Tailoring Treatment for Patients With HR+/HER2– Metastatic Breast Cancer: Examining the Role of Current and Emerging Endocrine Therapies

PRE-READ MATERIALS

Educational Resources for Clinicians and Patients

EMPOWER

https://empower-breast.com/

HR+/HER2− Breast Cancer: At a Glance

- HR+, HER2− is the most common breast cancer subtype in the US.[1]
- What do we mean by HER2−?
  - "Non-amplified", or no abnormal increase in HER2 gene copies
  - Includes HER2 low, HER2 ultralow, null

Age-adjusted rate of new breast cases per 100,000 women, SEER 22 2017–2021	
Subtype	**New cases**
HR+/HER2−	90.0
HR−/HER2−	13.6
HR+/HER2+	12.4
HR−/HER2+	5.1
Unknown	7.9
Total	**129.4**

5-year relative survival %t, female breast subtypes by SEER combined summary stage			
Subtype	**Localized**	**Regional**	**Distant**
HR+/HER2−	100.0%	90.5%	35.4%
HR−/HER2−	92.0%	66.8%	14.3%
HR+/HER2+	99.3%	90.4%	45.8%
HR−/HER2+	97.3%	84.2%	39.7%
Unknown	96.6%	77.4%	16.8%
Total	**99.6%**	**86.7%**	**31.9%**

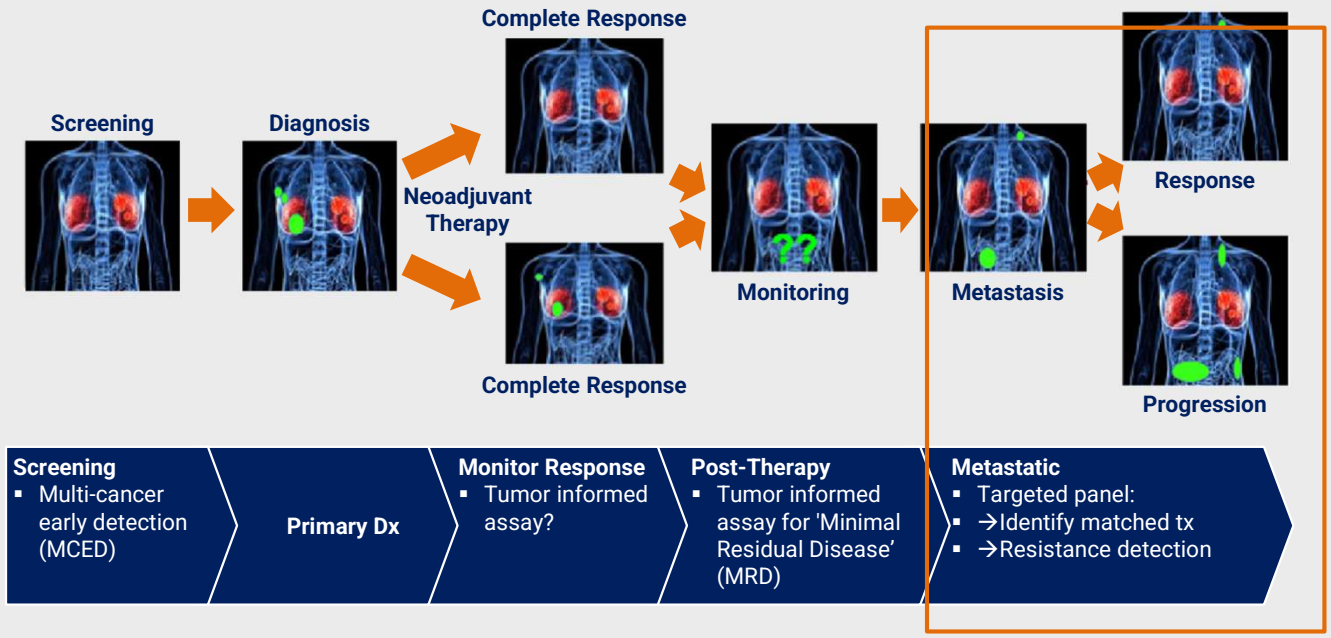
SEER = Surveillance, Epidemiology, and End Results (a program of the NCI).

1. National Cancer Institute (NCI). Cancer stat facts: female breast cancer subtypes (https://seer.cancer.gov/statfacts/html/breast-subtypes.html). Accessed 3/28/2025.

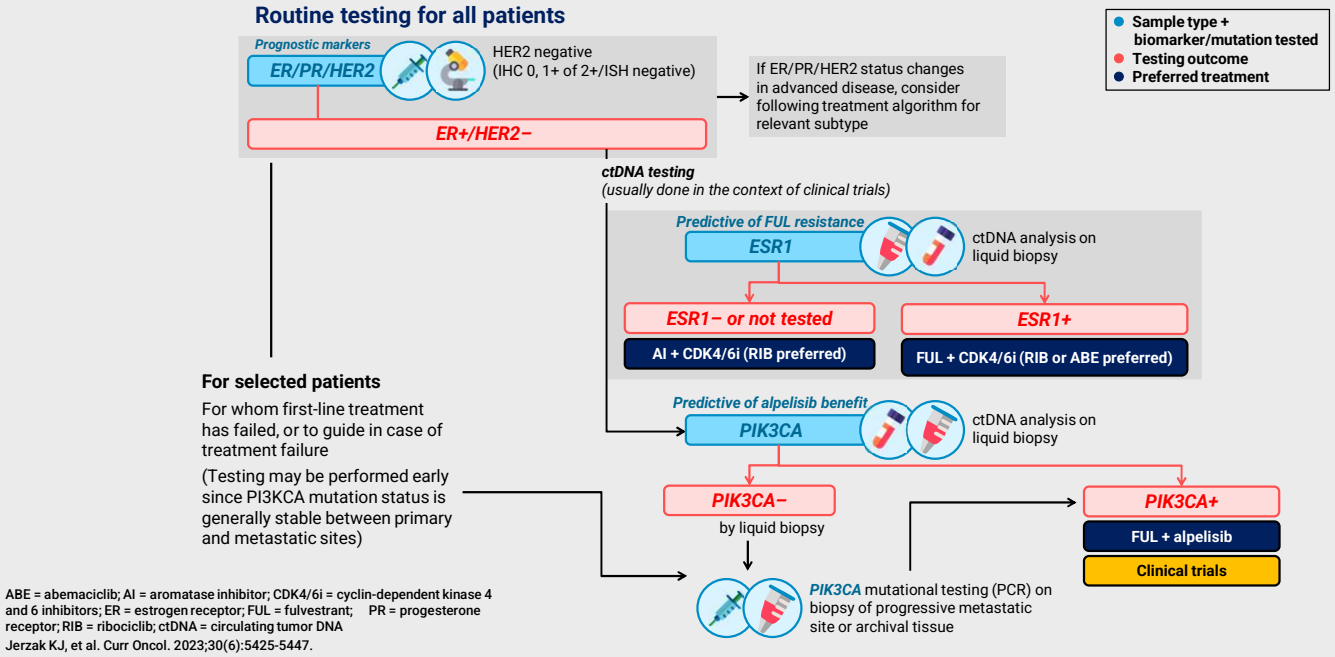
Growing List of Mutation-matched Therapies

Genomic Alteration	Potential FDA-Approved Therapy
***ESR1* mutations**	Elacestrant
***AKT1* pathway alterations**	Alpelisib (*PIK3CA*), Capivasertib
***ERBB2* mutations**	Neratinib
Germline *BRCA1* or *BRCA2* alterations	Olaparib, Talazoparib
Germline *PALB2* or somatic *BRCA1/2*	Olaparib
Microsatellite instability*	Pembrolizumab
High tumor mutational burden*	Pembrolizumab
***NTRK* fusions**	Entrectinib, Larotrectinib

'Liquid Biopsy': Clinical Application



Mutational Testing at Diagnosis of Advanced/Metastatic Disease



ABE = abemaciclib; AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase 4 and 6 inhibitors; ER = estrogen receptor; FUL = fulvestrant; PR = progesterone receptor; RIB = ribociclib; ctDNA = circulating tumor DNA

Jerzak KJ, et al. Curr Oncol. 2023;30(6):5425-5447.

Tumor Agnostic Findings That Can Be Actionable

Mutational testing (PCR) on tissue biopsy

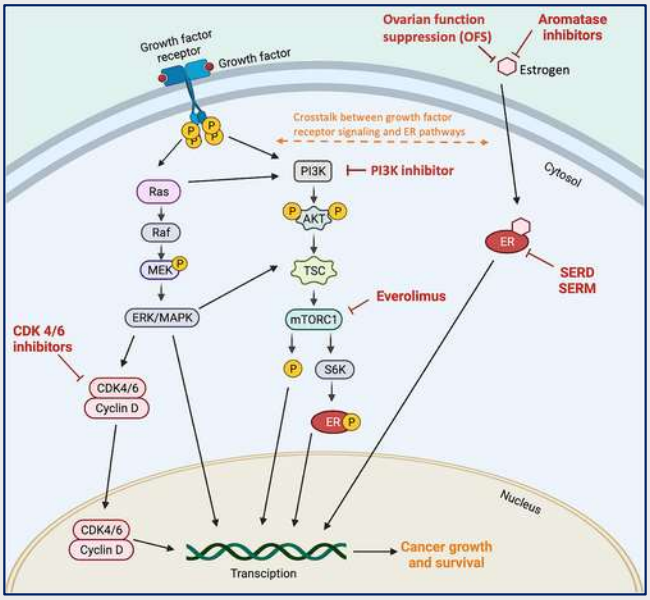
NTRK	MSI-H/dMMR
Larotrectinib	Pembrolizumab
Entrectinib	Dostarlimab

Next-generation sequencing (NGS)

TMB-H	*RET*-fusion
Pembrolizumab	Selpercatinib

MSI-H/dMMR = microsatellite instability-high/mismatch repair deficient; TMB-H =high tumor mutational burden.
Jerzak K, et al. Curr Oncol. 2023;30(6):5425-5447.

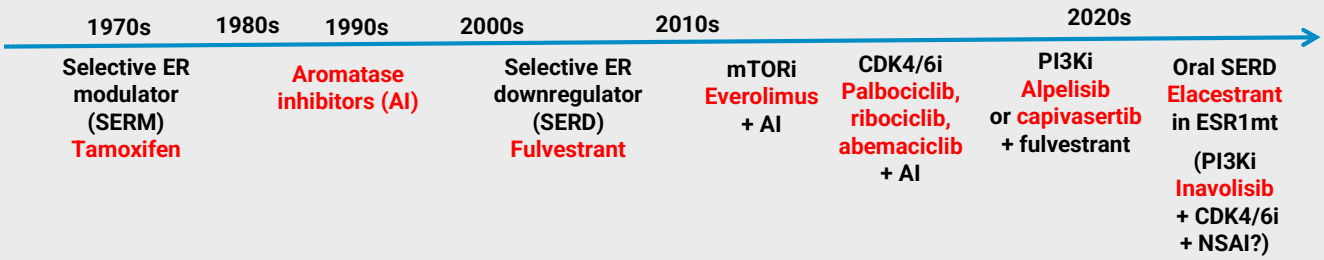
Treatment Pathway: HR+/HER2–



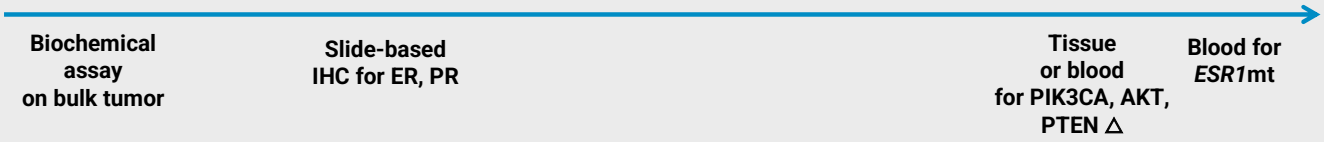
HR+ = hormone receptor-positive; HER2– = human epidermal growth factor receptor 2- negative ; SERM = selective estrogen receptor modulator; SERD = selective estrogen receptor down regulator; CDK4/6 inhibitor = Cyclin-dependent kinase 4 and 6 inhibitor.
Huppert LA, et al. *CA*. 2023; 73(5):480-515.

Recent Evolution in Approaches to Advanced HR+ HER2– BC

MBC drug approvals (examples in red)



Predictive biomarkers



NSAI = nonsteroidal aromatase inhibitor; SERD = selective estrogen receptor degrader; SERM = selective estrogen receptor modulator.

Limitations/Challenges With First-Generation Endocrine Therapies

Endocrine therapy resistance

- Acquired somatic mutations in the ER gene, *ESR1*
- Altered expression of transcription factors, tyrosine kinase receptors, or cell cycle proteins
- Modification of the ER by miRNAs
- Increased crosstalk between HER2, SRC3, and the ER

Intramuscular administration

- Restricts the dose and offers only modest benefit in the second-line setting

Injection site reactions

Modest ability to downregulate the ER

SRC3 = steroid receptor coactivator-3

Rugo H, et al. Clin Adv Hematol Oncol. 2023;21:623-32. Neupane N, et al. Cancers. 2024;16:619. Sharaf B, et al. Front Oncol. 2024;14:1385577.

Treatment Options

HR+/HER2– mBC

Class	Agents
Aromatase inhibitors	Anastrozole, letrozole, exemestane
SERD	Fulvestrant, elacestrant
SERM	Tamoxifen
CDK4/6 inhibitors	Abemaciclib, palbociclib, ribociclib
***PI3K* inhibitor**	Alpelisib, inavolisib
***AKT* inhibitor**	Capivasertib
mTOR	Everolimus

HR+: hormone receptor-positive
HER2–: human epidermal growth factor receptor 2- negative
mBC: metastatic breast cancer
SERM: selective estrogen receptor modulator; SERD: selective estrogen receptor down regulator
CDK4/6 inhibitor: Cyclin-dependent kinase 4 and 6 inhibitor

NCCN. Breast Cancer (version 1. 2025).

Treatment Recommendations

1L

- CDK4/6 inhibitor + ET
- Inavolisib/palbociclib/fulvestrant*

Subsequent Lines

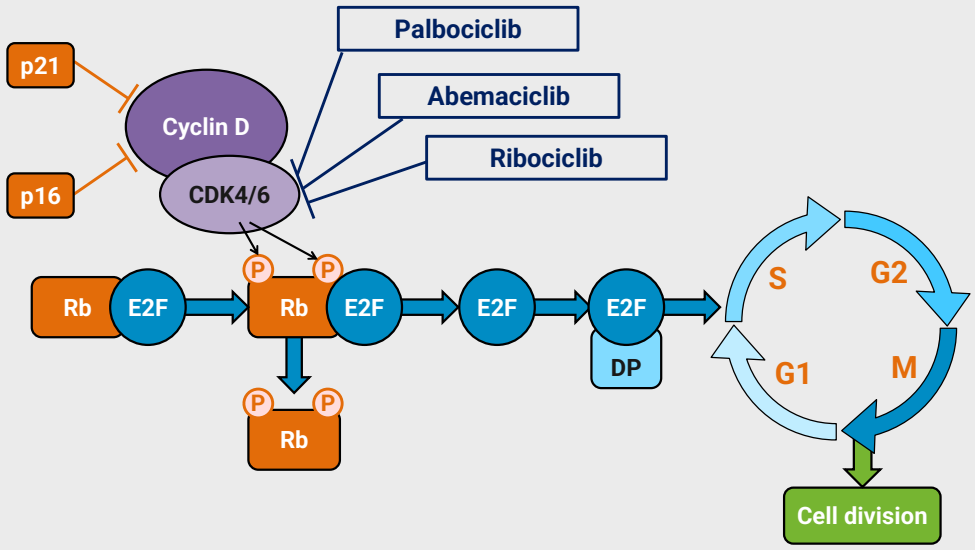
Endocrine-Targeted Therapies

- CDK4/6 inhibitor + fulvestrant (if not used first-line)
- Everolimus + ET
- Targeted therapy (*PI3K*/*AKT1*/mTOR, *PTEN*, *ESR1*, etc.)
- Endocrine monotherapy (fulvestrant, aromatase inhibitor, or tamoxifen)

*if recurrence on/within 12 months of adjuvant AI treatment.
HR = hormone receptor; HER2– = human epidermal growth factor receptor 2; ET = endocrine therapy; CDK4/6 inhibitor = Cyclin-dependent kinase 4 and 6 inhibitor; ESR1 = estrogen receptor 1

Burstein HJ, et al. *J Clin Oncol*. 2024;42(12):1450-53. NCCN. Breast Cancer (version 1. 2025).

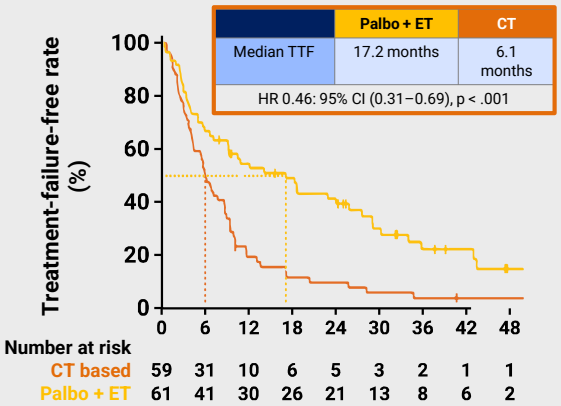
Inhibition of CDK4/6 Is Critical to Improving Outcomes in ER+ Breast Cancer

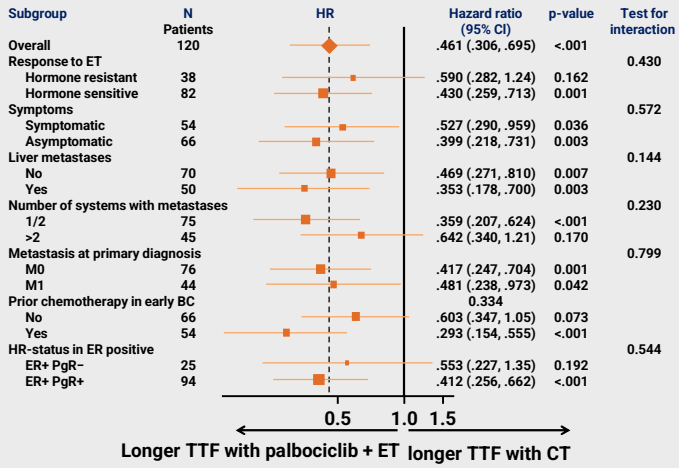


M = mitosis; P = phosphorylation; Rb = retinoblastoma gene product.

Modified from Finn RS, et al. N Engl J Med. 2016;375:1925-1936.

PADMA: Results at 37 Months





- Similar findings for PFS (19 mo vs 8 mo), OS (46 mo vs 37 mo, not significant)
- Heme toxicity worse in ET arm, non-heme toxicity similar in 2 arms (1 grade 5 in ET arm)
- Supports RIGHT Choice—first-line optimized ET > chemotherapy

Very few patients should receive first-line chemotherapy.

CI = confidence interval; Palbo = palbociclib; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure.

Loibl S, et al. SABCS 2024; Abstract LB1-03.

RIGHT Choice: First-Line Ribociclib + ET vs CT for High-Risk HR+/HER2− MBC

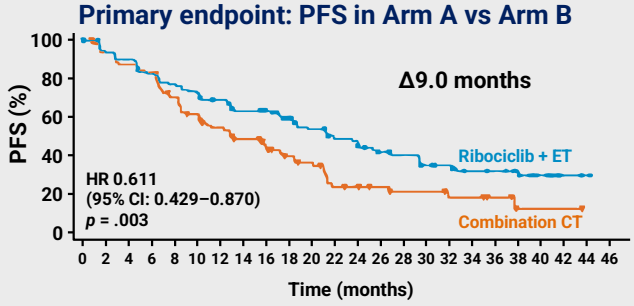
- Pre- and perimenopausal women
- HR+/HER2− ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease
- Aggressive disease
- ECOG PS ≤2
- Total bilirubin ≤1.5 x ULN

→ **R** N = 222 → 1:1

- **Ribociclib (600 mg, 3 weeks on/1 week off) + ET**
- **Physician's choice of combination CT**
  - Docetaxel + capecitabine
  - Paclitaxel + gemcitabine
  - Capecitabine + vinorelbine

Patient population
- **ER-positivity ≥50%: 86.0%**
- ***de novo* metastatic: 64.4%**
- **Rapid progression: 18.5%**
- **Visceral crisis: 47.7%**

Primary endpoint: PFS in Arm A vs Arm B



- OS data are immature
- Patients on the ribociclib + ET arm had lower symptomatic AE rates and fewer discontinuations

Ribociclib + ET resulted in a significant improvement in mPFS in premenopausal women with clinically aggressive HR+/HER2− MBC compared to combination CT.

ABC = advanced breast cancer; AE = adverse event; ECOG PS = Eastern Cooperative Oncology Group Performance Status; mPFS = median PFS; ULN = upper limit of normal.
Lu Y, et al. *J Clin Oncol*. 2024;42(23):2812-2821.

Summary

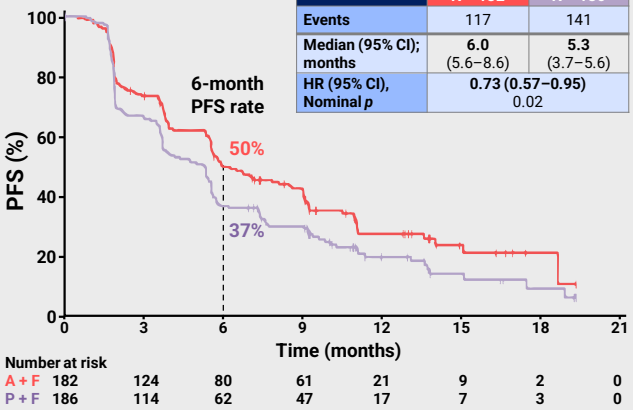
✓ Data from separate trials evaluating CDK4/6i + ET have demonstrated that this combination is superior to chemotherapy as first-line therapy for HR+/HER2− MBC, even in patients with aggressive disease

✓ Given the known survival benefit with CDK4/6i + ET in the first-line setting, almost ALL patients should be treated with this combination in first line, reserving chemotherapy only for patients in visceral crisis and/or after exhausting ET options

postMONARCH: Efficacy Endpoints

Primary EP: Investigator-assessed PFS

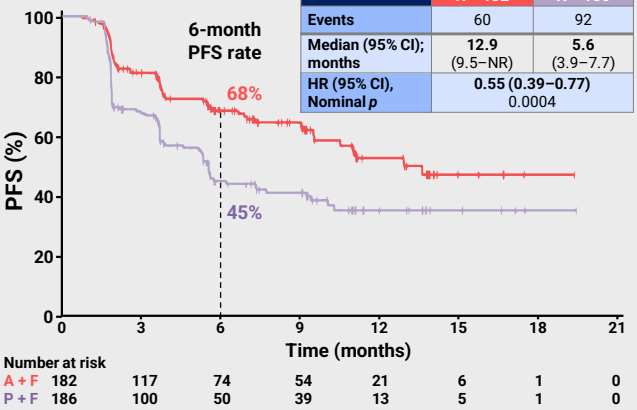
	Abemaciclib + fulvestrant N = 182	Placebo + fulvestrant N = 186
Events	117	141
Median (95% CI); months	6.0 (5.6–8.6)	5.3 (3.7–5.6)
HR (95% CI), Nominal *p*	0.73 (0.57–0.95) 0.02	



Abemaciclib led to 27% reduction in the risk of developing PFS event.

Secondary EP: BICR-assessed PFS

	Abemaciclib + fulvestrant N = 182	Placebo + fulvestrant N = 186
Events	60	92
Median (95% CI); months	12.9 (9.5–NR)	5.6 (3.9–7.7)
HR (95% CI), Nominal *p*	0.55 (0.39–0.77) 0.0004	



Abemaciclib led to 45% reduction in the risk of developing PFS event per BICR.

Estimates impacted by informative censoring (discordance with investigator events): 51% abemaciclib arm, 38% placebo arm

Kalinsky K, et al. *J Clin Oncol*. 2025;43(9)1101-1112.

postMONARCH: Summary

- First randomized phase 3 trial in ER+/HER2− MBC to confirm efficacy of continuing CDK4/6i after progression on CDK4/6i and switching ET
- Abemaciclib + fulvestrant improved PFS in patients who had previously been treated with prior palbociclib or ribociclib
  - 27% reduction in risk of progression or death
  - Benefit seen in all prespecified subgroups regardless of biomarker
- Abemaciclib + fulvestrant is a reasonable second-line option for patients who have done well on first-line CDK4/6i and may be most appropriate for those without PIK3CA or ESR1 mutations

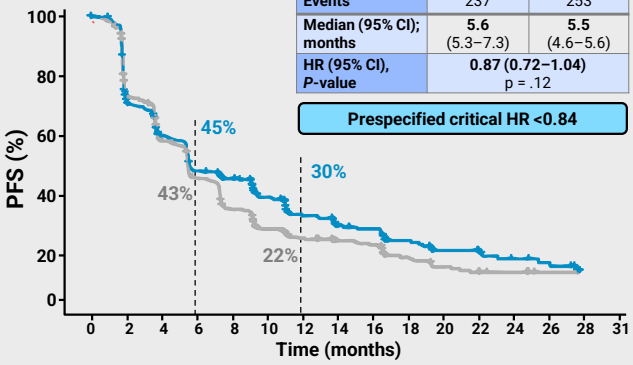
Kalinsky K, et al. *J Clin Oncol*. 2025;43(9)1101-1112.

EMBER-3: Imlunestrant vs SOC for ER+/HER2− MBC

Primary endpoint:
PFS in all patients – Arm A vs Arm B

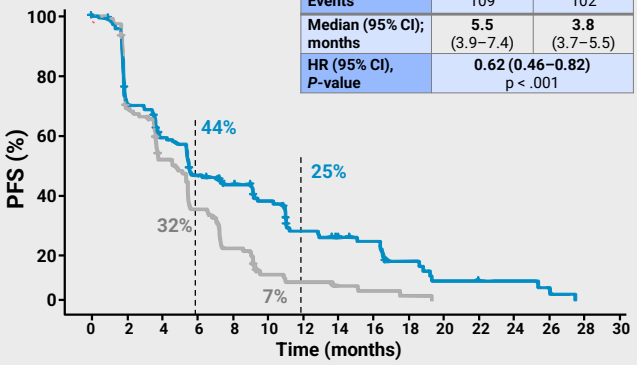
	Imlunestrant N = 331	SOC ET N = 330
Events	237	253
Median (95% CI); months	5.6 (5.3–7.3)	5.5 (4.6–5.6)
HR (95% CI), *P*-value	0.87 (0.72–1.04) p = .12	

Prespecified critical HR <0.84



Primary endpoint:
PFS in *ESR1 mutant* – Arm A vs Arm B

	Imlunestrant N = 138	SOC ET N = 118
Events	109	102
Median (95% CI); months	5.5 (3.9–7.4)	3.8 (3.7–5.5)
HR (95% CI), *P*-value	0.62 (0.46–0.82) p < .001	



Arm A: Imlunestrant Arm B: Fulvestrant or exemestane

Significant difference in PFS with imlunestrant observed ***only*** in *ESR1* mutant subset.

Jhaveri K, et al. NEJM. 2025;392(12):1189-1202.

Not yet FDA approved for breast cancer treatment.

EMBER-3 Summary

- Imlunestrant monotherapy significantly improved PFS vs SOC ET in the *ESR1* mutant patient population but not in the overall population
- The PFS benefit in *ESR1* mutant population with imlunestrant is in line with that reported for other oral SERDs
- Imlunestrant + abemaciclib significantly improved PFS irrespective of *ESR1* mutation status in patients with ER+/HER2− MBC
- This mPFS of 9.1 months in an unselected population is higher than that reported for fulvestrant/abemaciclib or fulvestrant/ribociclib combinations (~5.6 months), suggesting that imlunestrant + abemaciclib is a reasonable second-line treatment option in CDK4/6i pretreated ER+/HER2− MBC

Not yet FDA approved for breast cancer treatment.

INAVO120

Key eligibility criteria

Enrichment of patients with poor prognosis

- *PIK3CA*-mutated, HR+, HER2− LA/MBC by central ctDNA or local tissue/ctDNA test
- Measurable disease
- Progression during/within 12 months of adjuvant ET completion
- Fasting glucose <126 mg/dL (<7.0 mmol/L) and HbA1C <6.0% (< 42 mmol/mol)

R 1:1

N = 325

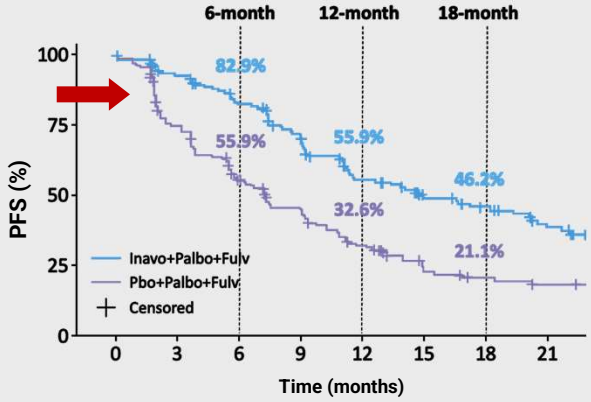
Enrollment period: December 2019 to September 2023

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD Day 1–21) + fulvestrant (500 mg Cycle 1 Day 1/ Day 15 and Q4W)

Placebo (PO QD) + palbociclib (125 mg PO QD Day 1–21) + fulvestrant (500 mg Cycle 1 Day 1/ Day 15 and Q4W)

Until PD or toxicity

SURVIVAL FOLLOW-UP



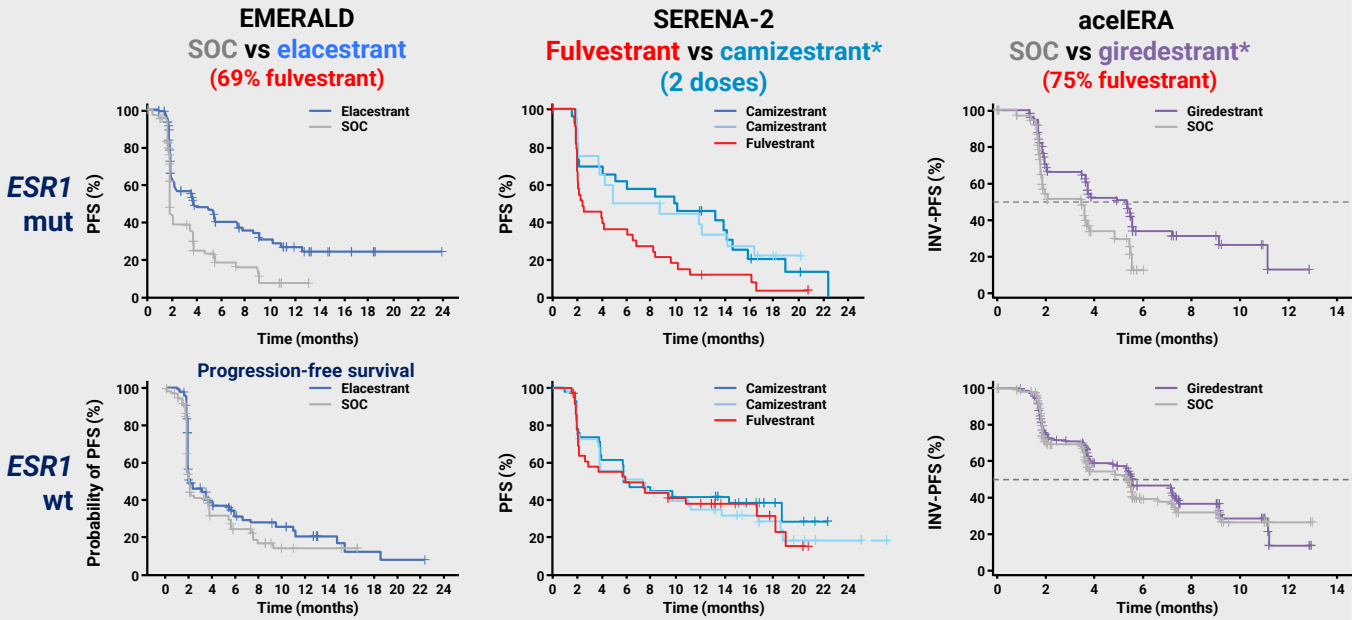
	Inavolisib + palbociclib + fulvestrant N = 161	Placebo + palbociclib + fulvestrant N = 164
Events	82 (50.9)	113 (68.9)
Median (95% CI); months	**15.0** (11.3–20.5)	**7.3** (5.6–9.3)
HR (95% CI), *p*-value	**0.43 (0.32–0.59)** p < .0001	

OS immature (HR 0.65, 0.43-0.97), ns

Approved October 2024
Who should you treat?

Turner NC, et al. N Engl J Med. 2024;391:1584-1596.

Other SERD Trials by *ESR1* Status



*Not FDA approved for breast cancer treatment. INV = investigator; mut = mutation; wt = wild-type.

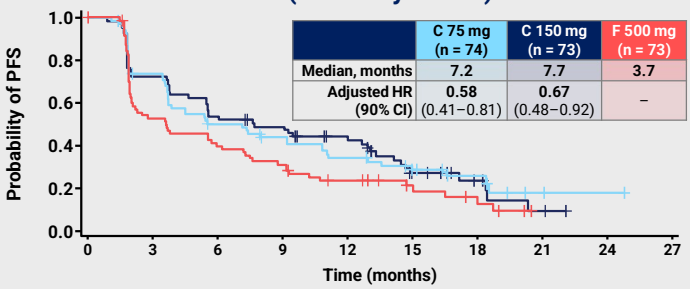
Bidard F-C, et al. *J Clin Oncol*. 2022;40(28):3246-3256. Oliveira M, et al. *Lancet Oncol*. 2024;25(11):1424-1439. Martin M, et al. *J Clin Oncol*. 2024;42:2149-2160.

SERENA-2

Randomized phase 2 trial of camizestrant vs fulvestrant in postmenopausal patients with ER+ HER2– ABC with recurrence or progression on SOC ET[1]

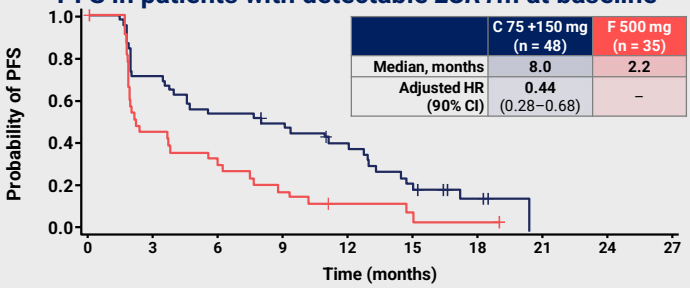
- Camizestrant (next-generation SERD and pure estrogen receptor antagonist) provided a statistically significant and clinically meaningful PFS benefit vs fulvestrant, regardless of dose[1]
- Median PFS with camizestrant was similar in patients with and without detectable *ESR1*m at baseline[2]
- Camizestrant demonstrated a well-tolerated safety profile[1]

PFS (full analysis set)



	C 75 mg (n = 74)	C 150 mg (n = 73)	F 500 mg (n = 73)
Median, months	7.2	7.7	3.7
Adjusted HR (90% CI)	0.58 (0.41–0.81)	0.67 (0.48–0.92)	–

PFS in patients with detectable *ESR1*m at baseline



	C 75 +150 mg (n = 48)	F 500 mg (n = 35)
Median, months	8.0	2.2
Adjusted HR (90% CI)	0.44 (0.28–0.68)	–

C = camizestrant; F = fulvestrant

1. Oliveira M, et al. Cancer Res. 2023;83(suppl 5):GS3-02. 2. Oliveria M, et al. J Clin Oncol. 2023;41(suppl 16):1066.

Not FDA approved for breast cancer treatment.

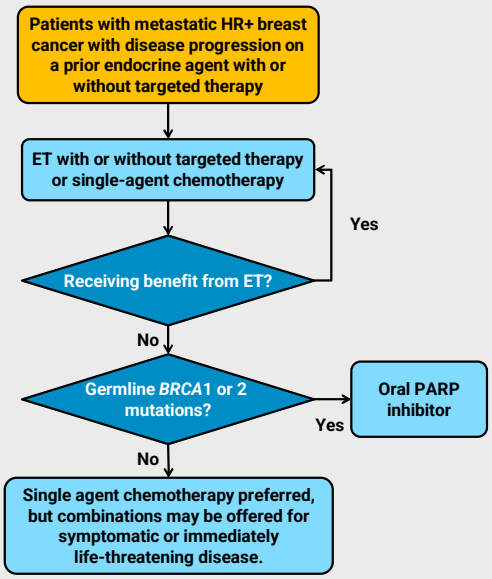
Common Adverse Events With Oral SERDs

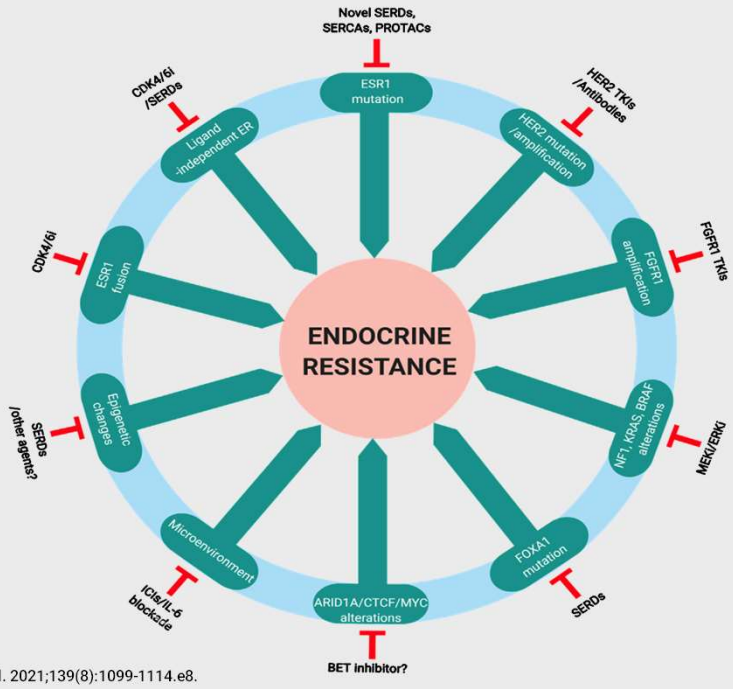
Side effect (vs SOC)	Elacestrant	Imlunestrant	Giredestrant	Camizestrant
Fatigue		X	X	X
Nausea	X	X	X	X
Vomiting	X		X	
Constipation	X	X		
Diarrhea	X	X		X
Bradycardia			X (3.3%)	
Photopsia (light flashes)				X (25%)
Transaminitis			X	
Musculoskeletal symptoms			X	X

Slide adapted from H Burstein.

Multiple Ways to Continue ET-Based Therapy…

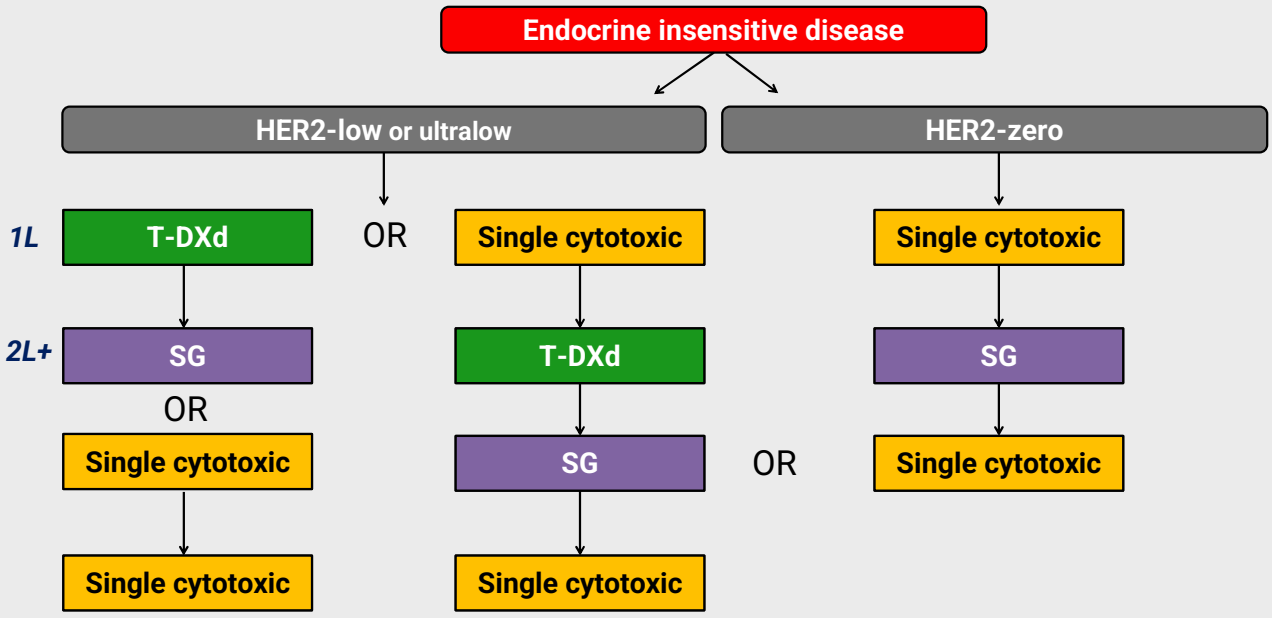
ASCO Clinical Practice Guidelines





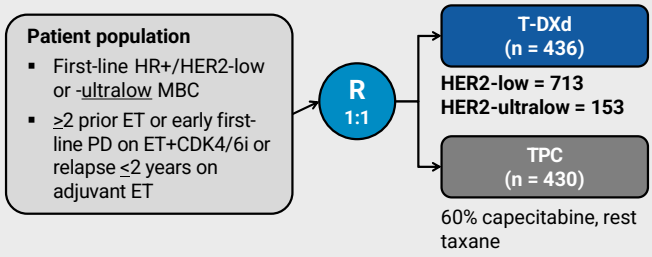
Moy B, et al. J Clin Oncol. 2021;39(35):3938-3958. Hanker AB, et al. Cancer Cell. 2021;139(8):1099-1114.e8.

What Are the Choices, and How Do You Make Them?



SG = sacituzumab govitecan; T-DXd = trastuzumab deruxtecan.

DESTINY Breast-06



Prior reports

- T-DXd > TPC for mPFS in HER2-low and ITT
- T-DXd > TPC for toxicity
- OS trend towards T-DXd (87% vs 82%; 12-month OS)

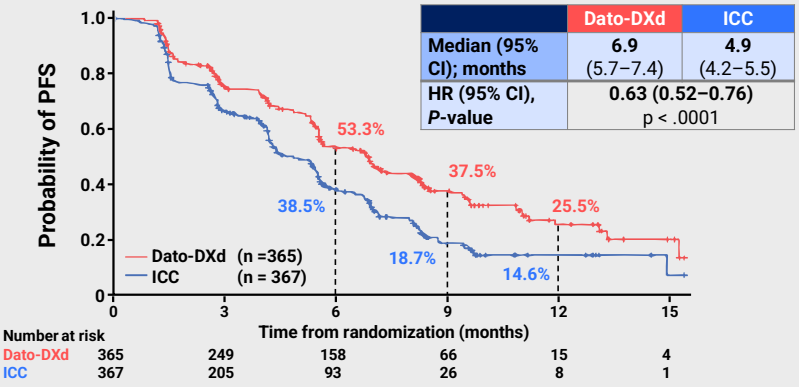
- **However, OS remains immature, toxicity is worse with T-DXd in all subgroups, and there are no data that T-DXd is better given in first line than second line+.**
- **T-DXd is a better choice as first-line chemotherapy in symptomatic, rapidly progressive disease.**

ITT = intent-to-treat; TPC = treatment of physician's choice.

Bardia A, et al. N Engl J Med. 2024;391(22):2110-2122. Bardia A, et al. ASCO 2024; Abstract 1075. Bardia A. SABCS 2024; Abstract LB1-04.

TROPION Breast01: Efficacy Outcomes

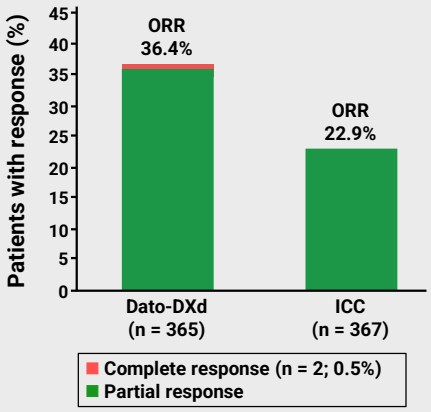
Primary EP: PFS by BICR



	Dato-DXd	ICC
Median (95% CI); months	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI), *P*-value	0.63 (0.52–0.76) p < .0001	

PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI, 0.53–0.76)

Response rate by BICR



OS (dual primary endpoint)
OS data were not mature (information fraction 39%): Median follow-up 9.7 months.
A trend favoring Dato-DXd was observed: HR 0.84 (95% CI 0.62–1.14).

Bardia A, et al. ESMO 2023; Abstract LBA11. Rugo HS, et al. Miami Breast Cancer Conference (MBCC) 2024; Abstract 30.

Datopotamab Deruxtecan: Where to Place in Algorithm

- No survival advantage, unique toxicity profile (stomatitis in >50%)
- Consider for second line (when you might use T-DXd) in
  - HER2-0 (recognizing the silliness of the IHC subcategories)
  - Underlying cardiac concerns
  - History of drug-induced pneumonitis (?)
- Probably would not use after T-DXd (would choose SG unless myelosuppression a big concern) because has same payload as T-DXd

Conclusions

- Many advances in metastatic breast cancer, especially in HR+ HER2− (which is more than half of MBC)
- ET-based treatment outperforms chemotherapy-based treatment in HR+ MBC
- Novel combinations and endocrine backbones now in second-line ER+ MBC
- Challenges remain in deciding when to use more effective, and more toxic, approaches given increasing longevity
- Patient-reported outcomes are a mechanism to better identify and address toxicity—and worthy of efforts to incorporate into clinical care

The survival curve continues to move in the right direction.
We need to make sure that is not at the expense of quality of life.