STANFORD
CANCER INSTITUTE

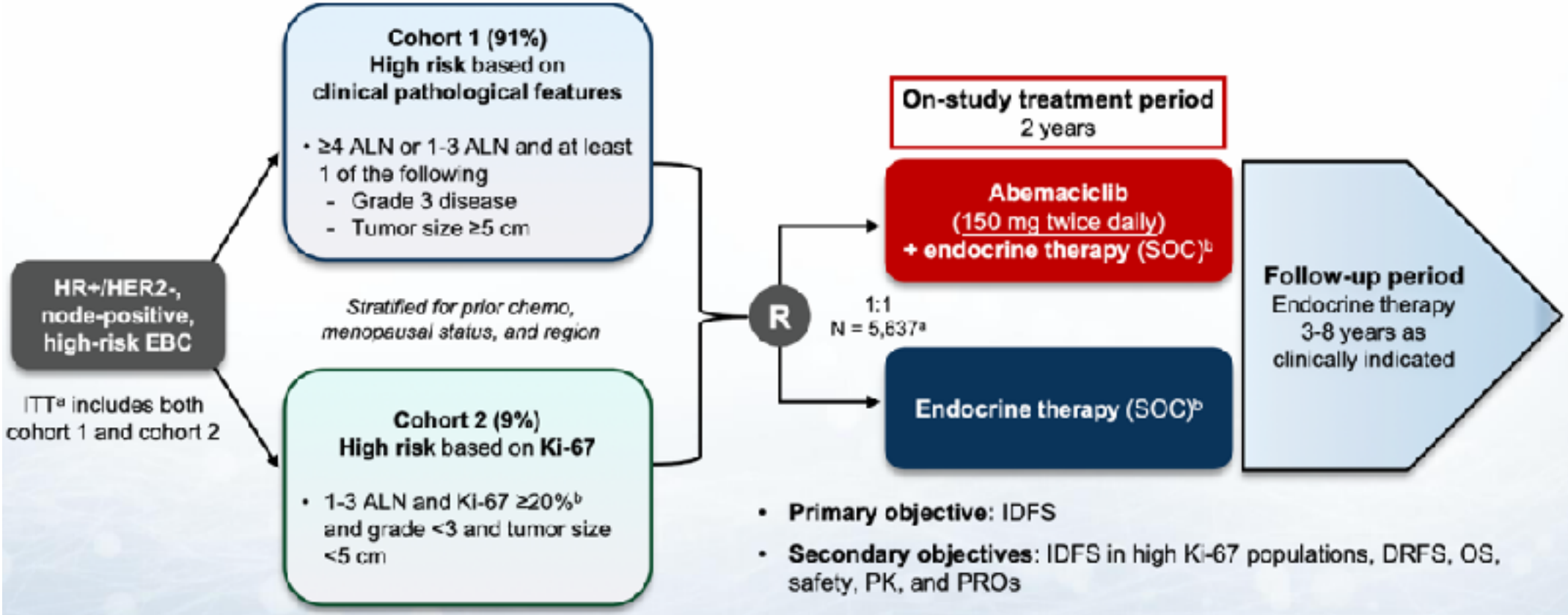
Updates in Breast Cancer Research and Treatment

November, 2025

Mark Pegram, M.D., FASCO
Susy Yuan-Huey Hung Endowed Professor of Oncology
Stanford University School of Medicine

Expanding Options for Intermediate to High-Risk HR+, HER2– Early Breast Cancer: CDK 4/6 Inhibition in the Adjuvant Setting

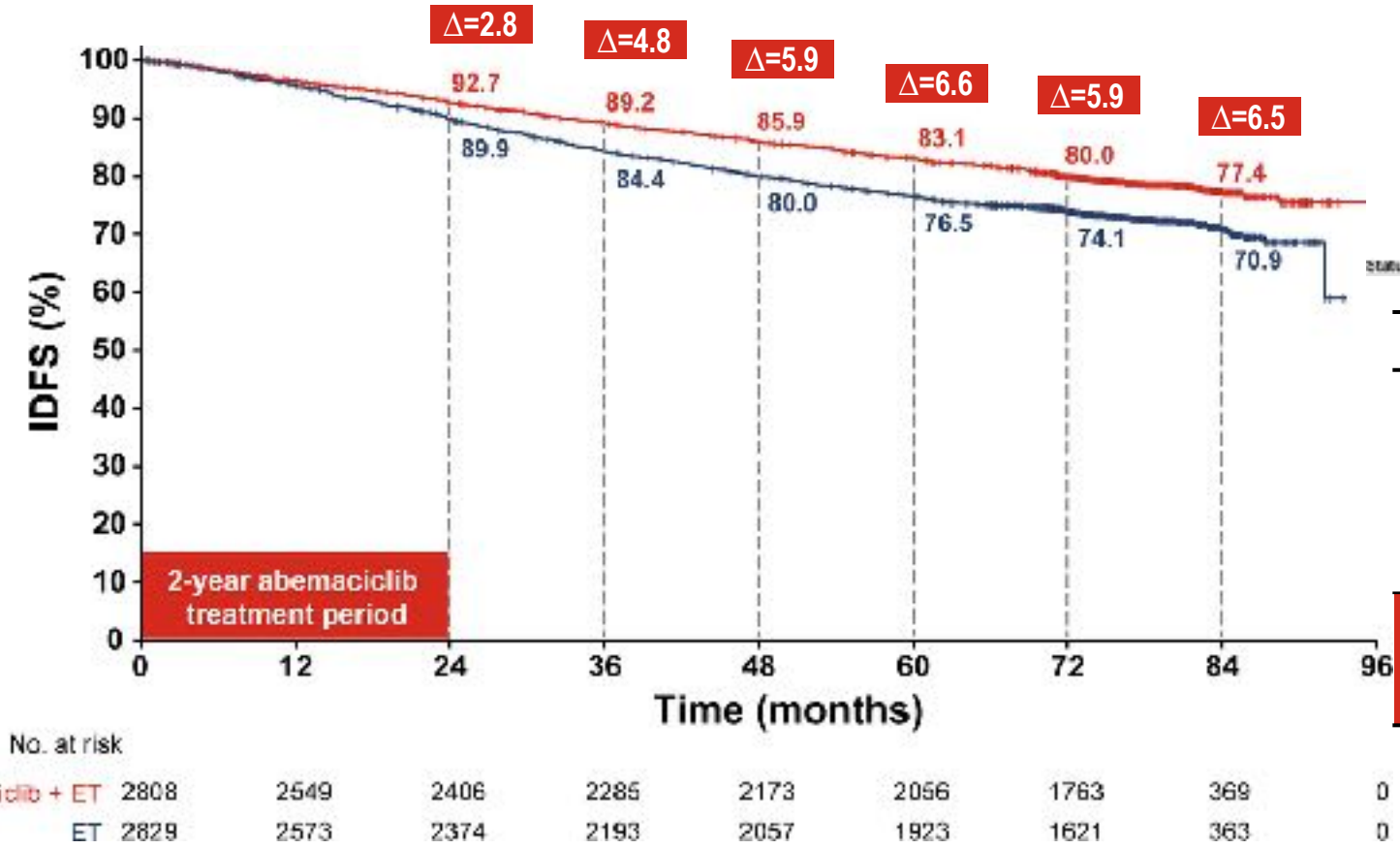
monarchE Study Design[1,2]

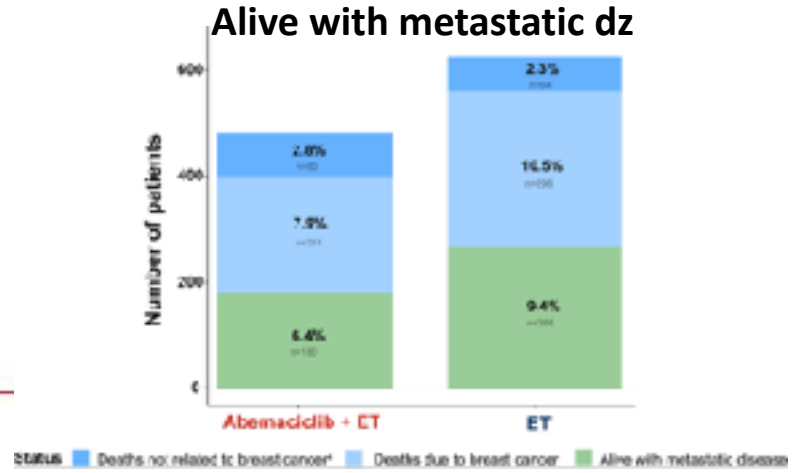


[a] Recruitment from July 2017 to August 2019. [b] Endocrine therapy of physician's choice (eg, aromatase inhibitors, tamoxifen, LHRH agonist).

1. Harbeck N. ESMO 2023. Abstract LBA17. 2. Rastogi P et al. *J Clin Oncol*. 2024;00:1-7.

Sustained IDFS Benefit in ITT: Evolution of Yearly Rates





Number of IDFS events	
Abemaciclib + ET	ET
722	722
54	
7	

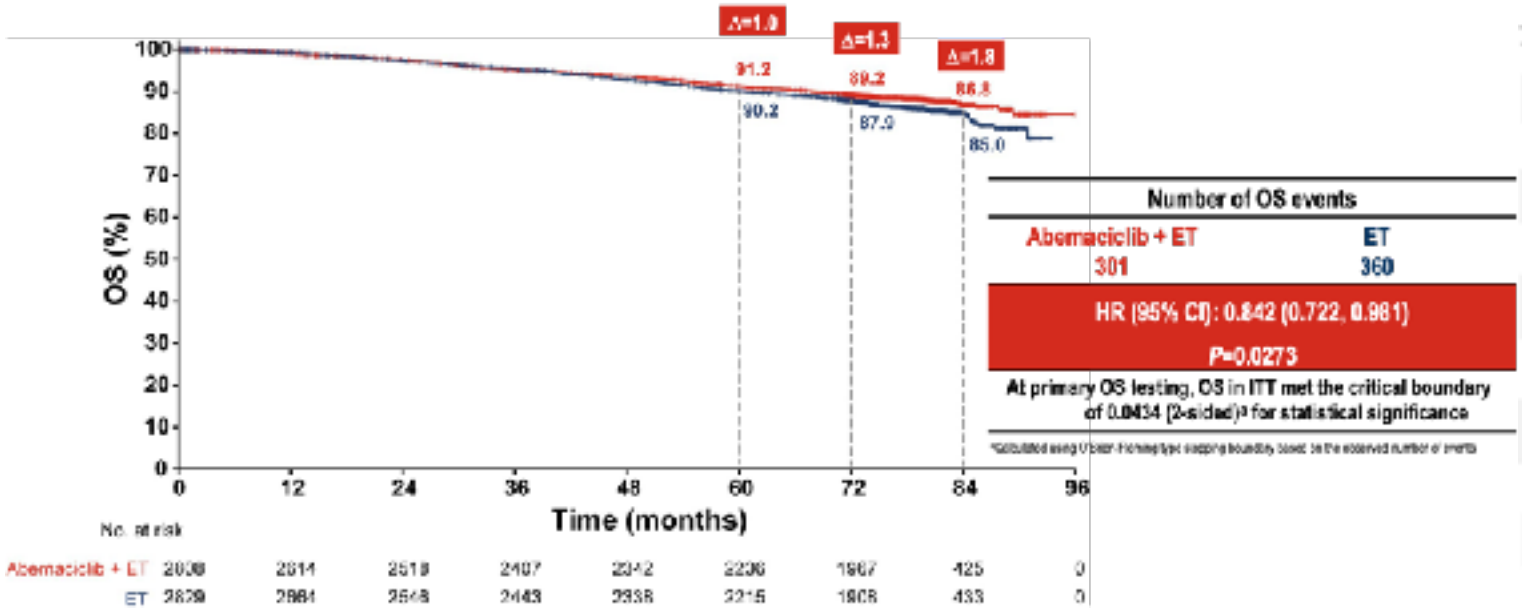
HR (95% CI): 0.734 (0.657, 0.820)

Nominal *P*<.0001

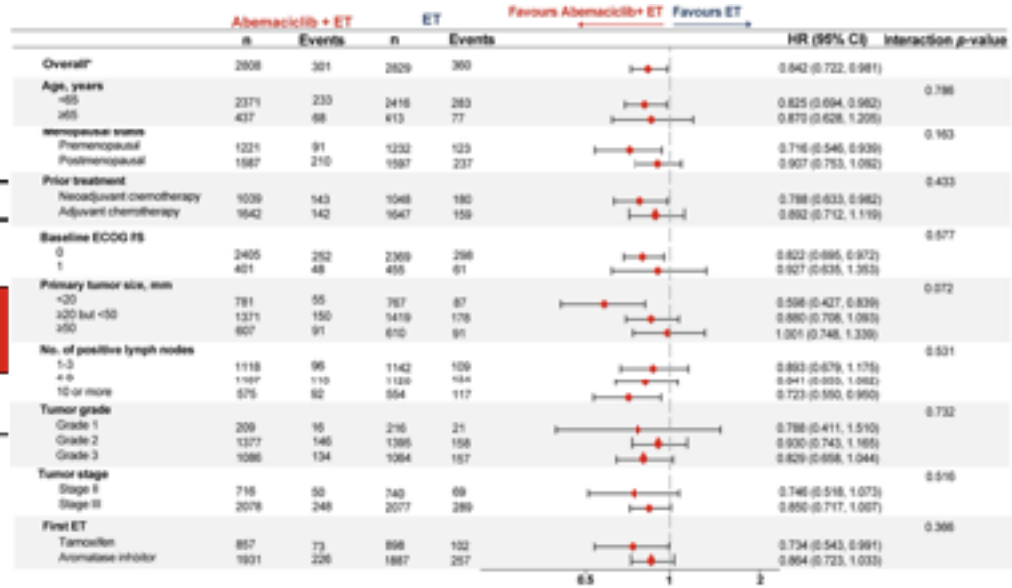
Abemaciclib + ET reduced the risk of IDFS events by 26.6% compared to ET alone

NO NEW SAFETY SIGNALS

Key Secondary Endpoint: Overall Survival in ITT



Consistent OS Benefit Across Prespecified Subgroups



Abemaciclib is the first CDK4/6 inhibitor to achieve a statistically significant improvement in OS for patients with HR+ HER2-, node-positive, high-risk EBC

At a median follow-up of 6.3 years, abemaciclib + ET reduced the risk of death by 15.8% compared to ET alone

Stephen Johnston, MD, PhD.

Study Design: NATALEE

An open-label, multicenter, randomized, phase 3 trial[1,2]

Adult patients with stage II and III HR+/HER2− EBC

- Prior ET allowed up to 12 months
- **Anatomical stage IIA**[a]
  - N0 with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - N1
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
- N0, N1, N2, or N3

R 1:1[c]

RIB
400 mg/day
3 weeks on/1 week off for **3 y**
+
NSAI
Letrozole or anastrozole[b] for **≥ 5 y**
+ goserelin in men and premenopausal women

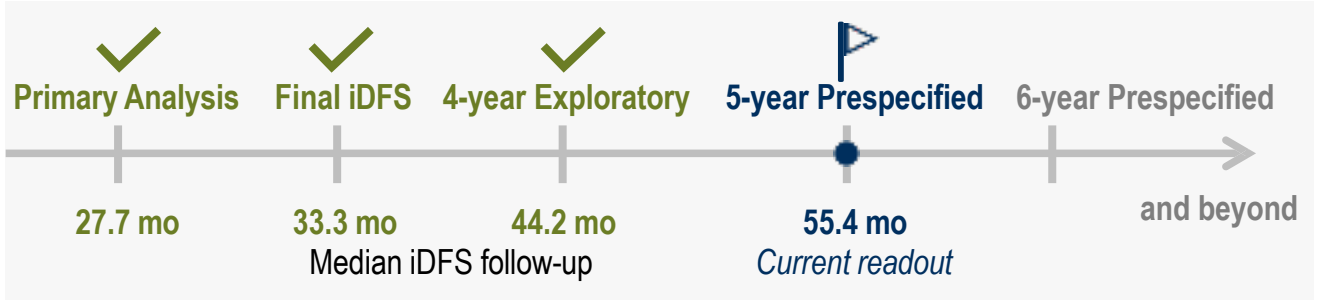
NSAI
Letrozole or anastrozole[b] for **≥ 5 y**
+ goserelin in men and premenopausal women

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- RFS, DDFS, OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- DRFS
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Efficacy outcomes for the 5-year analysis were estimated by the Kaplan-Meier method, and results are descriptive. The Cox proportional hazards model was used to estimate the HRs and 95% CIs.



[a]Enrollment of patients with stage II disease was capped at 40%. [b]Per investigator choice. CI, confidence interval; ctDNA/RNA, circulating tumor DNA/RNA; DDFS, distant disease-free survival; DRFS, distant recurrence-free survival; EBC, early breast cancer; HR, hazard ratio; iDFS, invasive disease-free survival; ITT, intention to treat; mo, months; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient reported outcomes; RIB, ribociclib; RFS, recurrence-free survival.

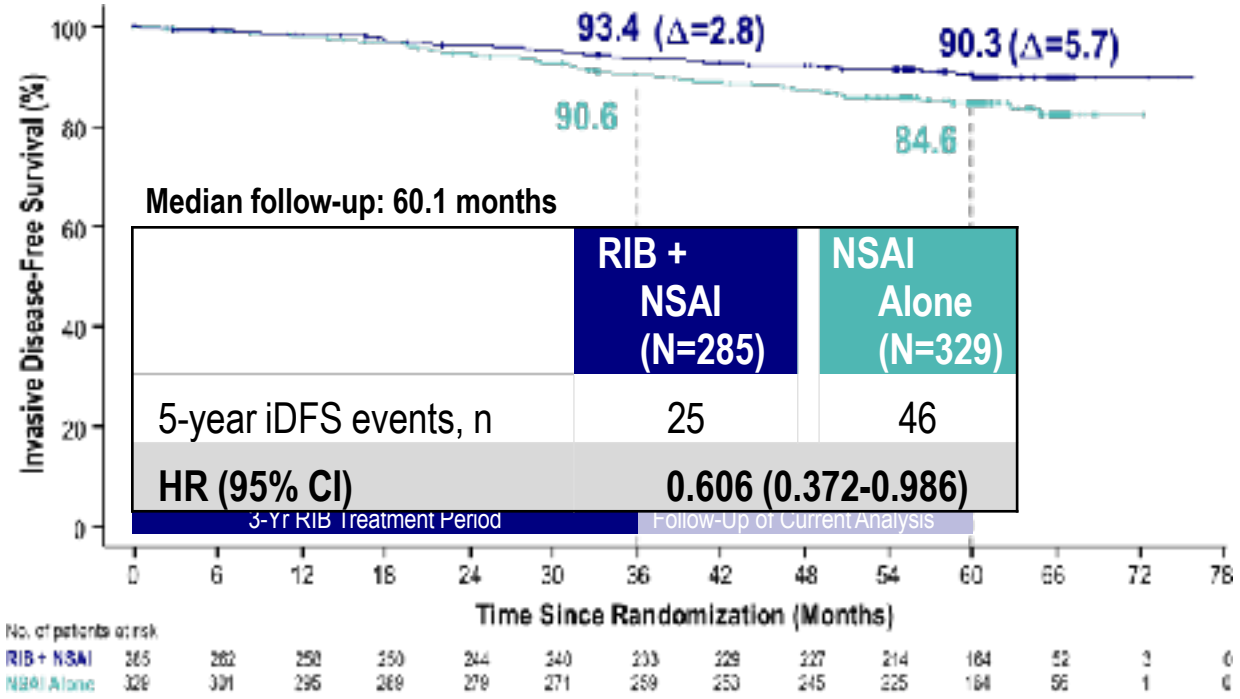
1. ClinicalTrials.gov. Accessed November 8, 2023. https://clinicaltrials.gov/study/NCT03701334.
2. Slamon D, et al. Ther Adv Med Oncol 2023;15:1-16.

John Crown, M.D.

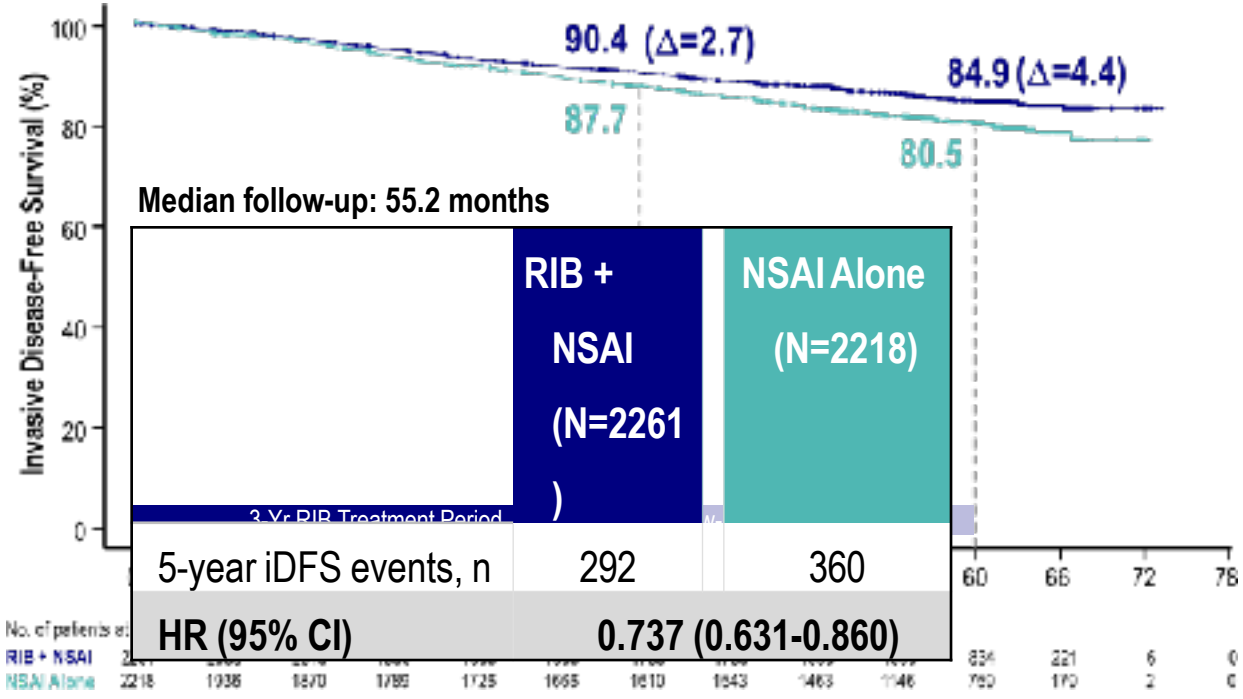
iDFS by Nodal Status

With a median of 2 years off RIB treatment, ***RIB continues to demonstrate persistent benefit in patients with high-risk N0 disease and N+ disease***

N0



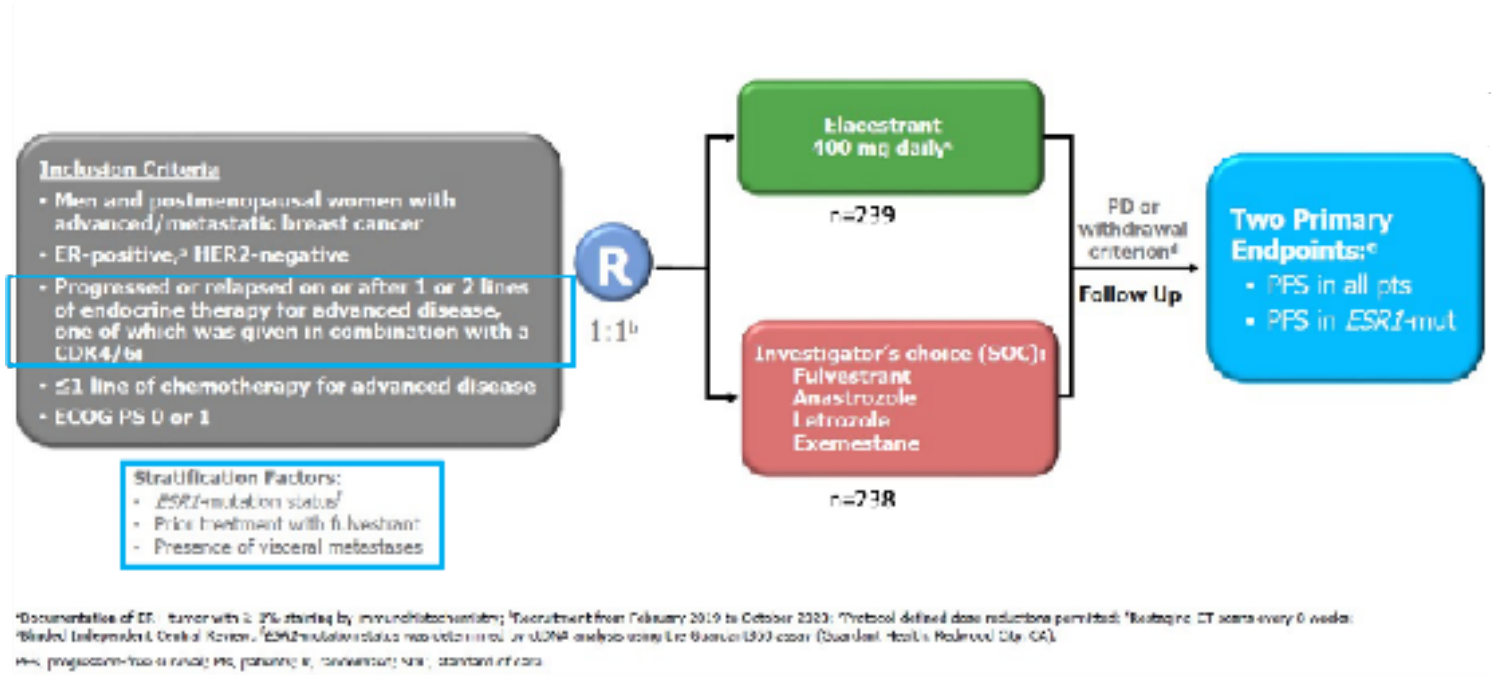
N+

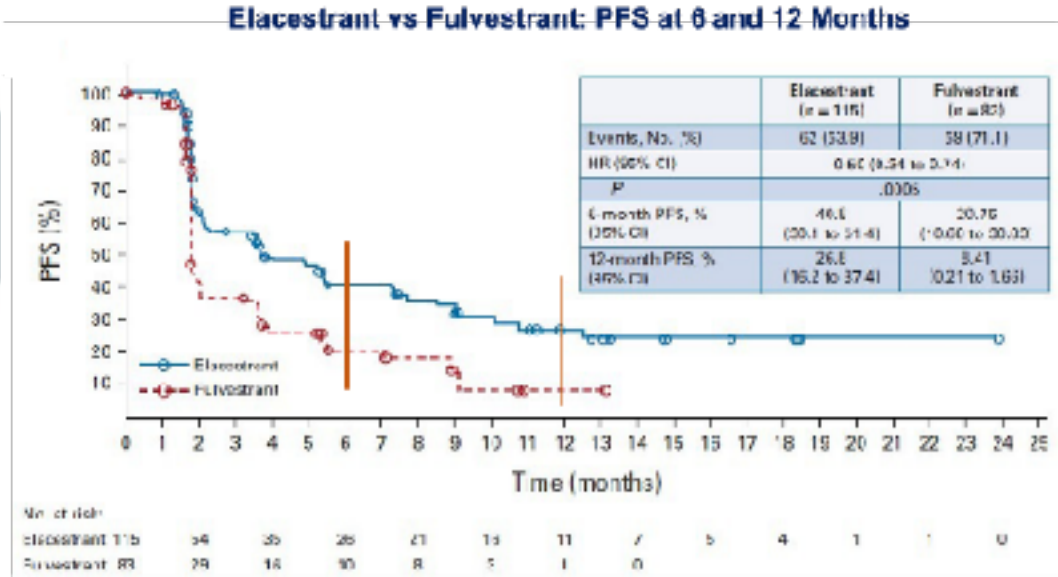


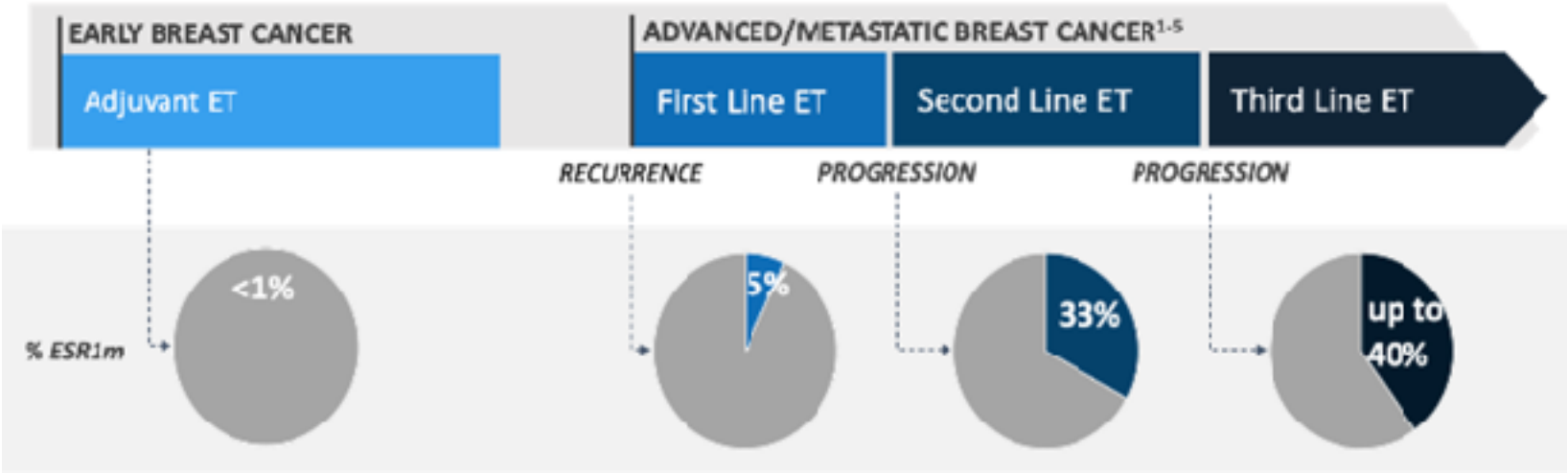
At this 5-year follow-up of NATALEE, RIB + NSAI continue to reduce the risk of recurrence beyond the 3-year treatment window, supporting its use as adjuvant therapy in patients with HR+/HER2− EBC at high-risk of recurrence, including those with high-risk N0 disease

CI, confidence interval; HR, hazard ratio; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Phase III EMERALD Clinical Trial: Study Design







Key baseline patient characteristics balanced:

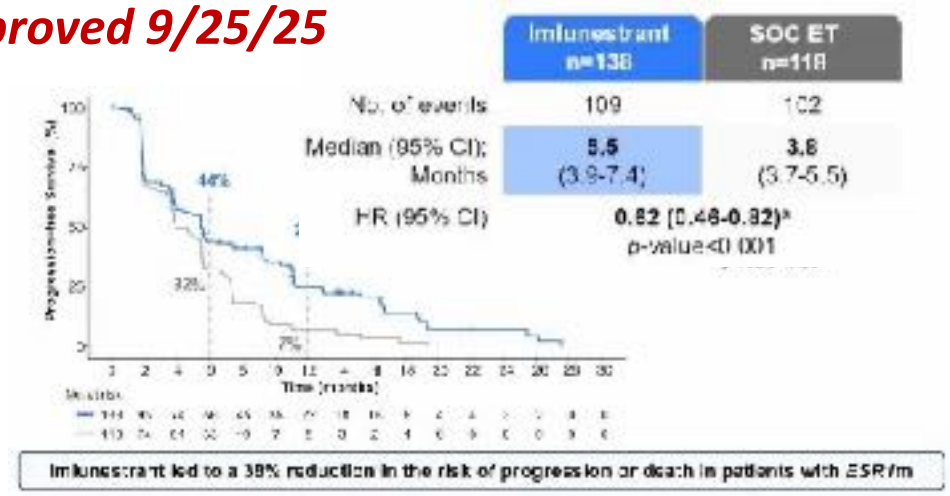
- Visceral Metastasis ~70%
- Prior Adjuvant Therapy ~55-65%
- Prior AI ~>80%
- Prior Fulvestrant ~25-30%

Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-3256.

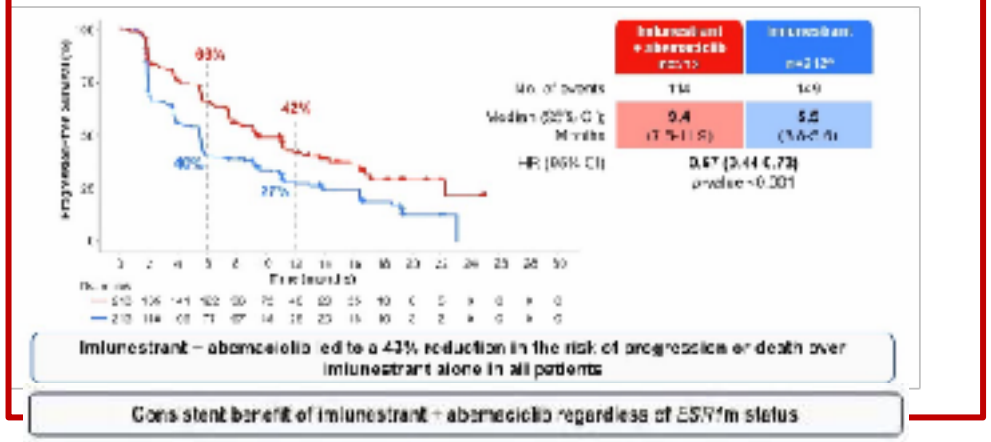
EMBER-3 Primary Endpoint: Investigator-Assessed PFS

Imlunestrant vs SOC ET (*ESR1*m patients)

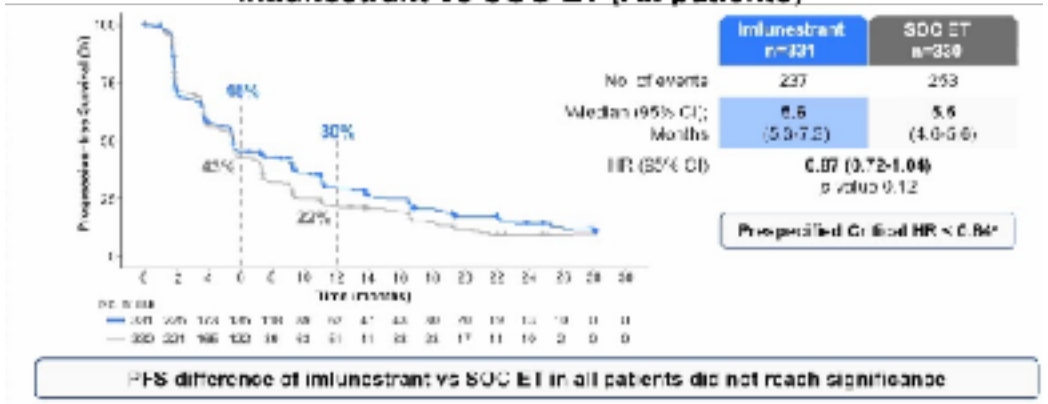
FDA Approved 9/25/25



Primary Endpoint: Imlunestrant + Abemaciclib vs Imlunestrant Investigator-assessed PFS in All Patients

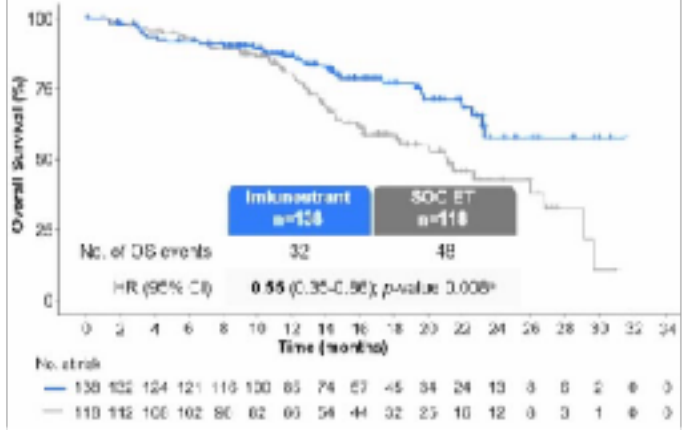


Imlunestrant vs SOC ET (All patients)



Patients with *ESR1*m (31% maturity)

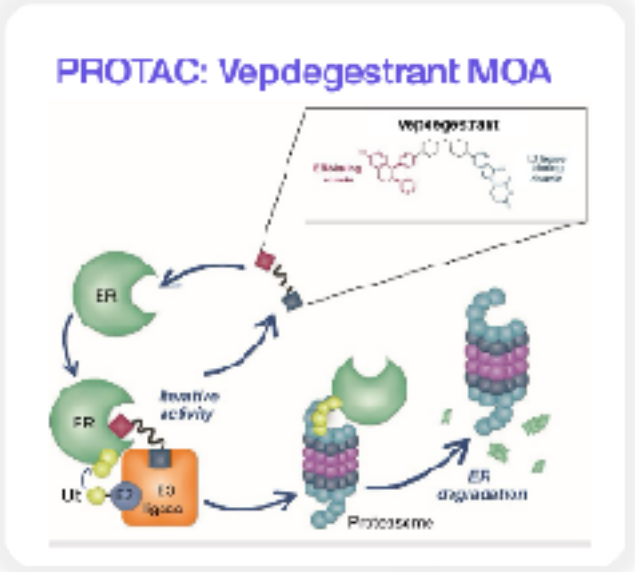
Interim OS



Jhaveri K, et al. SABCS 2024. Abstract GS1-01; Jhaveri K, et al. *N Engl J Med*. 2025;392:1189-1202.

VERITAC-2: Investigator-Assessed PFS

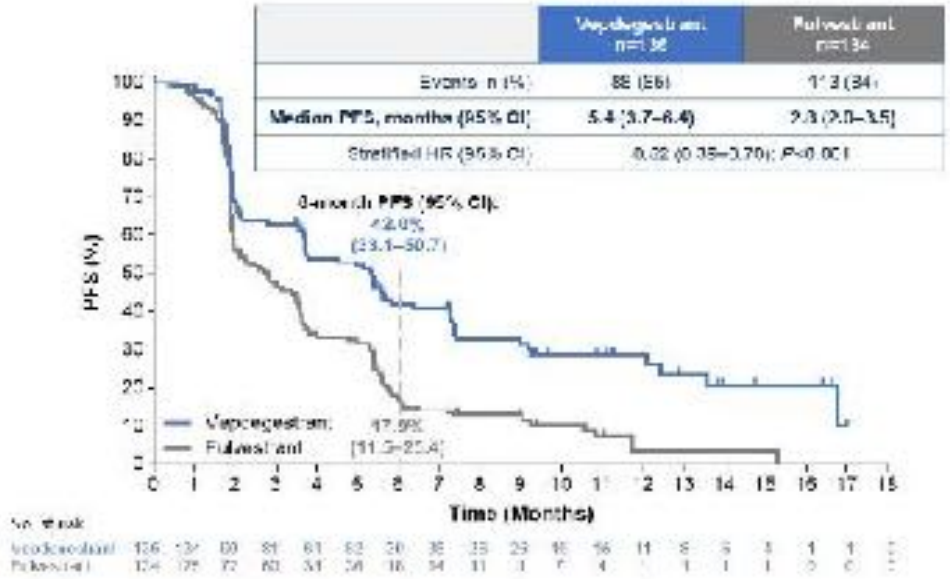
MOA:
Bifunctional small molecule binds ER and E3 Ubiquitin Ligase, targeting ER for proteosome degradation



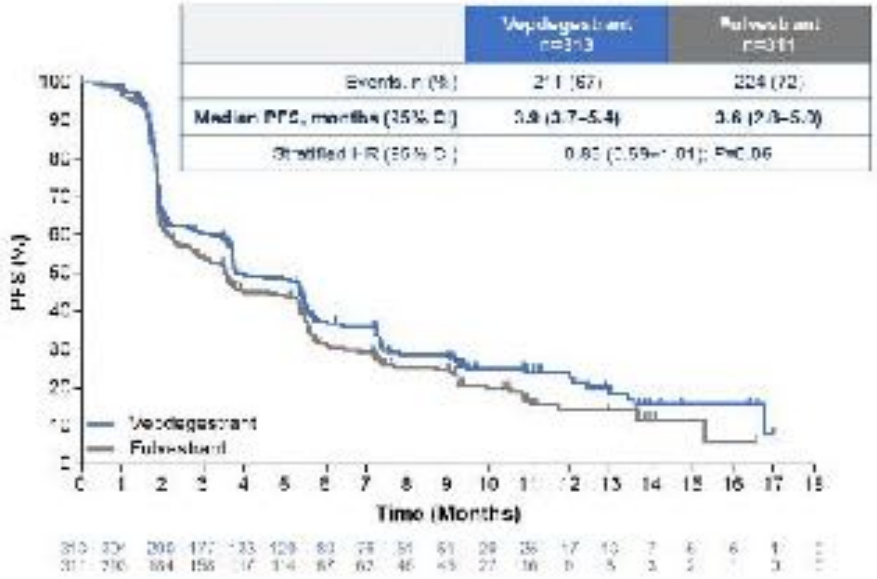
TEAEs in >10% of Patients in Either Group

TEAE, %	Vepdegestrant (n = 312)		Fulvestrant (n = 307)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Fatigue[a]	27	1	16	[illegible]
ALT increased[a]	14	1	10	[illegible]
AST increased[a]	14	1	10	3
Nausea	13	0	9	[illegible]
Anemia[a,b]	12	2	8	3
Neutropenia[a]	12	2[c]	5	1[c]
Back pain	11	1	7	<1
Arthralgia	11	1	11	0
Decreased appetite	11	<1	6	0

Patients With *ESR1*m



All Patients



Hamilton E, et al ASCO 2025. Abstract LBA1000; Campone M, et al. *N Engl J Med*. 2025;393:556-568.

SERENA-6 Study Design

Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)

- Female/male patients with ER+, HER2– aBC*
- All patients who have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for aBC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

R 1:1

N = 315

Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI

STATS: 195 PFS events: Power = 0.93 for HR = 0.61 at 5% 2-sided significance. Planned interim after 135 events, at *P* <.0001

Palbociclib vs ribociclib vs abemaciclib

Continuing AI (anastrozole/letrozole) + CDK4/6i + placebo for camizestrant

Treatment continued until disease progression, unacceptable toxicity, patient withdrawal, or death

Primary endpoint*

PFS by investigator assessment (RECIST v1.1)

Secondary endpoints

- PFS2
- OS
- Safety
- Patient-reported outcomes

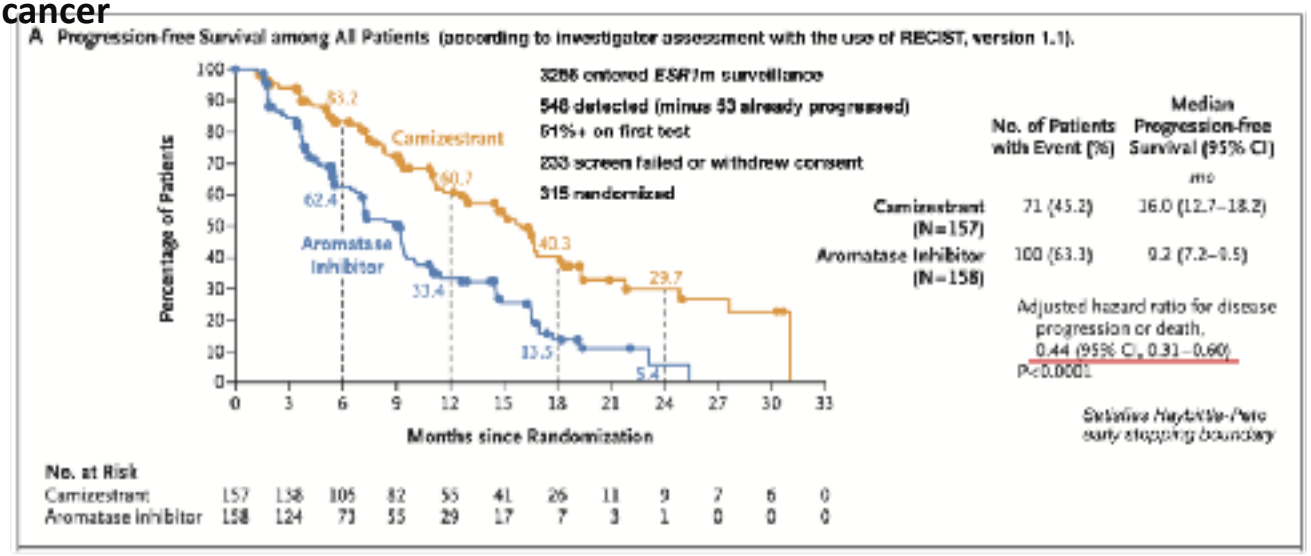
*F/U every 8 weeks for the first 18 months, then every 12 weeks until disease progression.

Groups well balanced for age (61), post-MP (~80%), ECOG 1 (31%–35%), visceral mets (42%–45%), median time for *ESR1* detection (22 months), median prior CDK4/6 inhibition (23 months), and *ESR1*m type (D538G: 45% vs 52%; Y537S: 39% vs 38%; Y537N: 19% vs 16% for camizestrant vs control, respectively).

Turner NC, et al. ASCO 2025. Abstract LBA4.

First-Line Camizestrant for Emerging *ESR1*-Mutated aBC

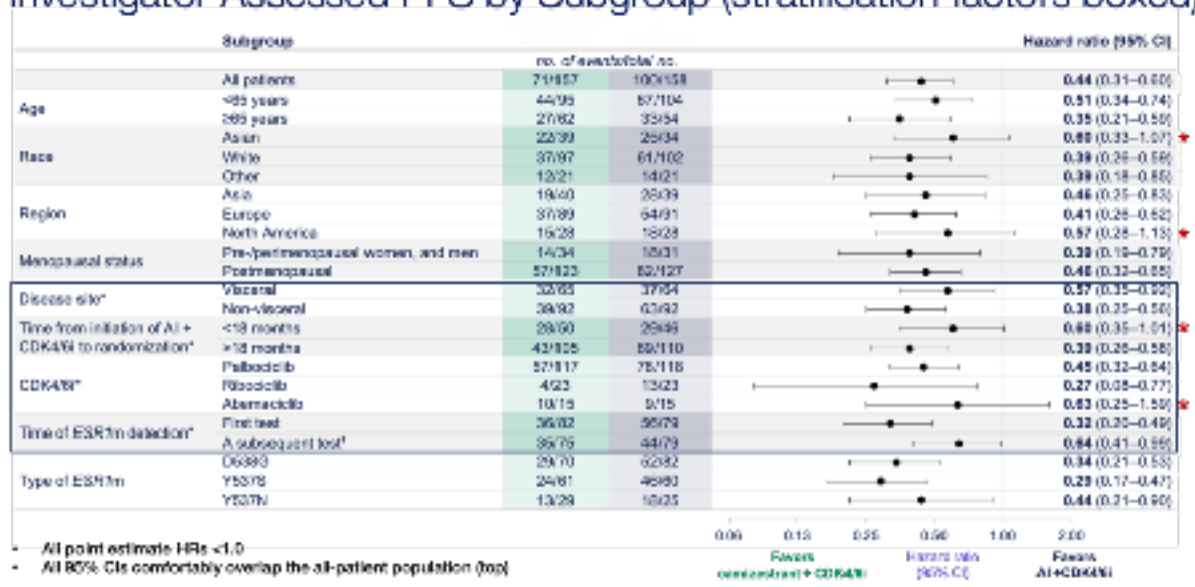
First global registration phase 3 trial to demonstrate clinical utility of ctDNA monitoring to detect and treat emergent resistance mutations in breast cancer



The median duration of follow-up was 18.1 and 12.1 months (for camizestrant and AI groups, respectively).

Bidard FC, et al. *N Engl J Med*. 2025;393:569-580.

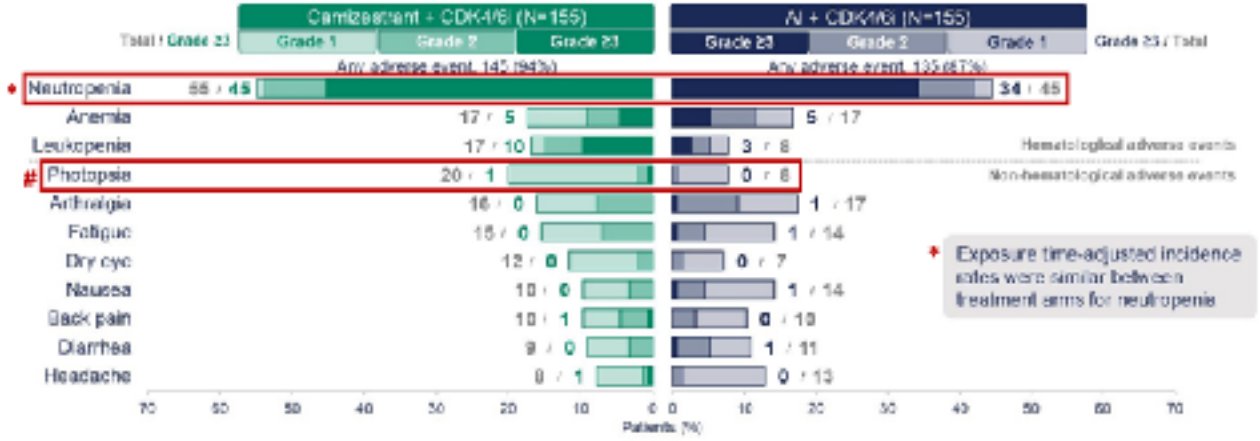
Investigator-Assessed PFS by Subgroup (stratification factors boxed)



- All point estimate HRs <1.0
- All 95% CIs comfortably overlap the all-patient population (top)

Turner NC, et al. ASCO 2025. Abstract LBA4.

*Note: 95% CIs crossing 1.0 have small N.

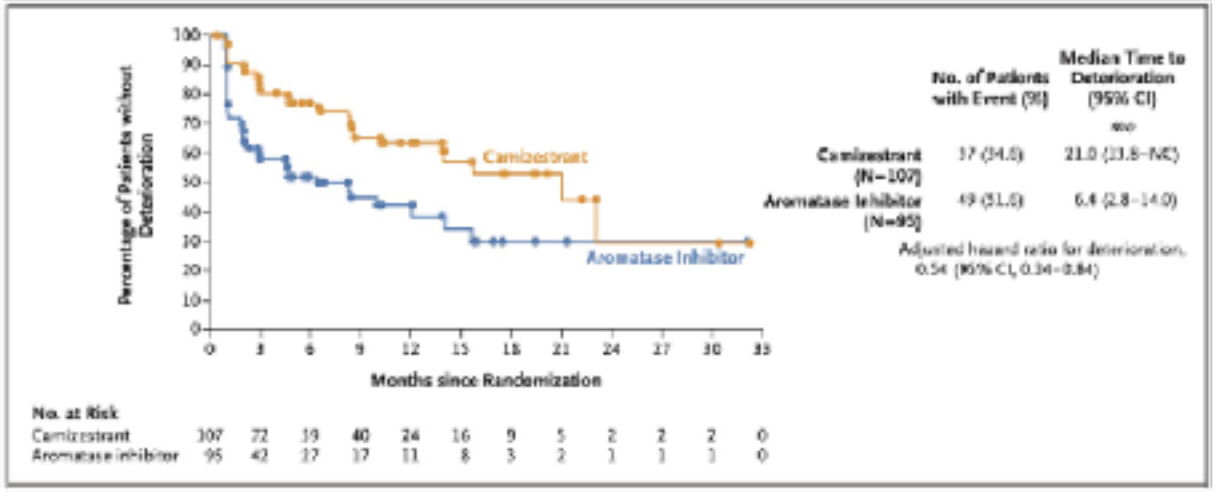


* Exposure time-adjusted incidence rates were similar between treatment arms for neutropenia

Photopsia (brief flashes of light in the peripheral vision) did not impact daily activities: if experienced, visual effects had no/minimal impact on daily activities, were typically ≤1 minute, ≤3 days/week, and reversible. There were no structural changes in the eye and no changes in visual acuity

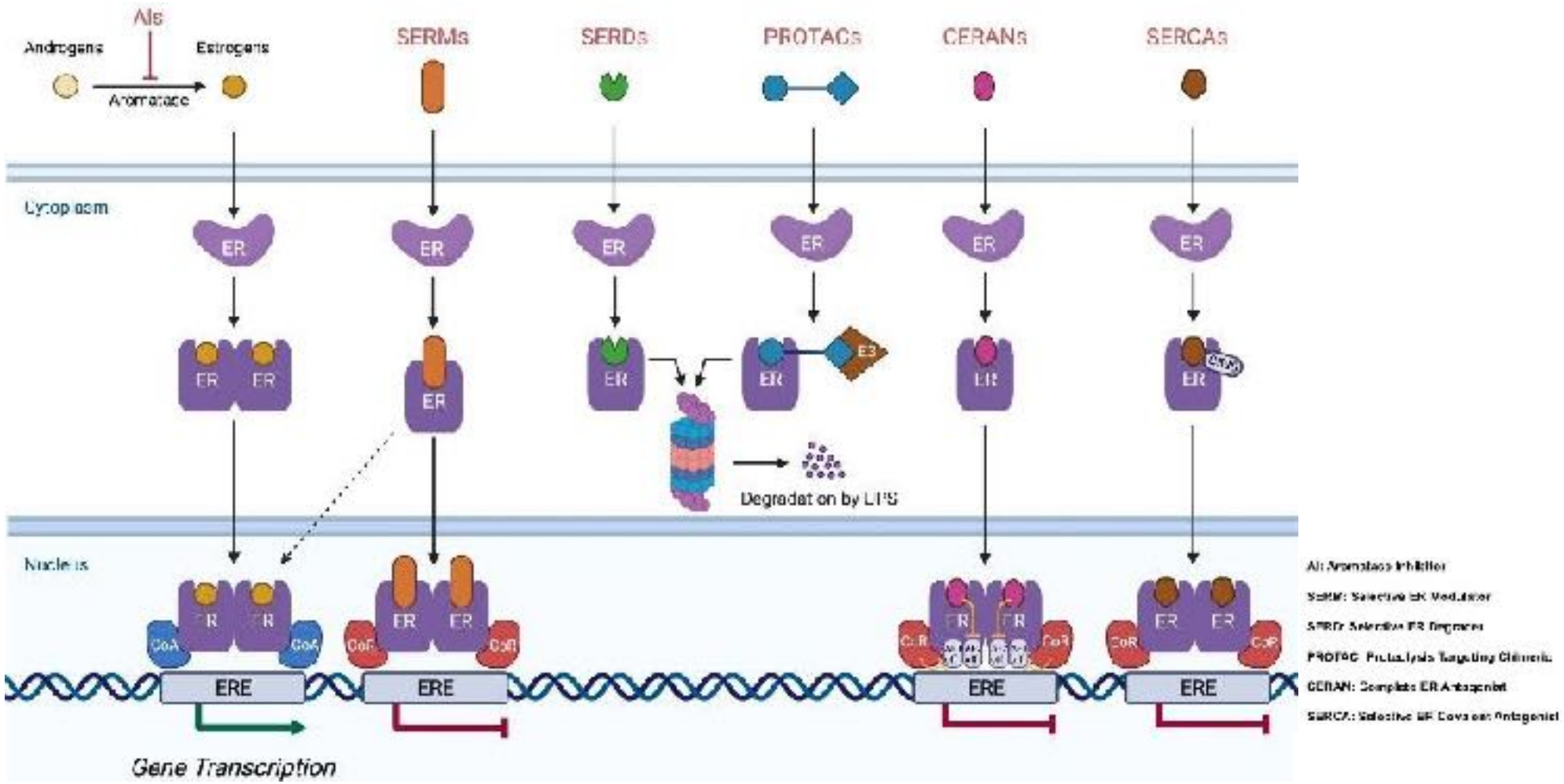
Bradycardia and sinus bradycardia were reported in the camizestrant group only, with 8 patients (5.2%) reporting bradycardia and 4 patients (2.6%) reporting sinus bradycardia; none of these events led to treatment discontinuation, and none were grade 3/4.

Exploratory Endpoint: Time until Deterioration in Global Health Status and Quality of Life



European Organization for Research and Treatment of Cancer 30-item quality-of-life questionnaire

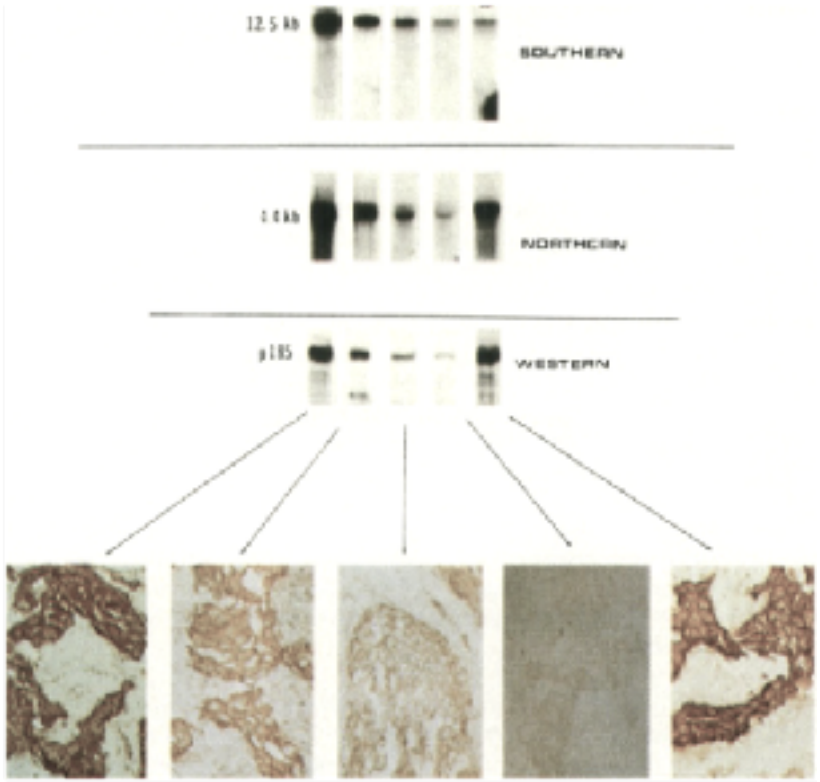
ER-Targeted Drug Classes: Summary



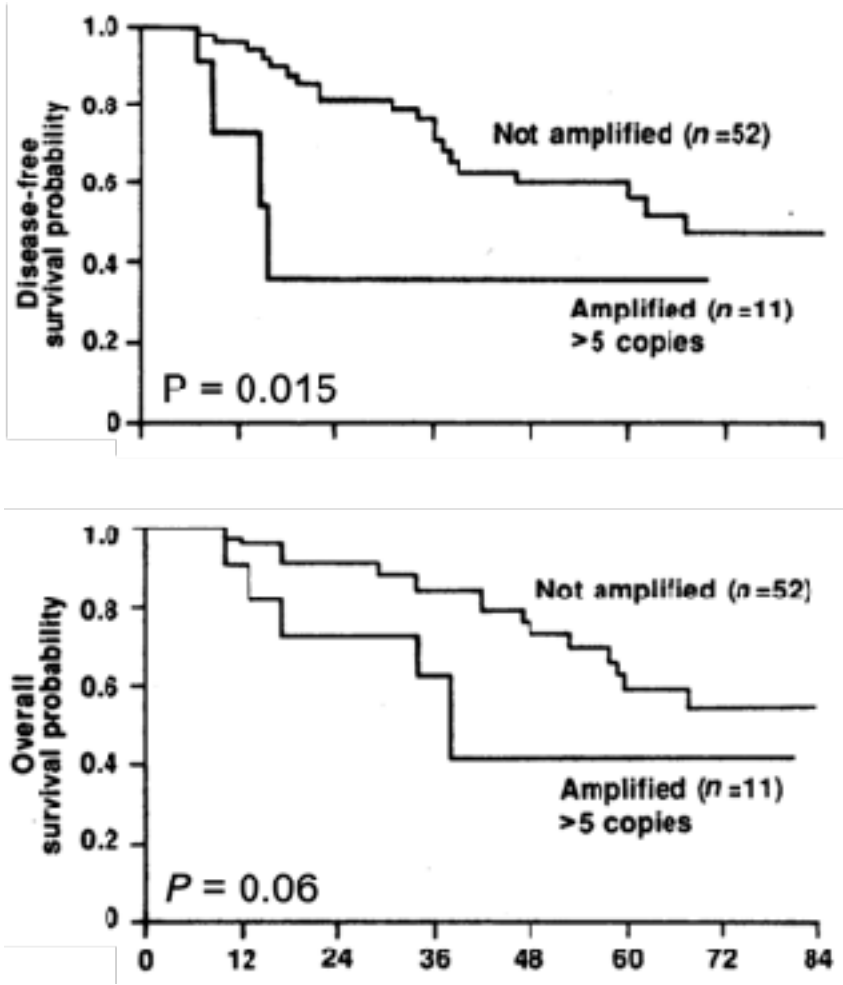
Patel R, et al. *NPJ Breast Cancer.* 2023;9:20.

Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene: Aggressive Biology = High Unmet Need

Correlation between HER-2/*neu* gene amplification and expression[1]



Disease-free and overall survival probability in lymph node positive breast cancer patients[2]



Overexpression of HER2/*neu* is associated with adverse prognostic factors, including:

- Advance pathologic stage[1]
- Number of metastatic axillary lymph nodes[3]
- Decreased estrogen and progesterone receptor expression[4]
- Increased S-phase fraction[5]
- DNA ploidy[6]
- High nuclear grade[7]

1. Slamon DJ, et al. Science. 1989 May 12;244(4905):707-12.
2. Slamon DJ, et al. Science. 1987 Jan 9;235(4785):177-82.
3. Seshadri R, et al. J Clin Oncol 11:1936-1942, 1993.
4. Konecny G, et al. J Natl Cancer Inst. 2003 Jan 15;95(2):142-53.
5. Borg A, et al. Oncogene 6:137-143, 1991.
6. Stal O, et al. Cytometry 16:160-168, 1994.
7. Berger MS, et al. Cancer Res 48:1238-1243, 1988.

DESTINY-Breast11 study design

A randomized, global, multicenter, open-label, Phase 3 study (NCT05113251)

Patient population
- Previously untreated HER2+ eBC
- HR-positive or HR-negative
- High-risk defined as:
  - ≥cT3 and N0–3 or cT0–4 and N1–3
  - Inflammatory BC

Randomized 1:1:1

- n=321 → **T-DXd* → THP†** 4 + 4 cycles
- n=320 → **ddAC‡ → THP§** 4 + 4 cycles
- n=286 → **T-DXd*** 8 cycles

→ **Surgery¶**

Recommended post-neoadjuvant treatment per study protocol‖

pCR: radiotherapy and concomitant trastuzumab ± pertuzumab for up to 1 year

No pCR: radiotherapy and T-DM1 for up to 14 cycles

HR-positive: endocrine therapy

Stratification factors
- HR status: ER and/or PR-positive or negative
- HER2 status: (IHC 3+ or ISH+ in the absence of IHC 3+ status)

The T-DXd alone arm closed on March 13 2024, following Independent Data Monitoring Committee recommendation
The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery

Data cutoff: March 12, 2025

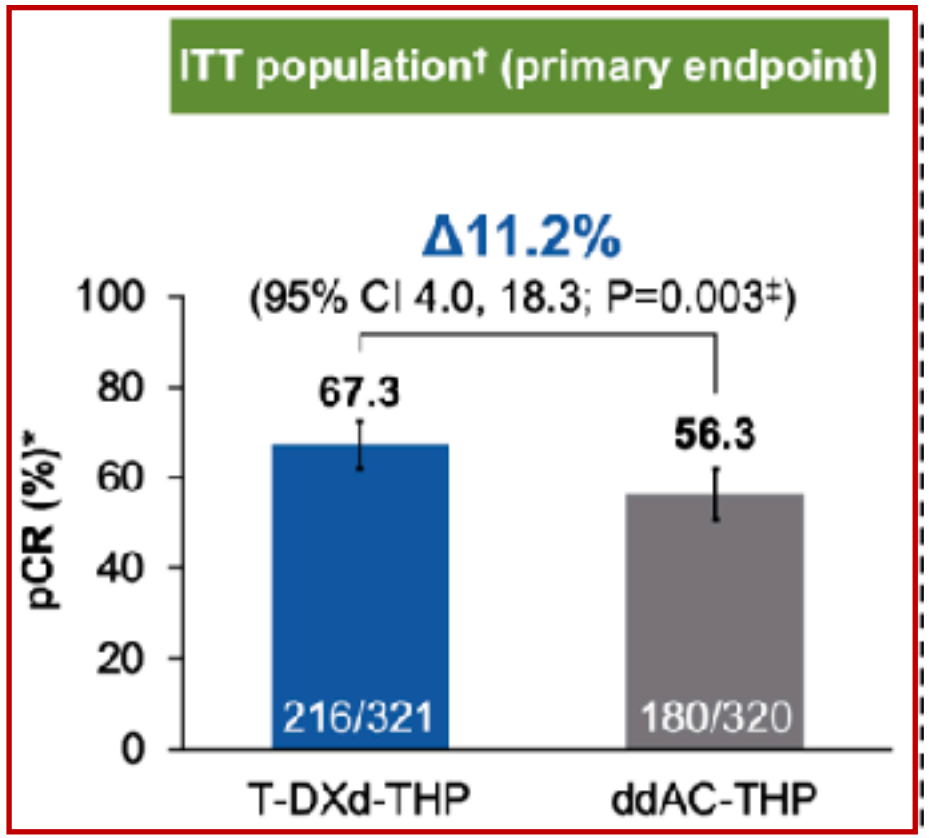
Primary endpoint
- pCR (ypT0/is ypN0) by blinded central review

Secondary endpoints
- pCR (ypT0 ypN0) by blinded central review
- EFS
- Safety
- Pharmacokinetics and immunogenicity
- Invasive disease-free survival
- Overall survival
- Health-related quality of life

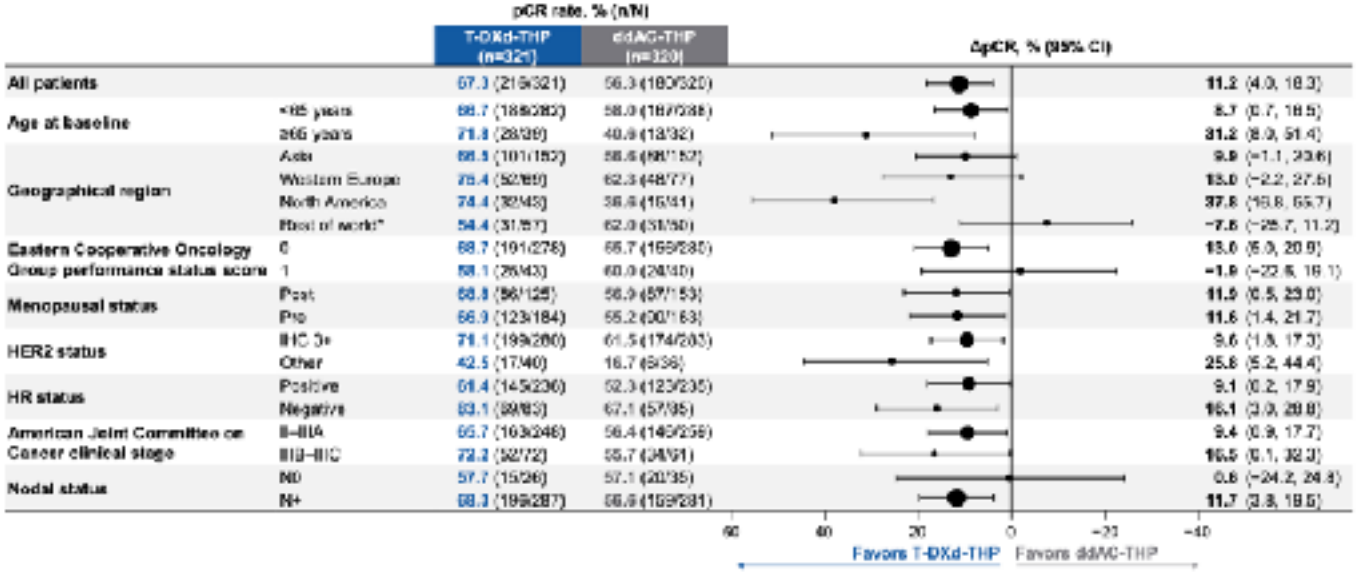
Additional outcome measures
- Residual cancer burden (RCB)

High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. *5.4 mg/kg Q3W; †paclitaxel (80 mg/m² QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ‡doxorubicin (60 mg/m² Q2W) + cyclophosphamide (600 mg/m² Q2W); §paclitaxel (80 mg/m² QW) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ¶the recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment; ‖administered as part of the patient's SOC at the investigator's discretion. cT, clinical tumor stage; ER, estrogen receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH+, in situ hybridization–positive; N, nodal stage; PR, progesterone receptor; Q3W, every 3 weeks. T-DM1, trastuzumab emtansine; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes; ypT0 ypN0, absence of invasive and in-situ cancer in the breast and axillary nodes

pCR (ypT0/is ypN0): primary endpoint (pathologic Complete Response)



pCR (ypT0/is ypN0) by subgroups



Improvement in pCR for T-DXd-THP vs ddAC-THP was observed across most pre-specified subgroups

Nadia Harbeck, MD

DESTINY-Breast11

ESMO congress

Neoadjuvant T-DXd-THP demonstrated a statistically significant and clinically meaningful improvement in pCR vs ddAC-THP

Improvement was observed in both the HR-positive and HR-negative subgroups

For the ITT population, treatment effects were estimated by the difference in pCR with 95% CIs and P-values based on the stratified Miettinen and Nurminen's method, with strata weighting by sample size (ie Mantel–Haenszel weights). Patients with no valid records regarding pCR status for any reason were considered to be non-responders (including but not limited to withdrawal from the study, progression of disease or death before surgery, lack of surgical specimen, or defined as not evaluable by the central pathologist). Subgroup analyses were unstratified. †By blinded central review. ‡pCR responders were defined as patients who only received randomized study treatment (at least one dose) and had pCR. §Two-sided P-value crossed the 0.03 prespecified boundary. ITT, intent-to-treat.

Nadia Harbeck, MD

After surgery, 81.3% of patients receiving T-DXd-THP had no or minimal residual invasive cancer (RCB-0+I) detected in the resected breast or lymph node tissue vs 69.1% of those receiving ddAC-THP

ESMO congress

Conclusions

- In DESTINY-Breast11, **T-DXd-THP showed the highest reported pCR rate in HER2+ eBC** for a registrational study in the neoadjuvant setting, despite a **high prevalence of HR-positive disease** and a **high-risk population**[1–3*]
- **T-DXd-THP showed a statistically significant and clinically meaningful improvement in pCR rate** vs ddAC-THP: Δ11.2% (95% CI 4.0, 18.3)
  - pCR benefit for T-DXd-THP vs ddAC-THP was independent of HR status and disease stage
- An **early positive trend in EFS** was observed, favoring T-DXd-THP vs ddAC-THP
  - Hazard ratio: 0.56 (95% CI 0.26, 1.17)
- The **safety profile of T-DXd-THP was favorable vs ddAC-THP**
  - Lower rates of Grade ≥3 AEs, serious AEs, and AEs leading to dose interruptions
  - Lower rates of hematological AEs, left-ventricular dysfunction, and fatigue
  - ILD rates were low and similar between arms (1 grade 5 ILD in each arm)

pCR rate

67.3%

More than two thirds of patients in the T-DXd-THP arm had a pCR

HR-positive: **61.4%**
HR-negative: **83.1%**

DESTINY-Breast11 results support T-DXd-THP as a more effective and less toxic neoadjuvant treatment compared with ddAC-THP, and it may become a preferred regimen for patients with high-risk HER2+ eBC

*Historical pCR rates (defined by ypT0/is ypN0) from other registrational studies for neoadjuvant SOC treatments in HER2+ eBC ranged from 39.3% to 62.7%, and HR-positive prevalence ranged from 46.7% to 52.4%[1–3]

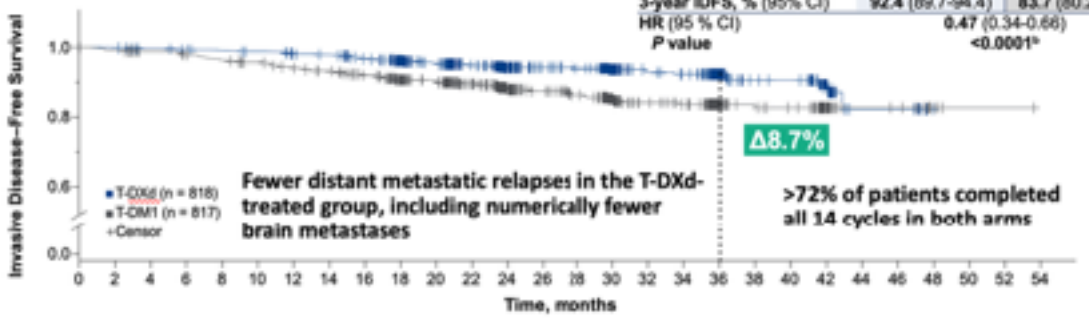
1. Huober J, et al. *J Clin Oncol*. 2022;40:2946–2956; 2. Hurvitz SA, et al. *Lancet Oncol*. 2013;19:115–126; 3. Gianni L, et al. *Lancet Oncol*. 2012;13:25–32

PHASE 3 DESTINY Breast05: PRIMARY ENDOINT AND SUBGROUP ANALYSIS (N=1600)

T-DXd vs. T-DM1 for residual disease following HER2-targeted NAT in high-risk patients: inoperable or operable eBC (cT1-3,N0-1,M0) with axillary LN+ disease after NAT

Primary endpoint: IDFS[a] (Invasive Disease-Free Survival)

	T-DXd n = 818	T-DM1 n = 817
Patients with events, n (%)	51 (6.2)	102 (12.5)
3-year IDFS, % (95% CI)	92.4 (89.7-94.4)	83.7 (80.2-86.7)
HR (95 % CI)	0.47 (0.34-0.66)	
P value	<0.0001[b]	



Number at Risk:

T-DXd	818	788	781	776	771	768	758	753	731	684	634	544	440	380	320	275	218	212	129	92	90	46	14	14	0	0	0	0
T-DM1	817	781	769	760	745	734	719	708	687	632	599	527	417	355	287	233	186	177	120	84	79	38	14	13	4	1	1	0

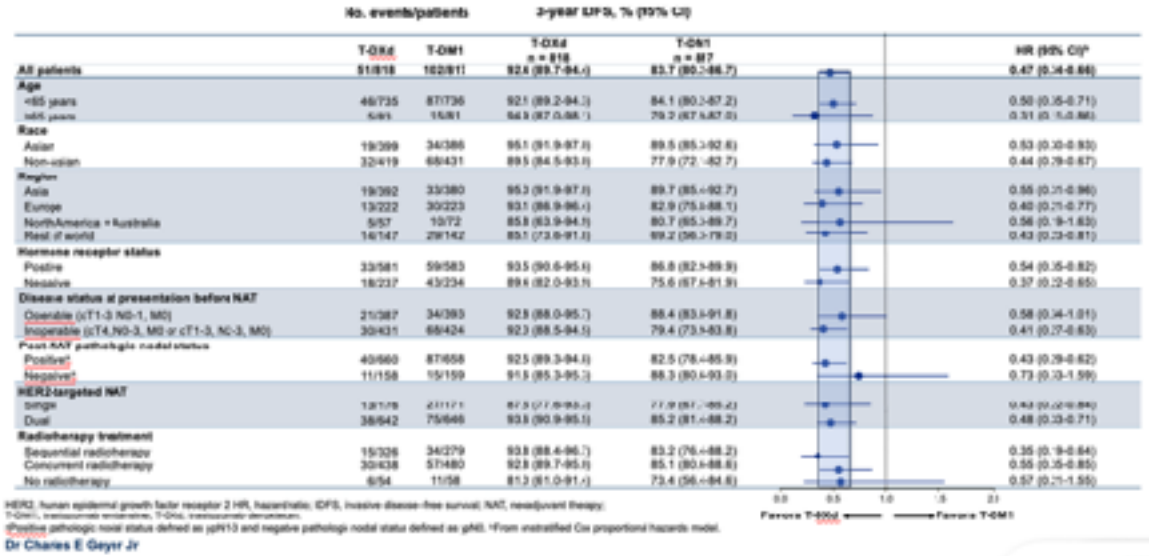
53% reduction in the risk of invasive disease recurrence or death for T-DXd compared with T-DM1

HR, hazard ratio; IDFS, invasive disease-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Efficacy stopping boundary, *P* = 0.0185.
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. [b]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.

Dr Charles E Geyer Jr

DESTINY-Breast05 ESMO congress

Primary endpoint subgroup analysis: IDFS (Invasive Disease-Free Survival)



HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDFS, invasive disease-free survival; NAT, neoadjuvant therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[b]Positive pathologic nodal status defined as ypN1/3 and negative pathologic nodal status defined as ypN0. [a]From unstratified Cox proportional hazards model.

Dr Charles E Geyer Jr

Shaded box indicates 95% CI, all pt population

DESTINY-Breast05 ESMO congress

SAFETY: 2 adjudicated grade 5 ILD events in the T-DXd arm (0.2%), none in the T-DM1 arm.
Numerically more low-grade (1/2) ↓LVEF in the T-DXd arm (2.6% vs. 1.4% for T-DXd and T-DM1, respectively.

Adjuvant radiotherapy timing (sequential or concurrent) showed no differences in adjudicated drug-related ILD

Similar distributions of any grade adjudicated drug-related ILD events were observed with sequential and concurrent radiotherapy in both treatment arms (T-DXd: 10.7% and 9.6.% vs T-DM1: 2.6% and 1.0%, respectively)

Adjuvant T-DXd demonstrated superior efficacy with manageable safety in patients with high-risk HER2+ eBC and residual invasive disease after NAT, representing a potential new standard of care in this post-neoadjuvant setting

The future of ADC in HER2+ eBC

NEOADJUVANT

- **DESTINY-Breast11**: T-DXd +/- sequential THP vs. AC-THP[1] — Ph III
- **ADAPT-HER2-IV:** T-DXd vs. chemo/H/P[2] — Ph II
- **APTneo:** Pertuzumab + trastuzumab + paclitaxel (HPCT) + atezolizumab vs. AC + HPCT + atezolizumab vs. HPCT[3] — Ph III

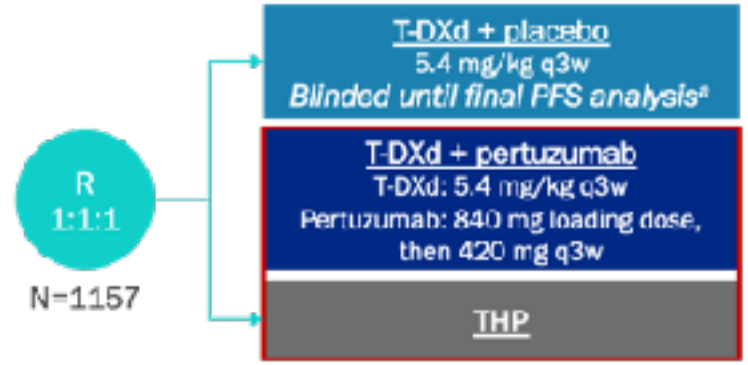
POST-NEOADJUVANT / ADJUVANT

- **DESTINY-Breast05:** T-DXd vs. T-DM1[4] — Ph III
- **ATEMPT 2.0:** T-DM1 + trastuzumab vs. trastuzumab + paclitaxel[5] — Ph II
- **ADEPT:** Pertuzumab + trastuzumab + ET[6] — Ph II
- **ASTEFANIA:** Atezolizumab + T-DM1 vs. placebo + T-DM1[7] — Ph III
- **COMPASSHER2-RD:** Tucatinib + T-DM1 vs. T-DM1 + placebo[8] — Ph III

- **COMPASSHER2-pCR:** Neoadjuvant trastuzumab + pertuzumab + paclitaxel/nab-paclitaxel or docetaxel -> surgery within 42 days, post-neoadjuvant trastuzumab + pertuzumab ± SOC radiotherapy (if pCR), or T-DM1 ± SOC chemotherapy/hormone therapy (if residual disease)[9] — Ph II
- **PHERGAIN-2:** Neoadjuvant FDC SC trastuzumab + pertuzumab (± ET) followed by post-neoadjuvant FDC SC trastuzumab + pertuzumab or T-DM1 or chemotherapy before adjuvant T-DM1 (± ET)[10] — Ph II
- **DECRESCENDO**: Neoadjuvant FDC SC trastuzumab + pertuzumab + paclitaxel or docetaxel followed by post-neoadjuvant FDC SC trastuzumab + pertuzumab (if RCB=0) or T-DM1 (if RCB ≥1) or anthracycline-based chemotherapy before T-DM1 (if RCB ≥2)[11] — Ph II

MBC: PFS

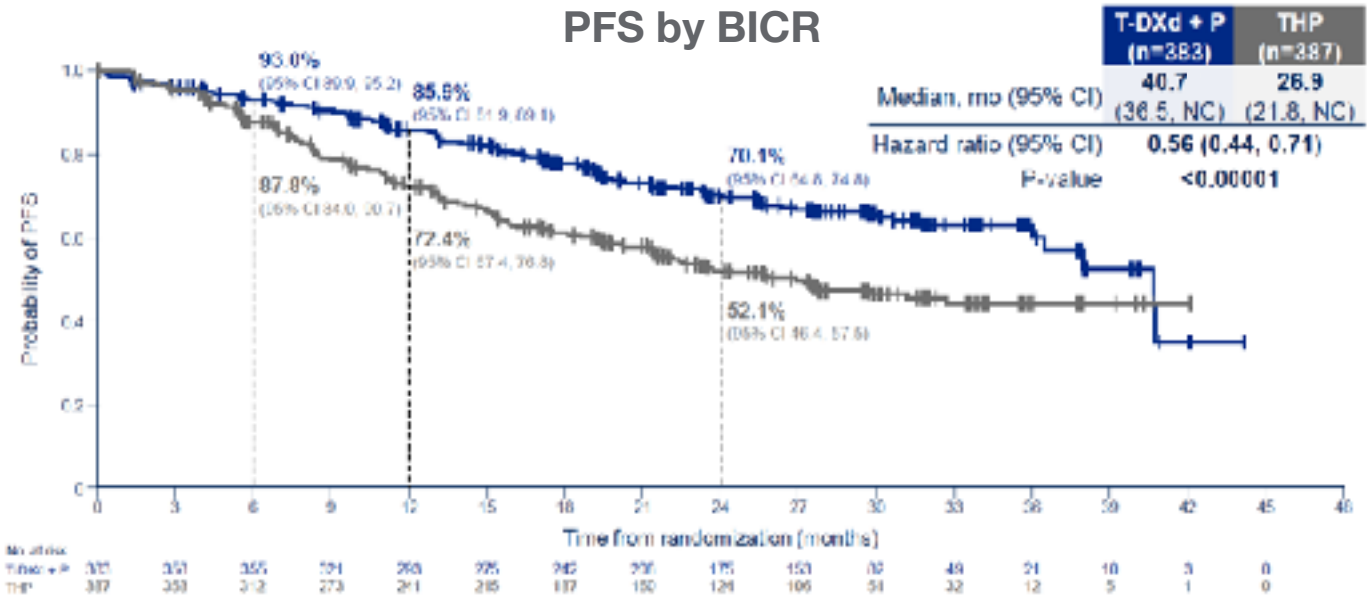
Key Eligibility Criteria
- HER2+ MBC
- Asymptomatic/inactive brain metastases allowed
- DFI >6 months from last chemotherapy or HER2-targeted therapy in (neo)adjuvant setting
- 1 prior line of ET in the metastatic setting permitted
- No other prior systemic therapy for MBC

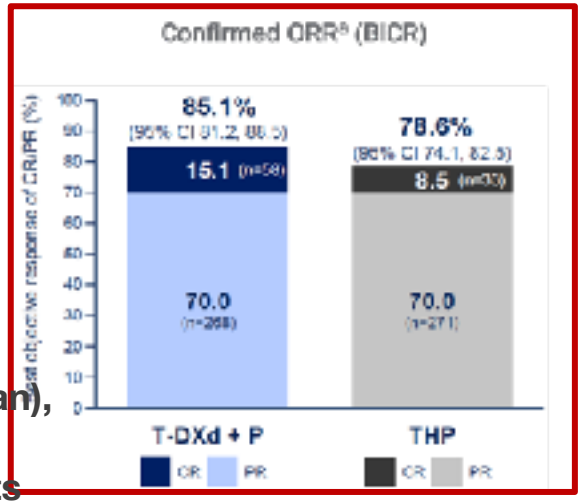


Stratification factors: De novo vs recurrent MBC, HR+ vs HR−, and PIK3CAmut

Primary endpoint: PFS (BICR)
Key secondary endpoint: OS
Other secondary endpoints: PFS by INV, ORR, DOR, PFS2, safety

Groups well-balanced for age (54), world region (49% Asian), ECOG 0 (64-67%), HER2 IHC 3+ (81-83%), HR+ (54%), de novo metastatic dz (52%), PIK3CAmut (30-31%), CNS mets (6%), visceral mets (69-73%).





- **PFS by INV was similar (HR=0.49; 95% CI, 0.39-0.61; *P*<0.00001)**
- **Benefit with T-DXd + P vs THP was consistent across prespecified subgroups, including stratification factors**
- **Median follow-up: 29.2 months**
- **2 grade 5 ILD events in the T-DXd + P arm, none in control**

PFS benefit with T-DXd + P vs THP was consistently observed across prespecified subgroups, including stratification factors

[a] Median PFS estimate for T-DXd is likely to change at updated analysis. [b] Stratified log-rank te

Tolaney SM, et al. ASCO 2025. Abstract LBA1008.

Primary Results From PATINA Phase 3 Trial of Palbociclib + Anti-HER2 Therapy + ET in HR+/HER2+ MBC

Key Eligibility Criteria

- HR+/HER2+ MBC
- No prior treatment in ABC setting beyond induction therapy
  - **6-8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine**
- **Completion of induction chemotherapy and no evidence of disease progression**

N=518

R 1:1

Palbo + Anti-HER2 + ET
Palbociclib (125 mg PO qd D1-D21) + trastuzumab ± pertuzumab + ET[a]

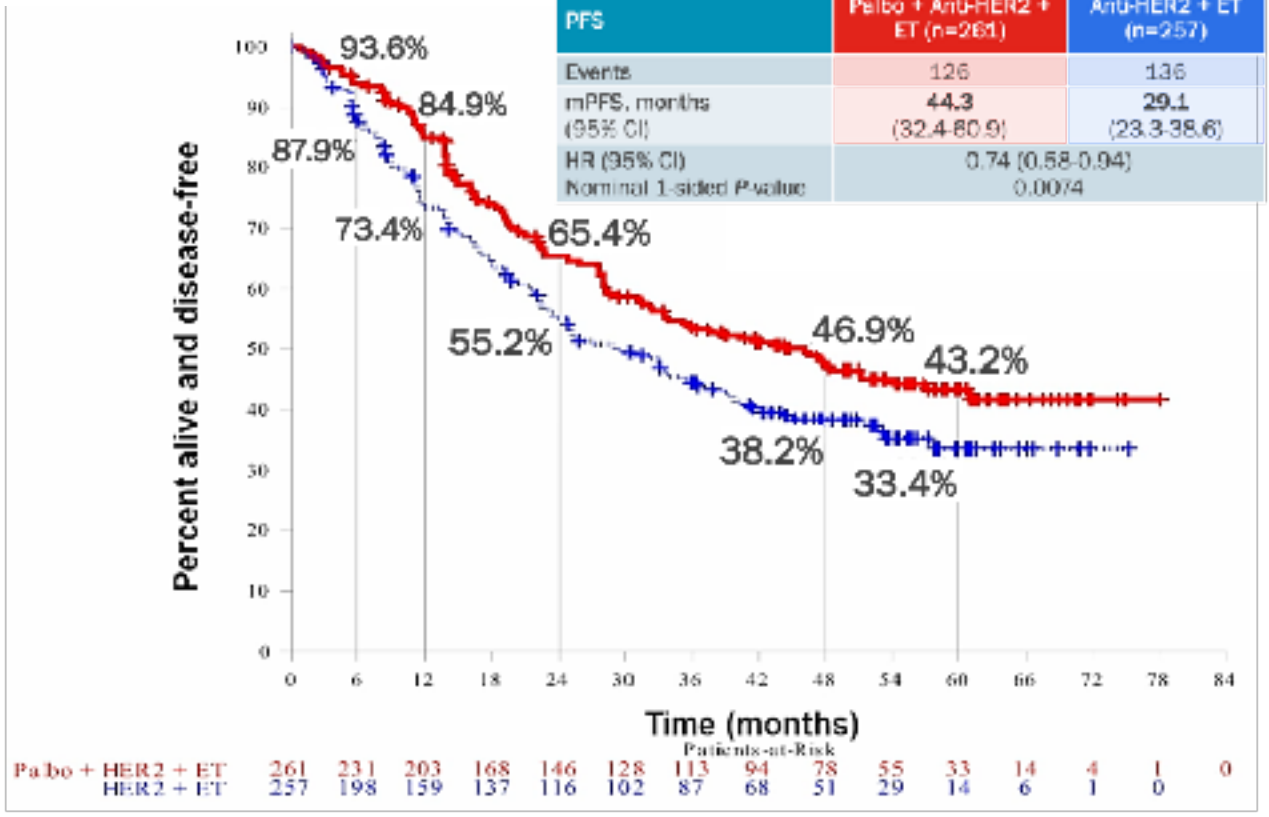
Anti-HER2 + ET
Trastuzumab ± pertuzumab + ET[a]

Until PD or toxicity

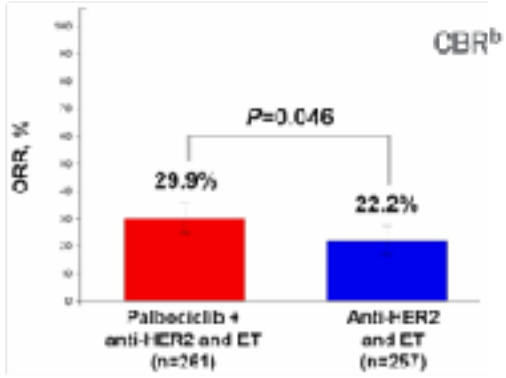
Stratification factors: pertuzumab use, prior (neo)adjuvant anti-HER2 therapy, response to induction therapy, type of ET

Primary endpoint: INV-assessed PFS
Key secondary endpoint: OS

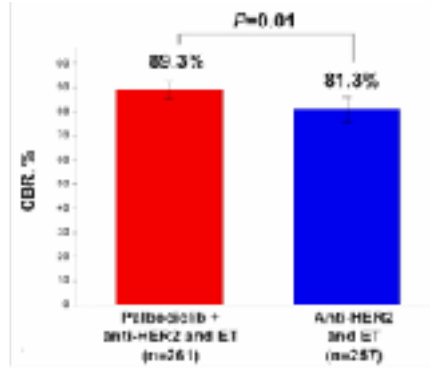
PFS	Palbo + Anti-HER2 + ET (n=261)	Anti-HER2 + ET (n=257)
Events	126	136
mPFS, months (95% CI)	44.3 (32.4-60.9)	29.1 (23.3-38.6)
HR (95% CI) Nominal 1-sided *P* value	0.74 (0.58-0.94) 0.0074	



Confirmed ORR[a]



CBR[b]

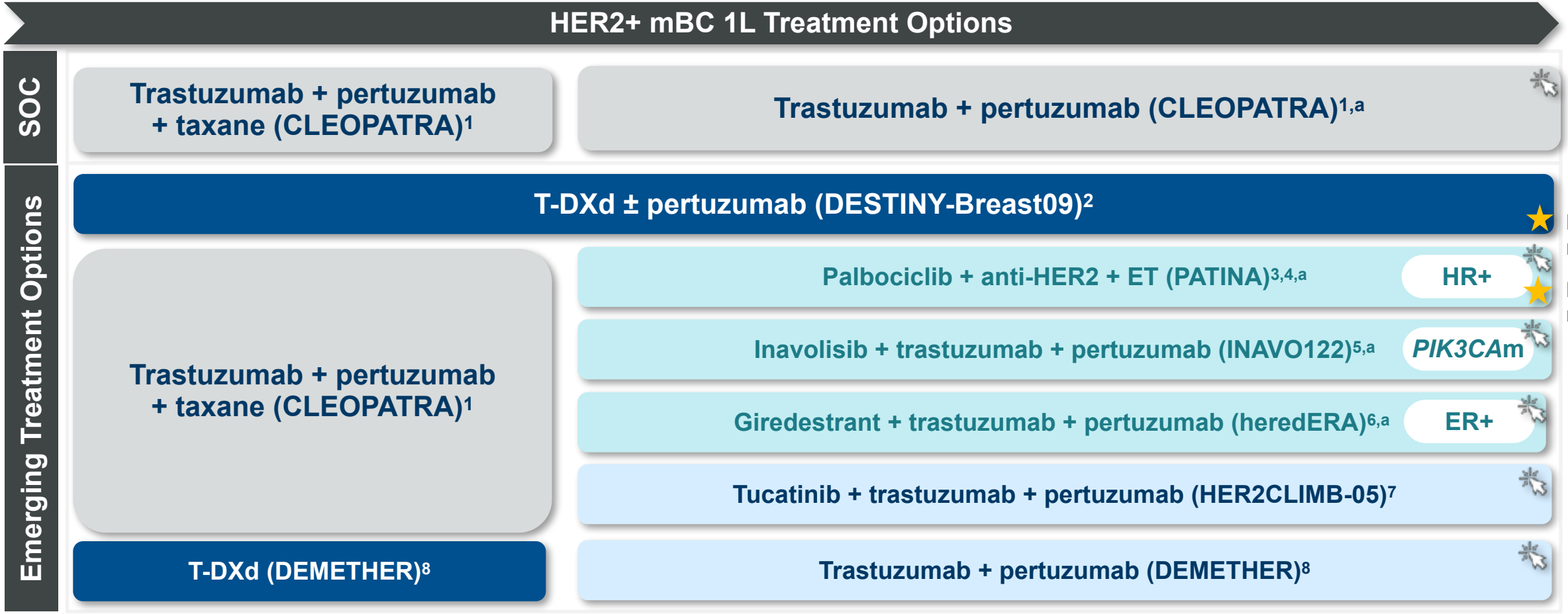


Groups well-balanced for age (53), median #cycles induction Rx (6), pertuzumab use (97%), prior AI (91%), prior (neo)adj anti-HER2 Rx (71-73%), best response to induction therapy (CR/PR = 68.5%)

[a] Trastuzumab and pertuzumab were administered per SOC. ET options include an AI or fulvestrant.

Metzger O, et al. SABCS 2024. Abstract GS2-12.

The HER2+ mBC 1L Treatment Landscape is Likely to Continue to Evolve With Emerging Data From Ongoing Trials – many are induction/maintenance design

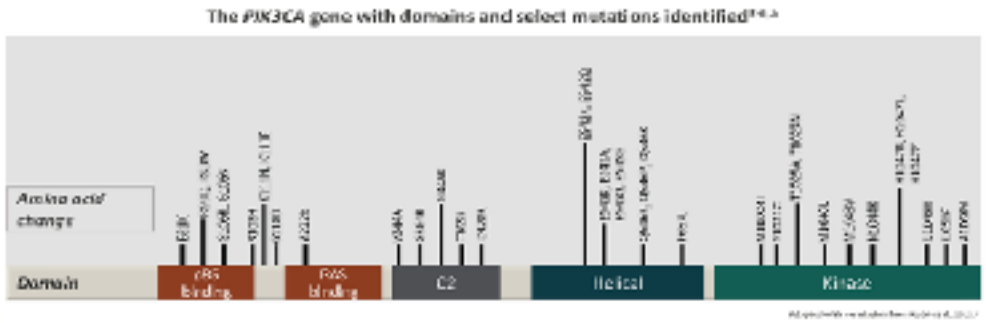


[a]ET can be added with maintenance trastuzumab + pertuzumab for patients with HR-positive disease as per guidelines.[9]

1L, first-line; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IA, interim analysis; mBC, metastatic breast cancer; *PIK3CA*m, *PIK3CA* mutation; SOC, standard of care; T-DXd, fam-trastuzumab deruxtecan-nxki.

Please see references in slide notes.

INAVO120: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study[1,2]



- Overall, PIK3CA mutations are the second most common mutation (~40% in ER+) observed in all breast cancer patients, second only to TP53 mutations[1]

INAVO120: A Phase III, randomized, double-blind, placebo-controlled study[1,2]

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2– aBC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **No prior therapy for aBC**
- **Fasting glucose <126 mg/dL and HbA_{1c} <6.0%**

Enrolment period: January 2020 to September 2023

N = 325

R 1:1

Inavolisib (9 mg PO QD)
+ palbociclib (125 mg PO QD D1–D21)
+ fulvestrant (500 mg C1D1/15 and Q4W)†

Placebo (PO QD)
+ palbociclib (125 mg PO QD D1–D21)
+ fulvestrant (500 mg C1D1/15 and Q4W)†

Until PD or toxicity

SURVIVAL FOLLOW-UP

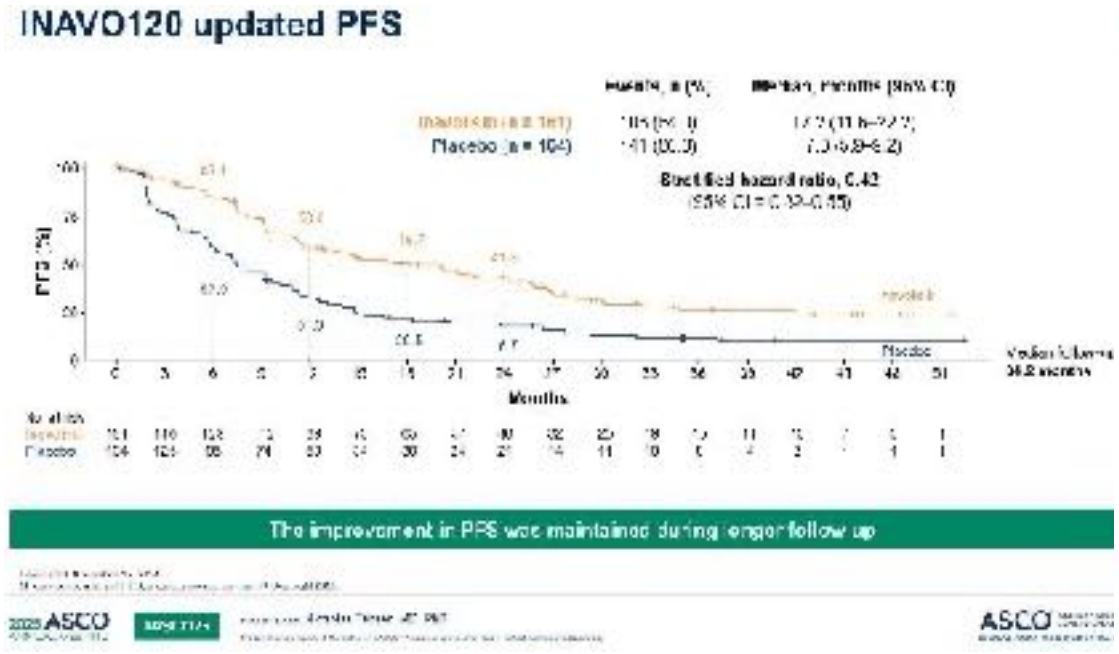
Stratification factors:
- Visceral disease (yes vs. no)
- Endocrine resistance (primary vs. secondary)‡
- Region (North America/Western Europe vs. Asia vs. Other)

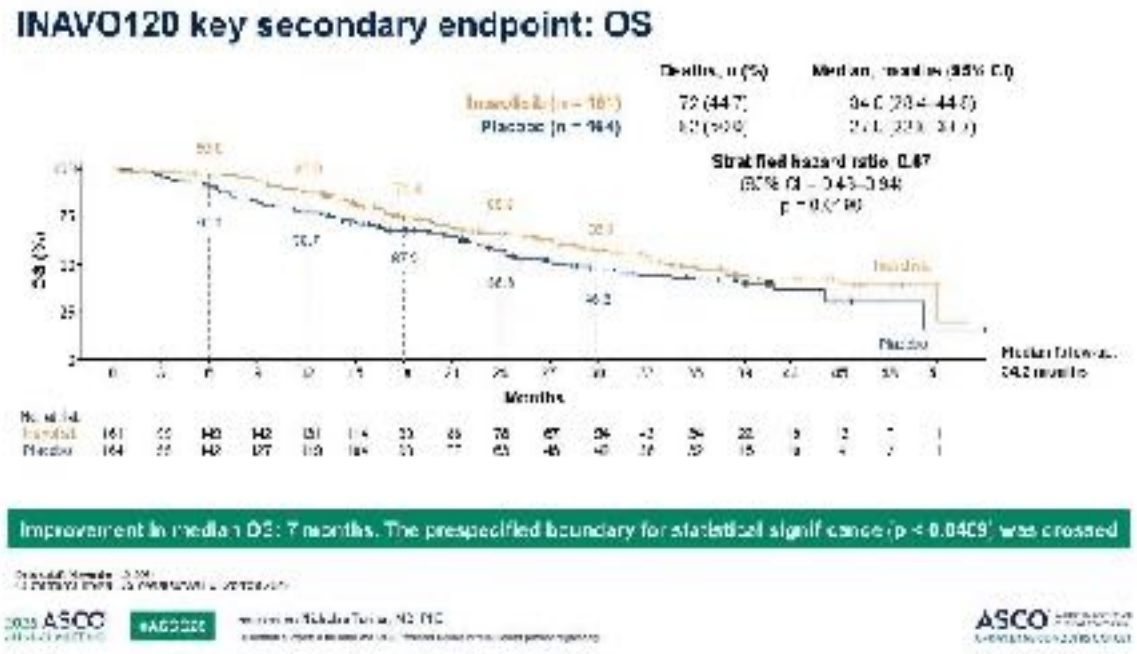
- Primary endpoint: Investigator-assessed PFS
- Secondary endpoints included: OS; investigator-assessed ORR, BOR, CBR, and DoR; PROs

➢ Inavolisib is a PI3Kα inhibitor with a high degree of selectivity over beta-, gamma-, and delta- PI3K isoforms

ClinicalTrials.gov number: NCT04191499.
Adapted from Turner NC, et al. SABCS 2023 (Abstract GS3-13); * Central testing for PIK3CA mutations was done on ctDNA using FoundationOne® liquid (FoundationMedicine, Inc., Cambridge, MA) and local ctDNA testing by the Roche cobas® PIK3CA mutation assay (Roche); † Pre-menopausal women received ovarian suppression; ‡ Defined per 4th European School of Oncology (ESO)-European Society for Medical Oncology (ESMO) international Consensus Guidelines for Advanced Breast Cancer.[3]
Primary: Relapse while on the first 2 years of adjuvant ET; secondary: Relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.
aBC, advanced breast cancer; BOR, best overall response; C, cycle; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; D, day; DoR, duration of response; ET, endocrine therapy; HbA_{1c}, glycated hemoglobin; HER2–, HER2-negative; HR+, hormone receptor-positive; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, by mouth; PRO, patient-reported outcome; QD/W, every 1 week/s; C1D1, cycle 1, day 1; R, randomization.
1. Turner NC, et al. *N Engl J Med* 2024; **391**:1584–1596. 2. Jhaveri KL, et al. SABCS 2023 (Abstract GS3-13). 3. Cardoso F, et al. *Ann Oncol* 2018; **29**:1634–1657.

INAVO120: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study





- This is the first time OS has been significantly improved by a PI3K pathway-targeted drug
- Median time to first subsequent chemotherapy = almost 2 years (23 months)
- Hyperglycemia, stomatitis, and dry eye/blurred vision were reported at a higher frequency in the inavolisib group, but discontinuation rate was low

Mutations in the PI3 Kinase/AKT Pathway Are Actionable: CAPItello-291 Phase III Trial of Capivasertib + Fulvestrant in AI-Resistant HR+, HER2– mBC

Most common adverse reactions (incidence ≥20%), were diarrhea, rash, hyperglycemia, lymphopenia, anemia, nausea, fatigue, leukocytosis, hypertriglyceridemia, neutropenia, ↑creatinine, vomiting, and stomatitis.

Key Eligibility Criteria

- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6i allowed (at least 51% required)

R — 1:1 — N=708

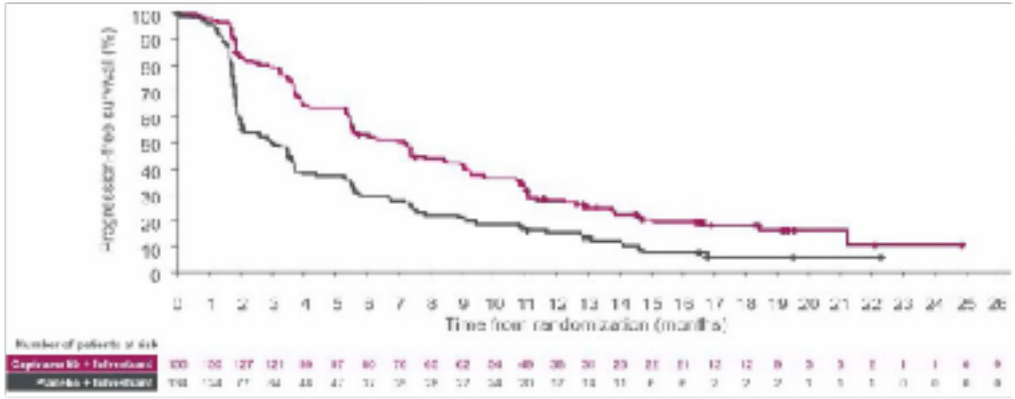
- **Capivasertib + Fulvestrant (n=355)**
  Capivasertib 400 mg bid[a]
  Fulvestrant 500 mg q4w[b]
- **Placebo + Fulvestrant (n=353)**
  Placebo bid[a]
  Fulvestrant 500 mg q4w[b]

Dual primary endpoints: PFS by investigator in overall and in AKT pathway-altered tumors[c]
Secondary endpoints: OS, ORR
Stratification Factors: Liver mets, prior CDK4/6i, region

[a]4 days on, 3 days off. [b]Cycle 1: days 1 and 15; then q4w. [c]AKT pathway-altered tumors: tumors carrying *PIK3CA*, *AKT1*, or *PTEN* alteration. [d]Baseline eGFR/BSA factor. [e]One patient in the C+F group was ER negative.

Turner NC, et al. SABCS 2022. Abstract GS3-04.

PFS by Investigator in the AKT Pathway-Altered Population



AKT Pathway-Altered Population	C+F (n=155)	P+F (n=134)
PFS events	121	115
Median PFS, mo (95% CI)	7.3 (5.5-9.0)	3.1 (2.0-3.7)
Adjusted HR (95% CI)	0.50 (0.38-0.65)	
Two-sided *P* value	<0.001	

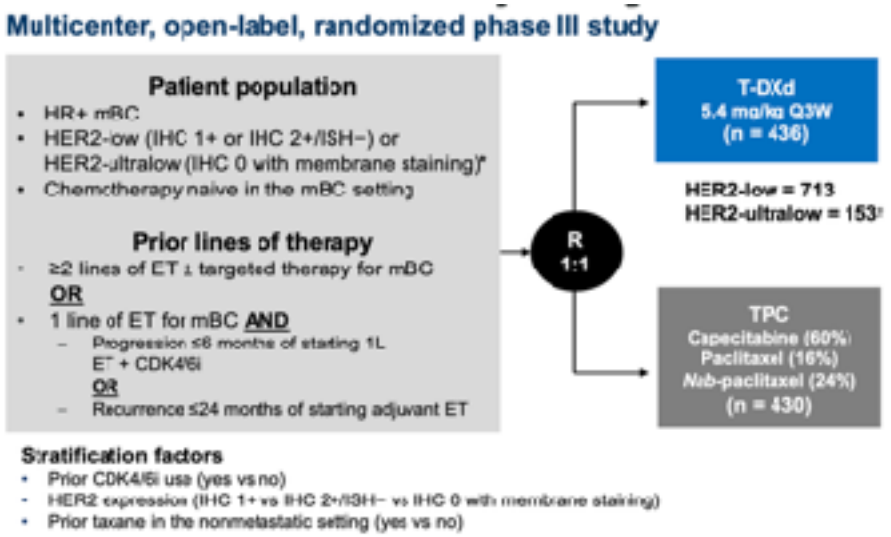
- PFS benefit was observed in all key subgroups, including prior use of CDK4/6i and liver metastases

Novel *PIK3CA/AKT/MTOR* Drugs in Clinical Trials

Target	Key Features	Name
PIK3CA	Allosteric, pan-mutant, isoform selective	RLY-2608
PIK3CA, MTORC1, MTORC2	Pan-class I isoform, multiple subunits, IV	Gedatolisib
PIK3CA	Mutant specific for *PIK3CA* H1047R	OKI-129
PIK3CA	Allosteric, mutant selective	STX-478
PIK3CA	Covalent	TOS-358
AKT	Pan-AKT inhibitor	Ipatasertib
AKT E17K	Mutant selective	ALTA 2618

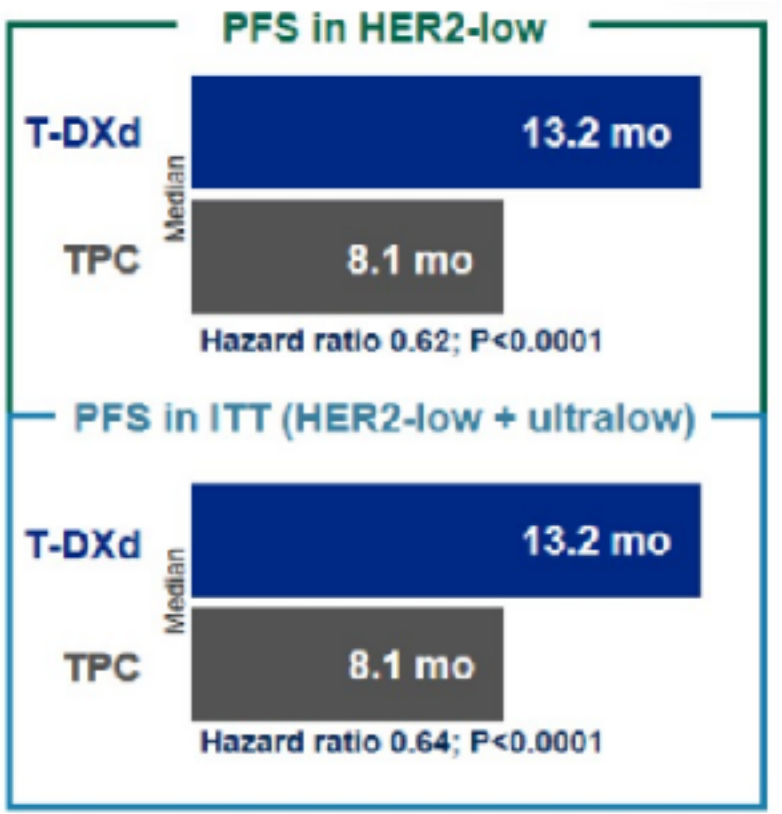
DESTINY-Breast06[1,2]

FDA approved January 27, 2025



HER2-ultralow = No staining OR faint/barely perceptible, incomplete membrane staining in ≤10% of tumor cells. NCCN defines HER2-ultralow as HER2 IHC 0+.5 The FDA label defines it as IHC 0 with membrane staining, as determined by an FDA-approved test.

- **T-DXd demonstrated a statistically significant and clinically meaningful PFS benefit vs TPC (conventional chemotherapy) in HR+, HER2-low mBC in an earlier line of treatment than in DESTINY-Breast04**
- **Results in HER2-ultralow patients were consistent with HER2-low**
- **Confirmed ORR was 57.3% (T-DXd) vs 31.2% (TPC) in ITT**
- **No new safety signals were identified; ILD remains an important safety risk of T-DXd**



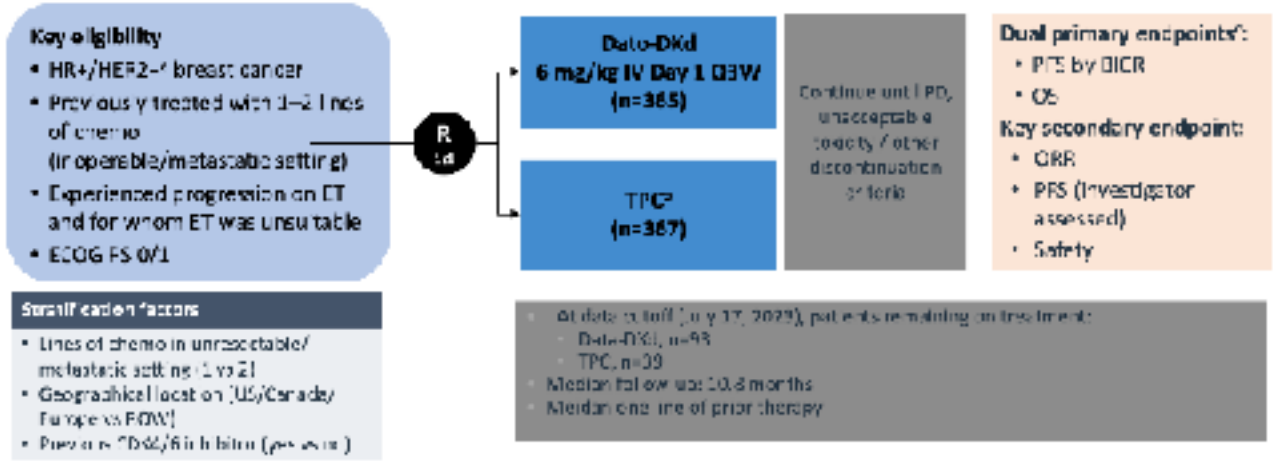
DESTINY-Breast06 establishes T-DXd as an effective new treatment option for patients with HR+, HER2-low and HER2-ultralow mBC following ≥1 endocrine-based therapy

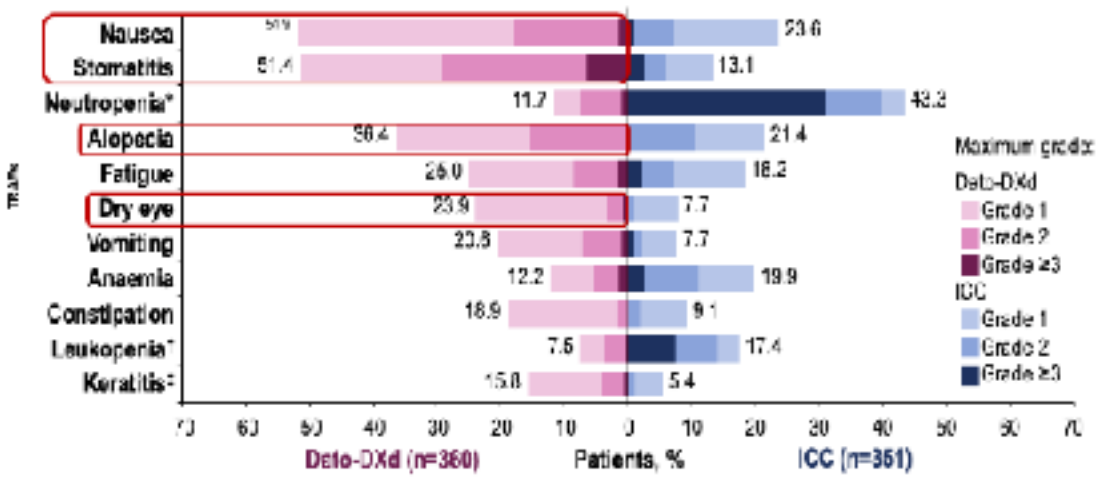
New FDA indication 1/27/25: HR+, HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on 1 or more endocrine therapies in the metastatic setting.

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ILD, interstitial lung disease; ITT, intention-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; T-DXd, fam-trastuzumab deruxtecan-nxki; TPC, treatment of physician's choice.

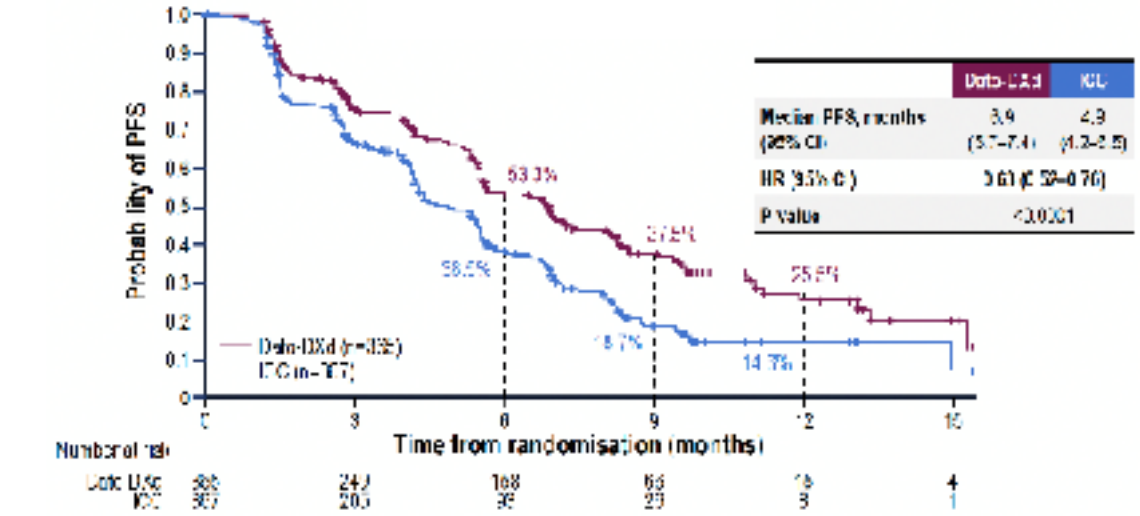
1. Curigliano G, et al. ASCO 2024. Abstract LBA1000; 2. Bardia A, et al. *N Engl J Med*. 2024;391:2110-2122.

TROPION-Breast01: Dato-DXd vs Chemo for 2–3L HR+, HER2– mBC





Dato-DXd, datopotamab deruxtecan; TPC, treatment of physician's choice.

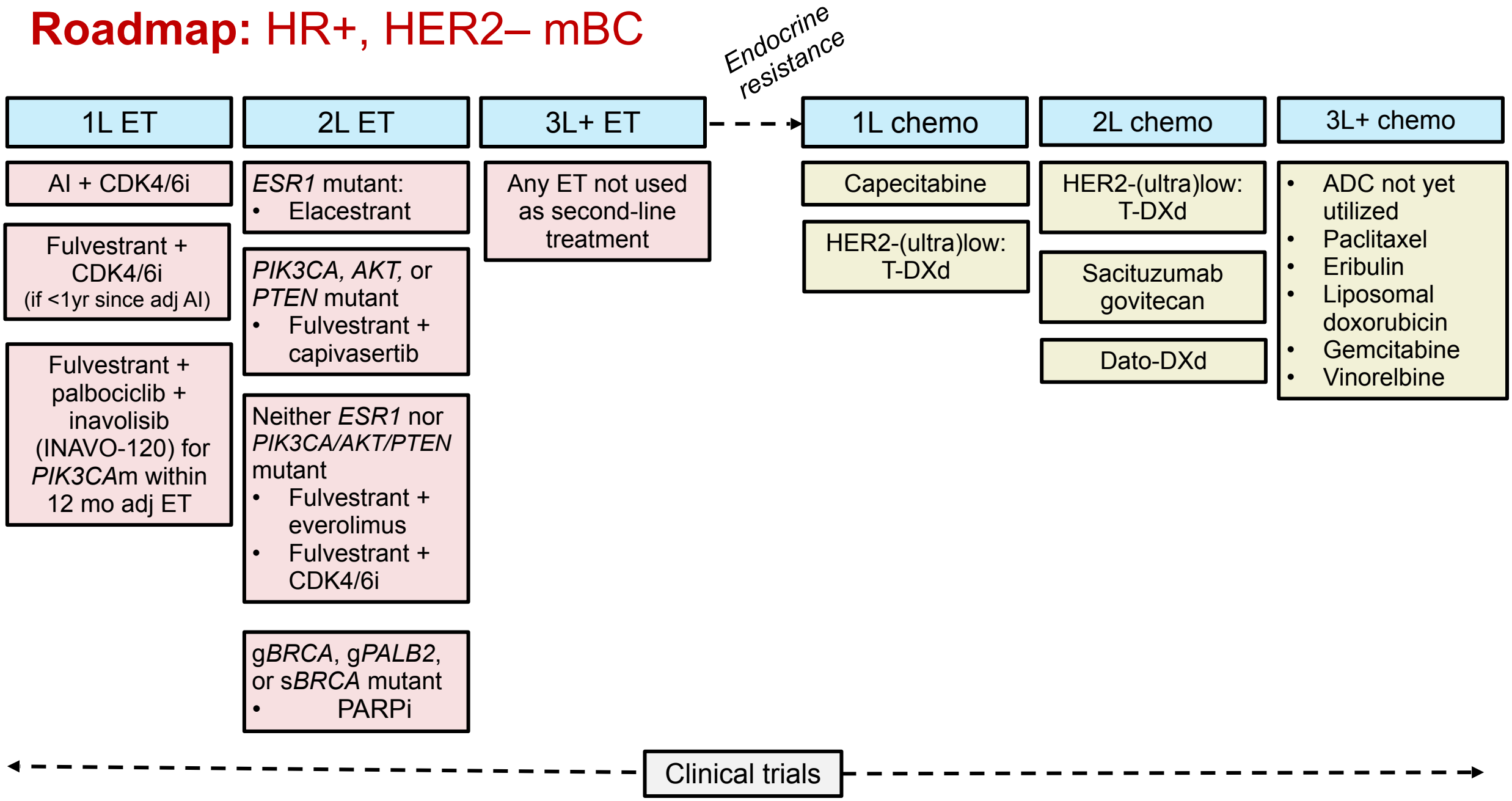


- **mPFS by BICR:** 6.9 mo vs 4.9 mo (HR 0.63)
- **mOS:** 18.6 mo vs 18.3 mo – not statistically significant
- Major toxicities: nausea, stomatitis, alopecia, dry eye, low-rate ILD

FDA approved January 17, 2025

Bardia A, et al. *J Clin Oncol.* 2024;42:2281-2294.

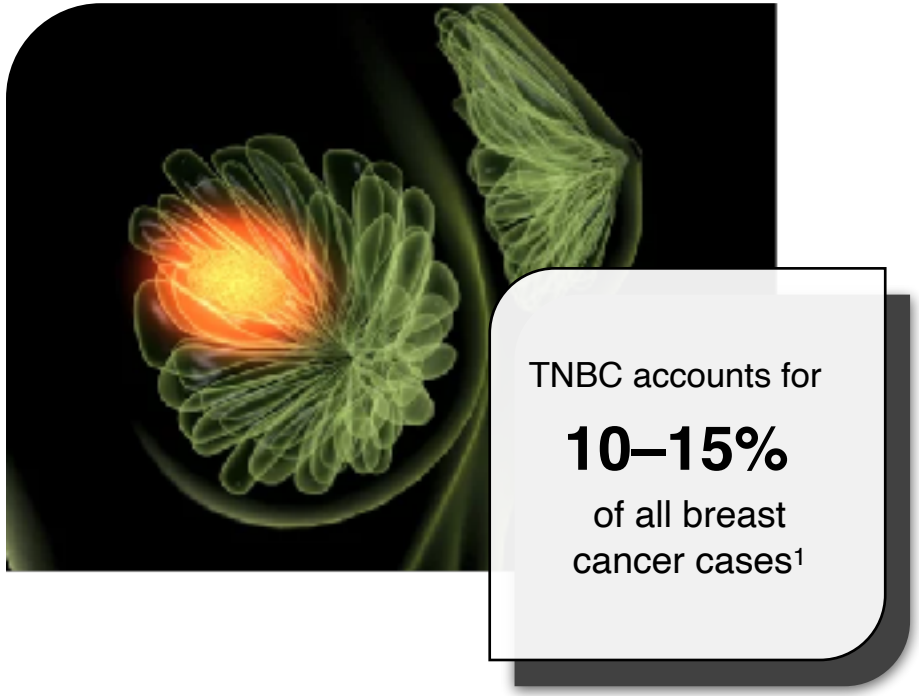
Roadmap: HR+, HER2– mBC



Source: Dr Laura Huppert, UCSF. 2025.

Triple-negative breast cancer (TNBC) is the most aggressive breast cancer subtype

TNBC is highly invasive, exhibiting high metastatic potential, early relapse and poor outcomes



More likely to occur in **premenopausal** women aged **40–50 years old**[1,2]

~46% of TNBC patients will have distant metastasis.[2] Median survival after metastasis is only **13.3 months**

Five-year mortality rate is **30%**[2]

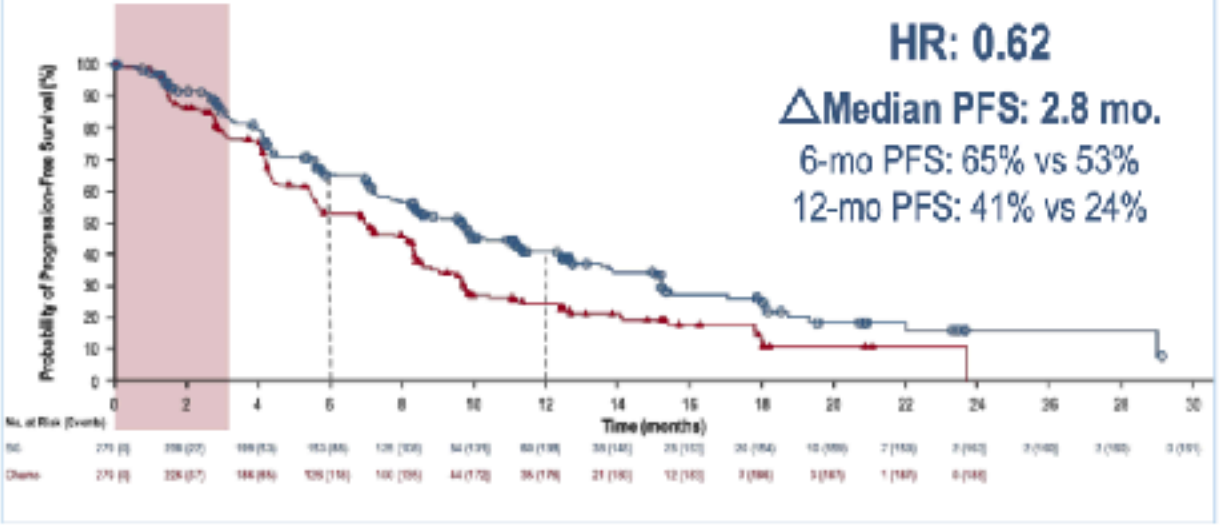
TNBC = triple-negative breast cancer.

1. Furlanetto J and Loibl S. *Breast Care* (Basel) 2020;15:217–226. 2. Schrodi S, et al. *Ann Oncol.* 2021;S0923-7534(21)04218-6. doi: 10.1016/j.annonc.2021.08.1988 [Online ahead of print]. 3. Villegas SL, et al. *Eur J Cancer* 2021;148:159–170.

TROP2 ADC IMPROVES PFS vs TPC in 1L mTNBC

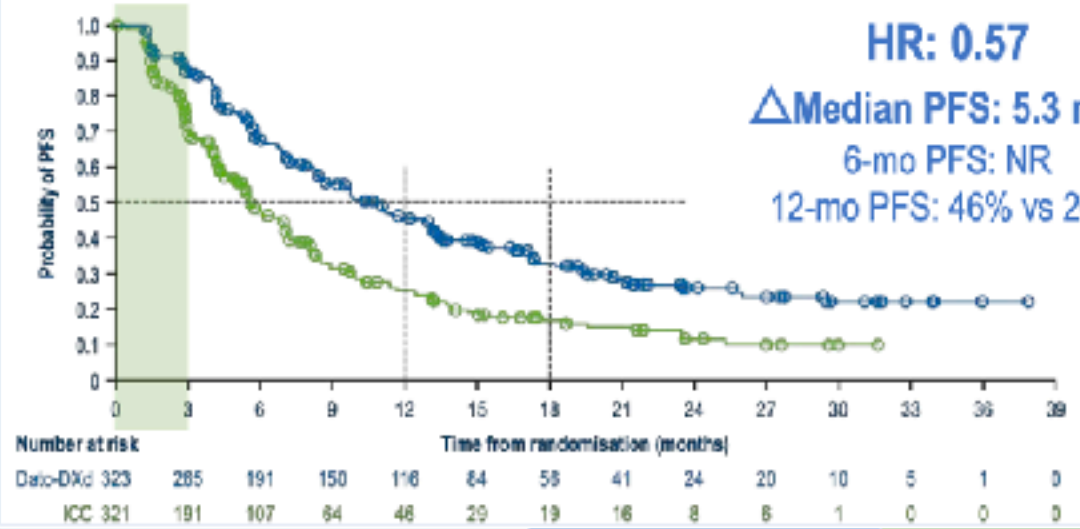
KN355
Median PFS (CPS<10)
TPC: 5.7 months

ASCENT-03



	SG	TPC
Median follow-up (range), mo	13.2 (<0.1-29.2)	
N PFS events (%)	349 (63)	
Median PFS (95% CI), mo	9.7 (8.1-11.1)	6.9 (5.6-8.2)
Stratified HR (95% CI)	0.62 (0.50-0.77), p <0.0001	

TROPION-Breast02



	Dato-DXd	ICC
Median follow-up (range), mo	27.5 (13.3-38.7)	
N PFS events (%)	408 (63)	
Median PFS* (95% CI), mo	10.8 (8.6-13.0)	5.6 (5.0-7.0)
Stratified HR (95% CI)	0.57 (0.47-0.69), p <0.0001	

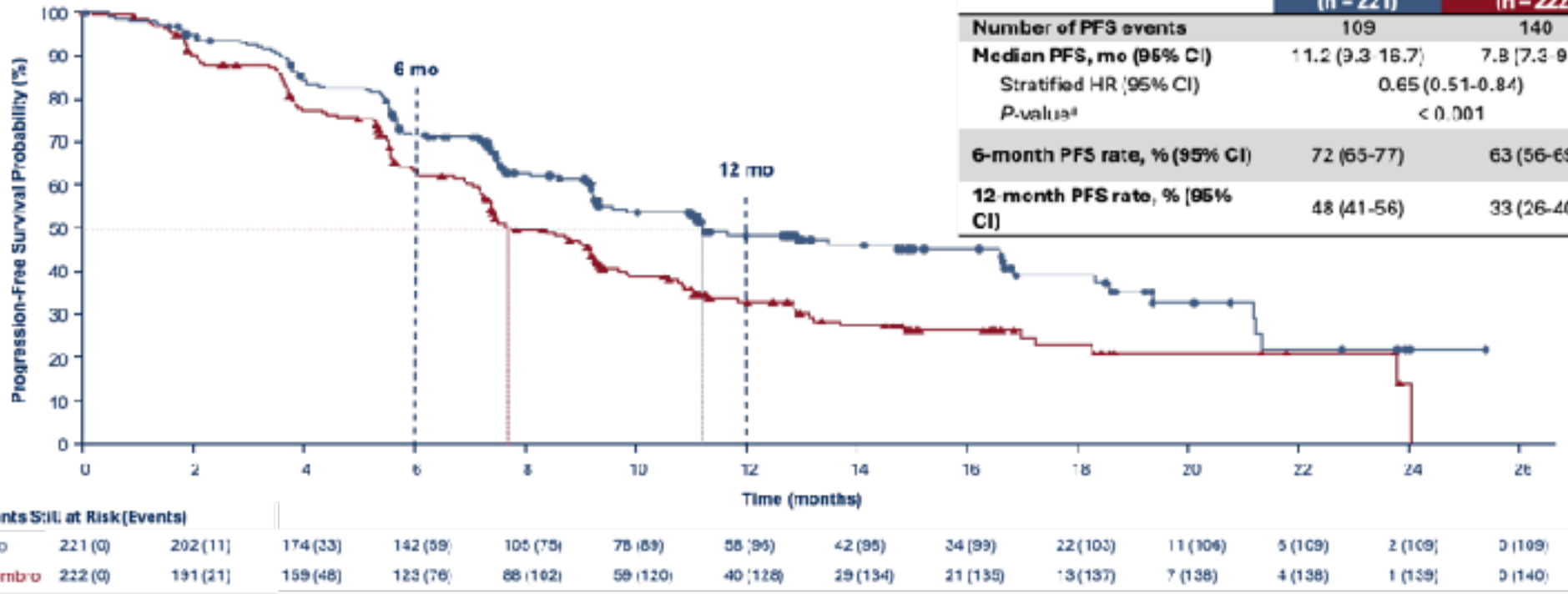
*Numbers shown in table are rounded: median PFS 10.84 with Dato-DXd; 5.55 with ICC; Δ 5.29 months

Ana C. Garrido-Castro, M.D.

The patient populations in the 2 trials were sufficiently different that the outcomes cannot be compared head-to-head.

ASCENT-04: SG+pembro vs. Chemo+pembro in PD-L1+ 1st-line Metastatic TNBC Progression-Free Survival by BICR

N=443



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of PFS events	109	140
Median PFS, mo (95% CI)	11.2 (9.3-16.7)	7.8 (7.3-9.3)
Stratified HR (95% CI)	0.65 (0.51-0.84)	
P-value[a]	< 0.001	
6-month PFS rate, % (95% CI)	72 (65-77)	63 (56-69)
12-month PFS rate, % (95% CI)	48 (41-56)	33 (26-40)

SG + pembro demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo + pembro by BICR analysis, with a 35% reduction in risk of disease progression or death

AISE were a composite of the known toxicities of each agent.

Results from ASCENT-04/KEYNOTE-D19 support the use of SG + pembro as a potential new standard of care for patients with previously untreated, PD-L1+, locally advanced unresectable or metastatic TNBC

Data cutoff date: March 3, 2025.
[a]Two-sided *P*-value from stratified log-rank test.
BICR, blinded independent central review; chemo, chemotherapy; HR, hazard ratio; PFS, progression-free survival; pembro, pembrolizumab; SG, sacituzumab govitecan.

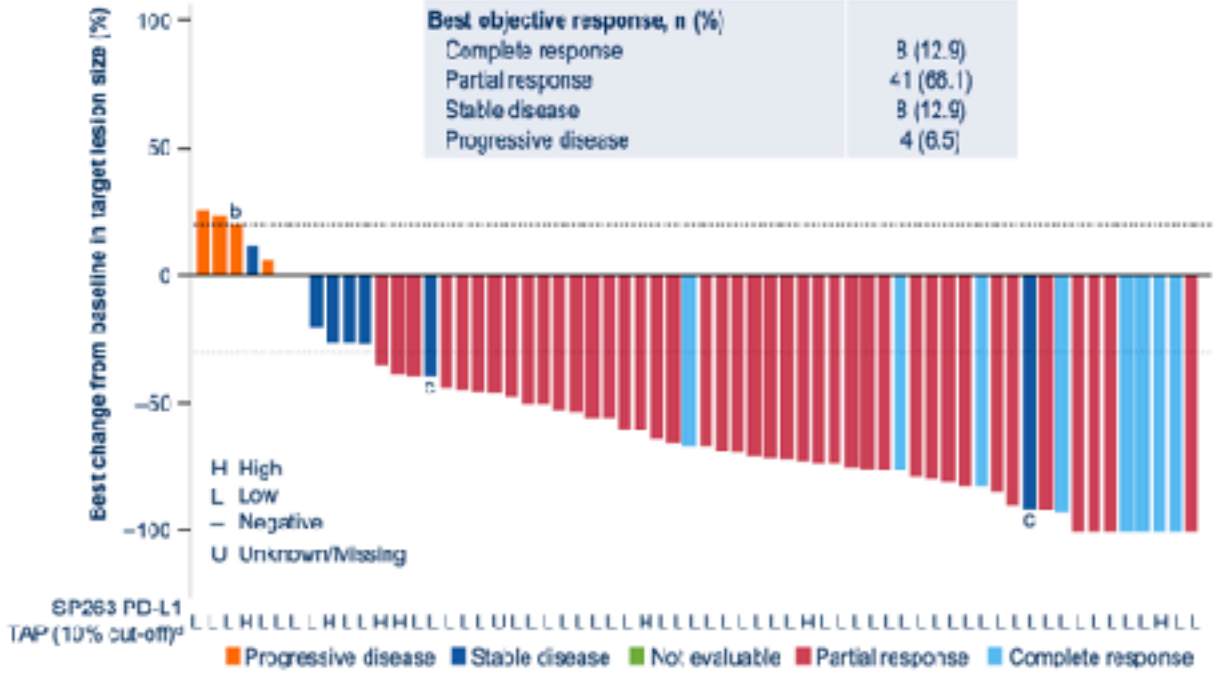
OS data were immature (26% of target event rate), HR=0.89.
SG was a subsequent Rx in 81% from the chemo+pembro control arm.

Tolaney SM et al. ASCO 2025;Abstract LBA109

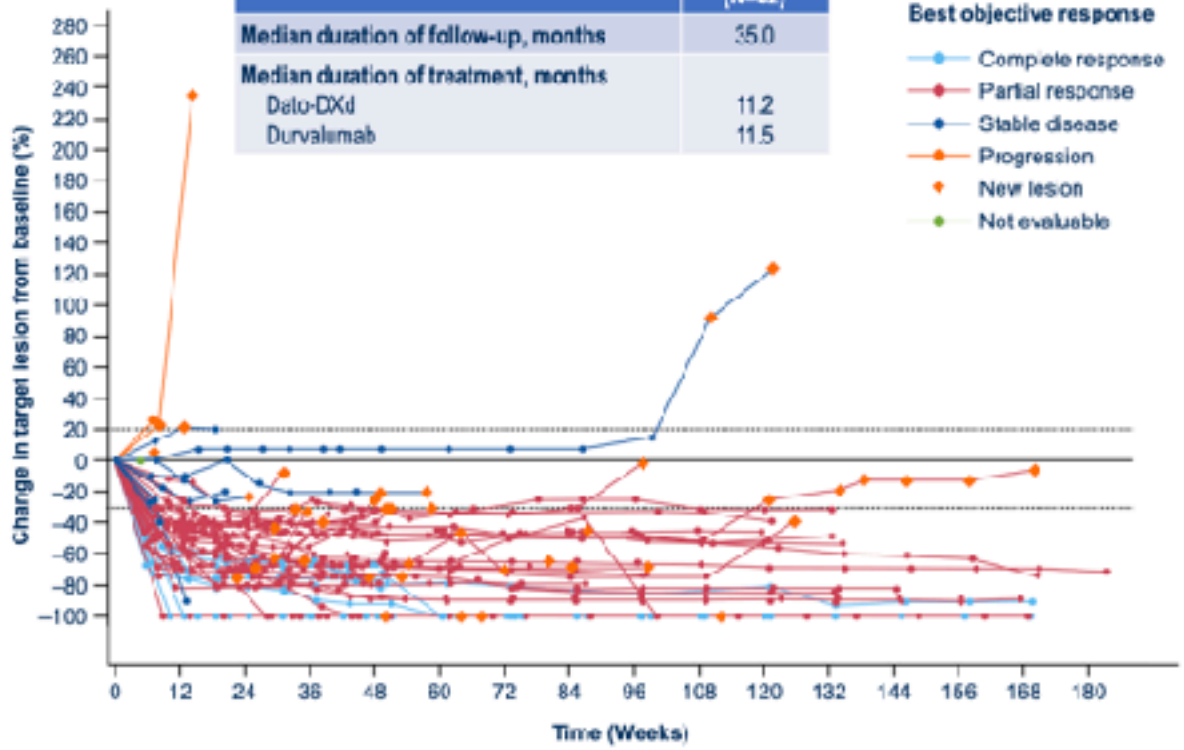
BEGONIA Study: DATO-DXd + Durvalumab
Overall Response and Duration of Response (Arm 7)

Overall, 11.3% patients had PD-L1 high tumours and 87.1% had PD-L1 low tumours

	Arm 7 (N=62)
Confirmed ORR,[a] % (95% CI)	49 (79.0) (66.6–88.3)
Best objective response, n (%)	
Complete response	8 (12.9)
Partial response	41 (66.1)
Stable disease	8 (12.9)
Progressive disease	4 (6.5)



	Arm 7 (N=62)
Median duration of follow-up, months	35.0
Median duration of treatment, months	
Dato-DXd	11.2
Durvalumab	11.5



Responses were observed in patients with PD-L1 high and PD-L1 low tumours

Median **DoR** was 17.6 months (95% CI 10.5–27.3)
Median **PFS** was 14.0 months (95% CI 11.0–21.1)

[a]Investigator-assessed, per RECIST v1.1. [b]Patient with imputed values. [c]Unconfirmed response. [d]PD-L1 status determined by central testing using the SP263 TAP 10% cut-off.

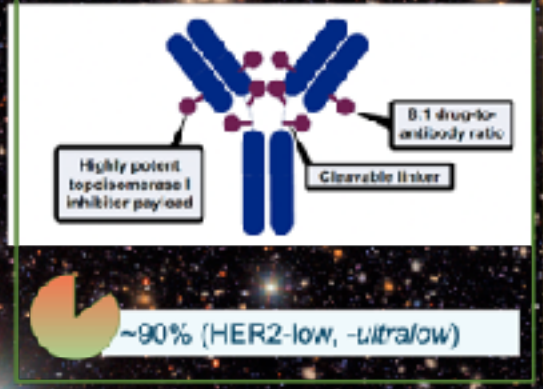
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ORR, objective response rate; PD-L1, programmed death ligand-1; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TAP, tumour area positivity.

ep·i·logue

/ˈepəˌlôg,ˈepəˌläg/

Noun, definition -- An epilogue is the final chapter at the end of a story that often serves to reveal the fates of the characters. Some epilogues may feature scenes only tangentially related to the subject of the story. They can be used to hint at a sequel or wrap up all the loose ends.

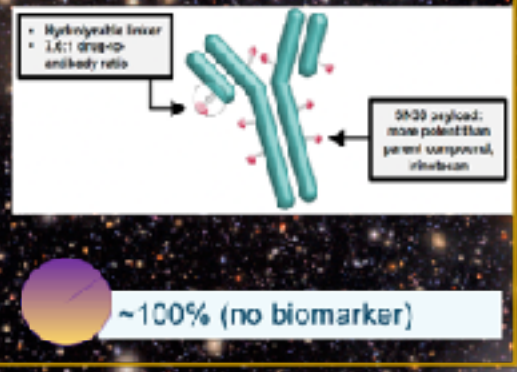
Trastuzumab deruxtecan (T-DXd)
Anti-HER2 ADC



Indicated for the treatment of:

- Adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting.
- HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting, or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

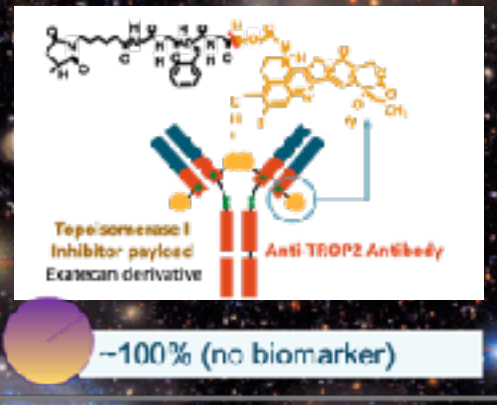
Sacituzumab Govitecan (SG)
Anti-TROP2 ADC



Indicated for the treatment of adult patients with:

- Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.
- Unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.

Datopotamab Deruxtecan (Dato-DXd)
Anti-TROP2 ADC



Indicated for the treatment of:

- Adult patients with unresectable or metastatic, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease.

Vera Ruben Observatory, Chile

BACK-UP SLIDES

NATALEE and monarchE Population Criteria

AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]	monarchE[4]
Stage IB	**T0N1mi/T1N1mi**	✗	Only if grade 3 or Ki-67 ≥20%
Stage IIA	**T0N1**	✓	Only if grade 3 or Ki-67 ≥20%
	T1N1	✓	Only if grade 3 or Ki-67 ≥20%
	T2N0	Only if grade 3 or grade 2 with Ki-67 ≥20% or high genomic risk[a]	✗
Stage IIB	**T2N1**	✓	Only if grade 3 or Ki-67 ≥20%
	T3N0	✓	✗
Stage IIIA	**T0N2**	✓	✓
	T1N2	✓	✓
	T2N2	✓	✓
	T3N1	✓	✓
	T3N2	✓	✓
Stage IIIB	**T4N0**	✓	✗
	T4N1	✓	Only if tumor size ≥5 cm or grade 3 or Ki-67 ≥20%
	T4N2	✓	✓
Stage IIIC	**Any TN3**	✓	✓
		NATALEE allowed[3]: • Any **N1**, **N2**, or **N3** • **N0: T2** (*G2 + high genomic risk or Ki-67 ≥20% or G3*), **T3**, or **T4**	monarchE allowed[4]: • Any **N2** or **N3** • **N1** only if G3 or tumor size ≥5 cm or Ki-67 ≥20%

N0 not allowed in monarchE

Table adapted from Slamon D et al. with permission.

AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; mi, micrometastasis; N, node; T, tumor; TN, tumor, node.

[a]High risk as determined by Oncotype DX/Prosigna/MammaPrint/EndoPredict.[2]

1. Amin MB et al. AJCC Cancer Staging Manual. 8th ed. Springer; 2017:587-636. 2. Slamon D et al. *Ther Adv Med Oncol*. 2023;15:17588359231178125. 3. Slamon D et al. *N Engl J Med*. 2024;390(12):1080-1091. 4. Harbeck N et al. *Ann Oncol*. 2021;32(12):1571-1581.