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Understanding ESR1 Mutations in Metastatic Breast Cancer

Testing and Implications Guide

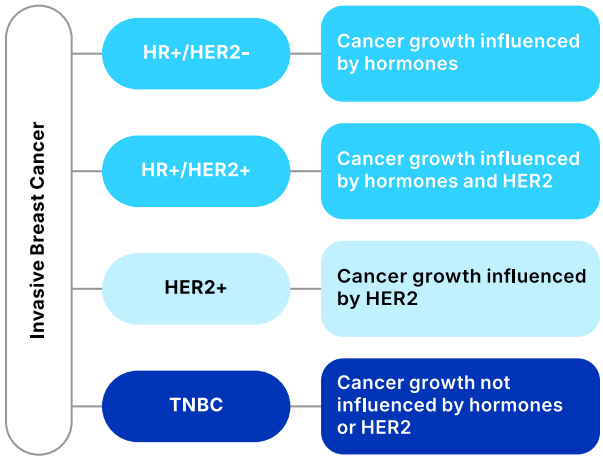


Introduction

Cancer represents the second highest cause of non-communicable death worldwide, only behind heart disease, with an estimated 10 million deaths globally every year.[1] The advent of precision therapeutics, specialized treatments which target an individual's specific tumor biology, has radically improved outcomes for patients with advanced cancer, adding years of disease-free life and offering hope to millions of patients around the world.[2] Unfortunately, many of these targeted therapies eventually fail due to acquired mechanisms of resistance that render these cutting-edge therapies ineffective.[2] In this educational backgrounder, we take a deeper look at acquired mutations in the *ESR1* gene, a common cause of treatment resistance and disease progression for patients with advanced breast cancer, and review how new approaches to *ESR1* mutation surveillance and intervention are aiming to rescue patients from treatment failure before it occurs.

Hormone Receptor-Positive Breast Cancer

Breast cancer is the most common cancer and second leading cancer-related cause of death in women around the world, with an estimated 2.3 million diagnoses and 670,000 deaths reported in 2022.[3] Over 99% of breast cancers occur in women with over 80% occurring in those without any known family history or hereditary risk.[1] Availability of non-invasive screening modalities, such as mammograms, has led to improvements in early breast cancer detection, with nearly two-thirds of newly diagnosed cases classified as localized disease.[4] Most breast cancers are diagnosed in post-menopausal women, with two-thirds of newly diagnosed patients being over the age of 55.[5]



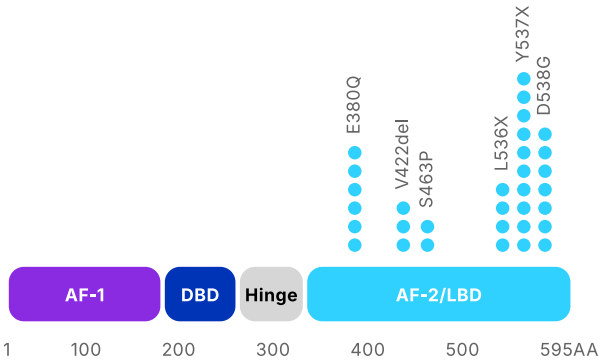
Breast cancer treatment is largely determined by biological subtyping, which is assigned by immunohistochemical assessment: estrogen receptor (ER) +/- progesterone receptor (PR)-expressing tumors, collectively regarded as hormone receptor-positive (HR+) subtype, human epidermal growth factor receptor 2-positive (HER2+) subtype, and those who show no ER, PR, or HER2 expression, known as the triple negative (TNBC) subtype.

The HR+/HER2- subtype is by far the most common form of breast cancer, accounting for approximately 70% of all breast cancers and conferring the most favorable prognosis.[6] If systemic treatment is warranted, patients with this subtype generally respond well to endocrine therapies aimed at interrupting the hormonal signaling pathways which play an active role in powering the disease.[4] Of these treatments, aromatase inhibitors (AIs), which interrupt the conversion of androgens to estrogens, are the most widely prescribed and generally best-tolerated, conferring durable responses in most patients.[7] Examples of AIs include anastrozole (Arimidex®), letrozole (Femara®), and exemestane (Aromasin®). For pre-menopausal patients, combination of these treatments with ovarian suppression therapy (leuproline (Lupron®), goserelin (Zoladex®) may be necessary to further deprive the cancer of estrogen.[8] This treatment approach is referred to as the ER blockade strategy. In metastatic disease, where the tumor has spread beyond the site of origin to other areas of the body, the addition of cyclin-dependent kinase 4/6-inhibitors (CDK4/6i), including palbociclib (Ibrance®), ribociclib (Kisqali®), and abemaciclib (Verzenio®), is considered standard of care to interrupt cell division and induce apoptosis in cancer cells.[4]

ESR1 Mutations in Advanced Breast Cancer

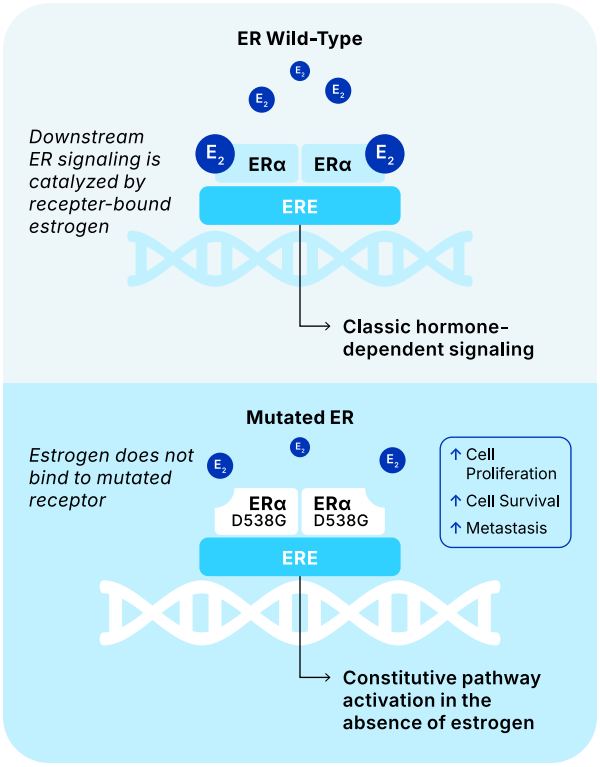
Although the ER blockade strategy confers durable responses in most patients, treatment resistance and failure does occur, resulting in disease recurrence and progression.[8,9] In advanced disease, the most common form of primary treatment resistance stems from the acquisition of point mutations in the ligand-binding domain (LBD) of the *ESR1* gene, which encodes for the alpha subunit of the ER.[10] These mutations account for roughly 40% of primary treatment resistance in this patient group and result in constitutive activation of the ER, catalyzing active downstream signaling even in the absence of ER-bound estrogen.[8] This estrogen-independent disease transformation induced by *ESR1* mutations therefore renders the cancer resistant to endocrine therapies which limit the body's production of estrogen, thus allowing the disease to progress.

Structural Diagram of ERα Protein



AF-1: activation function-1 | **AF-2:** activation function-2
DBD: DNA-binding domain | **LBD:** ligand-binding domain
ESR1 mutations associated with primary treatment resistance are concentrated in the ligand binding domain of the *ESR1* gene.

ESR1 LBD Mutations Confer Constitutive Activation of ER Signaling



ESR1 ligand binding domain mutations confer constitutive activation of the ER signaling pathway even in the absence of bound estrogen.
ERα: estrogen receptor alpha | **E2:** estrogen | **ERE:** estrogen receptor element | **ERα D538G:** ERα with *ESR1* D538G mutation

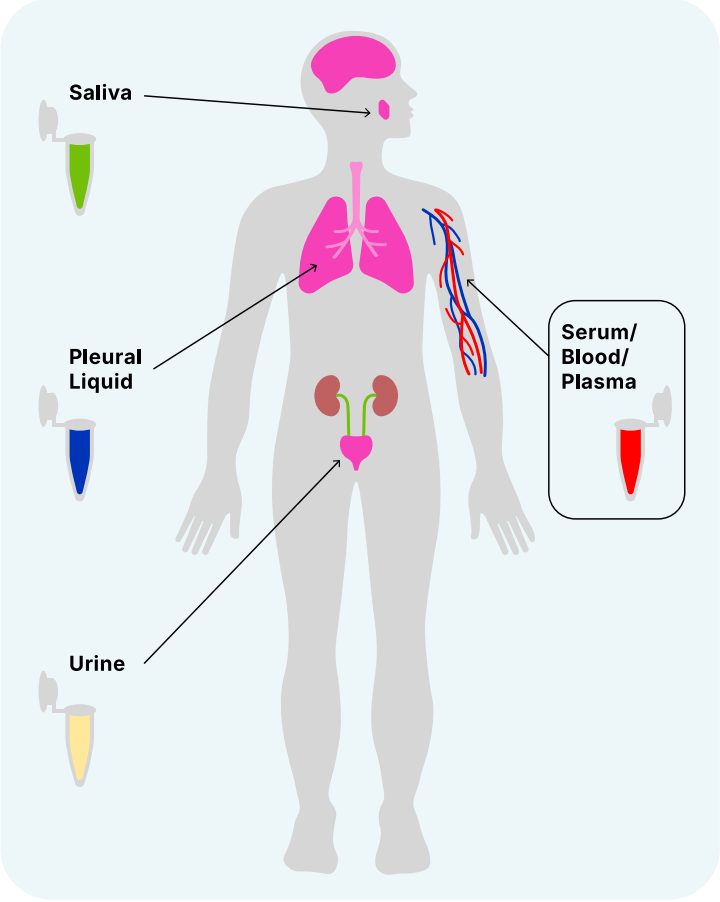
In January 2023, the US Food & Drug Administration approved elacestrant (Orserdu®), the first targeted therapy for HR+, metastatic breast cancer (mBC) patients presenting with any one or more of a number of *ESR1* mutations who have progressed following treatment with endocrine therapy.[11] In the registrational, Phase III EMERALD trial, HR+ mBC patients with at least 12 months prior exposure to CDK4/6i, experienced a significant improvement in median progression-free survival (mPFS) taking monotherapy elacestrant compared to those taking fulvestrant (Faslodex®), an injectable, selective ER degrader (SERD), or an AI (mPFS of 8.61 vs 1.91 months, HR 0.41).[12] Subsequently, in September 2025, the FDA also approved imlunestrant (Inluriyo™) as a monotherapy for patients who have progressed following treatment with an AI + CDK4/6i, highlighting an mPFS improvement of 5.5 months for imlunestrant compared to 3.8 months for patients continuing on investigator's choice of endocrine therapy.[13]

More recently, in May 2026, the FDA approved vepdegestrant (Veppanu™), a first-in-class PROTAC (proteolysis-targeting chimera) degrader, which actively binds and destroys the ER on cancer cells, for patients harboring an *ESR1* mutation following frontline AI+CDK4/6i therapy. In the registrational VERITAC-2 trial, vepdegestrant reduced the risk of progression or death by 43%, with patients receiving the novel drug exhibiting a mPFS of 5.0 months compared to 2.1 months for those receiving fulvestrant.[14]

Molecular Surveillance via Liquid Biopsy

The recommended testing approach for *ESR1* mutations is a "liquid biopsy," a laboratory test done on a sample of blood, urine, or other body fluid to look for cancer cells from a tumor or small pieces of DNA, RNA, or other molecules released by tumor cells into a person's body fluids.[15] Since *ESR1* mutations are extraordinarily rare in treatment-naïve patients and typically arise from selective pressure on the ER from sustained endocrine therapy exposure, liquid biopsy testing presents a highly sensitive, minimally-invasive means of testing for clinically meaningful *ESR1* mutations without the need for surgical tissue resection.[8] To date, most testing for *ESR1* mutations is performed on circulating tumor DNA (ctDNA), fragments of DNA shed from tumor cells into the bloodstream via apoptosis and necrosis, in human plasma.[8] Various molecular technologies, including real-time, quantitative polymerase chain reaction (qPCR), digital PCR (dPCR), and next-generation sequencing (NGS), have demonstrated the ability to accurately detect *ESR1* mutations from human plasma, reaching sensitivity of ≤1% variant allele frequency (VAF).[8]

Liquid Biopsy Samples



Emerging Need for *ESR1* Mutation Surveillance

The emergence of novel, oral SERDs has cemented *ESR1* mutation testing in key breast cancer clinical practice guidelines, including those curated by the National Comprehensive Cancer Network (NCCN), the American Society for Clinical Oncology (ASCO), and the European Society for Medical Oncology (ESMO).[16] While these guidelines currently recommend *ESR1* mutation testing at clinical progression following frontline AI + CDK4/6i treatment, emerging clinical data is paving the way for *ESR1* mutation surveillance during frontline therapy to intervene with effective therapies *before* a patient experiences anatomical progression.

The first of these studies, PADA-1 (NCT03079011), was sponsored by UNICANCER and was conducted over several public hospitals in France beginning in 2017. In this Phase III, proof-of-concept study, over 1,000 HR+/HER2- mBC patients on frontline endocrine therapy were tested every 2 months for the presence of an *ESR1* mutation from a plasma specimen using droplet digital PCR (ddPCR). If a mutation was detected, patients were then randomized 1:1 to either continue on AI + CDK4/6i treatment or instead switch to fulvestrant + CDK4/6i. The primary endpoint explored in this study was whether a statistically significant extension of median progression-free survival (mPFS) would be observed in patients receiving fulvestrant early based on serial *ESR1* mutation surveillance.[17]



The results were impressive and provocative. In evaluating the mPFS data, the fulvestrant arm of patients experienced a near doubling of mPFS compared to those who remained on standard of care therapy [12.8mos vs 5.8mos; HR: 0.54].[17]

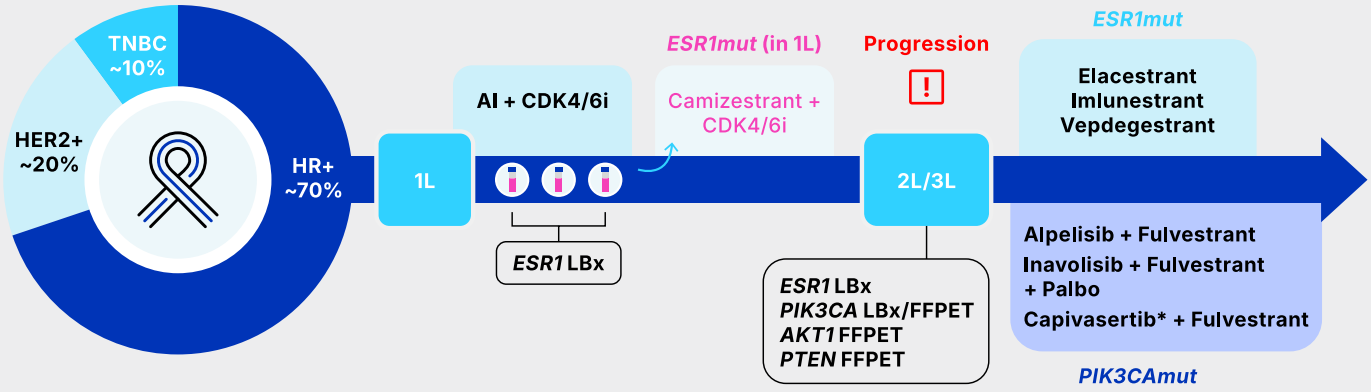
This observed improvement in mPFS was also clearly attributable to the early switching strategy, with patients switching to fulvestrant once radiological progression had occurred was a mere 3.5mos.[17] Furthermore, early intervention seemed to provide a protective benefit to patients; those who switched to fulvestrant early also saw a delayed time to the second progression event (mPFS2) by nearly 16 months [29.4mos vs 14.0mos; HR: 0.37].[17] While Overall Survival (OS) data remains immature, these preliminary metrics certainly suggest that the liquid biopsy-powered early switching strategies employed in these studies may confer significant improvements to patient outcomes.

This promise of extended mPFS via early treatment switching was expanded upon in the Phase III SERENA-6 (NCT04964934) trial, which substituted fulvestrant for camizestrant, an investigational, oral SERD developed by AstraZeneca. The trial followed a similar schema to PADA-1 in that patients were routinely monitored for the presence of *ESR1* mutations via plasma every 2–3 months; patients (n=315) with detectable mutations were similarly randomized 1:1 to either continue on existing frontline therapy (n=158) or switch to camizestrant + CDK4/6i (n=157).[18] In this study, a centralized NGS panel was used to screen for the 11 most prevalent *ESR1* mutations associated with endocrine therapy resistance from plasma specimens.[19]

SERENA-6 read out its updated median PFS data at the 2026 American Society of Clinical Oncology (ASCO) Annual Meeting further confirming that the trial has met its primary endpoint of statistically improved mPFS in the early switching arm. In this interim analysis, patients who switched to camizestrant early following a detectable *ESR1* mutation exhibited a mPFS of 16.8 months, compared to just 9.2 months for those who remained on the standard of care [HR: 0.45, 55% reduction in risk of death or progression].[18] Also at the 2026 ASCO Annual Meeting median PFS2 data was presented for the SERENA-6 trial, showing that patients who switched to caminzestrant early, beginning from the start of second-line therapy following a detectable *ESR1* mutation, experienced a mPFS2 of 25.7 months, compared to 19.1 months for those who remained on standard of care with an aromatase inhibitor [HR: 0.63, 37% reduction in risk of progression or death]. While the OS data remains immature, based on what has been observed with PADA-1 and SERENA-6 thus far, there is understandably much excitement around the promise this strategy holds for patients with advanced breast cancer.

SERENA-6 is a landmark study in that it is the first registrational trial for a novel therapy to be approved based on routine monitoring for treatment resistance events—in this case, *ESR1* mutations—and administering treatment in *advance* of radiological progression. Camizestrant was granted fast-track designation from the FDA, and the promising data from SERENA-6 is highly supportive of drug approval. During the months of May - August, 2026 Camizestrant (Etcamah™) has been approved in UAE, Saudi Arabia, Japan, the European Union, and Canada. In September the FDA in the United States also approved the drug for use, subject to the future completion of an additional clinical trial. Furthermore, since administration of the drug in the trial was based on *ESR1* mutations detected while on frontline therapy (i.e., in advance of progression), this approval will usher in a new era of testing for patients with advanced disease: catching signs of early treatment resistance and rescuing the patient with an effective therapy before their condition worsens.

Emerging Testing Paradigm in HR+/HER2- mB



Conclusion

ESR1 mutations have emerged as a core predictive biomarker to guide downstream treatment decisions in HR+/HER2- mBC. Given their acquired, subclonal nature, testing is recommended to be performed on liquid biopsy specimens using highly sensitive assays capable of detecting these low-level mutations from plasma. While current clinical practice guidelines endorse *ESR1* mutation testing at progression following endocrine therapy failure, emerging clinical data from the PADA-1 and SERENA-6 trials are catalyzing the need for *ESR1* mutation surveillance in routine clinical practice. Liquid biopsy testing may be a relatively novel tool in the battalion against cancer, but its impact is already transforming the way patients are tested, treated, and managed.

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