Resistance to Endocrine Therapy in ER+, HER2-Metastatic Breast Cancer

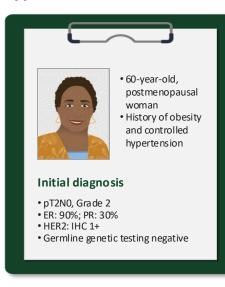
ER+, HER2- MBC and Progression on 1L SOC



The current first-line (1L) standard of care (SOC) for estrogen receptor–positive (ER+), human epidermal growth factor receptor 2–negative (HER2-) metastatic breast cancer (MBC) includes endocrine therapy (ET) + cyclin-dependent kinase 4/6 inhibitor (CDK4/6i)^{1,2}

While 1L SOC is effective, MBC will inevitably progress during treatment due to the rise of genetic mutations, such as *ESR1*.^{3,4} There is currently no consensus on optimal second-line treatment strategy^{1,3}

Hypothetical Patient Case: ESR1m



2016

- Underwent lumpectomy, adjuvant chemotherapy, and radiotherapy
- Initiated aromatase inhibitor (AI) and continued for 5 years

2023

- · Presented with back pain 2 years after completion of AI
- Imaging revealed lytic bone lesions in spine and pelvis
- Started AI + CDK4/6i and achieved partial response

2025

- Worsening disease (new bone lesions) detected 18 months into AI + CDK4/6i treatment
- Willing to undergo further treatment

The patient underwent liquid biopsy, which revealed ESR1m

Between 20-40% of patients who have received AI develop *ESR1*m⁵

Approximately 10% of patients with ER+, HER2- MBC harbor both ESR1m and PIK3CAm⁶



Guidelines recommend genomic profiling at **disease recurrence** or **disease progression on ET** to identify actionable biomarkers and potential resistance mechanisms^{1,7}

Understanding genetic alterations and their impact on ET sensitivity helps healthcare providers maximize clinical outcomes in patients with ER+, HER2- MBC

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Abbreviations: ESR1 m = ESR1 m ut ation; IHC = im munohistochemistry; PIK3CAm = PIK3CAm ut ation; PR = progesterone receptor.

