Endocrine Sequencing in *ESR1*-Mutant HR+/HER2− Metastatic Breast Cancer: A Two-Case Series

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Abstract

Background: Breast cancer is the most common cancer and the leading cause of cancer-related death in women worldwide, with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) tumors comprising approximately 70% of breast cancer. Endocrine therapy combined with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors is standard for advanced disease; however, resistance often develops, frequently driven by estrogen receptor 1 (*ESR1*) mutations. Emerging therapies, such as the oral selective estrogen receptor degraders (SERDs) Elacestrant, demonstrate significant benefit, particularly in *ESR1*-mutated tumors. We report two HR+/HER2− metastatic cases illustrating endocrine resistance and the evolving role of SERDs in management.

Case presentations: Case 1 involved a premenopausal, breast cancer gene (BRCA) wild-type woman diagnosed in 2013 with estrogen receptor−positive (ER+)/progesterone receptor−positive (PR+)/HER2-negative/invasive lobular carcinoma (ILC) of the left breast, who developed bone metastases three years after initial therapy; sequential endocrine therapy with Palbociclib and Denosumab maintained disease control, and Elacestrant was initiated in 2023 to overcome emerging *ESR1* mutations (Y537N, Y537S), achieving 11 months of progression-free survival (PFS) until temporary interruption for spinal surgery; subsequent progression required Capecitabine and palliative radiotherapy. Case 2 involved a 46-year-old woman diagnosed in 2020 with de novo bilateral breast cancer harboring *ESR1* (Y537S, D538G), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) E545K, and GATA-binding protein 3 (GATA3) S427fs mutations. She was started on Goserelin, Ribociclib (CDK4/6 inhibitor), Letrozole (aromatase inhibitor), and Denosumab. Disease progression in the bone was observed in May 2024, prompting a switch to Elacestrant in June 2024. This resulted in disease control for 15 months. Subsequent progression in October 2025 was managed with Capivasertib plus Fulvestrant.

Conclusion: Carefully selected endocrine therapies can provide meaningful disease control in metastatic hormone receptor-positive breast cancer, even in the presence of resistance-associated mutations. Real-world evidence demonstrates that Elacestrant is effective in ER-positive, HER2-negative, *ESR1* mutant disease, particularly when used earlier in the metastatic course. These findings highlight the clinical value of Elacestrant and underscore that the therapeutic potential of endocrine therapy should not be underestimated, with genomic profiling and prior treatment history guiding optimal sequencing.

Keywords: ER-positive breast cancer, *ESR1* mutation, Elacestrant, Endocrine therapy resistance, SERDs.

Abbreviations

- ANC: Absolute Neutrophil Count
- BRCA: Breast Cancer gene
- CAP: CT Chest, Abdomen, and Pelvis
- CDK4/6: Cyclin-Dependent Kinases 4 and 6
- CT: Computed Tomography
- CtDNA: Circulating Tumor DNA
- DCIS: Ductal Carcinoma in Situ
- ECG: Electrocardiogram
- ER: Estrogen Receptor
- *ESR1*: Estrogen Receptor 1 gene
- FDG - Fluorodeoxyglucose
- GATA3 - GATA binding protein 3
- HER2: Human Epidermal Growth Factor Receptor 2
- IDC: Invasive Ductal Carcinoma
- ILC: Invasive Lobular Carcinoma
- LBD: Ligand Binding Domain
- MRI: Magnetic Resonance Imaging
- PET-CT: Positron Emission Tomography−Computed Tomography
- PFS: Progression-Free Survival
- PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
- PR: Progesterone Receptor
- SBRT: Stereotactic Body Radiotherapy
- US: Ultrasound

Introduction

Breast cancer is the leading cause of cancer-related death for women worldwide and the most frequently diagnosed cancer [1]. Approximately 70% of breast cancer cases are Hormone Receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-), which typically have a good prognosis [2]. Endocrine-based therapies, especially in combination with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, remain the recommended first-line treatment for advanced disease and provide significant clinical benefits [3]. However, endocrine resistance often develops over time, resulting in disease progression or recurrence [2,4].

Mutations in the ligand-binding domain (LBD) of the estrogen receptor 1 (*ESR1*) gene are a well-known mechanism of acquired resistance in estrogen receptor-positive (ER+) breast cancer [5,6]. These mutations result in constitutive, ligand-independent activation and stabilise the receptor in an active conformation, which decreases the effectiveness of conventional endocrine therapies [5,6]. In ER-positive breast cancer, aromatase inhibitor therapy can select for acquired *ESR1* mutations, which are linked to endocrine resistance and disease progression [6]. In metastatic hormone receptor–positive breast cancer, *ESR1* mutations commonly emerge during endocrine therapy and are most reliably detected through liquid biopsy through circulating tumour DNA (ctDNA), which allows real-time monitoring of acquired resistance [5-7].

Additional actionable mutations, such as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), which can co-occur with other mutations, including *ESR1*, can be identified through tumour tissue analysis. Tumour-based sequencing studies have characterised the frequency and distribution of PIK3CA somatic alterations in breast cancer [8]. Furthermore, ctDNA exhibits good diagnostic accuracy for PIK3CA detection, which supports the complementary role as a minimally invasive tool to assess tumour heterogeneity and guide targeted therapy [9]. Mutations in GATA binding protein 3 (GATA3), particularly those affecting exon 6, have also been linked to altered tumor behavior and breast cancer progression, indicating their relevance in disease biology [10].

Invasive ductal carcinoma (IDC) is the most common subtype of invasive breast cancer, accounting for approximately 70-80% of cases [11]. IDC commonly arises from ductal carcinoma in situ (DCIS) and shares key driver mutations with *DCIS*, including *PIK3CA, TP53*, and *GATA3*, supporting a clonal evolutionary relationship. This progression involves additional molecular changes that enable invasion, such as the activation of oncogenic signaling pathways, epithelial–mesenchymal transition, and interactions within the tumor microenvironment [12]. Invasive lobular carcinoma (ILC) is less common and accounts for 5–15% [13-15]. ILCs exhibit distinct histopathologic and molecular characteristics, including discohesive growth with single-file ('Indian file') infiltration and loss of E-cadherin (CDH1) expression [14,15]. These tumors are typically ER–positive, progesterone receptor–positive (PR+), and HER2-negative, and frequently present as diffuse, ill-defined lesions, contributing to lower mammographic detectability [14,15]. ILC is also associated with higher rates of multifocal and bilateral disease and demonstrates distinct metastatic patterns, preferentially involving the peritoneum, gastrointestinal tract, ovaries, retroperitoneum, and meninges, as well as a propensity for late recurrence [14,15]. Molecular analyses further reveal recurrent co-alterations in *PIK3CA, AKT1, ERBB2*, *ESR1*, and *FGFR1*, which may inform targeted therapy approaches and explain variability in clinical outcomes [14]. Approximately 70% of patients with advanced breast cancer will develop bone metastasis [16]. These differences necessitate individualized treatment strategies and extended surveillance.

In recent years, significant improvements in progression-free survival (PFS) and overall survival (OS) have been achieved in HR+/HER2– metastatic breast cancer with the introduction of CDK4/6 inhibitors, such as Palbociclib, Ribociclib, and Abemaciclib, in combination with endocrine therapy [3]. Despite these advances, resistance to CDK4/6 inhibitors involves alterations in cell cycle regulators and activation of compensatory signaling pathways, including cell cycle specific and non specific mechanisms such as changes in the CDK4/6–retinoblastoma (Rb) protein axis, where phosphorylation of Rb by cyclin D–CDK4/6 normally controls the G1-to-S phase transition and other proliferative pathways necessitating the development of novel therapeutic approaches [17,18]. In the phase III EMERALD trial, Elacestrant significantly improved PFS compared with standard-of-care endocrine therapy in patients with ER-positive/HER2-negative advanced or metastatic breast cancer who had previously received endocrine therapy and a CDK4/6 inhibitor. The benefit was particularly pronounced in patients with *ESR1*-mutated tumors, demonstrating the clinical relevance of targeting estrogen receptor mutations [19]. Subgroup analyses of the EMERALD trial showed that Elacestrant provided the greatest PFS benefit in patients with *ESR1*-mutated tumors who retained endocrine sensitivity following prior CDK4/6 inhibitor therapy, including those with longer durations of prior endocrine treatment [20].

We describe two cases of HR+/HER2– metastatic breast cancer with *ESR1* mutations: one a recurrent metastatic ILC and the other a de novo bilateral breast cancer of mixed ductal and lobular histology. These cases illustrate patterns of endocrine resistance and the evolving role of SERDs in disease management.

Case presentations

Case 1

Left ILC, ER+/PR+/HER2-, breast cancer gene (BRCA) negative with *ESR1* (Y537N, Y537S), CTNNB1 T41A

A premenopausal woman, BRCA wild-type, was initially diagnosed in July 2013 with left breast ILC (ER 90%, PR 80%, HER2-negative), staged cT2N1M0. She received neoadjuvant chemotherapy with Fluorouracil, Epirubicin, and Cyclophosphamide ×4 cycles, followed by Paclitaxel ×12 weekly doses.

In March 2014, she underwent a left lumpectomy with axillary lymph node dissection (ALND). Postoperative pathology confirmed a 3 cm residual invasive lobular carcinoma with associated ductal carcinoma in situ, and eight of nine lymph nodes were positive for metastasis. Because margins were initially involved, a re-excision achieved clear margins. She completed adjuvant radiotherapy and was started on adjuvant Tamoxifen.

Two years later, in July 2016, she developed severe back pain. Imaging revealed an L5 vertebral fracture and diffuse bone metastases, for which she underwent spinal decompression and palliative radiotherapy. Computed tomography (CT) also showed small liver lesions that remained stable. In September 2016, treatment was switched to Goserelin, Letrozole, Palbociclib, and Denosumab. Follow-up CT in May 2019 revealed no new lesions, stable compared to October 2018. In November 2019, CT showed increasing anterior and right lateral compression of T11 with no new lesions. She received palliative radiotherapy to T11 and completed therapy by March 2020. She continued the same

medications - Goserelin, Letrozole, Palbociclib, and Denosumab and remained stable until October 2023.

In October 2023, CT chest, abdomen, and pelvis (CAP) showed a right iliac lytic bone lesion with a surrounding soft-tissue component, likely metastatic, and lytic bone lesions involving the left acetabular and ischium. The *ESR1* (Y537N, Y537S) mutation was positive.

In November 2023, her therapy was changed to Elacestrant 345 mg/day, with continued Goserelin and Denosumab until March 2025. She also received palliative pelvic radiotherapy in December 2023.

She remained progression-free on Elacestrant for approximately 11 months until March 2025, when spinal trauma led to pathological fractures of L2 and L3. She underwent extensive spinal surgery, including L2 and L3 corpectomies with tumor mass excision, anterior L1–L4 interbody cage implantation, and lumbar spinal canal decompression with L1–L4 discectomies. Posterior T12–S1 pedicle instrumentation and fixation were performed, along with complete excision of lumbar spine and flank soft tissue dermal tumors. Biopsies were taken from the L2 vertebral bone, L2–L3 intervertebral disc, and posterior tumor excision, and Elacestrant was discontinued for more than three months.

By May 2025, positron emission tomography/computed tomography (PET-CT) revealed widespread disease progression, including diffuse bone metastases, new lymphadenopathy, bilateral pleural effusions, and soft tissue deposits. She was subsequently started on oral Capecitabine alongside ongoing Denosumab, with palliative radiotherapy to the spine recommended for symptom control (Figure 1, 2 & 3).

Case 2

ER-positive, HER2-negative bilateral breast carcinoma with *ESR1* (Y537S, D538G) and PIK3CA (E545K) mutations; GATA3 S427fs mutation (Guardant360 ctDNA testing); NF1 variant of uncertain significance; BRCA1/2 negative

A 46-year-old woman first noticed a right breast lump during the ninth month of pregnancy in July 2019, but ignored further evaluation until she delivered in August 2019. In October 2019, breast magnetic resonance imaging (MRI) and ultrasound (US) revealed a suspicious right upper outer quadrant mass; biopsy confirmed ILC (ER+, PR−, HER2++). She was first seen in the oncology clinic in January 2020. Mammogram showed a spiculated right upper outer quadrant lesion measuring 34 × 50 × 37 mm with no axillary lymphadenopathy; US showed a right

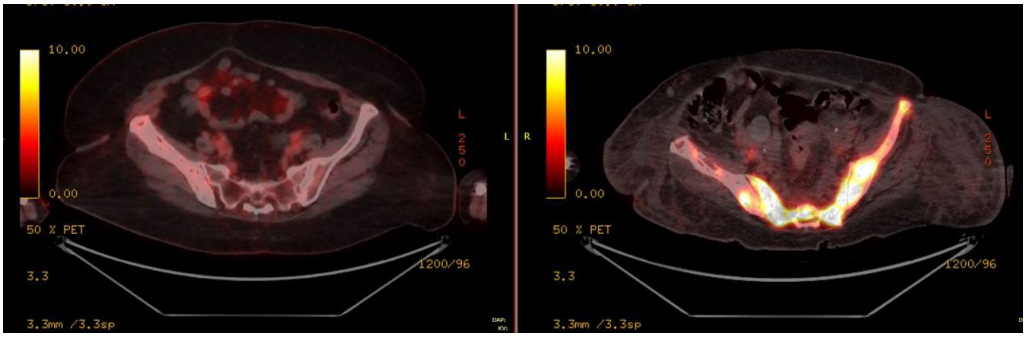

Figure 1. Comparison of lesions before and after Elacestrant therapy (Right vs Left).

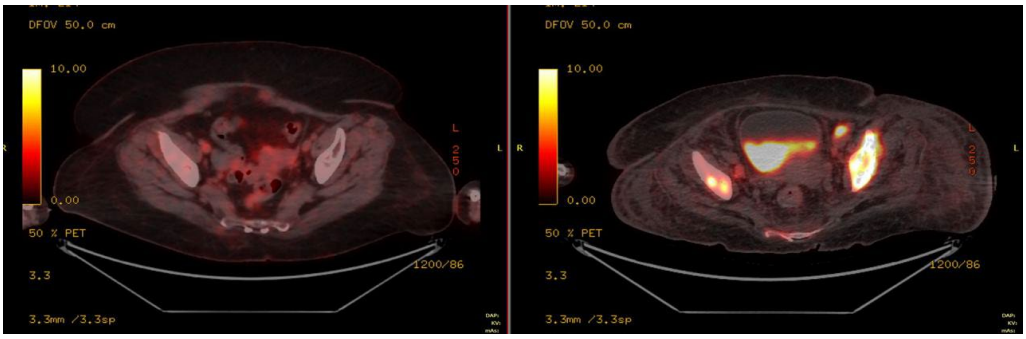

Figure 2. Comparison of lesions before and after Elacestrant therapy (Right vs Left).

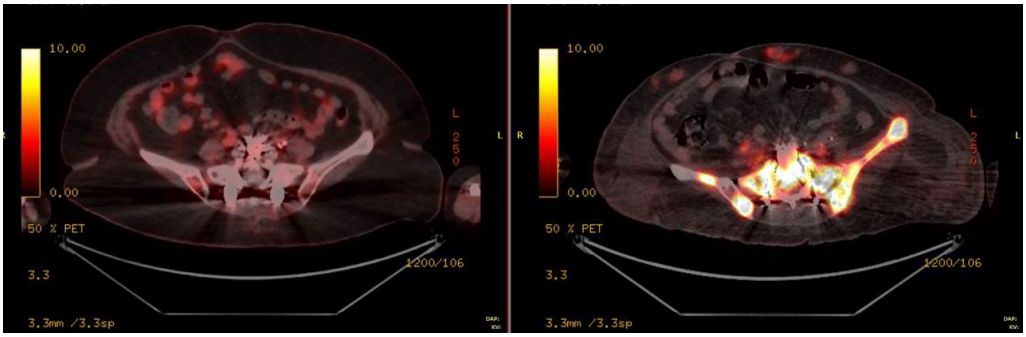

Figure 3. Comparison of lesions before and after Elacestrant therapy (Right vs Left).

breast lesion 77 × 22 × 47 mm and a left breast lesion 20 × 14 × 13 mm. CT and bone scan were negative for metastases. Bilateral breast biopsies confirmed IDC in the left breast (grade 3, ER 90%, PR 30%, HER2 equivocal, fluorescence in situ hybridization (FISH) negative, Ki-67 30–40%) and ILC in the right breast (grade 2, ER 80%, PR <1%, HER2 equivocal, FISH negative, Ki-67 5–10%). She was found to be pregnant again in March 2020 and deferred a planned bilateral mastectomy, delivering her second child in August 2020.

Follow-up imaging in November 2020 showed an interval increase in size of bilateral breast lesions with a newly developed left breast lesion. CT in December 2020 revealed aggressive lytic lesions in the sternum, left iliac bone, and T10 vertebral body; bone scan confirmed metastasis in the manubrium. She was started on Goserelin 3.6 mg, Ribociclib (CDK4/6 inhibitor), Letrozole (aromatase inhibitor), and Denosumab. Baseline electrocardiogram (ECG) showed QTc 418 ms and Estradiol 216.

Treatment was delayed six weeks in February 2021 due to COVID-19 infection, and therapy was restarted in March 2021 with Anastrazole and Ribociclib. MRI spine in April 2021 showed metastatic lesions in L3, L4, and both iliac bones. CT in May 2021 showed an interval decrease in breast lesions and sclerosis of bony metastases, suggestive of a healing flare. Absolute Neutrophil count (ANC) at that time was 0.82 ×10 /L, improving to 1.24 ×10 /L in June 2021, allowing continuation of therapy. Ribociclib dosing was adjusted due to vaginal bleeding and severe itching, with subsequent cycles (C5–C10) continued along with Goserelin, Letrozole, and Denosumab. PET/CT in December 2021 showed no fluorodeoxyglucose (FDG)-avid disease.

In 2022, PET/CT in April and breast US from April to June demonstrated a partial response in breast lesions with stable treated bone metastases. MRI spine in June 2022 showed a mild increase in T9 and L4 metastatic deposits without fractures. PET/CT in August 2022 showed treated bone metastases but progression in the right breast, leading to surgical consultation. Breast US in September 2022 demonstrated a partial response of left breast lesions and stable right breast lesions. PET/CT in December 2022 confirmed decreased metabolic activity of right breast lesions with stable bone metastases.

In 2023, the patient remained on Ribociclib, Letrozole, and Goserelin until mid-March, managing chronic knee pain, weight gain, and dental issues. PET/CTs and breast US in March, April, and July 2023 showed regressive breast lesions and stable bone metastases. Denosumab was held intermittently for dental procedures, and ANC remained within normal limits. Ribociclib was held in December 2023 for surgery.

In January 2024, stereotactic body radiation therapy (SBRT) to oligometastatic lesions in the right acetabulum and T9 spine had been completed. Following evidence of progressive bone metastases on PET/CT in May 2024 (Figure 4), the patient was transitioned to Elacestrant in the last week of June 2024. PET/CT in September 2024 showed a response in treated lesions, with stable disease elsewhere. MRI brain in October 2024 showed no metastases, though idiopathic intracranial hypertension was suspected. MRI of the thoracolumbar spine/pelvis in November 2024 revealed stable, known lesions.

In 2025, an MRI of the spine/pelvis in January showed known vertebral and pelvic metastases without new lesions. PET/CT in February 2025 demonstrated continued metabolic response with decreased activity in the right breast and stable pelvic metastases (Figure 5). PET/CT in May 2025 demonstrated a mixed response with no rise in tumor marker CA 15-3 with no new symptoms clinically, and the patient continued on her treatment. PET/CT in October 2025 confirmed progression of metabolically active bony metastases (Figure 6). Overall, Elacestrant provided

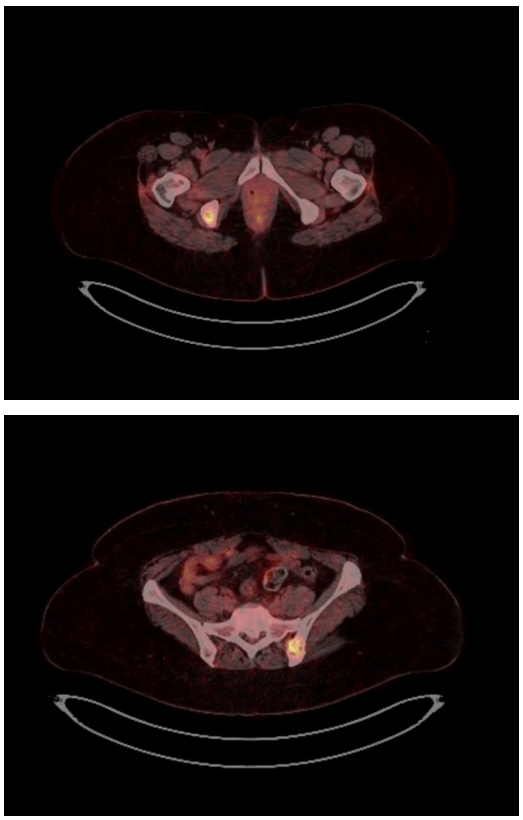

Figure 4. PET scan showing bone pelvic disease progression on CDK4/6 inhibitors, May 2024.

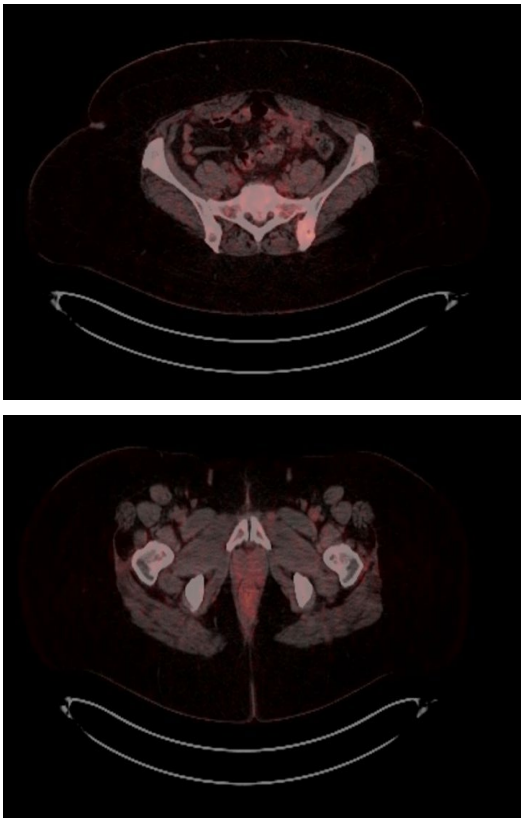

Figure 5. PET scan showing decreased FDG uptake with increased sclerotic in pelvic bones, indicating treatment response, February 2025.

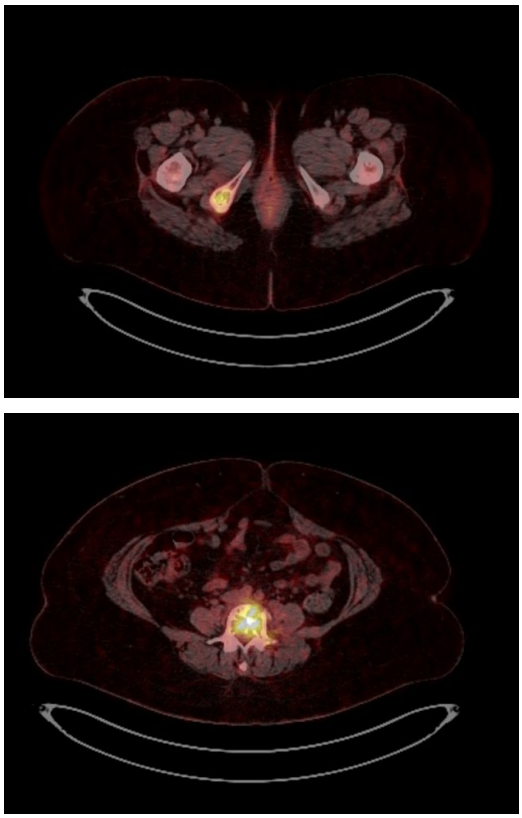

Figure 6. PET scan showing increased FDG uptake in pelvic bone disease, indicating disease progression, October 2025.

Table 1: Clinical and molecular characteristics of two *ESR1*-mutant ER+/HER2- metastatic breast cancer.

	Case 1	**Case 2**
Patient age / menopausal status	Premenopausal	46 years, premenopausal
Histology	ILC (left breast)	Bilateral breast cancer: Left IDC, Right ILC
Molecular profile	*ESR1 (Y537N, Y537S), CTNNB1 T41A*; *BRCA* wild-type	*ESR1 Y537S, ESR1 D538G; PIK3CA E545K; GATA3 S427fs; BRCA1/2* negative
Prior therapy duration before Elacestrant	~7 years	~3.5 years
Sites of metastasis at the start of Elacestrant	Bone: L2, L3, L5, T11, pelvis (iliac bone, acetabulum, ischium); Soft tissue deposits near the spine and pelvis; Liver: small lesions (stable)	Bone: T9, L3, L4, pelvis (iliac bones, right acetabulum); Bilateral breast lesions
Elacestrant PFS (months)	11	15
Type of response to Elacestrant	Stable disease while on therapy; progression occurred after Elacestrant was stopped due to spinal surgery.	Reduction in spine and pelvic bone metastases; breast lesions remained stable; progression occurred while on therapy, likely driven by PIK3CA co-mutation
Key outcomes	Durable disease control on Elacestrant	Radiological response with clinical benefit

approximately 15 months of progression-free disease control (Table 1).

In November 2025, therapy was transitioned to Capivasertib 400 mg orally twice daily (4 days on, 3 days off) in combination with Fulvestrant and Denosumab 120 mg due to disease progression and PIK3CA co-mutation.

Discussion

The two cases presented here illustrate the variable but often prolonged clinical course of ER-positive, HER2-negative metastatic breast cancer with *ESR1* mutations. Both patients demonstrated sustained endocrine sensitivity despite resistance-associated genomic alterations. Case 1 involved a premenopausal woman initially diagnosed with early-stage left ILC who developed bone metastases approximately three years later. She achieved disease control for several years on sequential endocrine therapy combined with a CDK4/6 inhibitor. Disease progression occurred after a temporary interruption of Elacestrant, which had previously provided around 11 months of PFS. Case 2 described a 46-year-old woman with de novo bilateral breast cancer diagnosed postpartum, who harbored *ESR1* (Y537S and D538G), PIK3CA (E545K), and GATA3 (S427fs) mutations detected via ctDNA next-generation sequencing. She

achieved a partial response to aromatase inhibitor plus CDK4/6 inhibitor therapy, followed by a favorable response to Elacestrant for approximately 15 months. Following disease progression, therapy was switched to AKT inhibitor-based treatment with Capivasertib plus Fulvestrant.

ESR1 mutations in the LBD are a common mechanism of acquired resistance to endocrine therapies in metastatic hormone receptor–positive breast cancer, leading to constitutive estrogen receptor activation and ligand-independent signaling [5,21]. Preclinical studies demonstrate reduced sensitivity of *ESR1*-mutant tumors to selective estrogen receptor modulators and degraders, but clinical evidence supports continued activity of Fulvestrant and newer oral selective estrogen receptor degraders in this setting [5,21]. Accordingly, molecular testing for *ESR1* mutations via ctDNA or tumor tissue next-generation sequencing is recommended to guide endocrine therapy sequencing in advanced ER-positive, HER2-negative breast cancer, reflecting the integration of this biomarker into current clinical practice guidelines [21]. Beyond endocrine resistance, *ESR1* activating mutations may also promote chemotherapy resistance by upregulating multidrug resistance protein 1 (MDR1) through the c-Jun N-terminal kinase (JNK)/c-Jun signaling pathway, suggesting a potential therapeutic strategy to restore chemosensitivity [22].

The two cases further illustrate the distinction between acquired and intrinsic endocrine resistance. Case 1 involved an acquired *ESR1* mutation that occurred after prolonged endocrine therapy, whereas Case 2 presented with de novo *ESR1* mutations (Y537S and D538G) along with PIK3CA and GATA3 mutations. Despite these resistance-associated mutations, both patients derived meaningful clinical benefit from Elacestrant, consistent with results from the phase III EMERALD trial. In the EMERALD trial, Elacestrant demonstrated improved PFS in patients with *ESR1*-mutant, ER-positive, HER2-negative metastatic breast cancer [19]. Subgroup analyses showed that patients previously treated with endocrine therapy plus CDK4/6 inhibitors for at least 12 months experienced a marked median PFS benefit (8.6 vs 1.9 months; HR 0.41), with consistent efficacy across *ESR1*(D538G) and *ESR1*(Y537S/N) mutations [20]. These findings support the use of Elacestrant after prior endocrine therapy and CDK4/6 inhibitors, including in patients harboring dual *ESR1* mutations, as illustrated in Case 2.

In Case 2, the PIK3CA E545K mutation indicated activation of the PI3K–AKT–mTOR pathway, a key driver of endocrine resistance in HR+/HER2− advanced breast cancer, and targeting this pathway with Capivasertib plus Fulvestrant significantly improved PFS in the phase III CAPItello 291 trial, particularly in tumors harboring PIK3CA, AKT1, or PTEN alterations [23, 24]. GATA3 mutations frequently co-occur with other driver alterations such as PIK3CA and may influence tumor behavior and response to therapy in metastatic HR-positive breast cancer [25].

Both patients had bone-predominant metastatic disease and prolonged sensitivity to sequential endocrine-based therapies. In endocrine-sensitive bone-only HR+/HER2− metastatic breast cancer, first-line treatment with CDK4/6 inhibitors combined with endocrine therapy provides prolonged disease control and delays the need for chemotherapy [26]. Local therapies such as SBRT have been shown to provide high and durable local control of spinal metastases from breast cancer, with acceptable toxicity [27].

Adherence to endocrine therapy remains critical. Eliassen et al. (2023) reported that non-adherence or early discontinuation of endocrine therapy in hormone receptor–positive breast cancer was associated with worse outcomes. Event-free survival was poorer in seven of ten studies (HR 1.39–2.44), and overall survival was reduced in seven of nine studies (HR 1.26–2.18) [28]. These cases demonstrate that carefully selected endocrine therapies can provide clinically meaningful disease control in metastatic hormone receptor-positive breast cancer, even in the presence of resistance-associated mutations. Real-world evidence from [29,30] demonstrated that Elacestrant provides meaningful benefit in patients with ER-positive, HER2-negative, *ESR1*-mutant metastatic breast cancer, with a median time to next treatment of six to eight months and longer durations when used earlier in the metastatic course.

Conclusion

Its activity is consistent across common *ESR1* variants and remains relevant even in the presence of co-occurring PI3K-pathway alterations, although higher *ESR1* polyclonality is associated with shorter treatment duration. These cases highlight the importance of routine molecular monitoring using ctDNA to detect *ESR1* mutations early and guide therapy sequencing. Thus, incorporating comprehensive molecular testing ensures the timely identification of actionable mutations and enables more precise treatment selection. Integrating genomic profiling with prior treatment history is essential to optimize endocrine therapy in clinical practice.

Ethics Approval: This report did not meet institutional criteria for IRB approval. The patient whose images are included provided consent for photo release.

Competing interests: The authors declare they have no competing interests

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Authors' Contribution

RB, MH and DH provided clinical review, data interpretation, and drafted and reviewed all versions of the manuscript

DH and MH conceptualized the study, provided data interpretation, editing, oversight, and reviewed all versions of the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Consent:

For Case 1, written informed consent for publication could not be obtained despite repeated attempts to contact the patient following relocation abroad. All patient information has been fully anonymized, and no identifiable details are included.

For Case 2, written informed consent for publication was obtained from the patient.

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