Applications for Community Oncology

SABCS 2025 Data Review

January 22, 2026

cornerstone specialty network™

2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
- ASCENT-07
- EMBER-3
- evERA
- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

CLINICAL QUESTION

ASCENT-03

Does sacituzumab govitecan (SG) benefit patients with untreated mTNBC unable to receive PD-L1 inhibitors when compared to single agent or combination chemotherapy?

(Sacituzumab govitecan vs chemo)

Updated safety data from SABCS

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KEY DATA

ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

Study Design: Open-label, phase III

- Previously untreated locally advanced, unresectable, or metastatic TNBC
- **Not candidates for PD-L1 inhibitors**
  - PD-L1-ve CPS <10
  - PD-L1+ve CPS ≥10 and previously treated with a PD-L1 agent in curative setting
  - Ineligible due to comorbidities
- **≥6 months since treatment in curative setting**
- Previously treated, stable CNS metastases allowed

N=558

Stratified by curative treatment-free interval (de novo vs recurrence within 6-12 mo vs recurrence after >12 mo), geographic region (US/Canada/W Europe vs RoW)

Sacituzumab govitecan
10 mg/kg IV
(days 1 and 8 of 21-day cycles)
(n=279)

→ *Standard of care*

Paclitaxel 90 mg/m² IV or **nab-Paclitaxel**
100 mg/m² IV Day 1, 8, and 15 of 28-day cycle or
Gemcitabine 1000 mg/m² + **Carboplatin**
AUC2 (days 1 and day 8 of 21-day cycles)
(n=279)

→ *Crossover to 2L SG permitted from chemotherapy arm upon progression*

Primary Endpoint: PFS by BICR

Secondary Endpoints: OS, ORR, DOR, TTR (time to response) by BICR, Safety,
PROs (QOL (EORTC QLQ-C30)
Exploratory: Additional QoL (EORTC QLQ-C30)

SABCS 2025

ESMO 2025. Abstr LBA20.
SABCS 2025. Abstract RF6-05.

KEY DATA

ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

Essentially all TNBC, PD-L1 negative

Primary Endpoint: PFS by BICR

Previously presented at ESMO 2025

Outcome	SG (n = 279)	CT (n = 279)
Median PFS, mo (95% CI)	**9.7** (8.1-11.1)	6.9 (5.6-8.2)
• Stratified HR (95% CI)	**0.62** (0.50-0.77)	
• P value	<.0001	
6-mo PFS, % (95% CI)	65 (59-71)	53 (47-59)
12-mo PFS, % (95% CI)	41 (34-47)	24 (19-30)

Data cutoff date: April 2, 2025

ESMO 2025. Abstr LBA20.

KEY DATA

ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

Patient-Reported Outcomes (EORTC QLQ-C30)

Key secondary end points	• **Change from baseline in physical functioning at week 25** • **Time to first deterioration in fatigue**
Exploratory end points	• **Change from baseline in at week 25 (excluding physical functioning)** • **Time to first deterioration (excluding fatigue)** • **Time to confirmed deterioration** • **Time to first improvement**

PRO Assessment Schedule for EORTC QLQ-30 (All Randomization Patients

	Completion Rate (% of eligible patients)	
	SG (n=279)	Chemo (n=279)
Baseline	98	98
Week 13	86	88
Week 25	85	82

Baseline Scores

- Domain scores were similar between treatment groups and largely comparable to the general population norms
- Several domains tended to have worse scores (e.g. physical functioning, role functioning, pain)

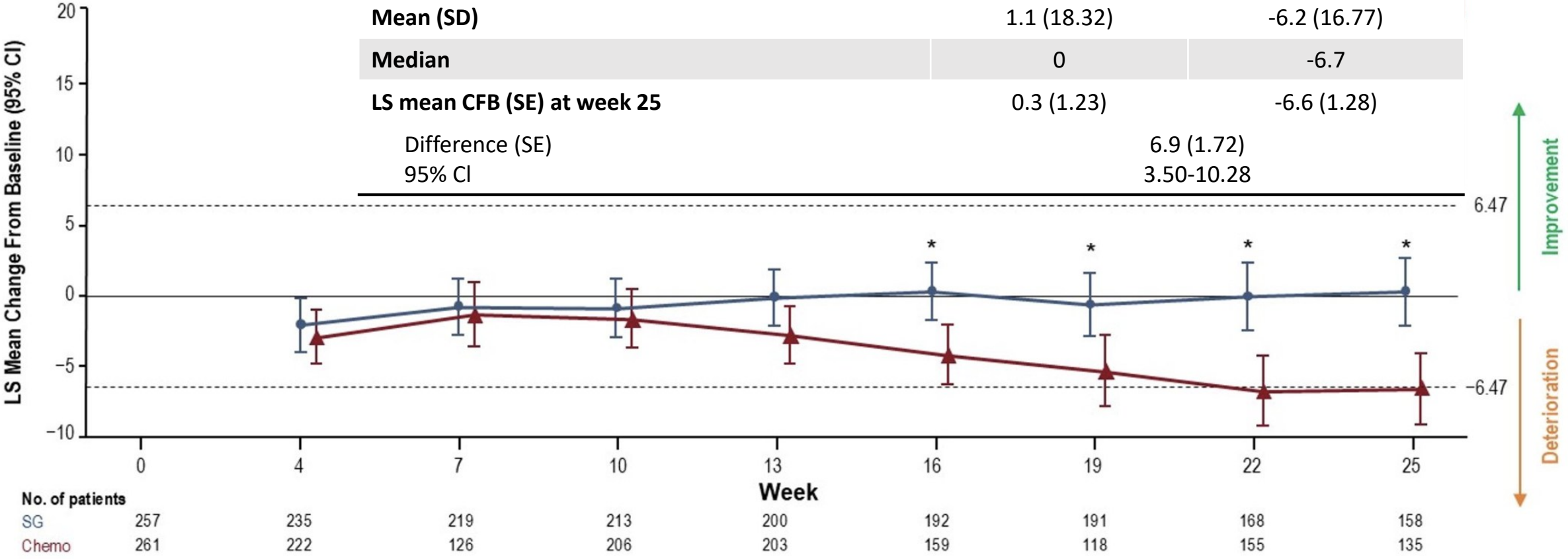
SABCS 2025. Abstract PRF6-05.

KEY DATA

ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

Mean Change from Baseline to Week 25 in Physical Functioning

	SG (n=279)	Chemo (n=279)
Number of patients with PRO assessment at week 25	158	135
Mean (SD)	1.1 (18.32)	-6.2 (16.77)
Median	0	-6.7
LS mean CFB (SE) at week 25	0.3 (1.23)	-6.6 (1.28)
Difference (SE)	6.9 (1.72)	
95% CI	3.50-10.28	



SABCS 2025. Abstract RF6-05.

KEY DATA

ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

Essentially all TNBC, PD-L1 negative

Safety Analysis: Exposure-Adjusted Incidence Rates

TEAE	Sacituzumab Govitecan (n = 275)		Chemotherapy (n = 276)		EAIR Difference (95% CI)
	N (%)	EAIR (95%CI)	N (%)	EAIR (95%CI)	
Grade ≥ 3	181 (66%)	1.85 (1.59-2.14)	171 (62)	2.02 (1.73-2.35)	-0.18 (-0.59 to 0.23)
Serious	71 (26)	0.40 (0.31-0.51)	67 (24)	0.49 (0.38-0.63)	-0.09 (-0.25 to 0.06)
Led to any dose interruption	181 (66)	2.05 (1.76 – 2.37)	171 (62)	2.14 (1.83-2.48)	-0.09 (-0.54 to 0.36)
Led to dose reduction	101 (37)	0.68 (0.55 – 0.82)	124 (45)	1.15 (0.96 – 1.37)	-0.48 (-0.73 to -0.23)
Led to treatment discontinuation	10 (4)	0.05 (0.02 – 0.09)	33 (12)	0.22 (0.15 -0.30)	-0.17 (-0.26 to -0.09)
Led to death	7 (3)	0.03 (0.01 -0.07)	1 (<1)	0.01 (0.00-0.06)	0.03 (-0.01 to 0.07)
Neutropenia	183 (67)	2.48 (2.13-2.87)	157 (57)	2.01 (1.71-2.35)	0.47 (-0.02 to 0.96)
Febrile Neutropenia	12 (4)	0.06 (0.03 -0.11)	3 (1)	0.02 (0.00-0.06)	0.04 (0.00 to 0.09)
Anemia	107 (39)	0.77 (0.63 – 0.93)	138 (50)	1.51 (1.27 – 1.78)	-0.74 (-1.05 to -0.45)
Thrombocytopenia	12 (4)	0.06 (0.03-0.11)	78 (28)	0.63 (0.50-0.78)	-0.57 (-0.73 to -0.43
Diarrhea	148 (54)	1.42 (1.20-1.67)	55 (20)	0.41 (0.31 – 0.54)	1.01 (0.76 to 1.28)
Fatigue	130 (47)	1.15 (0.96 – 1.37)	129 (47)	1.24 (1.03 – 1.47)	-0.08 (-0.38 to 0.21)
Peripheral Neuropathy	12 (4)	0.06 (0.03 – 0.11)	35 (13)	0.25 (0.17 – 0.34)	-0.18 (0.28 to -0.10)

SABCS 2025. Abstract RF6-05.

KEY DATA

ASCENT-03: 1st-line Sacituzumab govitecan (SG) vs chemo in untreated mTNBC with tumors lacking PD-L1 expression *or* previously treated with anti-PD-L1 in early-stage setting

Essentially all TNBC, PD-L1 negative

Safety Analysis: Time to Onset, Duration of Neutropenia and Diarrhea

	Sacituzumab Govitecan (n = 275)				Chemotherapy (n = 276)			
	Any grade		Grade ≥ 3		Any grade		Grade ≥ 3	
	n	Days (Range)	n	Days (Range)	n	Days (Range)	n	Days (Range)
Median time to onset								
• **Neutropenia**	187	22 (6-274)	124	22 (7-720)	158	22 (6-406)	113	29 (7-295)
• **Diarrhea**	148	13 (1-427)	25	67 (6-356)	55	26 (1-296)	2	210 (110-310)
Median duration								
• **Neutropenia**	183	9 (2-49	122	8 (1-36)	155	14 (1-179)	112	8 (1-25)
• **Diarrhea**	139	6 (1-273)	24	6 (1-18)	48	6 (1-370)	2	1 (1-1)

- Rates of neutropenia and diarrhea associated with sacituzumab govitecan were greatest during the initial phases of therapy
- In sacituzumab govitecan and chemotherapy arms, most diarrhea events were grade 1/2 (45% and 19%, respectively)
- Antidiarrheal medications used in 137 patients (50%) receiving SG and 35 (13%) receiving chemotherapy
  - Loperamide was the most frequently used agent in both groups (90% in sacituzumab govitecan arm and 77% in chemotherapy arm); 20% of participants in both groups required >1 antidiarrheal agent
  - In sacituzumab govitecan arm, diarrhea prompted dose reduction in 15 patients (5%) and treatment discontinuation in 1 (<1%)
  - In chemotherapy arm, diarrhea led to dose reduction in 3 patients (1%) and did not result in any treatment discontinuations

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Essentially all TNBC, PD-L1 negative

Safety Analysis: Management of Neutropenia

Neutropenia Management, n (%)	Sacituzumab Govitecan (n=275)		Chemotherapy (n=276)	
Primary G-CSF Prophylaxis	Yes (n=54)	No (n=221)	Yes (n=28)	No (n= 248)
• **Any grade**	28 (52)	159 (72)	21 (75)	137 (55)
• **Grade ≥ 3**	15 (28)	109 (49)	14 (50)	99 (40)
Secondary G-CSF Prophylaxis*	Yes (n=81)	No (n = 75)	Yes (n= 51)	No (n=85)
• **Any grade**	46 (57)	52 (69)	38 (75)	50 (59)
• **Grade ≥ 3**	30 (37)	20 (27)	29 (57)	39 (46)

* Excludes participants who received G-CSF prophylaxis

- Neutropenia resulted in dose reductions for 54 patients (20%) in both treatment arms and treatment discontinuation in 1 (<1%) receiving sacituzumab govitecan and 3 (1%) receiving chemotherapy

SUMMARY

ASCENT-03

- SG demonstrated improved PFS and QoL vs chemotherapy in patients with previously untreated advanced TNBC ineligible for PD-1/PD-L1 inhibitors
  - Physical functioning were maintained in the SG group and deteriorated in the chemo group
  - Time to deterioration in fatigue were similar between treatment groups
  - Additional QoL elements favored SG
  - GI symptom burden worse with SG

IMPACT

Sacituzumab govitecan is a potential new 1L treatment option for patients with PD-L1 negative, IO-ineligible TNBC addressing an unmet need for patients who cannot receive immunotherapy

Not yet FDA approved in this setting

cornerstone specialty network™

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HER2Climb-05

- *Polling Question*

TROPION-Breast02

Does datopotamab deruxtecan (Dato-DXd) benefit patients with untreated mTNBC unable to receive PD-L1 inhibitors vs single agent chemotherapy?

Dato-DXd vs chemo

Additional safety update

KEY DATA

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

Study Design: Open-label, randomized phase III study

Stratified by Geographic region (US/Canada/Europe vs other geographic regions); PD-L1 status (high [CPS ≥10] vs low [CPS <10]); DFI history (de novo vs prior DFI 0–12 months vs prior DFI >12 months)

- Recurrent inoperable or metastatic TNBC*
- No prior chemotherapy or targeted therapy in locally recurrent inoperable or metastatic setting
- Unsuitable for immunotherapy†
- ECOG PS ≤1
- No minimum disease-free interval (DFI‡)

N=558

Dato-DXd
6 mg/kg IV Day 1 q3w
(n=323)

Investigator's choice of chemotherapy (ICC)
Paclitaxel, nab-paclitaxel, capecitabine, eribulin mesylate/eribulin, carboplatin
(n=321)

Following progression or discontinuation of study treatment, patients could receive subsequent therapies, including approved ADCs or chemotherapy, at the investigator's discretion

*According to ASCO/CAP criteria.
†Including patients with PD-L1-low tumors, or patients with PD-L1-high tumors with (a) disease relapse after prior PD-(L)1 inhibitor therapy for early-stage breast cancer (b) comorbidities precluding PD-(L)1 inhibitor therapy, or (c) no regulatory access to PD-(L)1 inhibitor therapy
‡**DFI defined as time between date of completion of treatment with curative intent and date of first documented local or distant disease recurrence.**

Primary Endpoint: Dual primary: OS and PFS by BICR per RECIST v1.1

Secondary Endpoints: PFS (investigator-assessed), ORR, DoR, **Safety** — **SABCS 2025**

ICC: If no prior taxane, or prior taxane in the (neo)adjuvant setting and DFI >12 months: paclitaxel 80 mg/m^2 IV, D1, 8, 15, Q3W, or nab-paclitaxel 100mg/m^2 IV, D1, 8, 15, Q4W; if prior taxane and DFI 0–12 months: capecitabine 1000 or 1250 mg/m^2 po bid, D1–14, q3w (dose determined by standard institutional practice), or eribulin mesylate 1.4 mg/m^2/ eribulin 1.23 mg/m^2 IV, Day 1, 8, q3w, or carboplatin AUC6 IV, D1, q3w.

In the Dato-DXd vs ICC arm, 65% vs 72% of patients received any subsequent therapy in any treatment line; 14% vs 30% received a subsequent ADC (sacituzumab govitecan, sacituzumab tirumotecan, trastuzumab deruxtecan).

ESMO 2025. Abstr LBA21.

KEY DATA

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

Previously present at ESMO 2025

90% TNBC, PD-L1 negative

Dual Primary Endpoint: PFS by BICR

	Dato-DXd	Investigator's Choice of CT
Median PFS	**10.8 mo** (8.6 – 13.0)	**5.6 mo** (5.0 – 7.0)
HR (95% CI)	**0.57 (0.47 – 0.69)**	
P-value	**< 0.0001**	
12-mo rate	**45.6%**	**25.6%**
18-mo rate	**32.7%**	**16.8%**

PFS benefit with Dato-DXd observed across all subgroups

Dual Primary Endpoint: OS by BICR

	Dato-DXd	Investigator's Choice of CT
Median OS	**23.7 mo** (19.8 – 25.6)	**18.7 mo** (16.0 – 21.8)
HR (95% CI)	**0.79 (0.64 – 0.98)**	
P-value	**0.0291**	
12-mo rate	**75.2%**	**67.8%**
18-mo rate	**61.2%**	**51.3%**

OS benefit with Dato-DXd observed across most subgroups; exception geographical region cohort US, Canada, Europe
Ad hoc analysis of the US Cohort showed comparable OS HR to the ITT population

ESMO 2025. Abstr LBA21.

KEY DATA

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

90% TNBC, PD-L1 negative

Previously present at ESMO 2025

Safety

TRAE, n (%)	Dato-DXd (n = 319)	Investigators Choice of CT (n = 309)
All grades	296 (93)	257 (83)
• Grade ≥3	**105 (33)**	**89 (29)**
Total treatment duration, mo (range)	**8.5** (0.7 - 38.0)	**4.1** (0.1-32.0)
Total exposure >12 mo, %	**35.1**	9.4

AE of special interest, n (%)	Dato-DXd (n = 319)			Investigator's Choice of CT (n = 309)		
	Grade 1	Grade 2	Grade ≥3	Grade 1	Grade 2	Grade ≥ 3
Oral mucositis/ stomatitis	78 (24)	87 (27)	27 (8)	22 (7)	8 (3)	0
• Stomatitis	72 (23)	83 (26)	27 (8)	19 (6)	8 (3)	0
Ocular surface events	76 (24)	50 (16)	23 (7)	9 (3)	5 (2)	1 (<1)
• Dry eye	51 (16)	21 (7)	4 (1)	6 (2)	3 (1)	0
• Keratitis	21 (7)	14 (4)	7 (2)	1 (<1)	0	0
• Conjunctivitis	7 (2)	13 (4)	1 (<1)	0	0	0
Adjudicated drug-related ILD/pneumonitis	1 (<1)	7 (2)	1 (<1)	1 (<1)	1 (<1)	0

Treatment-related oral mucositis/stomatitis:

- In the Dato-DXd arm, events led to dose interruption, reduction, and discontinuation in 11 (3%), 36 (11%), and 0 patients, respectively
- Grade ≥2 events resolved to grade ≤1 in 103/114 patients (90%) at data cutoff

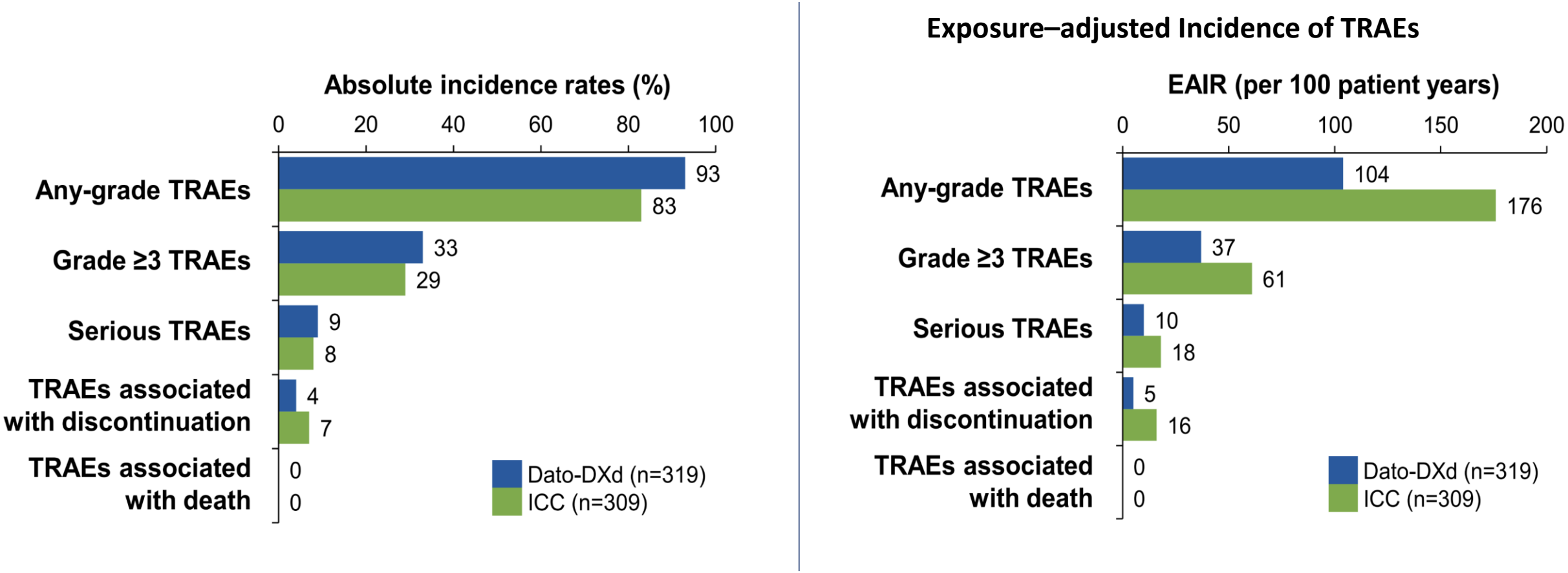
Treatment-related ocular surface events:

- In the Dato-DXd arm, events led to dose interruption, reduction, and discontinuation in 18 (6%), 14 (4%), and 3 (<1%) patients, respectively
- Grade ≥2 events resolved to grade ≤1 in 49/73 patients (67%) at data cutoff

ESMO 2025. Abstr LBA21.

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

Safety Analysis: Treatment-Related Adverse Events



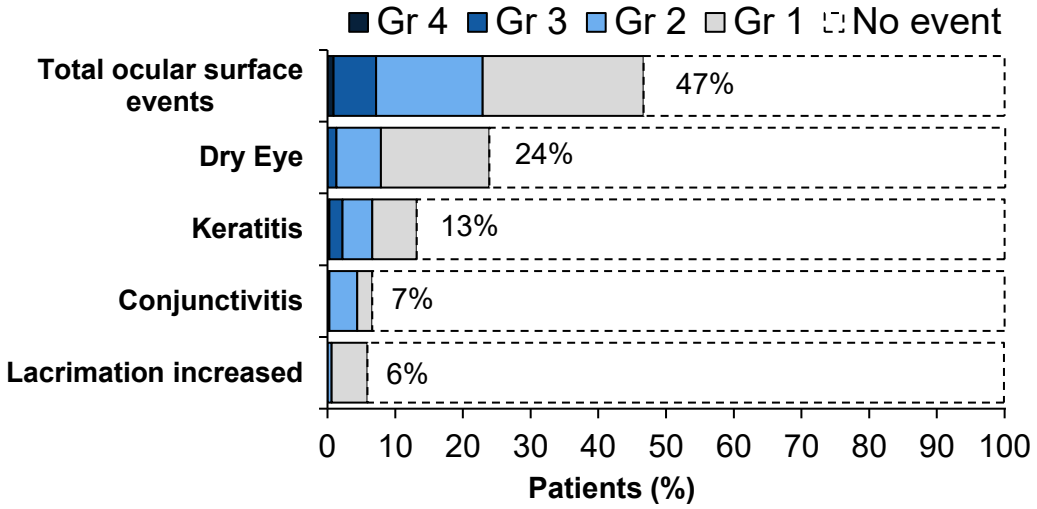
Exposure adjusted incidence rates (EAIRs) of ages derive from post hoc analysis (per 100 patient-year); based on number of patients with AEs by end of treatment and across all patients (x100).

SABCS 2025. Abstr PS5-03-05.

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

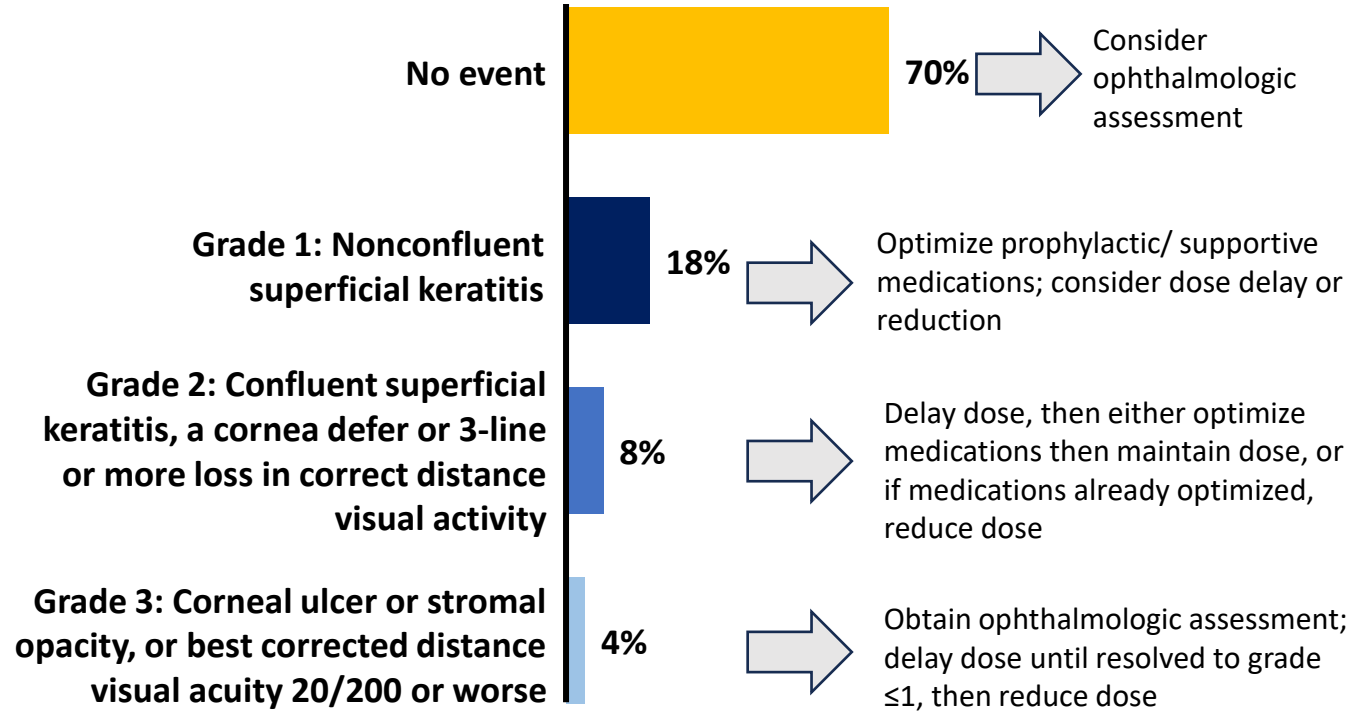
Safety Analysis: Adverse Events of Special Interest

Treatment-related ocular surface events* by CTCAE grade



Treatment-Related Ocular Events	Dato-DXd (n = 319)
Median time to onset, days	77.5
Median time to resolution†, days	64
Events leading to treatment discontinuation, n (%)	3 (0.9%)

Treatment-related ocular surface events* by corneal toxicity severity grade



*Comprising the preferred terms of acquired corneal dystrophy, blepharitis, conjunctivitis, corneal disorder, corneal epithelium defect, corneal erosion, corneal exfoliation, corneal lesion, corneal toxicity, dellen, dry eye, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, meibomian gland dysfunction, photophobia, punctate keratitis, ulcerative keratitis, vision blurred, visual acuity reduced, visual impairment, and xerophthalmia. †Resolution of events may only have been captured at a scheduled visit, which took place every 3 weeks for patients in the Dato-DXd arm.

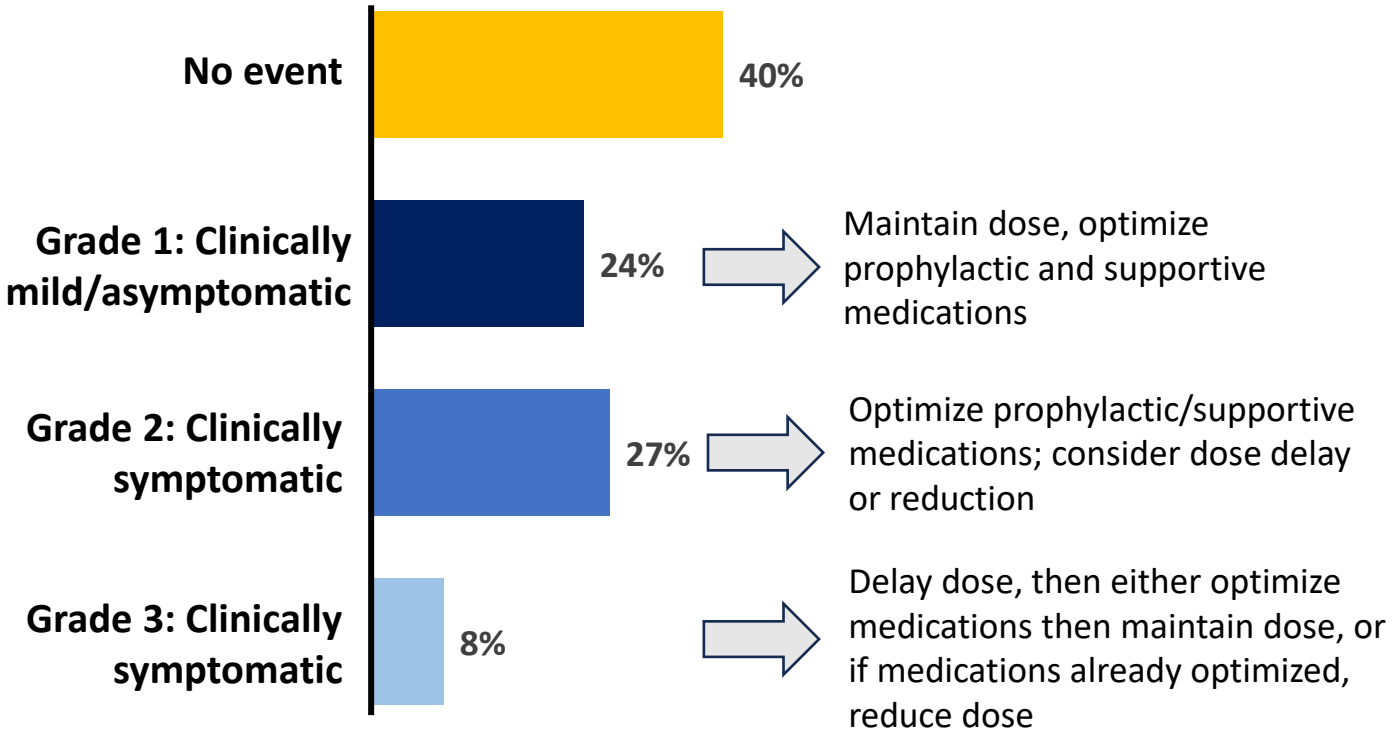
SABCS 2025. Abstr PS5-03-05.

KEY DATA

TROPION-Breast02: 1st-line Dato-DXd vs chemo in untreated mTNBC and unsuitable for anti-PD-L1

Safety Analysis: Adverse Events of Special interest

Treatment-related oral mucositis/ stomatitis* by CTCAE grade



Treatment-Related AESIs Oral mucositis/stomatitis	**Dato-DXd (n = 319)**
Median time to onset, days	26
Median time to resolution†, days	40.5
Events leading to treatment discontinuation, n (%)	0

Grade ≥2 events resolved to grade ≤1 at data cutoff: **103/114 (90%)**

Data cutoff is a snapshot in time; 45 patients remained on Dato-DXd treatment at the time of data cut off

*Comprising the preferred terms of aphthous ulcer, mouth ulceration, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis.
†Resolution of events may only have been captured at a scheduled visit, which took place every 3 weeks for patients in the Dato-DXd arm.

SUMMARY

TROPION-Breast02

- Exposure-adjusted incidence rates of TRAEs were lower with Dato-DXd vs investigator's choice CT in patients receiving 1L treatment for locally recurrent inoperable or metastatic TNBC unsuitable for immunotherapy
  - Most patients were on T-DXd therapy 2x as long as in the investigator's choice CT arm
  - Absolute incidence rates of grade ≥3 and serious TRAEs were similar, but rates of discontinuation were lower with Dato-DXd
- Most treatment-related AEs of special interest were grade 1/2 and seldom led to discontinuation of treatment; most grade ≥2 events resolved to grade ≤1 by data cutoff

IMPACT

Datopotomab deruxtecan is a potential new 1L treatment option for patients with PD-L1 negative metastatic TNBC

Not yet FDA approved in this setting

cornerstone specialty network™

Traina. SABCS 2025. Abstr PS5-03-05.

Cross-study comparisons

	TROPION-Breast02[1] (N=644) Datopotamab deruxtecan	ASCENT-03[2] (N=558) Sacituzumab govitecan
mPFS (months)	**10.8 vs 5.6 (HR=0.57)**	**9.7 vs 6.9 (HR=0.62)**
mOS (months)	**23.7 vs 18.7** (HR=0.79)	**21.5 vs 20.2** (HR = 0.98, 37% maturity)
ORR	**62.5% vs 29.3%**	**48.4% vs 45.5%**
mDOR (months)	12.3 vs 7.1	12.2 vs 7.2
mDOT (months)	8.5 vs 4.1	8.3 vs taxane (6.3), gem/carbo (5.8)
Subsequent Treatment Rate	65% vs 72%	45 vs 64%
Subsequent ADC use	ITT: 14% vs 30% Subsequent SG, T-DXd, or Sac-TMT	Chemo arm ITT: 53% subsequent SG
Discontinuation rate	**4% vs 7%**	**4% vs 12%**
Dose reduction	**27% vs 18%**	**37% vs 45%**
Dose interruption	**24% vs 19%**	**66% vs 62%**
Serious TEAEs	**9% vs 8%**	**17% vs 13%**
Grade ≥3 TRAEs	**33% vs 29%**	**66% vs 62%**
Treatment Related Deaths	**0**	**6 (2%) vs 1 (<1%) due to infection**

Carbo, carboplatin; gem, gemcitabine; Sac-TMT, Sacituzumab tirumotecan; T-DXd, trastuzumab deruxtecan.

1. Dent R, et al. Presented at: European Society for Medical Oncology (ESMO) Congress; October 17-21, 2025; Berlin, Germany. LBA21. **2.** Cortes J, et al. Presented at: European Society for Medical Oncology (ESMO) Congress; October 17-21, 2025; Berlin, Germany. LBA20

Polling question

Considering similar efficacy and the presented updated safety and PRO data in ASCENT03 and TROPION-Breast02, what will be your first-line treatment choice for PD-L1–negative, IO-ineligible TNBC if both agents are approved?

1. More likely to prescribe SG based on the ASCENT03 trial
2. More likely to prescribe Dato-DXd based on the TROPION-Breast02 trial
3. Unsure

Polling question

Does the safety data:

1. Allow me to feel more comfortable using SG
2. Allow me to feel more comfortable using Dato
3. Does not influence me either way
4. Unsure

Polling question

What is the biggest factor(s) that would influence my choice for either use of SG / Dato-DXd in PD1 neg, IO ineligible patient population? (pick the top two)

1. Payor / pathway mandates
2. Comfortable using SG in other disease states or lines of therapy
3. Comfortable using Dato-DXd in other disease states or lines of therapy
4. Efficacy
5. Safety
6. Rebates / NCR

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  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

Does Datopotamab Deruxtecan (Dato-DXd) benefit patients with HER2-Negative Metastatic Breast Cancer With Leptomeningeal Disease?

DATO-Base Cohort C

KEY DATA

DATO-Base: Dato-DXd, HER2-ve mBC and leptomeningeal disease

Study Design: Multicenter, multicohort, open-label phase II trial

Stratified by Geographic region (US/Canada/Europe vs other geographic regions); PD-L1 status (high [CPS ≥10] vs low [CPS <10]); DFI history (de novo vs prior DFI 0–12 months vs prior DFI >12 months)

- Cohort C (exploratory):
- Adults with HER2-negative, ER+/- MBC with leptomeningeal metastases (LMD)
- Prior ADCs and systemic therapy for LMD permitted
- ECOG 0-2

(N = 10)

→ **Dato-DXd** 6 mg/kg IV Q3W* → *Until PD, unacceptable toxicity, or withdrawal*

- Chest, abdomen, and pelvis CT at baseline and Q6W for first 24 wk, then Q9W
- Brain MRI at baseline and Q6W for first 24 wk, then Q9W
- cfDNA at baseline, C2D1, and when progression or off-protocol therapy occurs
- Optional biopsy of extracranial disease at baseline and progression.
- CSF collected at baseline, C2D2, and when progression or off-protocol therapy occurs (mandatory for Cohort C; optional for Cohort A/B)

Other cohorts with active CNS metastases:
Cohort A: ER+/HER2-negative MBC; ≥1 prior line of ET
Cohort B: metastatic TNBC; no prior tx needed

Exploratory endpoints: OS, radiographic/clinical response (Leptomeningeal Assessment in Neuro-Oncology [LANO] criteria), intracranial PFS, safety, neurologic function and biomarker analyses

SABCS 2025. Abstr PS1-09-02

KEY DATA

DATO-Base: Dato-DXd, HER2-ve mBC and leptomeningeal disease

Baseline Characteristics

Characteristic, n (%)	Dato-DXd (N = 10)
Age at enrollment, median yr (range)	48.9 (39.8-76.3)
Female	10 (100)
Neuro symptoms at baseline	
• Yes	7 (70)
• No	2 (20)
• Missing	1 (10)
ER status	
• Positive (≥10%)	7 (70)
• Low	1 (10)
• Negative	2 (20)
HER2 status	
• Negative	9 (90)
• Unknown	1 (10)
Extracranial disease at time of LMD diagnosis	
• Yes	9 (90)
• No	1 (10)

Characteristic, n %	Dato-DXd (N = 10)
MRI evidence of LM	
• Brain and spine	3 (30)
• Brain only	4 (40)
• Spine only	3 (30)
Prior local therapy for CNS disease	
• No prior treatment	2 (20)
• SRS/SRT + surgery	2 (20)
• Surgery	3 (30)
• WBRT	3 (30)
Prior lines of cytotoxic treatment, median (range)	2.5 (0-6.0)
Prior lines of ADC, median (range)	1.0 (0-2.0)

SABCS 2025. Abstr PS1-09-02.

DATO-Base: Dato-DXd, HER2-ve mBC and leptomeningeal disease

Efficacy: ORR, Intracranial-PFS, and OS

Median follow-up: 8.1 months

	Dato-DXd (N = 10)	ADC Naïve (n = 3)	ADC Pretreated (n = 7)
ORR by LANO criteria, n (%)	3 (30.0)	-	-
• CR	1 (10.0)	-	-
• PR	2 (20.0)	-	-
• SD	5 (50.0)	-	-
• Unknown	1 (10.0)	-	-
• Not evaluable	1 (10.0)	-	-
Median intracranial PFS, mo (95% CI)	4.1 (0.7-NR)	5.9	1.4
Median OS, mo (95% CI)	4.7 (0.7-NR)	13.3	3.7

- Of 8 evaluable patients, n = 8 had HS-TROP2-high disease and n = 4 had HS-HER2-high disease

SABCS 2025. Abstr PS1-09-02.

DATO-Base: Dato-DXd, HER2-ve mBC and leptomeningeal disease

Safety

TEAE in ≥20%, n (%)	Dato-DXd (N = 10)	
	All Grades	Grade ≥3
Fatigue	5 (50)	2 (20)
Oral mucositis	4 (40)	2 (20)
Nausea	4 (40)	2 (20)
Vomiting	3 (30)	2 (20)
Headache	3 (30)	2 (20)
Anemia	3 (30)	0 (0)
Thrush	3 (30)	0 (0)
Dyspnea	2 (20)	1 (10)
Hydrocephalus	2 (20)	2 (20)
Seizure	2 (20)	1 (10)
Cough	2 (20)	1 (10)
Thromboembolic event	2 (20)	1 (10)
Decreased neutrophil count	2 (20)	0 (0)

- Serious AEs: n = 4 (40%) with n = 2 (20%) considered treatment related
- No reported ILD nor grade 5 TRAEs
- 7 patients with neurologic symptoms at baseline
  - n = 5 reported improvement in at least 1 neurologic symptom
  - n = 1 patient stable
  - n = 1 one patient missing for follow-up NANO assessment

SABCS 2025. Abstr PS1-09-02.

SUMMARY

DATO-base

- Dato-DXd shows encouraging preliminary intracranial efficacy in HER2-negative MBC and LMD, with signals of greater benefit in ADC-naïve patients
  - ORR by LANO criteria was 30%, with responses observed in both ADC-naïve and ADC-pretreated patients
  - mOS was 4.7 months in the overall population, with longer survival observed in ADC-naïve patients (13.3 months) compared with ADC-pretreated patients (3.7 months)
  - IC-PFS was 4.1 months overall, with numerically longer disease control in ADC-naïve patients (5.9 months) versus ADC-pretreated patients (1.4 months)

IMPACT

Dato-DXd demonstrates early intracranial activity in HER2-negative metastatic breast cancer with leptomeningeal disease

Very small numbers…

cornerstone specialty network™

2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
- ASCENT-07
- EMBER-3
- evERA
- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

ASCENT-04

Does the combination of Pembrolizumab With Sacituzumab Govitecan benefit patients with Previously Untreated PD-L1+ Metastatic TNBC?

ASCENT-04: Updated Safety Analysis

KEY DATA

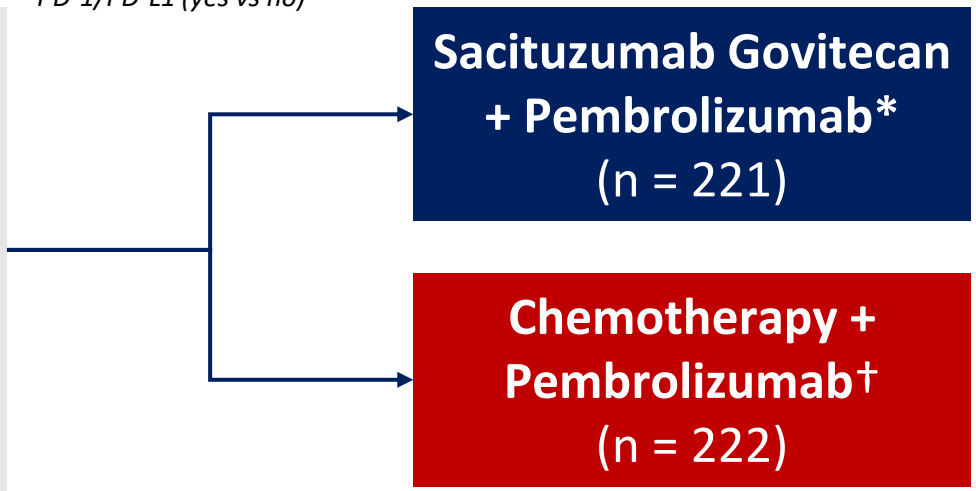
ASCENT-04: Sacituzumab Govitecan + Pembrolizumab in 1L setting for patient with PD-L1–Positive Advanced TNBC

Study Design: Global, multicenter, randomized, phase III trial

- Previously untreated, locally advanced unresectable or metastatic TNBC
- PD-L1 positive (CPS ≥10 using 22C3 assay)
- ≥6 mo since curative treatment (prior anti–PD-1/PD-L1 therapy allowed)

(N = 443)

Stratified by curative treatment-free interval (de novo vs recurrence within 6-12 mo vs recurrence in >12 mo); region (US/Canada/W Europe vs RoW); prior anti–PD-1/PD-L1 (yes vs no)



Treatment continued until BICR-verified disease progression or unacceptable toxicity

Crossover to 2L SG permitted upon progression
Note: (96 / 119 pts (81%) received SG monotherapy)

*SG 10 mg/kg IV D1, 8 + Pembro 200 mg D1 of 21-day cycle.
†Paclitaxel 90 mg/m^2 or nab-paclitaxel 100 mg/m^2 D1, 8, 15 of 28-day cycle or gemcitabine 1000 mg/m^2 + carboplatin AUC 2 D1, 8 of 21-day cycle; Pembro 200 mg D1 of 21-day cycle.

Primary endpoint: PFS by BICR
Secondary endpoints: OS and ORR by BICR (hierarchical testing), DoR by BICR, safety, QoL

ASCENT-04: Sacituzumab Govitecan + Pembrolizumab in 1L setting for patient with PD-L1–Positive Advanced TNBC

Primary Endpoint: PFS by BICR (ITT population) presented at ASCO 2025

	SG + Pembro (n = 221)	CT + Pembro (n = 222)
Events, n	109	140
Median PFS, mo (95% CI)	**11.2** (9.3-16.7)	**7.8** (7.3-9.3)
HR (CI)	**0.65** (95% CI: 0.51-0.84) *P* < .001	
6-mo PFS, % (95% CI)	72% (65-77)	63% (56-69)
12-mo PFS, % (95% CI)	48% (41-56)	33% (26-40)

Median follow-up: 14.0 mo (range: 0.1-28.6)

ASCENT-04: Sacituzumab Govitecan + Pembrolizumab in 1L setting for patient with PD-L1–Positive Advanced TNBC

Safety: TEAEs and Exposure-Adjusted Incidence Rates

TEAEs	SG + Pembro (n = 221)		Chemo + Pembro (n = 220)		EAIR Difference (95% CI)
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	
Grade ≥3	158 (71)	2.19 (1.86-2.56)	154 (70)	2.13 (1.81-2.49)	0.06 (-0.43, 0.55)
• Related to treatment	149 (67)	1.95 (1.65-2.29)	141 (64)	1.76 (1.48-2.07)	0.20 (-0.24, 0.64)
Serious	84 (38)	0.59 (0.47-0.73)	68 (31)	0.52 (0.41-0.66)	0.06 (-0.12, 0.25)
• Related to treatment	61 (28)	0.41 (0.31-0.52)	42 (19)	0.29 (0.21-0.40)	0.11 (-0.03, 0.25)
Led to any dose interruption	171 (77)	2.75 (2.35-3.19)	162 (74)	2.59 (2.21-3.02)	0.16 (-0.43, 0.75)
Led to any dose reduction	78 (35)	0.62 (0.49-0.78)	96 (44)	0.94 (0.76-1.14)	-0.31 (-0.56, -0.08)
Led to any treatment discontinuation	26 (12)	0.15 (0.10-0.21)	68 (31)	0.53 (0.41-0.67)	-0.38 (-0.53, -0.25)

SABCS 2025. Abstr PS5-02-28.

ASCENT-04: Sacituzumab Govitecan + Pembrolizumab in 1L setting for patient with PD-L1–Positive Advanced TNBC

TEAEs of Special Interest With Pembrolizumab

AEOSI Category, n (%)	SG + Pembro (n = 221)		Chemo + Pembro (n = 220)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hypothyroidism	16 (7)	1 (<1)	35 (16)	0
Colitis	13 (6)	4 (2)	3 (1)	1 (<1)
Infusion reactions	11 (5)	3 (1)	19 (9)	5 (2)
Hyperthyroidism	8 (4)	0	14 (6)	0
Pneumonitis	6 (3)	4 (2)	17 (8)	3 (1)

- Immune-mediated AEs reported in 30% of patients on the SG + pembro arm and 40% of patients on the chemo + pembro arm
- The most common TEAE of special interest in both groups was hypothyroidism
- Most cases of colitis (9/13) were non severe; 1 led to treatment discontinuation in SG + pembro arm; colitis was managed according to the PI for pembrolizumab

SABCS 2025. Abstr PS5-02-28.

ASCENT-04: Sacituzumab Govitecan + Pembrolizumab in 1L setting for patient with PD-L1–Positive Advanced TNBC

Time to onset and duration of neutropenia and diarrhea

	SG + Pembro (n = 221)				Chemo + Pembro (n = 220)			
	Any Grade		Grade ≥3		Any Grade		Grade ≥3	
	n	Days (Range)	n	Days (Range)	n	Days (Range)	n	Days (Range)
Median time to onset								
• Neutropenia	143	19 (6-624)	104	21 (7-624)	132	27 (7-366)	100	29 (7-378)
• Diarrhea	155	14 (1-462)	22	17 (1-715)	63	64 (1-496)	5	299 (202-513)
Median duration								
• Neutropenia	140	9 (2-72)	102	8 (1-22)	131	12 (2-61)	100	8 (1-21)
• Diarrhea	140	7 (1-709)	22	8 (1-98)	57	6 (1-117)	5	4 (1-11)

- Incidences of neutropenia and diarrhea (any grade and grade ≥3) with SG + pembro were highest early in the treatment course

SABCS 2025. Abstr PS5-02-28.

ASCENT-04: Sacituzumab Govitecan + Pembrolizumab in 1L setting for patient with PD-L1–Positive Advanced TNBC

Primary vs Secondary G-CSF Prophylaxis for management of neutropenia

Primary G-CSF Prophylaxis, n (%)	SG + Pembro (n = 221)		Chemo + Pembro (n = 220)	
	Yes (n = 43)	No (n = 178)	Yes (n = 20)	No (n = 200)
Any grade	20 (47)	123 (69)	13 (65)	119 (60)
Grade ≥3	15 (35)	89 (50)	10 (50)	90 (45)

Secondary G-CSF Prophylaxis, n (%)*	Yes (n = 75)	No (n = 47)	Yes (n = 37)	No (n = 81)
Any grade	55 (73)	30 (64)	20 (54)	49 (60)
Grade ≥3	34 (45)	16 (34)	11 (30)	36 (44)

*Includes patients eligible for secondary G-CSF and excludes patients who received primary G-CSF prophylaxis.

- In patients treated with SG + pembro, use of primary G-CSF was associated with less frequent and severe neutropenia

SABCS 2025. Abstr PS5-02-28.

SUMMARY

ASCENT-04

- Updated safety findings from ASCENT-04 show SG + pembrolizumab a consistent, expected profile in PD-L1–positive mTNBC

- After exposure adjustment (SG + pembro vs chemo + pembro):
  - Discontinuations: 12% vs 31%
  - Dose reductions: 35% vs 44%
  - Diarrhea/colitis: 70% vs 29% / 6% vs 1%
  - Immune-mediated AEs: 30% vs 40%

- Diarrhea occurred earlier with SG + pembro
- Use of primary G-CSF was associated with less frequent and severe neutropenia

IMPACT

Sacituzumab Govitecan + pembrolizumab offers a potential effective first-line treatment option for PD-L1 positive mTNBC

Combination ADC + IO, not yet approved

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Polling question

Based on the ASCENT-04 safety findings, how would you characterize the overall tolerability of SG + pembrolizumab in first-line PD-L1–positive mTNBC?

1. Very manageable, with a favorable safety profile compared with chemo + pembrolizumab
2. Manageable overall, with some notable but expected toxicities
3. Challenging to manage due to higher rates of GI events
4. Uncertain / need more data to assess tolerability

cornerstone specialty network™

Polling question

If approved SG + Pembro will be my…

1. Go-to first line treatment in eligible patients (90-100% of patients)
2. Used in majority (65-90%) of patients
3. Used in some 35-65% of patients
4. Used occasionally 0-35%

Polling question

If my patients get diarrhea with SG + Pembro I will manage it by…

1. Dose delay both drugs to see if it improves
2. Treat with Imodium / Lomotil - because I think it will be the likely related to SG
3. Treat with prednisone because I think it is related to Pembro
4. Treat with both Prednisone and Anti-diarrheals because it could be either
5. If it occurs early (favor 14 days), think it is related to SG and therefore tx with standard Anti-diarrheals

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2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
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- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

HALLOW

Does Trastuzumab Deruxtecan benefit Patients with HER2-Low Breast Cancer and Brain Metastases?

Interim analysis

KEY DATA

HALLOW: T-DXd, HER2-low Breast Cancer and Brain Metastases

Study Design: Multicenter, prospective observational study in real-world setting

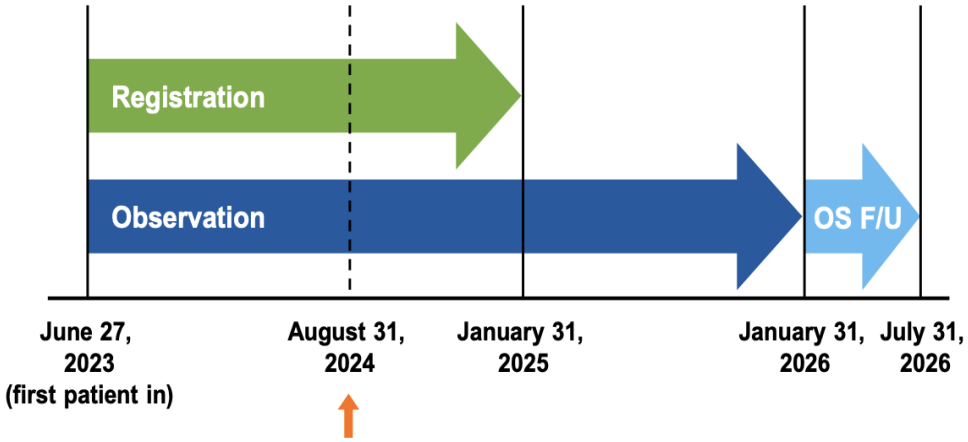
- HER2-low (IHC 1+, IHC 2+/ISH–) diagnosed at local sites before T-DXd treatment
- Metastatic breast cancer: HR- or HR+, with or without brain metastases
- Previously treated with chemotherapy with T-DXd treatment scheduled

→ **T-DXd**

Enrollment plan

- Cohort 1 (HR-/HER2-low): 200 patients
- Cohort 2 (HR+/HER2-low): 400 patients

Study period



Data cutoff date for the IA in patients with brain metastases

Endpoints

Effectiveness: OS,PFS, ORR, TTF, TTNT, PFS2, TTF2, TTNT2, DCR, CBR, DOR

✓ **Patients with brain metastases:** IC-PFS, IC-ORR, IC-CBR, MDASI-BT (QOL)

Safety: AEs of grade >3, ILD of grade >1, serious AEs, AEs leading to discontinuation of T-DXd, dose reduction of T-DXd, delay of T-DXd, and death

QOL assessment: EORTC GLQ-C30, QLQ-BR45

KEY DATA

HALLOW: T-DXd, HER2-low Breast Cancer and Brain Metastases

Baseline Characteristics

n (%)	All (n = 33)	HR– (n = 8)	HR+ (n = 25)
Age (years), Median (Q1 - Q3)	55 (47-65)	63 (49-70)	54 (47-58)
Sex, Female	33 (100)	8 (100)	25 (100)
HER2 status			
• IHC 2+/ISH–	7 (21.2)	3 (37.5)	4 (16.0)
• IHC 1+	26 (78.8)	5 (62.5)	21 (84.0)
ECOG – PS			
• 0	18 (54.5)	4 (50.0)	14 (56.0)
• 1	12 (36.4)	4 (50.0)	8 (32.0)
• 2	2 (6.1)	0 (0)	2 (8.0)
• Unknown	1 (3.0)	0 (0)	1 (4.0)

n (%)	All (n = 33)	HR– (n = 8)	HR+ (n = 25)
Metastasis			
• Yes	33 (100)	8 (100)	25 (100)
• Liver	21 (63.6)	3 (37.5)	18 (72.0)
• Lung	20 (60.6)	4 (50.0)	18 (64.0)
• Bone	21 (63.6)	2 (25.0)	19 (76.0)
Prior surgery for breast cancer			
• Yes	25 (75.8)	6 (75.0)	19 (76.0)
• No	8 (24.2)	2 (25.0)	6 (24.0)
Lines of systemic therapy (metastatic setting), Median (Q1- Q3)	5 (3-7)	3 (1-5)	5 (3-7)
Lines of Chemotherapy (metastatic setting), Median (Q1-Q3)	2 (1-3)	3 (1-4)	2 (1-2)

*Small numbers of patients received prior anti-PD-L1 data
Q1-Q3: Quartile 1-Quartile 3

[a]HER2 and HR status were based on historical results at each local site.

KEY DATA

HALLOW: T-DXd, HER2-low Breast Cancer and Brain Metastases

Baseline IC evaluation

By physician, n (%)	All (n = 33)	HR– (n = 8)	HR+ (n = 25)
Time BMs to start of T-DXd Tx (mo) Median (Q1, Q3)	2.3 (1.1, 10.4)	3.0 (0.8, 10.4)	2.1 (1.1, 10.5)
Symptomatic BM (epilepsy, convulsions, carcinomatous meningitis, etc)[b]	6/19 (31.6)	0/3 (0)	6/16 (37.5)
Steroid Tx for BM symptoms	10/32 (31.3)	2/8 (25.0)	8/24 (33.3)
Leptomeningeal dissemination (LMD)[c]	5/32 (15.6)	3/8 (37.5)	2/24 (8.3)
History of local therapy for BMs	27/32 (84.4)	5/8 (62.5)	22/24 (91.7)
• Whole-brain radiation	13/32 (40.6)	3/8 (37.5)	10/24 (41.7)
• Stereotactic radiation	15/32 (46.9)	2/8 (25.0)	13/24 (54.2)
• Tumor excision surgery	1/32 (3.1)	0/8 (0)	1/24 (4.2)

By Brain-ICR, n (%)	All (n = 33)	HR– (n = 8)	HR+ (n = 25)
Sum of diameter of baseline (mm) (RECIST v1.1), Median (Q1, Q3)	31.5 (18.4, 49.7) n = 17	25.0 (14.9, 40.6) n = 4	33.6 (21.2, 53.3) n = 13
No. of BMs [d]			
1–9	15 (45.5)	5 (62.5)	10 (40.0)
≥10	18 (54.5)	3 (37.5)	15 (60.0)
Meningeal carcinomatosis [e]	5 (15.2)	4 (50.0)	1 (4.0)
Active BMs[f]	33 (100)	8 (100)	25 (100)

[b]Subgroup was limited to patients with confirmed concomitant symptoms. [c]LMD is based on historical diagnosis, not only based on imaging at each local site. [d]Based on the results of a Japanese prospective observational study, categorized patients into two groups. [e]Meningeal carcinomatosis was evaluated on imaging by Brain-ICR. [f]Active BMs were defined as those meeting at least one of the following criteria:- No local treatment (surgery, radiation therapy) was performed on the brain lesion.- Regrowth of the brain lesion, or worsening of symptoms due to the brain lesion, after local treatment (surgery, radiation therapy) for the brain lesion

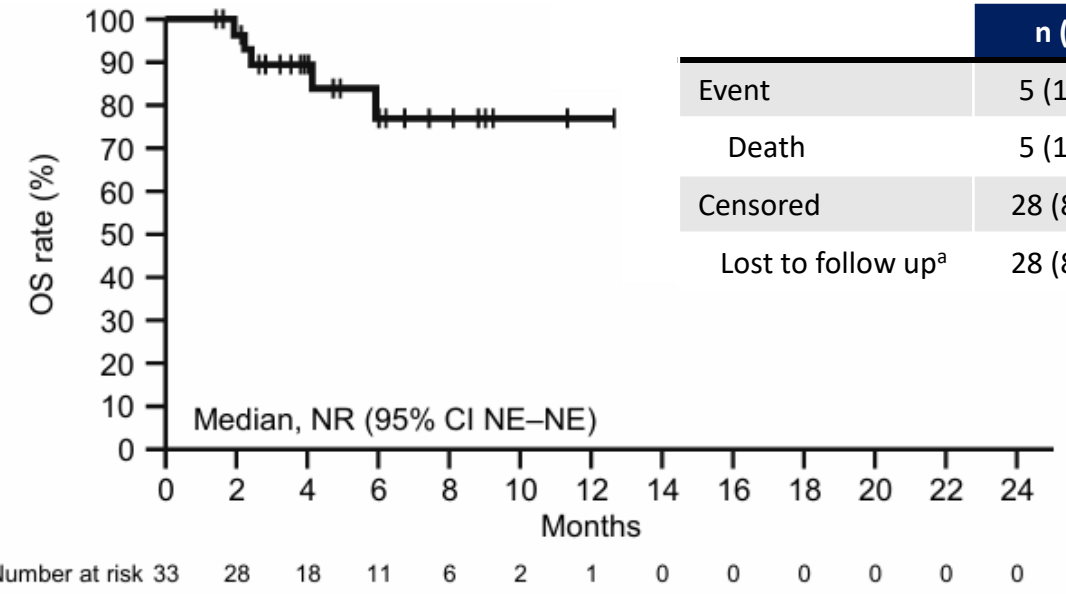
KEY DATA

HALLOW: T-DXd, HER2-low Breast Cancer and Brain Metastases

Outcomes

Overall Survival (OS)

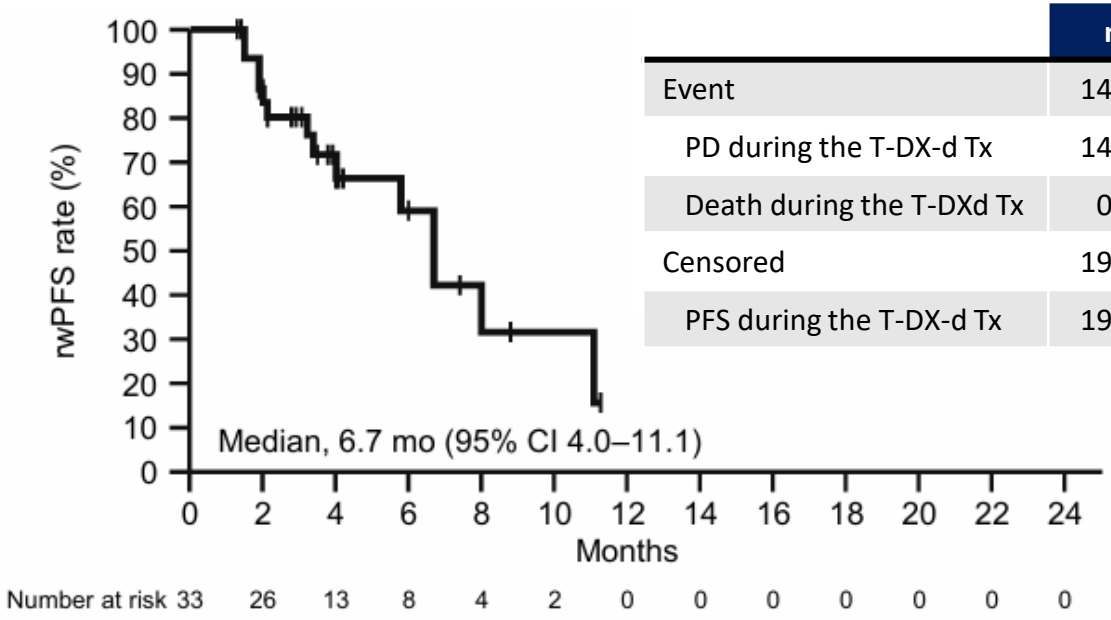
	All (n = 33)	HR– (n = 8)	HR+ (n = 25)
Rate at 6 mo (95% CI)	77.1 (51.5–90.3)	80.0 (20.4–96.9)	77.3 (48.1, 91.4)



	n (%)
Event	5 (15.2)
Death	5 (15.2)
Censored	28 (84.8)
Lost to follow up[a]	28 (84.8)

Real-world Progression Free Survival (rwPFS)

	All (n = 33)	HR– (n = 8)	HR+ (n = 25)
Rate at 6 mo (95% CI)	59.0 (34.9–76.7)	85.7 (33.4–97.9)	46.6 (18.8, 70.6)



	n (%)
Event	14 (42.4)
PD during the T-DX-d Tx	14 (42.4)
Death during the T-DXd Tx	0 (0.0)
Censored	19 (57.6)
PFS during the T-DX-d Tx	19 (57.6)

Median follow-up: 4.1 mo[a]

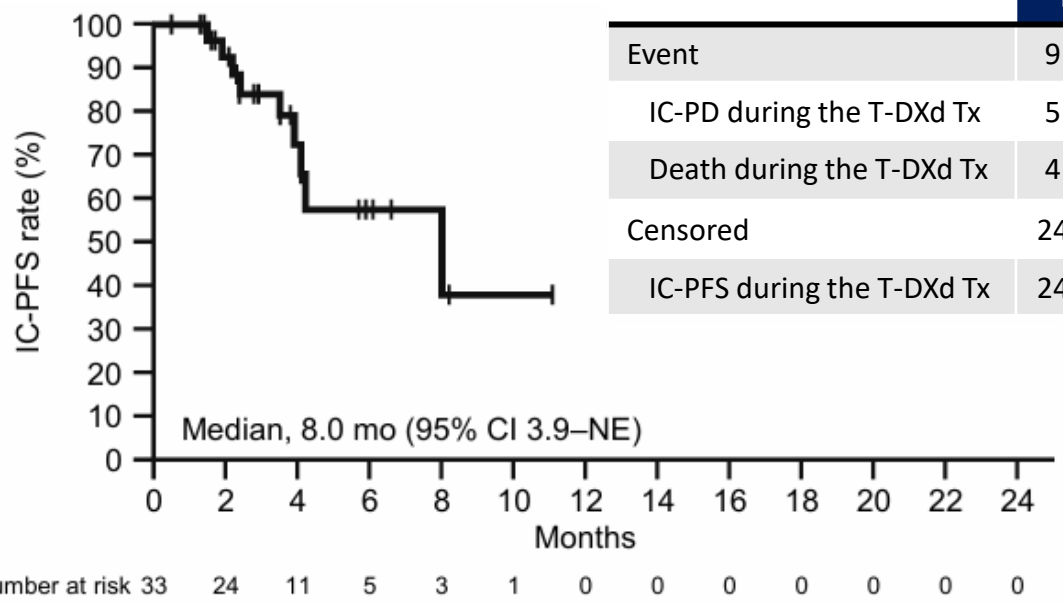
[a]At data cutoff (August 31, 2024), most patients are either currently receiving T-DXd or remain under ongoing observation

HALLOW: T-DXd, HER2-low Breast Cancer and Brain Metastases

IC-PFS: Evaluation by Brain-ICR per RECIST 1.1

Effective analysis set

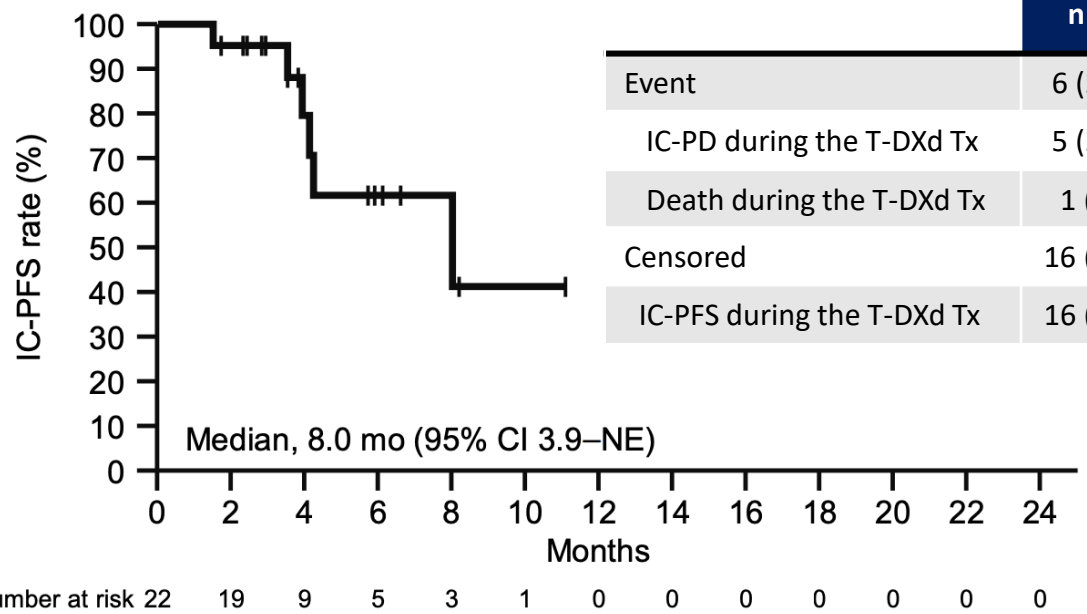
	All n = 33	(HR–) n = 8	(HR+) n = 25
Rate at 6 mo (95% CI)	57.6 (30.7–77.4)	71.4 (25.8–92.0)	46.8 (13.7–74.8)



	n (%)
Event	9 (27.3)
IC-PD during the T-DXd Tx	5 (15.2)
Death during the T-DXd Tx	4 (12.1)
Censored	24 (72.7)
IC-PFS during the T-DXd Tx	24 (72.7)

Effectiveness analysis set (Reliably evaluable per RECIST v1.1 only)

	All n = 22	(HR–) n = 6	(HR+) n = 16
Rate at 6 mo (95% CI)	61.9 (30.0–82.6)	66.7 (19.5–90.4)	53.3 (12.5–82.7)



	n (%)
Event	6 (27.3)
IC-PD during the T-DXd Tx	5 (22.7)
Death during the T-DXd Tx	1 (4.5)
Censored	16 (72.7)
IC-PFS during the T-DXd Tx	16 (72.7)

Median follow-up: 4.1 mo[a]

[a]At data cutoff (August 31, 2024), most patients are either currently receiving T-DXd or remain under ongoing observation. [b]Excluding patients determined to be NE by Brian-ICR.

HALLOW: T-DXd, HER2-low Breast Cancer and Brain Metastases

ORR and IC-ORR

	ORR			Intracranial-ORR					
	Effectiveness analysis set			Effectiveness analysis set			Effectiveness analysis set (Reliably evaluable per RECIST v1.1 only)		
	All (n = 33)	Cohort 1 (HR−) (n = 8)	Cohort 2 (HR+) (n = 25)	All [a] (n = 32)	Cohort 1 (HR−) (n = 8)	Cohort 2 (HR+)[a] (n = 24)	All (n = 22)	Cohort 1 (HR−) (n = 6)	Cohort 2 (HR+) (n = 16)
ORR, % (95% CI)	18.2 (7.0–35.5)	0.0 (0.0–36.9)	24.0 (9.4–45.1	6.3 (0.8–20.8)	12.5 (0.3–52.7)	4.2 (0.1–21.1)	9.1 (1.1–29.2)	16.7 (0.4–64.1)	6.3 (0.2–30.2)
CR, n (%)	1 (3.0)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR, n (%)	5 (15.2)	0 (0.0)	5 (20.0)	2 (6.3)	1 (12.5)	1 (4.2)	2 (9.1)	1 (16.7)	1 (6.3)

[a]One case was excluded from the analysis of IC-ORR, because BMs were confirmed by Brain-ICR, but IC-ORR could not be calculated

HALLOW: T-DXd, HER2-low Breast Cancer and Brain Metastases

Safety

n (%)	All (n = 42)	HR– (n = 11)	HR+ (n = 31)
AE of grade ≥3 • Related to T-DXd treatment	18 (42.9) 11 (26.2)	5 (45.5) 3 (27.3)	13 (41.9) 8 (25.8)
Serious AE • Related to T-DXd treatment	14 (33.3) 7 (16.7)	3 (27.3) 1 (9.1)	11 (35.5) 6 (19.4)
Interstitial lung disease (ILD) of grade ≥1 • Related to T-DXd treatment • T-DXd treatment-related ILD led to death	2 (4.8) 2 (4.8) 1 (2.4)	1 (9.1) 1 (9.1) 1 (9.1)	1 (3.2) 1 (3.2) 0 (0.0)
AE led to discontinuation of T-DXd	3 (7.1)	1 (9.1)	2 (6.5)
AE led to dose reduction of T-DXd (AE of grade ≥3 / ILD of grade ≥1)	1 (2.4)	1 (9.1)	0 (0.0)
AE led to delay of T-DXd (AE of grade ≥3 / ILD of grade ≥1)	7 (16.7)	2 (18.2)	5 (16.1)
AE led to death	1 (2.4)	1 (9.1)	0 (0.0)

SUMMARY

HALLOW

- T-DXd improved intracranial activity in patients with active brain metastases :
  - Median real-world PFS was 6.7 months
  - Estimated ORR was 18.2% at data cutoff (August 31, 2024)
  - Estimated 6 months OS rate was 77.1%
- Among 33 patients with active brain metastases, median IC-PFS was 8.0 months with an IC-ORR of 6.3%
- Consistent with known T-DXd experience; no new safety signals identified

IMPACT

T-DXd demonstrated meaningful real-world intracranial activity further supporting its potential clinical value in patients with HER2-low breast cancer and brain metastases

Small numbers…

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Kalinsky. SABCS 2025. Abstr PS5-02-28.

Polling question

Based on these early efficacy and safety findings in patients with active brain metastases, how would you characterize the overall clinical profile of T-DXd in this setting?

1. Promising intracranial activity with an acceptable safety profile
2. Moderate activity with safety concerns that warrant caution
3. Limited activity with safety risks outweighing potential benefit
4. Too early to assess given small numbers and short follow-up

Polling question

What is your current standard of care for Leptomeningeal disease?

1. WBRT or Cranial Spinal XRT
2. Intrathecal chemotherapy
3. New ADC
4. Don't have a SOC - normally refer to hospice

NCCN Guidelines Version 1.2026 – Jan 16, 2026

CYTOTOXIC REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)

See BINV-Q 1 of 15 for Considerations for systemic therapy.

Setting	Subtype/Biomarker	Regimen
First Line	PD-L1 CPS ≥10[i] regardless of germline *BRCA1/2* PV status[b]	• Chemotherapy (Albumin-bound Paclitaxel, Carboplatin/Gemcitabine, or Paclitaxel,)[j] + Pembrolizumab (category 1, preferred) • Sacituzumab govitecan-hziy + Pembrolizumab (preferred)
	PD-L1 CPS <10[i] and no germline *BRCA1/2* PV[b]	• Sacituzumab govitecan-hziy (category 1, preferred)[k] • Datopotamab deruxtecan-dlnk (other recommended) • Systemic chemotherapy BINV-Q 5 of 15
	PD-L1 CPS <10[i] and germline *BRCA1/2* PV[b]	• PARPi (Olaparib or Talazoparib) (category 1, preferred) • Platinum (Carboplatin or Cisplatin) (category 1, preferred)
Second Line	Germline *BRCA1/2* PV[b]	PARPi (category 1, preferred)
	Any	Sacituzumab govitecan-hziy[l] (category 1, preferred)
		Systemic chemotherapy BINV-Q 5 of 15 or targeted agents BINV-Q 7 of 15
	No germline *BRCA1/2* PV[b] and HER2 (*ERBB2*) IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[m] (other recommended)
Third Line and Beyond	Biomarker positive (ie, MSI-H, *NTRK1/2/3* and *RET* gene fusions, TMB-H)	Targeted agents and emerging biomarker options BINV-Q 7 of 15 and BINV-Q 8 of 15
	Any	Systemic chemotherapy BINV-Q 5 of 15

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SABCS 2025

HER2- & TNBC

Key Takeaways

Q&A

@EricSchaeferMD

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ASCENT-03: In first-line metastatic TNBC patients ineligible for PD-1/PD-L1 inhibitors, sacituzumab govitecan reduced the risk of progression or death by 38% vs standard chemotherapy (median PFS 9.7 vs 6.9 months; HR 0.62) – *not yet approved in this setting*

TROPION-Breast02: In first-line metastatic TNBC patients ineligible for PD-1/PD-L1 inhibitors, datopotamab deruxtecan improved OS (23.7 vs 18.7 mo, HR: 0.79) and PFS (10.8 vs 5.6 mo, HR: 0.57) by ~5 months, with unique adverse events (stomatitis and ocular) that require extra attention – *not yet approved in this setting*

DATO-Base: In patients with HER2-negative metastatic breast cancer and leptomeningeal disease, datopotamab deruxtecan demonstrated early intracranial and systemic activity, with responses observed by LANO criteria and prolonged intracranial disease control in some patients

ASCENT-04: In previously untreated PD-L1+ metastatic TNBC, sacituzumab govitecan plus pembrolizumab reduced the risk of disease progression compared with chemotherapy plus pembrolizumab (median PFS 11.2 vs 7.8 months; HR 0.65), with an expected safety profile – *combination not yet approved*

HALLOW: Interim real-world data suggest that trastuzumab deruxtecan provides intracranial disease control in patients with HER2-low metastatic breast cancer and active brain metastases, with no new safety signals observed

2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
- ASCENT-07
- EMBER-3
- evERA
- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

CLINICAL QUESTION

lidERA: Giredestrant in ER+, HER2- early breast cancer, adjuvant

Does the next-generation oral SERD giredestrant benefit patients with ER+, HER2- early breast cancer in the adjuvant setting versus standard of care endocrine therapy?

KEY DATA

lidERA: Giredestrant in ER+, HER2- early breast cancer, adjuvant

Study Design: International, multicenter, open-label, randomized phase III trial

- Patients with ER+ HER2- negative EBC; stage I-III disease*
- Surgery for breast cancer in ≤12 mo
- Neoadjuvant/adjuvant CT permitted
- ECOG PS 0-2

(N = 4170)

Stratified by risk (medium vs high); region (US/Canada/Western Europe vs Asia-Pacific vs ROW); prior CT (no vs yes); menopausal status (premenopausal vs postmenopausal)

Giredestrant 30 mg PO QD
(n = 2084)

SoC ET†
(n = 2086)

At least 5-yr treatment duration → *5-yr long term follow-up*

*Defined as either pN0 and pT >1 cm with grade 3, or Ki67 ≥20%, or high genomic assay score, or pT4N0; node positive.

†Permitted ET: tamoxifen, anastrozole, letrozole, or exemestane (*no CDK4/6i*)

Primary endpoint: Invasive disease-free survival (IDFS - not including second primary cancer outside breast) in ITT group

Secondary endpoints: Disease-free survival (DFS), distant recurrence-free interval (DRFI), IDFS (including second primary cancer outside breast‡), LRRFI, OS, safety

Cutoff date: August 8, 2025

Bardia. SABCS 2025. Abstr GS1-10.

KEY DATA

lidERA: Giredestrant in ER+, HER2- early breast cancer, adjuvant

Baseline Characteristics

Characteristic, n (%)	Giredestrant (n = 2084)	SoC ET (n = 2086)
Median age, yr (range)	54.0 (22-91)	54.0 (25-89)
Female	2073 (99.5)	2075 (99.5)
Race		
• American Indian or Alaska Native	77 (3.7)	62 (3.0)
• Asian	461 (22.1)	467 (22.4)
• Black	50 (2.4)	50 (2.4)
• Other	263 (12.6)	232 (11.1)
• White	1233 (59.2)	1275 (61.1)
Region		
• Asia-Pacific	544 (26.1)	544 (26.1)
• USA/Canada/Western Europe	860 (41.3)	905 (43.4)
• Latin America/Africa/Eastern Europe	680 (32.6)	637 (30.5)
Menopausal status*		
• Premenopausal	849 (41.0)	838 (40.4)
• Postmenopausal	1220 (59.0)	1236 (59.6)

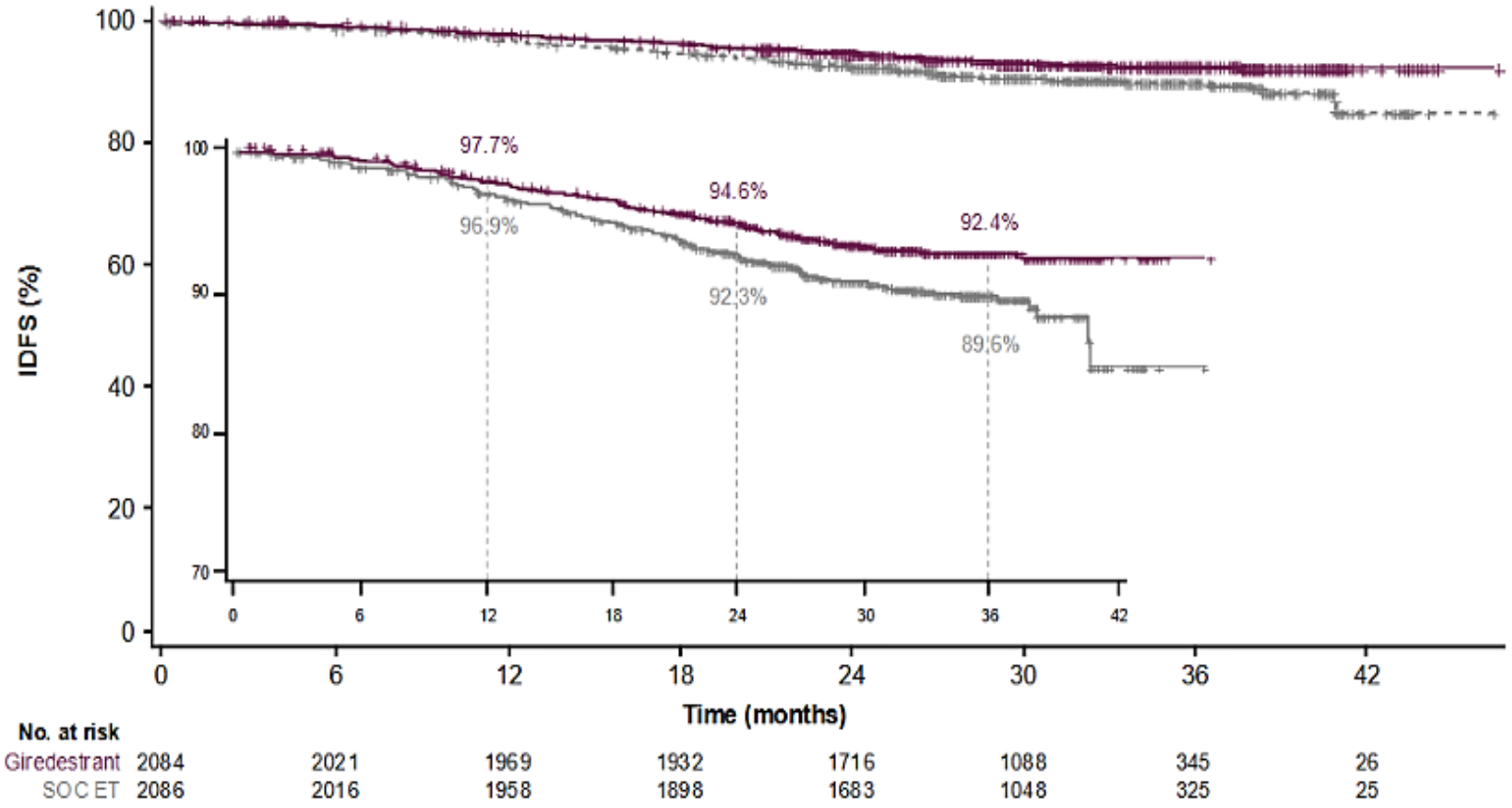
Characteristic, n (%)	Giredestrant (n = 2084)	SoC ET (n = 2086)
ER status†		
• Low positive	45 (2.2)	52 (2.5)
• Positive	2030 (97.8)	2031 (97.5)
AJCC stage at surgery‡		
• I	254 (12.3)	283 (13.6)
• II	1013 (49.0)	950 (45.7)
• III	799 (38.7)	844 (40.6)
Nodal stage on surgical specimen§		
• pN0	449 (21.6)	441 (21.2)
• pN1	968 (46.6)	953 (45.7)
• pN2-3	662 (31.8)	691 (33.1)
Risk		
• High	1448 (69.5)	1447 (69.4)
• Medium	636 (30.5)	639 (30.6)
Prior chemotherapy		
• No	396 (19.0)	450 (21.6)
• Yes	1688 (81.0)	1636 (78.4)

*n = 27 patients with unknown menopausal status (giredestrant: n = 15; SoC: n = 12). †Low positive = 1-10% of cells positive; positive = >10% of cells positive. ‡n=1 patient with stage 0 disease and n = 26 in whom stage was unknown (giredestrant: n = 18; SoC: n = 8). §n = 6 patients with unknown nodal status (giredestrant: n = 5; SoC: n = 1).

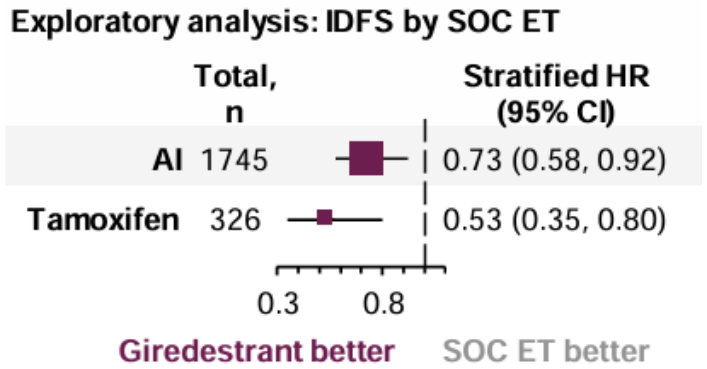
KEY DATA

lidERA: Giredestrant in ER+, HER2- early breast cancer, adjuvant

Primary Endpoint: Invasive disease-free survival (IDFS)



	Giredestrant (n = 2084)	SoC ET (n = 2086)
Events, n (%)	140 (6.7)	196 (9.4)
Stratified HR (95% CI)	**0.70** (0.57, 0.87); **p = 0.0014**	



Median follow-up at data cutoff:

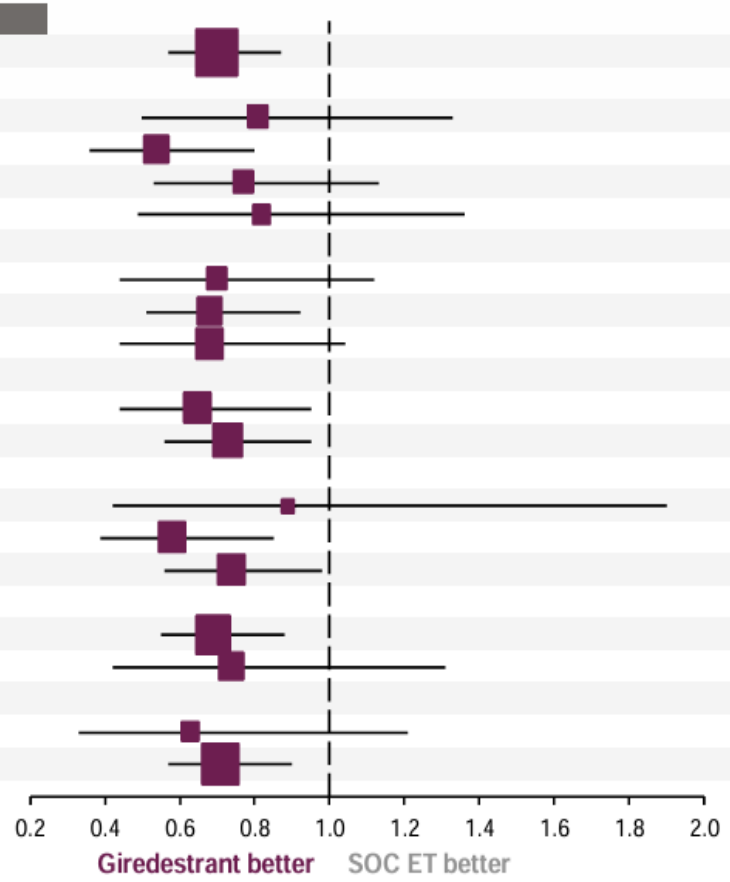
- 32.4 months in the giredestrant arm
- 32.3 months in the SoC ET arm

Bardia. SABCS 2025. Abstr GS1-10.

lidERA: Giredestrant in ER+, HER2- early breast cancer, adjuvant

IDFS by Subgroups

	Total, n	Patients, n: Giredestrant	Patients, n: SOC ET	HR (95% CI)
All patients	4170	2084	2086	0.70 (0.57, 0.87)
Age group, years				
≤ 45	906	472	434	0.81 (0.50, 1.33)
> 45 to ≤ 55	1355	660	695	0.54 (0.36, 0.80)
> 55 to ≤ 65	1118	567	551	0.77 (0.53, 1.13)
> 65	791	385	406	0.82 (0.49, 1.36)
Region				
Asia–Pacific	1088	544	544	0.70 (0.44, 1.12)
Latin America/Africa/Eastern Europe	1317	680	637	0.68 (0.51, 0.92)
USA/Canada/Western Europe	1765	860	905	0.68 (0.44, 1.04)
Menopausal status				
Pre-menopausal	1680	841	839	0.65 (0.44, 0.95)
Post-menopausal	2490	1243	1247	0.73 (0.56, 0.95)
AJCC stage at surgery*				
I	537	254	283	0.89 (0.42, 1.90)
II	1963	1013	950	0.58 (0.39, 0.85)
III	1643	799	844	0.74 (0.56, 0.98)
Risk				
High	2895	1448	1447	0.69 (0.55, 0.88)
Medium	1275	636	639	0.74 (0.42, 1.31)
Previous chemotherapy				
No	787	392	395	0.63 (0.33, 1.21)
Yes	3383	1692	1691	0.71 (0.57, 0.90)

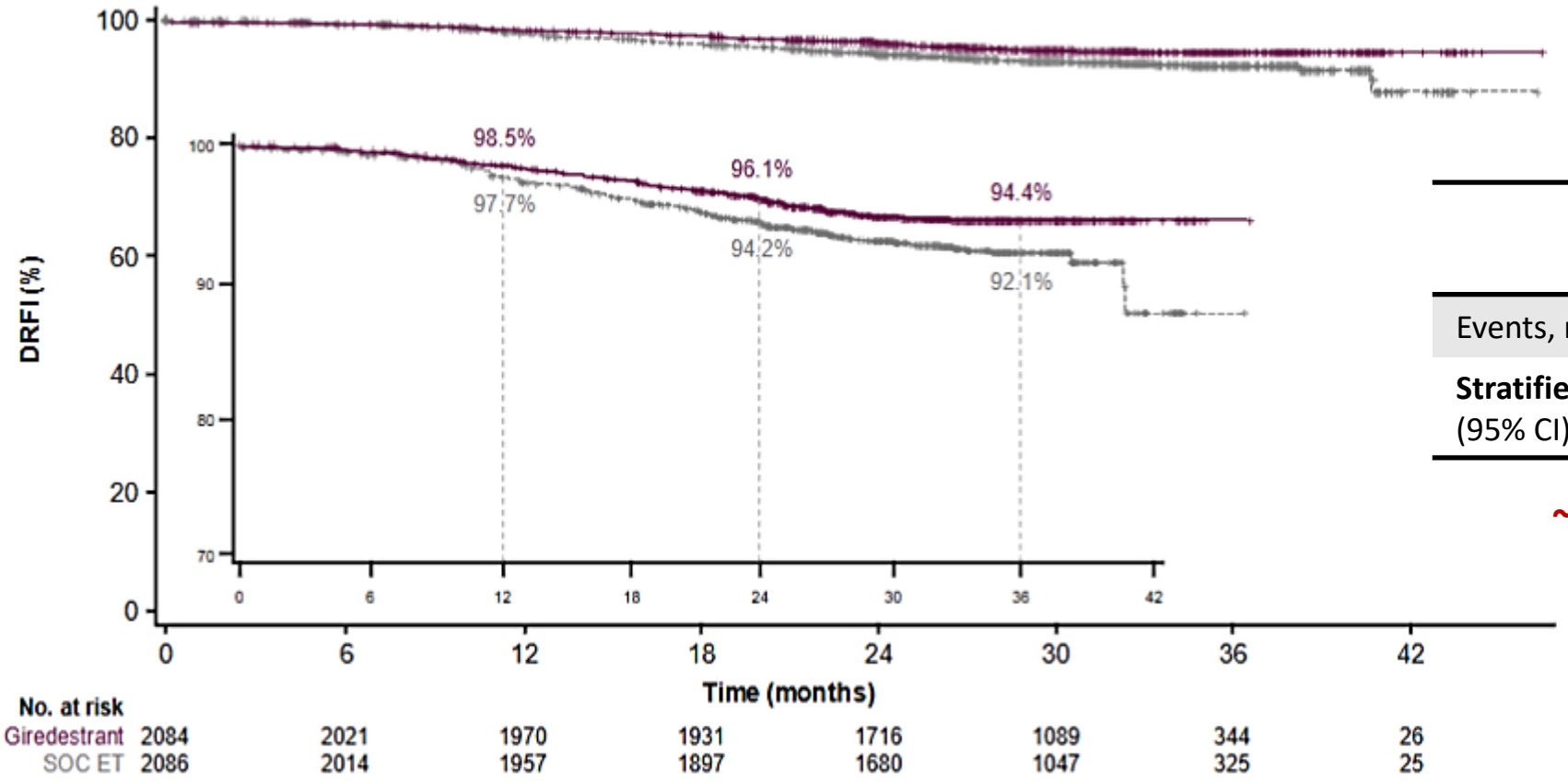


Data cutoff: August 8, 2025. HR estimates are unstratified. Median follow-up of 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively.* One patient had Stage 0 disease (SOC ET arm); 26 had unknown Stage (18 in the giredestrant arm and eight in the SOC ET arm). AJCC, American Joint Committee on Cancer; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; SOC, standard-of-care

Bardia. SABCS 2025. Abstr GS1-10.

lidERA: Giredestrant in ER+, HER2- early breast cancer, adjuvant

Distant recurrence-free interval



	Giredestrant (n = 2084)	SoC ET (n = 2086)
Events, n (%)	102 (4.9)	145 (7.0)
Stratified HR (95% CI)	**0.69** (0.54, 0.89)	

~2% difference at 36 months

Median follow-up: 32.3 mo

Data cutoff: August 8, 2025. Median follow-up, 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively. CI, confidence interval; DRFI, distant recurrence-free interval; ET, endocrine therapy; HR, hazard ratio; SOC, standard-of-care.

Bardia. SABCS 2025. Abstr GS1-10.

lidERA: Giredestrant in ER+, HER2- early breast cancer, adjuvant

Safety

Safety Outcome	Giredestrant (n = 2060)	SoC ET (n = 2074)
Median treatment duration, mo (range)	31.64 (0.03-46.36)	30.88 (0.03-46.26)
Mean dose intensity, % (SD)	98.77 (3.07)	98.68 (3.73)
Patients with ≥1 AE, n (%)		
• Any-grade AE	1955 (94.9)	1957 (94.4)
• TRAEs	1510 (73.3)	1498 (72.2)
• Fatal AEs	6 (0.3)	16 (0.8)
• Fatal TRAEs	0	1 (<0.1)
• Grade 3/4 AEs	407 (19.8)	372 (17.9)
• Serious AEs	223 (10.8)	209 (10.1)
• **AEs leading to dose interruption**	**261 (12.7)**	**136 (6.6)**
• **AEs leading to treatment discontinuation**	**110 (5.3)**	**171 (8.2)**

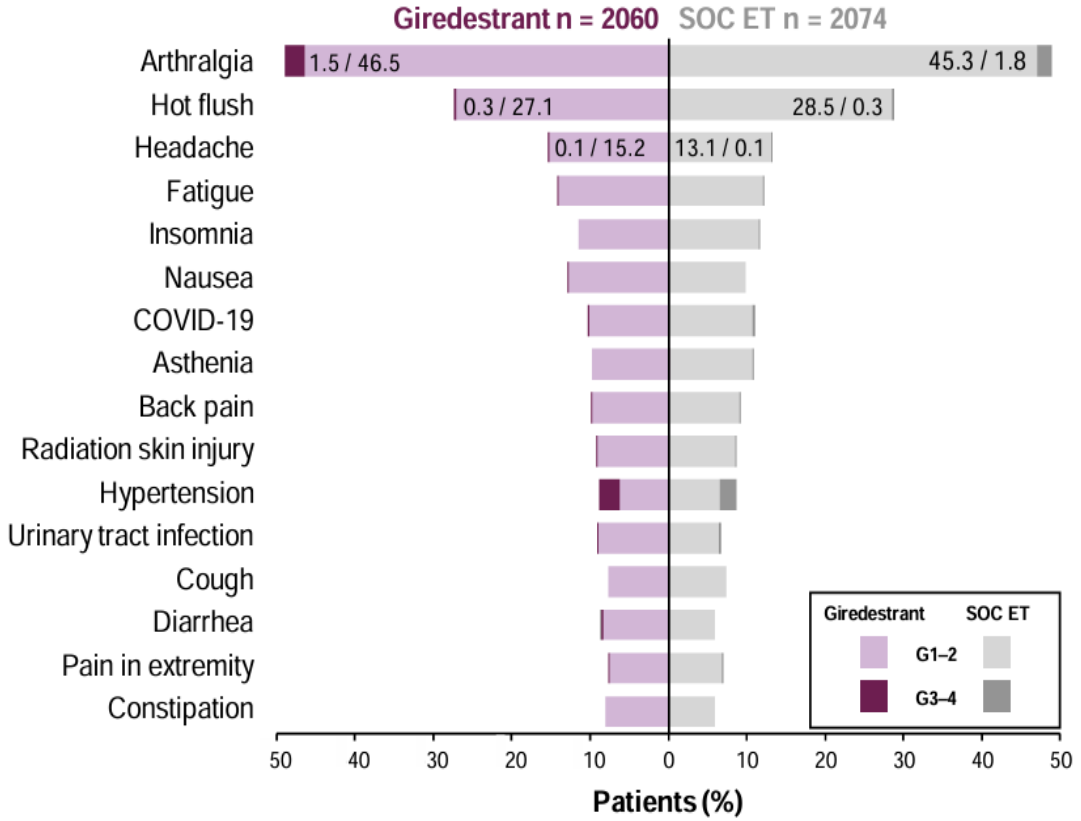
Bardia. SABCS 2025. Abstr GS1-10.

KEY DATA

lidERA: Giredestrant in ER+, HER2- early breast cancer, adjuvant

Safety

Common TEAEs (≥ 7.5% of patients in either arm at any grade)



Select AEs, n (%)	Giredestrant (n = 2060)			SoC ET (n = 2074)		
	Gr 1	Gr 2	Gr 3-4	Gr 1	Gr 2	Gr 3-4
Bradycardia†	217 (10.5)	15 (0.7)	0	64 (3.1)	2 (<0.1)	0
Venous thromboembolic events	4 (0.2)	12 (0.6)	2 (<0.1)‡	3 (0.1)	7 (0.3)	7 (0.3)

†G2 events occurred in 17 patients; 13 resolved, four patients discontinued treatment and the events resolved.
‡ G3 only.

Bardia. SABCS 2025. Abstr GS1-10.

SUMMARY

lidERA

- Adjuvant giredestrant reduced risk of disease recurrence vs SoC ET in patients with ER+/HER2- negative EBC
  - Invasive disease-free survival 36-mo rate:
    - 92.4% vs 89.6%; HR: 0.70 (95% CI: 0.57-0.87; *P* = .0014)
- Interim OS data favored giredestrant (HR: 0.79)
- Safety profile – mainly grade 1 bradycardia
  - Less discontinuation with giredestrant vs SoC ET
- *Challenge in trial – ET arm SoC is not current SoC in USA*

IMPACT

Giredestrant provides benefit to patients with ER+/HER2- early breast cancer in the adjuvant setting over (an older) standard of care endocrine therapy

Not yet approved

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Polling question

Based on the lidERA trial results comparing giredestrant with standard-of-care endocrine therapy, how do you view the clinical role of giredestrant in your future practice?

1. Will adopt widely on approval
2. Will not adopt on approval in view of the addition of CDK4/6i for high-risk HR+ disease
3. Will only use in patients with lower-risk disease
4. Unsure

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2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
- ASCENT-07
- EMBER-3
- evERA
- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

CLINICAL QUESTION

ASCENT-07: 1L metastatic HR+/HER2- breast cancer, no prior chemo

Does sacituzumab govitecan benefit patients with HR+/HER2- (IHC 0, 1+, 2+ / ISH-) metastatic breast cancer after endocrine therapy and no prior chemotherapy?

KEY DATA

ASCENT-07: 1L metastatic HR+/HER2- breast cancer, no prior chemo

Study Design: Randomized, open-label, phase 3 study

Stratification factors: Duration of prior CDK4/6i[d] for mBC (none vs ≤ 12 mo vs > 12 mo); HER2 IHC (HER2 IHC 0 vs HER2 IHC-low [IHC 1+ or IHC 2+/ISH–]); Geographic region (US/Canada/UK/EU vs ROW)

- Locally advanced unresectable or metastatic HR+/HER2− BC
- No prior chemotherapy for locally advanced or metastatic HR+/HER2− BC
- Measurable disease per RECIST v1.1
- Must have at least 1 of the following:
  - Progression on ≥ 2 previous lines of ET ± targeted therapy for mBC[a]
  - Progression < 6 mo of starting 1L ET ± CDK4/6i for mBC
  - Recurrence < 24 mo of starting adjuvant ET + CDK4/6i and no longer a candidate for additional ET for mBC

N=690

R 2:1

Sacituzumab govitecan 10 mg/kg IV Days 1 and 8, every 21 days n = 456

Treatment of physician's choice (capecitabine, paclitaxel, nab-paclitaxel)[b] n = 234

Treatment continued until disease progression[c] or unacceptable toxicity

aDisease recurrence while on the first 24 months of starting adjuvant ET will be considered a line of therapy; these participants will only require 1 line of ET in the metastatic setting.
bPaclitaxel 80 mg/m^2 or nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 of 28-day cycles, or capecitabine oral 1000 or 1250 mg/m^2 twice daily for first 2 weeks of 21-day cycles.
cPer RECIST v1.1.
dEnrollment of CDK4/6i-naïve participants was capped at 10%.

Primary endpoint: PFS by BICR
Secondary endpoints: OS, ORR by BICR, QOL
Other Secondary endpoints: PFS by INV, ORR by INV, DOR by BICR and INV, Safety

Data cutoff for primary PFS analysis (planned after ~415 events): September 15, 2025
Median duration of follow-up: 15.4 months

KEY DATA

ASCENT-07: 1L metastatic HR+/HER2- breast cancer, no prior chemo

Baseline Characteristics

Characteristic, n (%)	SG (n = 456)	TPC (n = 234)
Median age, yr (range)	57 (29-88)	58 (27-80)
• ≥65 yr	106 (23)	74 (32)
Female sex	452 (99)	232 (99)
Geographic region		
• US/Canada/UK/EU	181 (40)	93 (40)
• Rest of the world	275 (60)	141 (60)
Race		
• White	227 (50)	106 (45)
• Asian	176 (39)	95 (41)
• Black	10 (2)	3 (1)
• Other/nonspecified	43 (9)	30 (13)
ECOG PS		
• 0	269 (59)	145 (62)
• 1	187 (41)	89 (38)
ER/PR status		
• ER+ and PR+	286 (63)	165 (71)
• ER+ and PR-	164 (36)	66 (28)
• ER- and PR+	2 (<1)	2 (1)

Characteristic, n (%)	SG (n = 456)	TPC (n = 234)
HER2 expression		
• IHC 0	192 (42)	100 (43)
• HER2 low (IHC 1+; IHC2+/ISH-)	264 (58)	134 (57)
Primary endocrine resistance	143 (31)	62 (26)
Median time from initial diagnosis of metastatic disease to randomization, mo (range)	23.9 (0.5-192.0)	26.2 (0.3-152.1)
De novo metastatic disease at diagnosis	111 (24)	48 (21)
Visceral disease	407 (89)	205 (88)
Liver metastasis	320 (70)	156 (67)
Brain metastasis	18 (4)	14 (6)
Bone-only disease	18 (4)	11 (5)

Jhaveri. SABCS 2025. Abstr GS1-09.

KEY DATA

ASCENT-07: 1L metastatic HR+/HER2- breast cancer, no prior chemo

Prior therapies

Metastatic Setting	SG (n = 456)	TPC (n = 234)
Median prior lines, n (range)	2 (0-8)	2 (0-4)
Lines of ET, n (%)		
• None	8 (2)	1 (<1)
• 1	122 (27)	63 (27)
• 2	263 (58)	139 (59)
• ≥3	63 (14)	31 (13)
Previous endocrine-based therapies[a], n (%)		
• ET + CDK4/6i	416 (91)	216 (92)
• ET + CDK4/6i ≤6 mo[b]	74 (16)	35 (15)
• ET monotherapy	182 (40)	95 (41)
• ET + other targeted therapy[c]	160 (35)	74 (32)

Prior CDK4/6i Use in Metastatic Setting, n (%)	SG (n = 456)	TPC (n = 234)
None	32 (7)	19 (8)
≤12 mo	197 (43)	98 (42)
>12 mo	227 (50)	117 (50)

Consistent with current USA population

aTherapies reported are not mutually exclusive.
bIn first line.
cOther targeted therapies in the SG and TPC groups included everolimus (25% and 22%), alpelisib (5% and 3%), and olaparib (2% and 3%).
dSome participants had unknown adjuvant therapy history.
eET includes ET monotherapy and combination therapy

KEY DATA

ASCENT-07: 1L metastatic HR+/HER2- breast cancer, no prior chemo

Primary Endpoint: Progression-free survival by BICR

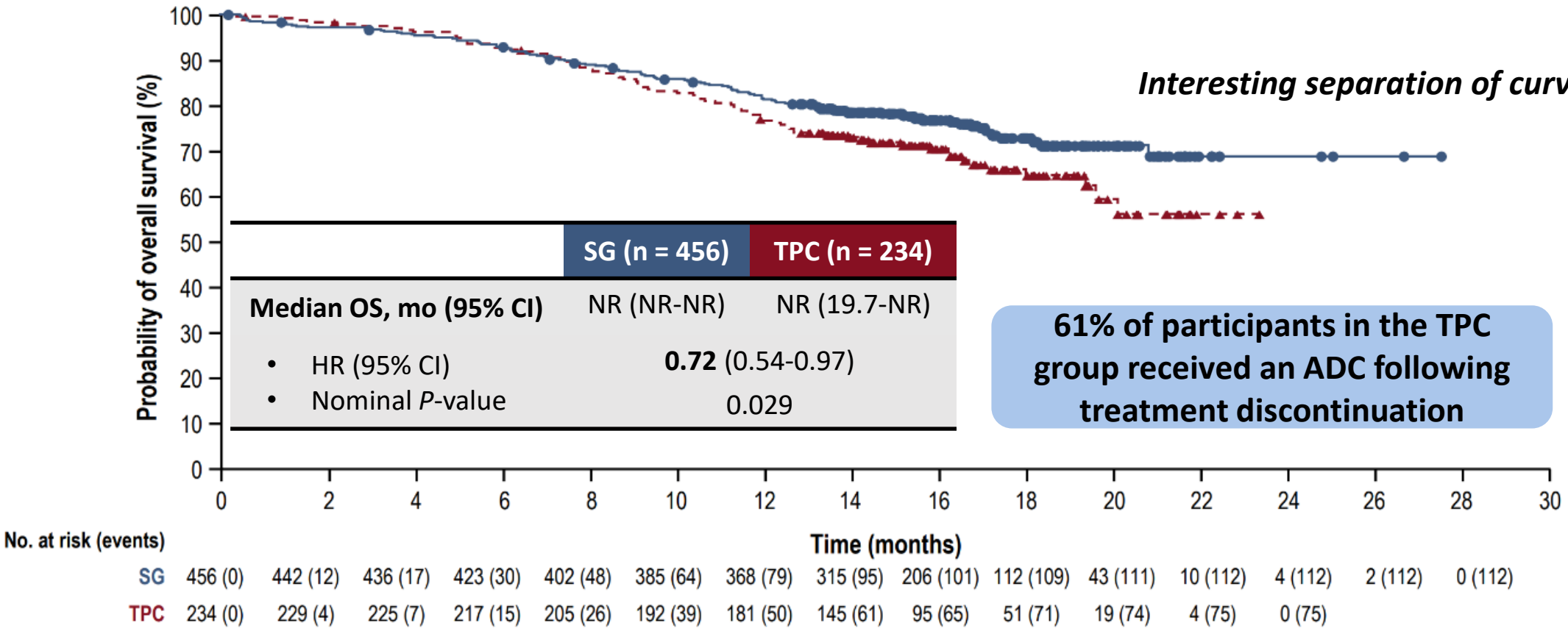
	SG (n = 456)	TPC (n = 234)
Median PFS, mo (95% CI)	**8.3** (8.1-10.3)	**8.3** (6.9-10.0)
• Stratified HR (95% CI) • *P*-value	0.85 (0.69-1.05) 0.130	
6-month PFS rate, % (95% CI)	71 (66-75)	64 (57-77)
12-month PFS rate, % (95% CI)	40 (35-45)	37 (29-44)

Jhaveri. SABCS 2025. Abstr GS1-09.

KEY DATA

ASCENT-07: 1L metastatic HR+/HER2- breast cancer, no prior chemo

Overall Survival at Primary Analysis (27% maturity)



	SG (n = 456)	TPC (n = 234)
Median OS, mo (95% CI)	NR (NR-NR)	NR (19.7-NR)
• HR (95% CI)	**0.72** (0.54-0.97)	
• Nominal *P*-value	0.029	

Interesting separation of curves

61% of participants in the TPC group received an ADC following treatment discontinuation

Jhaveri. SABCS 2025. Abstr GS1-09.

SUMMARY

ASCENT-07

- The ASCENT-07 study in participants with HR+/HER2- mBC did not meet statistical significance for the primary end point of PFS by BICR
  - At a median follow-up of 15.4 months, the median PFS was 8.3 months in both the SG and chemotherapy arm
- OS data immature (27% maturity), trend favoring SG over chemotherapy
- *<u>To put SG HR+ 1L data in perspective</u>: SG has been approved by the FDA and remains SoC for HR+, 2L+ metastatic breast cancer after prior endocrine therapy and chemotherapy (TROPICS-02)*
  - *PFS: 5.5 vs 4.0 mos*
  - *OS: 14.4 vs 11.2 mos (SG vs chemotherapy)*

IMPACT

Sacituzumab govitecan does not provide benefit over first-line chemotherapy (post endocrine therapy) for patients with HR+ HER2- mBC

2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
- ASCENT-07
- EMBER-3
- evERA
- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

CLINICAL QUESTION

EMBER-3: Imlunestrant ± abemaciclib vs SOC ET for ABC

Is Imlunestrant (SERD) with or without abemaciclib a beneficial treatment option for patients with advanced breast cancer after progression on endocrine therapy?

Updated efficacy results – 14 mos of additional follow-up

On September 25, 2025, the FDA approved imlunestrant (Inluriyo, Eli Lilly and Company), an estrogen receptor antagonist, for adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

cornerstone specialty network™

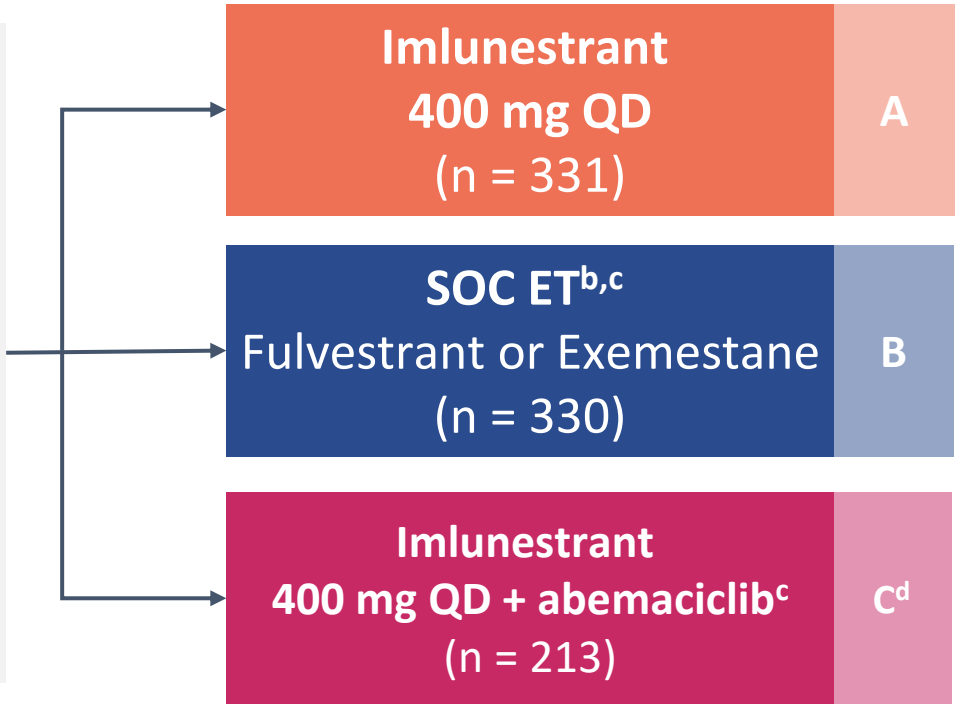
KEY DATA

EMBER-3: Imlunestrant ± abemaciclib vs SOC ET for ABC

Study Design: Open-label, randomized phase III study

Stratified by prior CDK4/6i therapy (Yes/No), visceral metastases (Yes/No), and Region (East Asia vs US/European Union vs others)

- Men and pre-[a]/post-menopausal women
- Prior therapy:
  - Adjuvant: recurrence on or within 12 months of completion of AI ± CDK4/6i
  - Advanced: Progression on first-line AI ± CDK4/6i
  - No other therapy for Adv BC



Primary Endpoints: Investigator-assessed PFS for[e]:

- A vs B in patients with ESR1m[f]
- A vs B in all patients
- C vs A in all patients[g]

Secondary endpoints: OS, PFS by BICR, ORR, and safety

Exploratory endpoints: Time to chemotherapy (TTC)[h], chemotherapy-free survival (CFS)[i], PFS2[j]

[a]A GnRH was required in men and premenopausal women. [b]Investigator's choice. [c]Labeled dose. [d]Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B). [e]Scans every 8 weeks for the first 12 months, then every 12 weeks. [f]*ESR1*m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rick Biotech) for patients from China. [g]Analysis conducted in all concurrently randomized patients. [h]Defined as the time form randomization to start of first chemotherapy (censoring patients who died prior to initiation of chemotherapy). [i]Defined as the time from randomization to initiation of first chemotherapy or death, whichever occurred first. [j]Defined as the time from randomization to progression on the next line of therapy or death from any cause.

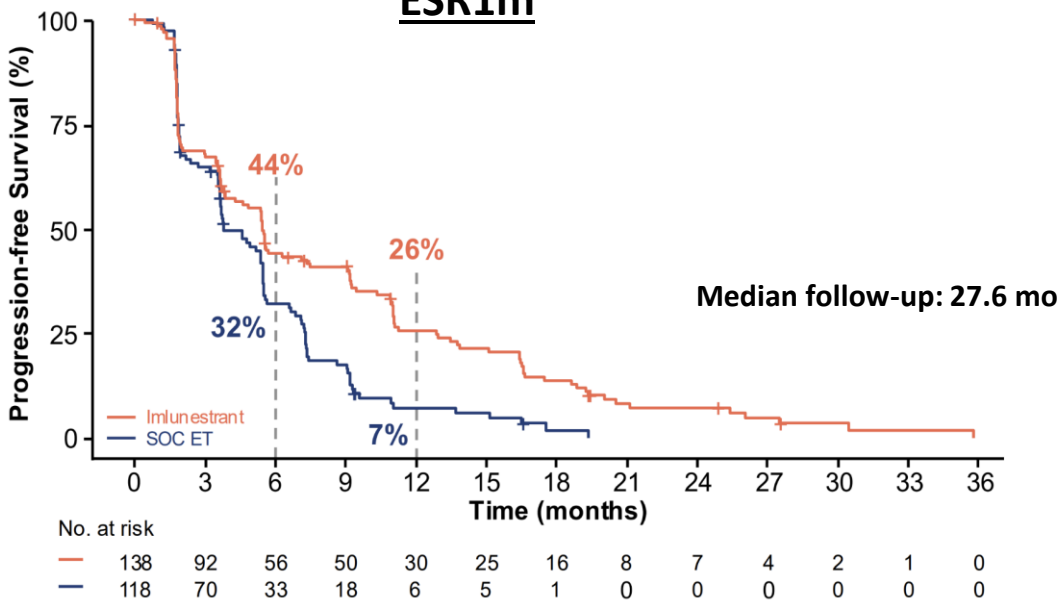
SABCS 2025. Abstract GS3-08.

KEY DATA

EMBER-3: Imlunestrant ± abemaciclib vs SOC ET for ABC

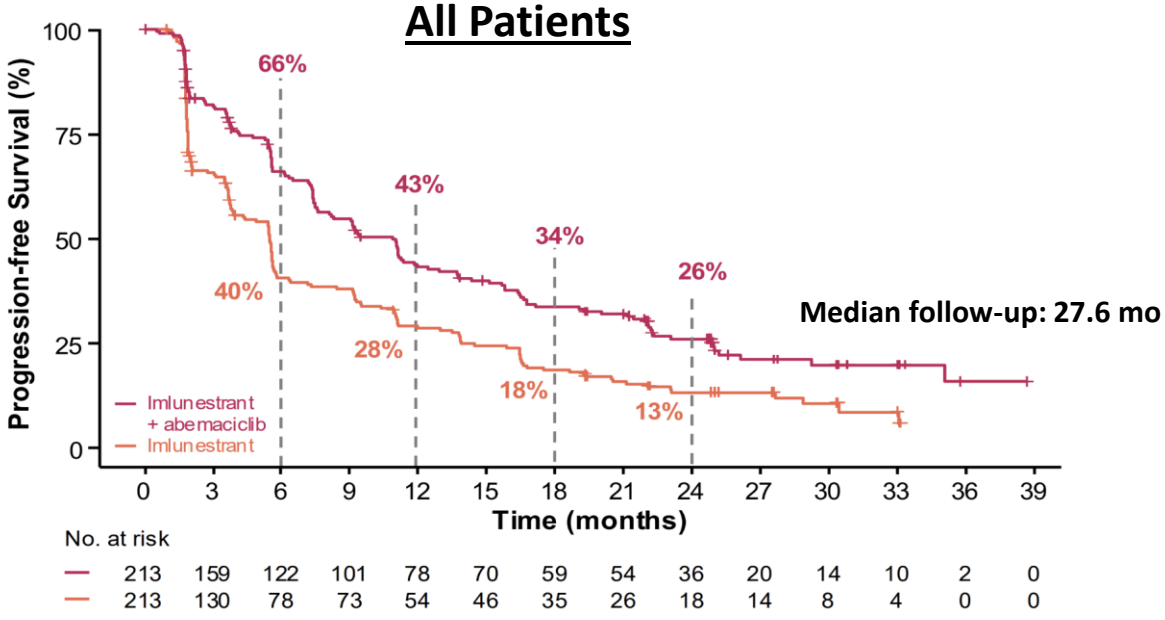
Primary Endpoints

A vs B: PFS of Imlunestrant vs SOC ET in patients with ESR1m



	Imlunestrant (n = 138)	SOC ET (n = 118)
PFS events	122	103
Median PFS (95% CI)	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
Hazard ratio (95% CI)	**0.62** (0.47-0.82) Nominal p-value[a] = 0.0007	

C vs A: PFS of Imlunestrant + Abemaciclib vs Imlunestrant in All Patients



	Imlunestrant + abemaciclib (n = 213)	Imlunestrant (n = 213[a])
PF events	144	174
Median PFS (95% CI)	**10.9** (7.5-12.5)	**5.5** (3.8-5.6)
Hazard ratio (95% CI)	**0.59** (0.47-0.74) Nominal p-value[a] <0.0001	

[a]Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm.

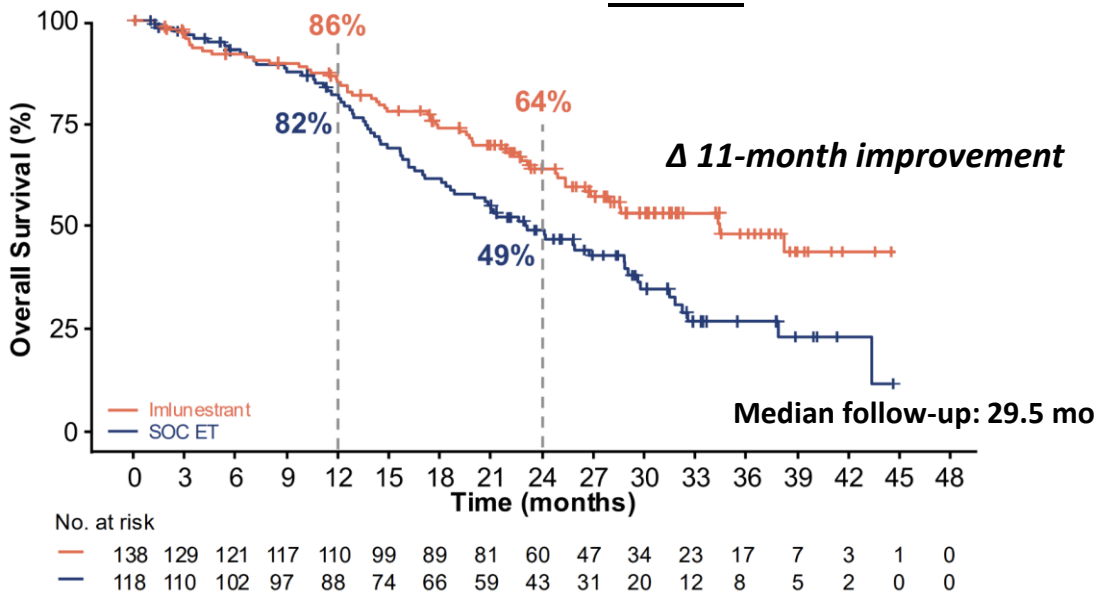
SABCS 2025. Abstract GS3-08.

KEY DATA

EMBER-3: Imlunestrant ± abemaciclib vs SOC ET for ABC

Secondary Endpoints

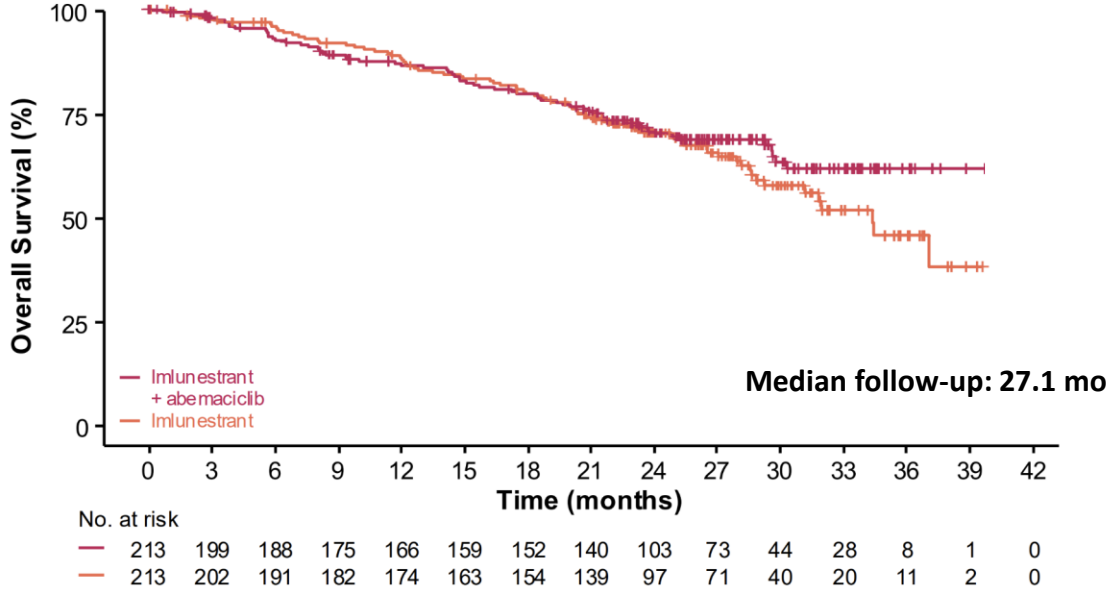
Interim OS of Imlunestrant vs SOC ET at 50% Maturity in Patients with *ESR1*m



	Imlunestrant (n = 138)	SOC ET (n = 118)
Deaths	57	71
Median OS (95% CI)	**34.5** (25.4-NR)	**23.1** (18.4-28.9)
Hazard ratio (95% CI)	**0.60 (0.43-0.86)** *p*-value = 0.0043*	

*p-value did not achieve prespecified threshold for significance (p=00000042 at interim analysis 2)

Interim OS of Imlunestrant + Abemaciclib vs Imlunestrant at 33% Maturity in All Patients



	Imlunestrant + abemaciclib (n = 213)	Imlunestrant (n = 213[a])
Deaths	64	76
Median OS (95% CI)	**NR**	**34.4** (29.3-NR)
Hazard ratio (95% CI)	**0.82 (0.59-1.16)** *p*-value = 0.2622*	

*p-value did not achieve prespecified threshold for significance (p < 0.0000001 at interim analysis 2)

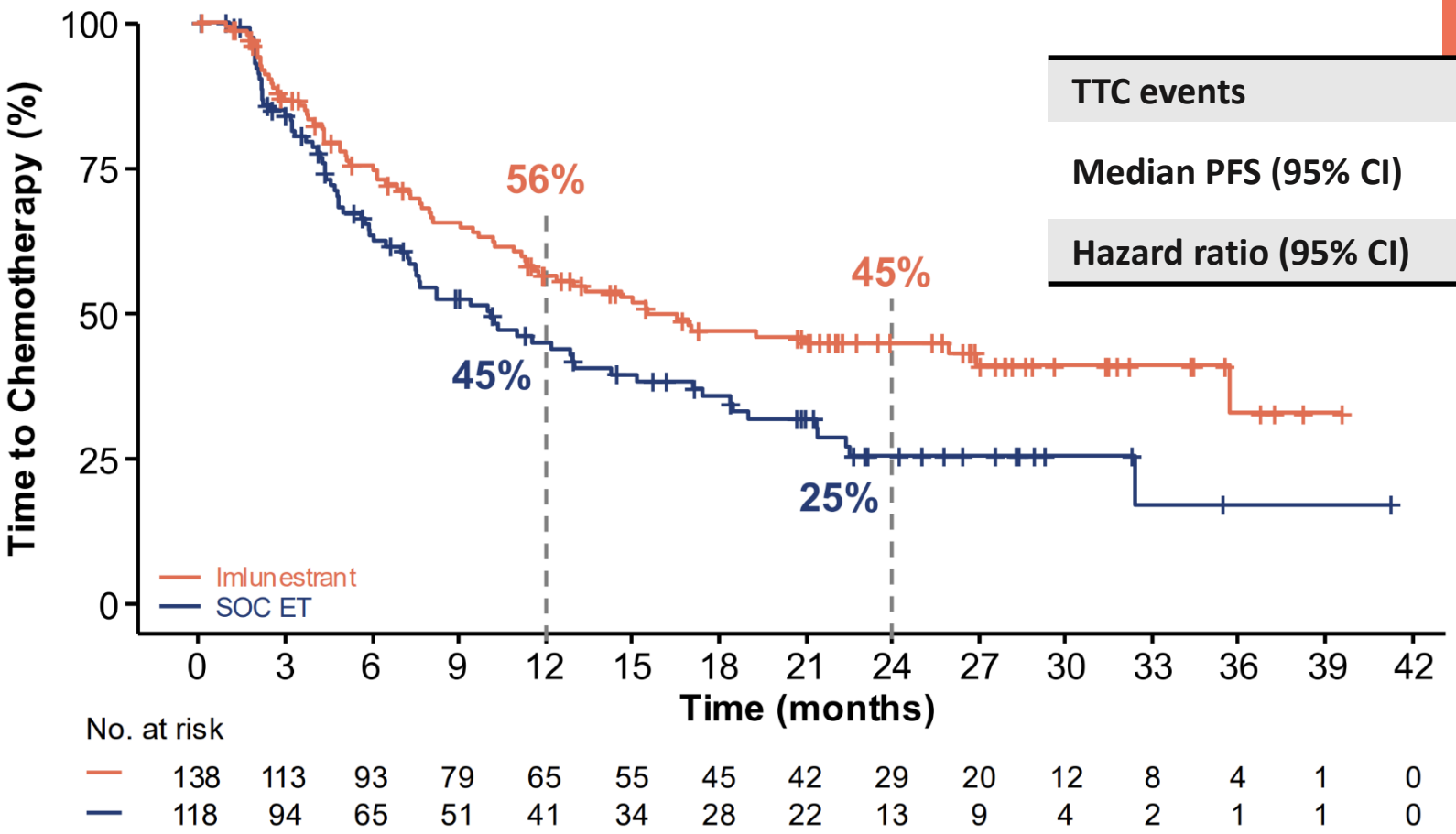
[a]Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm.

SABCS 2025. Abstract GS3-08.

KEY DATA

EMBER-3: Imlunestrant ± abemaciclib vs SOC ET for ABC

Exploratory Analysis: Time to chemotherapy (TTC) of single agent Imlunestrant vs SOC ET in patients with *ESR1*m



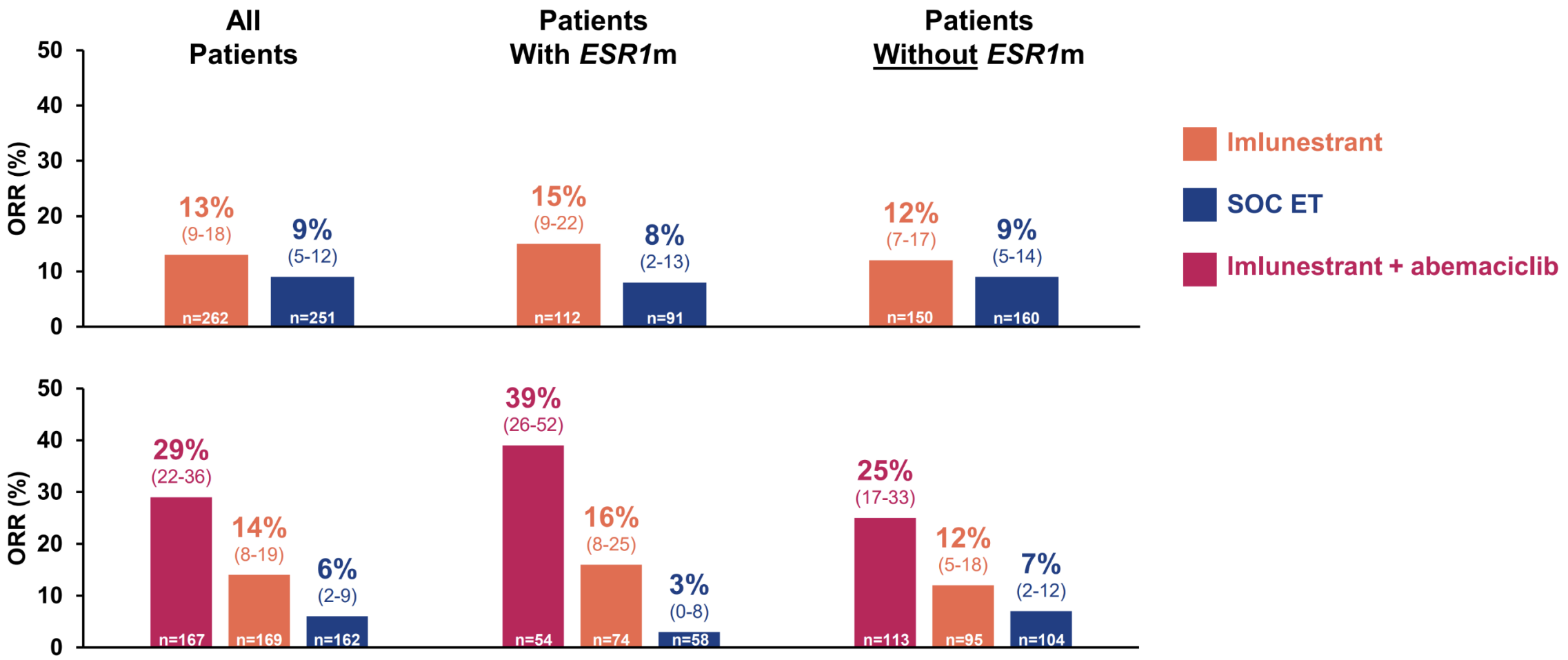
	Imlunestrant (n = 138)	SOC ET (n = 118)
TTC events	70	74
Median PFS (95% CI)	**15.6** (11.4-35.8)	**10.2** (7.3-13.0)
Hazard ratio (95% CI)	**0.66 (0.48-0.92)**	

SABCS 2025. Abstract GS3-08.

KEY DATA

EMBER-3: Imlunestrant ± abemaciclib vs SOC ET for ABC

Secondary endpoint: ORR in Patients with Measurable Disease



Patients without ESR1m included those with unknown ESR1m status (top bars: imlunestrant, n=13; SOC ET, n=7; bottom bars: imlunestrant +abemaciclib, n=1; imlunestrant, n=7; SOC ET, n=4). Bottom bars: analyses confined to the imlunestrant/SOC ET population concurrently randomized. The values indicated in parentheses represent the 95% confidence intervals.

SABCS 2025. Abstract GS3-08.

KEY DATA

EMBER-3: Imlunestrant ± abemaciclib vs SOC ET for ABC

Safety

TEAEs in ≥25% of Patients	Imlunestrant + abemaciclib (n = 208)		Imlunestrant (n = 327)		SOC ET (n=324)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 TEAE	98%	54%	85%	20%	85%	22%
• Diarrhea	**86%**	**9%**	**23%**	<1%	12%	0%
• Neutropenia	**50%**	**22%**	6%	3%	5%	2%
• Nausea	50%	2%	18%	<1%	14%	0%
• Anemia	46%	10%	11%	2%	13%	3%
• Fatigue	41%	5%	**24%**	<1%	14%	1%
• Vomiting	32%	<1%	9%	1%	5%	<1%
• Leukopenia	29%	4%	6%	1%	5%	0%
• Hypercreatininemia	25%	1%	4%	<1%	3%	0%
TEAEs leading to discontinuation	9%		5%		1%	
• Treatment-related	5%		2%		0%	

SOC ET = standard of care endocrine therapy; TEAE = treatment-emergent adverse event

SUMMARY

EMBER-3

IMPACT

- With an additional 14 month of follow-up**, Imlunestrant monotherapy** in patients with *ESR1*m vs standard of care endocrine therapy:
  - Improved OS (11.4 months difference; HR=0.60; p=0.0043); boundary for significance was not achieved (*p*=0.0000004)
  - Minor PFS benefit and delay to subsequent receipt of chemotherapy by 5.4 months (*ESR1*m only)

- **Imlunestrant + abemaciclib**
  - Median PFS benefit in patients with *ESR1*m or *ESR1*wt HR+ BC
  - Consistent benefit across key subgroups including patients previously treated with CDK4/6i (results not shown)
  - Median OS not reached

- Low discontinuation rates in the imlunestrant + abemaciclib arm relative to available combination regimens

Imlunestrant monotherapy or in combination with abemaciclib may provide a treatment option after progression on endocrine therapy for patients with ER+, HER2- advanced breast cancer

FDA approved only single agent imlunestrant for ESR1m

September 25, 2025

cornerstone specialty network™

2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
- ASCENT-07
- EMBER-3
- evERA
- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

CLINICAL QUESTION

evERA BC

HR+ metastatic

Does giredestrant (GIRE+ everolimus (E)) benefit patients with ER-positive, HER2-negative metastatic breast cancer (ER+, HER2– aBC) previously treated with a CDK4/6 inhibitor?

Giredestrant: investigational oral SERD (selective estrogen antagonist and degrader)

evERA BC: Everolimus with Giredestrant or SoC ET in previously treated ER+ HER2- mBC

Study Design: Global, open-label, randomized phase III

Stratified by prior treatment with fulvestrant (yes/no), ESR1m (yes/no), site of disease (visceral vs non-visceral)

- ER+/HER2- aBC
- 1-3 prior lines of therapy with ≤2 prior lines of ET for aBC
- PD or relapse during/after CDK4/6i + ET
- No prior CT for aBC
- Measurable disease or evaluable bone mets

N=373

Giredestrant (30 mg) + everolimus (10 mg)† (n=183)

SOC ET (Exemestane/fulvestrant/tamoxifen) + everolimus (10 mg)† (n=190)

Until PD or unacceptable toxicity

† Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol

SOC ET: 141 exemestane; 39 fulvestrant; 6 tamoxifen; 4 not treated

Co-Primary Endpoint: Investigator-assessed (INV)-PFS in ESR1m and in the ITT population

Secondary Endpoints: OS, INV-assessed ORR, DoR

SOC = standard of care

ET = endocrine therapy

SABCS 2025. Abstract GS3-09.

evERA BC: Everolimus with Giredestrant or SoC ET in previously treated ER+ HER2- mBC

Baseline Characteristics

Characteristic, n (%)	Giredestrant + Everolimus (n = 183)	SoC ET + Everolimus (n = 190)
Median age, yr (range)	62.0 (27-83)	60.0 (28-84)
Female sex	182 (99.5)	187 (98.4)
Race		
• White	103 (56.3)	119 (62.6)
• Asian	66 (36.1)	57 (30.0)
• Black	9 (4.9)	9 (4.7)
• Other	5 (2.7)	5 (2.6)
Region		
• Asia-Pacific	58 (31.7)	49 (25.8)
• North America	69 (37.7)	75 (39.5)
• Western Europe	36 (19.7)	43 (22.6)
• Other	20 (10.9)	23 (12.1)
Visceral disease	126 (68.9)	131 (68.9)
• Disease involving the liver	89 (48.6)	100 (52.6)
Post-menopausal at screening	156 (85.2)	159 (83.7)

Characteristic, n (%)	Giredestrant + Everolimus (n = 183)	SoC ET + Everolimus (n = 190)
***ESR1*m detected at baseline**	**102 (55.7)**	**105 (55.3)**
***PIK3CA/AKT1/PTEN* alteration**	82 (44.8)	80 (42.1)
• *PIK3CA*m	64 (35.0)	51 (26.8)
• *AKT1 E17K* alteration	14 (7.7)	12 (6.3)
• *PTEN* alteration	13 (7.1)	28 (14.7)
Duration of prior CDK4/6i		
• <12 mo	44 (24.0)	50 (26.3)
• >12 months	136 (74.3)	135 (71.0)
• 12 to <24 mo	61 (33.3)	60 (31.6)
• >24 mon	75 (41.0)	75 (39.5)
Prior CDK4/6i	183 (100)	190 (100)
• Abemaciclib	53 (29.0)	49 (25.8)
• Palbociclib	104 (56.8)	119 (62.6)
• Ribociclib	52 (28.4)	54 (28.4)
Prior fulvestrant treatment	86 (47.0)	89 (46.8)
• First line with CDK4/6i	53 (29.0)	42 (22.1)

KEY DATA

evERA BC: Everolimus with Giredestrant or SoC ET in previously treated ER+ HER2- mBC

Co-Primary Endpoint: investigator assessed PFS in *ESR1*m population

	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	5.45 (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < .0001	

PFS benefit with giredestrant + everolimus observed across all subgroups in ESR1m population

Co-Primary Endpoint: investigator assessed PFS in ITT population

	Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190
Events, n (%)	126 (68.9)	163 (85.8)
Median, mo (95% CI)	**8.77** (6.60, 9.59)	5.49 (4.01, 5. 59)
Stratified HR (95% CI)	**0.56** (0.44, 0.71); P <.0001	

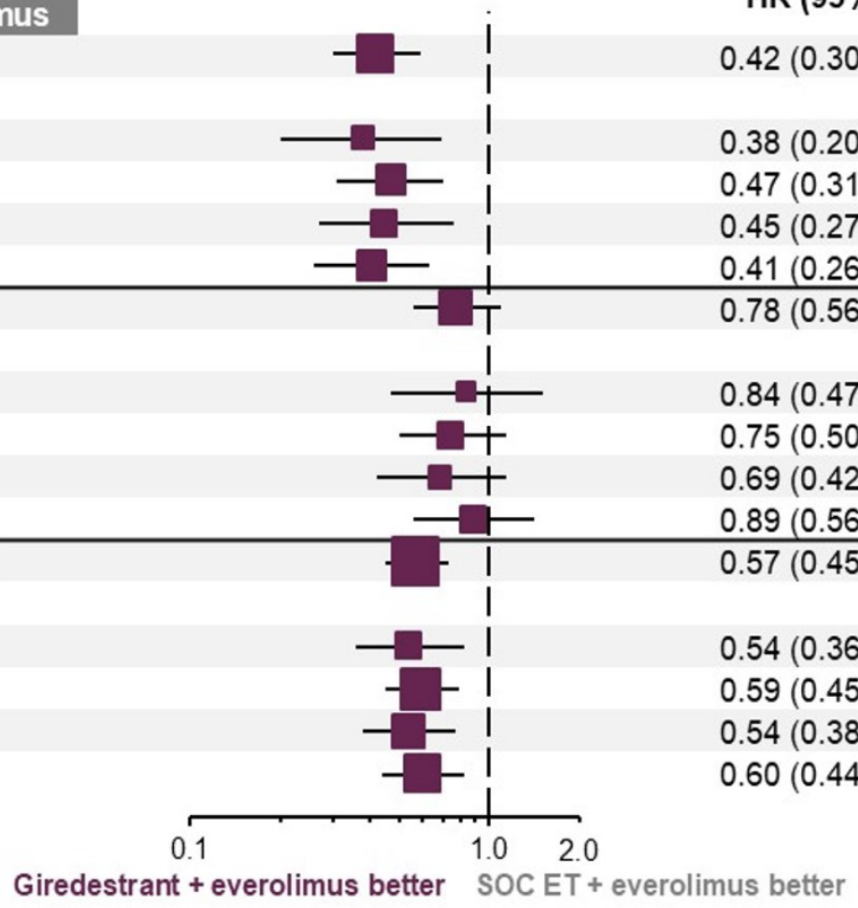
PFS benefit with giredestrant + everolimus observed across all subgroups in ITT population

SABCS 2025. Abstract GS3-09.

evERA BC: Everolimus with Giredestrant or SoC ET in previously treated ER+ HER2- mBC

Investigator-PFS by PIK3CA/AKT1/PTEN alteration status

	Total, n	Patients, n: Giredestrant + everolimus	Patients, n: SOC ET + everolimus	HR (95% CI)
All patients with *ESR1*m[1]	207	102	105	0.42 (0.30, 0.59)
Genomic alteration				
*PIK3CA*m detected	64	35	29	0.38 (0.20, 0.69)
*PIK3CA*m not detected	143	67	76	0.47 (0.31, 0.70)
PIK3CA/AKT1/PTEN alteration detected	89	47	42	0.45 (0.27, 0.76)
PIK3CA/AKT1/PTEN alteration not detected	118	55	63	0.41 (0.26, 0.63)
All patients with *ESR1*m not detected	166	81	85	0.78 (0.56, 1.10)
Genomic alteration				
*PIK3CA*m detected	51	29	22	0.84 (0.47, 1.52)
*PIK3CA*m not detected	115	52	63	0.75 (0.50, 1.14)
PIK3CA/AKT1/PTEN alteration detected	73	35	38	0.69 (0.42, 1.14)
PIK3CA/AKT1/PTEN alteration not detected	93	46	47	0.89 (0.56, 1.41)
All ITT patients[1]	373	183	190	0.57 (0.45, 0.73)
Genomic alteration				
*PIK3CA*m detected	115	64	51	0.54 (0.36, 0.83)
*PIK3CA*m not detected	258	119	139	0.59 (0.45, 0.79)
PIK3CA/AKT1/PTEN alteration detected	162	82	80	0.54 (0.38, 0.77)
PIK3CA/AKT1/PTEN alteration not detected	211	101	110	0.60 (0.44, 0.83)



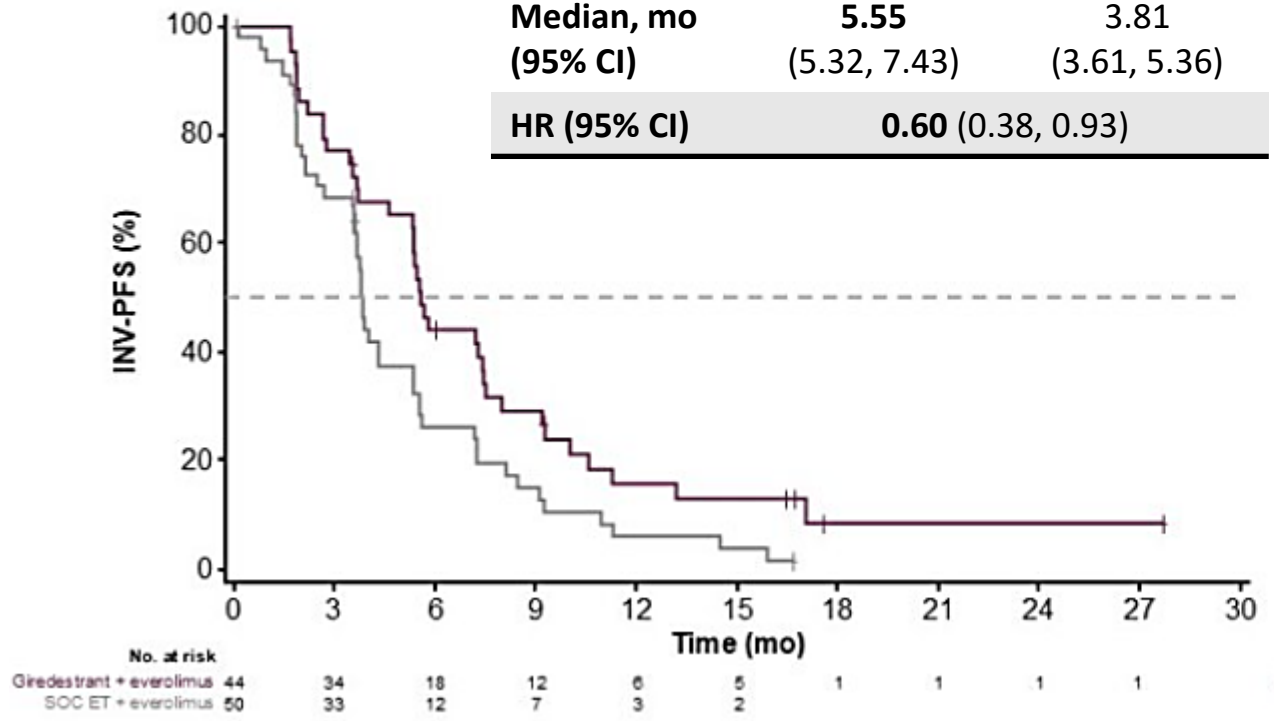
SABCS 2025. Abstract GS3-09.

evERA BC: Everolimus with Giredestrant or SoC ET in previously treated ER+ HER2- mBC

Investigator-PFS by duration of prior CDK4/6i (ITT population)

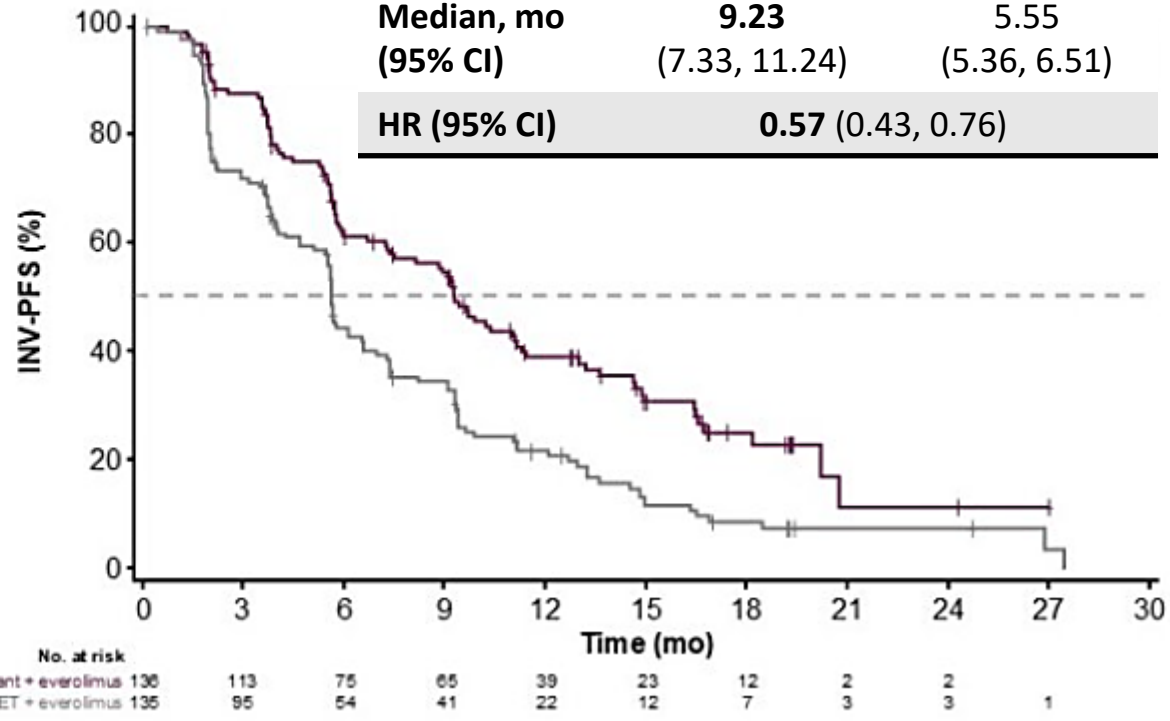
< 12 mo*

	Giredestrant + everolimus n = 44	SOC ET + everolimus n = 50
Events, n (%)	37 (84.1)	45 (90.0)
Median, mo (95% CI)	**5.55** (5.32, 7.43)	3.81 (3.61, 5.36)
HR (95% CI)	**0.60** (0.38, 0.93)	



≥ 12 mo*

	Giredestrant + everolimus n = 136	SOC ET + everolimus n = 135
Events, n (%)	88 (64.7)	115 (85.2)
Median, mo (95% CI)	**9.23** (7.33, 11.24)	5.55 (5.36, 6.51)
HR (95% CI)	**0.57** (0.43, 0.76)	

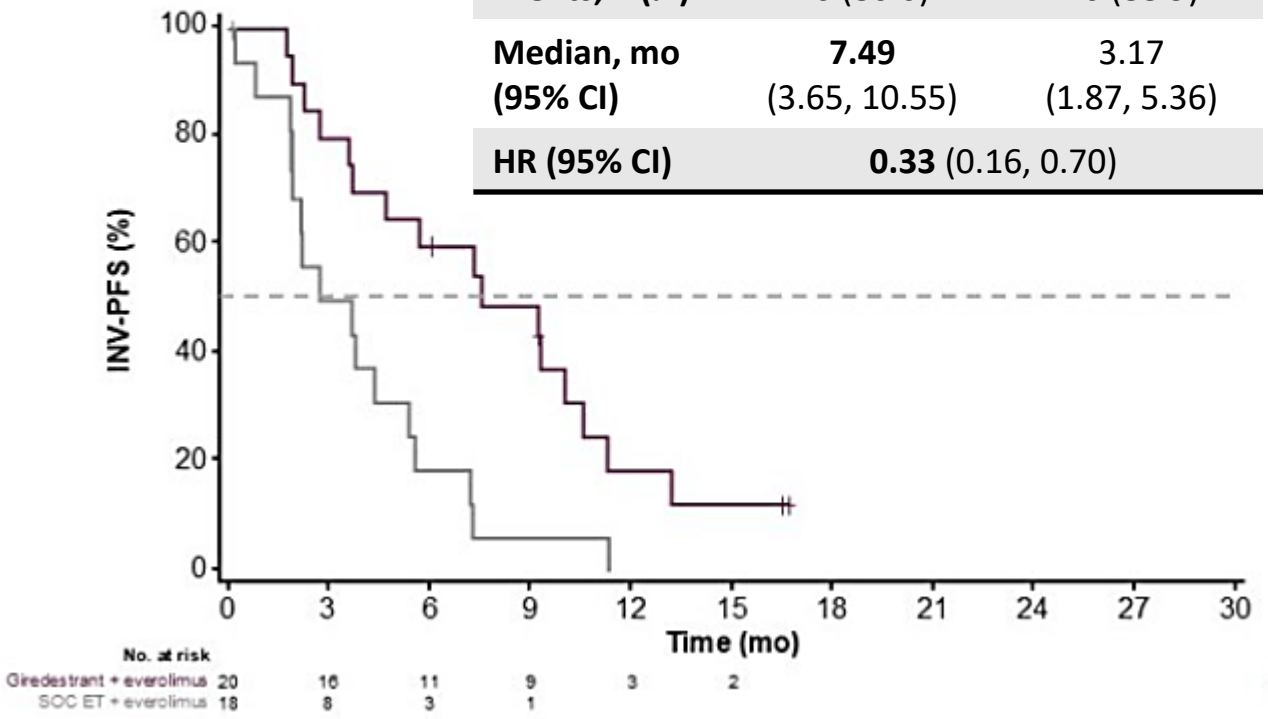


evERA BC: Everolimus with Giredestrant or SoC ET in previously treated ER+ HER2- mBC

INV-PFS by duration of prior CDK4/6i (ESR1m population)

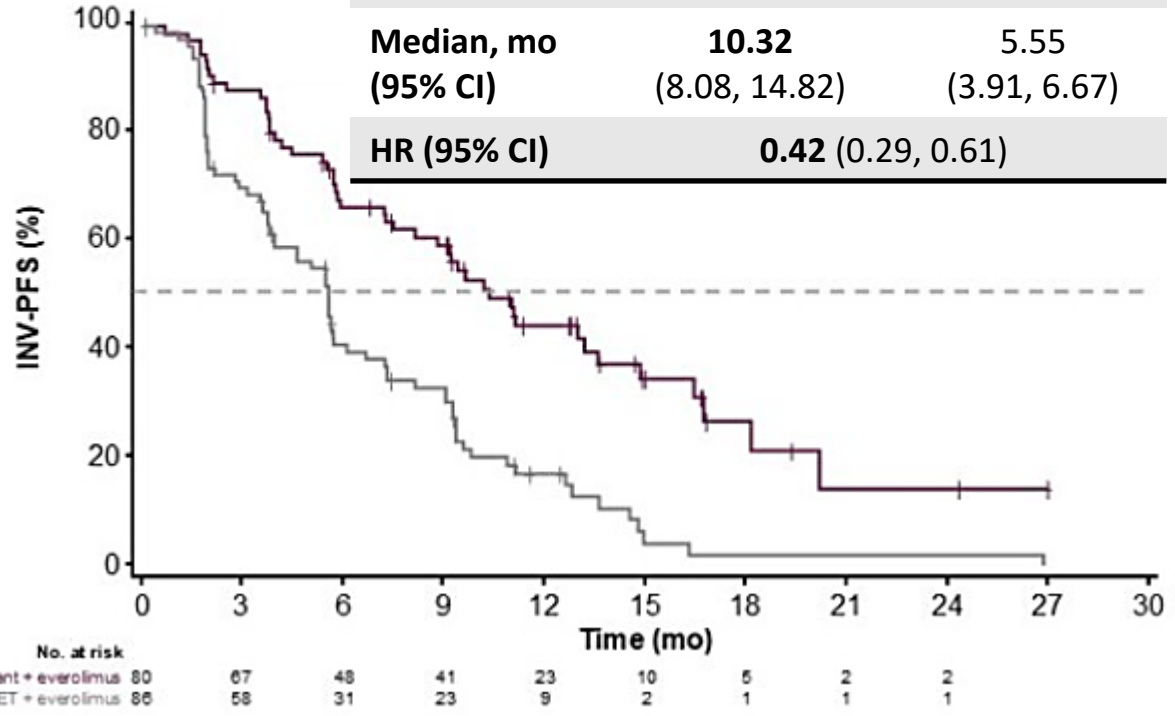
< 12 mo*

	Giredestrant + everolimus n = 20	SOC ET + everolimus n = 18
Events, n (%)	16 (80.0)	16 (88.9)
Median, mo (95% CI)	**7.49** (3.65, 10.55)	3.17 (1.87, 5.36)
HR (95% CI)	**0.33** (0.16, 0.70)	



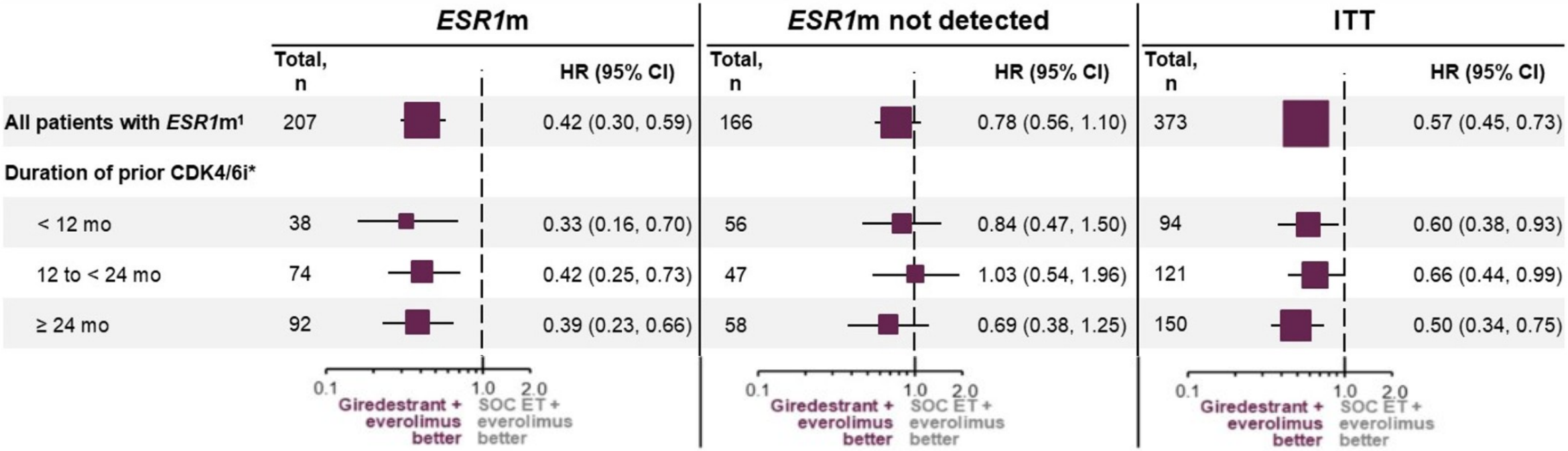
≥ 12 mo*

	Giredestrant + everolimus n = 80	SOC ET + everolimus n = 86
Events, n (%)	47 (58.8)	73 (84.9)
Median, mo (95% CI)	**10.32** (8.08, 14.82)	5.55 (3.91, 6.67)
HR (95% CI)	**0.42** (0.29, 0.61)	



evERA BC: Everolimus with Giredestrant or SoC ET in previously treated ER+ HER2- mBC

Investigator-PFS by duration of prior CDK4/6i



SUMMARY

evERA BC

- Giredestrant + everolimus improved investigator-assessed PFS vs SoC ET + everolimus in patients with ER+/HER2- aBC who had previously received CDK4/6i therapy
  - In ESR1m population, the combination led to 62% lower risk of disease progression or death (HR: **0.38**), with median INV-PFS of **9.99** mo vs 5.45 mo for the control arm
  - In ITT population, regimen achieved 44% lower risk of progression or death (HR: **0.56**), corresponding to median INV-PFS of **8.77** mo vs 5.49 mo for standard therapy
- Both *ESR1*m and ITT populations benefited from giredestrant + everolimus

IMPACT

Giredestrant + everolimus may be a new oral therapy option for ER+/HER2- metastatic breast cancer after CDK4/6i therapy

Not yet FDA approved

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2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
- ASCENT-07
- EMBER-3
- evERA
- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

EPIK-B5: Alpelisib + fulvestrant in *PIK3CA*m HR+, HER2- mBC

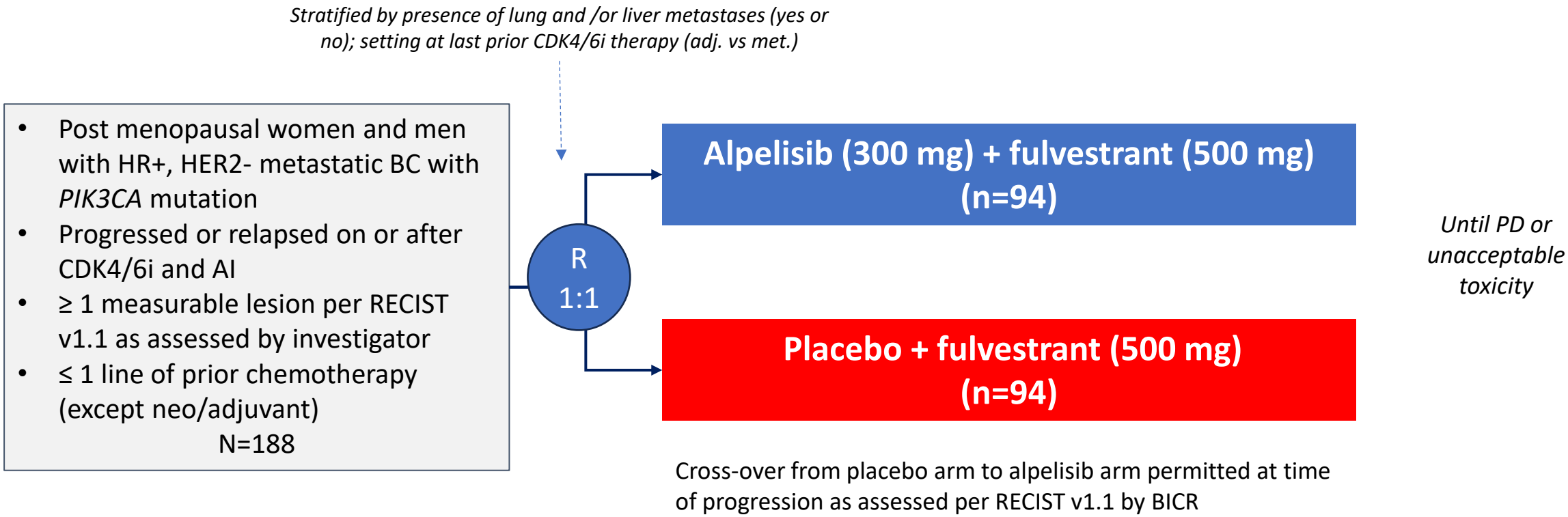
Does alpelisib plus fulvestrant benefit patients with PIK3CA-mutated, HR+, HER2- mBC after a CDK4/6 inhibitor?

Updated Overall Survival

KEY DATA

EPIK-B5: Alpelisib + fulvestrant in *PIK3CA*m HR+, HER2- mBC

Study Design: International, randomized phase III study



Primary Endpoint: PFS by BICR
Secondary Endpoints: OS, ORR, Clinical Benefit Rate (CBR), DOR, TTR by BICR, PFS by BICR by *PICK3CA* mutation status in ctDNA, Safety, ECOG, QoL,PFS2

Data cutoff: 15 Oct, 2024

SABCS 2025. Abstr RF7-02.

EPIK-B5: Alpelisib + fulvestrant in *PIK3CA*m HR+, HER2- mBC

Baseline Characteristics

	Alpelisib + Fulvestrant (n=94)	Placebo + Fulvestrant (n=94)
Median age (years)	62.0	61.5
ECOG 0 | 1 (%)	56.4 | 41.5	63.8 | 35.1
Visceral metastasis (%)	78.7	76.6
• Liver and/or lung metastasis (%)	71.3	71.3
Prior therapy (%)		
• Prior CDK4/6i in any setting	100	100
• Adjuvant chemotherapy	28.7	31.9
• Metastatic chemotherapy	12.8	18.1
Duration of prior CDK4/6i in metastatic setting		
• < 6 months (%)	11.7	10.6
• ≥ 6 months (%)	86.2	89.4
Number of metastatic sites (%)		
• 1	16.0	23.4
• 2	45.7	42.6
• ≥3	37.2	34.0

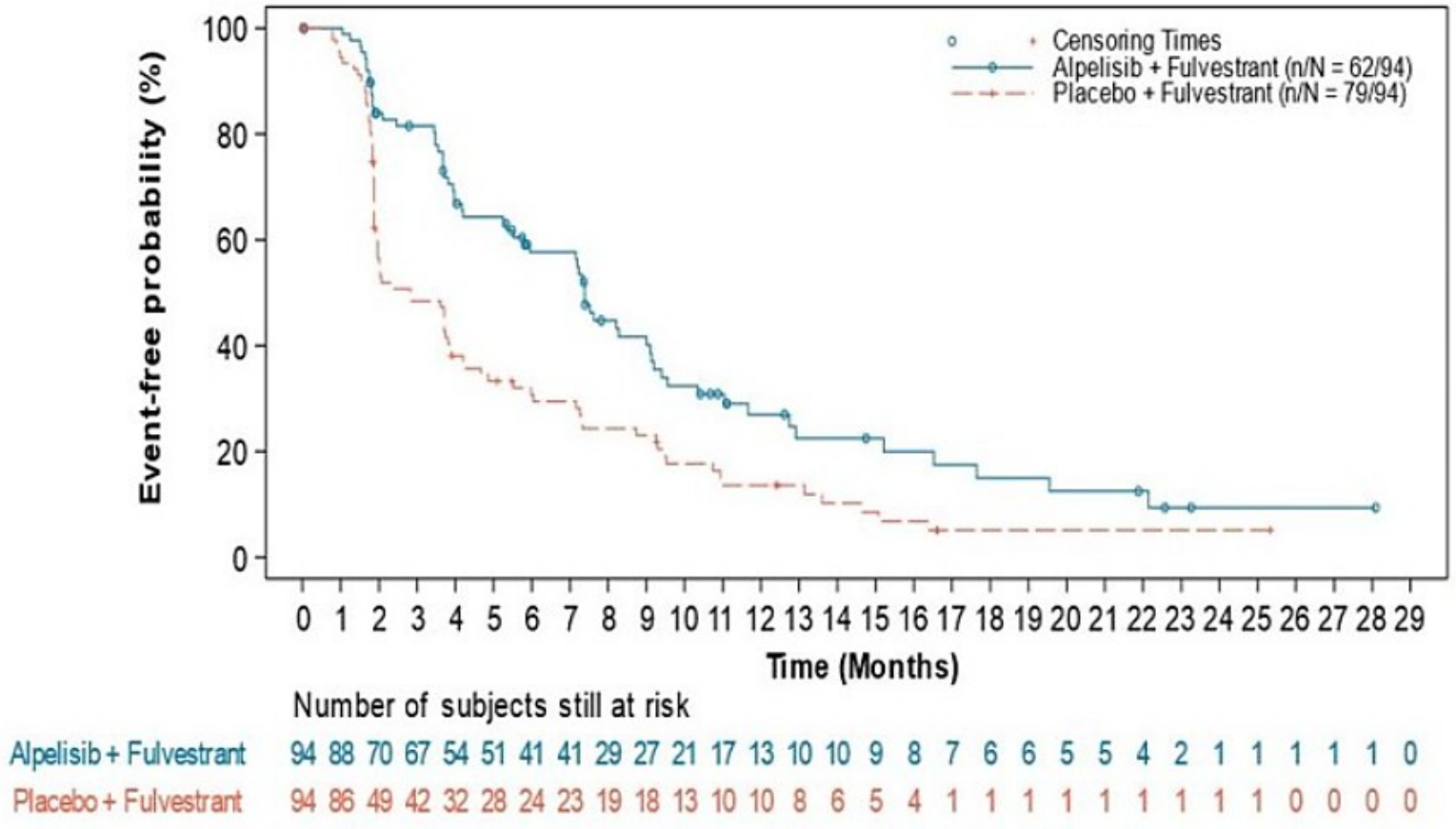
Data cutoff: 15 Oct, 2024

SABCS 2025. Abstr RF7-02.

KEY DATA

EPIK-B5: Alpelisib + fulvestrant in *PIK3CA*m HR+, HER2- mBC

Primary Endpoint: PFS by BICR per RECIST 1.1 during double-blind treatment



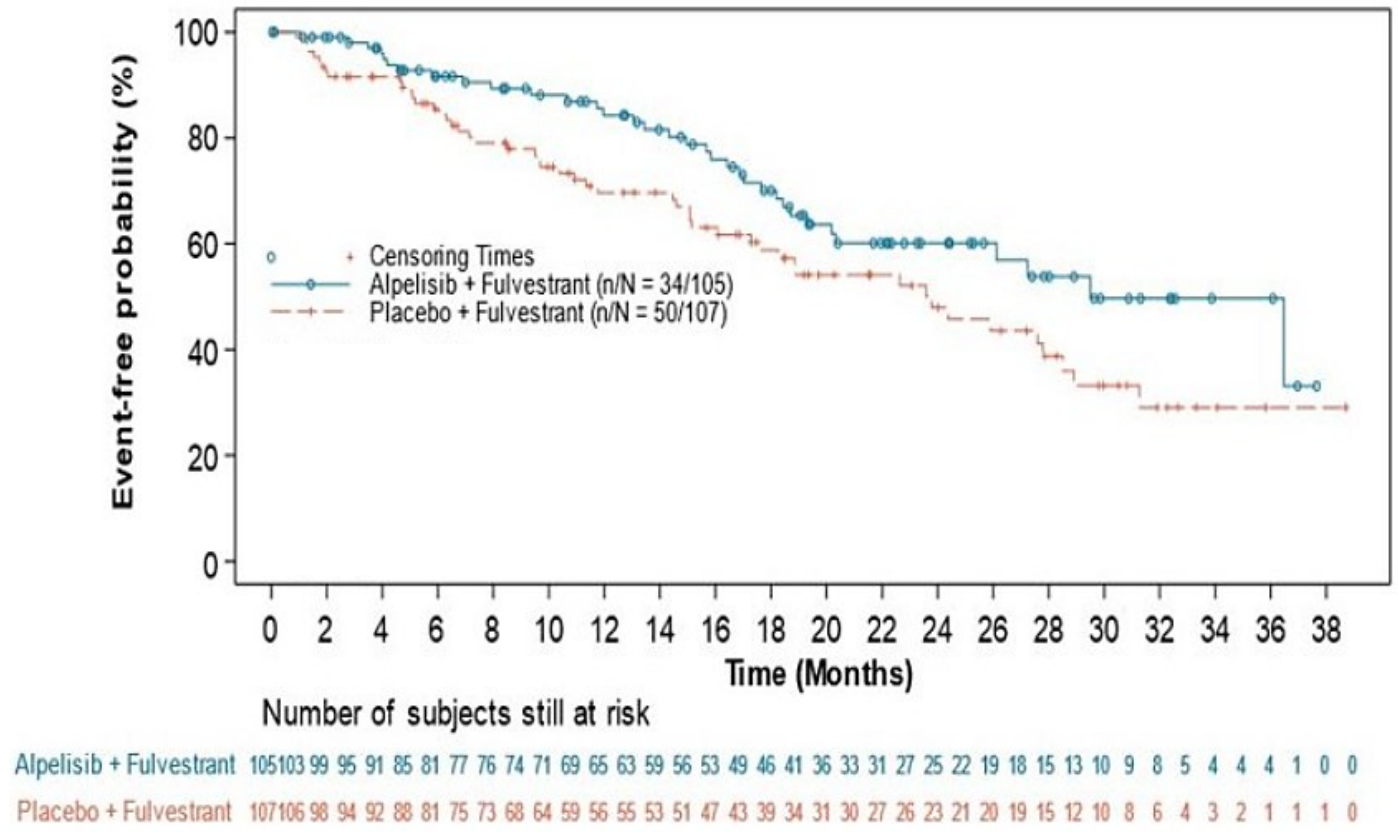
Data cutoff: 15 Oct, 2024	Alpelisib + Fulvestrant (n=94)	Placebo + Fulvestrant (n=94)
Events, n (%)	62 (66.0%)	79 (84.0%)
• **Progression**	56 (59.6%)	70 (74.5%)
• **Death**	6 (6.4%)	9 (9.6%)
• **Censored**	32 (34.0%)	15 (16.0%)
Median PFS (95% CI)	**7.4** (5.52 – 9.10)	**2.8** (1.94 – 3.84)
HR (95% CI)	**0.52** (0.37 – 0.72)	
P-value	**< 0.0001**	

SABCS 2025. Abstr RF7-02.

KEY DATA

EPIK-B5: Alpelisib + fulvestrant in *PIK3CA*m HR+, HER2- mBC

Secondary Endpoints:
Updated Overall survival (ITT analysis: includes 43 (40.2%) cross over)



	Alpelisib + Fulvestrant (n=94)	Placebo + Fulvestrant (n=94)
Data cutoff: 26 May, 2025		
Events, n (%) • **Death** • **Censored**	34 (32.4%) 71 (67.6%)	50 (46.7%) 57 (53.3%)
Median OS	**29.5**	**23.8**
HR (95% CI)	**0.64** (0.41 – 0.99)	
P-value	**0.021**	

*For Alpelisib and placebo
** Those reductions were primarily attributable to AEs (45.7% vs. 0%) in patients receiving alpelisib and placebo, respectively
***Dose interruptions were primarily attributable to AEs (68.5% vs. 13.8%) in patients receiving alpelisib and placebo, respectively
****Permanent alpelisib and placebo discontinuations were primarily attributable to progressive disease (40.2% vs. 75.5%) and AEs (27.2% vs. 2.1%)

SABCS 2025. Abstr RF7-02.

EPIK-B5: Alpelisib + fulvestrant in *PIK3CA*m HR+, HER2- mBC

Safety: Most common AEs (>10% in any arm, double blinded period)

	Alpelisib + Fulvestrant (N=94)		Placebo + Fulvestrant (n=94)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
At least one AE	92 (100)	65 (70.7)	81 (86.2)	31 (33.0)
Hyperglycemia	67 (72.8)	30 (32.6)	11 (11.7)	0
Diarrhea	47 (51.1)	2 (2.2)	11 (11.7)	0
Nausea	41 (44.6)	1 (1.1)	13 (13.8)	0
Decreased appetite	28 (30.4)	4 (4.3)	6 (6.4)	0
Rash	28 (30.4)	12 (13.0)	1 (1.1)	0
Asthenia	25 (27.2)	4 (4.3)	15 (16.0)	0
Muscosal inflammation	20 (21.7)	3 (3.3)	0	0
Vomiting	17 (18.5)	0	6 (6.4)	0
Stomatitis	15 (16.3)	4 (4.3)	2 (2.1)	1 (1.1)
Decreased weight	14 (15.2)	5 (5.4)	1 (1.1)	0
Fatigue	13 (14.1)	0	8 (8.5)	1 (1.1)

	Alpelisib + Fulvestrant (N=94)		Placebo + Fulvestrant (n=94)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Pyrexia	13 (14.1)	1 (1.1)	7 (7.4)	0
Anemia	12 (13.0)	0	12 (12.8)	1 (1.1)
Blood Creatinine increased	11 (12.0)	0	1 (1.1)	0
Rash Maculo-papular	10 (10.9)	7 (7.6)	0	0
Aspartate aminotransferase increased	9 (9.8)	3 (3.3)	13 (13.8)	6 (6.4)
Arthralgia	8 (8.7)	1 (1.1)	15 (16.0)	0
Alanine aminotransferase increased	7 (7.6)	3 (3.3)	14 (14.9)	5 (5.3)
Constipation	3 (3.3)	0	10 (10.6)	1 (1.1)
Gamm-glutamyl transferase increased	3 (3.3)	1 (1.1)	14 (14.9)	7 (7.4)

Data cutoff: 15 Oct, 2024

SABCS 2025. Abstr RF7-02.

SUMMARY

EPIK-B5

- Alpelisib + fulvestrant improved investigator-assessed PFS vs placebo + fulvestrant in patients with PIK3CA-mutated, HR+, HER2- mBC who had previously received AI and CDK4/6i therapy
  - The combination led lower risk of disease progression or death (HR: 0.52), with median PFS of 7.4 mo vs 2.8 mo for the control arm
- A 5.7 months improvement in median OS was observed (HR: 0.64, 95% CI: 0.41-0.99) in favor of the alpelisib + fulvestrant arm
- Notable adverse events require proactive monitoring / management and careful patient selection

IMPACT

Alpelisib plus fulvestrant provides benefit to patients with PIK3CA-mutated, HR+, HER2- metastatic breast cancer after a CDK4/6 inhibitor

Toxicity requires special consideration

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Polling question

Have you prescribed alpelisib?

1. Never used
2. Used in 1 patient
3. Used in 1-3 patient
4. Used in more than 3 patients

Polling question

Based on the EPIK-B5 data, how are you most likely to incorporate alpelisib + fulvestrant in patients with HR+/HER2−, PIK3CA-mutated metastatic breast cancer who have progressed on a CDK4/6 inhibitor?

1. As my preferred next-line therapy
2. After failure of another endocrine-based regimen
3. Only in select patients due to tolerability concerns
4. Unlikely to use; I favor alternative options

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NCCN Guidelines Version 1.2026 - Jan 16, 2026

CYTOTOXIC REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
See BINV-Q 1 of 15 for Considerations for Systemic Therapy.		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* PV[b] and/or HER2 (*ERBB2*) IHC 0+, 1+, or 2+/ISH negative[d]	Systemic chemotherapy[e] (category 1, preferred) (BINV-Q 5 of 15), or Fam-trastuzumab deruxtecan-nxki[e,f] (other recommended)
	Germline *BRCA1/2* PV[b]	PARPi (Olaparib or Talazoparib)[c] (category 1, preferred)
Second Line	HER2 (*ERBB2*) IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[f] (category 1, preferred)
	HER2 (*ERBB2*) IHC 0+[d]	Fam-trastuzumab deruxtecan-nxki[f] (other recommended)
	Not a candidate for Fam-trastuzumab deruxtecan-nxki	Sacituzumab govitecan-hziy[g] (category 1, preferred)
		Systemic chemotherapy (BINV-Q 5 of 15)
		Targeted therapy (BINV-Q 6 of 15 and BINV-Q 7 of 15)
		For HER2 (*ERBB2*) IHC 0, 1+, or 2+/ISH negative:[d] Datopotamab deruxtecan-dlnk[h] (other recommended)
Third Line and Beyond	Any	Systemic chemotherapy (BINV-Q 5 of 15)
	Biomarker positive (ie, MSI-H, *NTRK1/2/3* and *RET* gene fusions, TMB-H)	Targeted agents and emerging biomarker options (BINV-Q 6 of 15, BINV-Q 7 of 15, and BINV-Q 8 of 15)

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SABCS 2025

HR+ Breast Cancer

Key Takeaways

Q&A

@SujithKalmadiMD

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lidERA*:* In ER+, HER2- early breast cancer adjuvant setting, giredestrant reduced the risk of recurrence, with a 36-mo invasive disease-free survival of rate 92.4% versus 89.6% with standard endocrine therapy – *not yet approved*

ASCENT-07*:* Sacituzumab govitecan as first-line post–endocrine therapy setting did not demonstrate benefit over chemotherapy and remains a later-line standard of care for HR+, HER2- metastatic breast cancer – *not yet approved in first-line setting*

EMBER-3: Imlunestrant monotherapy provided 11.4-month benefit in overall survival vs standard of care (HR: 0.60; 95% CI, 0.42-0.86; p=0.0043) in ER+, HER2-, *ESR1*m advanced breast cancer, supporting its potential as a new standard of care – *FDA approved September 2025*

evERA*:* In ER+/HER2– advanced breast cancer, post-CDK4/6 inhibitors treatment with giredestrant plus everolimus reduced the risk of progression by ~44% overall and ~62% in *ESR1*-mutant patients versus standard endocrine therapy + everolimus – *not yet approved*

EPIK-B5*:* Alpelisib plus fulvestrant after a CDK4/6 inhibitor, lowered the risk of disease progression or death (median PFS of 7.4 mo vs 2.8 mo) and improving median overall survival by 5.7 months for patients with PIK3CA-mutated, HR+, HER2- mBC after a CDK4/6 inhibitor; notable adverse events require proactive monitoring / management and careful patient selection – *FDA approved May 2019*

Setting the Stage for our Discussion of 2025 SABCS Data for HER2+ Breast Cancer

- Impactful practice changing studies presented at **ESMO 2025** in
  - Neoadjuvant (DESTINY-Breast11)
  - Post neoadjuvant (DESTINY-Breast05)
  - First line metastatic setting (DESTINY-Breast09)
- One FDA approval since ESMO 2025
  - DESTINY-Breast09 (T-DXd + pertuzumab) – 1L metastatic HER2+ BC

*At **SABCS 2025***

- More detailed safety and PRO data from ASCO and ESMO 2025 studies
- New data in the 1L metastatic HER2+ setting – HER2Climb05

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2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
- ASCENT-07
- EMBER-3
- evERA
- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

CLINICAL QUESTION

DESTINY-Breast11

HER2+ neoadjuvant

Does neoadjuvant trastuzumab deruxtecan followed by paclitaxel + trastuzumab + pertuzumab (T-DXd-THP) vs anthracycline-cyclophosphamide ddAC-THP benefit patients with high-risk HER2+ primary breast cancer?

(T-DXd x4 → THP x4) *vs* (ddAC x4→ THP x4)

Additional safety and PRO data

KEY DATA

DESTINY-Breast11, neoadjuvant T-DXd x4 → THP x4 vs ddAC x4 → THP x4

Study Design: Open-label, randomized phase III study

- HER2+ early breast cancer (eBC) considered high risk, defined as ≥cT3 and N0-3 or cT0-4 and N1-3 or with inflammatory BC
- (N = 927)

Stratified by HR status (ER and/or PR pos vs neg), HER2 status (IHC 3+ vs ISH+ without IHC 3+)

T-DXd, 5.4 mg/kg IV q3w (4 cycles) → **THP**[†] (4 cycles) (n = 321)

ddAC[‡] (4 cycles) → **THP**[§] (4 cycles) (n = 320)

T-DXd* (8 cycles) (n = 286)

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

Primary endpoint: pCR (ypT0/is ypN0) by blinded central review
Secondary endpoints: pCR (ypT0 ypN0) by blinded central review, EFS, Safety, PK and immunogenicity, Invasive DFS, Overall survival, Health-related quality of life
Additional outcome measures: Residual cancer burden (RCB)

***T-DXd alone arm** closed following IDMC recommendation on March 13, 2024, due to lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, surgery time

[†] Paclitaxel 80 mg/m^2 IV qw, trastuzumab 6 mg/kg IV q3w, pertuzumab 840 mg → 420 mg IV q3w. [‡]Doxorubicin 60 mg/m^2 IV q2w, cyclophosphamide 600 mg/m^2 IV q2w. [§]Paclitaxel 80 mg/m^2 IV qw, trastuzumab 8 mg/kg → 6 mg/kg IV q3w, pertuzumab 840 mg → 420 mg IV q3w.

ESMO 2025. Abstr 291O. Harbeck. Ann Oncol. 2025 [Epub].

KEY DATA

DESTINY-Breast11, neoadjuvant T-DXd x4 → THP x4 vs ddAC x4 → THP x4

Primary Endpoint: pCR presented at ESMO 2025

pCR rate	T-DXd–THP	ddAC-THP
ITT population	**67.3%** (216/321)	**56.%** (180/320)
	Δ 11.2% (95% CI 4.0, 18.3; P=0.003)	
HR-Positive	**61.4%** (145/236)	**52.3%** (123/235)
	Δ 9.1% (95% CI 0.2, 17.9)	
HR-Negative	**83.1%** (69/83)	**67.1%** (57/85)
	Δ 16.1% (95% CI 3.0, 28.8)	

ESMO 2025. Abstr 291O. Harbeck. Ann Oncol. 2025 [Epub];
SABCS 2025. Abstract RF6-02.

KEY DATA

DESTINY-Breast11, neoadjuvant T-DXd x4 → THP x4 vs ddAC x4 → THP x4

Additional safety screening recommendations and data presented at SABCS 2025

- HER2+ early breast cancer (eBC) considered high risk, defined as ≥cT3 and N0-3 or cT0-4 and N1-3 or with inflammatory BC
- (N = 927)

T-DXd, 5.4 mg/kg IV q3w (4 cycles) → **THP**[†] (4 cycles) (n = 321)

ddAC[‡] (4 cycles) → **THP**[§] (4 cycles) (n = 320)

T-DXd (8 cycles) (n = 286) (*Arm closed early – will share safety data*)

Surgery + post-neoadjuvant treatment

Chest HRCT scans were performed at screening, Q6W until end of treatment, at safety follow up, and if ILD/pneumonitis was suspected

- If ILD/pneumonitis was confirmed, follow up continued until resolution; potential cases were retrospectively evaluated by an independent ILD Adjudication Committee

Heart failure adverse events were recoded until end of treatment and at end of study (up to 6 years' follow up)

Safety follow-up: 40+7 days from last dose of study treatment

HRCT = high resolution CT
ILD = interstitial lung disease

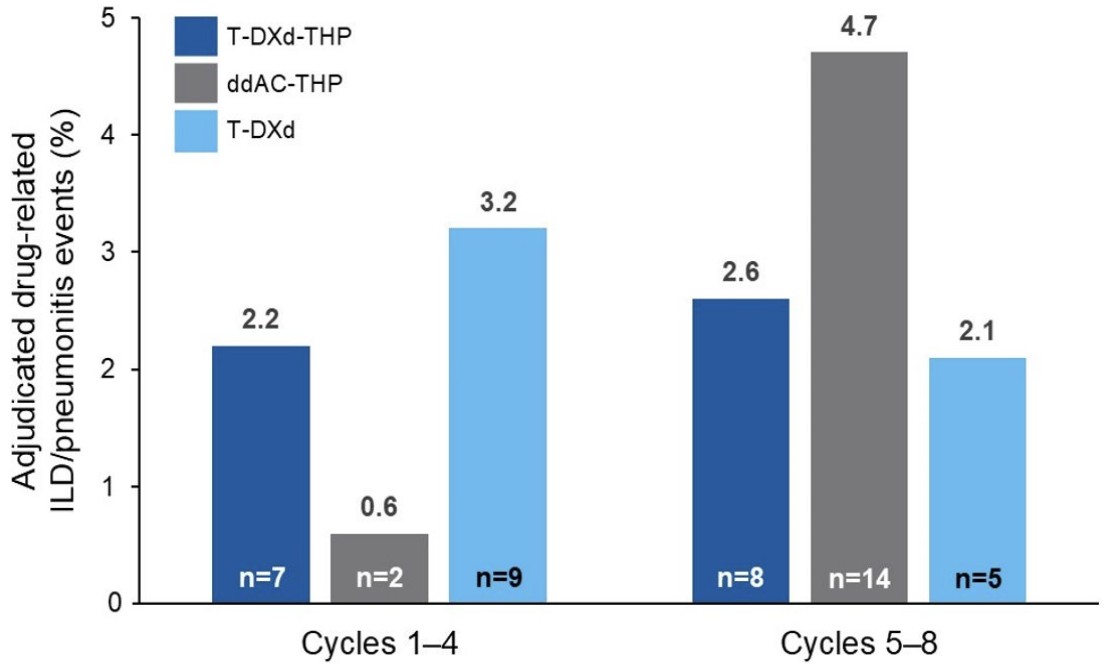
SABCS 2025. Abstract RF6-02.

DESTINY-Breast11, neoadjuvant T-DXd x4 → THP x4 vs ddAC x4 → THP x4

Adjudicated drug-related ILD/pneumonitis: event by cycle

n, (%)	T-DXd–THP (n=320)	ddAC-THP (n=312)	T-DXd (n = 283)
All grade	**14 (4.4)**	**16 (5.1)**	**14 (4.9)**
• Grade 1	4 (1.3)	4 (1.3)	2 (0.7)
• Grade 2	8 (2.5)	6 (1.9)	12 (4.2)
• Grade 3	1 (0.3)	5 (1.6)	0
• Grade 4	0	0	0
• Grade 5	1 (0.3)	1 (0.3)	0
• Grade ≥3 AEs	2 (0.6)	6 (1.9)	0
• **Median Time to Onset (range)**	82.5 (32 – 184) n=14	77.0 (41 – 149) n=16	78.0 (25 – 155) n=14

Adjudicated drug-related ILD/pneumonitis by cycle of onset[++]



[++] percentages are calculated using the number of patients at risk at any point in the cycle window as the denominator, and patients may be counted twice if they had multiple events in different cycles

DESTINY-Breast11, neoadjuvant T-DXd x4 → THP x4 vs ddAC x4 → THP x4

Additional Safety Data: Left ventricular dysfunction

n, (%)	T-DXd–THP (n=320)	ddAC-THP (n=312)	T-DXd (n = 283)
Left ventricular dysfunction	4 (1.3)	19 (6.1)	2 (0.7)
• Grade 1	0	3 (1.0)	0
• Grade 2	3 (0.9)	10 (3.2)	2 (0.7)
• Grade 3	1 (0.3)	6 (1.9)	0
• Grade ≥3	1 (0.3)	6 (1.9)	0
Ejection fraction decreased	4 (1.4)	15 (4.8)	2 (0.7)
• Grade 2	3 (0.9)	9 (1.9)	2 (0.7)
• Grade 3	1 (0.3)	6 (1.9)	0
• Grade ≥3	1 (0.3)	6 (1.9)	0
Cardiac failure	0	4 (1.3)	0
• Grade 1	0	3 (1.0)	0
• Grade 2	0	1 (0.3)	0

SABCS 2025. Abstract RF6-02.

DESTINY-Breast11, neoadjuvant T-DXd x4 → THP x4 vs ddAC x4 → THP x4

Additional Safety Data: Nausea and vomiting, events by cycle and antiemetic use

n, (%)	T-DXd–THP (n=320)	ddAC-THP (n=312)	T-DXd (n = 283)
All-grade nausea	207 (64.7)	161 (51.6)	193 (68.2)
• Grade ≥3	6 (1.9)	1 (0.3)	3 (1.1)
All-grade vomiting	92 (28.8)	66 (21.2)	88 (31.1)
• Grade ≥3	3 (0.9)	2 (0.6)	3 (1.1)

Per protocol, prophylaxis with 2-3 antiemetics* prior to each dose of T-DXd was recommended, but not mandated

Protocol-recommended antiemetics on or prior to Cycle 1 Day 1*			
• 3-antiemetic regimen	54 (16.9)	124 (39.7)	40 (14.1)
• 2-antiemetic regimen	183 (57.2)	126 (40.4)	157 (55.5)

*Use of 2 or more of the following was recommended by the protocol: a glucocorticoid, serotonin (5-HT3) receptor antagonist, and a neurokinin-1 receptor antagonist

SUMMARY

DESTINY-Breast11

- Neoadjuvant T-DXd x4 → THP x4 demonstrated low rates of adjudicated drug-related ILD/pneumonitis across arms and fewer Grade ≥3 events compared to ddACx4 → THP x4

- Rates of overall and Grade ≥3 left ventricular dysfunction were lower (0.3% vs 1.9%)
  - No events of cardiac failure in T-DXd arms

- Rates of nausea and vomiting were higher with T-DXD x 4 →THP x4, highlighting the importance of following guideline recommendations for antiemetics
  - Events were generally low grade, and rates decreased after Cycles 1-4

IMPACT

Trastuzumab deruxtecan followed by THP is a potential new neoadjuvant treatment option for patients with high-risk HER2+ early breast cancer

Additional safety data support becoming a new standard of care -- not yet FDA approved

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Polling question: neoadjuvant HER2+

*Based on the presented **DB-11 trial** additional safety data, and if approved by the FDA: does the additional safety data increase your comfort for prescribing T-DXd x4 → THP x4 in the <u>neoadjuvant</u> HER2+ setting?*

1. Yes
2. No
3. Unsure

2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
- ASCENT-07
- EMBER-3
- evERA
- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

CLINICAL QUESTION

DESTINY-Breast05

HER2+ post neoadjuvant

Does post-neoadjuvant trastuzumab deruxtecan vs trastuzumab emtansine (T-DM1) benefit patients with high-risk HER2+ primary early breast cancer with residual invasive disease after neoadjuvant Tx?

Additional efficacy and safety data

KEY DATA

DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

Study Design: Open-label, randomized phase III

- Residual invasive disease in breast and/or axillary LNs after neoadjuvant chemo with HER2-directed therapy (NAT*)
- High-risk defined as presentation prior to NAT with
  - inoperable early BC (cT4, N0-3, M0 or cT1-3, N2-3, M0) OR
  - operable early BC (cT1-3, N0-1, M0) with axillary node-positive disease (ypN1-3) after NAT
- HER2+ (IHC 3+ or ISH+) early BC
- ECOG PS 0-1

*NAT=neoadjuvant therapy: ≥16 wks NAT with ≥9 wks trastuzumab ± pertuzumab and ≥9 wks taxane-based chemotherapy

T-DXd 5.4 mg/kg IV q3w for 14 cycles N ≅ 800

T-DM1 3.6 mg/kg IV q3w for 14 cycles N ≅ 800

Concomitant adjuvant endocrine therapy (ET) allowed. If administered, RT could be initiated concurrently with study therapy or completed prior to initiation of study therapy (sequential) per investigator.

40-day safety follow-up

Stratified by extent of disease at presentation (inoperable vs operable), HER2-targeted NAT (single vs dual), HR status (pos vs neg), post-NAT pathologic nodal status (pos vs neg)

Primary endpoint:

- Invasive disease–free survival (IDFS)

Secondary endpoints:

- Disease-free survival (DFS)
- Overall survival (OS)
- Distant recurrence–free interval (DRFI)
- Brain metastasis–free interval (BMFI)
- Safety

Interim analysis timeline
Data Cutoff: 2 July 2025

KEY DATA

DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

Primary Endpoint: Invasive disease–free survival (IDFS) at ESMO 2025

	T-DXd (n = 818)		T-DM1 (n = 817)
3-yr IDFS	**92.4%** (89.7-94.4)	**Δ 8.7%**	**83.7%** (80.2-86.7)
HR (95% CI)	**0.47** (0.34-0.66)		
P Value	**<0.0001**		

>72% of patients in each arm completed the planned 14 cycles of therapy

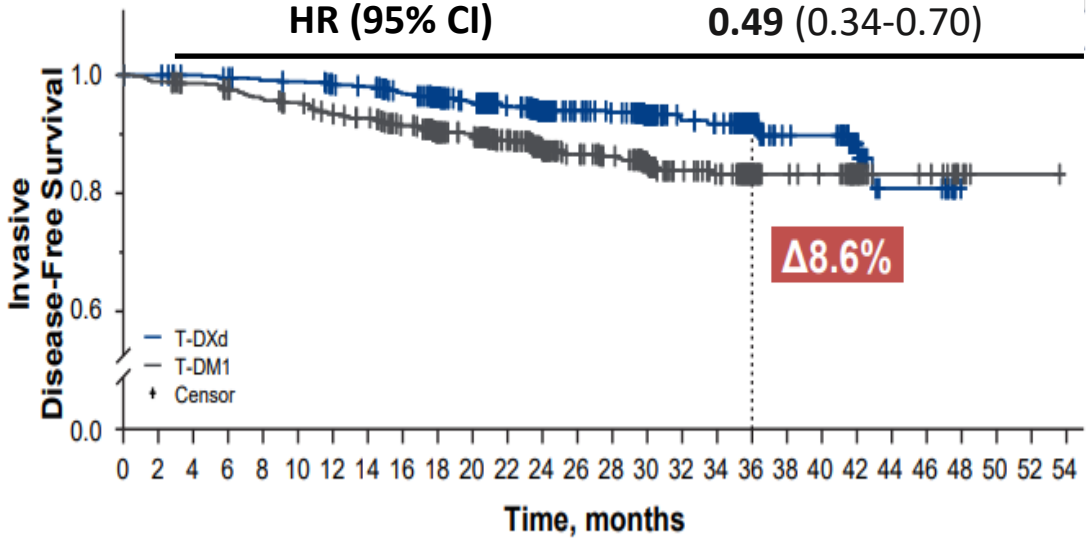
IDFS: time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause

DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

Invasive disease–free survival (IDFS) subgroup analysis: by HER2 testing status

HER2 IHC 3+

	T-DXd (n = 676)	T-DM1 (n = 670)
Pts with events, n (%)	**46** (6.8)	**86** (12.8)
3-yr IDFS, % (95% CI)	**91.8%** (88.7-94.1)	**83.2%** (79.2-86.5)
HR (95% CI)	**0.49** (0.34-0.70)	

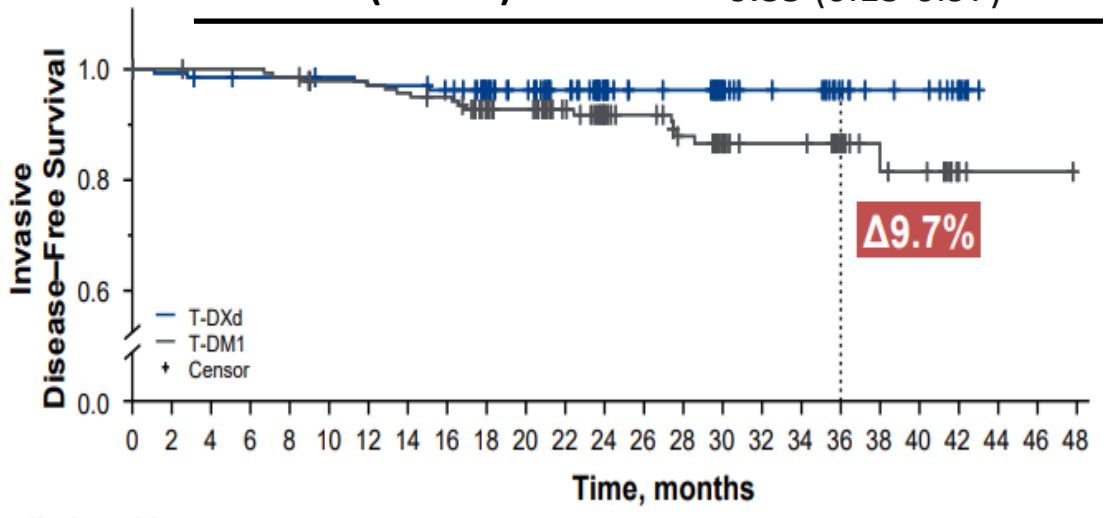


Number at risk

T-DXd	676	655	650	646	641	639	631	626	607	570	532	458	376	329	320	239	239	184	110	80	79	40	14	14	0	0	0	0
T-DM1	670	640	629	620	607	600	586	577	558	515	491	433	339	282	271	189	189	144	97	67	64	34	13	12	4	1	1	0

HER2 ISH+

	T-DXd (n = 140)	T-DM1 (n = 147)
Pts with events, n (%)	**5** (3.6)	**16** (10.9)
3-yr IDFS, % (95% CI)	**96.2%** (91.0-98.4)	**86.5%** (78.1-91.8)
HR (95% CI)	**0.35** (0.13-0.97)	



Number at risk

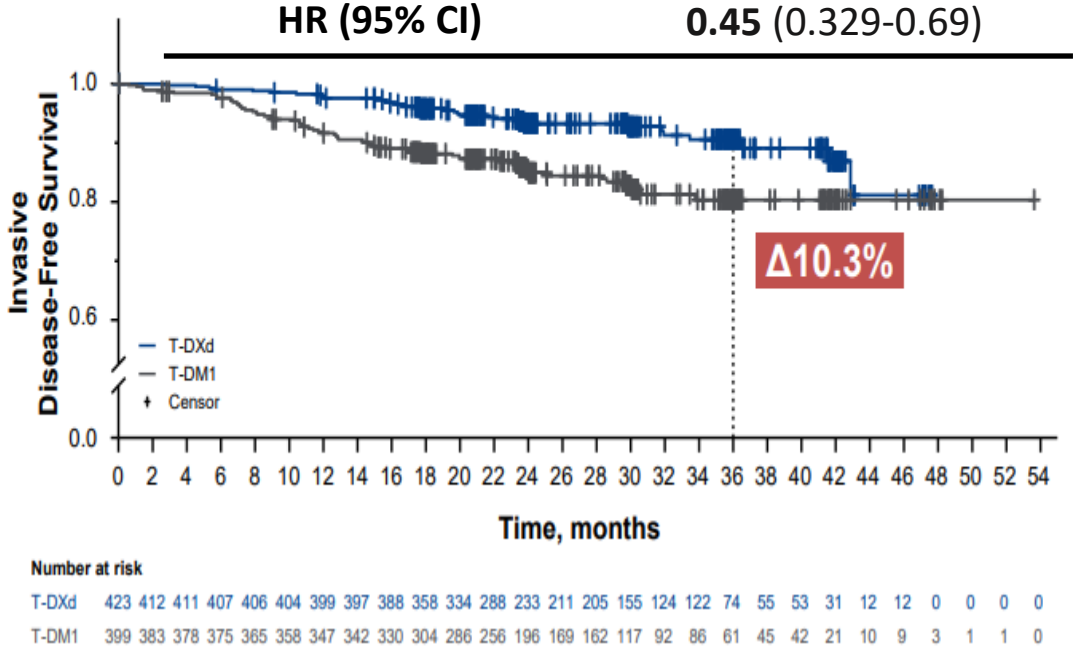
T-DXd	140	131	129	128	128	127	125	125	122	112	100	84	62	51	50	36	29	28	19	12	11	6	0	0	0
T-DM1	147	141	140	140	138	134	133	131	129	117	108	94	78	73	66	44	33	33	23	17	15	4	1	1	0

DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

Invasive disease–free survival (IDFS) subgroup analysis: prior neoadjuvant chemotherapy

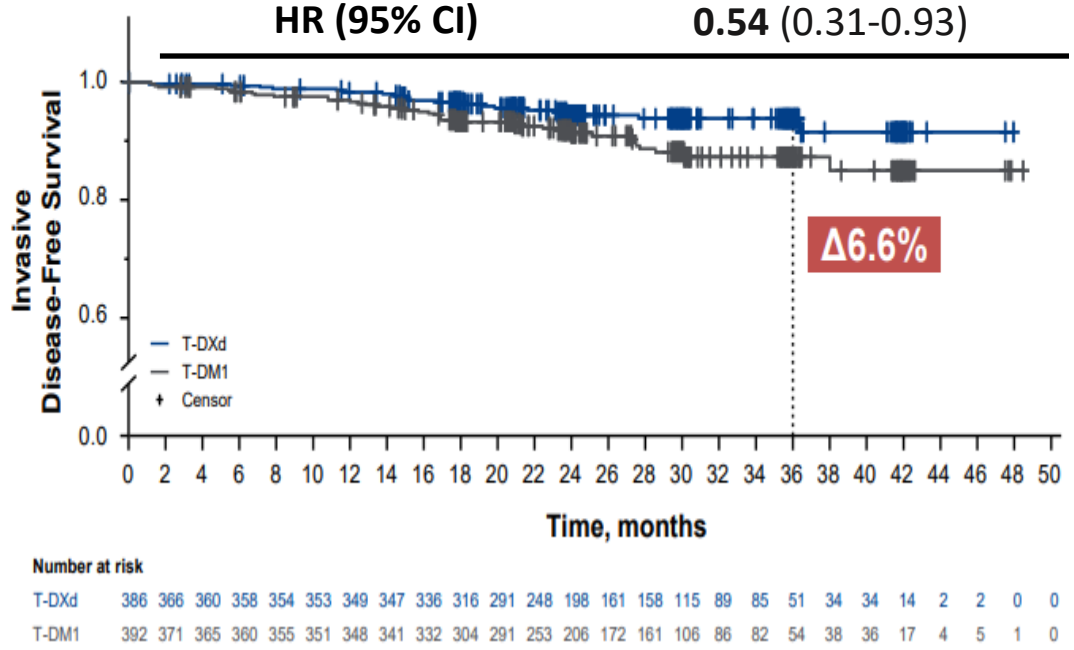
Prior anthracyclines

	T-DXd (n = 423)	T-DM1 (n = 670)
Pts with events, n (%)	**32** (7.6)	**61** (15.3)
3-yr IDFS, % (95% CI)	**90.6%** (86.1-93.6)	**80.3%** (74.8-84.8)
HR (95% CI)	**0.45** (0.329-0.69)	



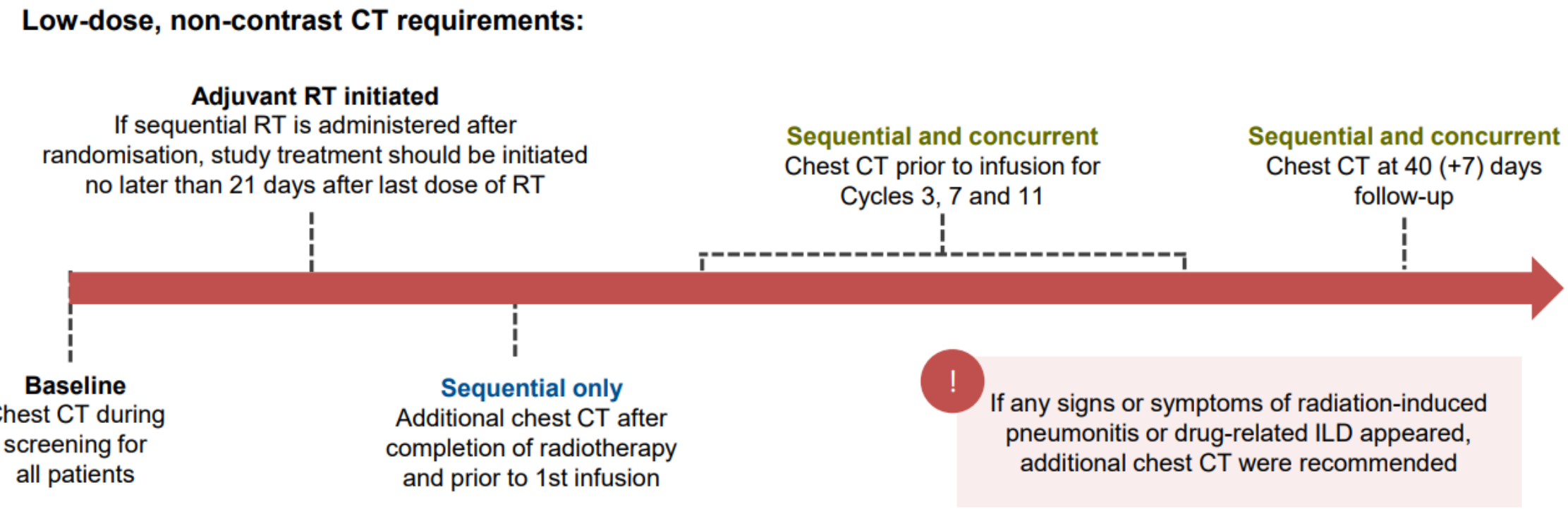
Prior platinum-based therapy

	T-DXd (n = 386)	T-DM1 (n = 392)
Pts with events, n (%)	**20** (5.2)	**37** (9.4)
3-yr IDFS, % (95% CI)	**93.9%** (90.4-96.1)	**87.3%** (82.4-90.9)
HR (95% CI)	**0.54** (0.31-0.93)	



DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

CT requirements for identifying ILD radiation pneumonitis, as per protocol



CT, computed tomography; ILD; interstitial lung disease; RT, radiotherapy

DESTINY-Breast05, post-neoadjuvant T-DXd vs T-DM1

Adjudicated drug-related ILD by timing of adjuvant RT sequential (prior to initiating T-DXd or T-DM1) or concurrent with the drugs

	T-DXd (n = 806)[a]			T-DM1 (n = 801)[a]		
Adjudicated drug-related ILD, any grade, overall, n (%)	77 (9.6)			13 (1.6)		
Adjudicated drug-related ILD, by adjuvant RT, n (%)	**Sequential (n = 319)**	**Concurrent (n = 438)**	**Sequential or concurrent (n = 757)**	**Sequential (n = 270)**	**Concurrent (n = 480)**	**Sequential or concurrent (n = 750)**
Any grade	34 (10.7)	42 (9.6)	76 (10.0)	7 (2.6)	5 (1.0)	12 (1.6)
Grade 1	6 (1.9)	10 (2.3)	16 (2.1)	4 (1.5)	3 (0.6)	7 (0.9)
Grade 2	24 (7.5)	27 (6.2)	51 (6.7)	3 (1.1)	2 (0.4)	5 (0.7)
Grade 3	3 (0.9)	4 (0.9)	7 (0.9)	0	0	0
Grade 4	0	0	0	0	0	0
Grade 5[b]	1 (0.3)	1 (0.2)	2 (0.3)	0	0	0
Grade ≥3	4 (1.3)	5 (1.1)	9 (1.2)	0	0	0
Time to onset, median (range), days[c]	122.0 (36-350)	124.5 (37-326)	123.5 (36-350)	79.0 (36-142)	121.0 (78-130)	121.0 (36-142)
Duration, median (95% CI), days[d,e]	77.0 (41-114)	67.0 (43-107)	74.0 (46-106)	114.0 (22-NE)	142.0 (51-NE)	114.0 (51-235)

- Most patients with drug-related ILD had recovered or were recovering at the data cutoff; in the T-DXd arm, the proportion of patients who had recovered from ILD was higher among those who received concurrent RT compared with sequential RT (69.0% vs 58.8%)

aAll patients who received at least one dose of study treatment. bGrade 5 adjudicated drug-related ILD was reported in 2 patients (0.2%) in the T-DXd arm, one at cycle 6 and one at cycle 7. In these 2 patients, treatment management guidelines were not appropriately followed, emphasizing the importance of appropriate identification of and adherence to guidelines. cTime to first adjudicated ILD onset = onset date of first ILD adjudicated as drug-related - first dose date + 1. dMedian is based on Kaplan-Meier Estimate. CIs were computed using the Brookmeyer-Crowley method. eDuration of first ILD = investigator reported end date - investigator reported onset date + 1. End date will be censored for ongoing ILDs.

SUMMARY

DESTINY-Breast05

- Post-neoadjuvant T-DXd vs T-DM1 resulted in IDFS improvement regardless of prior chemotherapy or HER2 status

- Timing of adjuvant RT (sequential or concurrent) did not impact incidence or severity of adjudicated drug-related ILD
  - Adjudicated drug-related ILD overall: 9.6% for T-DXd vs 1.6% for T-DM1
  - Grade ≥3 ILD by adjuvant RT (sequential or concurrent) 1.2% for T-DXd vs 0% for T-DM1

IMPACT

Trastuzumab deruxtecan is a potential new post-neoadjuvant treatment option for patients with high-risk HER2+ early breast cancer

Additional safety data support becoming a new standard of care -- not yet FDA approved

cornerstone specialty network™

Polling question: post-neoadjuvant HER2+

*Based on the presented **DB-05 trial** additional safety data, and if approved by the FDA: does the additional safety data increase your comfort for prescribing T-DXd instead of T-DM1 in the post-<u>neoadjuvant</u> HER2+ setting if patients have residual disease after neoadjuvant Tx?*

1. Yes
2. No
3. Unsure

cornerstone specialty network™

2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
- ASCENT-07
- EMBER-3
- evERA
- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

CLINICAL QUESTION

DESTINY-Breast09

HER2+ 1L metastatic

PFS benefit to risk ratio of trastuzumab deruxtecan + pertuzumab (T-DXd + P) vs THP seen in DB-09: patient reported outcomes (PRO) data for first-line HER2+ advanced/metastatic breast cancer

Now FDA Approved!

*On **December 15, 2025**, the FDA approved **fam-trastuzumab deruxtecan-nxki** (Enhertu, Daiichi Sankyo, Inc.) in combination **with pertuzumab** for the first-line treatment of adults with **unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer** as determined by an FDA-approved test evaluated in the **DESTINY-Breast09 trial.***

PFS = progression free survival

KEY DATA

DESTINY-Breast09: 1L T-DXd + Pertuzumab vs Pertuzumab + Trastuzumab + Taxane in HER2+ mBC

Study Design: Open label, phase 3 study

- HER2+* (IHC3+ or ISH+) advanced or mBC
- No previous chemo or HER2-targeted therapy for advanced or metastatic disease
- Previous chemo/HER2-targeted therapy allowed in neoadjuvant setting if >6 mo from metastatic disease diagnosis
- One prior line of ET for mBC permitted
- Asymptomatic/inactive brain mets allowed
- ECOG PS 0/1

(N = 1157)

Stratified by de novo vs recurrent mBC
HR+ or HR-; PIK3CAm detected vs non-detected

T-DXd 5.4 mg/kg q3w
(Blinded until final PFS analysis)
(n=387)

T-DXd 5.4 mg/kg q3w **+ Pertuzumab (n=383)**

Taxane + Pertuzumab + Trastuzumab (THP)†ǂ (n=387)

*Locally assessed and prospectively centrally confirmed.
†Investigator's choice: docetaxel or paclitaxel IV.
Concurrent use of ET (AI or tamoxifen) was allowed for those with HR+ disease after six cycles of T-DXd or discontinuation of taxane in the THP arm

Primary endpoint: PFS by BICR (per RECIST 1.1) up to 5 yr
Secondary endpoints: PFS by investigator, OS, ORR (BICR and investigator), DoR (BICR and investigator), PFS2, safety, **PROs (Reported Secondary endpoints at interim analysis February 26, 2025)**

Primary Endpoint: PFS by BICR Interim analysis presented at ASCO 2025

	T-DXd + Pertuzumab (n=383)	**THP (n=387)**
Median PFS	**40.7** (36.5 – NC)	**26.69** (21.8 – NC)
HR (95% CI)	**0.56** (0.44 – 0.77)	
P-value	**<0.00001**	

Subgroup analysis:

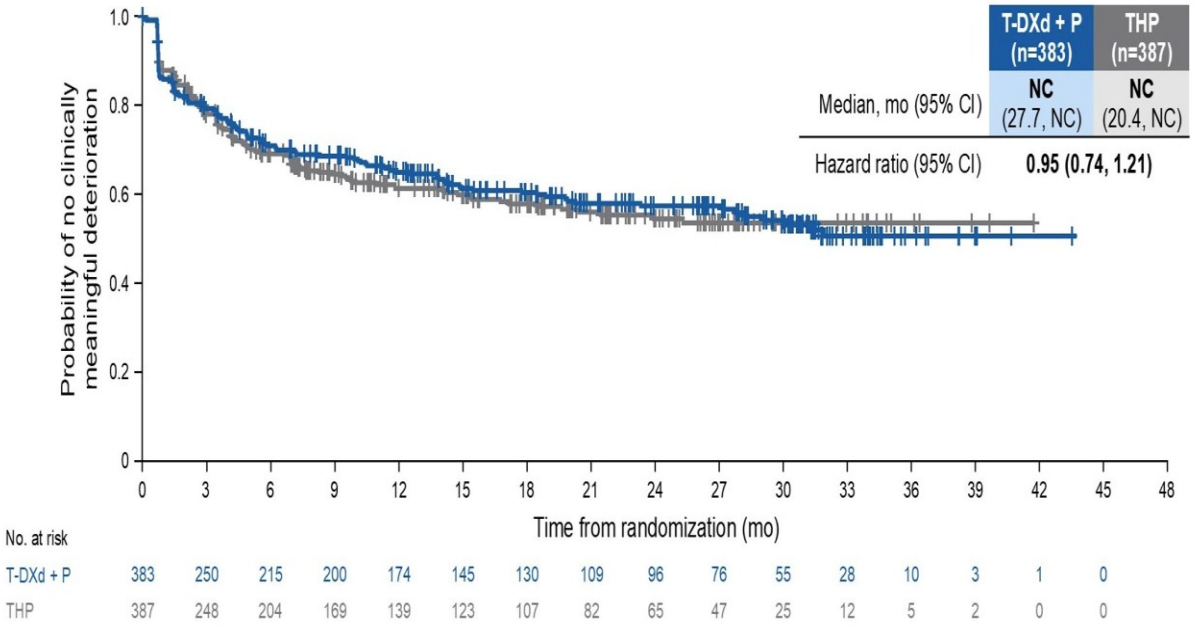
- Benefit regardless of treatment status
  - De novo disease or recurrent
- Benefit regardless of HR status
  - HR-positive or HR-negative
- Benefit regardless of *PIK3CA* mutation status
  - Mutation or wild-type

SABCS 2025 Abstract RF6-07.

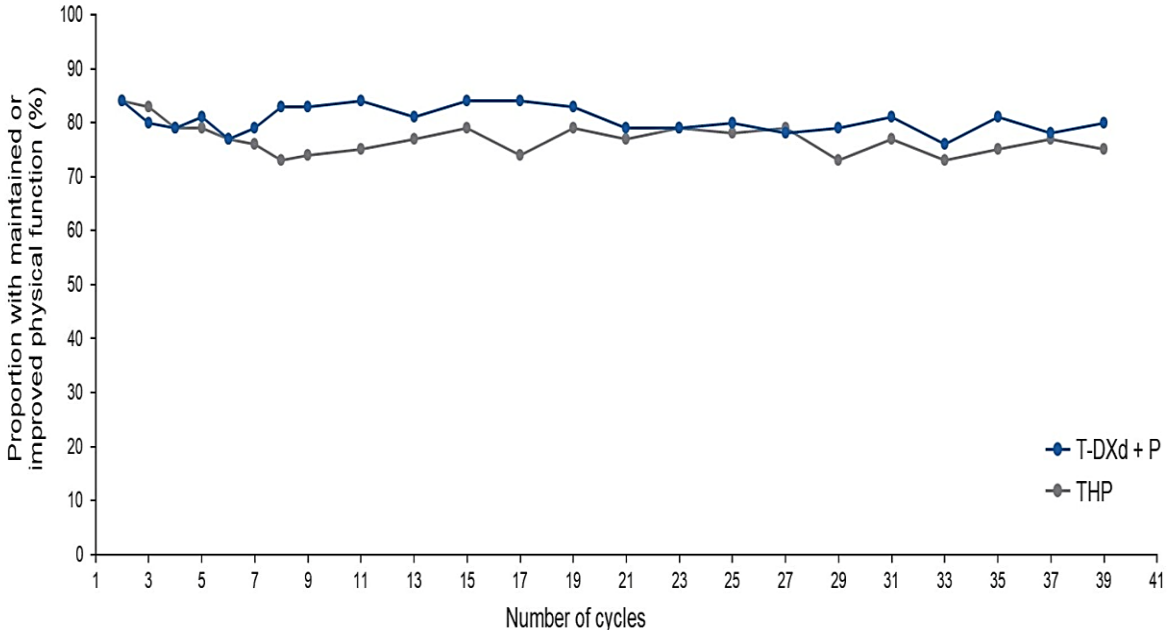
KEY DATA

DESTINY-Breast09: 1L T-DXd + Pertuzumab vs Pertuzumab + Trastuzumab + Taxane in HER2+ mBC, Patient Reported Outcomes at SABCS 2025

Time to deterioration in pain symptoms (EORTC QLQ-C30)



Change in physical function from baseline (EORTC QLQ-C30)

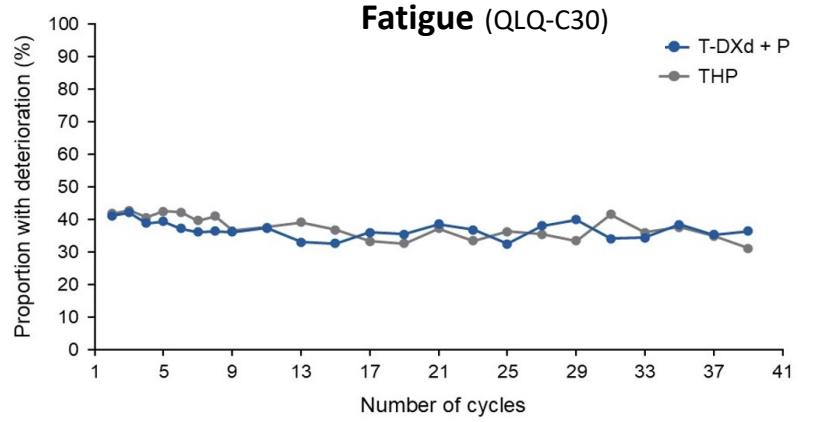


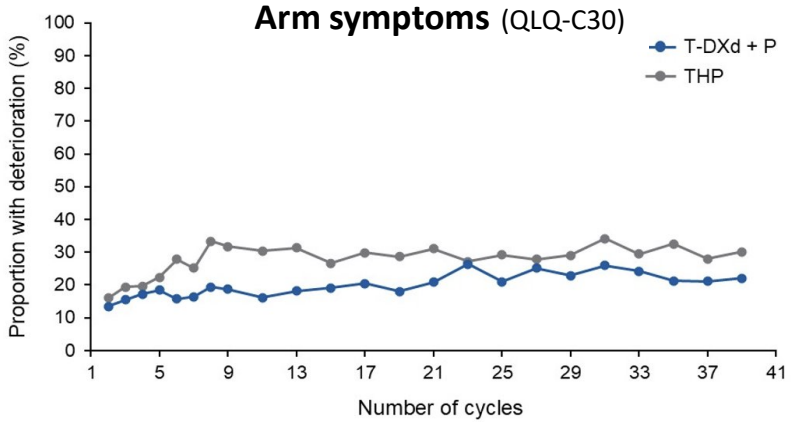
SABCS 2025 Abstract RF6-07.

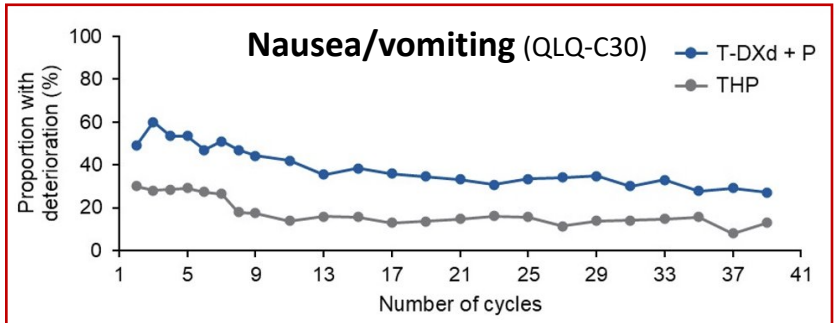
KEY DATA

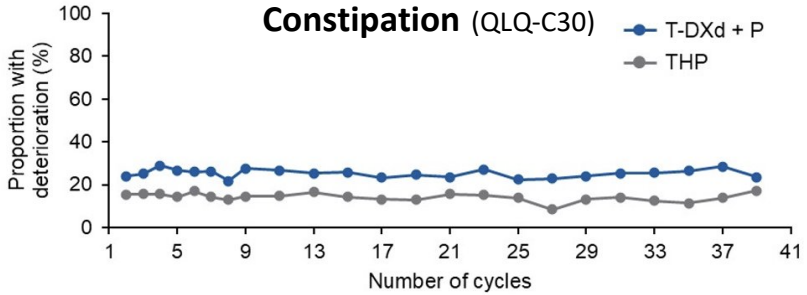
DESTINY-Breast09: 1L T-DXd + Pertuzumab vs Pertuzumab + Trastuzumab + Taxane in HER2+ mBC, Patient Reported Outcomes at SABCS 2025

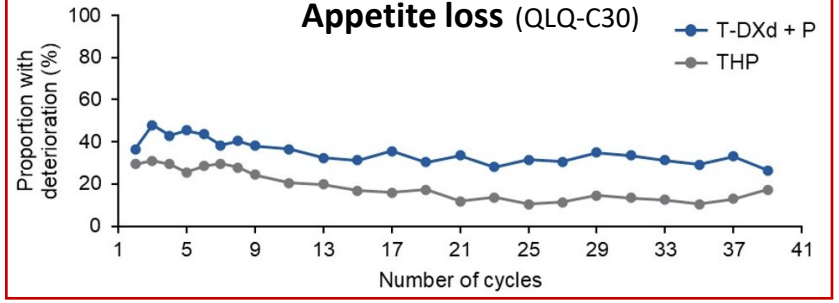
Treatment-related symptoms (EORTC QLQ-C30 + QLQ-BR45)

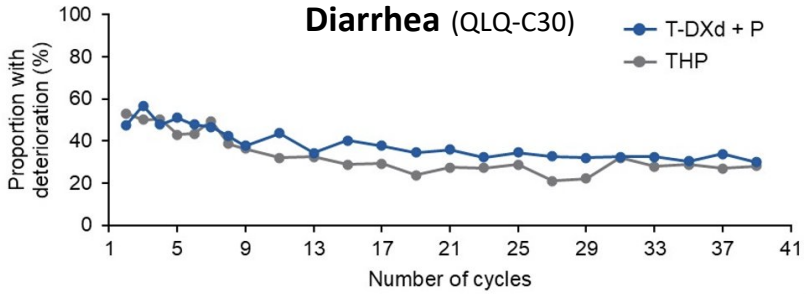












SABCS 2025 Abstract RF6-07.

SUMMARY

DESTINY-Breast09

- Maintained or improved physical function was consistent between the two arms
- T-DXd + P resulted in comparable impact on fatigue and diarrhea, but more nausea/vomiting and appetite loss vs THP
- The new regimen requires careful attention to prevention of nausea and vomiting

IMPACT

Trastuzumab deruxtecan with Pertuzumab is an effective treatment option, with a favorable benefit to risk profile for patients with HER2+ metastatic breast cancer in the 1L setting

FDA approved - December 15, 2025

cornerstone specialty network™

Polling question: 1L metastatic

*Based on the presented **DB-09 trial** and with recent approval by the FDA: how likely are you to now prescribe T-DXd + P in first-line HER2+ disease until tumor progression?*

1. Very likely – for all patients
2. Somewhat likely – for select patients
3. Not likely

cornerstone specialty network™

2025 SABCS Key Studies

HER2- and TNBC

- ASCENT-03
- TROPION-Breast02
  - *Polling Question*
- DATO-Base
- ASCENT-04
  - *Polling Question*
- HALLOW
  - *Polling Question*

HR+ Breast Cancer

- lidERA
  - *Polling Question*
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- EMBER-3
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- EPIK-B5
  - *Polling Question*

HER2+ Breast Cancer

- DESTINY-Breast11
  - *Polling Question*
- DESTINY-Breast05
  - *Polling Question*
- DESTINY-Breast09
  - *Polling Question*

HER2Climb-05

- *Polling Question*

CLINICAL QUESTION

HER2Climb-05

HER2+ 1st-line metastatic

Does adding tucatinib (TUC) to trastuzumab and pertuzumab (HP) in 1L maintenance improve progression-free survival in patients with HER2+ metastatic breast cancer following induction therapy?

KEY DATA

HER2Climb-05, 1L maintenance TUC + HP vs placebo + HP

Study Design: Randomized, double-blind, placebo controlled, interventional, phase 3 study

- Centrally confirmed HER2+ MBC
- No evidence of progression after THP (4 to 8 cycles)
- ECOG PS of 0 or 1
- No or asymptomatic brain metastases confirmed by contrast-enhanced MRI at screening

Stratified by diagnosis (de novo or recurrent), HR status (positive or negative), and presence or history of BM (yes or no)

Tucatinib (TUC) 300 mg po bid
+ HP*
Once every 21 days
± ET
(n = 326)

Placebo (PBO) po bid
+ **HP***
Once every 21 days
± ET
(n = 328)

Study treatment continues until unacceptable toxicity, disease progression consent withdrawal, or study closure. No crossover from PBO to TUC was allowed.

*H (6 mg/kg IV or 600 mg SC) and P (420 mg IV) or fixed dose combination (SC) of H (600 mg), and hyaluronidase (20,000 units)

Primary endpoint: Investigator-assessed PFS by RECIST v1.1
Secondary endpoints: OS (key secondary), PFS per BICR, CNS-PFS, Safety, HRQoL, Pharmacokinetics

HP = trastuzumab/pertuzumab
ET = endocrine therapy
BICR = blinded independent committee review
PFS = progression free survival
HRQoL = health related quality of life

KEY DATA

HER2Climb-05, 1L maintenance TUC + HP vs placebo + HP

Baseline Characteristics

Characteristic	TUC + HP (n = 326)	PBO + HP (n = 328)
Age, yr, median (range)	54.0 (24-82)	54.0 (29-83)
Race, n (%)		
• White	147 (45.1)	147 (44.8)
• Asian	119 (36.5)	111 (33.8)
• Black/African American	10 (3.1)	9 (2.7)
• Multiple or other	10 (3.1)	15 (4.6)
• Not reportable/unknown	40 (12.3)	46 (14.0)
ECOG Status, n (%)		
• 0	215 (66.0)	204 (62.2)
• 1	110 (33.7)	123 (37.5)
HR Status, n (%)		
• Positive	168 (51.5)	176 (53.7)
Received ET	74 (44.0)	81 (46.0)
• Negative	158 (48.5)	152 (46.3)
Presence or history of brain metastases, n (%)	41 (12.6)	40 (12.2)
Visceral disease, n (%)	194 (59.5)	172 (52.4)

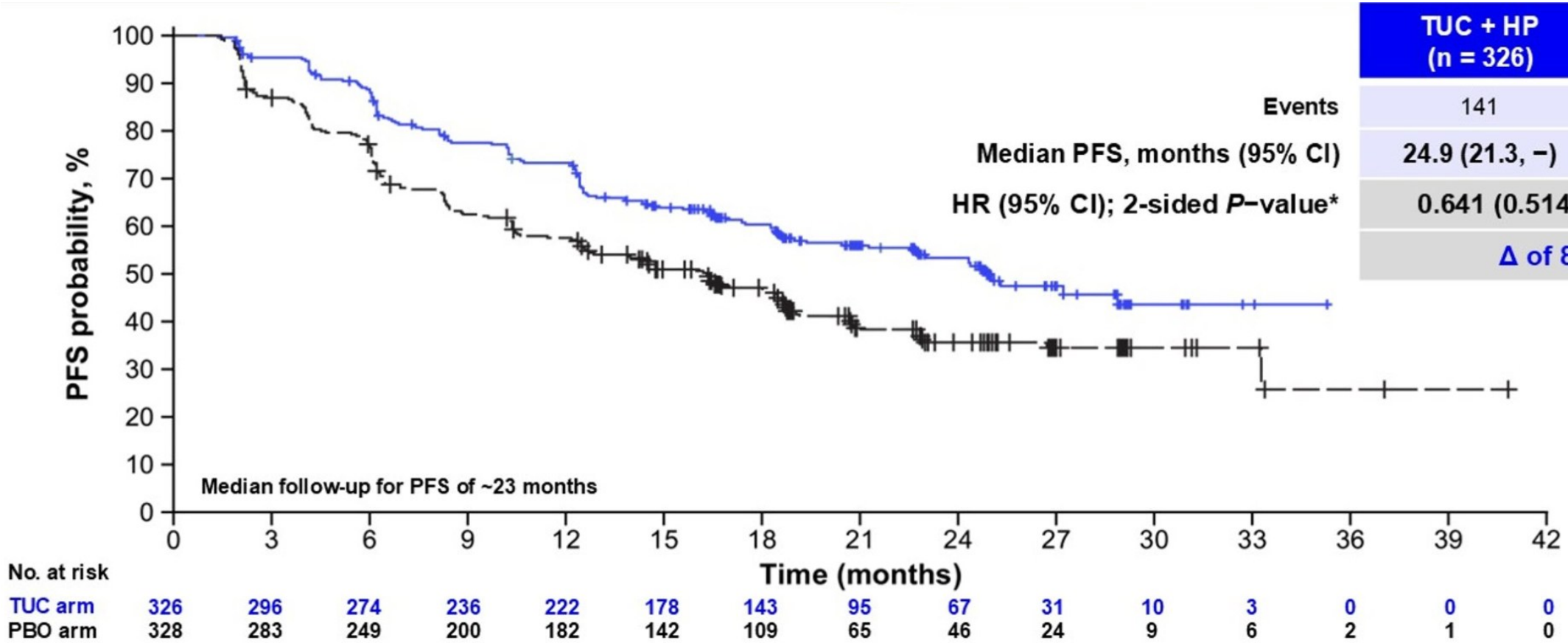
Characteristic	TUC + HP (n = 326)	PBO + HP (n = 328)
Disease status, n (%)		
• De *novo*	227 (69.6)	226 (68.9)
• Recurrent	99 (30.4)	102 (31.1)
Any prior (neo)adjuvant systemic therapy, n (%)	87 (26.7)	91 (27.7)
• Prior trastuzumab*	60 (69.0)	67 (73.6)
• Prior pertuzumab*	16 (18.4)	15 (16.5)
Induction HP cycle, median (range)	6 (4-10)	6 (4-11)
Induction T cycle, median (range)	6 (4-9)	6 (3-8)
Best response to induction THP, n (%)		
• CR	30 (9.2)	32 (9.8)
• PR	204 (62.6)	208 (63.4)
• SD	77 (23.6)	75 (22.9)
• Non-CR/Non-PD	15 (4.6)	13 (4.0)

SABCS 2025. Abstract GS1-01.

KEY DATA

HER2Climb-05, 1L maintenance TUC + HP vs placebo + HP

Primary Endpoint: Investigator-Assessed PFS



	TUC + HP (n = 326)	PBO + HP (n = 328)
Events	141	191
Median PFS, months (95% CI)	24.9 (21.3, –)	16.3 (12.6, 18.7)
HR (95% CI); 2-sided *P*–value*	0.641 (0.514, 0.799); < 0.0001	
	Δ of 8.6 months	

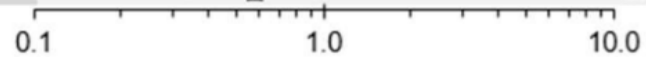
SABCS 2025. Abstract GS1-01.

KEY DATA

HER2Climb-05, 1L maintenance TUC + HP vs placebo + HP

PFS in Prespecified Patient Subgroups

Patient Groups		TUC + HP Events/No.	PBO + HP Events/No.	Favors TUC + HP ←	Favors PBO + HP →	TUC + HP vs PBO + HP HR (95% CI)
	ITT analysis	141/326	191/328			0.641 (0.514, 0.799)
Diagnosis	De novo	93/227	129/226			0.621 (0.475, 0.813)
	Recurrent	48/99	62/102			0.671 (0.457, 0.986)
Hormone receptor status	Negative	68/158	92/152			0.554 (0.403, 0.761)
	Positive	73/168	99/176			0.725 (0.535, 0.983)
Brain metastases at baseline	Yes	26/41	34/40			0.640 (0.373, 1.097)
	No	115/285	157/288			0.640 (0.503, 0.816)
Prior anti-HER2 therapy	Yes	27/62	45/69			0.569 (0.347, 0.934)
	No	114/264	146/259			0.666 (0.519, 0.854)
Best response to induction THP	CR or PR	101/234	135/240			0.695 (0.535, 0.902)
	SD or Non-CR/Non-PD	40/92	56/88			0.594 (0.377, 0.938)
Disease type	Visceral	96/194	107/172			0.642 (0.484, 0.852)
	Nonvisceral	45/132	84/156			0.561 (0.387, 0.813)
ECOG PS	0	89/215	114/204			0.637 (0.480, 0.846)
	1	52/110	76/123			0.591 (0.408, 0.857)
Region	North America	14/41	23/48			0.808 (0.392, 1.667)
	Europe	52/116	66/114			0.769 (0.529, 1.117)
	Asia–Pacific	47/121	70/113			0.469 (0.320, 0.688)
	Rest of World	28/48	32/53			0.710 (0.408, 1.233)
Age, years	< 65	124/274	161/272			0.655 (0.517, 0.831)
	≥ 65	17/52	30/56			0.447 (0.226, 0.883)
Race	White	68/147	81/147			0.829 (0.596, 1.153)
	Asian	48/119	70/111			0.481 (0.329, 0.702)
	Other	25/60	40/70			0.576 (0.339, 0.978)



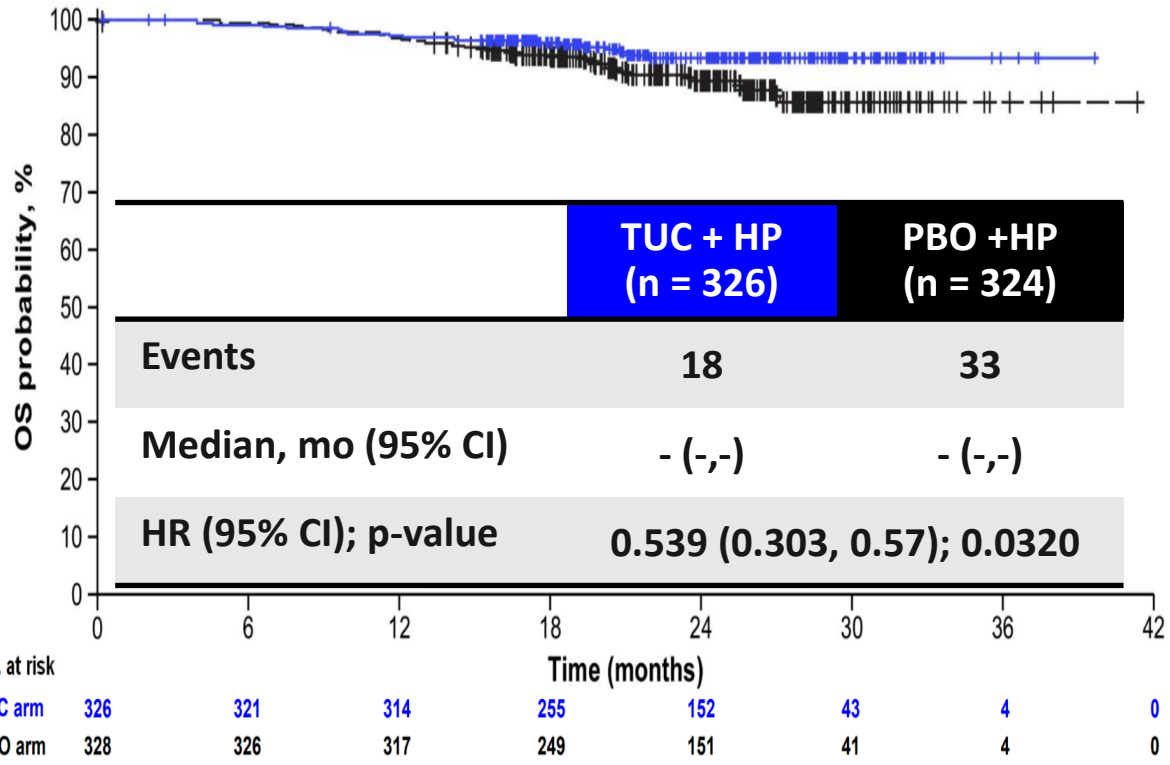
SABCS 2025. Abstract GS1-01.

KEY DATA

HER2Climb-05, 1L maintenance TUC + HP vs placebo + HP

Key Secondary Endpoints

Overall Survival



	TUC + HP (n = 326)	PBO +HP (n = 324)
Events	18	33
Median, mo (95% CI)	- (-,-)	- (-,-)
HR (95% CI); p-value	0.539 (0.303, 0.57); 0.0320	

CNS-PFS

ITT population

	TUC + HP (n = 326)	PBO +HP (n = 324)
Events	77	80
Median, mo (95% CI)	- (-,-)	- (-,-)
HR (95% CI)	0.846 (0.616, 1.162)	

Patients with baseline brain metastases

	TUC + HP (n = 41)	PBO +HP (n = 40)
Events	24	28
Median, mo (95% CI)	8.5 (4.4, 22.8)	4.3 (2.3, 10.6)
HR (95% CI)	0.716 (0.406, 1.273)	

Δ of 4.2 months

SABCS 2025. Abstract GS1-01.

KEY DATA

HER2Climb-05, 1L maintenance TUC + HP vs placebo + HP

Secondary Endpoint: Safety

n (%)	TUC + HP (n = 326)*	PBO + HP (n = 324)*
Duration of TUC/PBO treatment, months, median (range)	17.1 (0.4-36.5)	15.5 (0.5-41.3)
Patients with TEAE – Any	323 (99.1)	313 (96.6)
• Grade ≥3	138 (42.3)	79 (24.4)
• Serious TEAE	55 (16.9)	26 (8.0)
• Leading to death	1 (0.3)	1 (0.3)
Discontinuation from study treatment due to TEAE† – Any	45 (13.5)	15 (4.6)
• TUC/PBO	44 (13.5)	7 (2.2)
• H or P individually	2 (0.6)	5 (1.5)
• H + P fixed dose combination	9 (2.8)	4 (1.2)
Most common TEAEs leading to TUC/PBO discontinuation		
• Hepatic events††	25 (7.7)	0
• Diarrhea	5 (1.5)	3 (0.9)
Dose modification due to TEAE – Any	182 (55.8)	112 (34.6)
• TUC/PBO dose hold	161 (49.4)	82 (25.3)
• TUC/PBO dose reduction	95 (29.1)	36 (11.1)

*The safety analysis set included all randomly assigned patients who received ≥1 dose of any study treatment. †If a patient discontinued H or P, they were required to discontinue both. Patients cold discontinue TUC/PBO but remain on HP (and vice versa). †† Includes (n) ALT increased (13), blood bilirubin increased (2), drug-induced liver injury (2), hepatic cytolysis (2), hypertransaminasaemia (2), liver injury (2), AST increased (1), hepatobiliary disease (1).

SABCS 2025. Abstract GS1-01.

SUMMARY

HER2Climb-05

- Tucatinib added to 1L maintenance therapy with HP demonstrated a statistically significant and clinically meaningful PFS of 24.9 months vs 15.3 months (8.6-month improvement)
  - 36% reduction in risk of disease progression or death
- Preliminary OS data suggest positive trend favoring TUC + HP
- Safety considerations: TUC + HP combination showed diarrhea, nausea, and elevated liver enzymes, although mostly low grade

IMPACT

Tucatinib added to trastuzumab and pertuzumab is a new potential post-induction maintenance therapy option for patients with 1L HER2+ metastatic breast cancer

Data showing promising results --not yet FDA approved

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Polling question: 1L maintenance

Based on the presented ***HER2Climb-05 trial*** *data, and if approved by the FDA: would you use this regimen for 1L maintenance for HER2+ metastatic disease after induction therapy?*

1. Yes
2. No
3. Unsure, need more data

Approved 1L HER2+ MBC trials – randomization from day 1 of treatment for metastatic breast cancer

CLEOPATRA THP		DESTINY-Breast09 T-DXd + Pertuzumab	
• **No prior chemotherapy or biological treatment for metastatic disease** • **HR pos or neg**		• **No previous chemo or HER2-targeted therapy for metastatic disease** • **HR pos or neg**	
Pertuzumab + trastuzumab + docetaxel (n=402)	Placebo + trastuzumab + docetaxel (n=406)	**T-DXd** + pertuzumab (n=383)	Taxane + pertuzumab + trastuzumab (TCP)† (n=387)
Medium follow-up: **99.9 months**	Medium follow-up: 98.7 mo	Medium follow-up: **29.2 mo**	
mPFS: **18.7**	12.4 months	**mPFS: 40.7**	26.9 months
8-year landmark PFS rates: **16%** vs 10%		**HR: 0.56** (0.44 – 0.71); P = 0.00001	
mOS: **57.1**	40.8 months	*Not calculable*	*Not calculable*
8-year landmark OS rate: **37%** vs 23%		HR 0.84 (*OS immature*)	

N Engl J Med. 2012;366(2):109-19.

ASCO 2025 Abstr. 1008; ESMO 2025 LBA18

1st-line HER2+ MBC trials *PATINA and HER2Climb05 start after 4-6 months of initial Rx*

PATINA **→ Palbociclib + HP + ET**		**HER2Climb05** **→ Tucatinib + HP**	
Not yet FDA approved			
• **Completion of induction chemotherapy and no evidence of disease progression (CR, PR, or SD)** • **HR pos**		• **No evidence of disease progression after THP (4 to 8 cycles)** • **HR pos or neg**	
Palbociclib + trastuzumab ± pertuzumab + endocrine therapy (n=261)	Placebo + trastuzumab ± pertuzumab + endocrine therapy (n=261)	**Tucatinib** + pertuzumab + trastuzumab ± endocrine therapy (n = 326)	Placebo pertuzumab + trastuzumab ± endocrine therapy (n = 328)
Medium follow-up: **52 mo**		Medium follow-up: **23 mo**	
mPFS: 44.3	29.1 months	**mPFS: 24.9**	16.3 months
HR: 0.74 (0.58 – 0.94); P = 0.0074		**HR: 0.64** (0.51 – 0.8); P = <0.0001	
Not evaluable	77 months *(OS immature)*	*Not calculable*	*Not calculable*
3-year OS rate: 87.0%	vs 84.7 %	HR: 0.54 (0.30 – 0.96); P = 0.0320	

SABCS 2024 Abstract GS2-12

SABCS 2025 Abstract GS1-01

DB-09 start randomization on D1

PATINA and HER2Climb05 start after 4-6 months of initial Rx

DESTINY-Breast09 T-DXd + Pertuzumab	PATINA → Palbociclib + HP+ ET	HER2Climb05 → Tucatinib + HP
Now FDA approved	***Not yet FDA approved***	
HR pos or neg	**HR pos**	**HR pos or neg**
T-DXd + pertuzumab (n=383) vs Taxane + pertuzumab + trastuzumab (TCP)† (n=387)	**Palbociclib** + trastuzumab ± pertuzumab + endocrine therapy (n=261) vs Placebo + trastuzumab ± pertuzumab + endocrine therapy (n=261)	**Tucatinib** + pertuzumab + trastuzumab ± endocrine therapy (n = 326) vs Placebo pertuzumab + trastuzumab ± endocrine therapy (n = 328)
Medium follow-up: **29.2 mo**	Medium follow-up: **52 mo**	Medium follow-up: **23 mo**
mPFS from Day 1: **40.7** vs 26.9 months **HR: 0.56** (0.44 – 0.71); P = 0.00001	**mPFS from Day ~120:** **44.3** vs 29.1 months **HR: 0.74** (0.58 – 0.94); P = 0.0074	**mPFS from Day~120:** **24.9** vs 16.3 months **HR: 0.64** (0.51 – 0.8); P = <0.0001
ASCO 2025 Abstr. 1008; ESMO 2025 LBA18; SABCS	SABCS 2024 Abstract GS2-12	SABCS 2025 Abstract GS1-01

In the context of DB09 and other studies, how likely are you to consider T-DXd + pertuzumab in the first line induction setting, and then switching to something else?

NCCN Guidelines Version 1.2026 – Jan 16, 2026

CYTOTOXIC REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a,n]

HR-Positive or -Negative and HER2-Positive	
See BINV-Q 1 of 15 for Considerations for systemic HER2-targeted therapy.	
Setting	**Regimen**
First Line	Docetaxel + Pertuzumab + Trastuzumab (category 1, preferred) with maintenance Pertuzumab + Trastuzumab If HR-positive: Aromatase inhibitor ± Palbociclib + Pertuzumab + Trastuzumab
	Paclitaxel + Pertuzumab + Trastuzumab (preferred) with maintenance Pertuzumab + Trastuzumab If HR-positive: Aromatase inhibitor ± Palbociclib + Pertuzumab + Trastuzumab
	Fam-trastuzumab deruxtecan-nxki[o] + Pertuzumab (other recommended)
Second Line/Third Line	Capecitabine/Tucatinib + Trastuzumab[p] (category 1, preferred)
	Fam-trastuzumab deruxtecan-nxki[o,q] (category 1, preferred)
	T-DM1[r]
Fourth Line and Beyond (optimal sequence is not known)[s]	Docetaxel or Vinorelbine + Trastuzumab
	Paclitaxel + Trastuzumab ± Carboplatin
	Capecitabine/Lapatinib or Capecitabine + Trastuzumab
	Lapatinib + Trastuzumab (without cytotoxic therapy)
	Other chemotherapy agents[t] + Trastuzumab
	Capecitabine/Neratinib
	Chemotherapy (Capecitabine, Eribulin, Gemcitabine, or Vinorelbine) + Margetuximab-cmkb
	Abemaciclib/Fulvestrant + Trastuzumab (for HR+ only) (category 2B)
	Targeted Therapy and emerging biomarker Options BINV-Q 7 of 15 and BINV-Q 8 of 15

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SABCS 2025

HER2+ Breast Cancer

Key Takeaways

Q&A

@EdithPerezMD

DESTINY-Breast11*:* Neoadjuvant T-DXd x4 →THP x4 achieved a 67.3% pCR rate (vs 56.3% with ddAC x4→ THP x4), improving response with fewer Grade ≥3 ILD adverse events and lower rates of cardiac events. Proactive antiemetic use is warranted for T-DXd

Potentially a new standard of care in the curative intent setting for HER2+ early breast cancer – *not yet approved*

DESTINY-Breast05: Post-neoadjuvant T-DXd improved invasive disease-free survival compared to T-DM1 (92.4% vs 83.7%) in patients with high-risk HER2+ early breast cancer with residual invasive disease after neoadjuvant therapy regardless of prior chemotherapy, HER2 status, or timing of adjuvant radiation therapy (T-DXd Grade ≥3 ILD was 1.2%)

Potentially a new standard of care in the curative intent setting for HER2+ early breast cancer – *not yet approved*

HER2Climb05: In first-line HER2+ metastatic breast cancer, the addition of tucatinib to trastuzumab and pertuzumab as maintenance therapy following taxane-based induction improved PFS (median ~ 24.9 months vs 16.3 months; HR 0.641) versus trastuzumab and pertuzumab alone with similar any grade toxicity rates but higher rates of grade ≥3 TEAEs for tucatinib combination (42.3% vs 24.4%) – *not yet approved*

DESTINY-Breast09: In first-line HER2+ metastatic breast cancer, T-DXd plus pertuzumab significantly improved PFS (median ~ 40.7 months vs 26.9 months; HR 0.56) versus THP with a favorable benefit to risk profile, with patient reported outcomes indicating similar tolerability and proactive management with antiemetics warranted → *FDA approved December 2025*

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