

UC San Diego Health

# Recent Advances in Systemic Treatment for Breast Cancer

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# Three shifts shaping breast oncology in 2026

## 1. Escalate where it helps

More precise adjuvant decisions in early-stage disease

## 2. Use biomarkers earlier

Blood and tumor testing now change treatment sequencing

## 3. Move ADCs earlier

New standards are emerging in metastatic and curative-intent care

# HR+/HER2- early-stage: adjuvant options expanded

FDA approved

## Adjuvant CDK4/6 Inhibitors in HR+/HER2- Early Breast Cancer

Two positive phase III trials • Different eligibility criteria, duration and toxicity

### ABEMACICLIB | monarchE

2 years • 150 mg twice daily • continuous dosing

#### POPULATION

High-risk, node-positive disease:

- ≥4 positive nodes, or
- 1–3 nodes + grade 3, tumor ≥5 cm, or Ki-67 ≥20%

#### EFFICACY

- 7-year OS: 86.8% vs 85.0%
- OS HR 0.842 (95% CI 0.722–0.981; P=.027)
- iDFS benefit sustained; ~7.6% absolute benefit at 5 years

#### KEY TOXICITIES

Diarrhea, neutropenia, fatigue; monitor CBC/LFTs and VTE risk.

### RIBOCICLIB | NATALEE

3 years • 400 mg daily • 21 days on / 7 days off

#### POPULATION

Stage II–III disease, broader risk range:

- Any involved nodes (except microscopic-only), or
- Selected node-negative tumors with high-risk features

#### EFFICACY

- 5-year absolute iDFS benefit: 4.5%
- iDFS HR ~0.72 in 5-year analysis
- OS trend favorable; not yet statistically significant in the reported analysis **6-year OS will be presented at ESMO 2026 (LBA26)**

#### KEY TOXICITIES

Neutropenia, elevated LFTs, QT prolongation; monitor CBC/LFTs, ECG and electrolytes.

## Why it matters

Abemaciclib and ribociclib both improve outcomes after standard local therapy and endocrine therapy. monarchE supports intensification for high-risk node-positive disease.

NATALEE broadens the population who may benefit from adjuvant CDK4/6 inhibition

Clinical selection: monarchE has mature, statistically significant OS benefit; NATALEE includes selected node-negative and broader stage II patients.

# lidERA: oral SERD may change adjuvant endocrine therapy

Under FDA review

## STUDY DESIGN · PHASE III / N=4,170

Stage I–III ER+/HER2–  
intermediate/high risk

**Giredestrant 30 mg/day**

vs

**Standard endocrine therapy**

Randomized 1:1  
Planned treatment: 5 years

**Primary endpoint: invasive disease-free survival**

## PRIMARY ENDPOINT: INVASIVE DISEASE-FREE SURVIVAL

**30%**

risk reduction  
HR=0.70, p=0.0014

## 3-YEAR DISEASE-FREE SURVIVAL

Giredestrant **92.4%**

Standard therapy **89.6%**

**31%**

reduction in  
distant metastasis  
HR=0.69

**5.3%**

vs  
8.2%

discontinuation  
due to side effects

**11.3%**

vs  
3.2%

bradycardia  
(mostly grade 1)

## Why this matters

- 30% relative reduction in invasive disease-free survival events (HR 0.70).
- 3-year iDFS: 92.4% with giredestrant vs 89.6% with standard endocrine therapy.
- Lower treatment discontinuation from side effects (5.3% vs 8.2%).
- Signals possible future expansion of oral SERDs into early-stage disease.

**Not yet standard of care.**

# HR+/HER2- metastatic: blood and tumor biomarkers matter

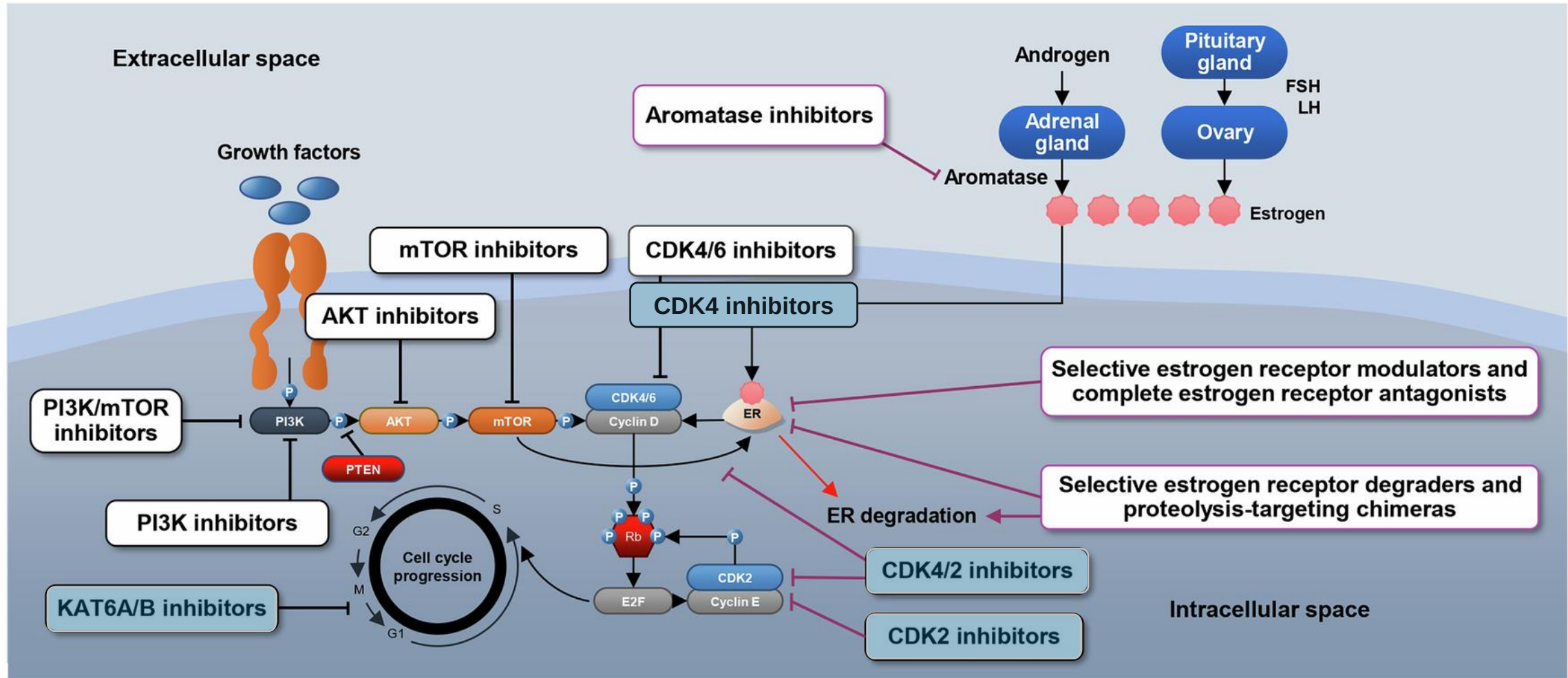
## Detecting Actionable Biomarkers is Standard of Care

- Both ESMO and ASCO recommend multi-gene panel testing for ESCAT I/II genomic alteration ( $\Delta$ ).
- ASCO and ESMO recommend serial ctDNA for ESR1mt in HR+ HER2-.
- Evolving: ~45 genetic aberrations in breast cancer meet OncoKb levels of evidence with FDA-approved drugs

| Genomic $\Delta$ | %           | FDA approved therapy                                     |
|------------------|-------------|----------------------------------------------------------|
| ESR1m            | $\leq 40\%$ | elacestrant, imlunestrant<br>vepedgestrant, camizestrant |
| AKT1, PTENm      | 20%         | capivasertib                                             |
| PIK3CAm          | 40%         | capivasertib, alpelisib, inavolisib                      |
| g(or s)BRCA1/2m  | 10%         | olaparib, talazoparib                                    |
| gPALB2m          | 2%          | olaparib                                                 |
| BRAFm            | 1%          | dabrafenib+trametinib                                    |
| NTRK fusion      | $<1\%$      | entrectinib, larotrectinib, repotrectinib                |
| RET fusion       | 1%          | seelpercatinib                                           |
| MSI-H            | 1%          | Pembrolizumab, dostarlimab                               |
| TMB-high         | 5%          | Pembrolizumab                                            |
| ErbB2m           | 2%          | neratinib                                                |

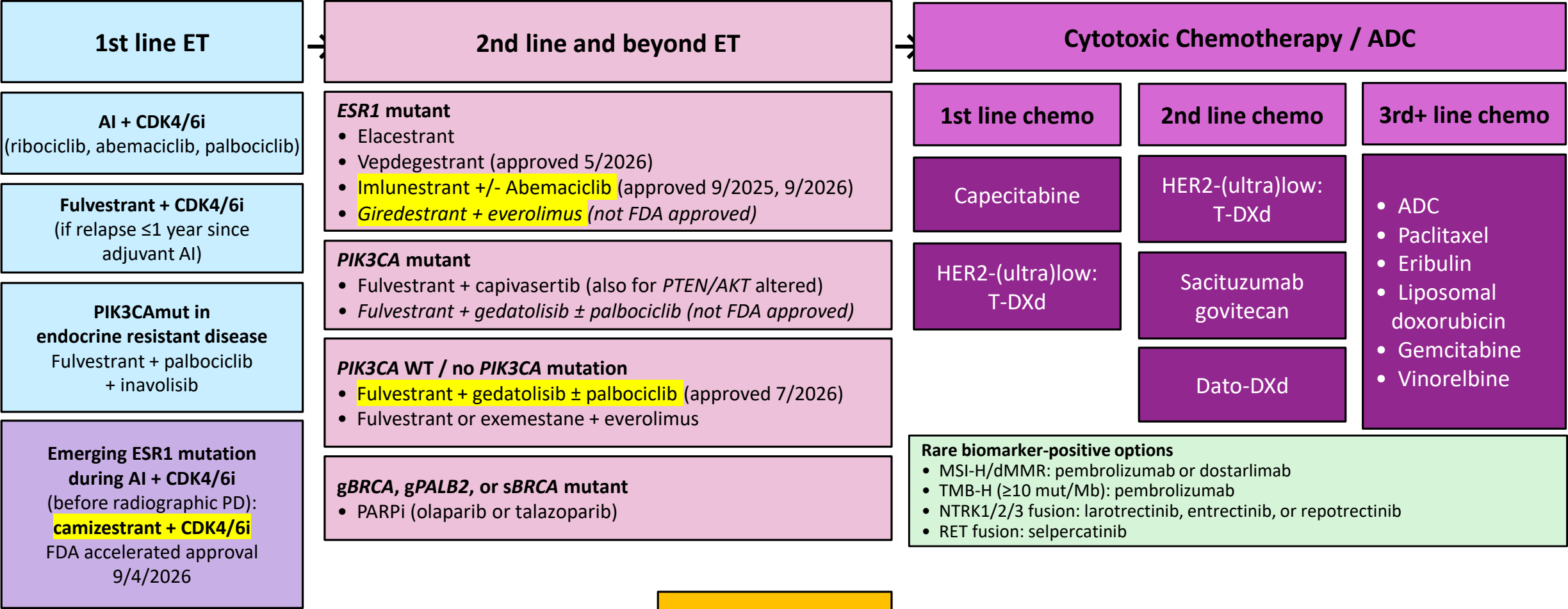
Re-biopsy or liquid biopsy at progression can reveal newly actionable resistance mechanisms.

# Molecular Targets in HR+ HER2- Breast Cancer



In Phase 3 studies; not yet FDA approved

# Updated Roadmap: ER/PR+ HER2– metastatic breast cancer (2026)



- This roadmap will continue to change!
- Novel combination endocrine therapies are coming! Will have to balance efficacy and toxicity of doublet vs triplet strategies
- Use of novel ET at molecular progression? (e.g. SERENA-6 strategy)
- Impact in mBC tx from adjuvant use of CDK4/6i and novel ET in early-stage BC
- Identifying biomarkers of response and resistance are critical
- Important to evaluate optimal sequencing of these agents
- Need for developing new ADCs or strategies for those with endocrine/ targeted therapy resistance

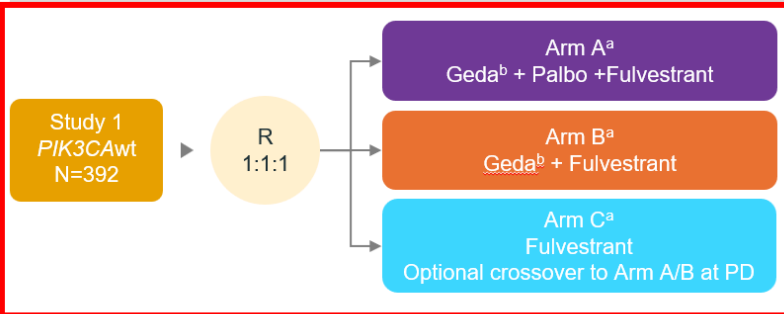
# Gedatolisib: new approval from VIKTORIA-1

Approved Jul 2026

- Gedatolisib is an IV dual PI3K/mTOR inhibitor
- Approval filled an important gap for patients without a detected *PIK3CA* mutation after CDK4/6 inhibitor + AI

## Key Eligibility Criteria

- Pre- and postmenopausal women and men
- Progression on/after CDK4/6i + NSAI
- ≤2 lines of prior ET for MBC; no prior mTORi, PI3Ki, AKTi; no prior Chemo for MBC
- No T2DM with HbA1c >6.4% or T1DM



**Primary endpoint:** PFS by BICR (Arm A vs Arm C; Arm B vs Arm C)

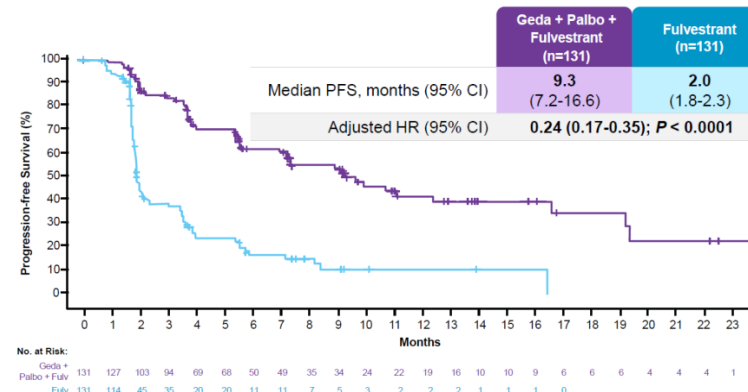
**Secondary endpoints:** OS, response, safety, QoL

<sup>a</sup> Gedatolisib 180 mg IV qw (3 weeks on, 1 week off); palbociclib 125 mg qd (21 days on, 7 days off); fulvestrant 500 mg C1 D1 and D15, then q4w.

<sup>b</sup> Prophylactic use of steroid-containing "swish and spit" regimen was protocol mandated; oral non-sedating antihistamine therapy was recommended.

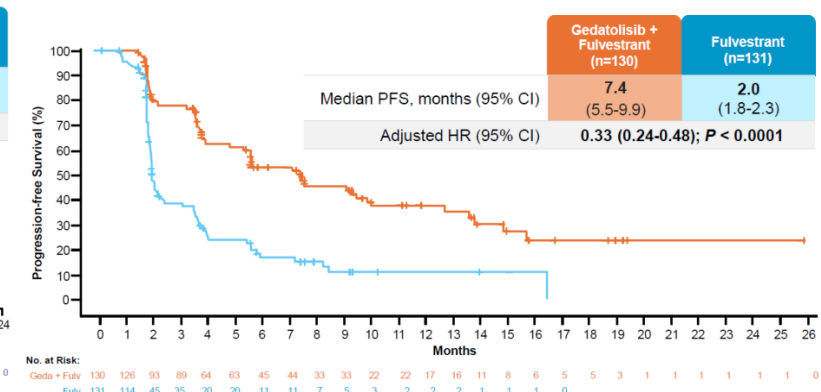
## Study 1 (PIK3CAwt): PFS

PFS by BICR (Coprimary Endpoint):  
Gedatolisib Triplet vs Fulvestrant



- Median follow-up: 10.1 months (IQR, 6.6-15.1)

PFS by BICR (Coprimary Endpoint):  
Gedatolisib Doublet vs Fulvestrant



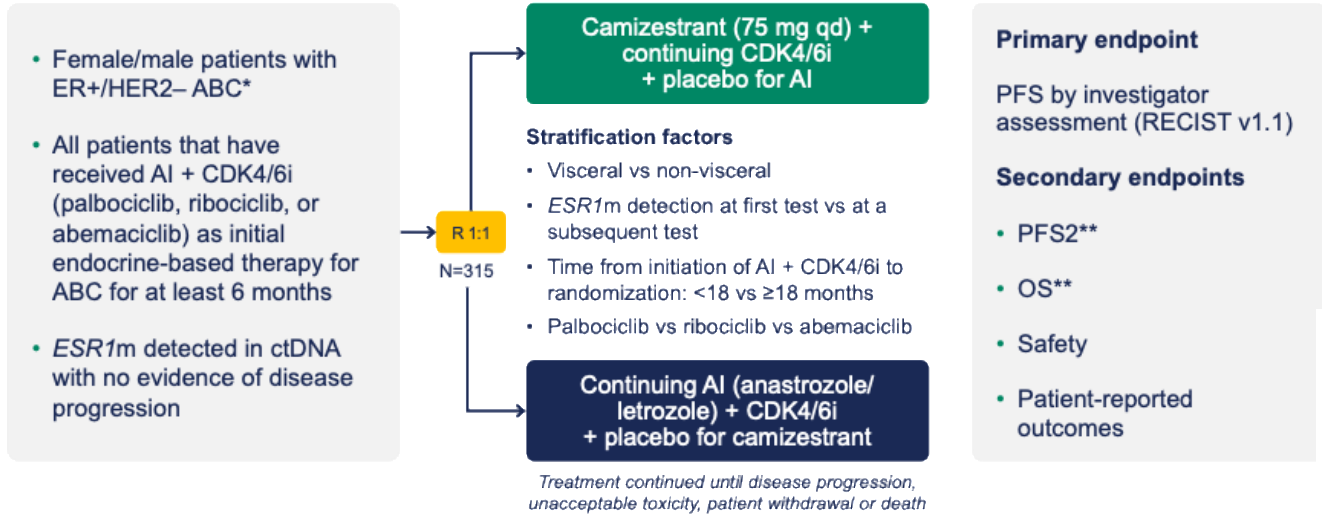
# Shifting paradigm: SERENA-6 and ESR1-guided switching

Approved Sept 2026

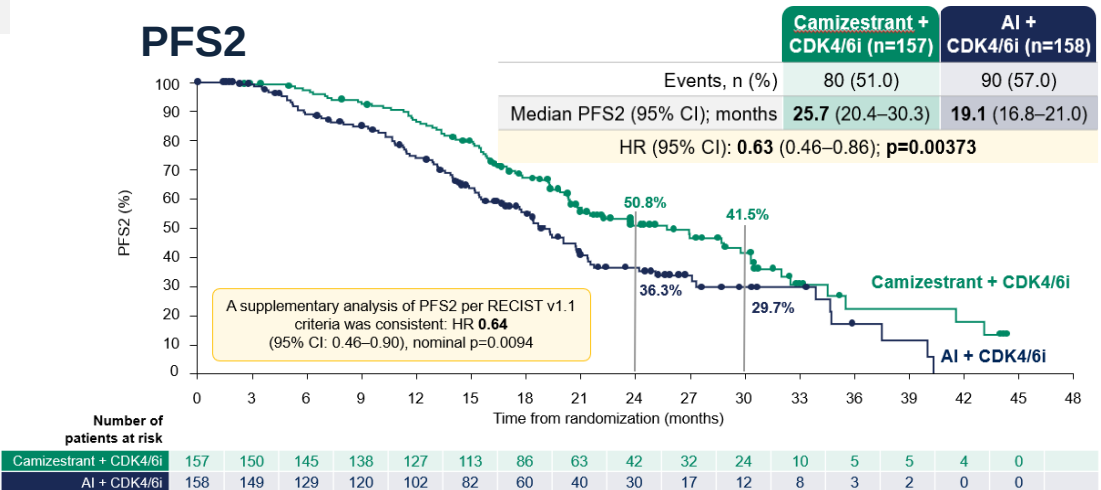
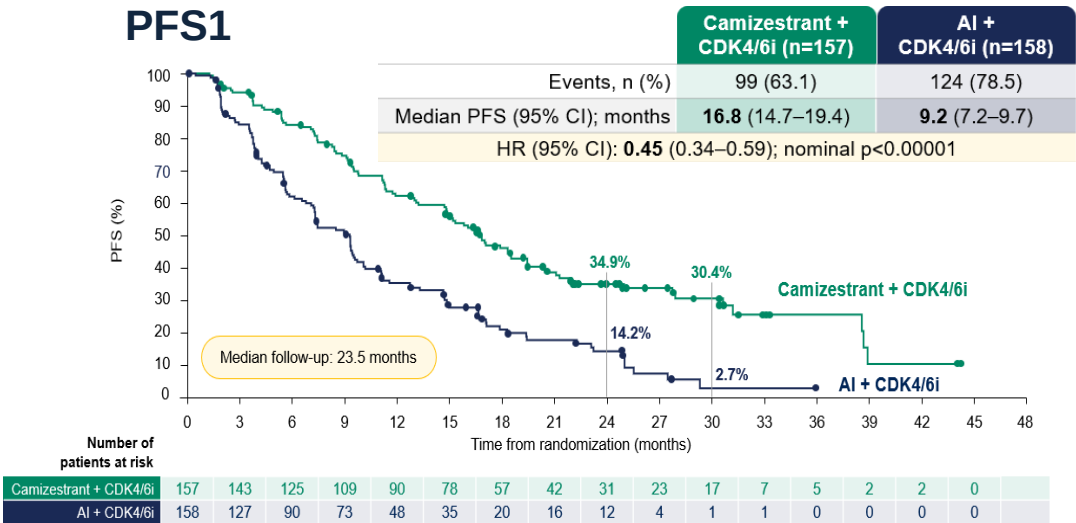
## The scenario

- Cancer remains controlled on aromatase inhibitor + CDK4/6 inhibitor
- Blood detects a new ESR1 mutation
- No radiographic progression

## SERENA-6 study design



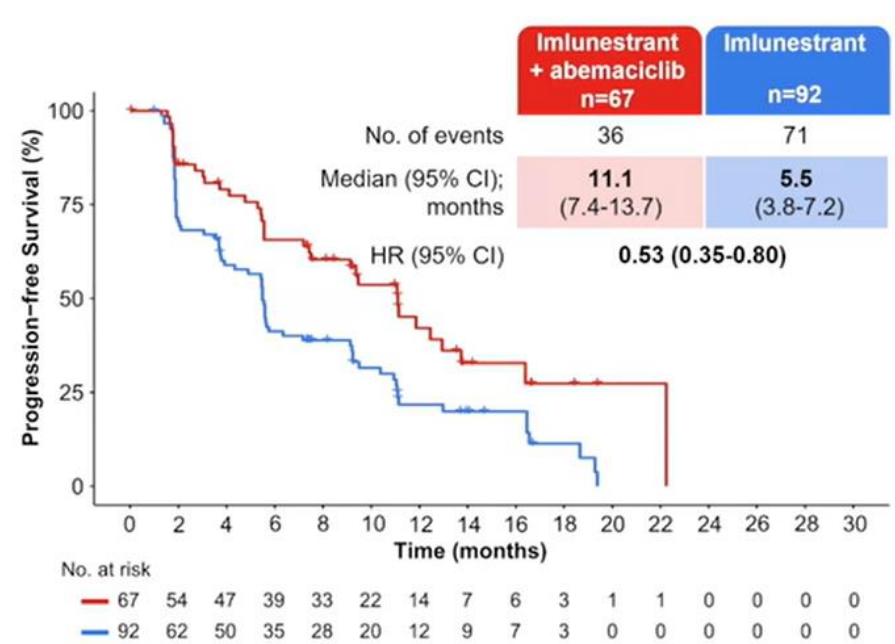
- NO cross-over after 1st disease progression
- Most patients did NOT get 2L oral SERDs for ESR1mut disease (which is standard therapy in US)
- Does not address whether treating early when ESR1mut is detected before clinical or imaging progression will lead to improvement in overall survival



# Oral SERD + CDK4/6i: imlunestrant + abemaciclib

Approved Sep 2026

## ESR1-mutant subgroup · progression-free survival



**11.1 vs 5.5 mo**  
**Median PFS · HR 0.53**

**FDA indication**  
ESR1-mutated ER+/HER2-  
advanced/metastatic disease  
after ≥1 endocrine line

- Imlunestrant + abemaciclib showed consistent benefit across all patients regardless of *ESR1*mut, *PIK3CA*mut, and including in **CDK4/6i pretreated subgroup**

| PFS in CDK4/6i Pretreated Patients | Imlunestrant + Abemaciclib<br>(n=139) | Imlunestrant<br>(n=140) |
|------------------------------------|---------------------------------------|-------------------------|
| Events, n                          | 97                                    | 120                     |
| Median PFS, mo (95% CI)            | 9.1 (7.2-11.3)                        | 3.7 (2.1-5.5)           |
| HR (95% CI)                        | 0.53 (0.40-0.69)                      |                         |
| Nominal <i>p</i> -value <0.0001    |                                       |                         |

# Giredestrant + everolimus after CDK4/6 inhibition: evERA

Under FDA review

**Key eligibility criteria\***

- ER+, HER2– aBC (1–3L of therapy)
- ≤ 2 prior lines of ET in the aBC setting
- PD or relapse during/post-CDK4/6i + ET
- No prior chemotherapy in the aBC setting
- Measurable disease per RECIST v1.1 or evaluable bone metastases

N = 373\*

R 1:1

Giredestrant (30 mg) + everolimus (10 mg)<sup>†</sup>

SOC ET<sup>‡</sup> + everolimus (10 mg)<sup>†</sup>  
<sup>‡</sup>Exemestane/fulvestrant/tamoxifen

Enrolment period: August 2022 to October 2024

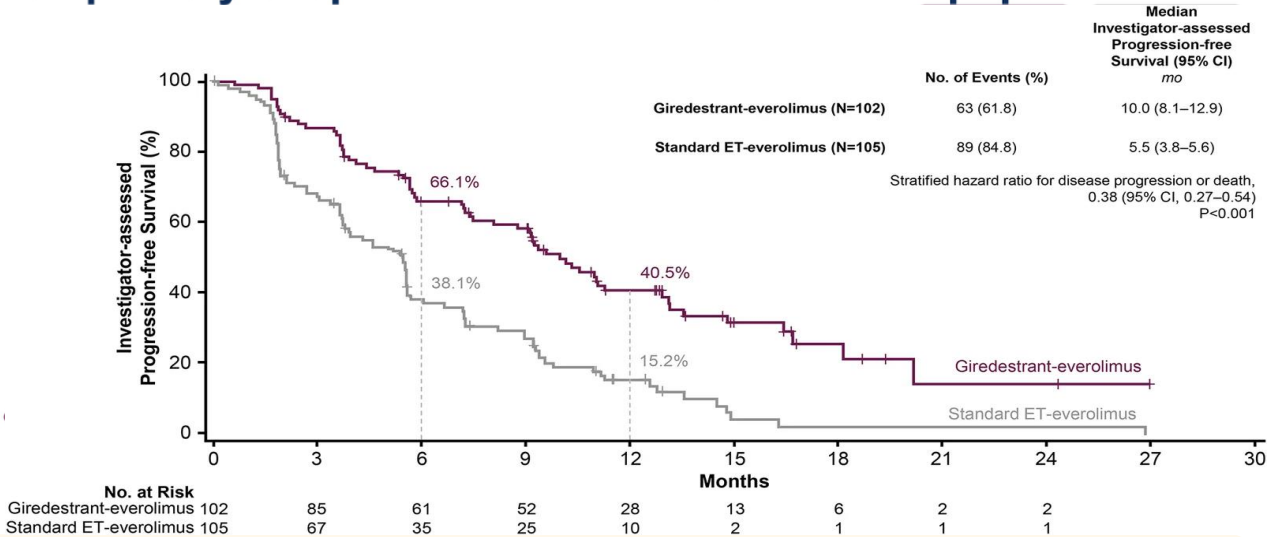
<sup>†</sup> Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol<sup>1</sup>

\* Trial was enriched to 55% of patients with *ESR1*m at baseline (centrally tested via circulating tumour DNA)

### Stratification factors

- Prior treatment with fulvestrant (yes vs no)
- ESR1*m (yes vs no/indeterminate)
- Site of disease (visceral [lung and/or liver involvement] vs non-visceral)

## Co-primary endpoint – INV-PFS in the *ESR1*m population



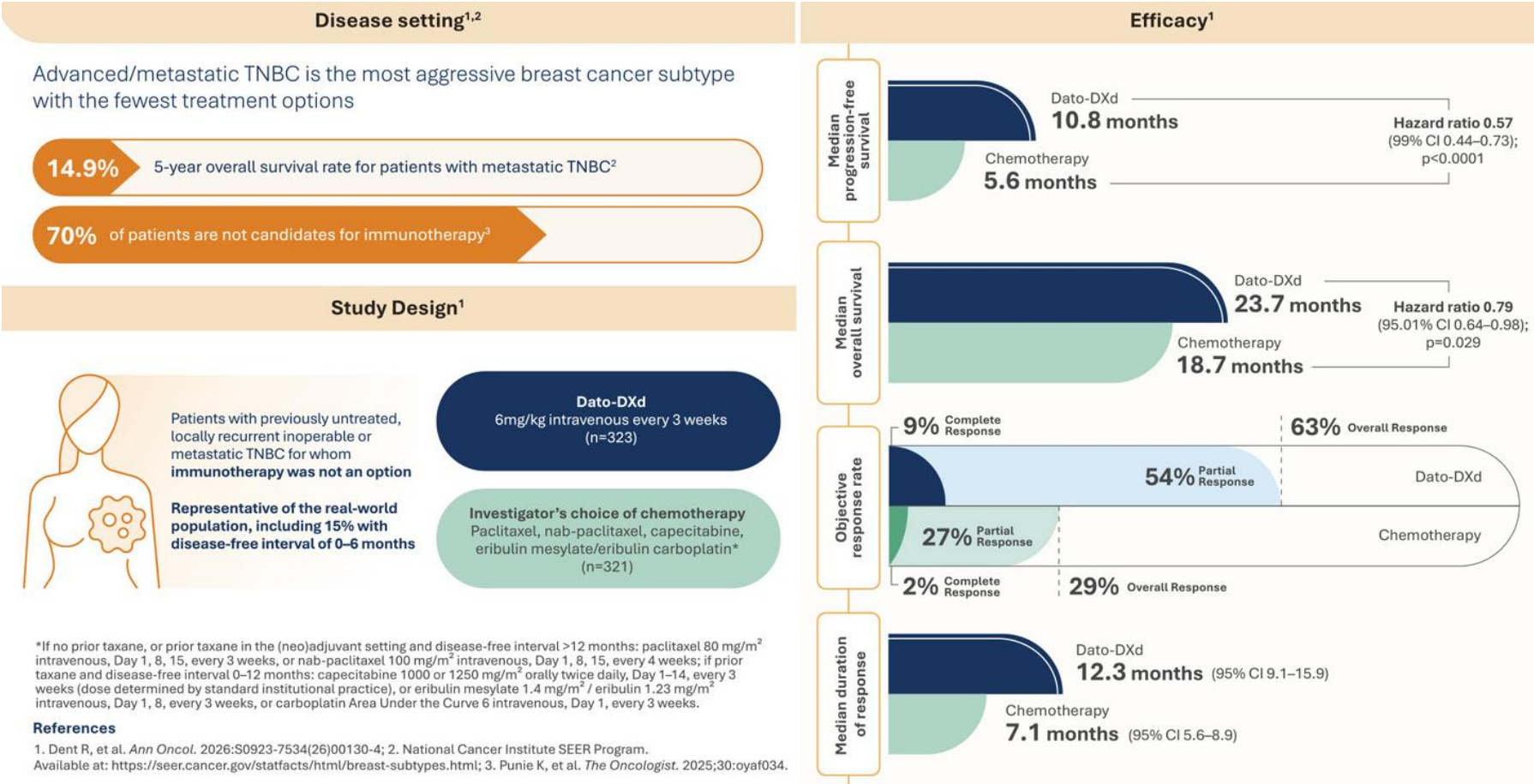
10.0 vs 5.5 mo  
Median PFS · HR 0.38

- Giredestrant + everolimus** improved PFS versus standard endocrine therapy + everolimus.
- The benefit appeared in *ESR1*-mutant disease but not *ESR1*-WT disease.
- Not ready for routine practice yet, but likely another near-future option for *ESR1*-mutant disease.

# Metastatic TNBC: ADCs are moving into first line

Approved May 2026

## TropionBreast-02: Datopotamab deruxtecan improved outcomes over chemo in PD-L1(-) or immunotherapy ineligible metastatic TNBC



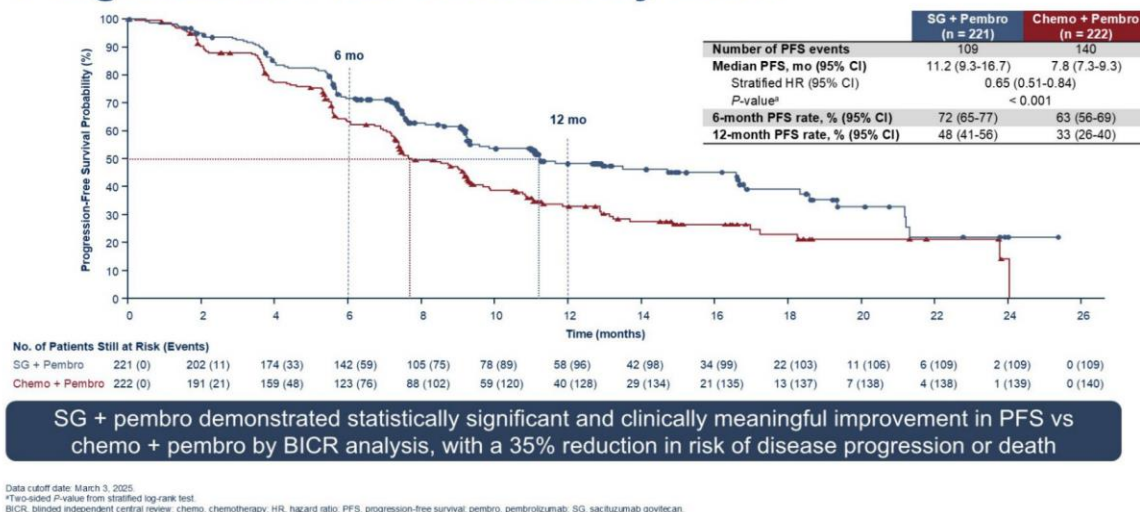
# Metastatic TNBC: ADCs are moving into first line

Approved June 2026

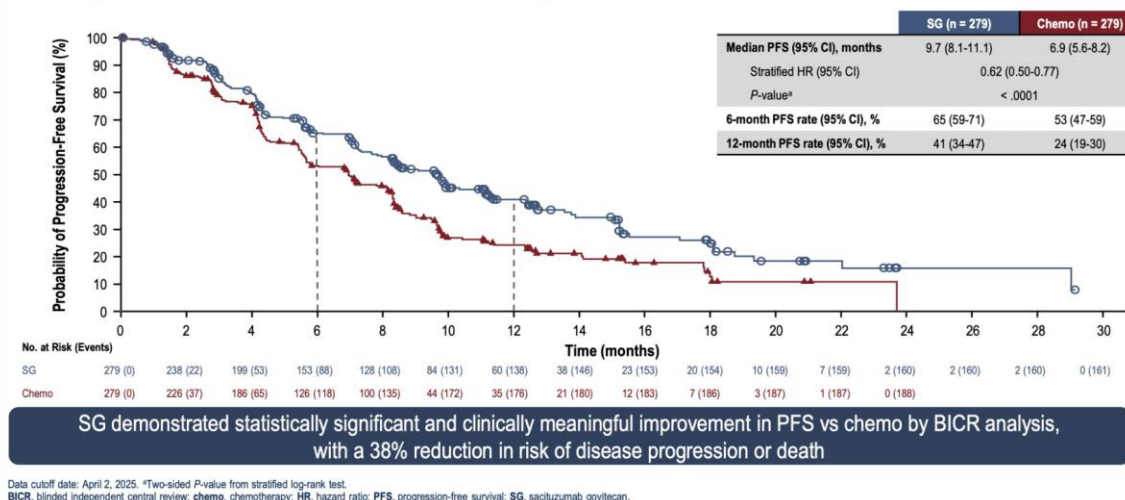
**ASCENT-04:** sacituzumab govitecan + pembrolizumab improved outcomes over chemo + pembrolizumab in PD-L1(+) metastatic TNBC.

**ASCENT-03:** Sacituzumab govitecan improved outcomes over chemo in PD-L1(-) metastatic TNBC

## Progression-Free Survival by BICR



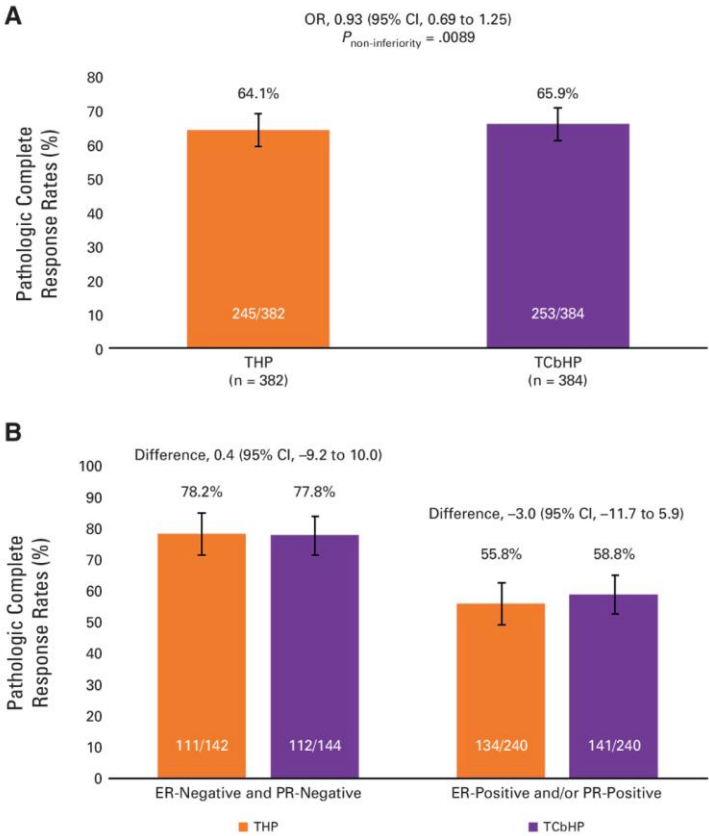
## Progression-Free Survival by BICR



# HER2-positive early-stage disease: de-escalation and escalation coexist

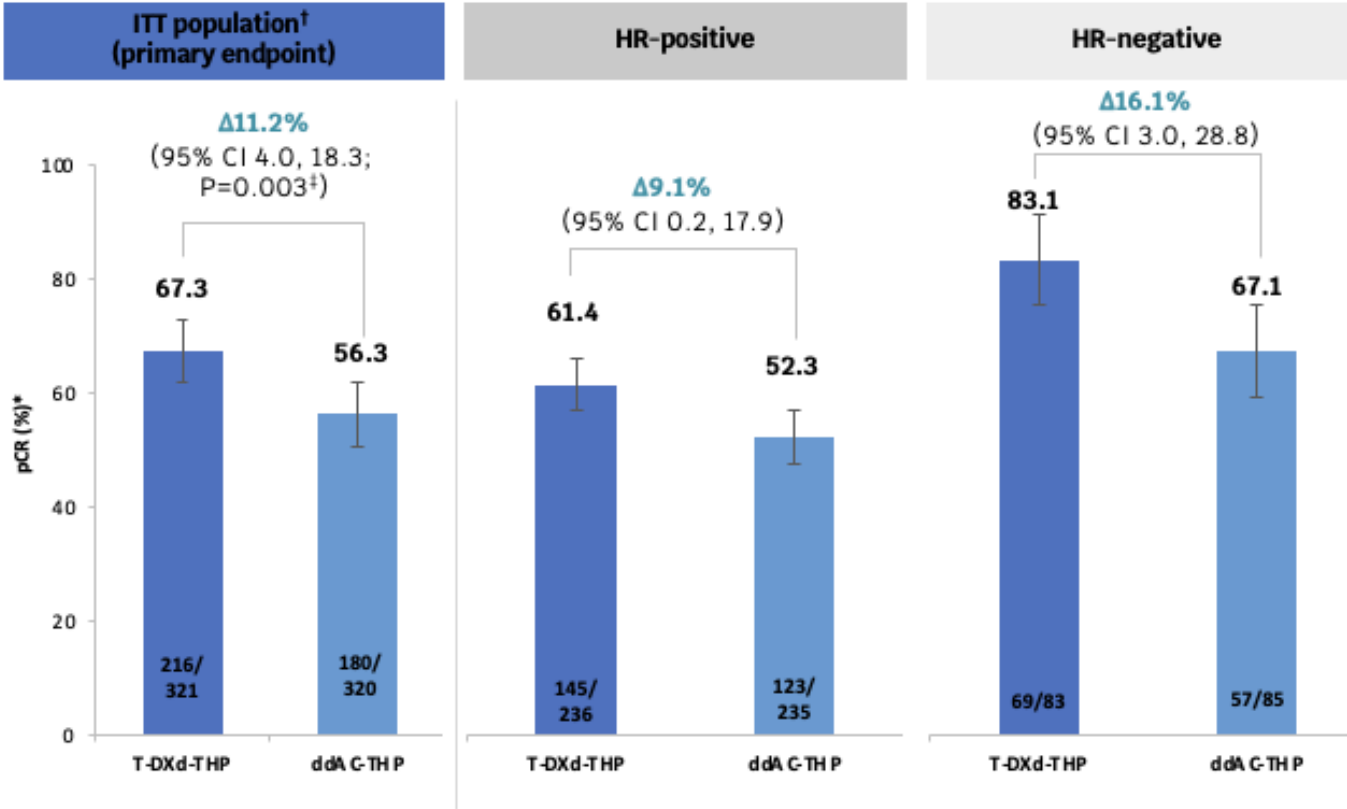
Approved May 2026

## neoCARHP: THP vs TCbHP



THP achieved noninferior pCR with better tolerability than TCHP in stage II–III disease.

## DESTINY Breast11: Trastuzumab deruxtecan (T-DXd) vs ddAC-THP



T-DXd-containing neoadjuvant therapy showed very strong pCR results and may change escalation strategies.

# Residual HER2-positive disease: DESTINY-Breast05

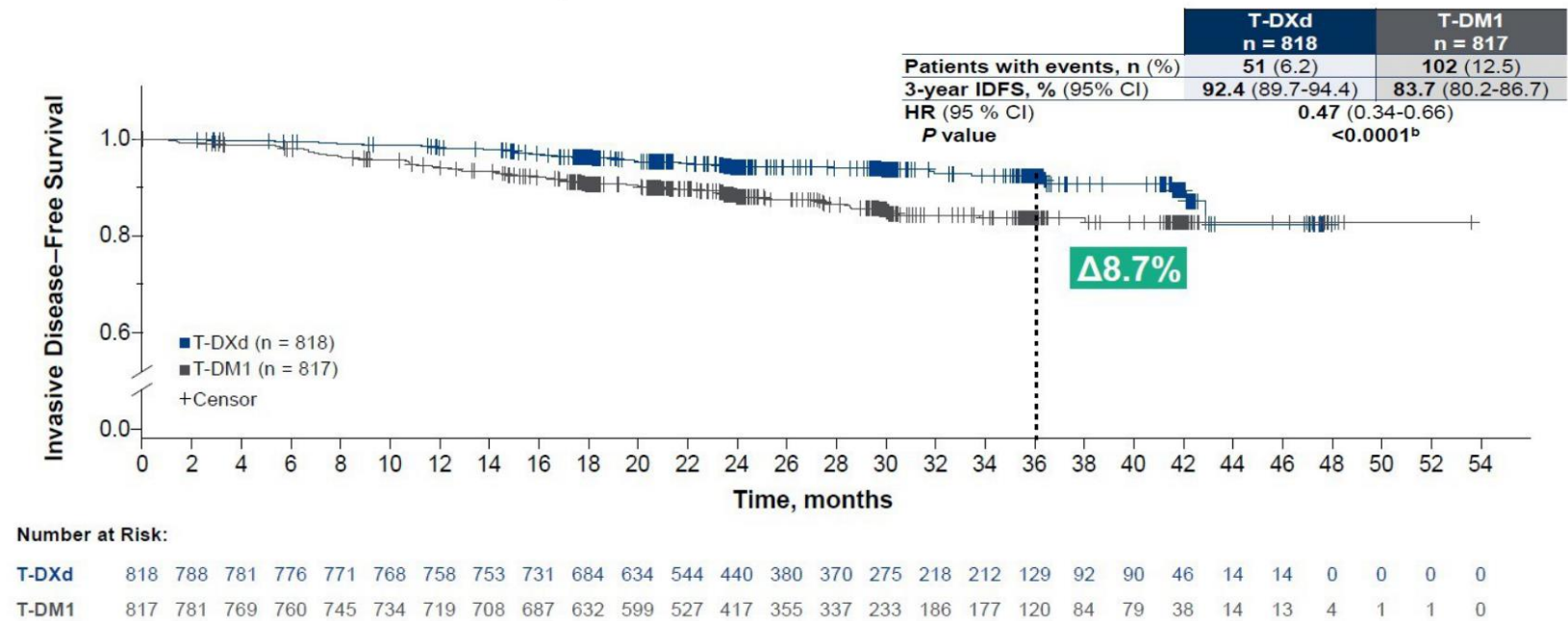
Approved May 2026

For patients with significant residual disease after neoadjuvant therapy, T-DXd beat T-DM1 in DESTINY-Breast05.

This is a major escalation in curative-intent HER2+ care.

Safety, pneumonitis awareness, and patient selection remain essential.

## DESTINY Breast05: Adjuvant T-DM1 vs T-DXd



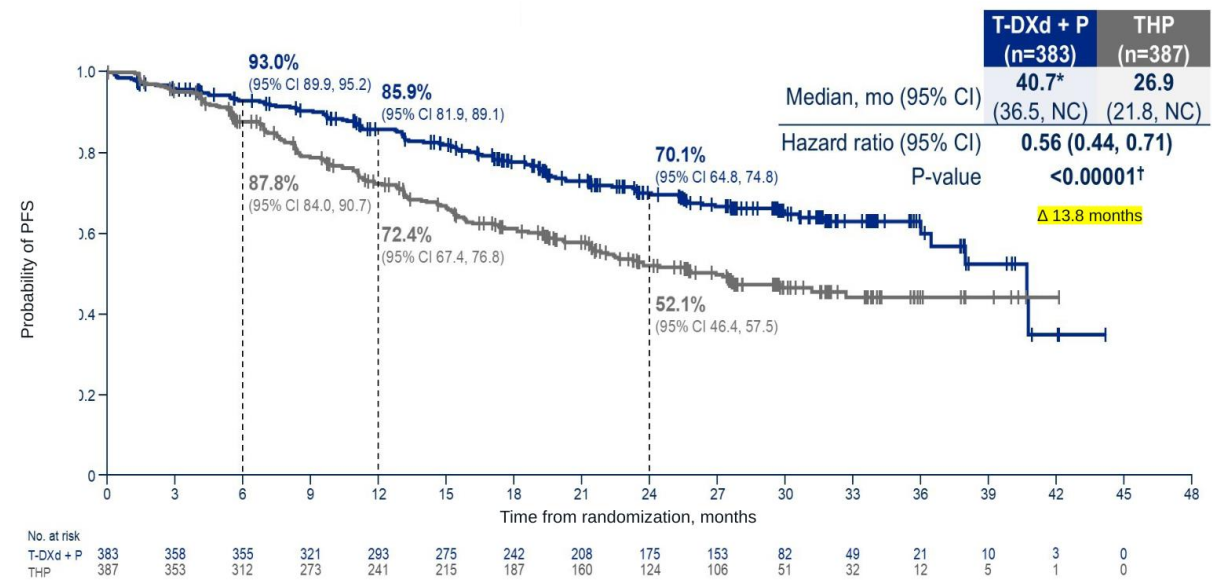
**53% reduction in the risk of invasive disease recurrence or death for T-DXd compared with T-DM1**

HR, hazard ratio; IDFS, invasive disease-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.  
Efficacy stopping boundary,  $P = 0.0183$ .  
<sup>a</sup>IDFS is defined as the time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. <sup>b</sup>Two-sided  $P$  value from stratified log-rank test. Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

# HER2+ metastatic disease: first line T-DXd + pertuzumab

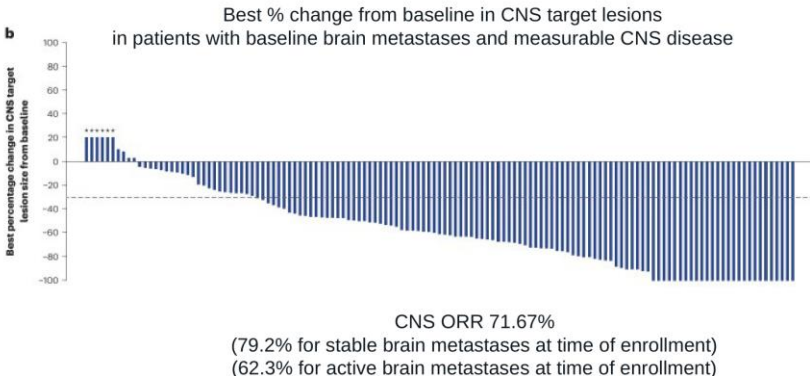
Approved Dec 2025

**DESTINY-Breast09:** phase III trial of trastuzumab deruxtecan + pertuzumab in the **first line** for HER2+ metastatic breast cancer



**DESTINY-Breast12:** Trastuzumab deruxtecan (T-DXd) treatment of HER2+ **brain metastases:** Phase 3b/4

- DESTINY-Breast12**
- Screened n=621
  - Treated n=504
  - Baseline brain metastases n=263
    - Stable brain metastases n=157
    - Active brain metastases n=106
  - No baseline brain metastases n=241

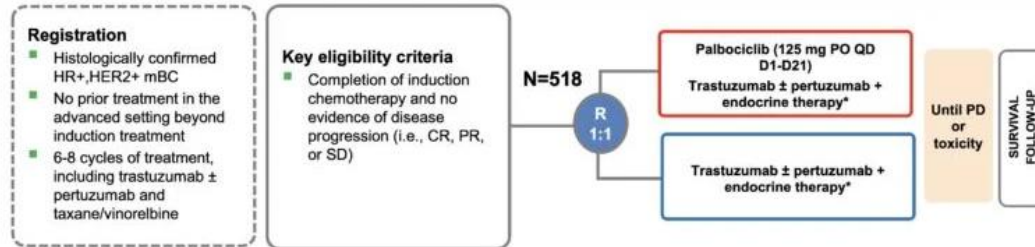


T-DXd + pertuzumab improved first-line outcomes versus THP and is reshaping metastatic HER2+ treatment.

# HER2+ metastatic disease: improving maintenance efficacy with palbociclib

Approved Jun 2026

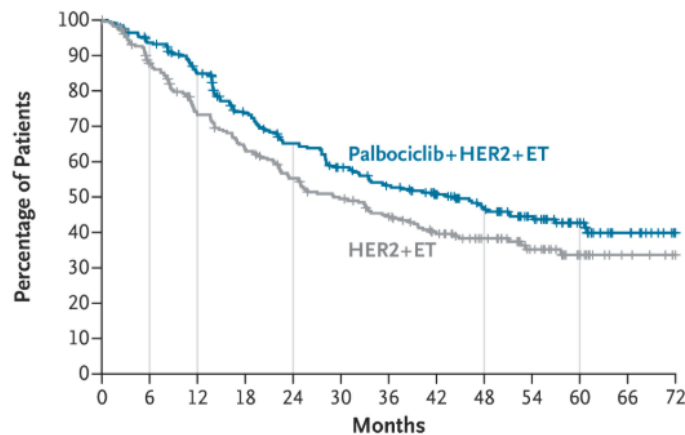
**PATINA**: phase III trial of anti-HER2 therapy + endocrine therapy + **palbociclib** as **maintenance therapy** after induction for HR+HER2+ metastatic breast cancer



## Stratification factors

- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)<sup>†</sup>
- Response to induction therapy (CR or PR vs SD) by investigator assessment<sup>†</sup>
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)

## A Progression-free Survival



| No. of Events/Total<br>No. of Patients | Median<br>Progression-free<br>Survival<br>(95% CI)<br>mo |
|----------------------------------------|----------------------------------------------------------|
| 127/261                                | 44.3 (32.4–56.8)                                         |
| 135/257                                | 29.1 (23.3–38.6)                                         |

Hazard ratio for disease progression or death, 0.75 (95% CI, 0.59–0.96)  
Two-sided unstratified P=0.02 by log-rank test

## No. at Risk

|                     |     |     |     |     |     |     |     |    |    |    |    |    |   |
|---------------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|---|
| Palbociclib+HER2+ET | 261 | 230 | 202 | 166 | 144 | 126 | 111 | 92 | 76 | 54 | 33 | 15 | 5 |
| HER2+ET             | 257 | 197 | 157 | 135 | 115 | 101 | 88  | 68 | 52 | 30 | 15 | 6  | 1 |

## PATINA

## 44.3 vs 29.1 months

HR 0.75 (95% CI 0.59–0.96)

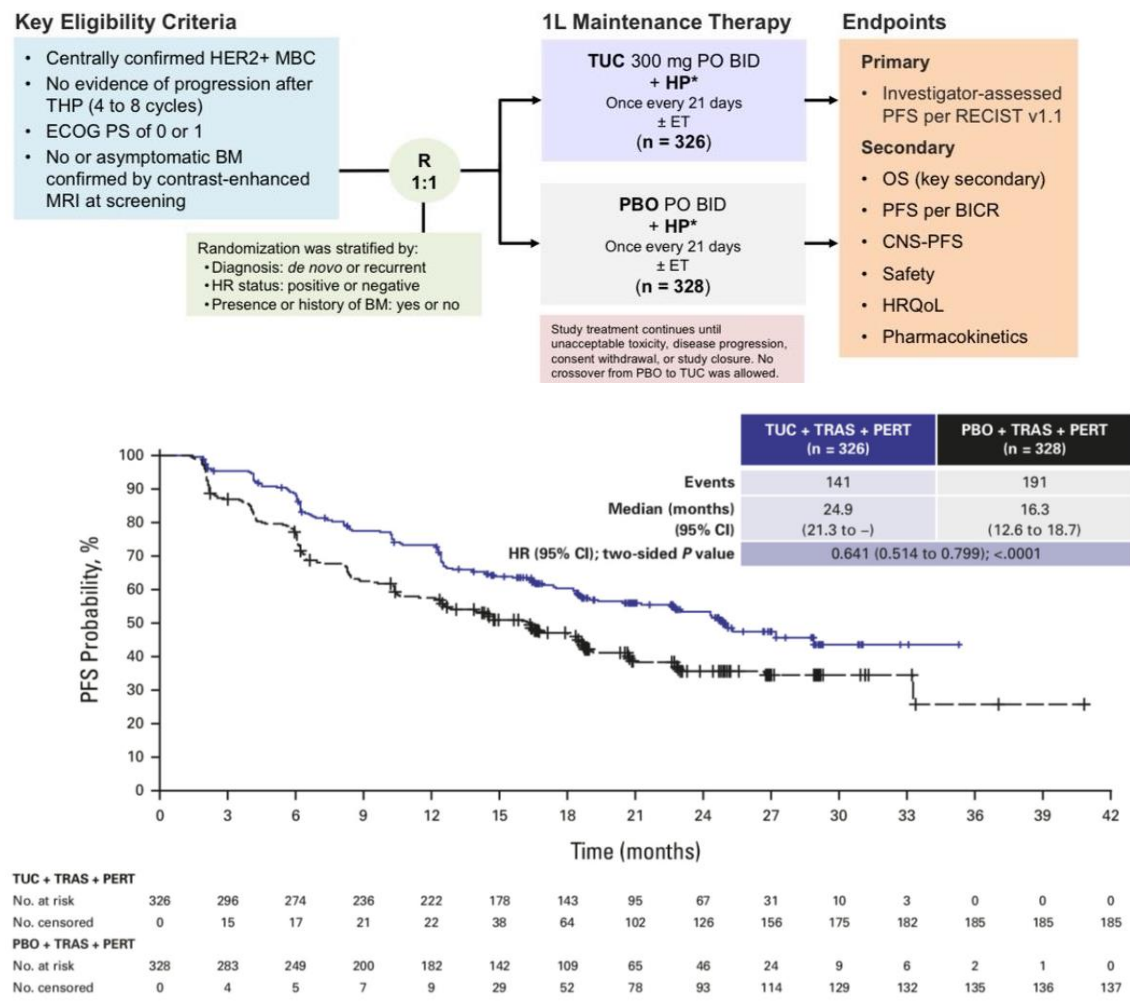
Palbociclib + endocrine therapy +  
trastuzumab ± pertuzumab.

Main side effect: neutropenia

# HER2+ metastatic disease: improving maintenance efficacy with tucatinib

Approved Oct 2026

**HER2CLIMB-05:** phase III trial of trastuzumab + pertuzumab +/- **tucatinib** as **maintenance therapy** after induction for HER2+ metastatic breast cancer



## HER2CLIMB-05

24.9 vs 16.3 months

HR 0.64 (95% CI 0.51–0.79)

Tucatinib 300mg twice daily + HP

Main side effects: hepatotoxicity, diarrhea, LFTs

# 5 take-home messages

*For patients, families, and the multidisciplinary care team*

- 1 Adjuvant therapy in HR+ /HER2– disease is becoming more individualized, with CDK4/6 inhibitors already standard for selected patients and oral SERDs potentially coming next.
- 2 In metastatic HR+ /HER2– disease, PIK3CA and ESR1 are the most immediately actionable biomarkers.
- 3 In HER2+ disease, 2025–2026 data support both de-escalation for some patients and more powerful escalation for others.
- 4 In TNBC, immunotherapy remains central in early-stage disease, while ADCs are increasingly reshaping first-line metastatic care
- 5 Individualized treatment requires efficacy, toxicity, goals and team coordination.

# HR+ HER2- Early Breast Cancer Clinical Trials at UCSD

## *Neoadjuvant*

### **I-SPY 2 NCT01042379**

*(PI: Anne Wallace)*

Block A: GSK5733584 (B7H4 topoADC) +/- Dosarlimab

Block A: Vidutolimab (TLR9 agonist) + cemiplimab

Block B: Paclitaxel

Block C: AC

## *Adjuvant*

### **CAMBRIA-2**

*(PI: Alyssa Beck)*

Ph III: oral SERD camizestrant vs AI or  
tamoxifen x 7 years

**\*\*On HOLD pending CDK4/6i substudy\*\***

# HR+ HER2- Early Breast Cancer Clinical Trials at UCSD

## 1<sup>st</sup> Line

**OPERA-02 (NCT07085767)**

(PI: Rebecca Shatsky)

Ph III: CERAN **palazestrant** + ribociclib vs letrozole + ribociclib

## Immediately After CDK4/6i; No prior chemo

**MoonRose (NCT07100106)**

(PI: Kay Yeung)

Ph Ib/II: **CDK2/4/6i vustanaciclib** + giredestrant vs abemaciclib + giredestrant

## After CDK4/6i; ≤1 chemo

**AIM-BRIGHT (NCT07227233)**

(PI: Kay Yeung)

Ph II: **CDK4/6i** + fulvestrant vs TPC

Must have palbociclib-sensitive disease per palbo-VNN model  
Nonmeasurable but evaluable disease allowed

**ReDiscover-2 (NCT06982521)**

(PI: Kay Yeung)

Ph III: **PI3Kalpha inhibitor** zovogalisib + fulvestrant vs capivasertib + fulvestrant  
**PIK3CAmut**; no prior PAM pathway inhibitors; No *PTEN*, *AKT1*, *RAS*, *BRAF* alterations

**ReDiscover-1 (NCT05216432)**

(PI: Kay Yeung)

Ph I/II: **PI3Kalpha inhibitor** zovogalisib + fulvestrant + CDK4i **atirmociclib**  
**PIK3CAmut**; no prior PAM pathway inhibitors; No *PTEN*, *AKT1*, *RAS*, *BRAF* alterations

**MEN2312-01 (NCT06638307)**

(PI: Rebecca Shatsky)

Up to 2 total lines (ET/ targeted/ 1 chemo)

Ph I: **KAT6 inhibitor MEN2312** with fulvestrant or elacestrant

## After CDK4/6i; ≤ 2 chemo

**NKT5097-101 (NCT07029399)**

(PI: Rebecca Shatsky)

Ph I: **CDK2/4 degrader** NKT5097

## No Limit on Prior Therapies

**BRIA-ABC (NCT06072612)**

(PI: Rebecca Shatsky)

Ph III: vaccine BC-IMT with pre-conditioning cyclophosphamide regimen and in combination with immune checkpoint inhibitor retifanlimab vs TPC

**IAM1363-01 (NCT0625387)**

(PI: Kay Yeung)

Ph II: **HER2 TKI IAM1363** as a monotherapy for **HER2 mutant** disease  
CNS mets allowed

**AMX1501-103 (NCT07287917)**

(PI: Rebecca Shatsky)

Ph I: **AMXT 1501** and oral **DFMO** in combo with fulvestrant + Capivasertib  
**PIK3CA/PTEN/AKT altered**  
prior PAM pathway inhibitors allowed

**TRACY-1 (NCT06590857)**

(PI: Teresa Helsten)

Ph II: **Radionuclide 225Ac-DOTATATE** (radioactive peptide that binds somatostatin receptors)  
Must be positive on pre-screening DOTATATE PET  
\*\*On HOLD\*\*

# HER2+ Breast Cancer Clinical Trials at UCSD

## Early Breast Cancer

### Neoadjuvant

**I-SPY 2 HER2+ NCT01042379**  
(PI: Anne Wallace)  
Block A: TBD  
Block B: THP  
Block C: T-DXd

### Adjuvant

**Shortstop-HER2 NCT06876714**  
(PI: Kay Yeung)  
Ph III: shortened duration of  
trastuzumab after pCR (6 vs 12  
months)

### Extended Adjuvant

**FLAMINGO-01  
NCT05232916**  
(PI: Rebecca Shatsky)  
Ph III: HER2 peptide vaccine vs  
placebo if non-pCR after  
completion of adjuvant therapy

## Metastatic Breast Cancer

### After prior T-DXd

**ASPEN-09-03  
NCT07007559**  
(PI: Kay Yeung)  
Ph II: macrophage-targeted ICI  
evorpaccept + trastuzumab + TPC  
(cape, eribulin, gem, paclitaxel,  
vinorelbine)  
≥1 prior line of treatment including  
T-DXd  
Stable, treated CNS mets allowed

**IAM1363-01  
NCT0625387**  
(PI: Kay Yeung)  
Ph II: HER2 TKI IAM1363 as a  
monotherapy or in combination with  
cape/tras, cape/zanidatamab, or T-DXd  
CNS mets allowed

### No Limit on Prior Therapies

**BRIA-ABC  
NCT06072612**  
(PI: Rebecca Shatsky)  
Ph III: vaccine BC-IMT with pre-  
conditioning cyclophosphamide  
regimen and in combination with  
immune checkpoint inhibitor  
retifanlimab vs TPC

# Triple Negative Breast Cancer Clinical Trials at UCSD

## Neoadjuvant

### **I-SPY 2 NCT01042379**

*(PI: Anne Wallace)*

Block A: GSK5733584 (B7H4 topoADC) +/- Dosarlimab

Block A: Vidutolimab (TLR9 agonist) + cemiplimab

Block B: Taxol/carbo/pembro

Block C: AC/pembro

## Metastatic

### ***1<sup>st</sup> Line***

#### **ROSETTA Breast-01 NCT07173751**

*(PI: Rebecca Shatsky)*

Ph III: Punitamig (bispecific PDL1/VEGF-A) + TPC  
(Taxol, Abraxane, gem/carbo, eribulin)  
PDL1- disease or PDL1 ineligible

### ***No Limit on Prior Therapies***

#### **BRIA-ABC NCT06072612**

*(PI: Rebecca Shatsky)*

Ph III: vaccine BC-IMT with pre-conditioning cyclophosphamide regimen and in combination with immune checkpoint inhibitor retifanlimab vs TPC

### ***After prior ADC***

#### **9MW2821-CP103 NCT06908928**

*(PI: Rebecca Shatsky)*

Ph Ib: ADC Bulumtatug fuvedotin targeting Nectin-4 with MMAE payload  
≤3 prior chemotherapies  
Stable CNS mets allowed