HYPOTHETICAL CASE #2

ER+, HER2- Metastatic Breast Cancer Case Challenge

Begin the case and learn more about patient selection considerations for second-line therapy in patients with ER+, HER2- metastatic breast cancer and *ESR1* mutation with *PIK3CA* wildtype.

Developed under the direction and sponsorship of Lilly Medical Affairs and intended for U.S. healthcare professionals only. The clinical case presented here is entirely fictional and is not based on any real patient.

Case Presentation Summary

This hypothetical patient is a 63-year-old postmenopausal woman who recently retired after 30 years as a high school biology teacher. She lives with her husband of 38 years and stays busy with her two adult children and her first grandchild, born last spring. She enjoys tending to her vegetable garden, walking her dog most mornings, and hosting Sunday dinners for her extended family. She has a history of obesity and controlled hypertension.

Initial presentation

Back in 2018, the 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**.

63 years

Postmenopausal woman
Maintains active lifestyle with family and home

Obesity

BMI: 33

Hypertension

BP: 128/78 mmHg on current management

BMI, body mass index; BP, blood pressure.

Initial Diagnosis — 2018

ADJUVANT MANAGEMENT

She underwent surgery and radiation therapy, followed by adjuvant chemotherapy, and then completed **5 years of aromatase inhibitor therapy**.

pT2N0, Grade 2
Stage and grade at diagnosis

ER 90% / PR 60%
Hormone receptor expression

HER2 IHC 1+
HER2 by immunohistochemistry

Recurrence Score 26
21-gene assay; germline genetic testing negative

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

2025 — Metastatic Recurrence

- 2 years after completing her adjuvant treatment, the patient presented with abdominal fullness and nausea
- Imaging revealed **lytic bone lesions** in her pelvis
- **Liver metastases** were also present, and biopsy showed adenocarcinoma consistent with breast cancer

First-line therapy

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

Abdominal fullness & nausea

2 years post-adjuvant treatment

Lytic bone lesions

Identified in the pelvis on imaging

Liver metastases

Biopsy showed adenocarcinoma consistent with breast cancer

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor.

2026 — Progression on First-Line Therapy

- After 10 months of treatment, the patient's imaging revealed new liver lesions
- A liquid biopsy was ordered, which revealed an ***ESR1* mutation with *PIK3CA* wildtype**

Patient goals

This patient confirmed she is willing to undergo further treatment, and expressed a preference to delay chemotherapy for as long as possible with an oral ET-based therapy.

10 months

On CDK4/6i + aromatase inhibitor, with a partial response before progression

ESR1 mutation

Detected on liquid biopsy at progression

PIK3CA wildtype

No *PIK3CA* alteration identified

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Endocrine Therapy Resistance

As with most patients with ER+, HER2- metastatic breast cancer, this patient developed resistance to endocrine therapy (ET). Specifically, she has **secondary ET resistance**, which is defined as:[1]

- Relapse while receiving adjuvant ET, after at least 2 years
- Progressive disease after at least 6 months of first-line ET-based therapy for metastatic breast cancer
- Progressive disease after any duration of second-line ET-based therapy for metastatic breast cancer
- Known *ESR1* mutation*

*Definition unaffected by therapy with CDK4/6i, mTOR/PI3Ki, or other adjunctive drugs.

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; PI3Ki, phosphatidylinositol 3-kinase inhibitor.

CASE CHALLENGE

Multiple-Choice Questions

Two questions on second-line treatment selection and *ESR1* mutation testing.

Question #1 Second-line treatment selection

Based on the patient's presentation, which second-line treatment regimen would you consider for her?

a ET + everolimus

b Intramuscular SERD + CDK4/6i

c Oral SERD monotherapy

d Chemotherapy

e Oral SERD + CDK4/6i

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; SERD, selective estrogen receptor degrader.

Question #1 — Best Option

Based on the patient's presentation, which second-line treatment regimen would you consider for her?

- a ET + everolimus
- b Intramuscular SERD + CDK4/6i
- c Oral SERD monotherapy
- d Chemotherapy
- **e Oral SERD + CDK4/6i**

Best Option: e. Oral SERD + CDK4/6i

As this hypothetical patient has liver metastases without visceral crisis, would like to continue care, and wishes to delay chemotherapy for as long as possible with an oral ET-based therapy, an all-oral, chemotherapy-free regimen is appropriate, particularly given her response to prior treatment and that acquired *ESR1* mutation is associated with shorter progression-free survival.[8]

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; SERD, selective estrogen receptor degrader.

Question #2 *ESR1* mutation testing

When should we test for *ESR1* mutations?

a At metastatic diagnosis

b At first metastatic progression

c At metastatic diagnosis and at each subsequent progression, if not detected previously

ESR1, estrogen receptor 1.

Question #2 — Best Option

When should we test for *ESR1* mutations?

a. At metastatic diagnosis

b. At first metastatic progression

c. At metastatic diagnosis and at each subsequent progression, if not detected previously

Best Option: c) At metastatic diagnosis and at each subsequent progression, if not detected previously

Guidelines recommend routine testing for detecting *ESR1* mutation at recurrence or progression on ET in ER+, HER2- metastatic breast cancer.[9] *ESR1* mutations emerge while on treatment (typically aromatase inhibitor) and are not usually detected before ET treatment.[9-11]

- Biomarker testing at progression can help identify the appropriate next line of therapy. The prevalence of *ESR1* mutation increases with time on treatment; it is important to repeat testing at metastatic diagnosis and subsequent progressions.[10,11]
- *ESR1* mutations are best detected by blood-based circulating tumor DNA analyses, which have greater sensitivity and are less invasive than tissue-based testing.[9-12] Among its disadvantages, tissue-based testing is impractical to repeat, requires longer turnaround time for analysis, may not reveal tumor heterogeneity, and/or requires biopsy of metastatic sites.[11,12]

ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2.

Key Takeaways

01

TESTING CADENCE

Test for *ESR1* mutation via circulating tumor DNA (next-generation sequencing or polymerase chain reaction) at recurrence after aromatase inhibitor treatment and at each progression on CDK4/6i-based therapy; retest when *ESR1* mutation is not yet detected, as mutations emerge while on treatment with ET.[2,3]

02

TREATMENT OPTIONS

Biomarker testing can help identify appropriate treatment options, such as elacestrant, imlunestrant alone or with abemaciclib, vepdegestrant, and camizestrant which are FDA approved for patients with *ESR1* mutation, ER+, HER2- metastatic breast cancer.[4-7]

03

REGIMEN CHOICE

Deciding between monotherapy vs. combination regimens hinges on patient performance status, organ function, and comorbidities against added toxicity (eg, diarrhea/neutropenia).[4-7]

04

ROUTE AND ACCESS

Factors such as patient preference, tolerability profile, financial impact, and access can help determine whether oral or intramuscular administration is appropriate for a patient.

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2.

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