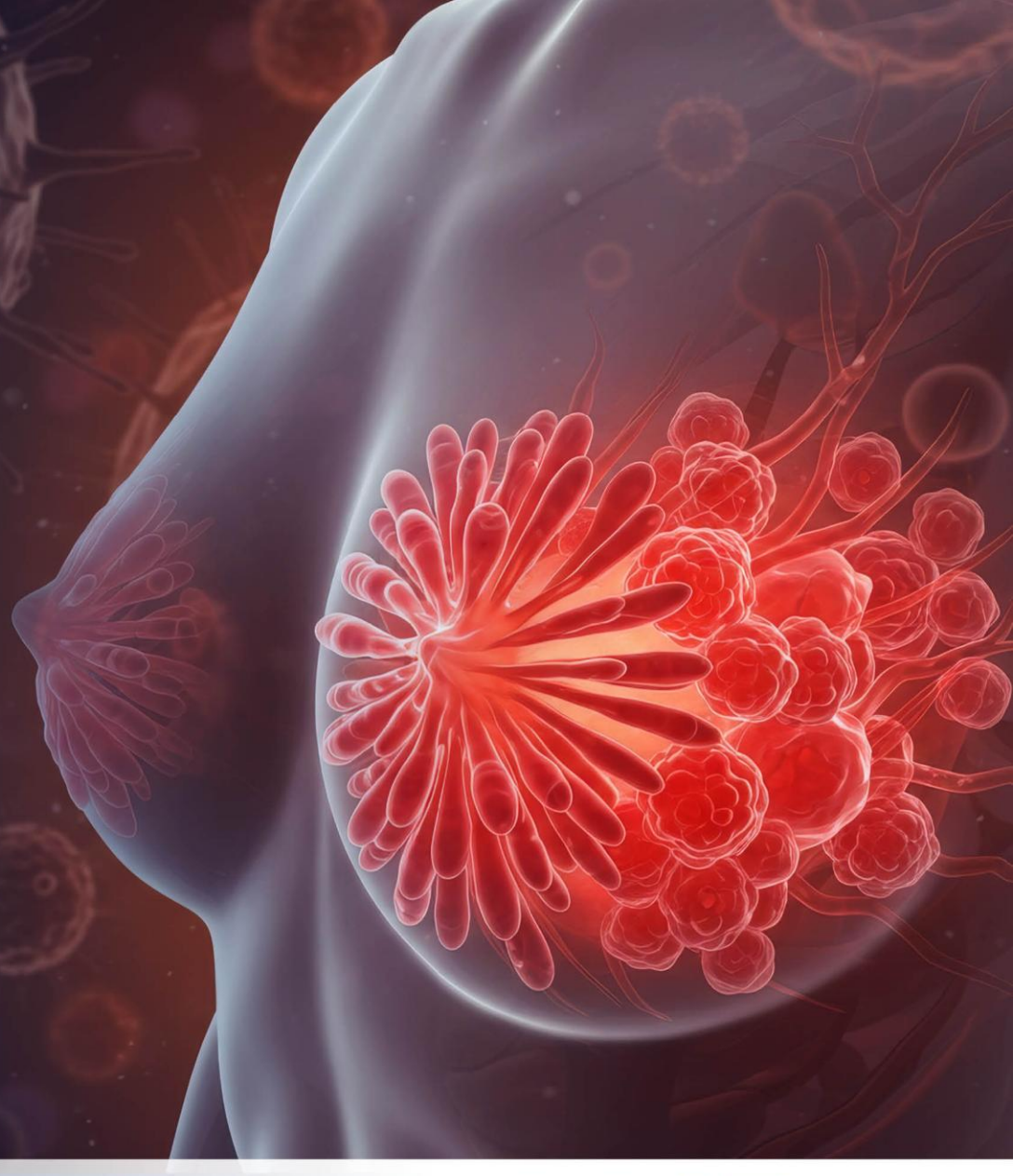
The Next Frontier:

Strategic Sequencing and Biomarker-Driven Therapy in HR+ Metastatic Breast Cancer



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The Next Frontier: Strategic Sequencing and Biomarker-Driven Therapy in HR+ Metastatic Breast Cancer

Danielle Roman, PharmD, BCOP

Educational Objectives

After completion of this activity, participants will be able to:

- Analyze the latest clinical trial data for current and emerging targeted therapies such as selective estrogen receptor degraders, PROTAC inhibitors, PI3Kα inhibitors, and AKT inhibitors in hormone receptor-positive (HR+) metastatic breast cancer, and their implications for treatment sequencing
- Determine how *PIK3CA* and *ESR1* mutation testing in clinical workflows can identify patients eligible for targeted therapies
- Explore the evolving role of circulating tumor DNA monitoring to inform treatment decisions throughout the course of HR+ metastatic breast cancer
- Apply practical, multidisciplinary approaches to anticipate, monitor, and manage treatment-related toxicities while maintaining adherence

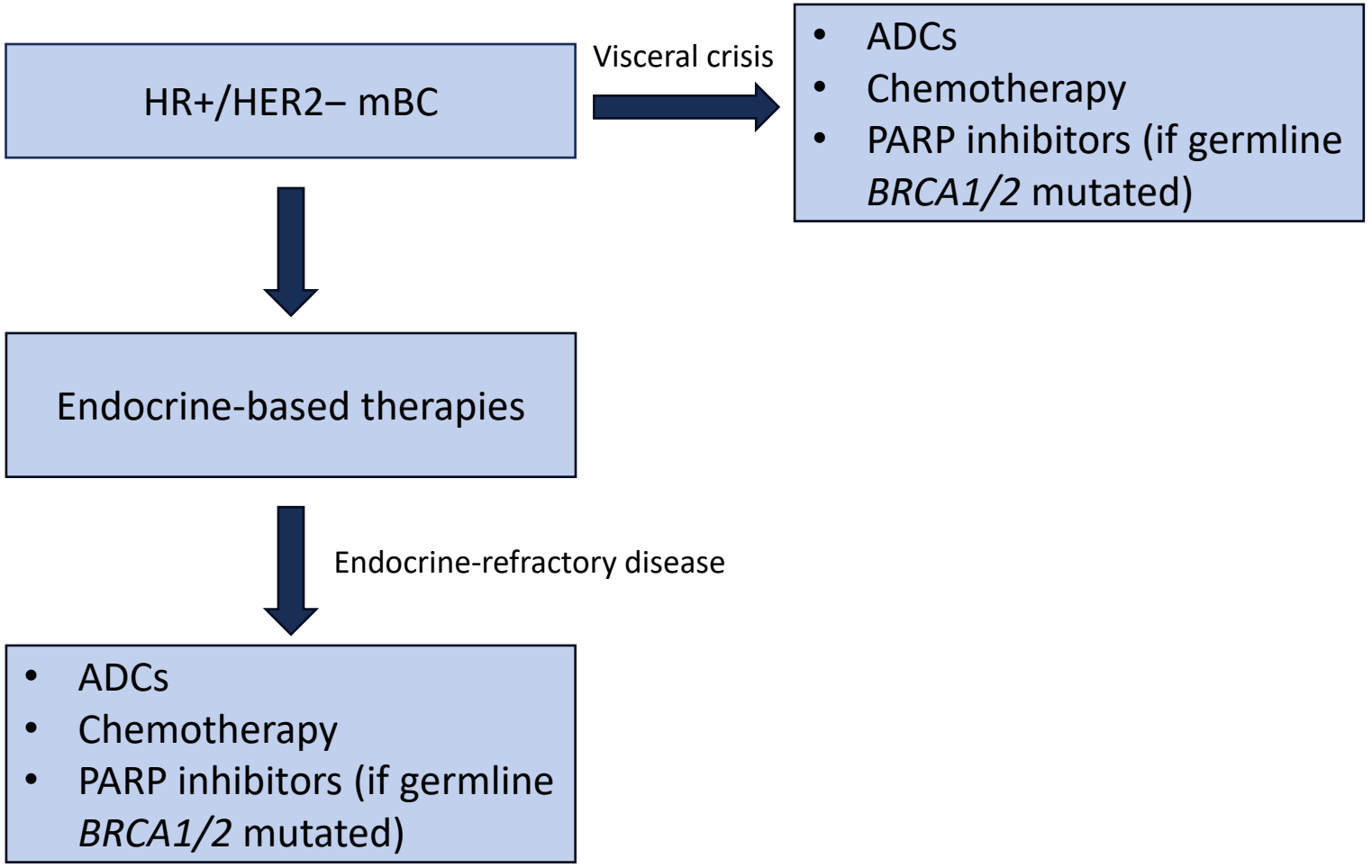
HR+/HER2– mBC:
Focus on Endocrine-Based Therapies

HR+/HER2– BC: Epidemiology and Treatment Overview

70%

of cases are HR+/HER2– subtype

HR+/HER2– → best survival pattern	
Stage at diagnosis	**5-year relative survival (%)**
All stages	95.6
Localized	100
Regional	90.8
Distant	36.5



ADC, antibody-drug conjugates; HR, hormone receptor; mBC, metastatic breast cancer.

NIH. Accessed March 17, 2026. seer.cancer.gov/statfacts/html/breast-subtypes.html; NCCN. Clinical Practice Guidelines in Oncology. Breast cancer, version 2.2026. Accessed March 17, 2026. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Biomarker Testing: Newly Diagnosed mBC

Biomarker	Detection	Treatment implications
HR status (ER/PR)	Tissue	Eligibility for ET
HER2 expression	Tissue	Eligibility for HER2-directed therapy
PIK3CA mutation	Tissue or ctDNA	Eligibility for first-line treatment with inavolisib if disease progression on adjuvant ET or relapse within 12 months of completing adjuvant ET
ESR1 mutation (if progression on/after adjuvant AI)	ctDNA preferred	Oral SERD • Elacestrant • Imlunestrant

AI, aromatase inhibitor; ctDNA, circulating tumor DNA; ER/PR, estrogen/progesterone; ET, endocrine therapy; SERD, selective estrogen receptor degrader.

NCCN. Clinical Practice Guidelines in Oncology. Breast cancer, version 2.2026. Accessed March 17, 2026. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Treatment Algorithm for Hormone Sensitive Disease

Preferred first line

- AI + CDK4/6i
- Fulvestrant + inavolisib + palbociclib (*PIK3CA* mutation)
- Fulvestrant + CDK4/6i (if disease progression on adjuvant ET or relapse within 12 months of adjuvant ET completion)

CDK4/6i, CDK4/6 inhibitor.

NCCN. Clinical Practice Guidelines in Oncology. Breast cancer, version 2.2026. Accessed March 17, 2026. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

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INAVO120: Fulvestrant + Inavolisib + Palbociclib

Phase 3, double-blind trial

- *PIK3CA*-mutated, HR+/HER2– aBC
- Measurable disease
- Progression during/within 12 months of adjuvant ET completion
- No prior treatment for aBC
- FBG <126 mg/dL and HbA_{1C} ≤6%

N = 325

RANDOMIZED

Inavolisib 9 mg oral daily + palbociclib 125 mg oral days 1-21 every 28 days + fulvestrant IM

Placebo + palbociclib 125 mg oral days 1-21 every 28 days + fulvestrant IM

Outcomes (months)			
Primary	**Inavolisib**	**Control**	**HR (95% CI)**
PFS	17.2	7.3	0.42 (0.32-0.55)
Secondary	**Inavolisib**	**Control**	**HR (95% CI)**
OS (median 34.2 months follow-up)	34	27	0.67 (0.48-0.94)
DOR	18.4	9.6	0.57 (0.33-0.99)
Median time to chemotherapy	35.6	12.6	0.43 (0.3-0.6)

Inavolisib is approved in combination with fulvestrant and palbociclib for endocrine-resistant, *PIK3CA*-mutated, HR+/HER2– aBC.

aBC, advanced breast cancer; DOR, duration of response; FBG, fasting blood glucose; HbA_{1C}, hemoglobin A_{1C}; IM, intramuscular; OS, overall survival; PFS, progression-free survival.

Jhaveri KI et al. *N Engl J Med.* 2025;393(2):151-161; Turner NC et al. *N Eng J Med.* 2024;391(17):1584-1596; Itovebi. Prescribing information. Genentech; December 2025.

Biomarker Testing: After First-Line Progression

Biomarker	Detection	Treatment implications
HER2 expression	Tissue	Eligibility for HER2-directed therapy
BRCA1/2 mutation (germline)	Tissue or ctDNA	PARP inhibitors • Olaparib • Talazoparib
PIK3CA mutation	Tissue or ctDNA	PI3K/AKT pathway inhibitors • Alpelisib + fulvestrant • Capivasertib + fulvestrant
PTEN alteration	Tissue or ctDNA	AKT pathway inhibitor • Capivasertib + fulvestrant
AKT1 mutation	Tissue or ctDNA	AKT pathway inhibitor • Capivasertib + fulvestrant
ESR1 mutation	ctDNA preferred	Oral SERD • Elacestrant • Imlunestrant

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Treatment Algorithm for Hormone Sensitive Disease

Preferred first line

- AI + CDK4/6i
- Fulvestrant + inavolisib + palbociclib (*PIK3CA* mutation)
- Fulvestrant + CDK4/6i (if disease progression on adjuvant ET or relapse within 12 months of adjuvant ET completion)

Preferred second line and subsequent

- Fulvestrant + CDK4/6i
- Fulvestrant + alpelisib (if *PIK3CA* mutation)
- Fulvestrant + capivasertib (if *PIK3CA* mutation, *AKT1* mutation, *PTEN* alteration)
- Everolimus + ET

Other recommended for first and/or subsequent line

- Elacestrant (*ESR1* mutation and progression on AI + CDK4/6i)
- Imlunestrant (*ESR1* mutation and progression on AI +/- CDK4/6i)
- Fulvestrant + AI
- Fulvestrant
- AI
- Tamoxifen

NCCN. Clinical Practice Guidelines in Oncology. Breast cancer, version 2.2026. Accessed March 17, 2026. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

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- Everolimus + ET

Other recommended for first and/or subsequent line

- Elacestrant (*ESR1* mutation and progression on AI + CDK4/6i)
- Imlunestrant (*ESR1* mutation and progression on AI +/- CDK4/6i)
- Fulvestrant + AI
- Fulvestrant
- AI
- Tamoxifen

NCCN. Clinical Practice Guidelines in Oncology. Breast cancer, version 2.2026. Accessed March 17, 2026. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

CAPItello-291: Capivasertib + Fulvestrant

Phase 3, double-blind trial

- HR+/HER2– aBC/mBC who progressed on AI +/- CDK4/6i or during/within 12 months of adjuvant AI
- Received ≤2 lines of ET and ≤1 line of chemotherapy
- Stratified based on *PIK3CA* mutation or *PTEN* or *AKT1* alteration
- Excluded if HbA_{1C} >8%

N = 708

RANDOMIZED

Capivasertib 400 mg oral twice a day x 4 days, followed by 3 days off + fulvestrant IM

Placebo + fulvestrant IM

Outcomes (months)			
Primary	**Capivasertib**	**Control**	**HR (95% CI)**
PFS (overall population)*	7.2	3.6	0.6 (0.51-0.71)
PFS (*AKT* altered)	7.3	3.1	0.5 (0.38-0.65)
Secondary	**Capivasertib**	**Control**	**HR (95% CI)**
PFS (*AKT* non-altered)	5.3	3.7	0.79 (0.61-1.02)
OS at 18 months (overall population)	73.9%	65%	0.74 0.56-0.98)
OS at 18 months (*AKT* altered)	73.2%	62.9%	0.69 (0.45-1.05)
ORR (overall population)	22.9%	12.2%	2.19 (1.42-3.36)
ORR (*AKT* altered)	28.8%	9.7%	3.93 (1.93-8.04)

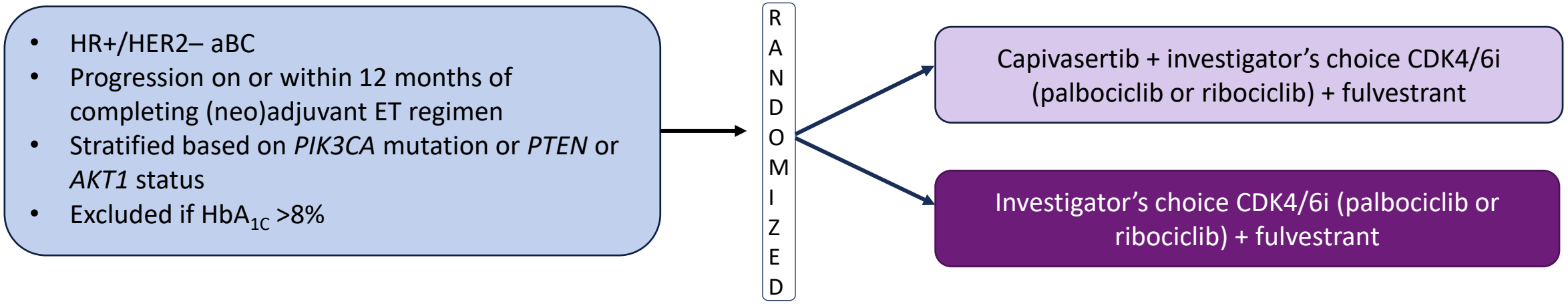
*PFS in overall population improved regardless of prior CDK4/6i exposure.

Capivasertib is approved in combination with fulvestrant for HR+/HER2– aBC with ≥1 *PIK3CA*, *AKT1*, or *PTEN* alterations following progression on ≥1 line ET for mBC or recurrence within 12 months of completing adjuvant ET.

Turner N et al; CAPItello-291 Study Group. *N Engl J Med.* 2023;388(22):2058-2070; Truqap. Prescribing Information. AstraZeneca; November 2025.

Moving Up in the Line of Therapy? CAPItello-292: Capivasertib + Fulvestrant in the First-Line Metastatic Setting

- Phase 1b/3 study to evaluate the efficacy, safety, and degree of added benefit of capivasertib added to CDK4/6i + fulvestrant for locally advanced (inoperable) or metastatic HR+/HER2– BC
  - Phase 1b → determine recommended phase 3 doses of the triplet combinations



Estimated study primary completion date: November 2027

AstraZeneca. Accessed March 17, 2026. https://www.astrazenecaclinicaltrials.com/study/D361DC00001/; NIH. Accessed March 17, 2026. https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCI-2021-06969

Treatment Algorithm for Hormone Sensitive Disease

Preferred first line

- AI + CDK4/6i
- Fulvestrant + inavolisib + palbociclib (*PIK3CA* mutation)
- Fulvestrant + CDK4/6i (if disease progression on adjuvant ET or relapse within 12 months of adjuvant ET completion)

Preferred second line and subsequent

- Fulvestrant + CDK4/6i
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- Fulvestrant + AI
- Fulvestrant
- AI
- Tamoxifen

NCCN. Clinical Practice Guidelines in Oncology. Breast cancer, version 2.2026. Accessed March 17, 2026. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Oral SERD Overview

FDA approved

- Elacestrant
- Imlunestrant

Investigational

- Camizestrant
- Giredestrant → Efficacy in HR+/HER2– early BC based on results of phase 3 lidERA trial (presented at SABCS 2025).
- Vepdegestrant *(PROTAC)*

PROTAC, proteolysis-targeting chimera; SABCS, San Antonio Breast Cancer Symposium.

Orserdu. Prescribing Information. Stemline Therapeutics, Inc; November 2023; Inluriyo. Prescribing Information. Eli Lilly and Company; September 2025; Bidard FC et al; SERENA-6 Study Group. *N Engl J Med*. 2025;393(6):569-580; Bardia A et al. SABCS 2025. Abstract GS1-10; Campone M et al; VERITAC-2 Study Group. *N Engl J Med.* 2025;393(6):556-568.

Trial Data Supporting Elacestrant

Elacestrant

ELEVATE Trial (phase 1b/2)

- Evaluated elacestrant in combination with various targeted therapies
- Objectives: to evaluate RP2D (phase 1b) and PFS (phase 2)

Combination	RP2D
Elacestrant In combination with:	345 mg oral daily
Ribociclib	400 mg oral daily
Everolimus	7.5 mg oral daily
Abemaciclib	150 mg twice daily
Capivasertib	320 mg oral 4 days on, 3 days off

RP2D, recommended phase 2 dose; SOC, standard of care.

EMERALD Trial (phase 3)

- HR+/HER2– aBC/mBC
- Progression on 1-2 lines ET (+ CDK4/6i) or progression on/within 12 months adjuvant ET
- 1 line chemotherapy allowed

R → Elacestrant

R → SOC (AI or fulvestrant)

End points	Elacestrant (N = 239)	SOC (N = 238)
Primary: median PFS all patients	2.8 months	1.9 months
	HR, 0.7 (95% CI, 0.55-0.88)	
Primary: median PFS *ESR1* mutated	3.8 months	1.9 months
	HR, 0.55 (95% CI, 0.39-0.77)	
Subgroup analysis: median PFS if prior ET+CDK4/6i ≥12 months	N = 78 8.6 months	N = 81 1.9 months
	HR, 0.41 (95% CI, 0.26-0.63)	

- Recommended for patients with *ESR1* mutation
- Improved efficacy if prior CDK4/6i + ET duration ≥12 months

Bidard FC et al. *J Clin Oncol*. 2022;40(28):3246-3256; Bardia A et al. *Clin Cancer Res.* 2024;30(19):4299-4309; Flaherty C. News release. *Targeted Oncology*. December 12, 2025. Accessed March 17, 2026. https://join.targetedonc.com/view/elevate-trial-elacestrant-combos-boost-pfs-in-er-her2--breast-cancer

Trial Data Supporting Imlunestrant

Imlunestrant → EMBER-3 Trial (phase 3)

- HR+/HER2– aBC
- Progression on AI +/- CDK4/6i in the first-line setting during or within 12 months of adjuvant therapy
- Stratified by previous CDK4/6i or visceral metastases

R
- Imlunestrant 400 mg oral once daily
- SOC (fulvestrant or exemestane)
- Imlunestrant + abemaciclib

Imlunestrant is approved as monotherapy for HR+/HER2– *ESR1* mutated mBC following ≥1 line ET.

End points	Imlunestrant (N = 331)	SOC (N = 330)	Results
Primary: mPFS, all patients	5.6 months	5.5 months	HR, 0.87 (95% CI, 0.72-1.04)
Primary: mPFS, patients with *ESR1* mutation	5.5 months	3.8 months	HR, 0.62 (95% CI, 0.46-0.82)
Secondary: OS at 18 months in with *ESR1* mutation	77%	58.6%	HR, 0.55 (95% CI, 0.35-0.86; *P* = .008); threshold 2.2 x 10^{-10}
End points	**Imlunestrant + abemaciclib (N = 213)**	**Imlunestrant (N = 213)**	**Results**
Primary: mPFS, all patients	9.4 months	5.5 months	HR, 0.57 (95% CI, 0.44-0.73; *P* <.001)

Jhaveri K et al; EMBER-3 Study Group. *N Engl J Med.* 2025;392(12):1189-1202; Inluriyo. Prescribing Information. Eli Lilly and Company; September 2025.

Trial Data Supporting Camizestrant

Camizestrant → SERENA-6 Trial (phase 3)

Phase 3 (N = 3256)
- HR+/HER2– men or women with locoregional recurrent or mBC
- Received at least 6 months of AI + CDK4/6i* in the first-line setting and no clinical/radiographic signs of progression

→ ctDNA *ESR1* mutation surveillance every 2-3 months*

→ *ESR1* mutation detected (n = 315)

→ R
- Camizestrant 75 mg oral once daily + CDK4/6i as prior
- Continue AI + CDK4/6i as prior

→ *ESR1* wild type: maintain current treatment

*53.3% had *ESR1* mutation on first ctDNA test.

Outcomes			
Primary	**Camizestrant**	**Control**	**HR (95% CI)**
mPFS (months)	16	9.2	0.44 (0.31-0.60); *P* <.001
Secondary	**Camizestrant**	**Control**	**HR (95% CI)**
OS (immature)	NR	NR	0.91 (0.48-1.73)

- Switching to camizestrant following detection of *ESR1* mutation before clinical disease progression improves mPFS
- Camizestrant PDUFA date = first half of 2026

PDUFA, Prescription Drug User Fee Act.

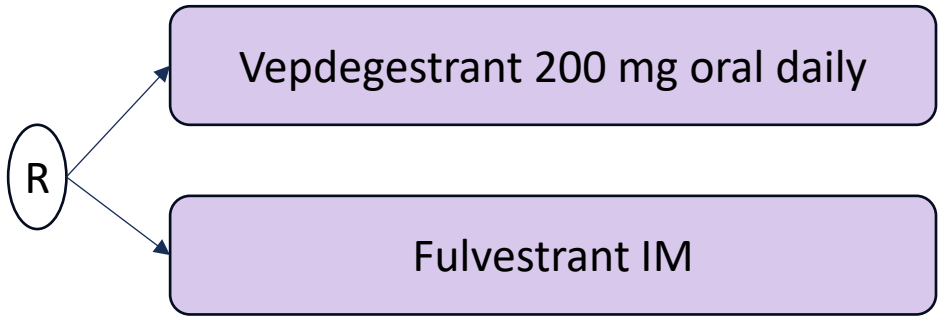
Bidard FC et al; SERENA-6 Study Group. *N Engl J Med*. 2025;393(6):569-580; Areitio B. ApexOnco. September 26, 2025. Accessed March 17, 2026. https://www.oncologypipeline.com/apexonco/second-line-esr1-mutant-patients

PROTAC: Vepdegestrant

VERITAC-2 Trial

Phase 3 (N = 624)

- HR+/HER2– locoregional recurrent or mBC
- Progressed on up to 2* prior line ET, 1 of which must include up to 1 CDK 4/6i for mBC or adjuvant setting if progression occurred during/within 12 months of treatment
- Received 6 months of most recent ET prior to progression
- Excluded prior fulvestrant, elacestrant, or chemotherapy for mBC



*79% of patients had received 1 line of ET; 49% received palbociclib as CDK4/6i.

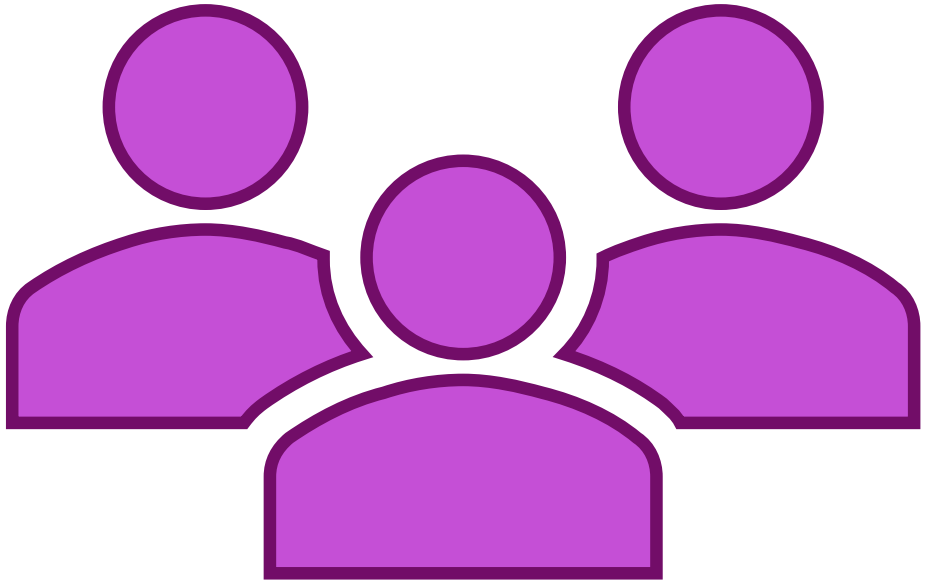
Outcomes			
Primary	**Vepdegestrant**	**Control**	**HR (95% CI)**
PFS (*ESR1* mutated; months)	5	2.1	0.58 (0.43-0.78)
PFS (overall; months)	3.8	3.6	0.83 (0.69-1.01)
Secondary	**Vepdegestrant**	**Control**	**HR (95% CI)**
OS (immature) ORR (*ESR1* mutated)	NR 18.6%	NR 4%	NR RR, 4.64 (1.63-13.22)

- Vepdegestrant improved mPFS for patients with an *ESR1* mutation
- PDUFA date = June 2026

43.3% of patients had an *ESR1* mutation.

Campone M et al; VERITAC-2 Study Group. *N Engl J Med.* 2025;393(6):556-568; News release. *Pharmaceutical Technology*. August 11, 2025. Accessed March 17, 2026. https://www.pharmaceutical-technology.com/news/arvinas-vepdegestrant-nda-fda-acceptance-breast-cancer/

Case Discussion



Case #1: DA

- DA is a 57-year-old postmenopausal woman who is on first-line treatment with ribociclib + fulvestrant for HR+/HER2– mBC. Unfortunately, her treatment has been complicated by hepatoxicity and neutropenia.
- Next-generation sequencing testing results show *PIK3CA* and *ESR1* mutations.

Audience Response Question

What therapy should be recommended for DA's *PIK3CA*- and *ESR1*-mutated HR+/HER2– mBC?

A. Alpelisib + fulvestrant
B. Capivasertib + fulvestrant
C. Elacestrant
D. Imlunestrant

Patient Case: Multiple Mutations

- How does a provider choose when a patient has multiple mutations?
- What are the differences in oral SERDs?

Oral SERDs

	Elacestrant (EMERALD)	Imlunestrant (EMBER-3)
Mechanism	Estrogen receptor antagonist and degrader	Estrogen receptor antagonist and degrader
Dosing	345 mg oral daily **with food**	400 mg oral daily **2 hours before or 1 hour after food**
Metabolism/DDI	• Major CYP3A4 substrate • Minor CYP2C9, CYP2A6 substrate • OATP2B1	• Major CYP3A4 substrate • UGT1A1 substrate • BCRP, PGP inhibitor
	Key AEs; all grade (grade 3/4)	
Nausea	35% (2.5%)	17.1% (0.3%)
Increased cholesterol	30% (1%)	10% (0%)
Increased triglycerides	27% (2%)	21% (0%)
Fatigue	26% (2%)	22.6% (0.3%)
Increased AST	13.1% (1.7%)	12.5% (0.9%)
Increased ALT	9.3% (2.1%)	10.4% (0.3%)
Arthralgia	14.3% (0.8%)	14.1% (0.6%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DDI, drug-drug interaction.

Bidard FC et al. *J Clin Oncol*. 2022;40(28):3246-3256; Orserdu. Prescribing Information. Stemline Therapeutics, Inc; November 2023; Inluriyo. Prescribing Information. Eli Lilly and Company; September 2025; Jhaveri K et al; EMBER-3 Study Group. *N Engl J Med.* 2025;392(12):1189-1202.

Patient Case: Multiple Mutations

- How does a provider choose when a patient has multiple mutations?
- What are the differences in oral SERDs?
- Concerns with previous treatment toxicity
- Investigational agents and combinations?

Investigational Oral Endocrine Therapies

	Vepdegestrant (VERITAC-2)	Camizetrant (SERENA-6)
Mechanism	PROTAC estrogen receptor degrader	Estrogen receptor antagonist and degrader
Dosing	200 mg oral daily **with food**	75 mg oral once daily **with or without food** in combination with a CDK4/6i
Metabolism/DDI	• PGPi • H_2 receptor antagonists/local antacids 10-12 hours before/after	• CYP2C9, CYP2C19, CYP3A4/5i • BCRPi
	Key AEs; all grade (grade 3/4)	
Nausea	13.5% (0%)	**Nausea** 9.7% (0%)
Fatigue	26.6% (1%)	**Fatigue** 15.5% (0%)
Increased AST	14.4% (1.3%)	**Photopsia** 20% (0.6%)
Increased ALT	14.4% (0.6%)	**Dry eye** 11.6% (0%)
Arthralgia	10.6% (1%)	**Arthralgia** 16.1% (0%)
Neutropenia	11.5% (1.9%)	**Neutropenia** 85% (45.2) **CDK4/6i combination**
QT prolongation	9.9% (1.6%)	**Bradycardia** 5.2% (0%)

Bidard FC et al; SERENA-6 Study Group. *N Engl J Med*. 2025;393(6):569-580; Campone M et al; VERITAC-2 Study Group. *N Engl J Med.* 2025;393(6):556-568.

Investigational Combinations

Updates From SABCS

EMBER-3

Imlunestrant + abemaciclib (N = 213) vs imlunestrant (N = 213)

- **mPFS (all patients)**: **10.9** months (95% CI, 7-5-12.5) vs **5.5** months (95% CI, 3.8-5.6) months
- **HR, 0.59** (95% CI, 0.47-0.74; *P* <.0001)
- **mPFS in patients with prior CDK4/6i**: **9.1** months (95% CI, 7-2-11.3) vs **3.7** months (95% CI, 2.1-5.5) months
- **HR, 0.53** (95% CI, 0.40-0.69; *P* <.0001)

ELEVATE Arm B

Elacestrant + everolimus (N = 50)

- Prior CDK4/6i required
- **mPFS**: **8.3** months (95% CI, 4.0-10.2)
- **ORR:** 19.5%
- **DCR:** 82.9%
- **mDOR**: 8.54 months

ELEVATE Arm D

Elacestrant + abemaciclib (N = 60)

- **mPFS: 14.3 months** (95% CI, 7.3-16.6)
- **ORR:** 24.6%
- **DCR:** 91.2%
- **mDOR**: 14.75 months

DCR, disease control rate.

Jhaveri KL et al. SABCS 2025. Abstract GS3-08; Jhaveri KL et al; EMBER-3 Study Group. *N Engl J Med.* 2025;392(12):1189-1202; Rugo HS et al. SABCS 2025. Abstract RF7-01.

Case #2: NS

- NS is a 64-year-old postmenopausal woman initially diagnosed in 2023 with HR+/HER2– (immunohistochemistry [IHC] 1+), Oncotype DX score 37. She was treated with a left mastectomy → docetaxel/cyclophosphamide x 4 cycles → exemestane x planned 5 years.
- 2 years into her ET course, she presents with metastatic disease to the liver that is HR+/HER2– (IHC 0).

Genetic testing

- *PIK3CA* mutation

Past medical history

- Hypertension
- Hyperlipidemia

Lab results

- Baseline HbA_{1C}: 4.5%
- FBG: 78 mg/dL
- Absolute neutrophil count (ANC): 1600

Audience Response Question

What therapy should be recommended for NS's *PIK3CA*-mutated HR+/HER2– mBC?

A. Abemaciclib + fulvestrant
B. Ribociclib + letrozole
C. Fulvestrant + inavolisib + palbociclib

Patient Case: Triple Therapy

- Triplet therapy eligibility
- Are there any situations where triplet therapy might be avoided in eligible patients?
- Hyperglycemia management

Case #2: NS continued

- Patient initiated inavolisib 9 mg oral daily, palbociclib 125 mg oral daily days 1-21 every 28 days, and standard dosing of fulvestrant.
- Treatment course:

Cycle	Lab value	Treatment modification
2	ANC 440	Palbociclib dose reduced to 100 mg
2	FBG: 210	Start metformin; hold inavolisib until FBG ≤160
5	--	Palbociclib dose reduced to 75 mg due to fatigue
5	FBG: 230	Increase metformin; hold inavolisib then resume at reduced dose of 6 mg
6	--	Inavolisib dose reduced to 3 mg due to diarrhea

PI3K/PTEN/AKT1 Pathway Inhibitors

	Alpelisib (SOLAR-1)	Capivasertib (CAPItello-291)	Inavolisib (INAVO120)
Mechanism	Inhibitor of PI3K p110α subunit	Inhibitor of AKT (AKT1, AKT2, AKT3)	Inhibitor of PI3K p110α subunit
Dosing	300 mg oral once daily **with food** in combination with fulvestrant	400 mg oral twice daily for 4 days **with or without food**, followed by 3 days off in combination with fulvestrant	9 mg oral once daily **with or without food** in combination with palbociclib + fulvestrant
Metabolism/DDI	• BCRP substrate • CYP2C9, CYP2B6, CYP3A4 inducer • CYP3A4, Pgp, OATP1B1/OCT2i	CYP3A4 substrate	• BCRP, Pgp substrate • Minimal CYP3A4 metabolism
	Key AEs; all grade (grade 3/4)		
Hyperglycemia	63.7% (36.6%); median onset 15 days	16.3% (2.3%); median onset 15 days	58.6% (5.6%); median onset 7 days
Diarrhea	57.7% (6.7%); median onset 46 days	72.4% (9.3%); median onset 8 days	48.1% (3.7%); median onset 15 days
Rash	53.9% (20%); median onset 13 days	38% (12.1%); median onset 12 days	25.3% (0%); median onset 29 days
Nausea	44.7% (2.5%)	34.6% (0.8%)	27.8% (0.6%)
Stomatitis	24.6% (2.5%)	14.6% (2%)	51.2% (5.6%)
Neutropenia	NR	NR	88.9% (80.2%) **Combination with palbociclib**

Andre F et al; SOLAR-1 Study Group. *N Engl J Med.* 2019;380(20):1929-1940; Turner NC et al; CAPItello-291 Study Group. *N Engl J Med.* 2023;388(22):2058-2070; Turner NC et al. *N Engl J Med.* 2024;391(17):1584-1596; Vijoice. Prescribing information. Novartis Pharmaceuticals Corporation; July 2025; Truqap. Prescribing Information. AstraZeneca; November 2025; Itovebi. Prescribing information. Genentech; December 2025; Rugo HS et al. *Ann Oncol.* 2020;31(8):1001-1010; Rugo HS et al. *ESMO Open.* 2024;9(9):103697; Genentech. Updated December 2025. Accessed March 17, 2026. https://www.itovebi-hcp.com/content/dam/gene/itovebi-hcp/pdfs/itovebi-safety-guide.pdf

Hyperglycemia Management

Ensure proactive monitoring. Consider prophylactic metformin.

Grade 1 FBG >ULN to 160 mg/dL **OR** HbA_{1C} >7% (for capivasertib)	**Alpelisib, capivasertib, and inavolisib**: continue and initiate/intensify anti-hyperglycemic regimen
Grade 2 FBG >160-250 mg/dL	**Alpelisib**: continue; if FBG does not decrease to ≤160 mg/dL within 21 days, reduce dose
	Capivasertib: hold until FBG ≤160 mg/dL. If recovery in ≤28 days, resume same dose but if >28 days, resume same dose
	Inavolisib: hold until FBG ≤160 mg/dL, then resume at same dose level; if FBG persists >200-250 mg/dL for 7 days, consider endocrine consult
Grade 3 FBG >250-500 mg/dL	**Alpelisib**: hold; if FBG ≤160 mg/dL within 3-5 days, resume at reduced dose. If not resolved within 21 days, d/c
	Capivasertib: hold until FBG ≤160 mg/dL. If recovery occurs ≤28 days, resume at reduced dose but if >28 days, d/c
	Inavolisib: hold; if FBG ≤160 mg/dL within 7 days, resume at same dose. If FBG ≤160 mg/dL for ≥8 days, resume at reduced dose. If >250-500 mg/dL recurs within 30 days, hold until ≤160 mg/dL, then resume at reduced dose.
Grade 4 FBG >500 mg/dL	**Alpelisib**: hold. If FBG ≤500 mg/dL, follow recommendations for grade 3: if FBG confirmed at >500 mg/dL, d/c
	Capivasertib: hold; if life-threatening sequelae or if FBG persists at ≥500 mg/dL after 24 hours, d/c. If FBG ≤500 m/dL within 24 hours, then follow guidance as above for relevant grade
	Inavolisib: hold; if FBG ≤160 mg/dL, resume at reduced dose. If FBG >500 mg/dL recurs within 30 days, d/c

d/c, discontinue; ULN, upper limit of normal.

Alpelisib. Prescribing Information. Novartis Pharmaceuticals; February 2025; Capivasertib. Prescribing Information. AstraZeneca; February 2025; Inavolisib. Prescribing Information, Genentech; January 2025;

Conclusion

Oral targeted therapies are important component of treatment for HR+/HER2– mBC.

Ensuring appropriate biomarker testing in HR+/HER2– mBC is critical to identify possible treatment targets in the first-line setting and beyond.

ctDNA is the preferred testing method for detecting an *ESR1* mutation. Switching to an oral SERD proactively at the development of an *ESR1* mutation (without clinical progression) may be an opportunity to improve PFS.

Proactive monitoring and management of AEs with oral targeted therapies are essential responsibilities of the health care team.

Additional Resources

Resources	
OncLive: Targeted Therapies in HR+/HER2– Breast Cancer	https://cdn.sanity.io/files/0vv8moc6/onclive/e1c578a007e40011889e4042fb5673734530d65b.pdf/02_OSP0125_BTG_Breast_Feb_2025.pdf
Oral Chemo Education Sheets	https://www.oralchemoedsheets.com/
Moore HN et al. Effective strategies for the prevention and mitigation of phosphatidylinositol-3-kinase inhibitor-associated hyperglycemia: optimizing patient care. *Clin Breast Cancer*. 2025;25(1):1-11.	

Thank you!

PTce ONCOLOGY