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: *ESR1*m

- 60-year-old, postmenopausal woman
- History of obesity and controlled hypertension

Initial diagnosis

- pT2N0, Grade 2
- ER: 90%; PR: 30%
- HER2: IHC 1+
- Germline genetic testing negative

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 *ESR1*m

Between 20-40% of patients who have received AI develop *ESR1*m[5]

Approximately 10% of patients with ER+, HER2- MBC harbor both *ESR1*m and *PIK3CA*m[6]

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

References: 1. Gennari A, et al. *Ann Oncol.* 2021;32(12):1475-1495. 2. Burstein HJ, et al. *J Clin Oncol.* 2021;39(35):3959-3977. 3. Zhou FH, et al. *Front Cell Dev Biol.* 2023;11:1148792. 4. Chen YC, et al. *Expert Opin Investig Drugs.* 2022;31(6):515-529. 5. Brett JO, et al. *Breast Cancer Res.* 2021;23(1):85. 6. Dempsey N, et al. *J Clin Oncol.* 2024;42(16_suppl):e13097-e13097. 7. Burstein HJ, et al. *J Clin Oncol.* 2023;41(18):3423-3425.

Abbreviations: *ESR1*m=*ESR1* mutation; IHC=immunohistochemistry; *PIK3CA*m=*PIK3CA*mutation ; PR=progesterone receptor.