelphia, PA]). Duplicates will be identified and removed using bibliographic information including title, author, journal, publication date, and doi. The remaining references will be uploaded using DistillerSR software (Evidence Partners, Ottawa, ON) for screening of the literature.
A data extraction template (DET) will be developed in MS Excel® to capture the data elements of interest from each study type. Before conducting full data extraction, the DET will be piloted with data extracted from 3 articles to ensure that all data elements of interest are captured. Then the DET will be finalized and full data extraction will be conducted by 1 researcher with full validation by a second independent researcher.

Quality assessment / Risk of bias analysis The Newcastle-Ottawa Scale will be used for prospective cohort studies, the Motheral et al. checklist for retrospective cohort and registry studies, the Joanna Briggs Institute (JBI) checklist for cross-sectional studies, and the Drummond Economic Evaluation Study Checklist for economic evaluations.

Strategy of data synthesis We will not conduct a feasibility assessment for any type of meta-analysis. Prevalence data may be combined if they are from similar data sources and have a similar study design. We would report combined prevalence data by country, if possible. If any clinical, economic, and societal burden data is reported by the same patient subgroup and with similar study designs (eg inclusion criteria), we may report combined data as appropriate, stratified by time on first line therapy, prior treatment, response to prior treatment, current treatment, line of therapy, and treatment resistance.

Subgroup analysis None planned.

Sensitivity analysis None planned.

Language restriction English language only.

Country(ies) involved United States.

Other relevant information The SLR will be conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (CHSRI, version 5.1.0) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The publications will be screened by 2 reviewers, with conflicts resolved by a third independent reviewer, at both the title/abstract and full-text screening levels. A preliminary list of included studies will be generated following title/abstract review. Then full-text review will be completed in order to narrow the results to the final list of included studies. Full manuscripts and

conferences abstracts will be evaluated using the same criteria, with the exception of an added publication date restriction for conference abstracts; only conference abstracts from the last 2 years will be included whereas there is no publication date limit for full manuscripts. Reason for exclusion will be documented at the full-text screening level. The reference lists of any included SLRs and meta-analyses will be checked against the final list of studies to ensure that all relevant publications have been identified.

Keywords Metastatic breast cancer; advanced breast cancer; ESR1 mutations; biomarker testing.

Dissemination plans Conference and manuscript submission will be considered.

Contributions of each author

Author 1 - Kimberly Ruiz - Kimberly co-designed the study, reviewed the protocol, and is leading the project team that is conducting the review.
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Author 2 - Stella Stergiopoulos - Stella co-designed the study, reviewed the protocol, and is providing regular review of deliverables and input to the team conducting the review.
Email: stella.stergiopoulos@pfizer.com
Author 3 - Chloe Grace Rose - Chloe co-designed the study, reviewed the protocol, and is providing regular review of deliverables and input to the team conducting the review.
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