Hypothetical Patient Case: ER+, HER2- Advanced Breast Cancer

Patient Case

Meet the patient

She is…

a 60-year-old woman with postmenopausal status

married with 3 adult children

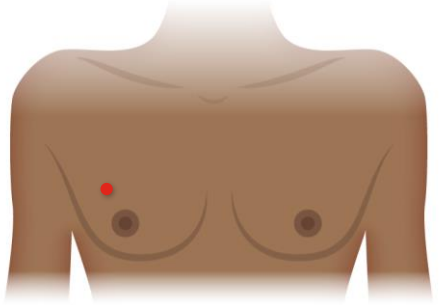
retired admin assistant

a volunteer at her local community center

with obesity and controlled hypertension

Patient Case

In 2017, this patient presented with a right breast mass detected during a routine mammogram



She underwent core biopsy followed by lumpectomy and was diagnosed with **invasive ductal carcinoma**

Staging	Grade	ER	PR	HER2	Germline Genetic Testing	21 Gene Recurrence Score
pT2N0	2	90%	30%	IHC 1+	Negative	27

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; N, node; p, pathologic stage; PR, progesterone receptor; T, tumor.

Patient Case

Initial diagnosis

- pT2N0, Grade 2
- ER: 90%; PR: 30%
- HER2: IHC 1+
- Germline negative
- 21 Gene Recurrence Score: 27

1

2016

This postmenopausal patient underwent lumpectomy, adjuvant chemotherapy, followed by radiotherapy

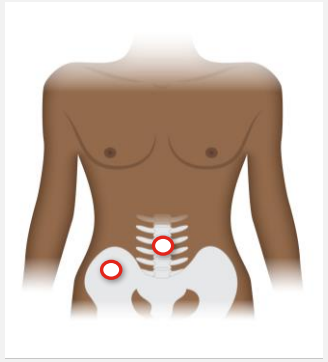
She completed 5 years of aromatase inhibitor therapy

2

2023

2 years after finishing her adjuvant treatment, she presented with persistent back pain

Imaging revealed lytic bone lesions in her spine and pelvis



3

She started treatment with CDK4/6i plus an aromatase inhibitor and had a partial response

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; N, node; p, pathologic stage; PR, progesterone receptor; T, tumor.

Patient Case

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- ER: 90%; PR: 30%
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- 21 Gene Recurrence Score: 27

2016: Underwent lumpectomy, adjuvant chemotherapy, and radiotherapy; she started an aromatase inhibitor

2023: Detection of lytic bone lesions 2 years after completion of an aromatase inhibitor; started CDK4/6i plus aromatase inhibitor therapy with partial response observed

4

2025

After 18 months of treatment, her imaging revealed worsening disease with new bone lesions

5

A liquid biopsy was ordered, which revealed an *ESR1* mutation

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; N, node; p, pathologic stage; PR, progesterone receptor; T, tumor.

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2023: Detection of lytic bone lesions 2 years after completion of an aromatase inhibitor; started CDK4/6i plus aromatase inhibitor therapy with partial response observed

2025: Detection of new bone lesions and ***ESR1* mutation**

6

This patient is willing to undergo further treatment

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; N, node; p, pathologic stage; PR, progesterone receptor; T, tumor.

Patient Case

Q1

For this patient with ER+, HER2- MBC, would you consider her to have primary or secondary ET resistance?

a. Primary ET resistance
b. Secondary ET resistance

ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer.

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The patient has **secondary ET resistance**.

- Primary ET resistance is defined as relapse while on the first 2 years of adjuvant ET, or progressive disease within the first 6 months of 1L ET-based therapy for ABC (regardless of prior CDK4/6i therapy)

- Secondary ET resistance, also known as acquired resistance, is defined as:
  - Relapse while receiving ≥2 years of adjuvant ET
  - Progressive disease after ≥6 months of 1L ET-based therapy for ABC
  - Progressive disease after any duration of 2L ET-based therapy for ABC
  - Known *ESR1* mutation (definition unaffected by therapy with CDK4/6i, mTORi/PI3Ki, or other adjunctive drugs)

1L, first line; 2L, second line; ABC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; mTORi, mammalian target of rapamycin inhibitor; PI3Ki, phosphatidylinositol 3-kinase inhibitor.

Cardoso F, et al. *Breast*. 2024;76:103756.

Patient Case

Q2

Approximately how many patients acquire resistance during their treatment with ET?

a. 0%-20%
b. 21%-40%
c. 41%-60%
d. 61%-80%
e. 81%-100%

ET, endocrine therapy.

Patient Case

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Most patients with ER+, HER2- MBC will develop resistance to their ET treatment, even if they were initially responsive.

While approximately **15%-30%** of patients will not benefit from standard-of-care treatments due to primary ET-resistance mechanisms, approximately **30%-40%** will acquire resistance during treatment.

ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer.

Chen YC, et al. *Expert Opin Investig Drugs*. 2022;31(6):515-529.

Patient Case

Q3

In ER+, HER2- MBC, how does prolonged exposure to AI impact the prevalence of *ESR1* mutations?

a. Prolonged exposure to AI reduces the prevalence of *ESR1* mutations
b. Prolonged exposure to AI has no measurable impact on the prevalence of *ESR1* mutations
c. Prolonged exposure to AI increases the prevalence of *ESR1* mutations

AI, aromatase inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer.

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ESR1 mutations in ER+ MBC occur almost exclusively after AI therapy. Approximately 20-40% of patients with MBC who have received AI treatment develop *ESR1* mutations, with prevalence varying by sites of metastatic disease.

In contrast, for patients with MBC who are ET naive, the prevalence of *ESR1* mutation is <1%.

AI, aromatase inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer.

Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85.

Patient Case

Q4

In ER+, HER2- MBC, what is the rate of co-occurring *ESR1* and *PIK3CA* mutations?

a. ≤20%
b. 21%-50%
c. 51%-80%
d. ≥81%

ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

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A study evaluating the co-occurrence of *ESR1* mutation and *PIK3CA* mutation via ctDNA in patients with ER+, HER2- MBC found a co-occurrence rate of **10.4%**.

ctDNA, circulating-tumor DNA; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Dempsey N, et al. *J Clin Oncol.* 2024;42:e13097-e13097.

Thank you!