National Comprehensive Cancer Network®

NCCN 2026 Breast Cancer Congress with Updates from the 2025 San Antonio Breast Cancer Symposium

Advances in the Management of Metastatic Breast Cancer with SABCS Updates

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AT THE FOREFRONT
UChicago Medicine

Updates in HER2+ Metastatic Breast Cancer

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Case Presentation: Polling Question

- A 60-year-old woman presents with new-onset fatigue, early satiety, and right upper-quadrant discomfort.
- She was treated 9 years ago for stage I HER2-positive, hormone receptor–negative breast cancer with lumpectomy followed by radiation and adjuvant paclitaxel and trastuzumab, completing 1 year of HER2-directed therapy.
- She remained disease-free until now. CT imaging reveals diffuse liver metastases and bilateral pulmonary nodules, and biopsy confirms hormone receptor-negative, HER2-positive metastatic breast cancer (IHC 3+).
- She has ECOG performance status 0, no underlying lung disease, no prior exposure to pertuzumab, and brain MRI reveals an 8mm enhancing lesion in the frontal lobe suspicious for brain metastasis, for which she is asymptomatic. She strongly wishes to avoid CNS radiation.

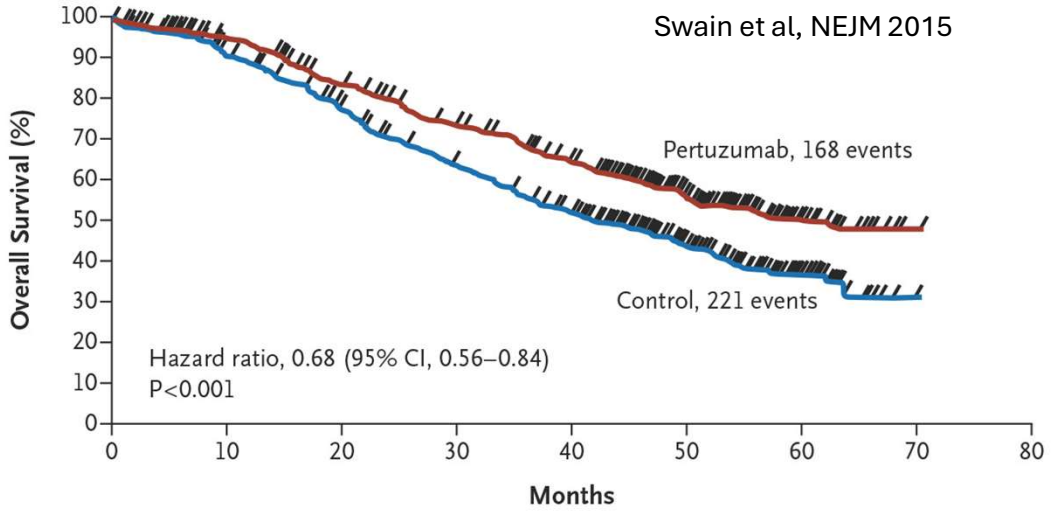
Given her high visceral tumor burden and CNS disease, which of the following is the most appropriate first-line systemic therapy?

A. Trastuzumab + pertuzumab + docetaxel
B. Trastuzumab emtansine (T-DM1)
C. Trastuzumab deruxtecan (T-DXd)
D. Trastuzumab deruxtecan (T-DXd) + pertuzumab
E. Single-agent taxane chemotherapy

Progress for HER2+ MBC

- **CLEOPATRA - 2012:** Established docetaxael + trastuzumab + pertuzumab → trastuzumab + pertuzumab maintenance as first line treatment for HER2+ MBC

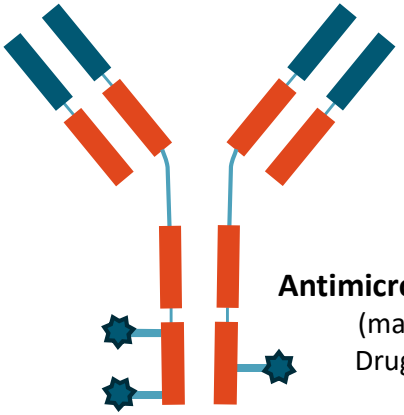
Swain et al, NEJM 2015



No. at Risk									
Pertuzumab	402	371	318	268	226	104	28	1	0
Control	406	350	289	230	179	91	23	0	0

ADCs for HER2+ Breast Cancer

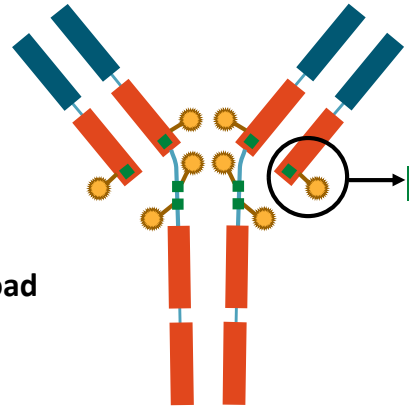
Trastuzumab Emtansine (T-DM1)



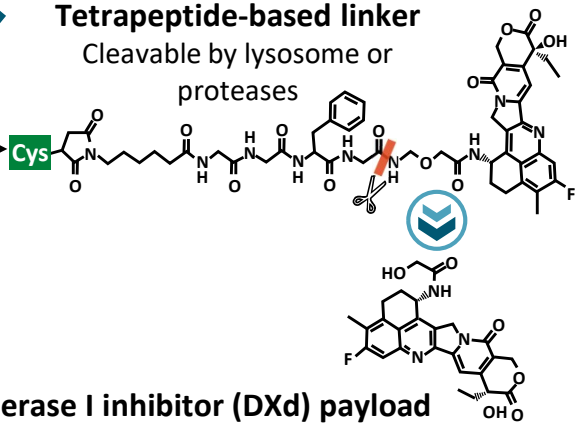
Antimicrotubule (DM1) payload
(maytansine derivative)
Drug-antibody ratio: 3.5

Thioether linker
Only cleaved in lysosome

Trastuzumab Deruxtecan (T-DXd)



Tetrapeptide-based linker
Cleavable by lysosome or proteases

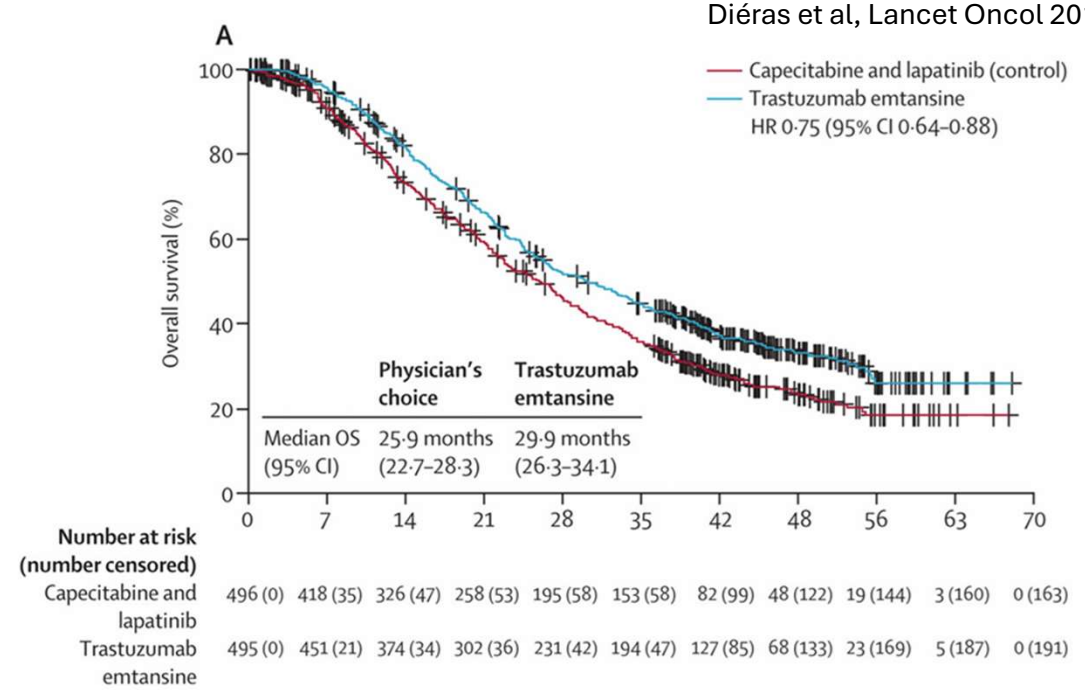


Topoisomerase I inhibitor (DXd) payload
(exatecan derivative)
Drug-antibody ratio: 8

Progress for HER2+ MBC

- **EMILIA - 2013:** Established T-DM1 as second line therapy

Diéras et al, Lancet Oncol 2017

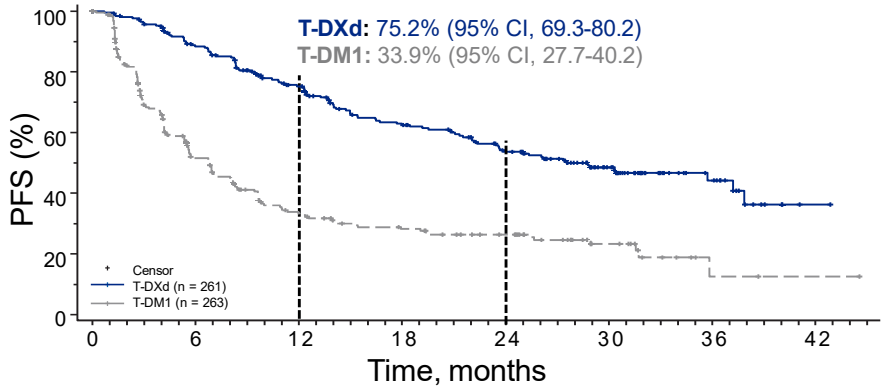


Progress for HER2+ MBC

- **DESTINY-Breast01 - 2019:** T-DXd approved as 3rd line
- **DESTINY-Breast02:** T-DXd effective after T-DM1
- **DESTINY-Breast03 - 2022:** T-DXd approved in the 2nd line setting

DESTINY-Breast03: T-DXd vs T-DM1

	T-DXd	T-DM1
Median (95% CI)	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	

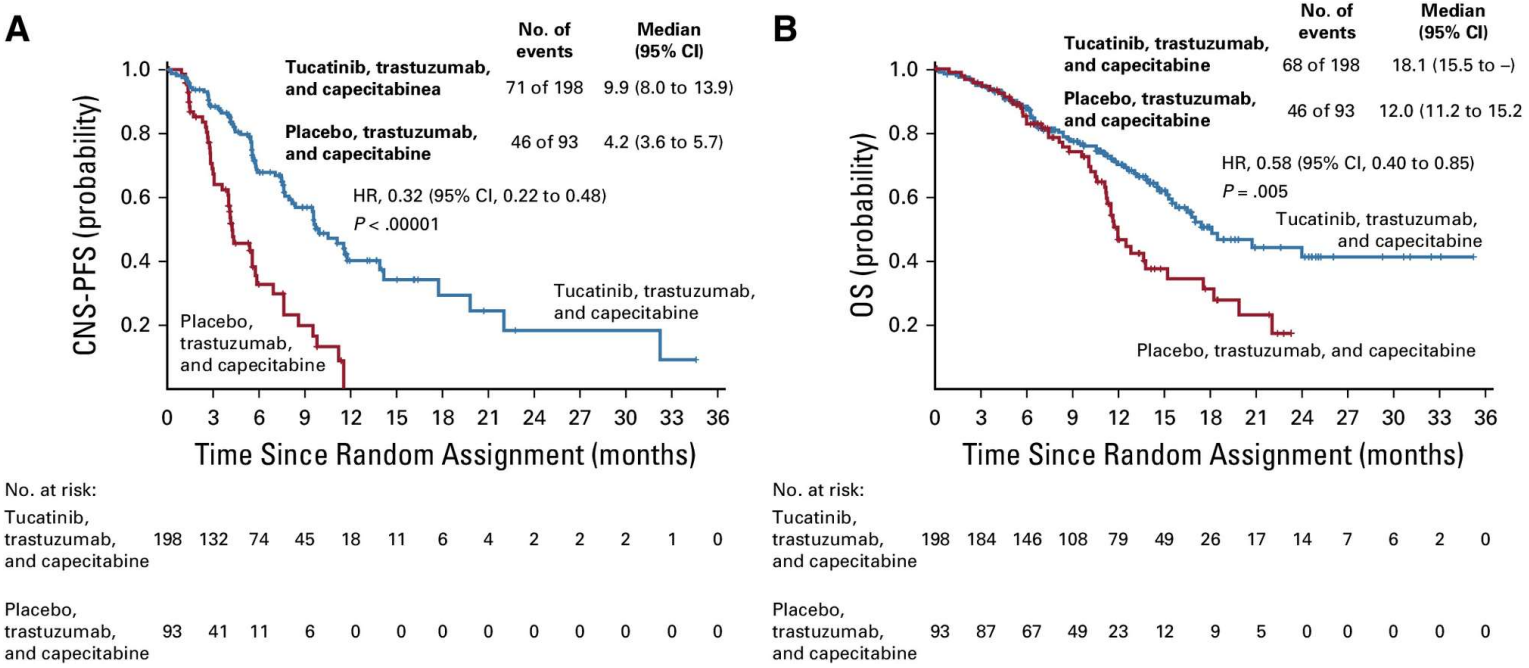


Hurvitz et al, SABCS 2022

Progress for HER2+ MBC – TKIs with CNS Activity

HER2CLIMB (Tucatinib, trastuzumab, capecitabine) – approved in 2020

- Enrolled patients post THP and T-DM1
- 291 with brain mets at enrollment (60% with active brain mets)



Lin et al, JCO 2020

NCCN Guidelines for HER2+ MBC

First Line	Second Line	Third Line
Taxane, Trastuzumab, Pertuzumab (THP)	Trastuzumab Deruxtecan	Tucatinib, Trastuzumab, Capecitabine
Maintenance:		
HP +/- ET		T-DM1

Adapted from Reid, SABCS 2025

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer (Version 5.2025).
© 2025 National Comprehensive Cancer Network, Inc. Available at www.NCCN.org/guidelines.

NCCN Guidelines for HER2+ MBC

First Line

Taxane, Trastuzumab, Pertuzumab (THP)

DESTINY-Breast09
Trastuzumab Deruxtecan + Pertuzumab

Maintenance:

HP +/- ET

PATINA
THP → HP + ET + Palbociclib

HER2-CLIMB05
THP → HP + Tucatinib ± ET

Second / Third Line

Trastuzumab Deruxtecan

Tucatinib, Trastuzumab, Capecitabine

T-DM1

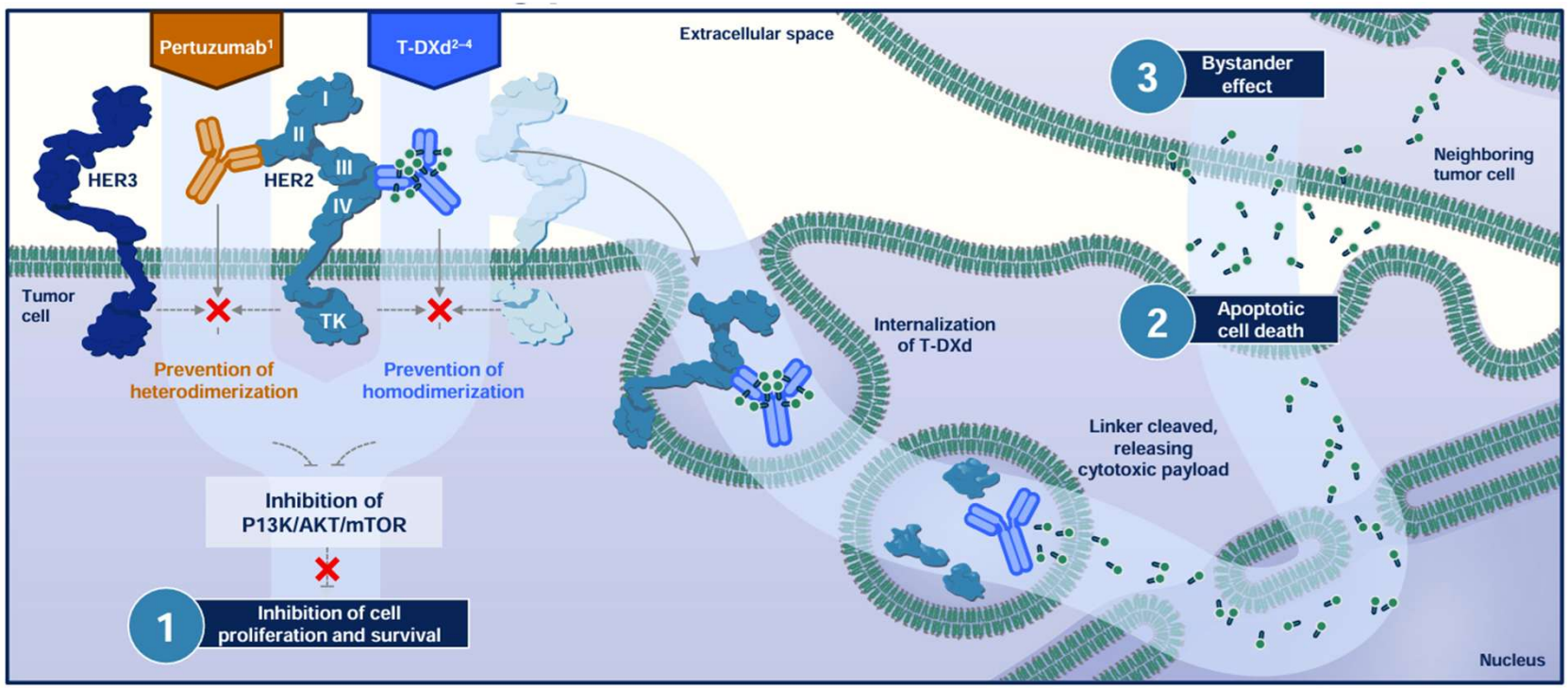
NCCN Recommended

Not Listed in NCCN Guidelines

Adapted from Reid, SABCS 2025

NCCN Guidelines® for Breast Cancer (Version 1.2026).

Rational for Combination of T-DXd + P



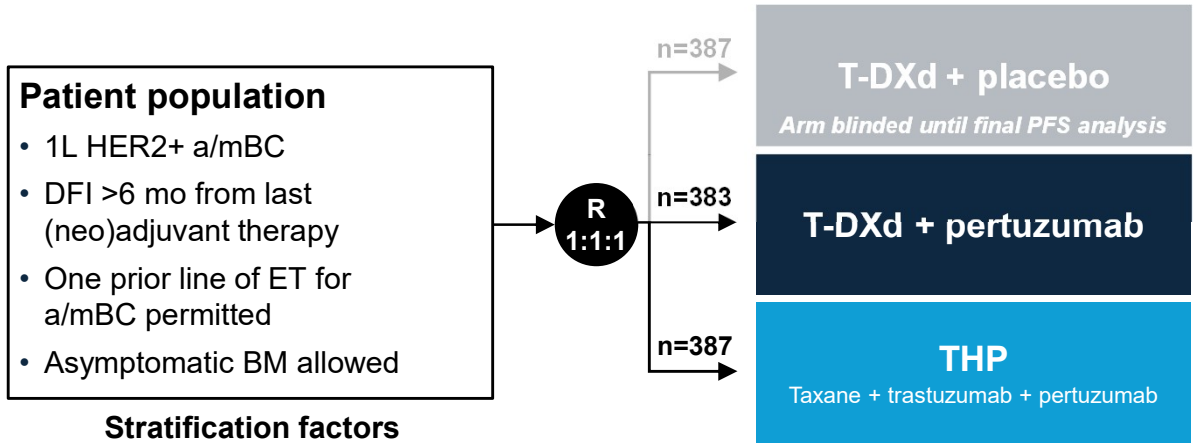
AKT, protein kinase B; HER2/3, human epidermal growth factor receptor 2/3; mTOR, mammalian target of rapamycin; P13K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TK, tyrosine kinase

1. Nami B, et al. *Cancers (Basel)*. 2018;10:342; 2. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185; 3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108; 4. Geng W, et al. *Eur J Pharmacol*. 2024:977:176725

Tolaney et al, ASCO 2025

DESTINY-Breast09 Study Design

A randomized, multicenter, open-label (for T-DXd vs THP) Phase 3 study (NCT04784715)



Stratification factors

- De-novo vs recurrent a/mBC
- HR+ or HR−
- *PIK3CA*m detected vs non-detected

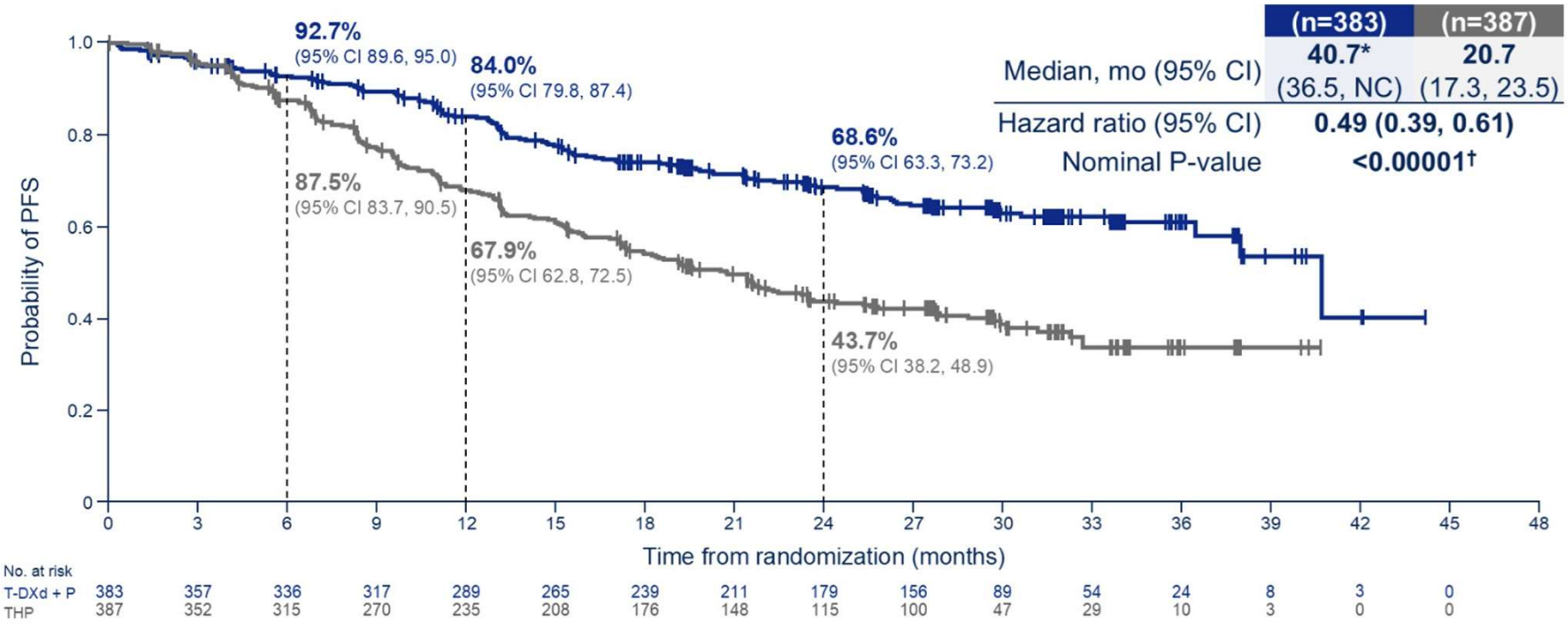
Key Demographics:

- 54% HR+
- 52% de-novo metastatic
- 30% with PIK3CAm
- 82% HER2 3+ by IHC

- **13.5% (T-DXd + P) and 38.3% (THP) of HR+ patients received concurrent ET after 6 cycles of T-DXd or discontinuation of taxane**
- **Median of 6 (paclitaxel) / 8 (docetaxel) cycles of taxane in THP arm**

Tolaney et al, ASCO 2025

DESTINY-Breast09 PFS by BICR

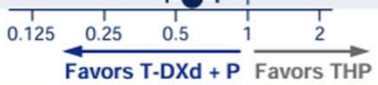


	(n=383)	(n=387)
Median, mo (95% CI)	40.7* (36.5, NC)	20.7 (17.3, 23.5)
Hazard ratio (95% CI)	0.49 (0.39, 0.61)	
Nominal P-value	<0.00001†	

Tolaney et al, ASCO 2025

PFS (BICR): Subgroup Analysis

	No. of events / no. of patients		mPFS, months (95% CI)		Hazard ratio (95% CI)
	T-DXd + P	THP	T-DXd + P	THP	
Prior treatment status					
De novo	52/200	85/200	NC (36.5, NC)	31.2 (23.5, NC)	0.49 (0.35, 0.70)
Recurrent	66/183	87/187	38.0 (26.9, NC)	22.5 (18.1, NC)	0.63 (0.46, 0.87)
HR status					
Positive	65/207	87/209	38.0 (36.0, NC)	27.7 (22.4, NC)	0.61 (0.44, 0.84)
Negative	53/176	85/178	40.7 (40.7, NC)	22.6 (17.3, 32.7)	0.52 (0.37, 0.73)
***PIK3CA* mutation status**					
Detected	41/116	64/121	36.0 (29.7, NC)	18.1 (15.1, 25.6)	0.52 (0.35, 0.77)
Not detected	76/266	108/266	40.7 (38.0, NC)	32.7 (24.4, NC)	0.57 (0.43, 0.77)
Age at randomization					
<65 years	90/315	139/315	40.7 (36.5, NC)	27.4 (22.4, NC)	0.50 (0.38, 0.65)
≥65 years	28/68	33/72	27.6 (14.9, NC)	21.5 (13.9, NC)	0.92 (0.55, 1.51)
Geographical region					
Asia	62/188	87/191	40.7 (36.5, NC)	27.2 (21.5, NC)	0.60 (0.43, 0.83)
Western Europe and North America	27/87	31/78	36.0 (30.6, NC)	31.2 (15.8, NC)	0.60 (0.35, 1.01)
Rest of World	29/108	54/118	NC (38.0, NC)	24.4 (14.8, NC)	0.48 (0.30, 0.76)
Brain metastases at baseline					
Present	10/25	15/22	31.8 (18.5, NC)	9.5 (5.6, 13.3)	0.30 (0.12, 0.68)
Not present	108/358	157/365	40.7 (36.5, NC)	27.6 (22.6, NC)	0.58 (0.45, 0.74)
Prior exposure to anti-HER2 therapies					
Yes	39/115	51/112	38.0 (26.9, NC)	21.5 (15.3, NC)	0.55 (0.36, 0.83)
No	79/268	121/275	40.7 (36.5, NC)	27.6 (22.5, NC)	0.56 (0.42, 0.74)
Prior exposure to pertuzumab					
Yes	5/31	12/26	40.8 (25.4, NC)	19.8 (7.5, NC)	NC
No	113/352	160/361	40.7 (36.0, NC)	27.4 (22.4, NC)	0.61 (0.48, 0.77)

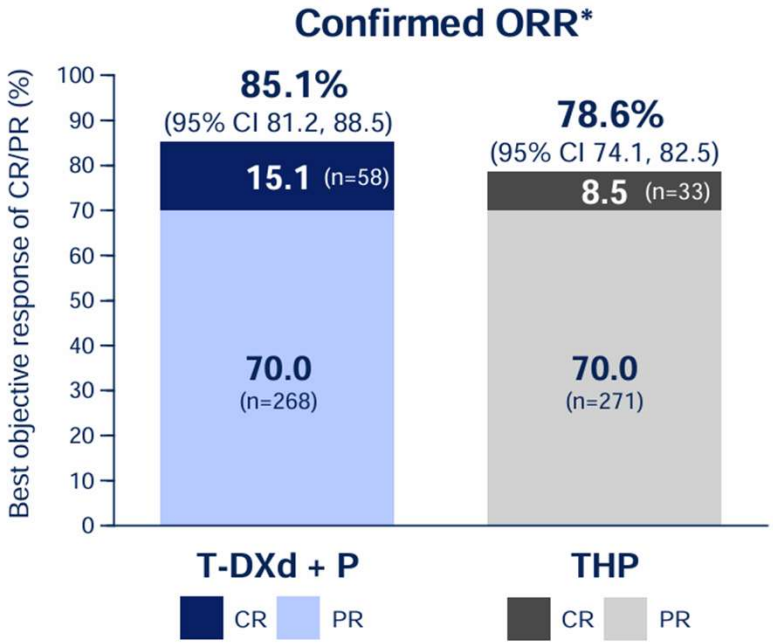


Size of circle is proportional to the number of events
BICR, blinded independent central review;
CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor;
NC, not calculable; P, pertuzumab;
(m)PFS, (median) progression-free survival;
T-DXd, trastuzumab deruxtecan;
THP, taxane + trastuzumab + pertuzumab

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

Tolaney et al, ASCO 2025

ORR per RECIST / DOR



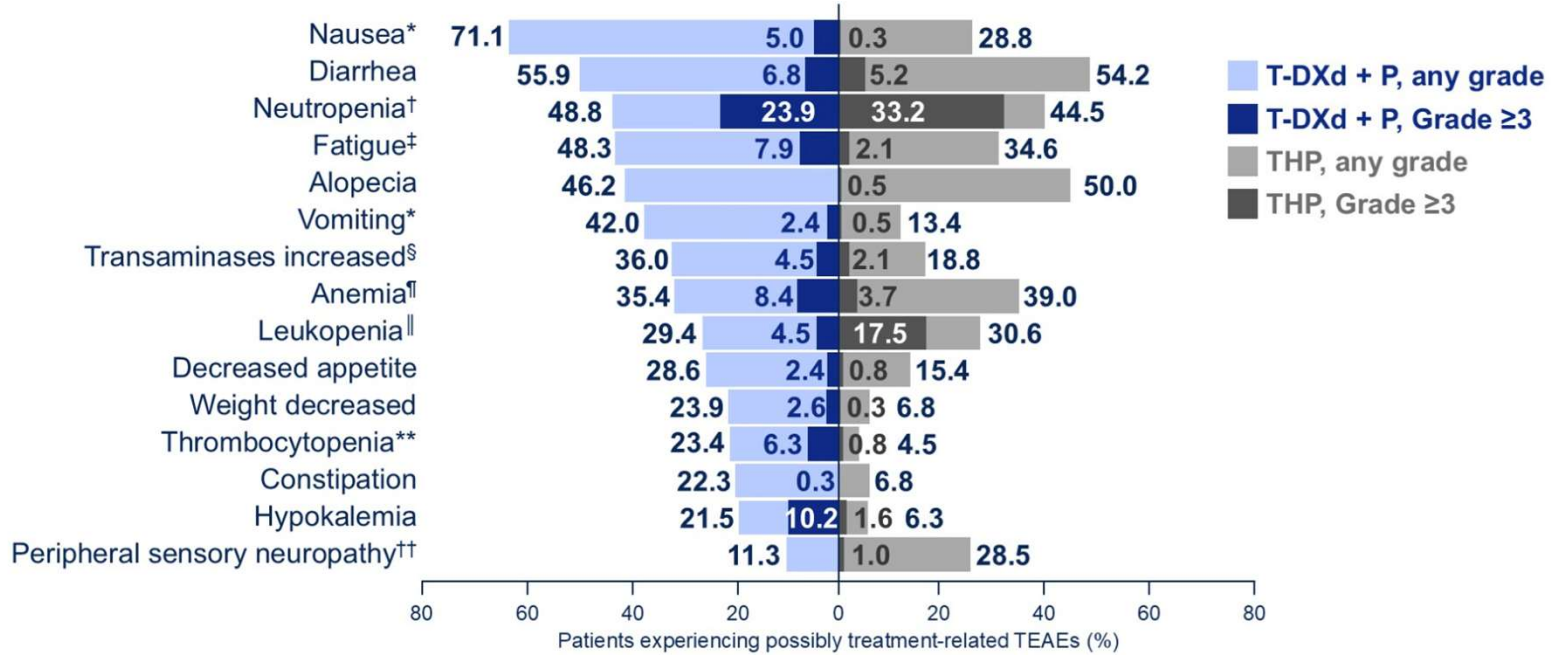
	T-DXd + P (n=383)	THP (n=387)
Median DOR, mo (95% CI)	39.2 (35.1, NC)	26.4 (22.3, NC)
Remaining in response at 24 mo (%)	73.3	54.9
Stable disease, n (%)	38 (9.9)	56 (14.5)

Response rates were greater with T-DXd + P vs THP and were durable

*Based on RECIST v1.1; response required confirmation after 4 weeks
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; mo, months; NC, not calculable; ORR, objective response rate; P, pertuzumab; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Tolaney et al, ASCO 2025

Possibly Treatment-related TEAEs



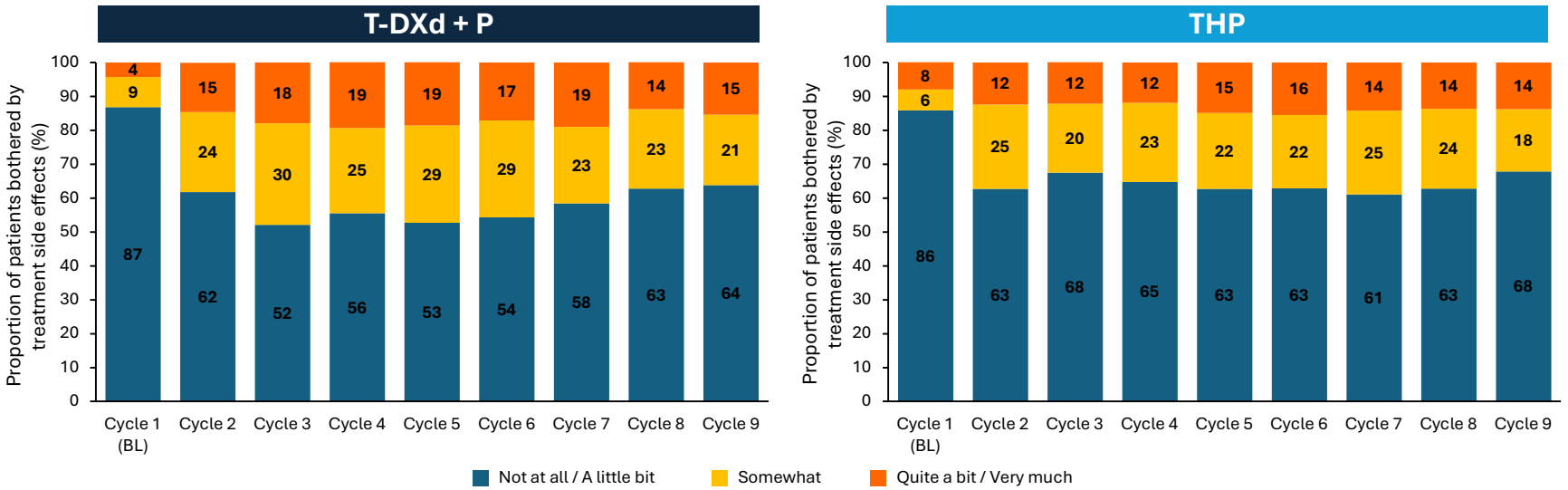
Adjudicated drug-related ILD/pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd + P (n=381)	17 (4.5)	27 (7.1)	0	0	2 (0.5)	46 (12.1)
THP (n=382)	2 (0.5)	2 (0.5)	0	0	0	4 (1.0)

Tolaney et al, ASCO 2025

DESTINY-Breast09 PROs

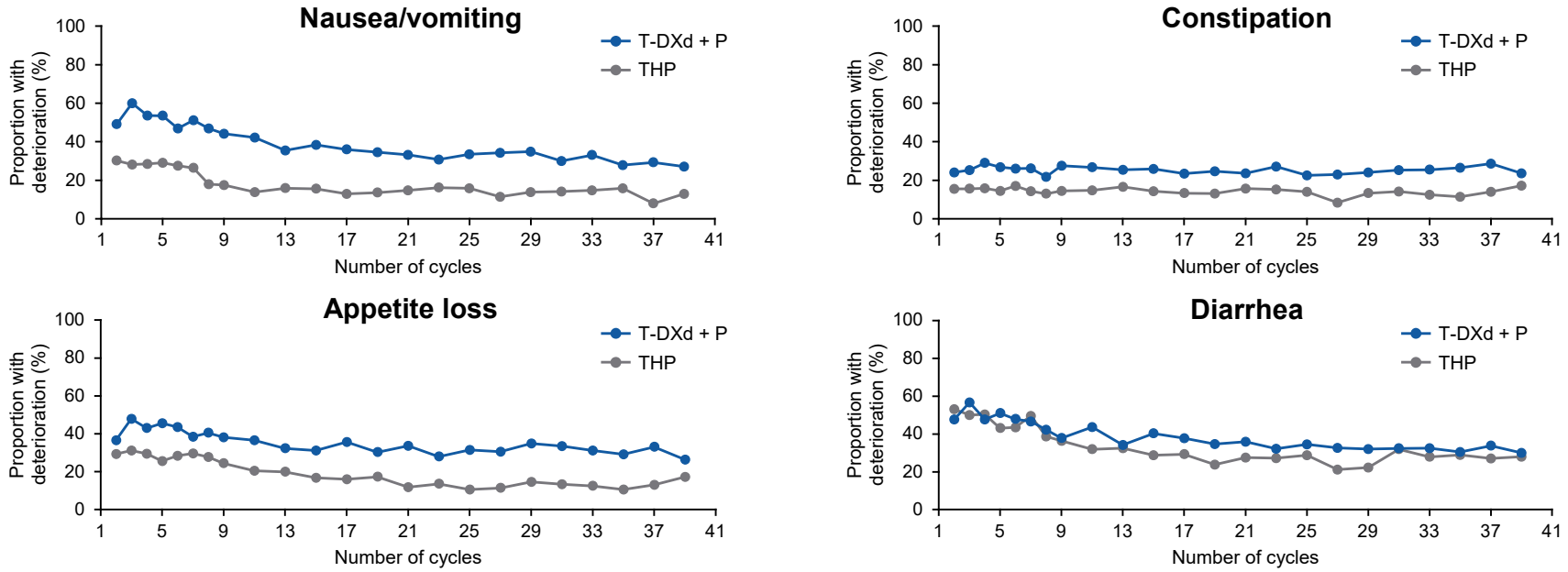
Overall treatment tolerability (PGI-TT)



- Post baseline, **52–64% (T-DXd + P)** vs **61–68% (THP)** of patients reported to be ‘Not at all’ or ‘A little bit’ bothered by treatment side effects
- Post baseline, **14–19% (T-DXd + P)** vs **12–16% (THP)** of patients reported to be ‘Quite a bit’ or ‘Very much’ bothered by treatment side effects

Rimawi et al, SABCS 2025

DESTINY-Breast09 PROs



T-DXd + P was associated with more nausea/vomiting, constipation, and appetite loss symptoms than THP, with similar impact on diarrhea

Patient compliance for the EORTC QLQ-C30: >92% at baseline, 63–68% by Cycle 17 (~12 mo), 43–59% by Cycle 39 (~26.9 mo),* and >90% overall (based on an evaluable baseline questionnaire and at least one evaluable post-baseline questionnaire)
*Cycle 39 is equivalent to approximately 26.9 mo, the observed median PFS in the THP arm, when a robust comparison could be made between arms without disease progression
EORTC, European Organisation for Research and Treatment of Cancer; GI, gastrointestinal; mo, months; P, pertuzumab; QLQ-C30, Quality of Life Questionnaire Core 30; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

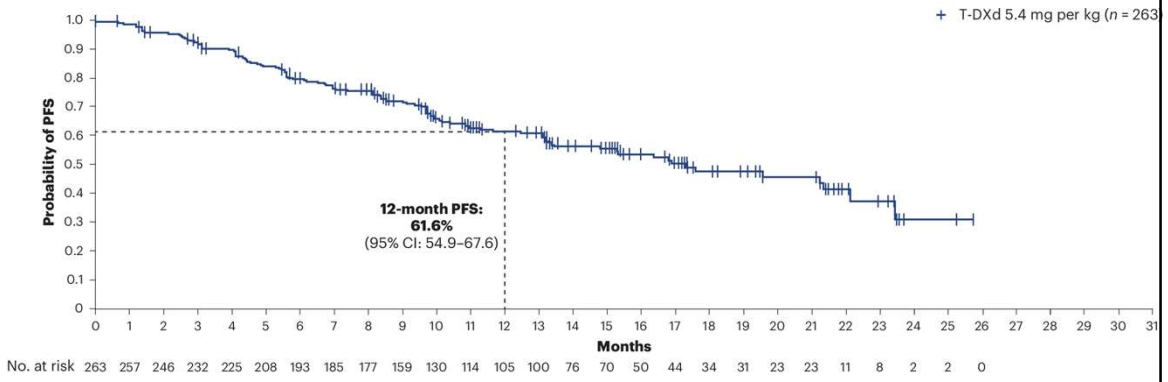
Rimawi et al, SABCS 2025

DESTINY-Breast12 – T-DXd with Baseline BMs

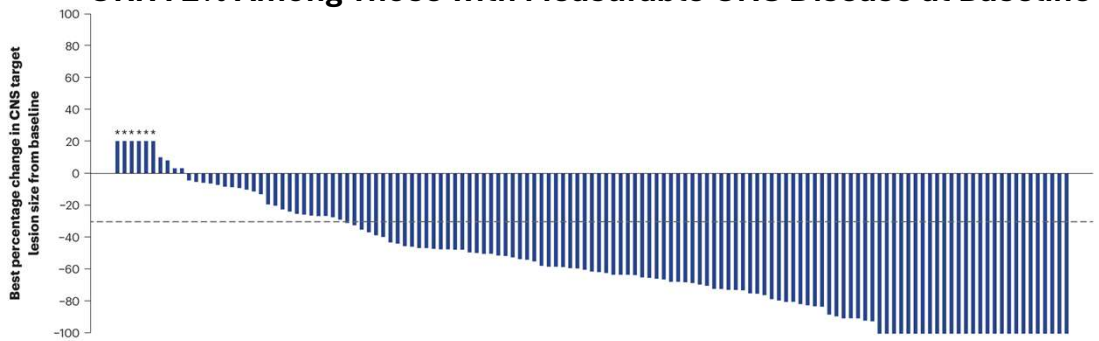
Enrollment of DESTINY-Breast12:

- Phase 3b/4 trial of HER2+ MBC with ≥ 1 prior regimen (90% had 1-2 lines)
- 263 enrolled with baseline brain mets
  - 157 with previously treated / stable brain mets
  - 106 with active brain mets
- All patients treated with T-DXd

Median PFS > 1 Year in Patients with Baseline Brain Metastasis



ORR 72% Among Those with Measurable CNS Disease at Baseline



Harbeck et al, Nat Med 2025

AFT-38 PATINA Study Design

Randomized, multicenter, open-label, Phase 3 study (NCT02947685)

Patient Population:
- HR+/HER2+ MBC
- Completed 6 – 8 cycles of first line taxane/vinorelbine + trastuzumab ± pertuzumab
- No evidence of disease progression

R
1:1

- Palbociclib (125mg PO QD D1-21) + endocrine therapy + trastuzumab ± pertuzumab
- Endocrine therapy + trastuzumab ± pertuzumab

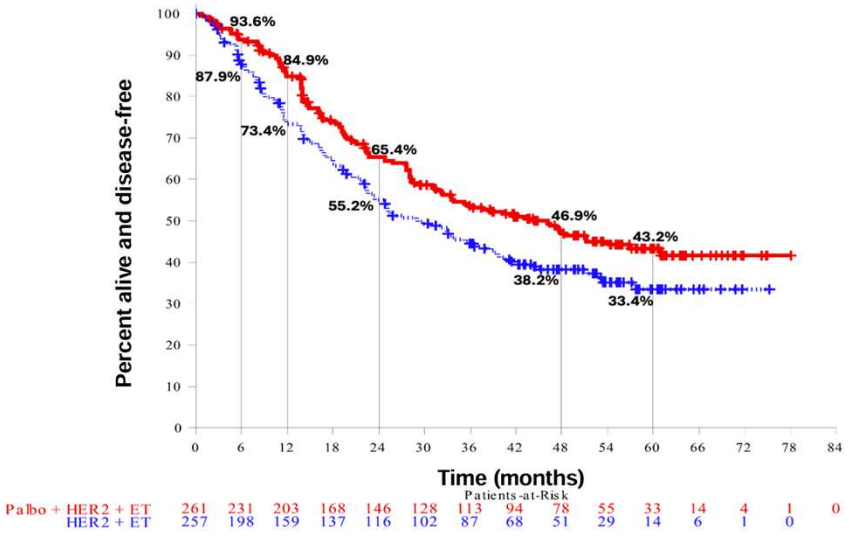
Stratification factors:
- Pertuzumab use
- Prior anti-HER2 therapy in the (neo)adjuvant setting
- Response to induction therapy (CR or PR vs SD) by investigator assessment
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)

Key Demographics: 518 patients enrolled
- 97% received pertuzumab
- 91% received aromatase inhibitor as endocrine therapy
- 28% with no prior therapy
- 69% with a CR or PR to induction therapy

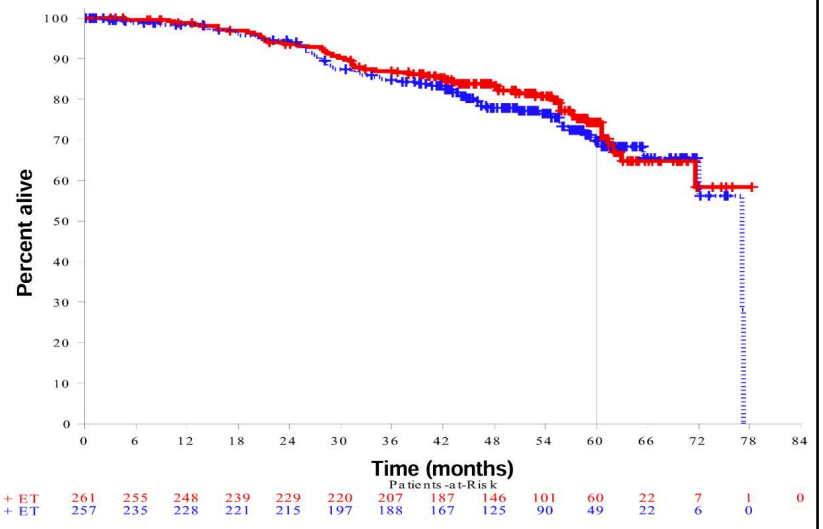
Metzger et al, SABCS 2024

AFT-38 PATINA Study Outcomes

Progression Free Survival



Overall Survival



	Palbo + anti-HER2 + ET	Anti-HER2 + ET
Median PFS, months (95% CI)	**44.3** (32.4 – 60.9)	**29.1** (23.3 – 38.6)
Hazard ratio (95% CI)	**0.74** (0.58 – 0.96)	

	Palbo + anti-HER2 + ET	Anti-HER2 + ET
5-yr OS, % (95% CI)	**74.3 (67.7 – 80.9)**	**69.8 (62.4 – 77.2)**
Hazard ratio (95% CI)	**0.86 (0.60 – 1.24)**	

Metzger et al, SABCS 2024

AFT-38 PATINA Adverse Events

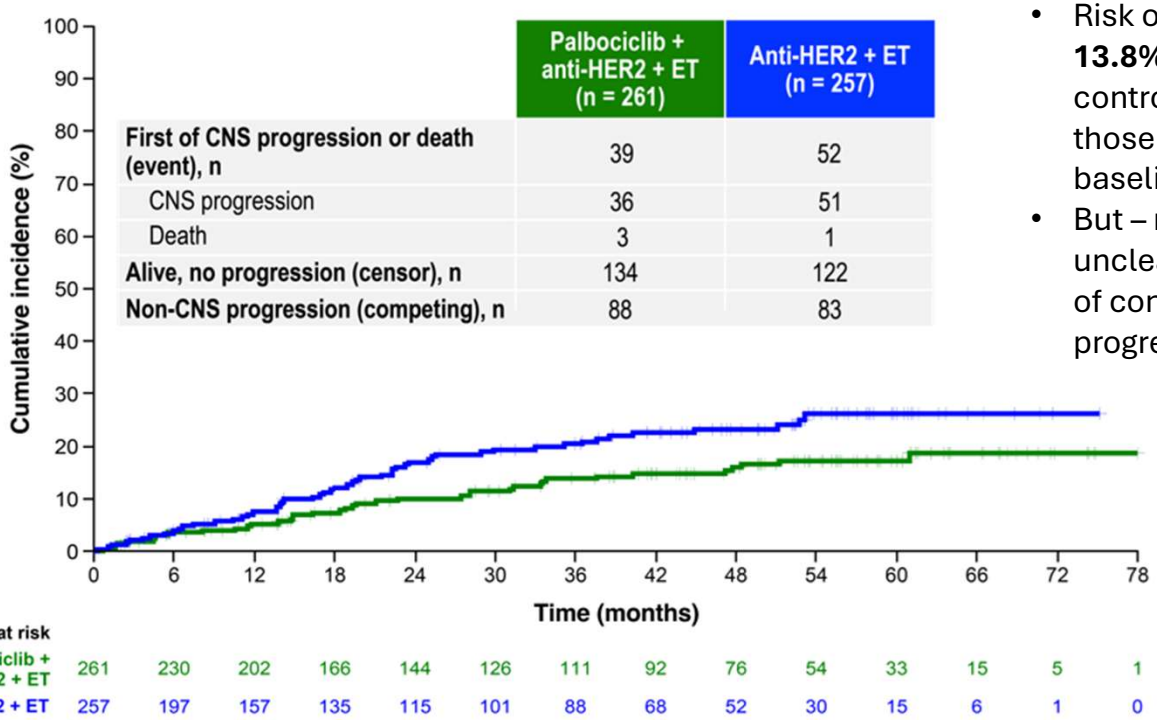
Adverse Event	Palbo + anti-HER2 + ET			Anti-HER2 + ET		
	Grade 2, %	Grade 3, %	Grade 4, %	Grade 2, %	Grade 3, %	Grade 4, %
Neutropenia	19.9	63.2	4.6	4.0	4.4	0.0
White blood cell count decreased	11.5	11.5	0.4	0.8	0.0	0.0
Fatigue	22.9	5.4	0.0	12.9	0.0	0.0
Stomatitis	17.2	4.2	0.0	1.2	0.0	0.0
Diarrhea	26.4	11.1	0.0	10.5	1.6	0.0
Upper respiratory tract infection	11.5	0.4	0.0	6.5	0.0	0.0
Urinary tract infection	10.0	0.8	0.0	7.7	0.4	0.0
Arthralgia	8.8	1.5	0.0	17.7	1.2	0.0
Ejection fraction decreased	8.4	0.4	0.0	8.5	3.2	0.0
Cardiac heart failure	0.0	0.0	0.0	0.4	0.4	0.0

Treatment discontinued due to AEs in **14 (7.5%) of the palbociclib arm**

Metzger et al, SABCS 2024

CNS Progression in PATINA

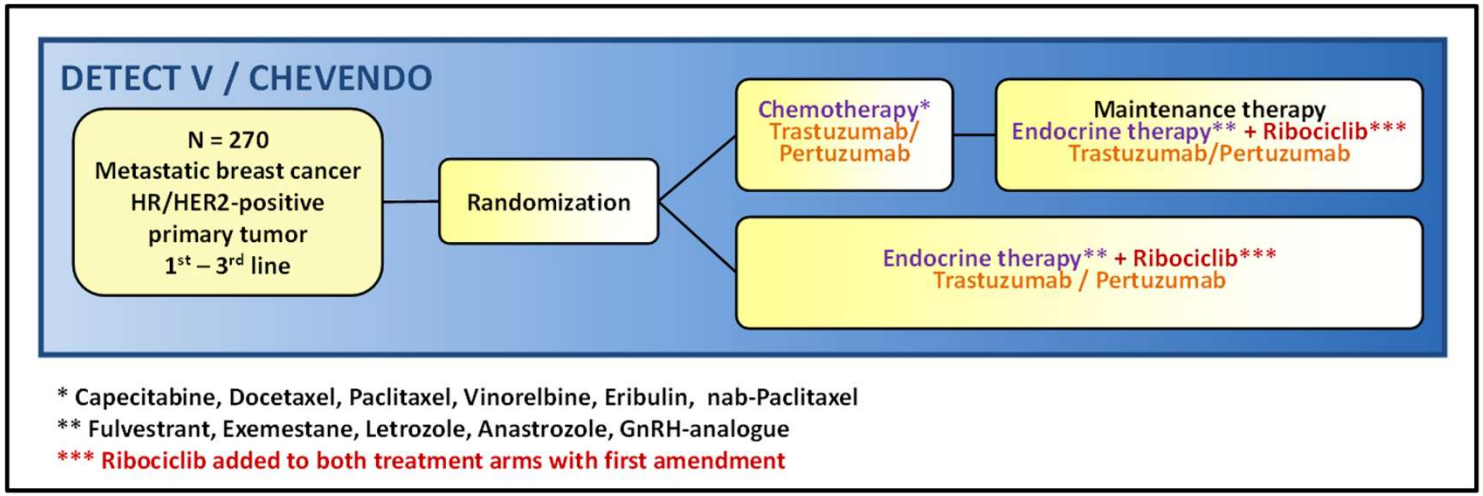
	Palbociclib + anti-HER2 + ET (n = 261)	Anti-HER2 + ET (n = 257)
First of CNS progression or death (event), n	39	52
CNS progression	36	51
Death	3	1
Alive, no progression (censor), n	134	122
Non-CNS progression (competing), n	88	83



- Risk of CNS Progression at 3 years was **13.8% vs 20.4%** for palbociclib vs control (P = 0.04); similar benefit in those without CNS metastasis at baseline
- But – no standardized CNS imaging, and unclear if benefit is driven by prevention of concurrent systemic + CNS progression

Metzger et al, SABCS 2025

Efficacy with Other CDK4/6 Inhibitors?

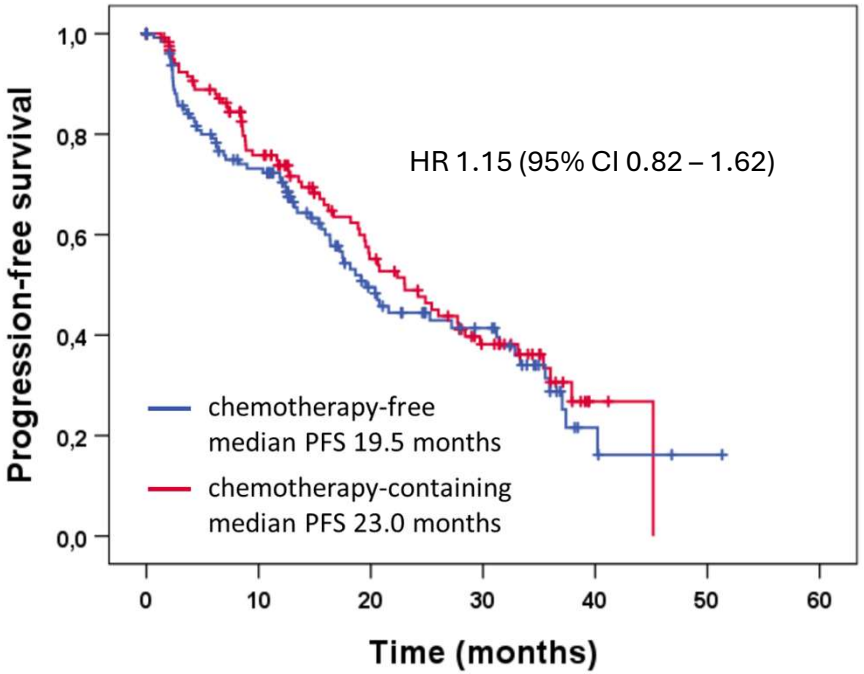


- Primary endpoint: Modified adverse event score
  (all adverse events grade 3 or higher, except for neutropenia, which is only included if rated grade 4, and alopecia, rash, peripheral neuropathy and hand-foot syndrome, all of which are included if rated grade 2 or higher)
- Important secondary endpoints: PFS, OS, Safety

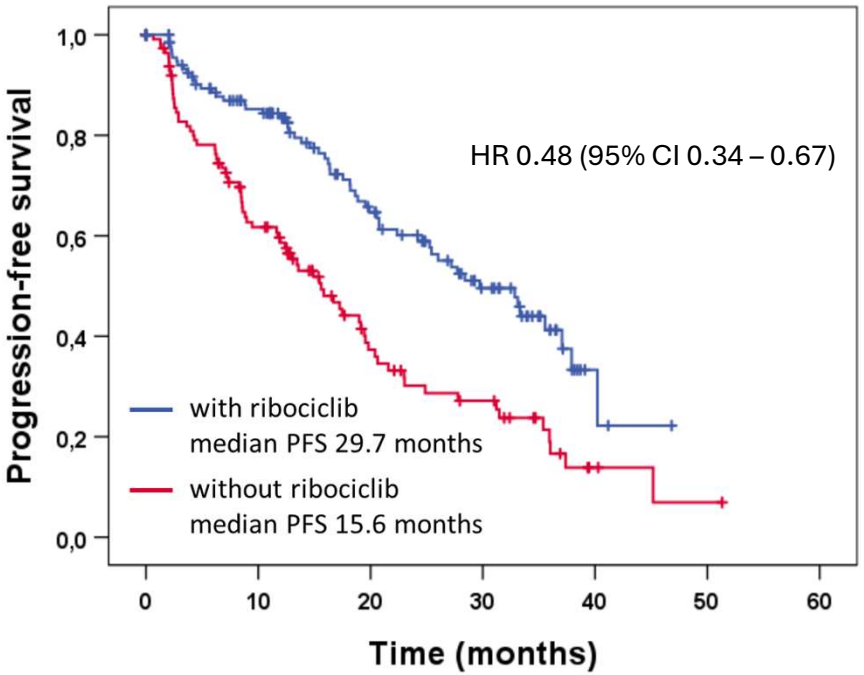
Janni et al, SABCS 2025

PFS Outcomes by Randomization / Treatment

Induction Chemo vs Not



Ribociclib + ET vs ET



- Chemotherapy was associated with more toxicity, nonsignificant improved PFS/OS
- Ribociclib + ET associated with more AEs than ET (25% G3 neutropenia; 10% G3 AST/ALT elevations)

Janni et al, SABCS 2025

HER2CLIMB-05

Randomized, multicenter, double-blind, Phase 3 study (NCT05132582)

Patient Population:
- HER2+ MBC
- No progression after THP (4 to 8 cycles)
- No or asymptomatic BM confirmed by contrast-enhanced MR at screening

R 1:1

- Tucatinib (300mg BID) + trastuzumab + pertuzumab ± endocrine therapy
- Placebo + trastuzumab + pertuzumab ± endocrine therapy

Stratification factors:
- Diagnosis: *de novo* or recurrent
- HR status: positive or negative
- Presence or history of BM: yes or no

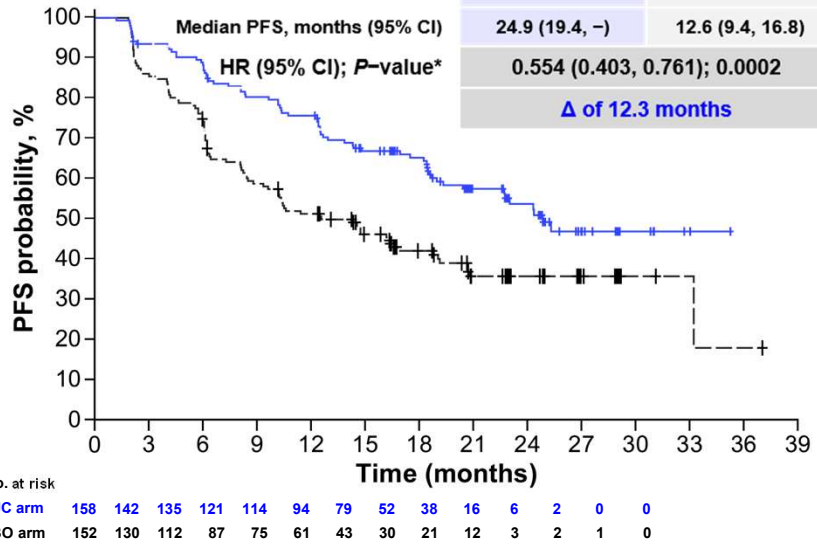
Key Demographics: 310 patients enrolled
- 53% HR+ (only 46% of whom received ET!)
- 12% with brain metastasis
- 69% with de novo disease
- 72% with a CR or PR to induction therapy

Hamilton et al, SABCS 2025

HER2CLIMB-05 – Outcomes by HR Status

Hormone receptor-negative

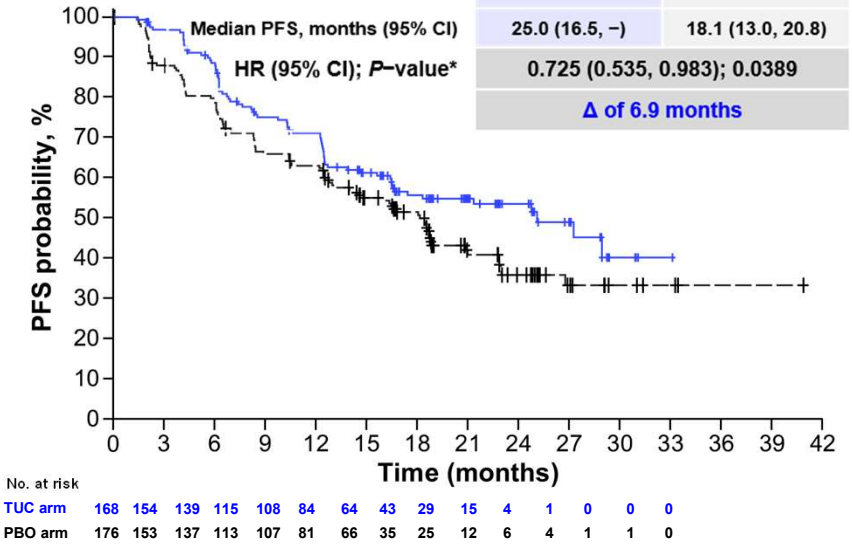
	TUC + HP (n = 158)	PBO + HP (n = 152)
Events	68	92
Median PFS, months (95% CI)	24.9 (19.4, –)	12.6 (9.4, 16.8)
HR (95% CI); *P*–value*	0.554 (0.403, 0.761); 0.0002	
	Δ of 12.3 months	



No. at risk													
TUC arm	158	142	135	121	114	94	79	52	38	16	6	2	0	0
PBO arm	152	130	112	87	75	61	43	30	21	12	3	2	1	0

Hormone receptor-positive

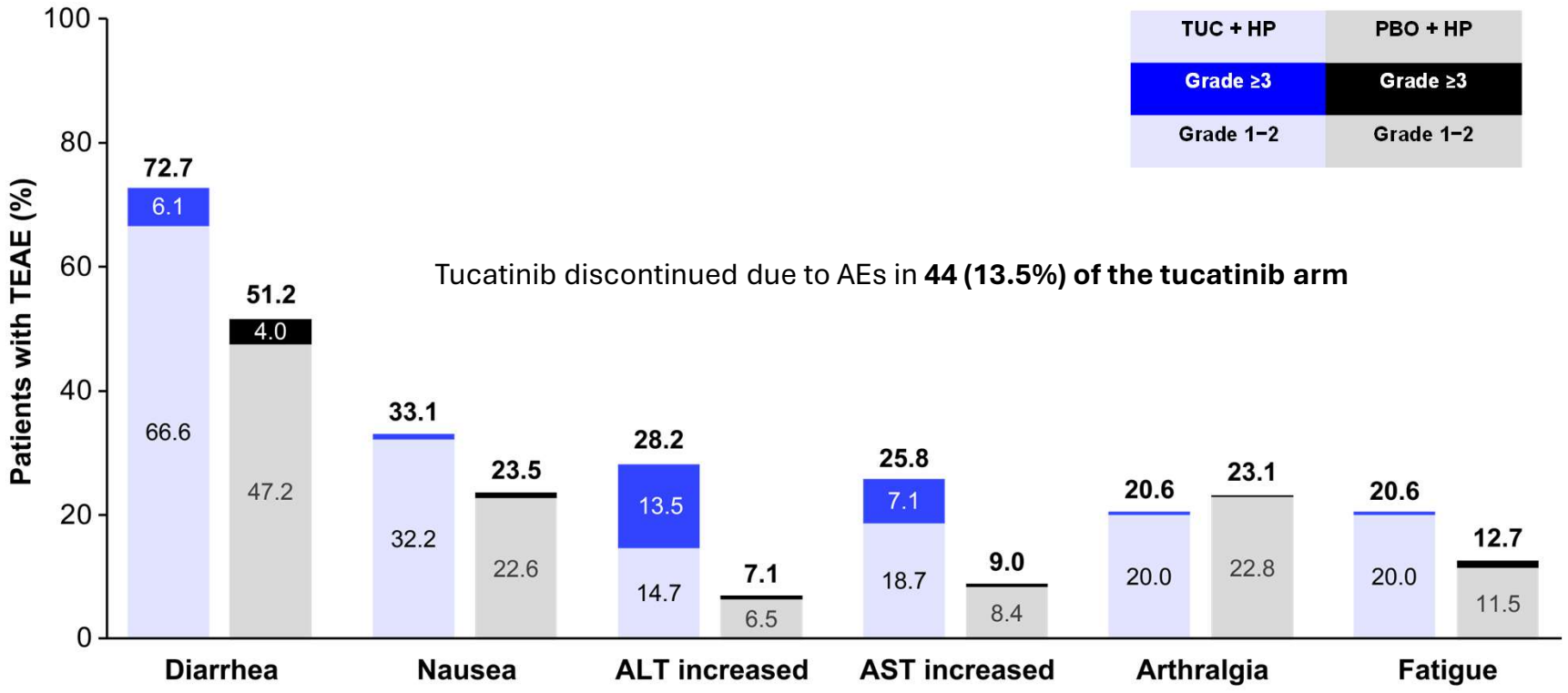
	TUC + HP (n = 168)	PBO + HP (n = 176)
Events	73	99
Median PFS, months (95% CI)	25.0 (16.5, –)	18.1 (13.0, 20.8)
HR (95% CI); *P*–value*	0.725 (0.535, 0.983); 0.0389	
	Δ of 6.9 months	



No. at risk														
TUC arm	168	154	139	115	108	84	64	43	29	15	4	1	0	0	0
PBO arm	176	153	137	113	107	81	66	35	25	12	6	4	1	1	0

Hamilton et al, SABCS 2025

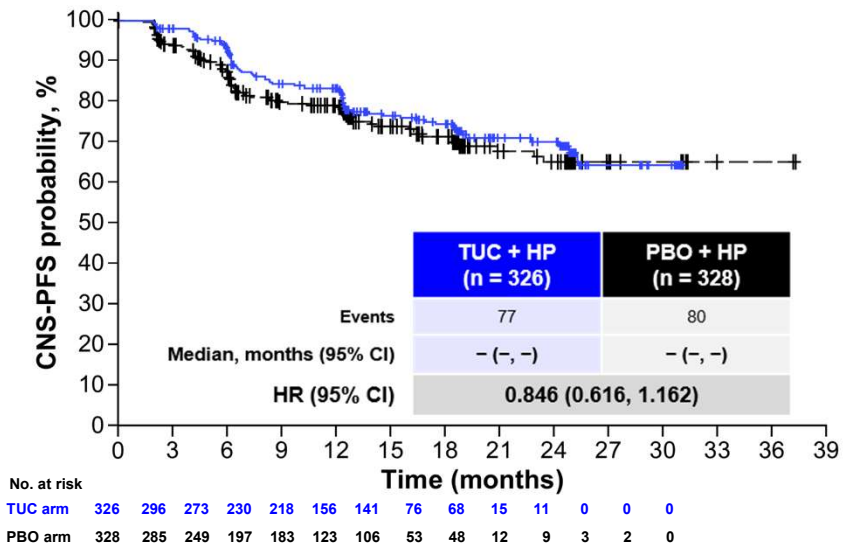
HER2CLIMB-05 – TEAEs



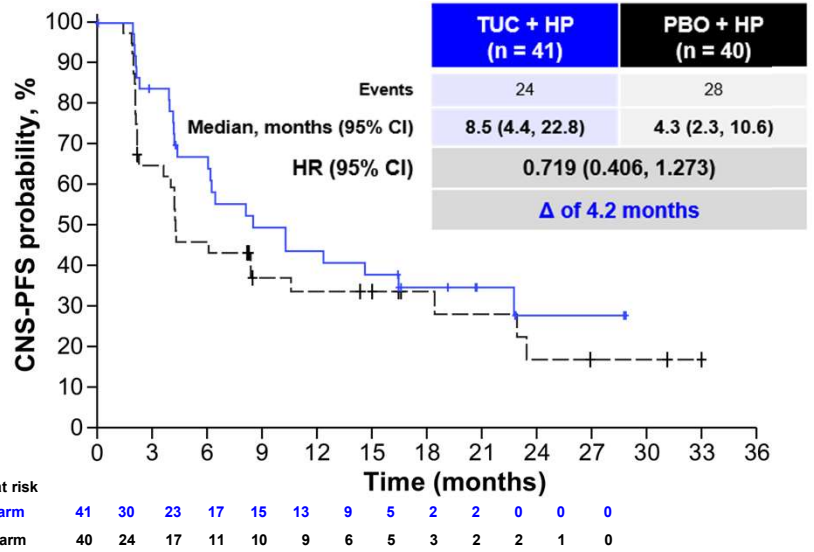
Hamilton et al, SABCS 2025

CNS Progression in HER2CLIMB-05

ITT population



Exploratory analysis: Patients with baseline BM



CNS-PFS was defined as the time from randomization to disease progression in the brain or death from any cause, whichever occurred first. Contrast-enhanced brain MRI was required for all patients at screening and end of treatment and was repeated for patients with presence or history of BM every 9 weeks. For patients without presence or history of BM at baseline, contrast-enhanced brain MRI was repeated every 27 weeks (~6 months).
BM = brain metastases; CI = confidence interval; CNS-PFS = central nervous system progression-free survival; H = trastuzumab; HR = hazard ratio; ITT = intent-to-treat; MRI = magnetic resonance imaging; P = pertuzumab; PBO = placebo; TUC = tucatinib.

Hamilton et al, SABCS 2025

Overview of 1L / Maintenance Strategies

	DESTINY-Breast09	PATINA	HER2CLIMB-05
Treatment	T-DXd + P vs THP	THP → HP + ET **± Palbociclib**	THP → HP (± ET) **± Tucatinib**
mPFS (mo) HR	**40.7** versus 20.7 0.56	**44.3** vs. 26.9 0.74 *Note: PFS measured from maintenance therapy	**24.9** vs. 16.3 0.64
HR+ mPFS (mo), HR	**38.0** vs 27.7 0.61	**44.3** vs. 26.9 0.74	**25.0** vs. 18.1 0.73
HR- mPFS (mo), HR	**40.7** vs 22.6 0.52	N/A	**24.9** vs 12.6 0.55
Adverse events	**Nausea (G1+: 71% vs 29%) / Vomiting / Diarrhea** Fatigue Cytopenias Transaminase Elevation **12% ILD (0.5% G5)**	**Neutropenia (G3+: 68% vs 4%)** Fatigue Stomatitis Diarrhea	**Diarrhea (G1+: 73% vs 51%)** / Nausea **AST / ALT elevation** Fatigue
Discontinuation for AEs	20.7% in T-DXd + P arm	7.5% in palbociclib arm	13.8% in tucatinib arm

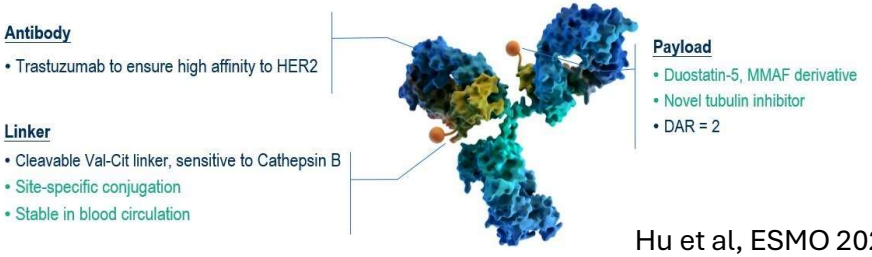
Adapted from Reid, SABCS 2025

Remaining Questions

- Continuous T-DXd + P, or Induction T-DXd + P followed by maintenance?
- What is the optimal maintenance strategy, and for whom is maintenance appropriate?
- Can we use biomarkers to select patients for less aggressive 1L treatments?

Emerging Therapies for HER2+ MBC

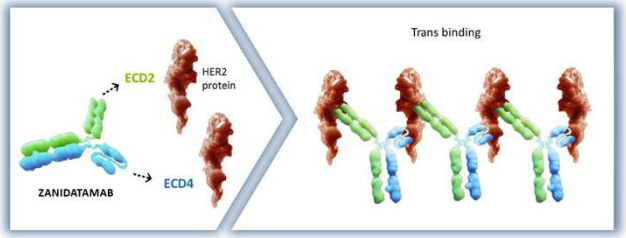
Novel HER2-Targeting ADCs



Hu et al, ESMO 2025

Drug / regimen	Phase	NCT registration
SHR-A1811 ± pertuzumab vs **THP**	3	NCT06057610
DP303c vs **T-DM1**	3	NCT06313086
JSKN003 vs **T-DM1**	3	NCT06846437
ARX788 (monotherapy post T-DXd)	2	NCT04829604
	2	NCT06578286
Disitamab vedotin (monotherapy and various combinations)	2	NCT03500380
	2	NCT06015113
	1/2	NCT06157892
	2	NCT07065435
	2	NCT06966453
MRG002 (monotherapy)	2	NCT04492488
	2	NCT05141747
ZW49 (zanidatamab zovodotin)	1	NCT03821233

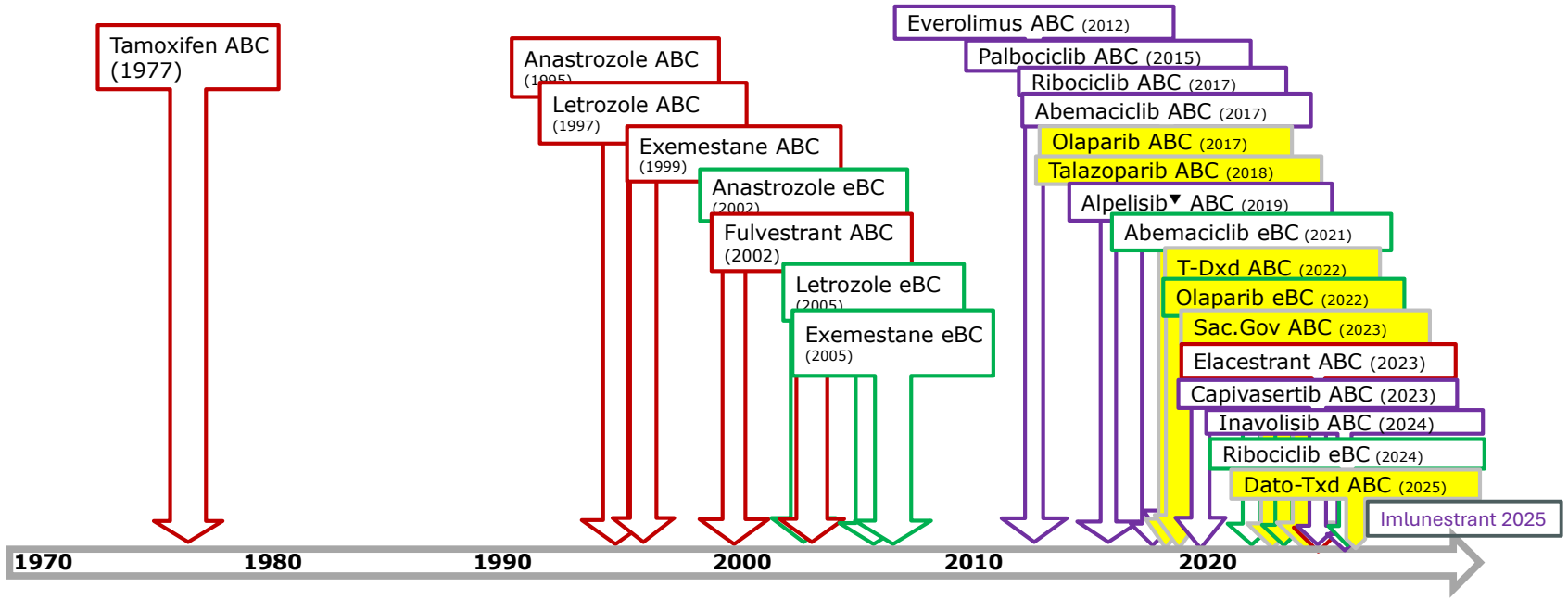
HER2-Targeting Bispecifics



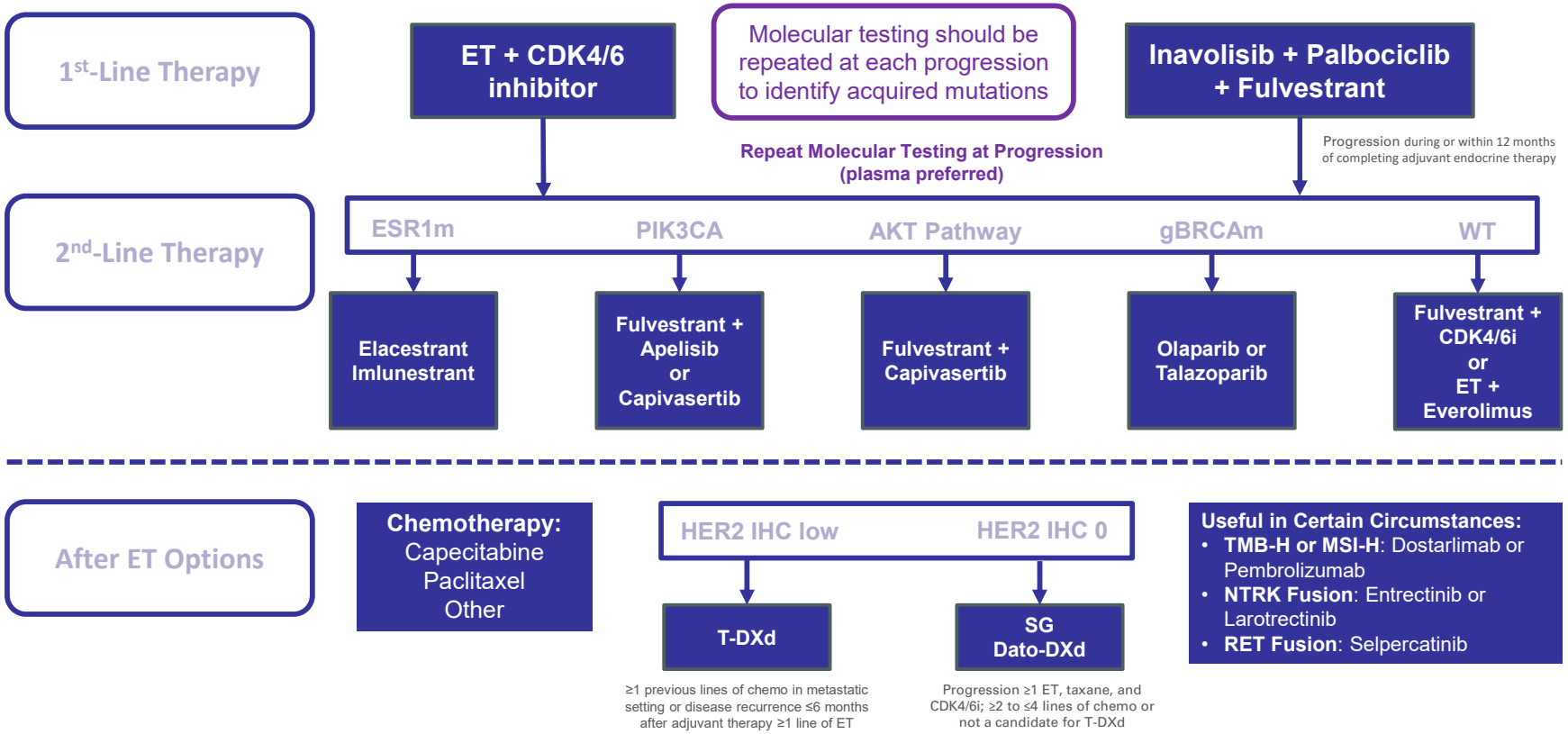
Pant et al, ASCO 2023

Drug / regimen	Phase	NCT registration
Zanidatamab vs trastuzumab (with chemo post T-Dxd)	3	NCT06435429
Zanidatamab + palbociclib + fulvestrant	2a	NCT04224272
Zanidatamab + evorpacept (ALX148, anti-CD47)	1b/2	NCT05027139
PRS-343 (HER2/4-1BB)	1	NCT03330561
PRS-343 + atezolizumab	1b	NCT03650348
YH32367 (HER2/4-1BB)	1/2	NCT05523947
KN026 (HER2 bispecific) + HB1801 (albumin bound docetaxel)	3	NCT05838066

Important milestones in the treatment of HR+ breast cancer
(Year of FDA Approval)



Managing HR+/HER2- mBC Patients in 2026



Detecting Actionable Biomarkers is Standard of Care

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

Genomic △	%	FDA approved therapy
ESR1m	≤40%	elacestrant, imlunestrant
AKT1, PTENm	20%	capivasertib
PIK3CAm	40%	capivasertib, alpelisib, inavolisib
g(or s)BRCA1/2m	10%	olaparib, talazoparib
gPALB2m	2%	olaparib
BRAFm	1%	dabrafinib+trametinib
NTRK fusion	<1%	entrectinib, larotrectinib, repotrectinib
RET fusion	1%	selpercatinib
MSI-H	1%	Pembrolizumab, dostarlimab
TMB-high	5%	Pembrolizumab
ErbB2m	2%	neratinib

https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-metastatic-breast-cancer

Chakravarty D et al, JCO 2022; https://www.oncokb.org/actionable-genes#cancerType=Breast%20Cancer&sections=Tx; Henry NL et al, JCO 2022; Burstein HJ et al, JCO 2023

TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	**Biomarker**	**Detection[u]**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
HR-positive, HER2-negative	*PIK3CA* activating mutation	NGS, PCR	Fulvestrant/Inavolisib/Palbociclib[x]	Category 1	Preferred
HR-positive/ HER2-negative	*PIK3CA* activating mutation	NGS, PCR	Alpelisib/Fulvestrant	Category 1	Preferred
HR-positive/ HER2-negative	*PIK3CA* or *AKT1* activating mutations or *PTEN*[w] inactivating mutations and genomic changes (eg, deletion)	NGS, PCR	Capivasertib/Fulvestrant[y]	Category 1	Preferred[y]
HR-positive/ HER2-negative[u,v]	*ESR1* mutation[v]	NGS, PCR	Elacestrant[z]	Category 2A	Other recommended
			Imlunestrant[aa]	Category 2A	Other recommended

Summary of CDK4/6i Combination Trials

	PALOMA-2 First Line N=666	MONALEES A-2 First Line N=668	MONARCH-3 First Line N=493	MONALEES A-7 First Line N=672	PALOMA-3 Post-ET N=521	MONARCH-2 First/Second Line N=669	MONALEES A-3 First/Second Line N=726
CDK4/6i	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Abemaciclib	Ribociclib
Endocrine Partner	AI	AI	AI	Tam or AI with OS	Fulvestrant	Fulvestrant	Fulvestrant
Menopause	Post	Post	Post	Pre/Peri	Pre/Peri/Post	Pre/Post	Post
ORR, %	55.3 vs 44	52.7 vs 37.1	59 vs 44	50.9 vs 36.5	25 vs 11	48.1 vs 21.3	40.9 vs 27.7
mPFS, mo • HR	27.6 vs 14.5 0.56, p<0.0001	25.3 vs 16.0 0.57, p<0.0001	29.0 vs 14.8 0.54, p<0.0001	23.8 vs 13.0 0.55, p<0.0001	9.5 vs 4.6 0.46, p<0.0001	16.4 vs 9.3 0.55, p<0.0001	33.6 vs 19.2 0.55, p<0.0001
mOS, mo • HR	53.9 vs 51.2 0.956, p=0.34	63.9 vs 51.4 **0.76, p=0.008**	66.8 vs 53.7 0.804, p=0.0664	58.7 vs 48 **0.763, p=0.00973**	34.9 vs 28.0 0.81, p=0.09	46.7 vs 37.3 **0.757, p=0.01**	67.6 vs 51.8 **0.67, p=0.00455**

Joyce O'Shaughnessy, DAVA Hawaii Breast 2023; Goetz M et al. SABCS 2023.

International Consensus Guidelines for Advanced Breast Cancer
ABC GUIDELINES

Lisbon 11/2025

ENDOCRINE SENSITIVITY/RESISTANCE
Collaboration work with the AURORA Molecular Screening Initiative (BIG 14-01)

PREMISES

- Endocrine resistance is a continuum and is a very complex, not yet fully understood biological phenomenon.
- These definitions may be helpful for clinical trials but not necessarily for clinical practice; they are general guidelines and are not truly distinct categories. Pragmatically, they can be associated with the likelihood of ET-benefit spectrum.
- This classification of levels of endocrine resistance has mostly prognostic value.
- Some biomarkers that predict resistance have both prognostic and predictive value (e.g. ESR1, PIK3CA).
- A given mechanism of resistance can occur in any of the types of endocrine resistance.
- In general, when resistance occurs, a change in the mechanism of action of the endocrine +/- targeted treatment is recommended; a possible exception is when relapse occurs 12 months or more after completion of adjuvant ET, when the same ET or the same targeted agent can be reused.

ENDOCRINE SENSITIVITY/RESISTANCE

PRIMARY ENDOCRINE RESISTANCE is defined as:

1) Relapse while on the first 2 years of adjuvant ET; or

2) PD within the first 6 months of 1st line ET-based therapy for ABC.

This definition is the same regardless of whether therapy included a CDK4/6i or not.

It is associated with a lower likelihood of ET-based therapy benefit.

SECONDARY or ACQUIRED ENDOCRINE RESISTANCE is defined as:

1) All other clinical situations of endocrine-resistance.

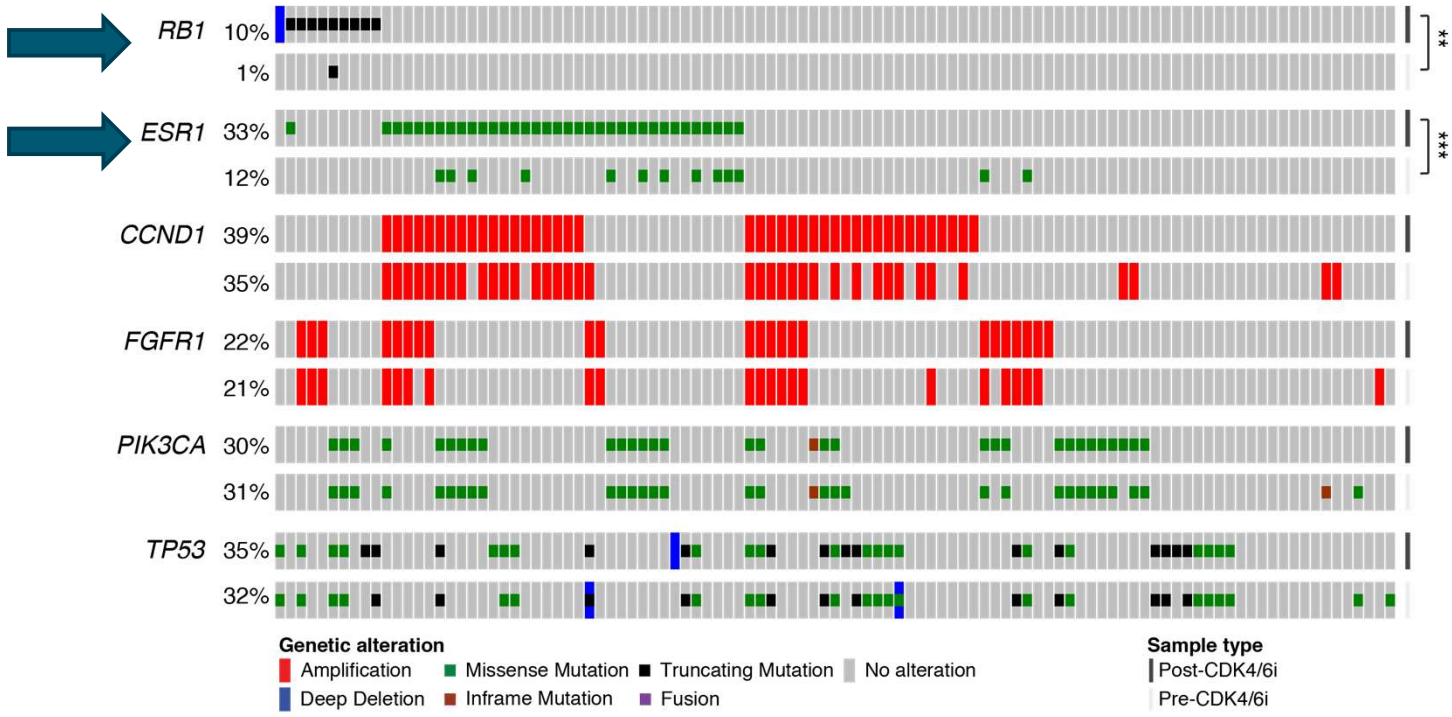
This definition is unaffected by therapy with CDK4/6i, mTOR/PI3Ki, or other adjunctive drugs.

EARLY ACQUIRED: 1) Relapse while receiving adjuvant ET but after at least 2 years; or 2) PD after at least 6 months but less than 12 months of 1st line ET-based therapy for ABC; or 3) PD after any duration of 2nd or later lines of ET-based therapy for ABC. It is associated with an intermediate likelihood of ET-based therapy benefit.

LATE ACQUIRED: 1) Relapse after 12 months of completing adjuvant ET; or 2) PD after at least 12 months of 1st line ET-based therapy for ABC. It is associated with a higher likelihood of ET-based therapy benefit.

(LoE: Expert opinion/NA or LoE/GoR: III B)

Comparison of Paired Post- vs Pre-CDK4/6i Breast Cancer Tumors



Razavi P et al. ASCO 2019. Abstract 1009.

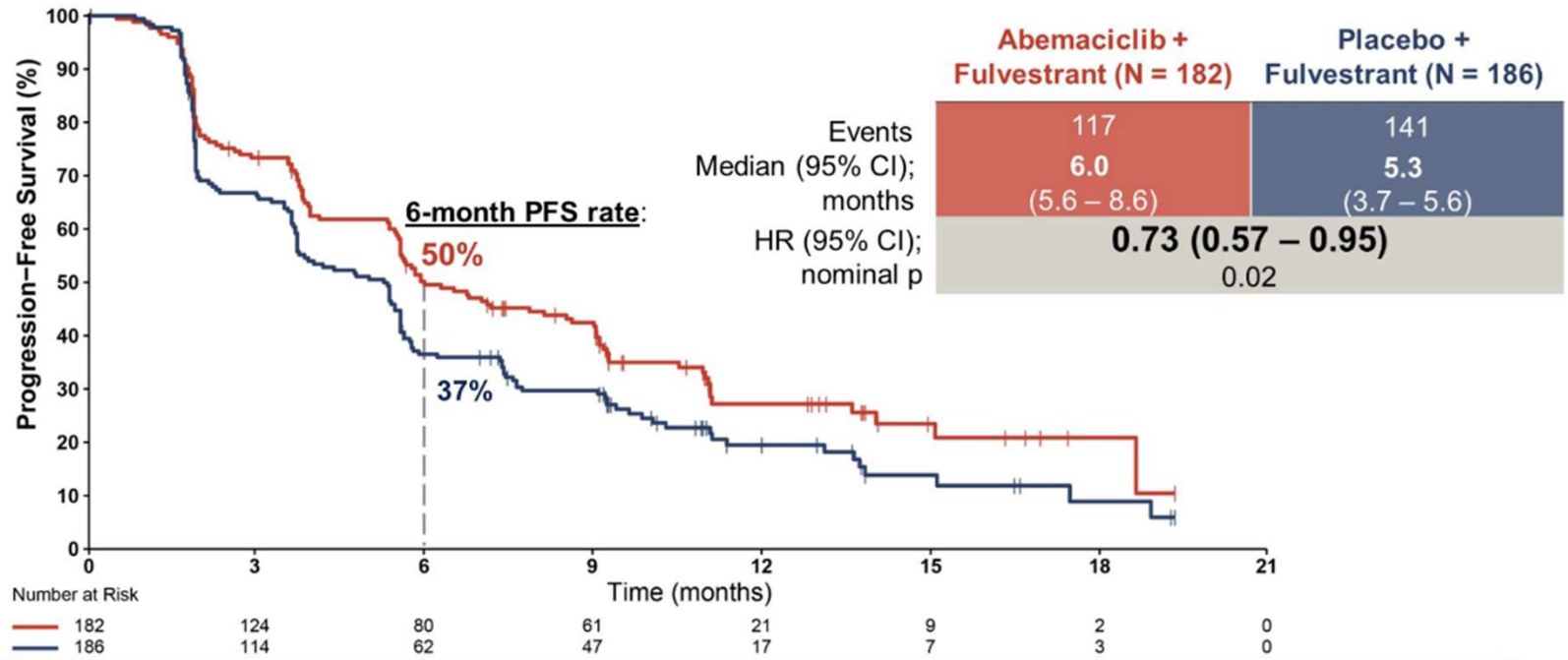
CDK 4/6 inhibitor after CDK 4/6 inhibitor

Switch Experience With CDK4/6 Inhibitors

	MAINTAIN	PACE	PALMIRA	Post MONARCH
Phase	II	II	II	III
Sample size	120 (1:1)	220 (1:1:1)	198 (2:1)	350
Design **HR+ MBC progression on iCDK 4/6+ET**	Fulvestrant or exemestane +/- ribociclib	Arm A: Fulvestrant Arm B: Fulvestrant + Palbociclib Arm C: Fulvestrant + Palbociclib + Avelumab	Fulvestrant or letrozole +/- palbociclib	Fulvestrant +/- abemaciclib
Initial CDK 4/6 inhibitor	Palbociclib (84%) Ribociclib (11%)	Palbociclib (90%)	Palbociclib (100%)	
Continuation iCDK 4/6	Ribociclib	Palbociclib	Palbociclib	Abemaciclib
% iCDK > 12mo	67%	75%	86%	
Continuation ET	Fulvestrant (83%), exemestane (17%)	Fulvestrant (100%)	Fulvestrant (90%), letrozole (10%)	ASCO 2024
PFS ET+CDK4/6 inhibitor vs. ET	5.3 vs. 2.8 months (HR 0.56)	4.6 vs. 4.8 months (HR 1.11)	4.9 vs. 3.6 months (HR 0.84)	

Kalinsky K et al. JCO 2023.
Mayer E et al. SABCS 2022.
Llombart-Cussac A et al. ASCO 2023.

postMONARCH: Investigator-Assessed PFS



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

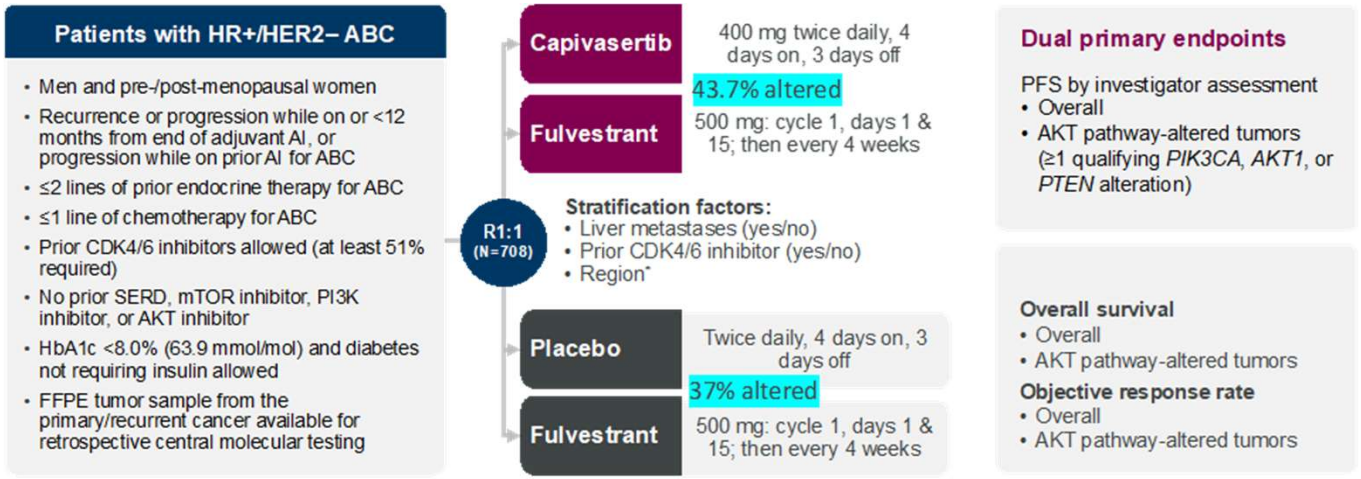
Kevin Kalinsky, ASCO 2024

Current Drugs Approved for the Treatment of MBC that Inhibit PIK3CA/AKT/mTOR Pathway

	Everolimus (BOLERO-2)	Alpelisib (SOLAR-1)	Capivasertib (CAPItello-291)
Mechanism of action	mTOR inhibitor	PI3Kα-specific inhibitor	AKT inhibitor
Design	Postmenopausal women (n=724), randomized 2:1 to exemestane + everolimus or placebo	n=572 (341 with PIK3CAm) randomized 1:1 to fulvestrant +alpelisib or placebo	n=708 (289 with AKT pathway alterations, 489 with prior iCDK4/6) randomized 1:1 to fulvestrant + capivasertib or placebo
Median PFS (months)	**10.6 vs 4.1 mo**	**PIK3CA WT: 7.4 vs. 5.6 mo** **PIK3CAm: 11 vs 5 mo**	**ITT 7.2 vs. 3.6 mo** **altered: 7.3 vs. 3.1**
HR (95%CI)	0.36 (0.27-0.47)	0.65 (0.5-0.85)	Altered 0.50 (0.38-0.65)
US FDA Approval	2012	2019 for patients with PIK3CA altered MBC HR+	2023 for patients with AKT, PTEN, PIK3CA altered HR+ breast cancer

Baselga J et al. *N Engl J Med*. 2012;366(2):109-119. André F et al. *N Engl J Med*. 2019;380(20):1929-1940.
Turner NC et al. *N Engl J Med*. 2023;388(22):2058-2070.

CAPItello-291: Phase III, randomized, double-blind, placebo-controlled study



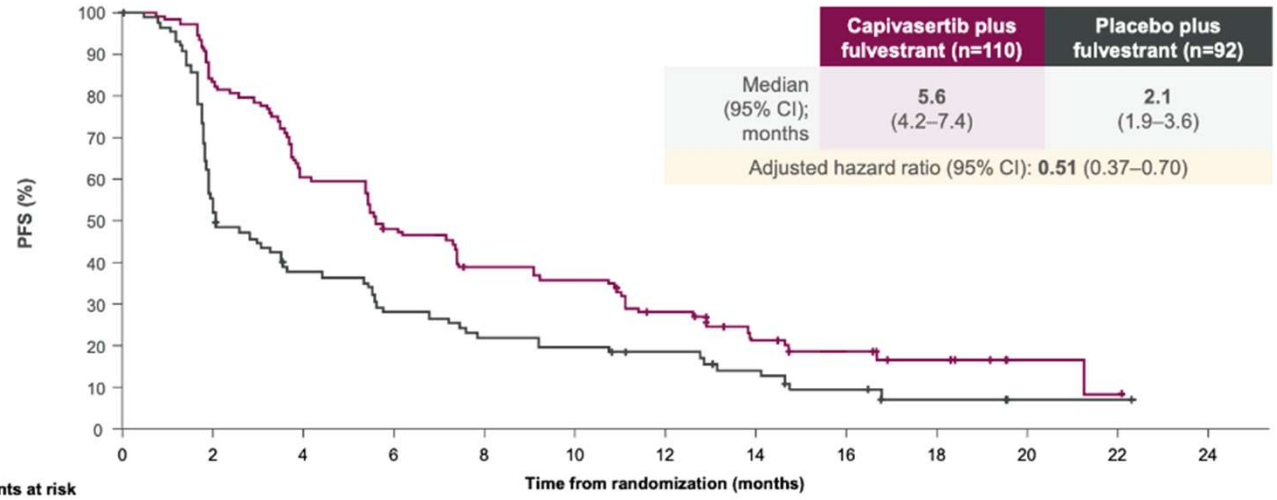
Summary of Demographics

- Median age ~59
- Asian 26%, Black 1%
- Primary ET resistance ~38%
- Visceral mets ~68%
- One line of prior ET for MBC ~75%
- Prior CDK4/6i for MBC ~70%
- Chemotherapy for ABC ~18%

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

Turner et al, SABCS 2022

SABCS 2023: CAPItello-291 PFS with PIK3CA Alterations



Number of patients at risk													
Capivasertib + fulvestrant	110	90	65	51	40	37	27	17	13	7	2	1	0
Placebo + fulvestrant	92	48	31	23	18	16	13	9	5	2	1	1	0

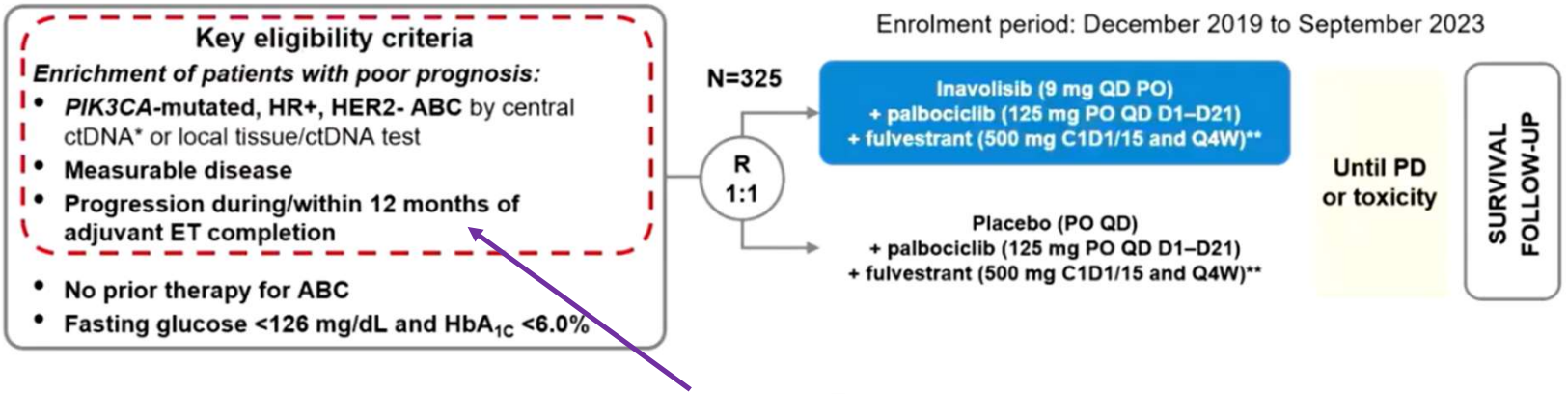
Northwestern Medicine®

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

Sacha Howell, SABCS 2023

SABCS 2023: INAVO120 Primary Analysis

- More effective treatments for patients with PIK3CA mutations are needed
- Inavolisib is a highly potent and selective PIK3α inhibitor that also promotes degradation of mutant p110α, which may improve the therapeutic window



Stratification factors:
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

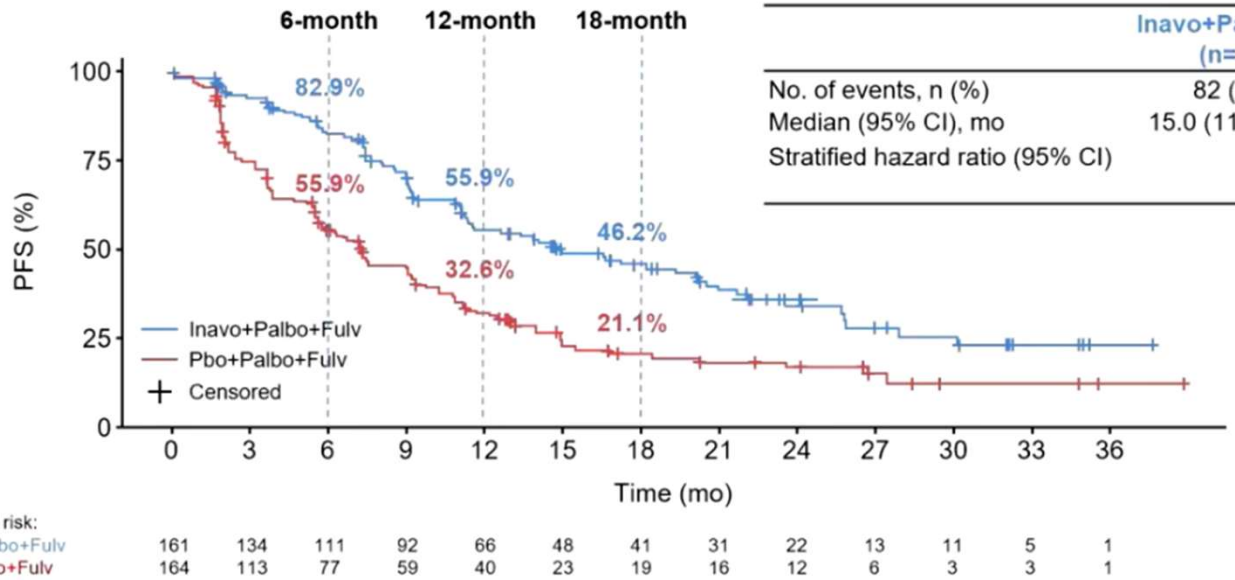
Endpoints
- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

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

Komal Jhaveri, SABCS 2023

Northwestern Medicine

SABCS 2023: INAVO120 PFS



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)** **p<0.0001**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

CCOD: 29th September 2023
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

Northwestern Medicine

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

Komal Jhaveri, SABCS 2023

Key Questions

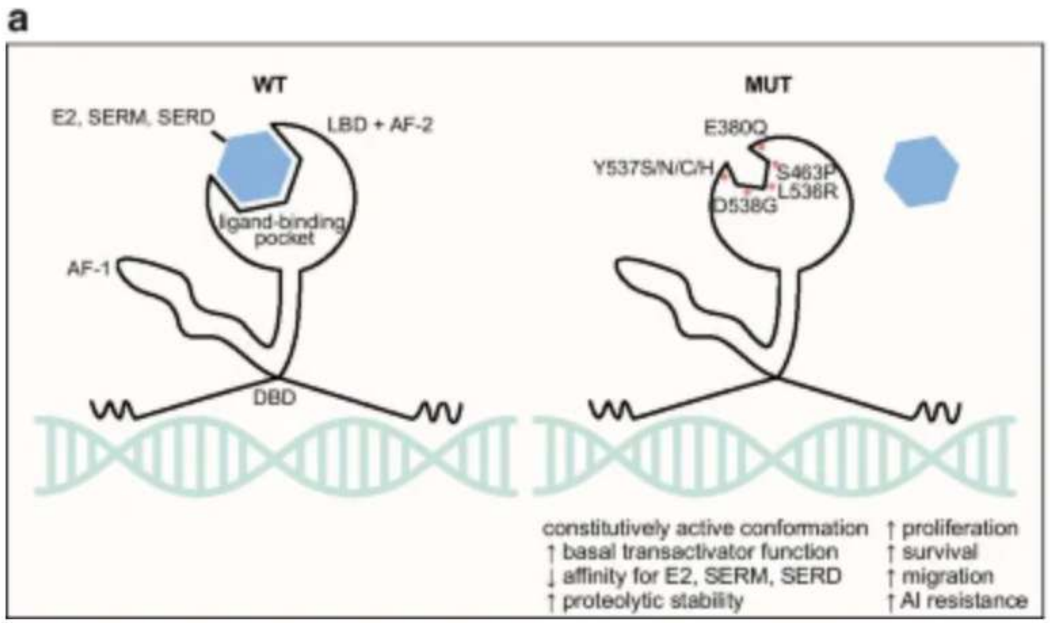
- How can we overcome endocrine resistance?
- How do we best utilize oral SERDs as monotherapy or in combination?
- How will novel endocrine therapy backbones be utilized?
- How can we best sequence these agents to optimize efficacy and minimize toxicity?

Prevalence of *ESR1* Mutations in Untreated vs Treated ER+/HER2- mBC

Treatment Setting	*ESR1* Mutation Prevalence[1-5]
At Initiation of First-Line ET	~5%
Second-Line	~33%
Third-Line	Up to 40%

1. Jeselsohn R et al. *Clin Cancer Res* 2014;20:1757-1767; **2.** Jeselsohn R et al. *Cancer Cell* 2018;33:173-186; **3.** Allouchery V et al. *Breast Cancer Res* 2018;20:40; **4.** Schiavon G et al. Sci Transl Med 2015;7(313):313ra182; **5.** Brett JO et al. *Breast Cancer Res* 2021;23(1):85.

ESR1 Mutations in Breast Cancer



Background: Alphabet soup of novel ER targeting agents

SERD
Serum estrogen receptors degrader

- Elacestrant
- Giredestrant
- Camizestrant
- Imlunestrant
- Amcenestrant
- Rintonestrant
- Borestrant
- ZN-C5

SERM
Serum estrogen receptors modulator

- Lasofoxifene
- Bazedozifene

PROTAC
Proteolysis targeted chimera agents

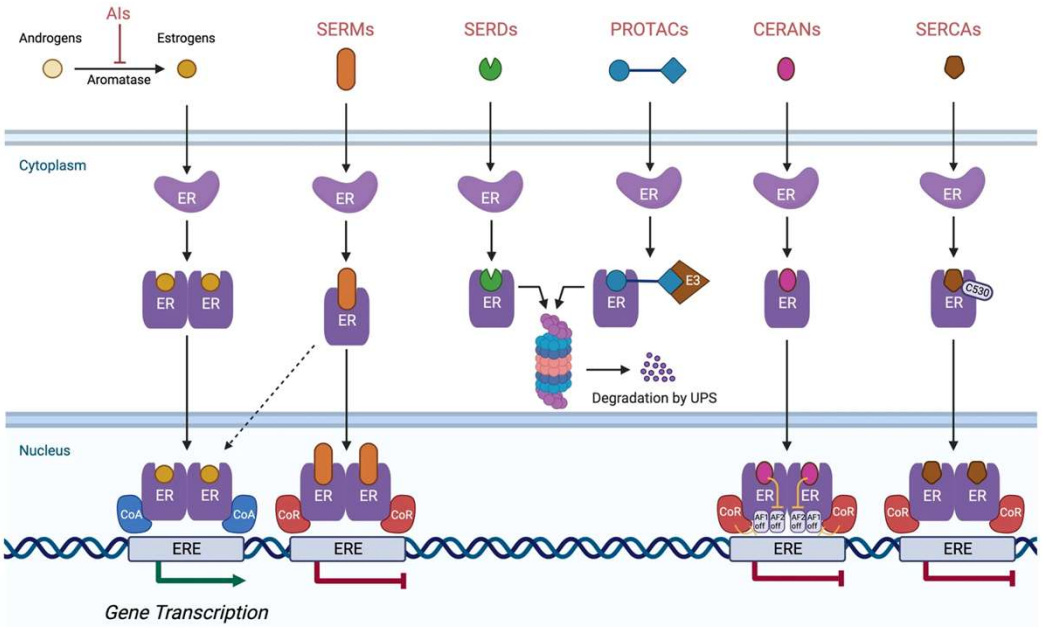
- Vepdegestrant (ARV-471)

CERAN
Complete estrogen receptor antagonist

- Palazestrant (OP-1250)

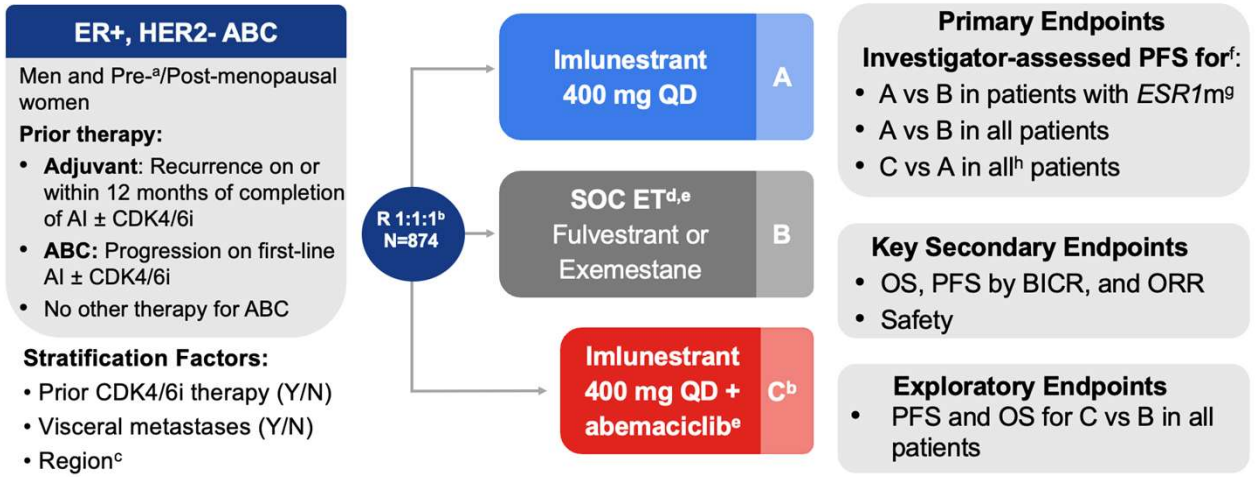
SERCA
Selective estrogen receptor covalent antagonist

- H3B-6545



Adapted from Patel et al. *NPJ Breast* 2023;9(1):20.

EMBER-3: Phase III trial of Imlunestrant +/- Abemaciclib vs. SOC ET



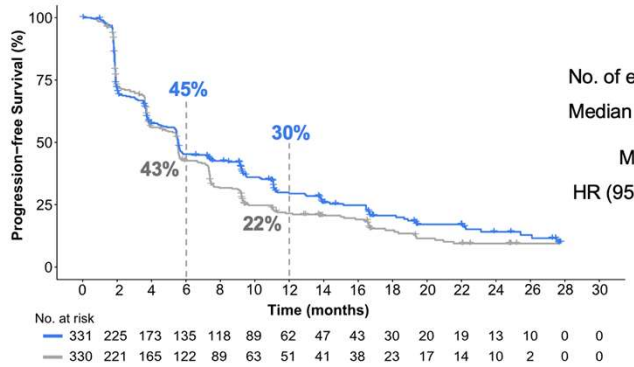
Key Demographics:

- Median age 62
- Prior Treatments
  - 1/3 adjuvant-only treatment; 2/3 1-line prior treatment for MBC
  - ~ 60% prior CDK4/6i treatment (nearly all palbociclib or ribociclib)
  - None with prior *PIK3CA*- or *AKT*-targeted treatments
- Tumors:
  - *ESR1* mutations: 32 to 42%
  - PI3K pathway mutation ~ 40%

Jhaveri et al. SABCS 2024. Abstract GS1-01.
Jhaveri et al. *N Engl J Med*. 2025;392(12):1189-1202.

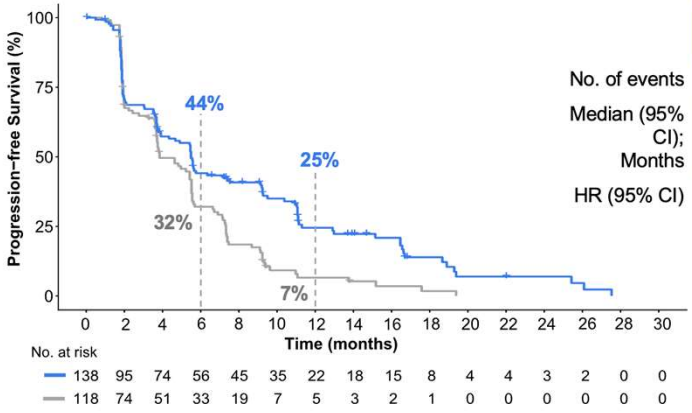
EMBER-3: Results mPFS Imlunestrant vs. SOC ET

***ESR1*wt**



	Imlunestrant n=331	SOC ET n=330
No. of events	237	253
Median (95% CI); Months	**5.6** (5.3-7.3)	**5.5** (4.6-5.6)
HR (95% CI)	**0.87 (0.72-1.04)** *p*-value 0.12	

***ESR1*mut**

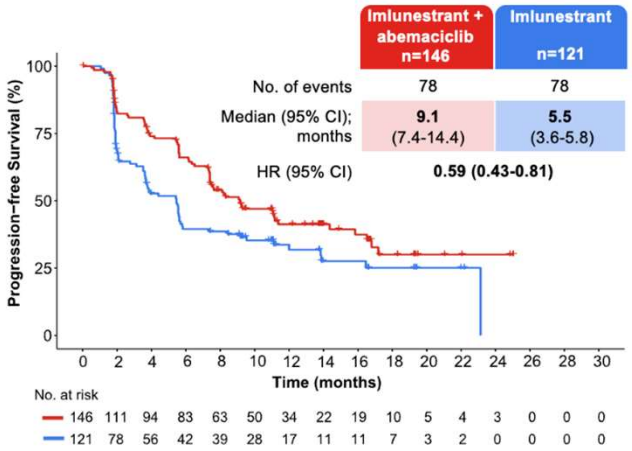


	Imlunestrant n=138	SOC ET n=118
No. of events	109	102
Median (95% CI); Months	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.46-0.82)**[a] *p*-value<0.001	

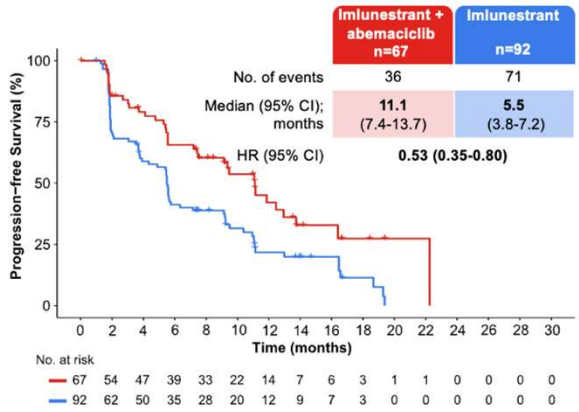
Jhaveri et al. SABCS 2024. Abstract GS1-01.
Jhaveri et al. *N Engl J Med*. 2025;392(12):1189-1202.

EMBER-3: Results mPFS Imlunestrant/abema vs. Imlunestrant

***ESR1*wt**



***ESR1*mut**



Results:

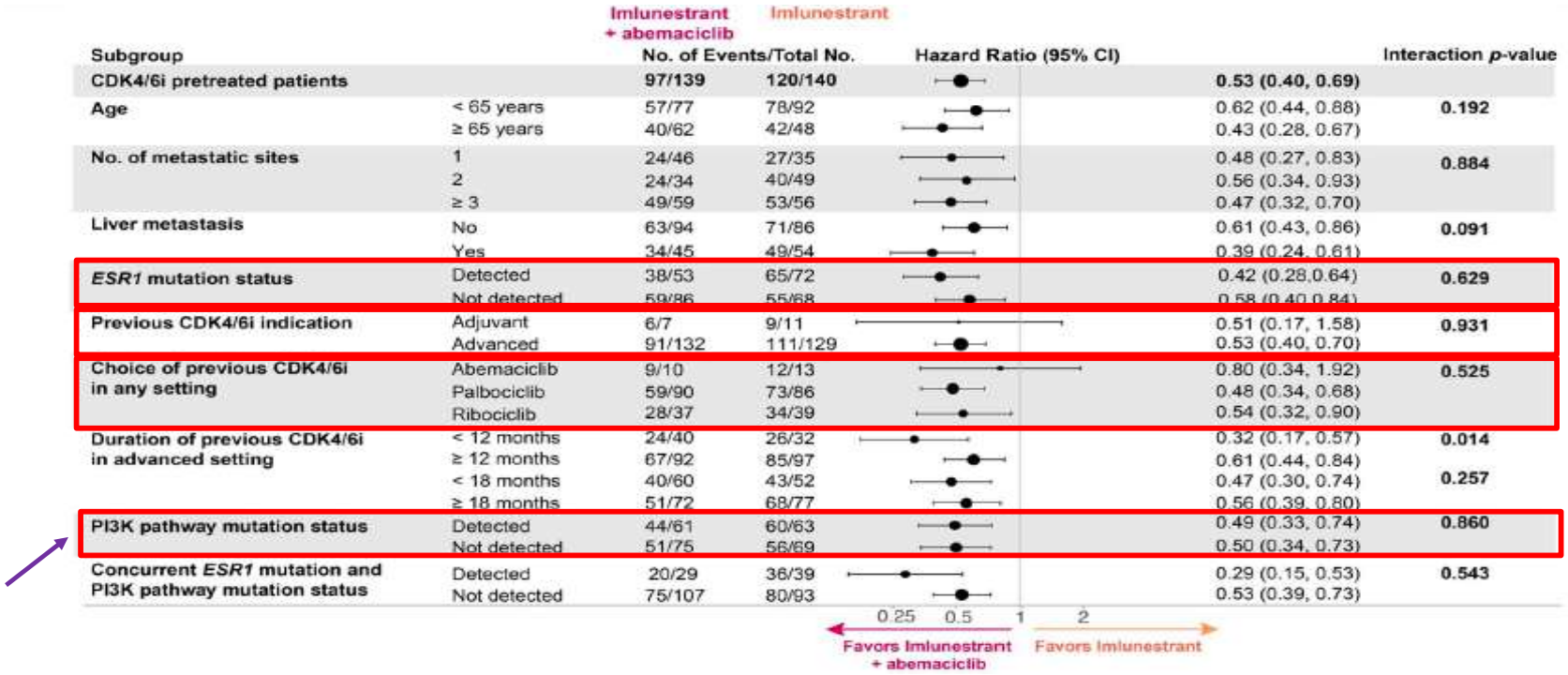
- Imlunestrant monotherapy > SOC ET in the m*ESR1* population only, similar to EMERALD and other oral SERD monotherapy trials

Clinical trial design considerations:

- Imlunestrant +/- abema vs. imlunestrant lacks a standard control arm (e.g., fulvestrant + capivasertib, fulvestrant + abemaciclib)
- Not all patients had prior CDK4/6 inhibitor **(only ~60%)** – would this change outcomes?

Jhaveri et al. SABCS 2024. Abstract GS1-01.
Jhaveri et al. *N Engl J Med*. 2025;392(12):1189-1202.

EMBER 3: PFS by subgroup in CDKi pre-treated population



Jhaveri et al SABCS 2025

Northwestern Medicine

EMBER-3: Safety and Tolerability

TEAEs in ≥ 10% of Patients, %	Imlunestrant n=327		SOC ET n=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	83	17	84	21
Fatigue[a]	23	<1	13	1
Diarrhea	21	<1	12	0
Nausea	17	<1	13	0
Arthralgia	14	1	14	<1
AST increased	13	1	13	1
Back pain	11	1	7	<1
ALT increased	10	<1	10	1
Anemia[a]	10	2	13	3
Constipation	10	0	6	<1

Patients with ≥ 1 SAE, %		10	12
Dose reductions due to AE, %		2	0
Discontinuations due to AE, %		4	1
Deaths due to AE on study, %		2	1
Injection Site Reaction[a]	TEAE, n/N (%)[b]	NA	27/292 (9%)
	PRO-CTCAE, n/N (%)[c]	NA	201/278 (72%)

TEAEs in ≥ 20% of Patients, %	Imlunestrant + abemaciclib n=208	
	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	98	49
Diarrhea	86	8
Nausea	49	2
Neutropenia[a]	48	20
Anemia[a]	44	8
Fatigue[a]	39	5
Vomiting	31	1
Leukopenia[a]	26	4
Hypercreatinemia[a]	22	1
Abdominal pain[a]	20	2
Decreased appetite	20	1

Patients with ≥ 1 SAE, %	17
Dose reductions due to AE, %[d]	39
Discontinuations due to AE, %	6
Deaths due to AE on study, %	1

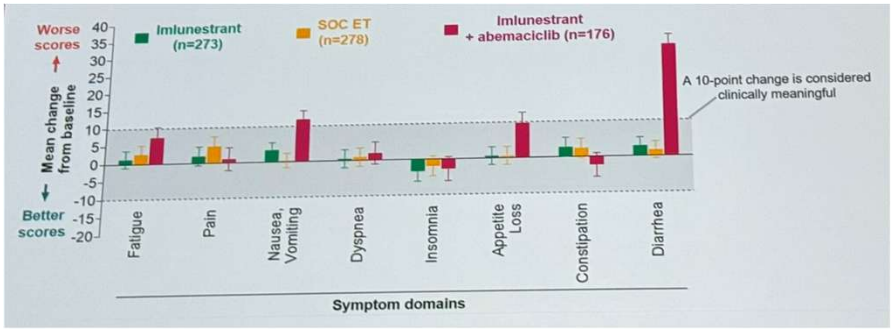
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; PRO-CTAE, Patient Reported Outcomes-Common Terminology Criteria for AEs; SAE, serious AEs; TEAE, treatment-emergent AE.
[a] Consolidated term; [b] N is the number of evaluable patients who received fulvestrant; [c] N is the number of evaluable patients who completed the PRO-CTCAE survey (answered "yes" or "no" to injection site pain, swelling, or redness).

Generally favorable safety profile. Safety consistent with the known abemaciclib profile.

Jhaveri et al. SABCS 2024. Abstract GS1-01.
Jhaveri et al. *N Engl J Med*. 2025;392(12):1189-1202.

EMBER-3: QOL and Safety Abstracts at ASCO 2025

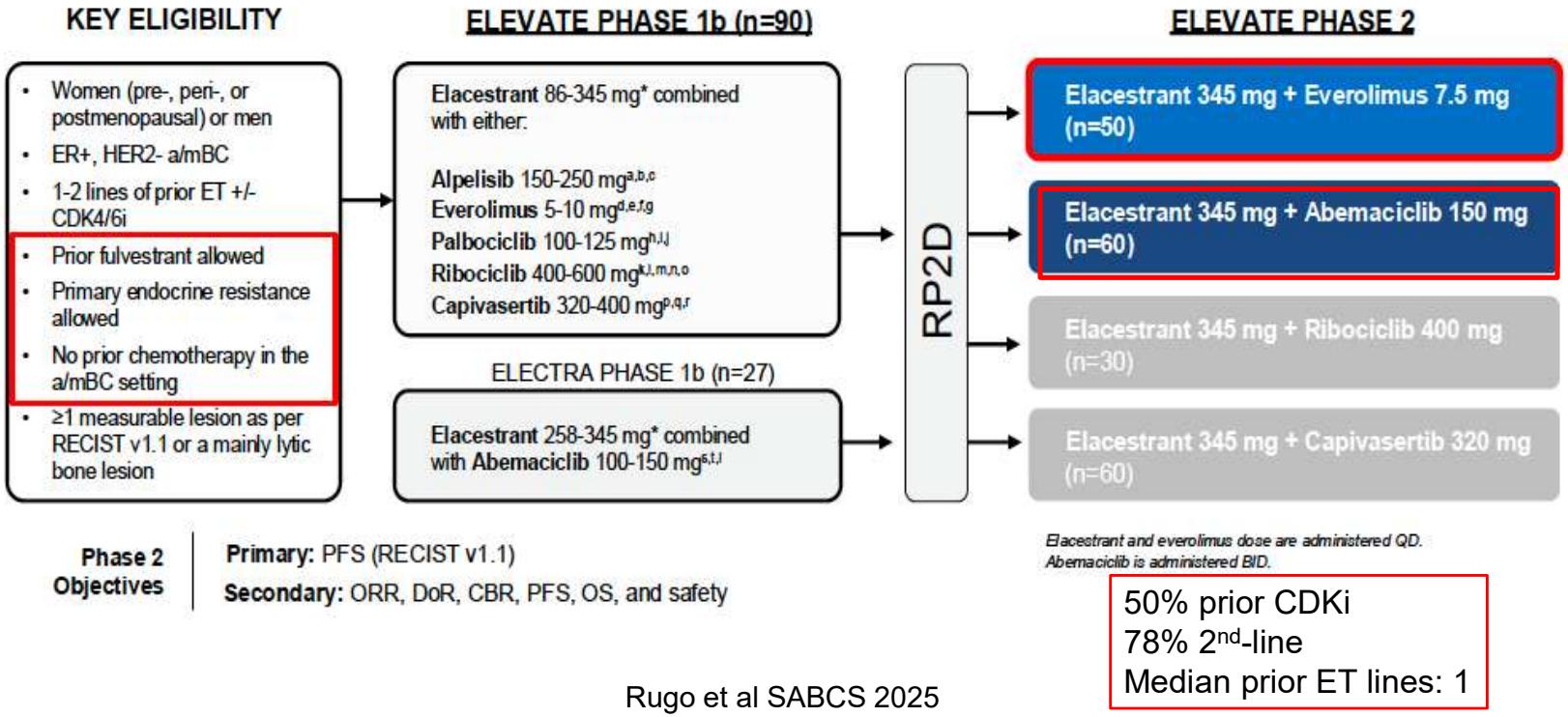
- **Abstract 1001:** Patient-reported outcomes (PROs) in patients with ER+, HER2- advanced breast cancer (ABC) treated with imlunestrant, investigator's choice standard endocrine therapy, or imlunestrant + abemaciclib: Results from the phase III EMBER-3 trial. Curigliano et al.



Symptom domains broadly similar across treatment arms except expected increase in diarrhea and N/V with imlunestrant + abemaciclib

- **Abstract 1060:** Imlunestrant with or without abemaciclib in advanced breast cancer (ABC): Safety analyses from the phase III EMBER-3 trial. O'Shaughnessy et al.

ELEVATE: Phase 2

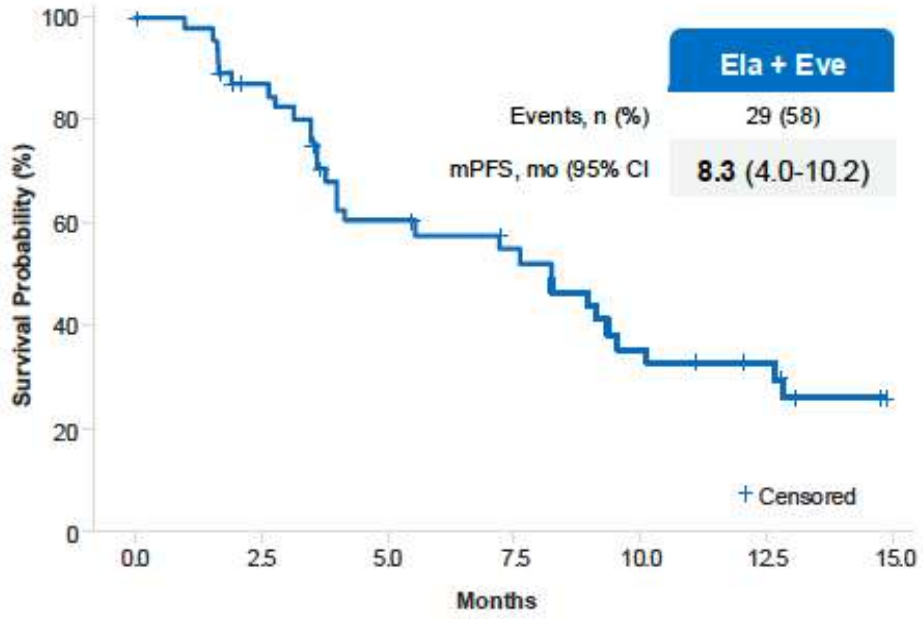


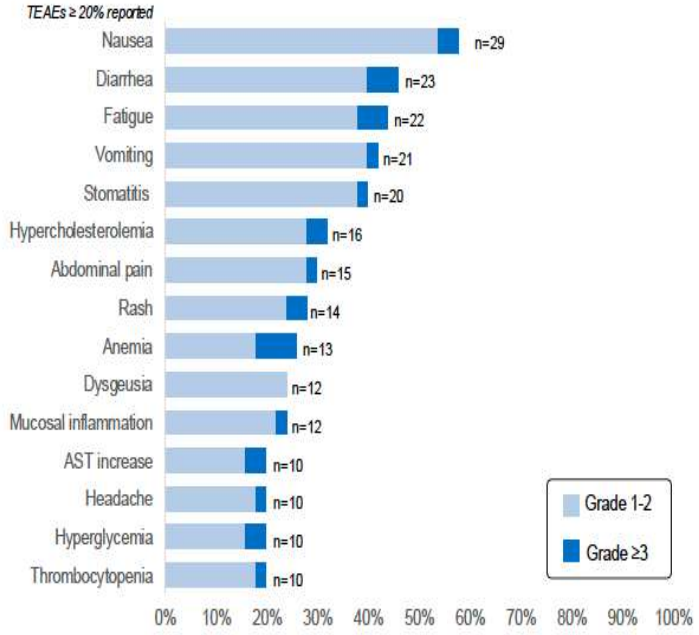
50% prior CDKi
78% 2nd-line
Median prior ET lines: 1

Rugo et al SABCS 2025

Northwestern Medicine

ELEVATE: Elacestrant + everolimus

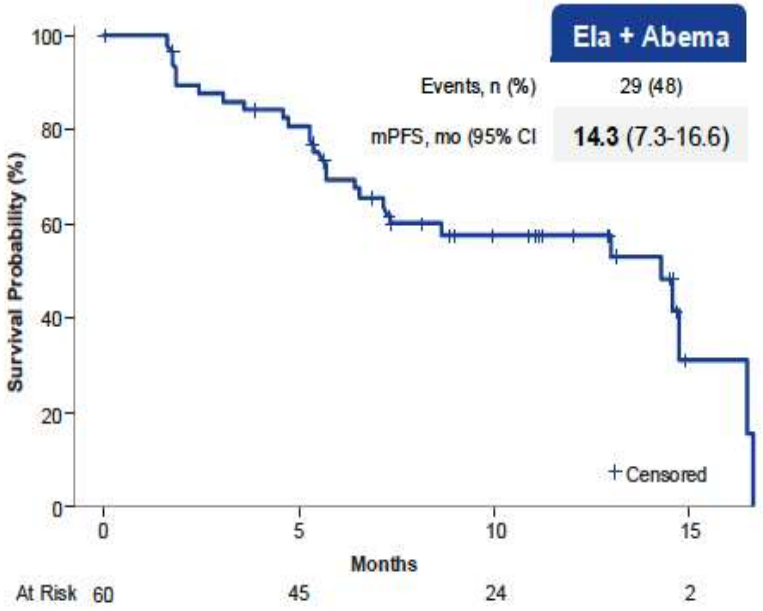


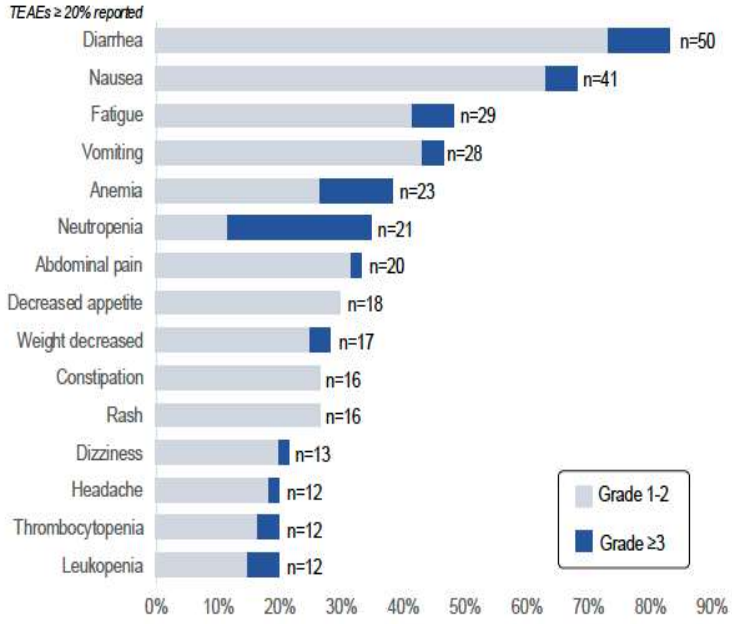


Rugo et al SABCS 2025

Northwestern Medicine

ELEVATE: Elacestrant + abemaciclib





Rugo et al 2025

Northwestern Medicine

MORPHEUS: Phase Ib/II umbrella study of various combinations

Many combination arms, including:

- Giredestrant + palbociclib
- Giredestrant + abemaciclib
- Giredestrant + ribociclib
- Giredestrant + everolimus
- Giredestrant + inavolosib
- Giredestrant + samuraciclib (CDK7i)

- No new safety signals in combination data presented to date
- Confirmatory efficacy analyses planned

Giredestrant + Abema (n=15) or Ribo (n=14)

	G	G + A	G + R
Tx-related adverse events (TRAEs) Grade 3–4	46% 0	80% 40%	100% 43%
AEs/TRAEs leading to tx discontinuation	0	0	7%
AEs leading to dose modification/interruption	18%	60%	64%
Fatal AEs	0	0	0
Most common TRAEs (≥ 20% of pts)	Fatigue	Diarrhea, nausea, abdominal pain, fatigue, neutropenia, vomiting, decreased appetite	Nausea, fatigue, neutropenia, asthenia, QT interval prolongation

NCT04802759

Giredestrant + Inavolisib (n = 15)

	GIR (n = 7)	GIR + INAVO (n = 15)
All-grade TRAEs	43%	100%
Grade 3 AEs (no Grade 4 or 5)	14%	33%
AE leading to tx discontinuation	0	7% (Grade 2 vomiting)
AEs leading to dose modification/interruption	14%	60%
Most common TRAEs (> 20% incidence rate)	Fatigue: 29%	Diarrhea: 60%; hyperglycemia: 53%; nausea: 47%; fatigue: 33%; decreased appetite: 33%; vomiting: 27%

Giredestrant + Everolimus (n = 15)

Pts with Adverse Events (AEs), n (%)	G + EVERO(n = 15)
Tx-related AEs (TRAEs)	14 (93.3)
Grade 3–4 AEs	3 (5.0)
Serious AEs	2 (13.3)
TRAE leading to tx discontinuation	1 (6.7)
TRAE leading to dose modification/interruption	6 (40.0)
Fatal AEs	0
Most common TRAEs (≥20% incidence rate)	Dysgeusia: 5 (33.3); nausea: 4 (26.7); asthenia: 3 (20.0); fatigue: 3 (20.0); mucosal inflammation: 3 (20.0); stomatitis: 3 (20.0); vomiting: 3 (20.0)

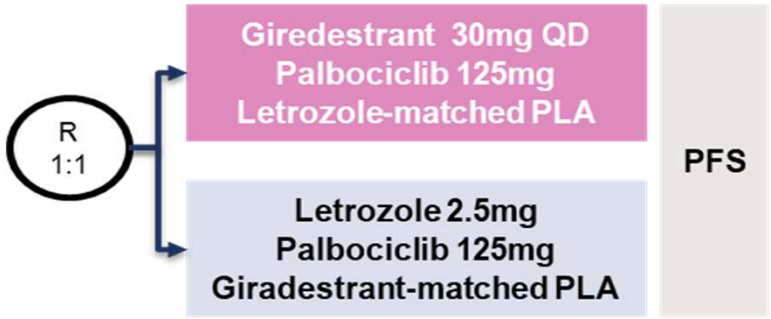
Oliveira et al. ASCO 2023. Abstract 1061; Rugo et al. SABCS 2023. Abstract PS12-08; Wanderer et al. ASCO 2024. Abstract 1059.

Oral SERDS in the 1L setting: Ongoing trials

persevERA NCT04546009

N=978

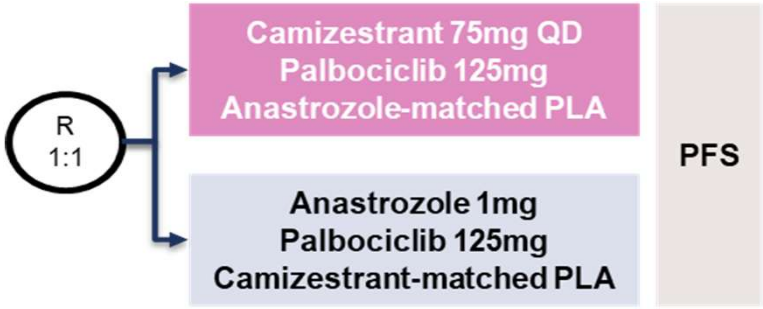
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC



SERENA-4 NCT04711252

N=1342

- ER+/HER2- LA/ABC
- No prior systemic tx for ABC



HR+ HER2- *metastatic* breast cancer

eVERA: Giredestrant + everolimus

Study design

A global, randomised, open-label, Phase III trial

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

Enrolment period: August 2022 to October 2024

N = 373* → R 1:1

- Giredestrant (30 mg) + everolimus (10 mg)†
- SOC ET‡ + everolimus (10 mg)†
  ‡Exemestane/fulvestrant/tamoxifen

Until PD or unacceptable toxicity

† Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol[1]

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

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

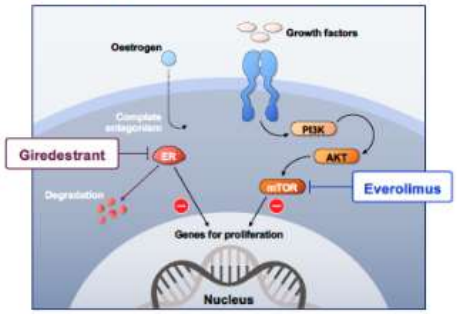
Coprimary endpoints (RECIST v1.1)
- INV-PFS in patients whose tumours had *ESR1*m
- INV-PFS in the ITT population

Key secondary endpoints
- OS
- INV-assessed ORR, DoR

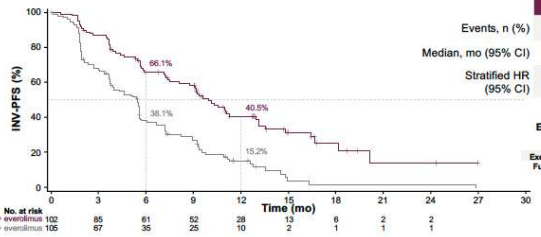
ClinicalTrials.gov number, NCT05306340. Adapted from Mayer EL, *et al.* SABCS 2022 (poster OT2-01-07) with permission.

1–3L, first to third line; aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER+, oestrogen receptor-positive; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; HER2–, HER2-negative; INV, investigator-assessed; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SOC ET, standard of care endocrine therapy.

Giredestrant + everolimus mechanism of action

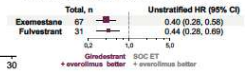


Co-primary endpoint – INV-PFS in the *ESR1*m population



	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 < 0.0001	

Exploratory analysis: INV-PFS by SOC ET



Combination therapy with giredestrant + everolimus led to a clinically meaningful 62% reduction in the risk of progression or death in patients with *ESR1*m

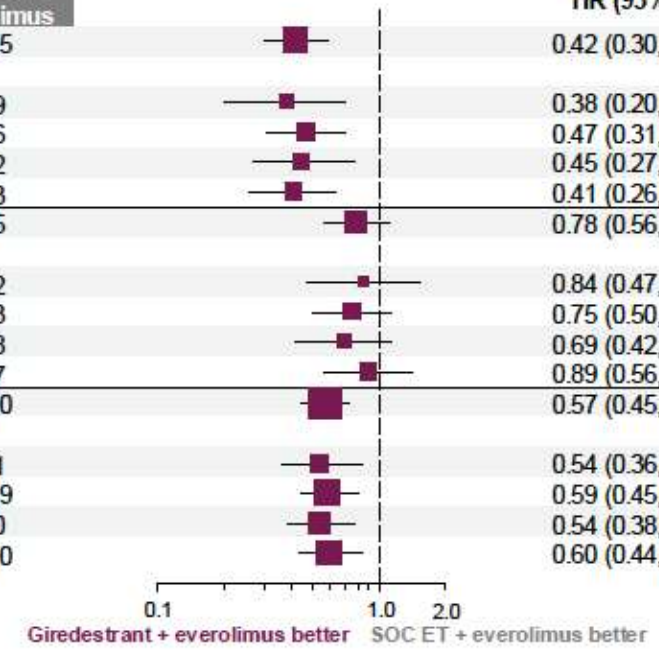
Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 11.14 mo (giredestrant + everolimus) and 5.68 mo (SOC ET + everolimus); stratified HR, 0.49; 95% CI: 0.34, 0.71.

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; INV, investigator-assessed; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

Mayer et al, ESMO 2025

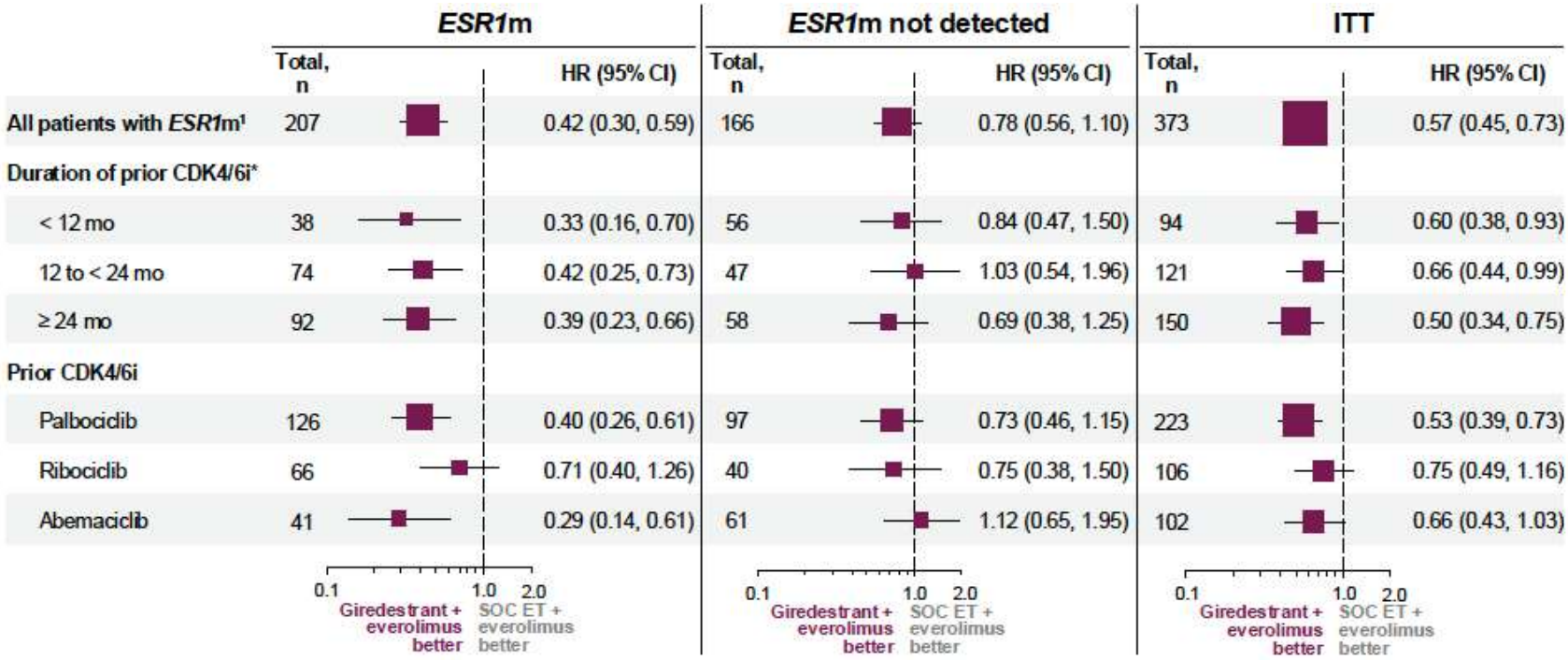
evERA: PFS based on PIK3CA/AKT1/PTEN tumor status

	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)



Rugo et al SABCS 2025

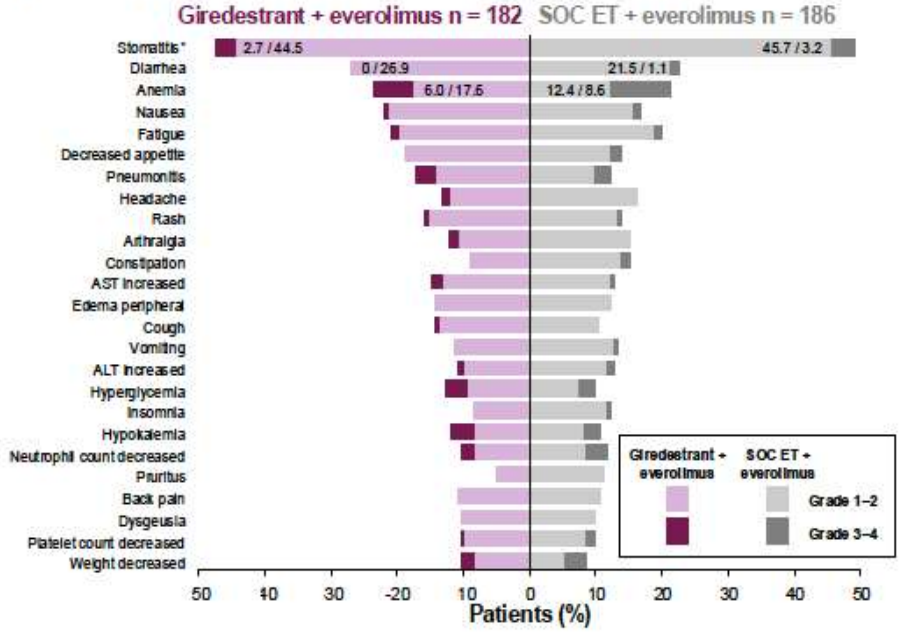
evERA: PFS based on prior CDKi type and duration



Rugo et al SABCS 2025

evERA: Adverse events

Common TEAEs (≥ 10% of patients in either arm)



Safety overview

Patients with AE, n (%)	Giredestrant + everolimus n = 182	SOC ET + everolimus n = 186
AEs with fatal outcome†	5 (2.7)	5 (2.7)
AEs leading to everolimus dose reduction‡	56 (30.8)	49 (26.3)
AEs leading to discontinuation from treatment§		
Giredestrant or SOC ET	15 (8.2)	12 (6.5)
Everolimus	31 (17.0)	22 (11.8)
Any	31 (17.0)	22 (11.8)

Selected AEs

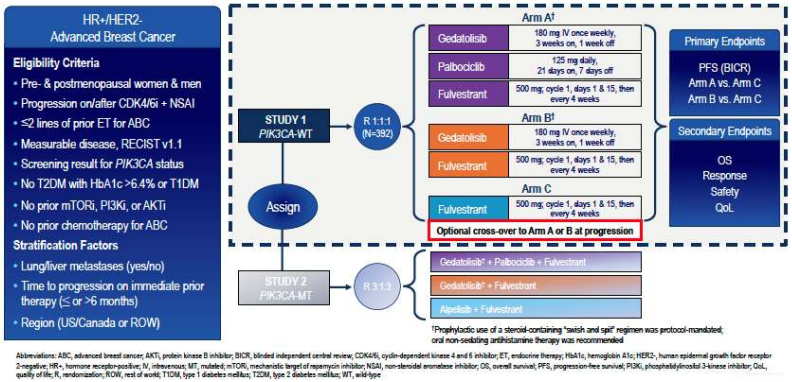
Patients with AE, n (%)	Giredestrant + everolimus n = 182		SOC ET + everolimus n = 186	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Bradycardia¶	7 (3.8)	0	1 (0.5)	0
Photopsia	0	0	0	0

Rugo et al SABCS 2025

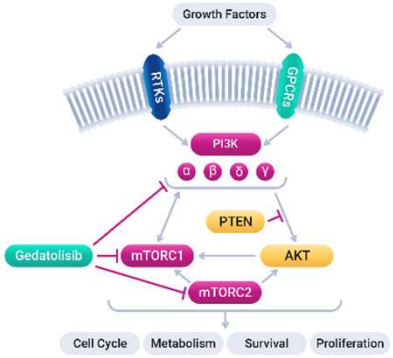
HR+ HER2- *metastatic* breast cancer

VIKTORIA-1: Gedatolisib

VIKTORIA-1 Study Design



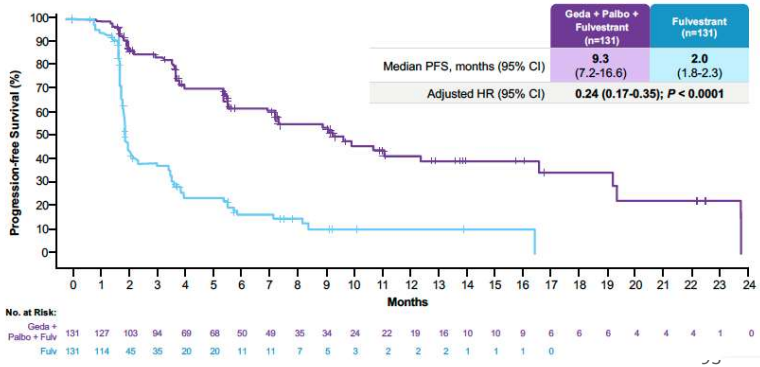
Abbreviations: ABC, advanced breast cancer; AKTi, protein kinase B inhibitor; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; ET, endocrine therapy; HbA1c, hemoglobin A1c; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; IV, intravenous; MT, mutated; mTORi, mechanistic target of rapamycin inhibitor; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PFS, progression-free survival; PI3Ki, phosphatidylinositol 3-kinase inhibitor; QoL, quality of life; R, randomization; ROW, rest of world; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; WT, wild-type



Gedatolisib, a highly potent **multitarget PAM inhibitor** of all class I PI3K isoforms, mTORC1, and mTORC2, has shown compelling preliminary clinical activity in combination with palbociclib & fulvestrant as 2L+ therapy in HR+/HER2- ABC

1st Co-Primary Endpoint: Progression-Free Survival

Gedatolisib Triplet vs. Fulvestrant, BICR Assessment



	Geda + Palbo + Fulvestrant (n=131)	Fulvestrant (n=131)
Median PFS, months (95% CI)	9.3 (7.2-16.6)	2.0 (1.8-2.3)
Adjusted HR (95% CI)	0.24 (0.17-0.35); *P* < 0.0001	

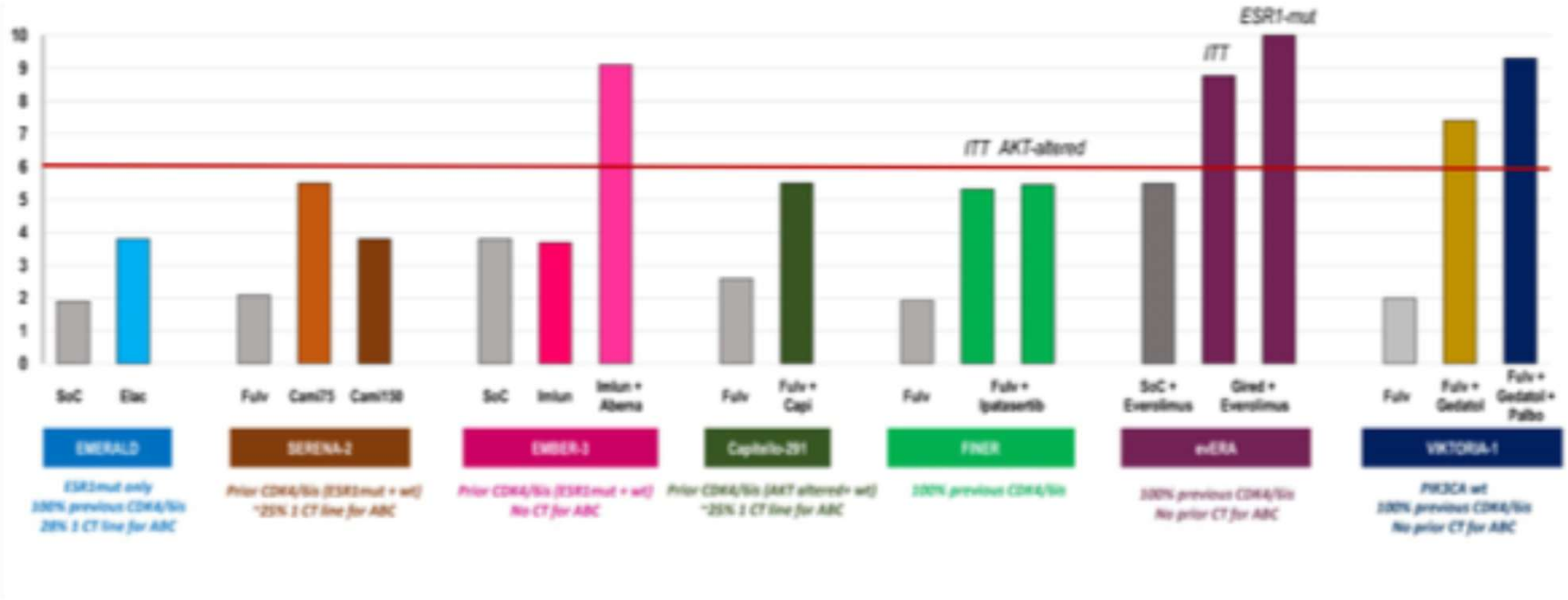
Hurvitz et al, ESMO 2025

Conclusions

- **VIKTORIA-1 is the first study to demonstrate a statistically significant and clinically meaningful improvement in PFS with PAM inhibition in patients with *PIK3CA*-WT disease, all of whom received prior CDK4/6i**
  - Gedatolisib triplet, mPFS 9.3 months (HR, 0.24; 95% CI, 0.17-0.35; $P < 0.0001$)
  - Gedatolisib doublet, mPFS 7.4 months (HR, 0.33; 95% CI, 0.24-0.48; $P < 0.0001$)
- **Efficacy of gedatolisib-based therapy was comparable regardless of which prior CDK4/6i was used**
- Adverse events associated with gedatolisib in VIKTORIA-1 were mainly Grade 1 or 2 in severity
  - **Hyperglycemia was low** (9.2% for triplet, 11.5% for doublet), **as was diarrhea** (16.9% and 12.3%, respectively), which is unexpected for a drug targeting the PAM pathway
  - Study treatment discontinuation due to TRAEs was reported in 2.3% (triplet) and 3.1% (doublet) of patients
- **These results validate the PAM pathway as a molecular driver in *PIK3CA*-WT disease**

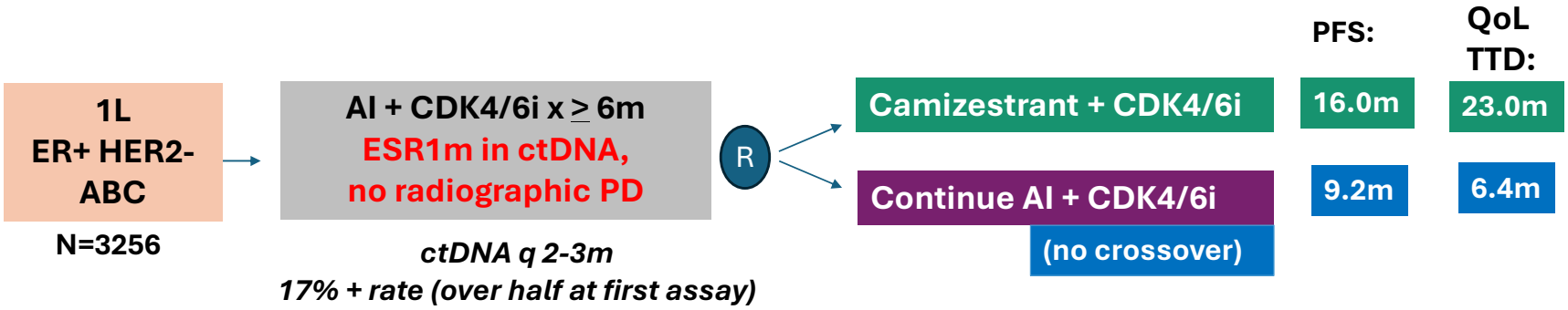
Gedatolisib plus fulvestrant, with or without palbociclib, represents a potential new standard of care for patients with HR+, HER2-negative, *PIK3CA*-WT ABC whose disease progressed on or after treatment with a CDK4/6 inhibitor

HR+/HER2- mBC: Novel ET and Oral SERD 2L+ Trials



A. Gennari ESMO 2025

Prospectively Intervening in ESR1m: SERENA-6



However, most patients on the control arm did not later receive camizestrant or any other SERD

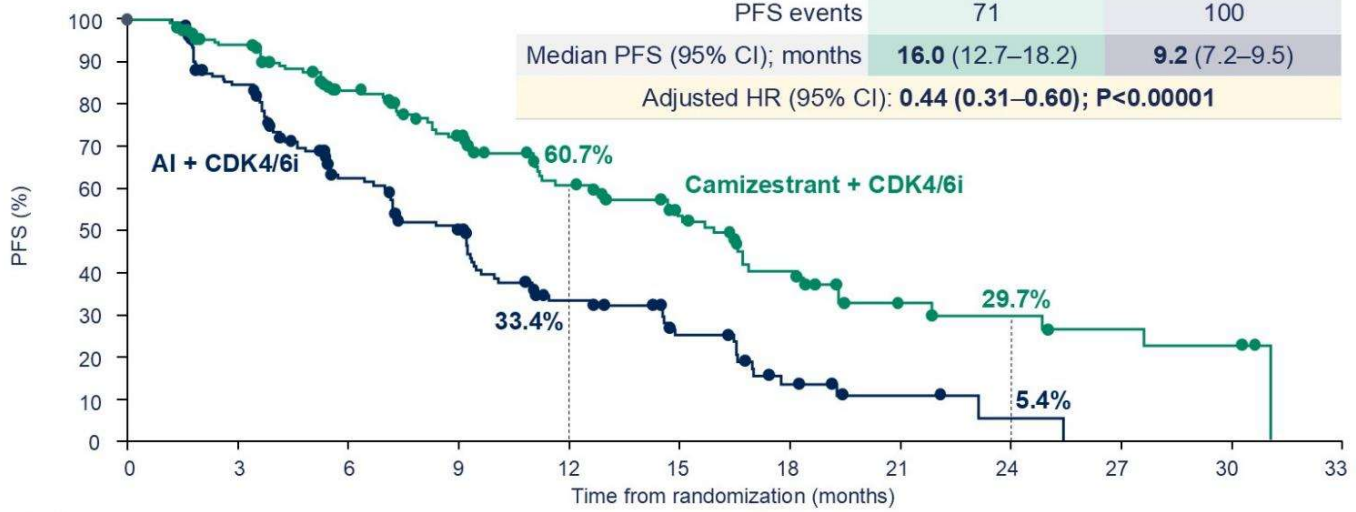
SERDs are better in ESR1m tumors
(but is early change better than change at PD?)

Bidard FC et al, NEJM 2025

Primary endpoint: Investigator-assessed PFS

SERENA-6

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS events	71	100
Median PFS (95% CI); months	**16.0** (12.7–18.2)	**9.2** (7.2–9.5)
Adjusted HR (95% CI): **0.44 (0.31–0.60); P<0.00001**		



Number of patients at risk

Camizestrant + CDK4/6i	157	138	105	82	55	41	26	11	9	7	6	0
AI + CDK4/6i	158	124	73	55	29	17	7	3	1	0	0	0

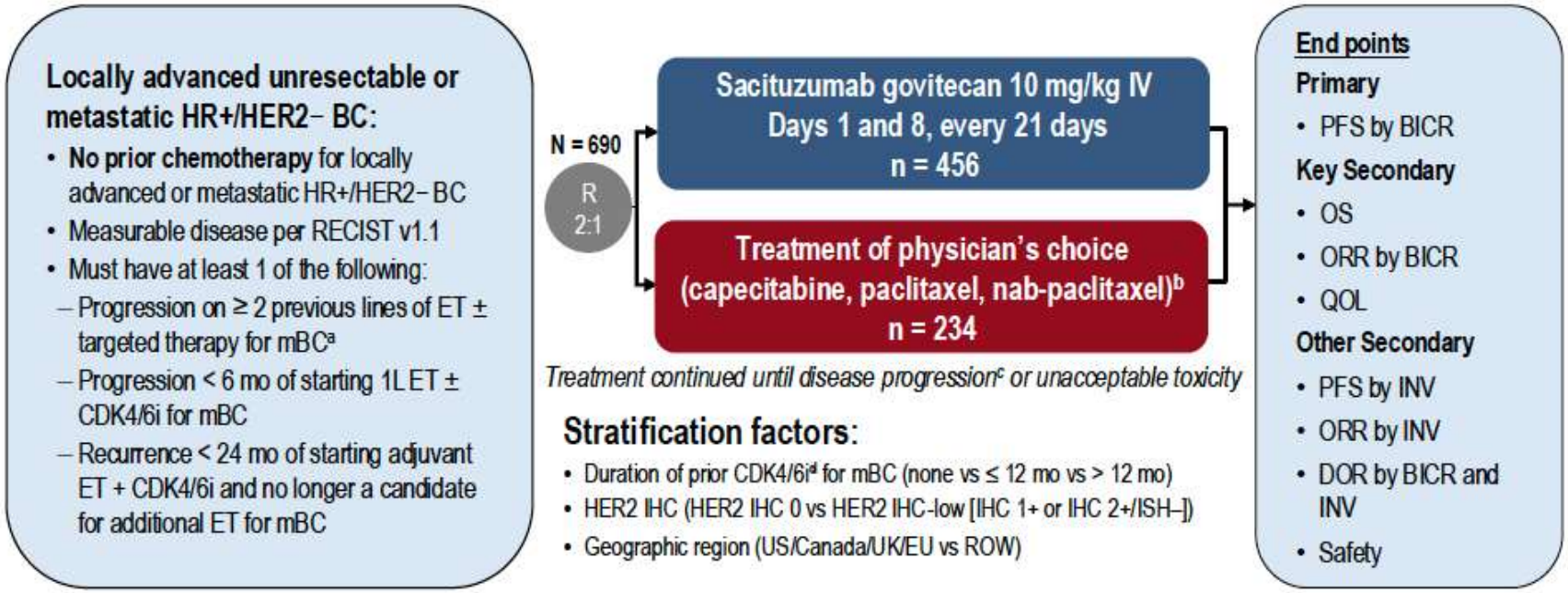
P-value crossed the threshold for significance (P=0.0001). PFS was defined per RECIST v1.1. HR was estimated using the Cox proportional hazard model adjusted for stratification factors.
CI, confidence interval; HR, hazard ratio.

2025 ASCO ANNUAL MEETING #ASCO25

PRESENTED BY: Nicholas Turner, MD, PhD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

ASCENT-07: Schema



Jhaveri et al SABCS 2025

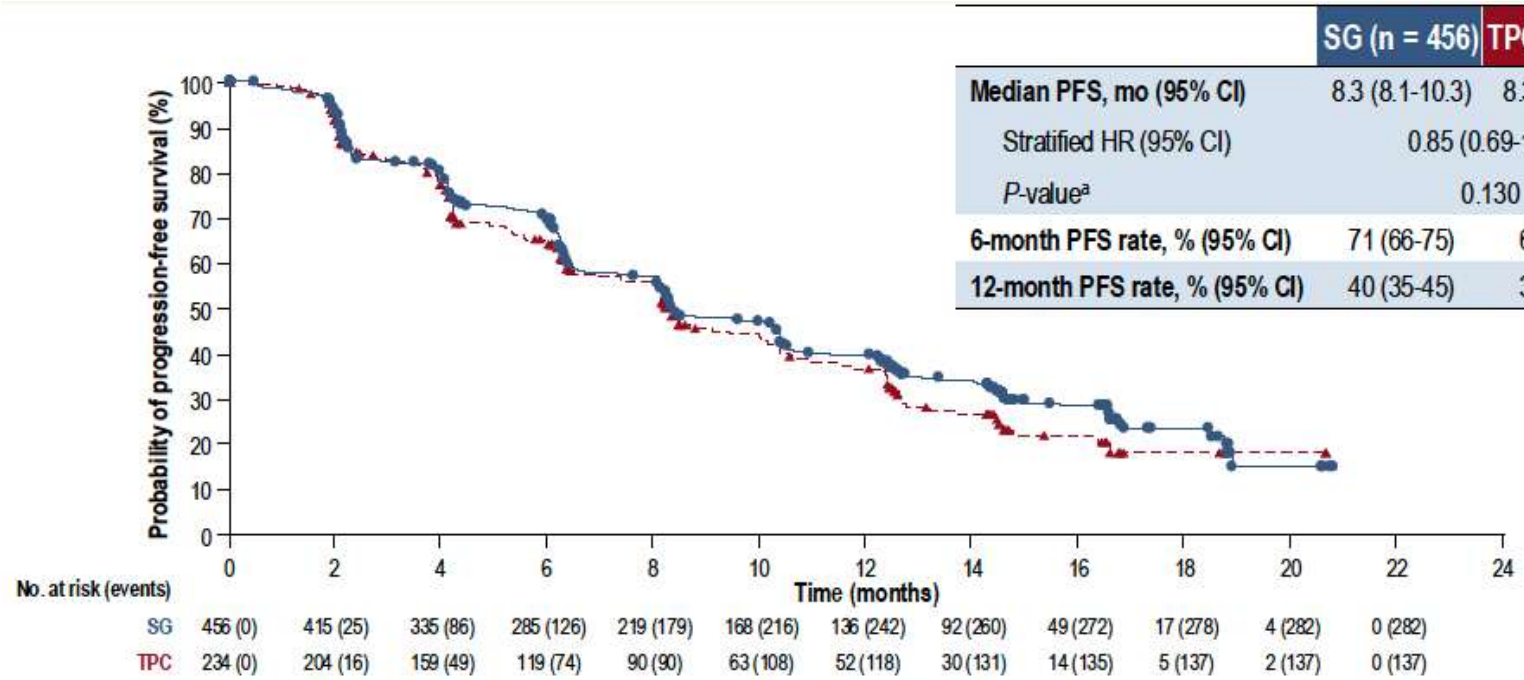
ASCENT-07: Prior therapies

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

ITT Population	SG (n = 456)	TPC (n = 234)
Adjuvant/neoadjuvant setting[a,d], n (%)		
ET[e]	295 (65)	158 (68)
ET with CDK4/6i	17 (4)	8 (3)
Chemotherapy	260 (57)	140 (60)
Taxane	211 (46)	115 (49)
Anthracycline	217 (48)	118 (50)
Prior CDK4/6i use in metastatic setting, n (%)		
None	32 (7)	19 (8)
≤ 12 months	197 (43)	98 (42)
> 12 months	227 (50)	117 (50)

Jhaveri et al SABCS 2025

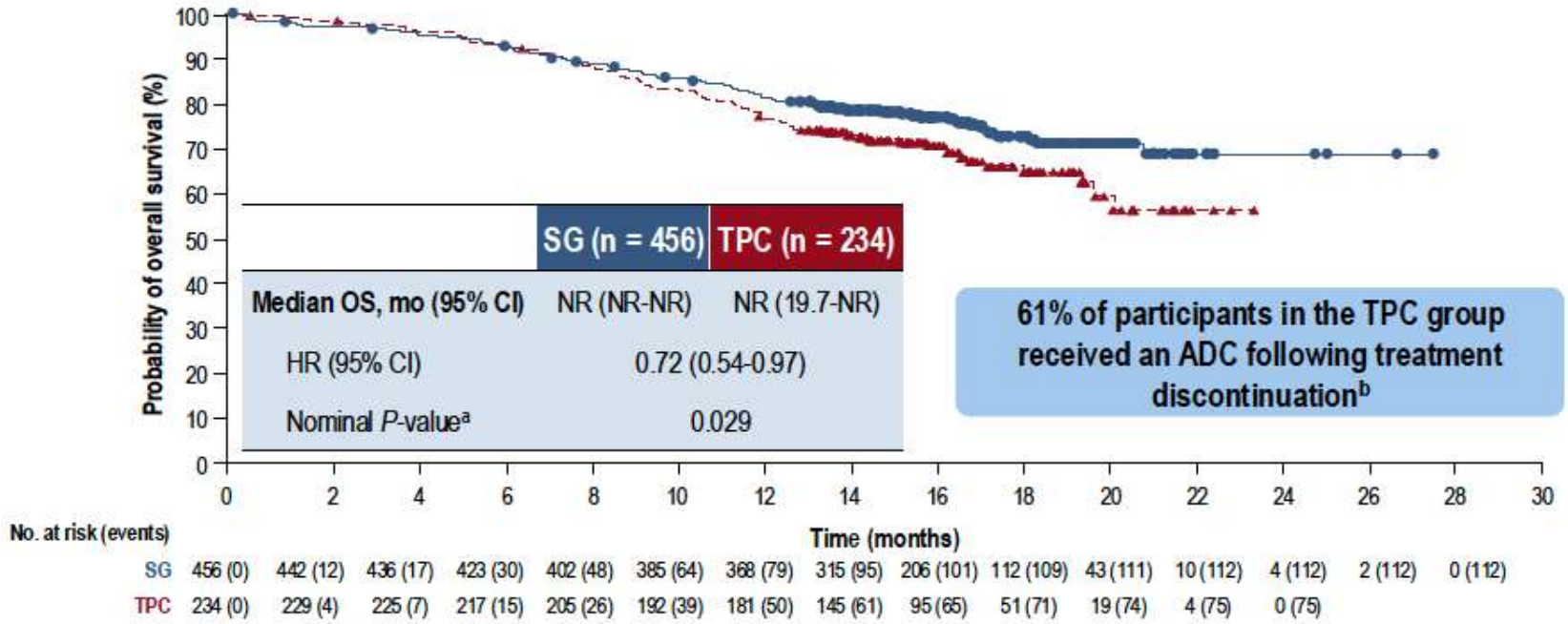
ASCENT-07: PFS by BICR



	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)	0.85 (0.69-1.05)	
P-value[a]	0.130	
6-month PFS rate, % (95% CI)	71 (66-75)	64 (57-71)
12-month PFS rate, % (95% CI)	40 (35-45)	37 (29-44)

Jhaveri et al SABCS 2025

ASCENT-07: Interim OS



Jhaveri et al SABCS 2025

ASCENT-07: Response and clinical benefit rate

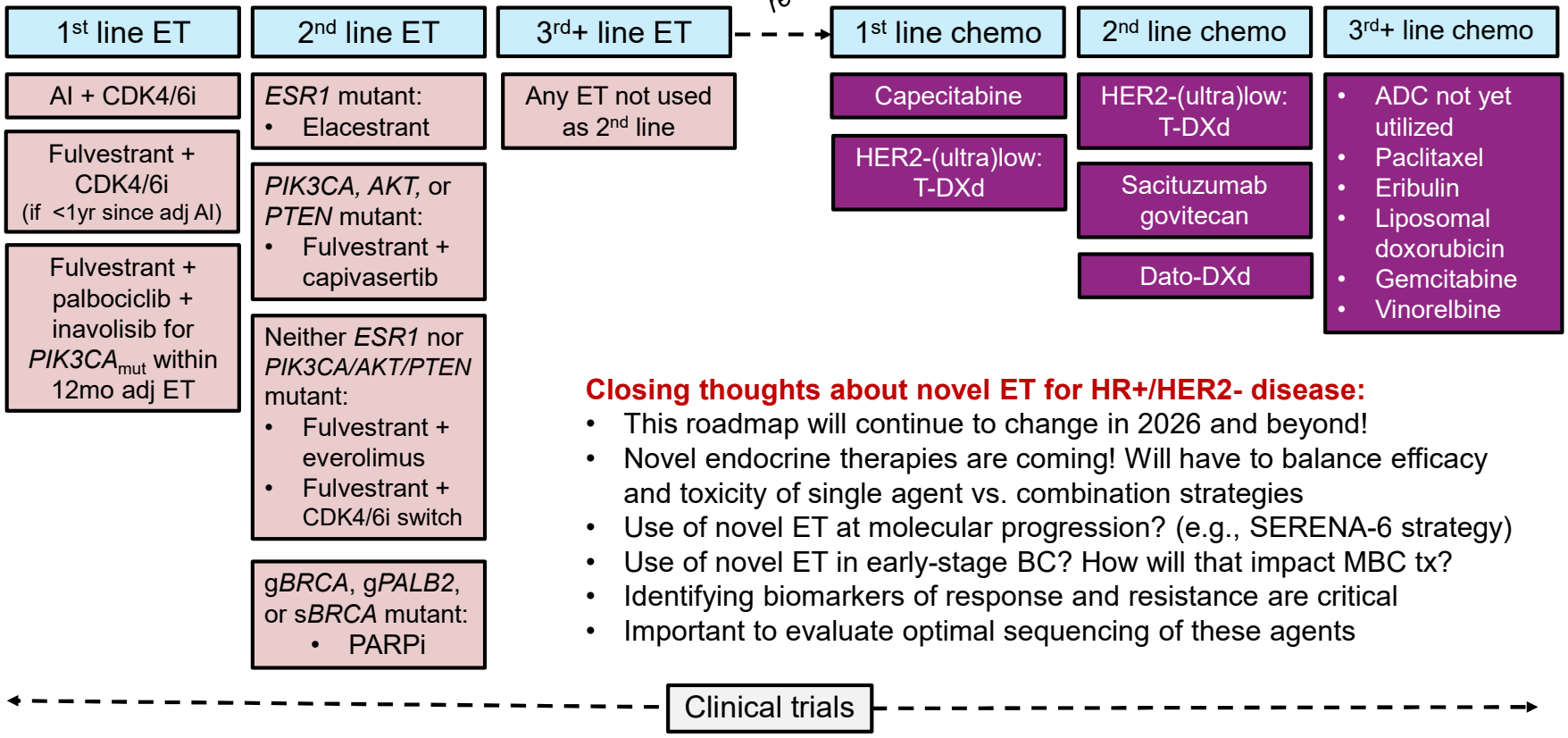
Variable	SG (n = 456)	TPC (n = 234)
Objective response rate[a], % (95% CI)	37 (32-42)	33 (27-39)
Stratified odds ratio (95% CI)	1.20 (0.86-1.69)	
Best overall response, n (%)		
Complete response	4 (1)	0 (0)
Partial response	164 (36)	77 (33)
Stable disease	202 (44)	112 (48)
Stable disease ≥ 6 months	126 (28)	48 (21)
Progressive disease	64 (14)	33 (14)
Not evaluable[b]	22 (5)	12 (5)

Variable	SG (n = 456)	TPC (n = 234)
Clinical benefit rate[c], % (95% CI)	65 (60-69)	53 (47-60)
Responders, n	**SG (n = 168)**	**TPC (n = 77)**
Median (range) time to response[d], mo	2.3 (1.2-14.6)	2.3 (1.4-12.5)
Median duration of response, mo (95% CI)	12.1 (8.5-13.8)	9.3 (6.5-14.3)

Jhaveri et al SABCS 2025

Bottom line: Sacituzumab not superior to chemotherapy in chemotherapy-naïve HR+ MBC

Roadmap: HR+/HER2- MBC



Closing thoughts about novel ET for HR+/HER2- disease:

- This roadmap will continue to change in 2026 and beyond!
- Novel endocrine therapies are coming! Will have to balance efficacy and toxicity of single agent vs. combination strategies
- Use of novel ET at molecular progression? (e.g., SERENA-6 strategy)
- Use of novel ET in early-stage BC? How will that impact MBC tx?
- Identifying biomarkers of response and resistance are critical
- Important to evaluate optimal sequencing of these agents

Advances in the management of metastatic triple-negative breast cancer

Melinda Telli, M.D.

Professor of Medicine
Stanford University School of Medicine
Director, Breast Cancer Program
Associate Director for Clinical Research
Stanford Cancer Institute

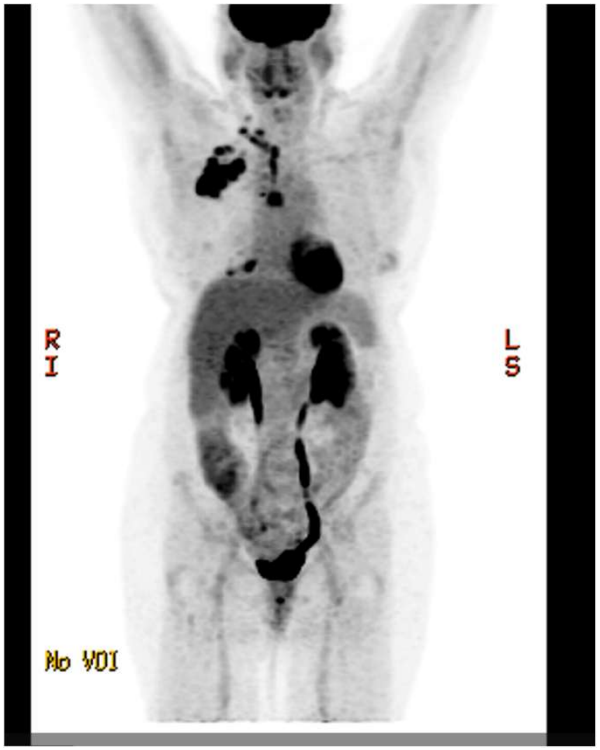
February 6, 2026

Patient Case:

- A 47-year-old premenopausal woman is diagnosed with a T1miN0M0 Stage I IDC of the right breast associated with a 4 cm area of DCIS
  - ER 0%
  - PR 0%
  - HER2-negative (0 by IHC; FISH negative)
- She is treated with lumpectomy surgery and completes whole breast irradiation.
- No systemic chemotherapy is recommended.
- She tests negative for pathogenic variants in *BRCA1* & *BRCA2*

Patient Case:

- 2 years later, she is found to have suspicious right axillary adenopathy on routine breast imaging.
- Core biopsy of the right axillary node reveals recurrent IDC ER 0%, PR 0%, and HER2 0 (FISH negative)
- She undergoes PET/CT imaging for systemic staging which reveals:
  - Hypermetabolic right lower cervical, supraclavicular, internal mammary, cardiophrenic, axillary, subpectoral and mediastinal lymphadenopathy concerning for nodal metastatic disease.
- Biopsy of a mediastinal node reveals recurrent TNBC
  - PD-L1 CPS = 1
  - NGS reveals a somatic *BRCA2* pathogenic variant

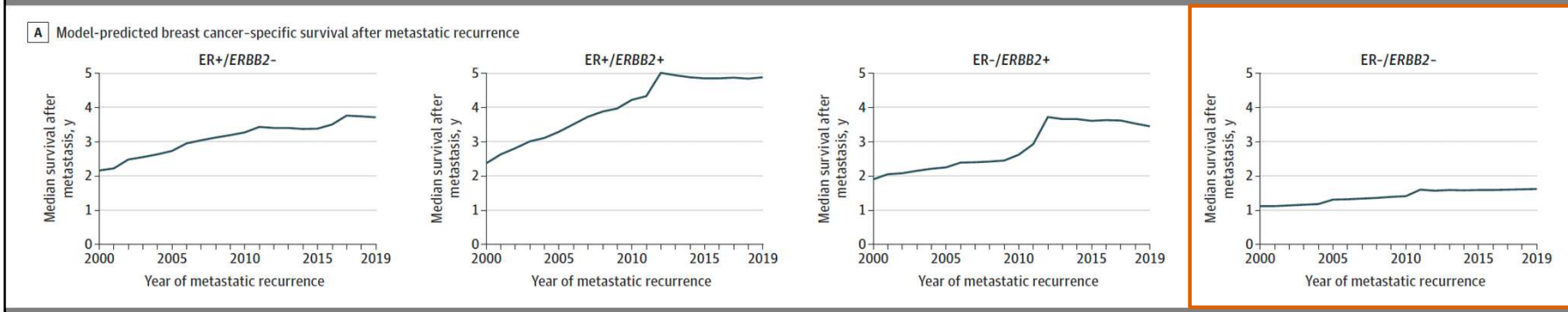


Case 1: Polling Question

As first-line therapy, what do you recommend?

A. Gemcitabine and carboplatin
B. Weekly paclitaxel
C. Sacituzumab govitecan
D. Olaparib
E. Datopotamab deruxtecan

Breast cancer-specific survival after metastatic relapse 2000 - 2019



Caswell-Jin J, et al. JAMA 2024; 331(3):233-241.

FDA approvals in the last decade

Advances in metastatic TNBC

2018: Olaparib & talazoparib improve progression-free survival in gBRCA1/2 mutation-associated breast cancer

2020: Pembrolizumab improves progression-free & overall survival in PD-L1+ advanced TNBC

2020: Sacituzumab govitecan improves progression-free & overall survival in pre-treated advanced TNBC

2022: Trastuzumab deruxtecan improves progression-free & overall survival in pre-treated advanced HER2 low breast cancer, including TNBC

NCCN Guidelines Version 1.2026

New recommended therapies

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
First line	PD-L1 ≥ 10 regardless of germline *BRCA1/2* PV status	• Chemotherapy (albumin-bound paclitaxel, carboplatin/gemcitabine, or paclitaxel) + Pembrolizumab (category 1, preferred) • **Sacituzumab govitecan-hziy + Pembrolizumab (preferred)**
	PD-L1 < 10 and no germline *BRCA1/2* PV	• **Sacituzumab govitecan-hziy (category 1, preferred)** • **Datopotamab deruxtecan-dlnk (other recommended)** • Systemic chemotherapy
	PD-L1 CPS < 10 and germline *BRCA1/2* PV	• PARPi (Olaparib or Talazoparib) (category 1, preferred) • Platinum (Carboplatin or Cisplatin) (category 1, preferred)
Second line	Germline *BRCA1/2* PV	PARPi (category 1, preferred)
	Any	Sacituzumab govitecan-hziy (category 1, preferred)
		Systemic chemotherapy or targeted agents
	No germline *BRCA1/2* PV and HER2 (ERBB2) IHC 1+ or 2+/ISH-negative	Fam-trastuzumab deruxtecan-nxki (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
	Any	Systemic chemotherapy

NCCN Breast Cancer Guideline Version 1.2026, BINV Q (3) available at nccn.org

PARP inhibitors in gBRCA1/2 mutant advanced breast cancer

Pivotal trials

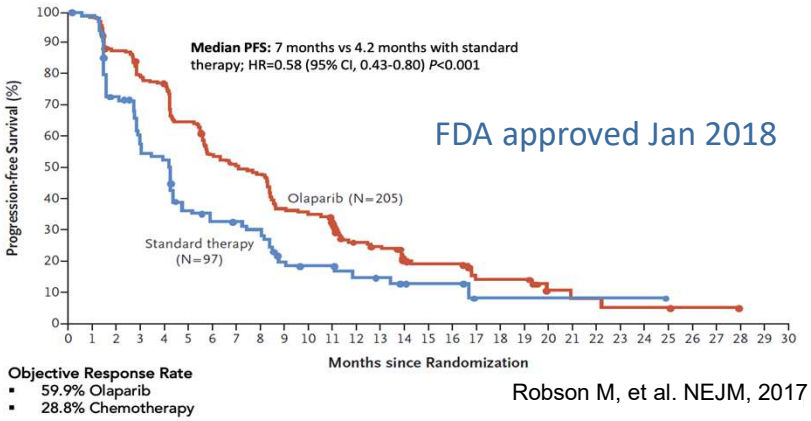
OlympiAD

gBRCA1/2, HER2-negative, Metastatic Breast Cancer
≤2 previous chemotherapy regimens
HR+ disease had to progress on at least 1 prior endocrine therapy

RANDOMIZED 2:1
n=302

Olaparib 300 mg BID n=205	MD Choice Chemotherapy* n=99

*Capecitabine, eribulin, or vinorelbine



FDA approved Jan 2018

Robson M, et al. NEJM, 2017

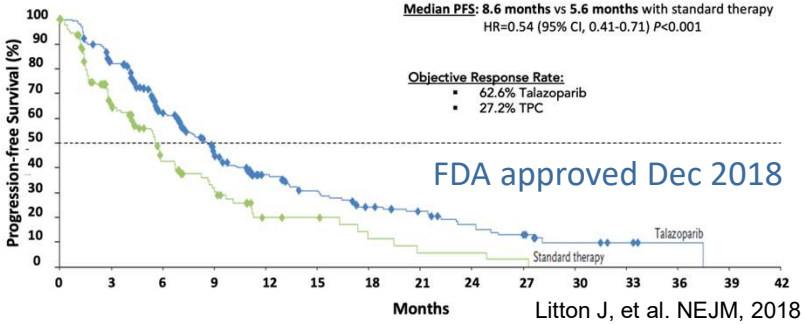
EMBRACA

gBRCA1/2, HER2-negative, Locally Advanced or Metastatic breast cancer
≤3 previous chemotherapy regimens
No limit on number of prior endocrine therapies

RANDOMIZED 2:1
N=431

Talazoparib 1 mg daily n=287	MD Choice Chemotherapy** n=144

**Capecitabine, eribulin, vinorelbine, or gemcitabine

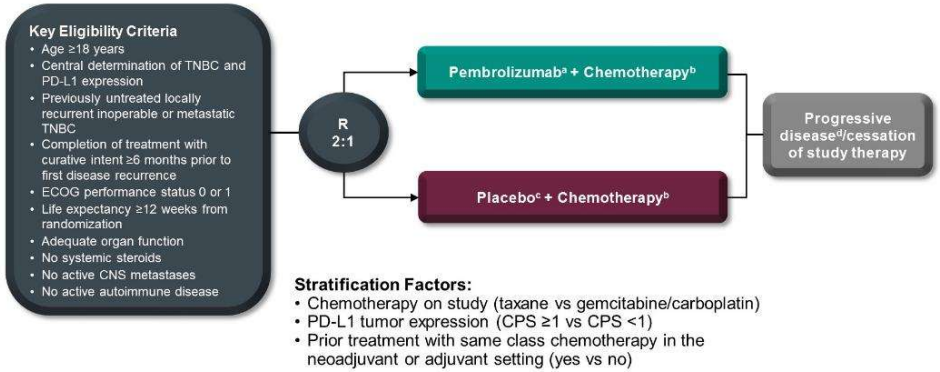


FDA approved Dec 2018

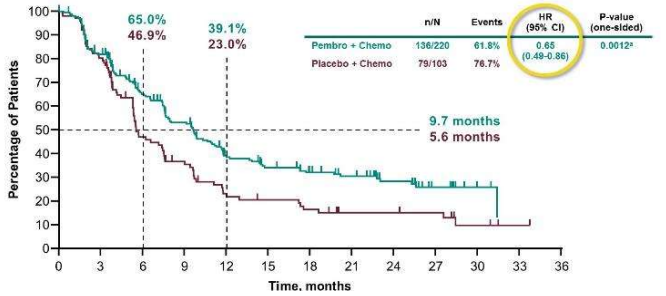
Litton J, et al. NEJM, 2018

Pembrolizumab added to 1st line chemotherapy in advanced TNBC

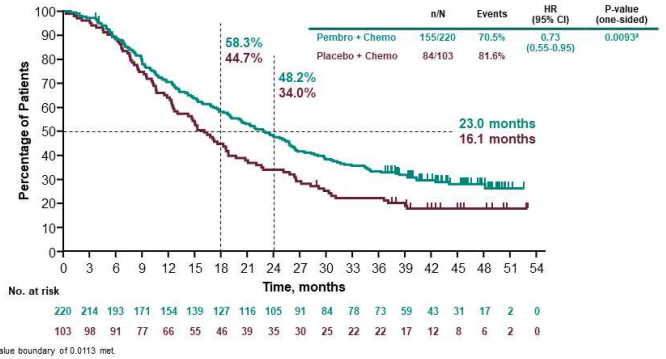
KEYNOTE-355



Progression-Free Survival: PD-L1 CPS ≥10



Overall Survival: PD-L1 CPS ≥10



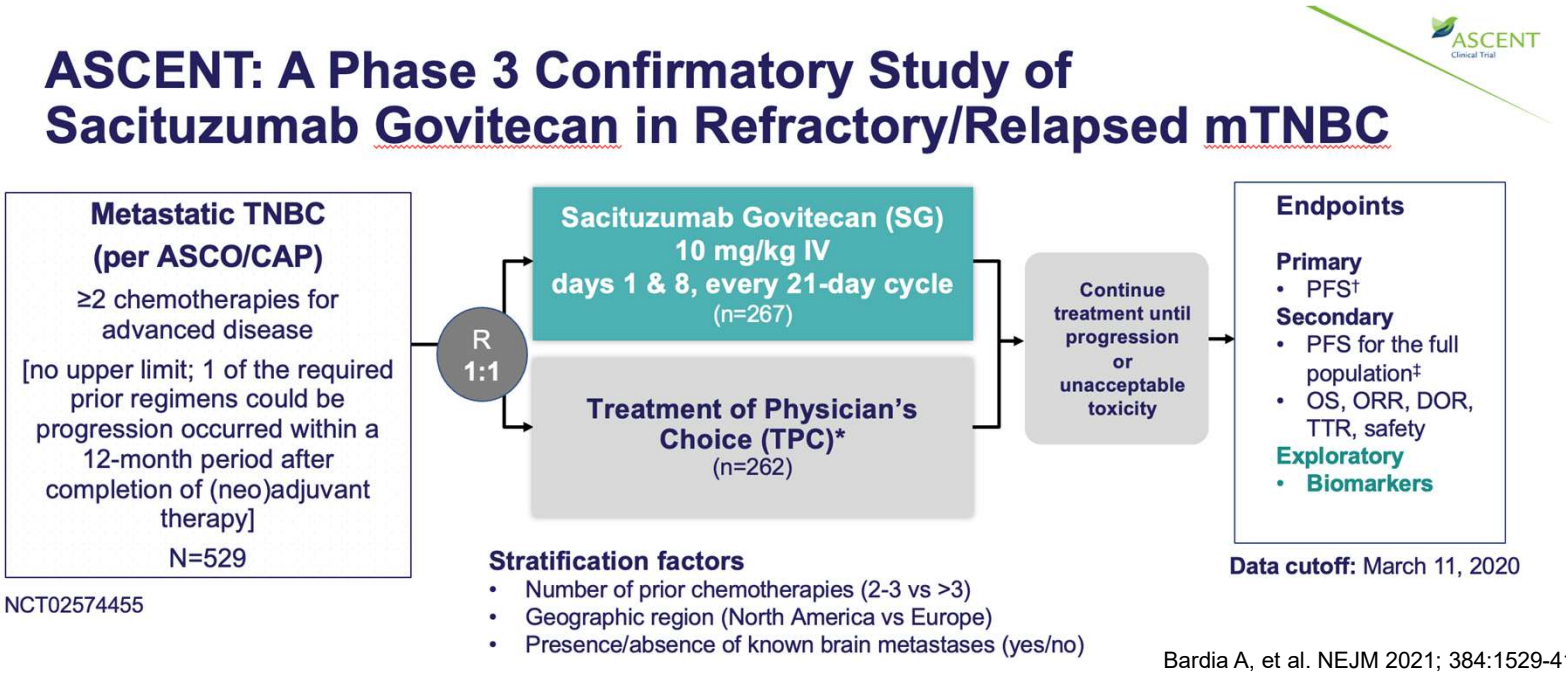
[a]Prespecified *P* value boundary of 0.0113 met.

- November 2020: Granted accelerated FDA approval for PD-L1+ metastatic TNBC with CPS ≥ 10
- July 2021: Granted full FDA approval

Cortes J, et al. Lancet. 2020;396(10265):1817-1828.
Cortes J, et al. N Engl J Med. 2022 Jul 21;387(3):217-226.

First antibody-drug conjugate in advanced TNBC

Sacituzumab govitecan

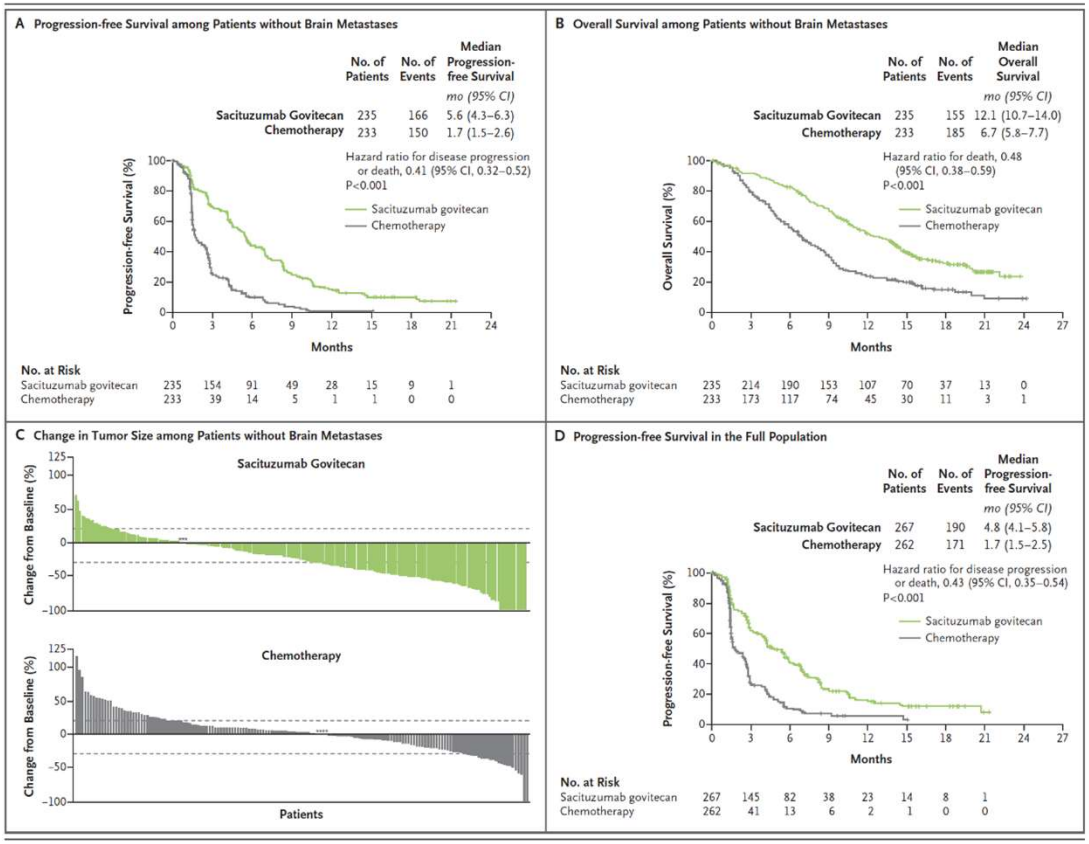


Bardia A, et al. NEJM 2021; 384:1529-41

Phase III ASCENT Trial Comparing Sacituzumab Govitecan to Chemotherapy in Metastatic TNBC

<u>April 2020</u>: Granted accelerated FDA approval

<u>April 2021</u>: Granted full FDA approval

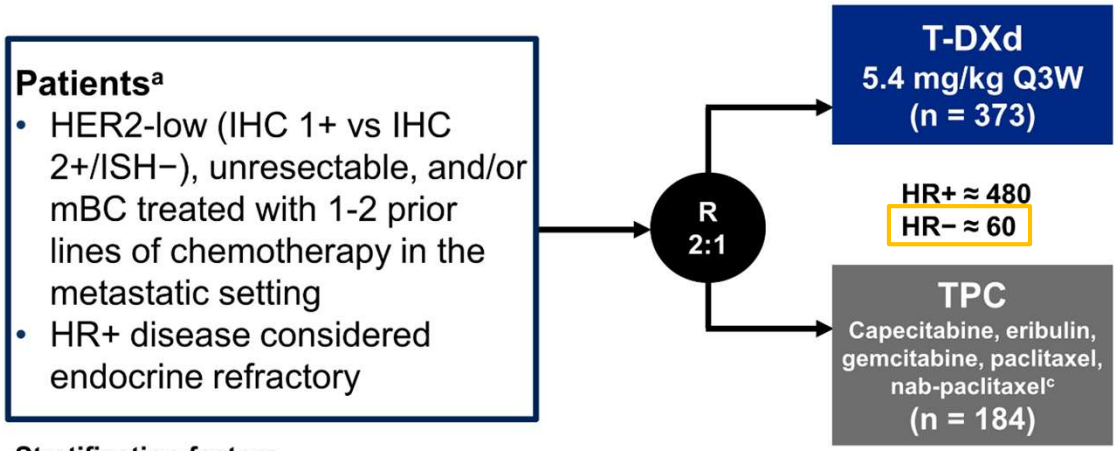


Bardia A, et al. NEJM 2021; 384:1529-41

DESTINY-Breast04

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

Primary endpoint

- PFS by BICR (HR+)

Key secondary endpoints[b]

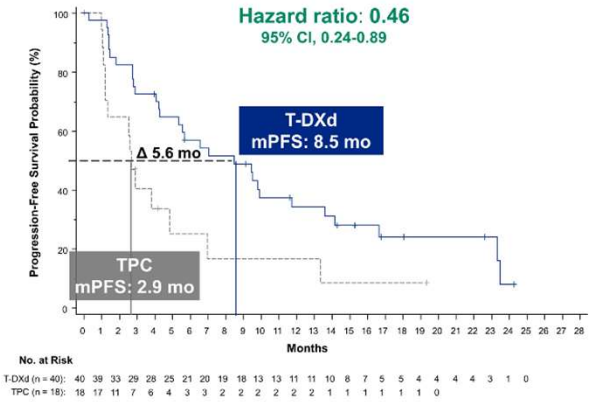
- PFS by BICR (all patients)
- OS (HR+ and all patients)

Modi S, et al. N Engl J Med. 2022 Jul 7;387(1):9-20.

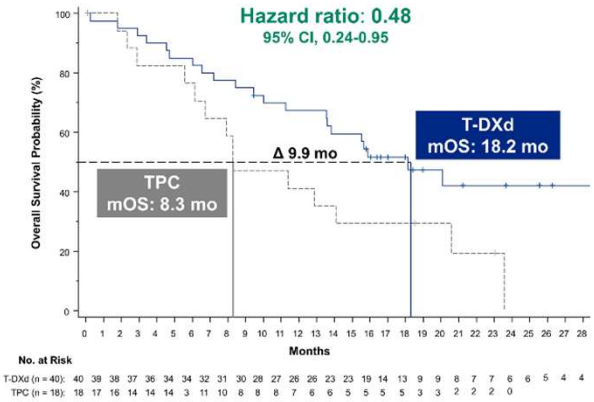
DESTINY-Breast04

PFS and OS in HR− (Exploratory Endpoints)

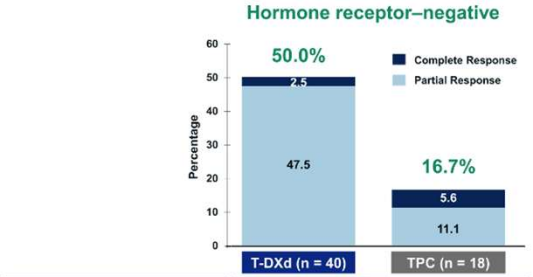
PFS



OS



Confirmed ORR



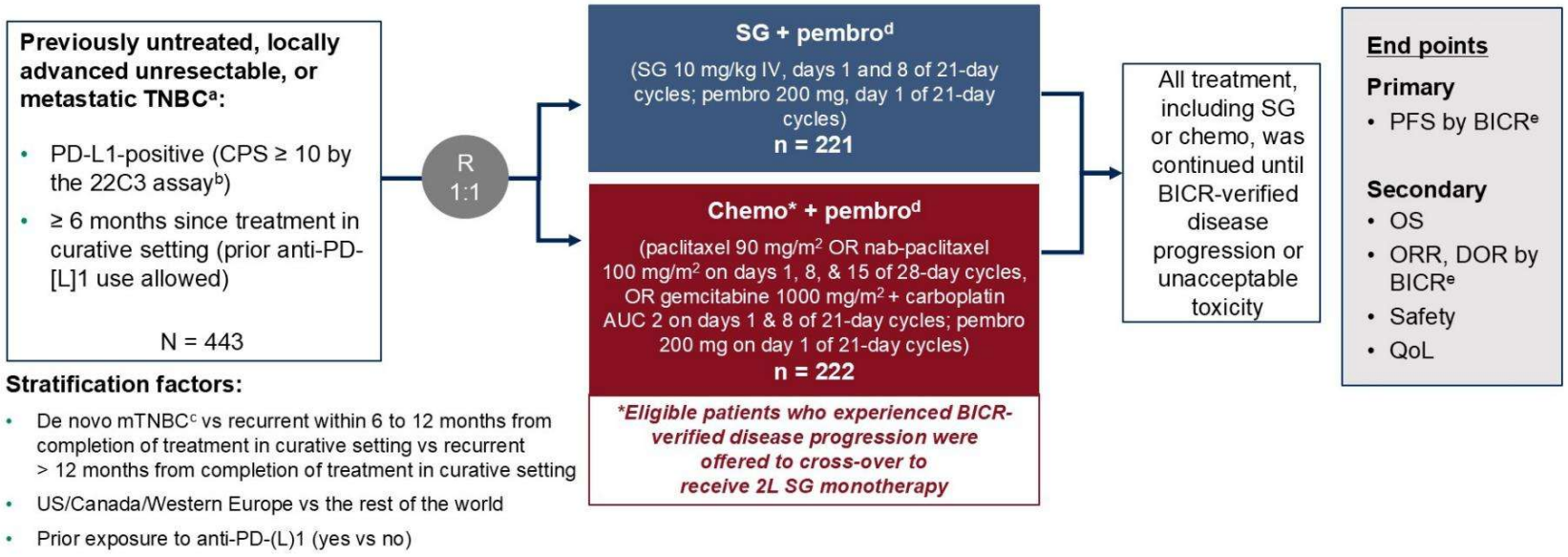
	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	12.5	33.3
Not evaluable, %	7.5	5.6
Clinical benefit rate,[b] %	62.5	27.8
Duration of response, months	8.6	4.9

FDA approved in August 2022 for advanced HER2 low breast cancer, including TNBC

Modi S, et al. N Engl J Med. 2022 Jul 7;387(1):9-20.

2025 New Data Releases

ASCENT-04/KEYNOTE-D19 Study Design



ClinicalTrials.gov identifier: NCT05382286.
[a]TNBC status determined according to standard American Society of Clinical Oncology-College of American Pathologists criteria. [b]Dako, Agilent Technologies. [c]Up to 35% de novo mTNBC. [d]Pembro was administered for a maximum of 35 cycles. [e]Per RECIST v1.1.
AUC, area under the curve; BICR, blinded independent central review; chemo, chemotherapy; CPS, combined positive score; DOR, duration of response; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; QoL, quality of life; R, randomized; RECIST v1.1; Response Evaluation Criteria in Solid Tumors, version 1.1; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TTR, time-to-response.

PRESENTED BY: Sara M Tolaney, MD, MPH

Demographics and Baseline Characteristics

ITT Population	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Female sex, n (%)	221 (100)	222 (100)
Median age, (range) yr	54 (23-88)	55 (27-82)
≥ 65 yr, n (%)	58 (26)	57 (26)
Race or ethnic group,[a] n (%)		
White	139 (63)	118 (53)
Asian	43 (19)	63 (28)
Black	13 (6)	11 (5)
Other/not specified	26 (12)	30 (14)
Geographic region, n (%)		
US/Canada/Western Europe	85 (38)	85 (38)
Rest of the world[b]	136 (62)	137 (62)
ECOG PS at baseline,[c] n (%)		
0	156 (71)	154 (69)
1	65 (29)	67 (30)
Curative treatment-free interval, n (%)		
De novo	75 (34)	75 (34)
Recurrent within 6-12 mo	40 (18)	40 (18)
Recurrent > 12 mo	106 (48)	107 (48)

ITT Population	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
PD-L1 CPS ≥ 10,[d] n (%)	221 (100)	222 (100)
Metastatic sites, n (%)		
Lymph node	159 (72)	154 (69)
Lung	111 (50)	95 (43)
Bone	61 (28)	45 (20)
Liver	55 (25)	57 (26)
Brain	8 (4)	6 (3)
Other[e]	81 (37)	71 (32)
Chemo selected prior to randomization,[f] n (%)		
Taxane	116 (52)	114 (51)
Gemcitabine/carboplatin	105 (48)	108 (49)
Prior anti-PD-(L)1 therapy,[g] n (%)	9 (4)	11 (5)

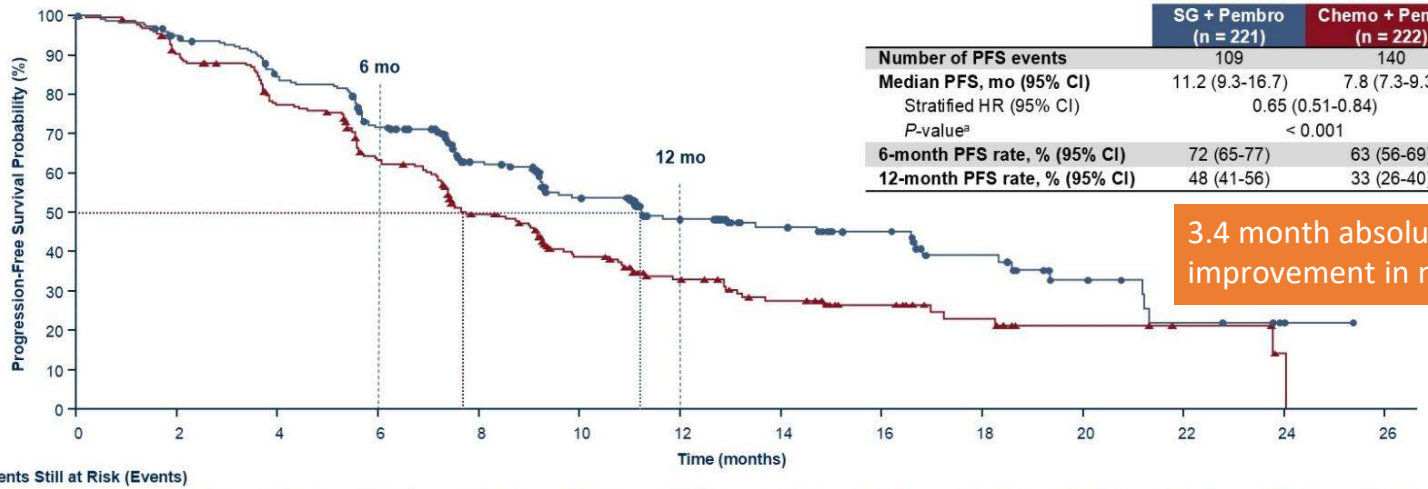
Data cutoff date: March 3, 2025.

[a]As reported by the patients; "other" includes American Indian or Alaska Native, other, and not permitted. [b]Rest of the world includes Argentina, Australia, Brazil, Chile, Czech Republic, Hong Kong, Hungary, Israel, Japan, Malaysia, Mexico, Poland, Singapore, South Africa, South Korea, Taiwan, and Turkey. [c]One patient in the chemo + pembro group had an ECOG PS ≥ 2. [d]PD-L1 status assessed using the PD-L1 IHC 22C3 assay (Dako, Agilent Technologies) at the time of enrollment. [e]Other metastatic sites includes pleura, pleural effusion, skin, soft tissue, chest wall, and muscle. [f]Actual chemo received was consistent with what was selected prior to randomization; however, two patients were randomized but did not receive treatment. [g]While 20 patients were included in the stratified subgroup of prior exposure to anti-PD-(L)1 therapy (yes) per the IRT system, only 6 patients received prior treatment with anti-PD-(L)1 agents per the clinical database.

Chemo, chemotherapy; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IRT, interactive response technology; ITT, intent-to-treat; PARPi, poly ADP-ribose polymerase inhibitor; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; SG, sacituzumab govitecan.

PRESENTED BY: Sara M Tolaney, MD, MPH

Progression-Free Survival by BICR



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

3.4 month absolute improvement in mPFS

No. of Patients Still at Risk (Events)

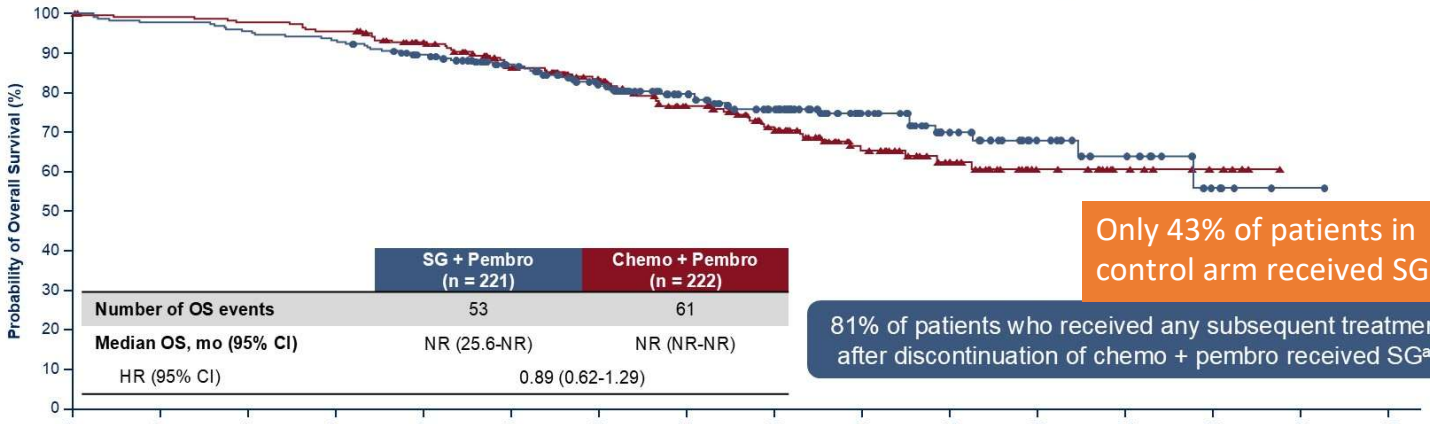
SG + Pembro	221 (0)	202 (11)	174 (33)	142 (59)	105 (75)	78 (89)	58 (96)	42 (98)	34 (99)	22 (103)	11 (106)	6 (109)	2 (109)	0 (109)
Chemo + Pembro	222 (0)	191 (21)	159 (48)	123 (76)	88 (102)	59 (120)	40 (128)	29 (134)	21 (135)	13 (137)	7 (138)	4 (138)	1 (139)	0 (140)

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

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

PRESENTED BY: Sara M Tolaney, MD, MPH

Descriptive Overall Survival at Primary Analysis



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of OS events	53	61
Median OS, mo (95% CI)	NR (25.6-NR)	NR (NR-NR)
HR (95% CI)	0.89 (0.62-1.29)	

Only 43% of patients in control arm received SG

81% of patients who received any subsequent treatment after discontinuation of chemo + pembro received SG[a]

No. of Patients Still at Risk (Events)																
SG + Pembro	221 (0)	216 (5)	211 (10)	206 (15)	190 (23)	162 (28)	138 (37)	111 (41)	88 (46)	55 (47)	36 (50)	21 (51)	14 (52)	5 (53)	1 (53)	0 (53)
Chemo + Pembro	222 (0)	218 (2)	215 (5)	210 (10)	193 (16)	166 (29)	142 (34)	111 (45)	87 (53)	56 (58)	38 (60)	19 (61)	11 (61)	6 (61)	0 (61)	

OS data were immature (maturity rate, 26%), however, a positive trend in improvement was observed for SG + pembro vs chemo + pembro

Data cutoff date: March 3, 2025. Median follow-up was 14.0 months (range, 0.1-28.6).
[a]Of the 96 patients who received SG monotherapy as subsequent anticancer therapy, 77 received it as part of the protocol-specified crossover after meeting all crossover eligibility criteria, including BICR-verification of disease progression; the remaining 19 patients received subsequent SG monotherapy as commercial supply.
2L, second line; chemo, chemotherapy; HR, hazard ratio; pembro, pembrolizumab; NR, not reached; OS, overall survival; SG, sacituzumab govitecan.

2025 ASCO ANNUAL MEETING #ASCO25

PRESENTED BY: Sara M Tolaney, MD, MPH

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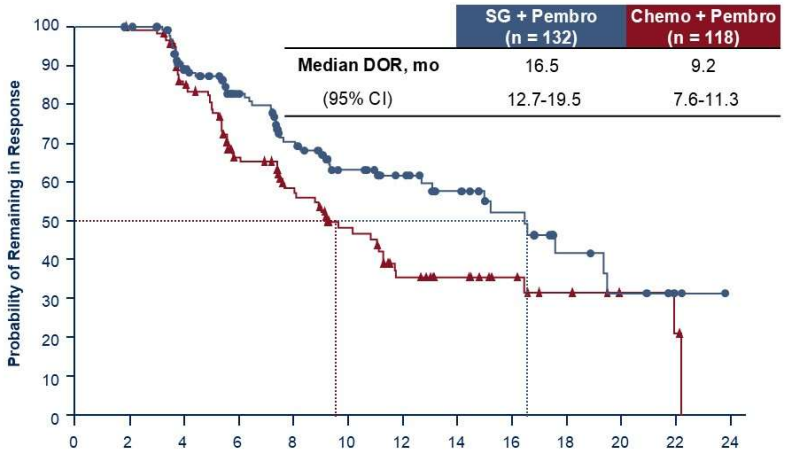
Tumor Responses and Duration of Response by BICR

Variable	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Objective response rate[a] (95% CI), %	60 (52.9-66.3)	53 (46.4-59.9)
Stratified odds ratio (95% CI)	1.3 (0.9-1.9)	
Best overall response, n (%)		
Complete response	28 (13)	18 (8)
Partial response	104 (47)	100 (45)
Stable disease	70 (32)	70 (32)
Stable disease ≥ 6 months	23 (10)	29 (13)
Progressive disease	9 (4)	26 (12)
Not evaluable	10 (5)	8 (4)
Time to response,[b] median (range), months	1.9 (1.0-9.3)	1.9 (1.1-11.4)



A substantially longer duration of response and a higher overall response rate (including an increased complete response rate) was observed for SG + pembro vs chemo + pembro

Data cutoff date: March 3, 2025.
[a]Objective response rate is defined as the proportion of patients who achieved a best overall response of complete response/partial response; [b]Time to response (months) = (date of first documented complete or partial response - date of randomization + 1)/30.4375.
BICR, blinded independent central review; DOR, duration of response; mo, months; pembro, pembrolizumab; SG, sacituzumab govitecan.

2025 ASCO ANNUAL MEETING #ASCO25

PRESENTED BY: Sara M Tolaney, MD, MPH

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
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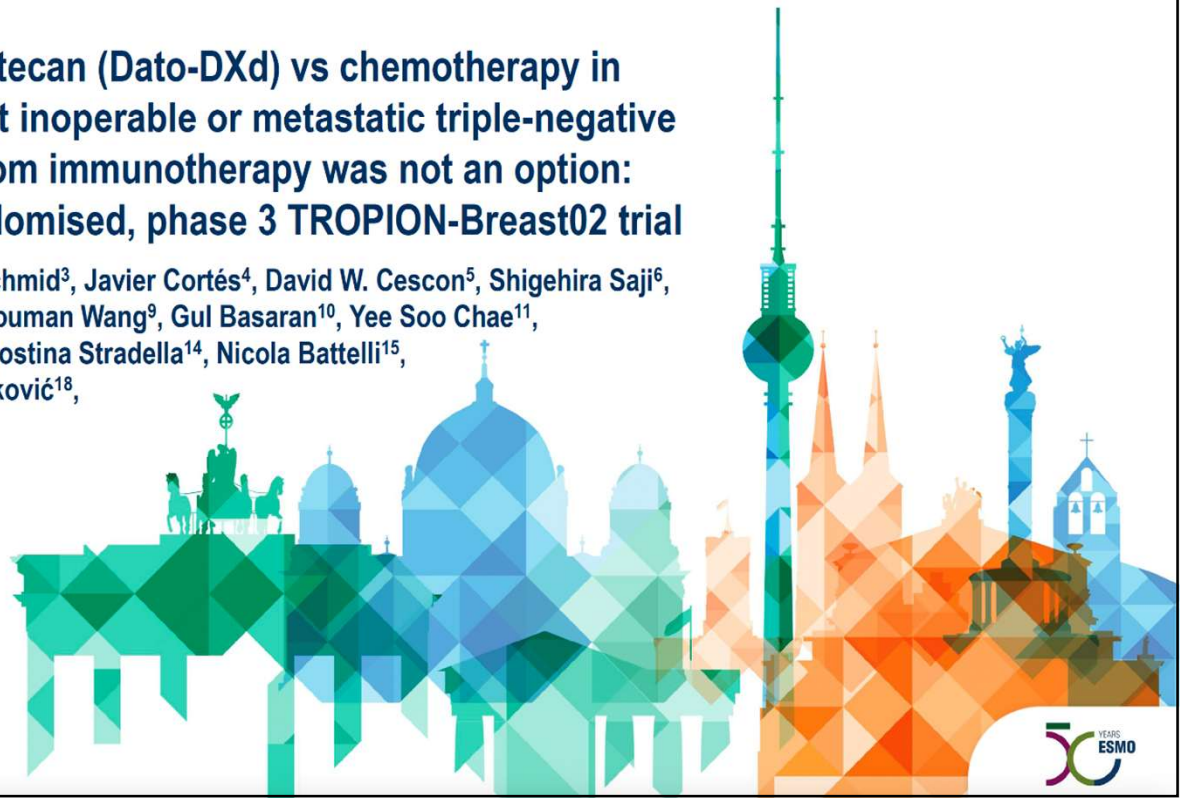
First-line datopotamab deruxtecan (Dato-DXd) vs chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) for whom immunotherapy was not an option: Primary results from the randomised, phase 3 TROPION-Breast02 trial

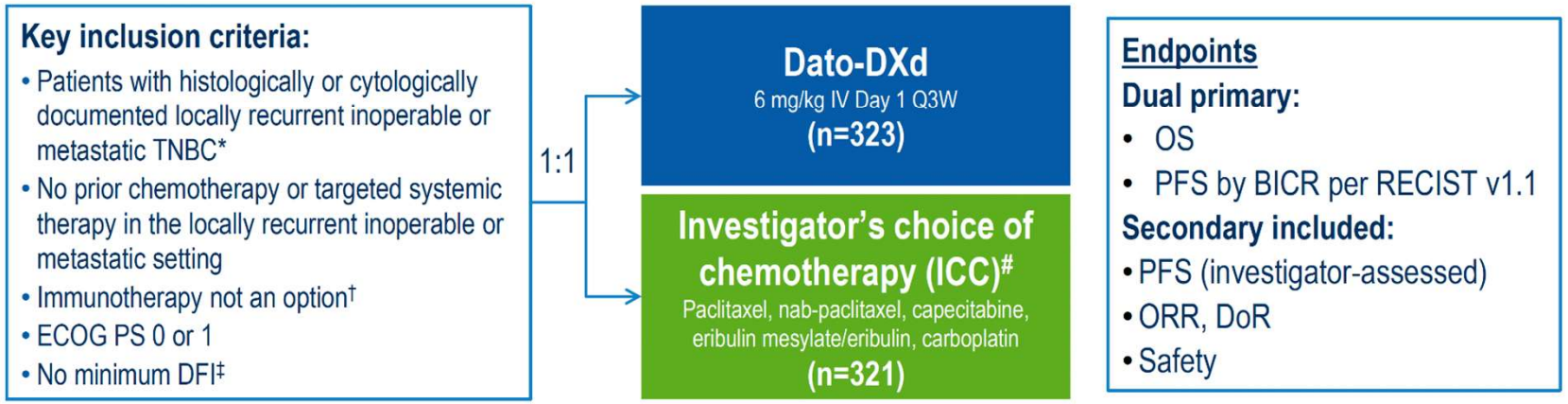
Rebecca A. Dent[1], Zhimin Shao[2], Peter Schmid[3], Javier Cortés[4], David W. Cescon[5], Shigehira Saji[6], Kyung Hae Jung[7], Thomas Bachelot[8], Shouman Wang[9], Gul Basaran[10], Yee Soo Chae[11], Rofhiwa Mathiba[12], Shin-Cheh Chen[13], Agostina Stradella[14], Nicola Battelli[15], Naoki Niikura[16], Kechen Zhao[17], Petra Vuković[18], Micah J. Maxwell[19], Tiffany A. Traina[20]

[1]National Cancer Center Singapore, Singapore; [2]Fudan University Shanghai Cancer Center, Fudan, China; [3]Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK; [4]International Breast Cancer Center (IBCC), Pangaea Oncology, Barcelona, Spain; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Fukushima Medical University, Fukushima, Japan; [7]Asan Medical Center – University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]Centre Léon Bérard, Lyon, France; [9]Xiangya Hospital of Central South University, Changsha, China; [10]MAA Acibadem University, School of Medicine, Medical Oncology Department, Istanbul, Türkiye; [11]Kyungpook National University Chilgok Hospital, Kyungpook National University School of Medicine, Kyungpook, Republic of Korea; [12]Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [13]Chang Gung Medical Foundation – Taipei Chang Gung Memorial Hospital, Taipei City, Taiwan; [14]Institut Catala d'Oncologia - Hospital Duran i Reynals (ICO L'Hospitalet), Barcelona, Spain; [15]Ospedale Generale Provinciale Macerata, Macerata, Italy; [16]Tokai University School of Medicine, Kanagawa, Japan; [17]Biometrics, Late-Stage Development, Oncology R&D, AstraZeneca, Wilmington, DE, USA; [18]Clinical Development, Late-Stage Development, Oncology R&D, AstraZeneca, Cambridge, UK; [19]Clinical Development, Late-Stage Development, Oncology R&D, AstraZeneca, Gaithersburg, MD, USA; [20]Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY, USA



TROPION-Breast02: Study Design

Randomised, phase 3, open-label, global study (NCT05374512)



Randomisation 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)¶

- Treatment continued until investigator-assessed RECIST v1.1 progressive disease, unacceptable toxicity, or another discontinuation criterion was met
- 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 tumours, or patients with PD-L1-high tumours 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. §Recruitment of patients with PD-L1-high tumours who would otherwise be eligible for pembrolizumab if regulatory access was available was capped at ~10% of randomised patients. ¶Recruitment of patients with DFI 0–12 months was capped at ~20% of randomised patients. #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 100 mg/m^2 IV, D1, 8, 15, Q4W; if prior taxane and DFI 0–12 months: capecitabine 1000 or 1250 mg/m^2 orally twice daily, 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).

ADC, antibody-drug conjugate; BICR, blinded independent central review; CPS, combined positive score; D, day; DFI, disease-free interval; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; ORR, objective response rate; PD-(L)1, programmed cell death (ligand) 1; PFS, progression-free survival; QXW, every X weeks.

Rebecca A. Dent

Demographics and Baseline Characteristics

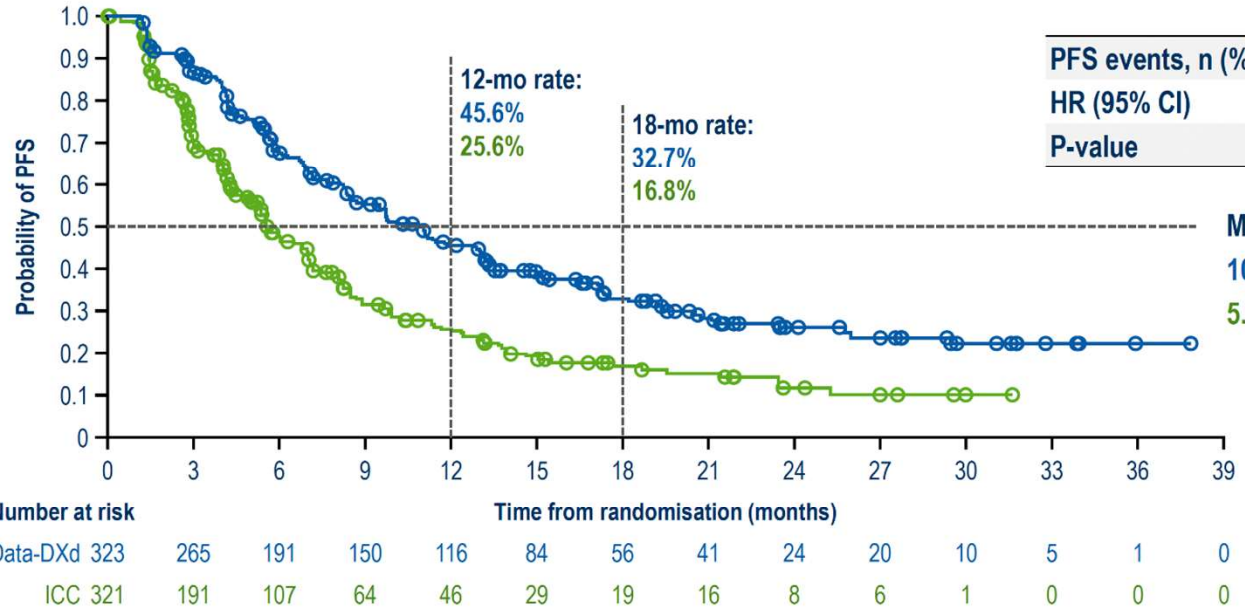
		Dato-DXd (n=323)	ICC (n=321)
Median age (range), years		56 (27–85)	57 (23–83)
Female, n (%)		323 (100)	319 (99)
Race, n (%)	Black or African American	13 (4)	14 (4)
	Asian	151 (47)	131 (41)
	White	131 (41)	153 (48)
	Other*	28 (9)	23 (7)
Geographic region, n (%)	US, Canada, Europe	120 (37)	120 (37)
	Other geographic regions	203 (63)	201 (63)
ECOG PS, n (%)	0	195 (60)	182 (57)
	1	128 (40)	139 (43)
DFI history, n (%)	*De novo*	109 (34)	110 (34)
	Prior DFI 0–12 months‡	67 (21)	66 (21)
	Prior DFI 0–6 months	***47 (15)***	***51 (16)***
	Prior DFI >12 months‡	147 (46)	145 (45)

		Dato-DXd (n=323)	ICC (n=321)
PD-L1 status,† n (%)	Low (CPS <10)	287 (89)	291 (91)
	High (CPS ≥10)	34 (11)	29 (9)
Metastases, n (%)	Visceral	253 (78)	233 (73)
	Liver	93 (29)	98 (31)
	Brain§	36 (11)	28 (9)
Number of metastatic sites, n (%)	<3	207 (64)	215 (67)
	≥3	116 (36)	106 (33)
Pre-selected choice of chemotherapy, n (%)	Nab-paclitaxel	180 (56)	172 (54)
	Paclitaxel	82 (25)	92 (29)
	Eribulin mesylate/eribulin	43 (13)	35 (11)
	Carboplatin	11 (3)	14 (4)
	Capecitabine	7 (2)	8 (2)

*Including not reported. †Based on central laboratory testing, using Agilent PD-L1 IHC 22C3 pharmDx Assay (Agilent Technologies, Santa Clara, CA); PD-L1 status missing/not applicable in 2 patients in the Dato-DXd arm and 1 patient in the ICC arm. ‡Prior (neo)adjuvant cancer therapy was received by 66% of patients, including nitrogen mustards (57%), taxanes (57%), anthracyclines (56%), pyrimidine analogues (27%), platinum compounds (16%), and PD-(L)1 inhibitors (5%). §Patients with asymptomatic, stable brain metastases were permitted in the study.

Rebecca A. Dent

Progression-Free Survival by BICR



	Dato-DXd	ICC
PFS events, n (%)	199 (62)	209 (65)
HR (95% CI)	0.57 (0.47–0.69)	
P-value	<0.0001	

Median PFS (95% CI)

10.8 mo (8.6–13.0)

5.6 mo (5.0–7.0)

Δ 5.3 mo*

Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with ICC, reducing the risk of progression or death by 43%

Rebecca A. Dent

*Numbers are rounded. To two decimal points: median PFS 10.84 (95% CI 8.57–12.98) with Dato-DXd, 5.55 (95% CI 4.96–6.97) with ICC; Δ 5.29 months.
CI, confidence interval; HR, hazard ratio; mo, months.

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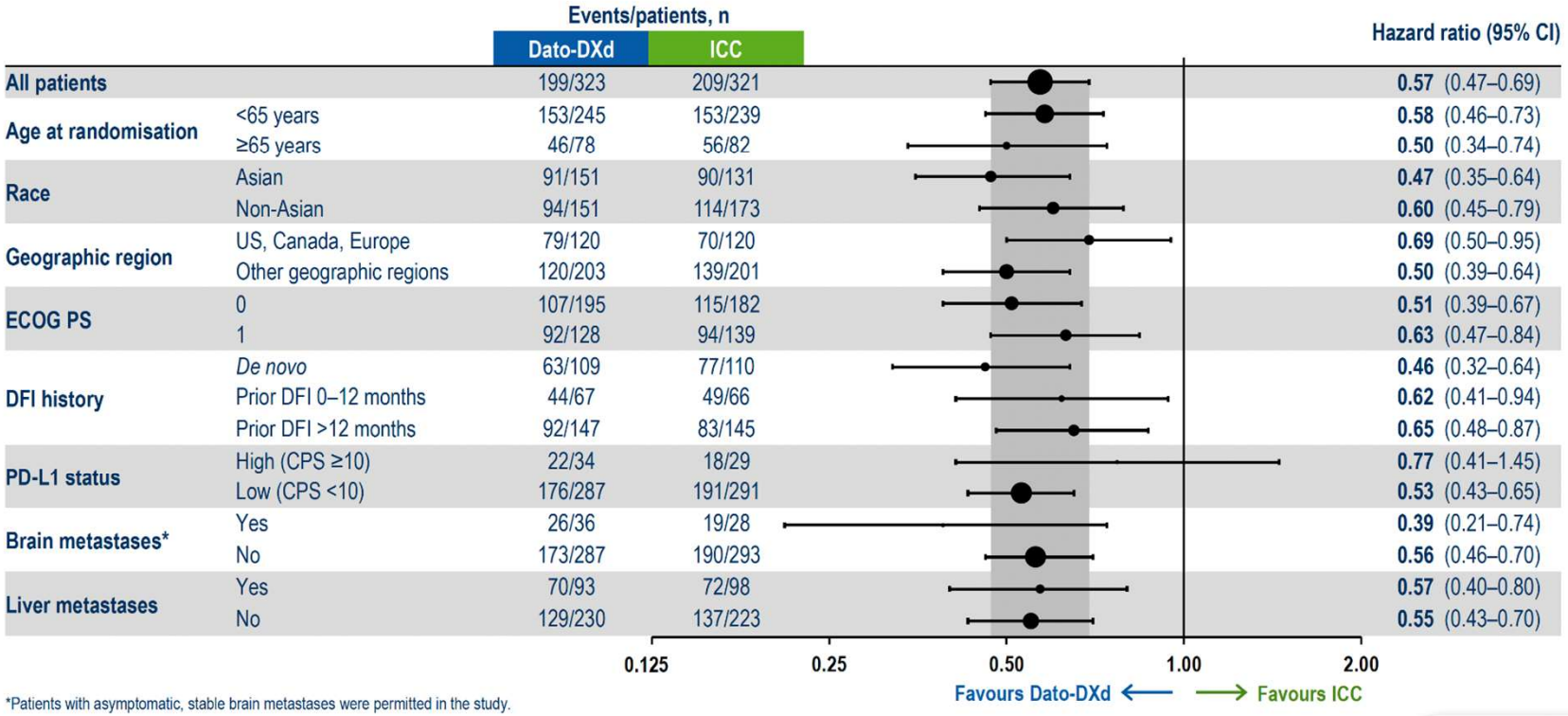
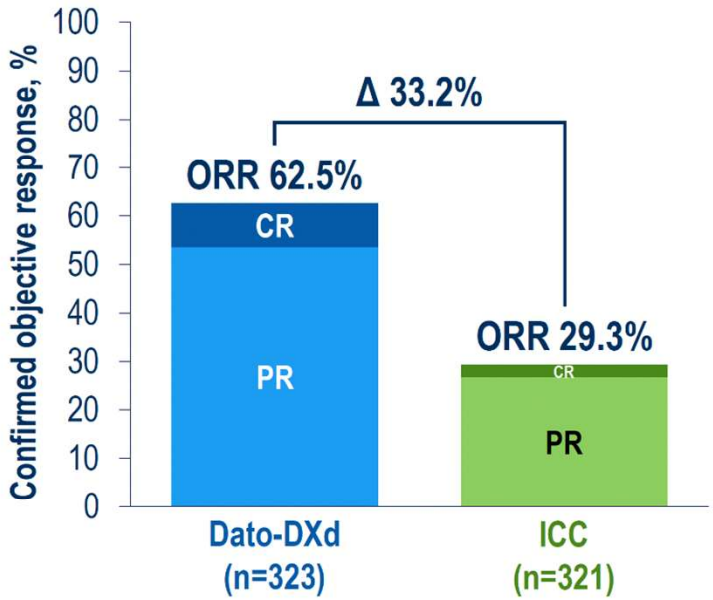
PFS by BICR Subgroup Analysis



*Patients with asymptomatic, stable brain metastases were permitted in the study.

Rebecca A. Dent

Response by BICR

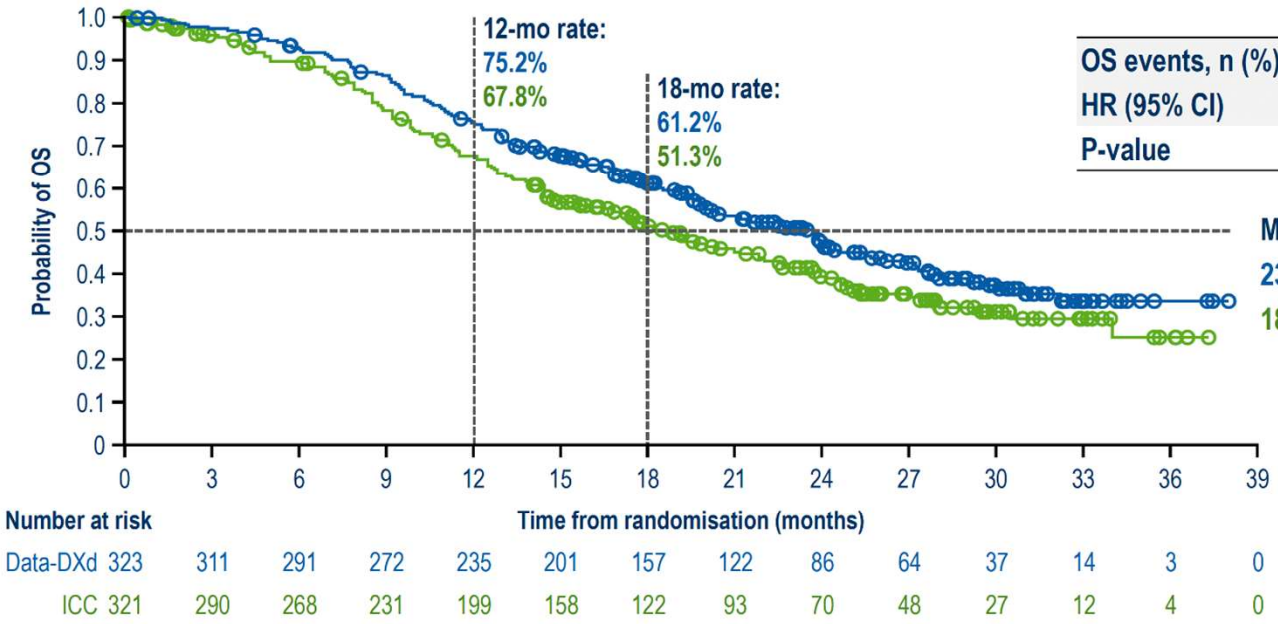


	Dato-DXd (n=323)	ICC (n=321)
Confirmed objective response, n (%)	202 (62.5)	94 (29.3)
Odds ratio (95% CI)	4.24 (3.03–5.95)	
Best confirmed objective response, n (%)		
Complete response	29 (9.0)	8 (2.5)
Partial response	173 (53.6)	86 (26.8)
Stable disease	87 (26.9)	151 (47.0)
Progressive disease	27 (8.4)	52 (16.2)
Not evaluable	7 (2.2)	24 (7.5)

With Dato-DXd, confirmed ORR was more than double that with ICC, and confirmed complete response rate was more than three times that with ICC

Rebecca A. Dent

Overall Survival



	Dato-DXd	ICC
OS events, n (%)	168 (52)	181 (56)
HR (95% CI)	0.79 (0.64–0.98)	
P-value	0.0291	

Median OS (95% CI)

23.7 mo (19.8–25.6)

18.7 mo (16.0–21.8)

Δ 5.0 mo

Number at risk														
Data-DXd	323	311	291	272	235	201	157	122	86	64	37	14	3	0
ICC	321	290	268	231	199	158	122	93	70	48	27	12	4	0

Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with ICC, reducing the risk of death by 21%

Rebecca A. Dent

Most Common Treatment-Related AEs (≥15% of Patients)

Treatment-related AEs, n (%)	Dato-DXd (n=319)		ICC (n=309)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Dry eye*	76 (24)	4 (1)	9 (3)	0
Stomatitis	182 (57)	27 (8)	27 (9)	0
Nausea	142 (45)	2 (<1)	53 (17)	2 (<1)
Constipation	72 (23)	1 (<1)	31 (10)	0
Vomiting	65 (20)	4 (1)	23 (7)	1 (<1)
Decreased appetite	49 (15)	1 (<1)	20 (6)	1 (<1)
Neutropenia†	39 (12)	10 (3)	90 (29)	40 (13)
Anaemia‡	48 (15)	6 (2)	64 (21)	10 (3)
Leukopenia§	27 (8)	3 (<1)	55 (18)	13 (4)
Peripheral neuropathy¶	14 (4)	0	75 (24)	5 (2)
Alopecia	130 (41)	0	96 (31)	1 (<1)‖
Fatigue#	101 (32)	8 (3)	86 (28)	9 (3)

*In the Dato-DXd arm only, ophthalmologic assessments were required every 3 cycles while on therapy; this was not required in the ICC arm. For all patients in both arms, ophthalmologic assessments were required at baseline, as clinically indicated, and at end of therapy.
†Grouped term comprising preferred terms of neutropenia and neutrophil count decreased. ‡Grouped term comprising preferred terms of haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased. §Grouped term comprising preferred terms of white blood cell count decreased and leukopenia. ¶Grouped term comprising preferred terms of neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, paraesthesia, and peripheral sensory neuropathy. #Grouped term comprising preferred terms of fatigue, asthenia, and malaise.
‖Per Common Terminology Criteria for Adverse Events version 5.0, the maximum grade for alopecia is grade 2.

Rebecca A. Dent

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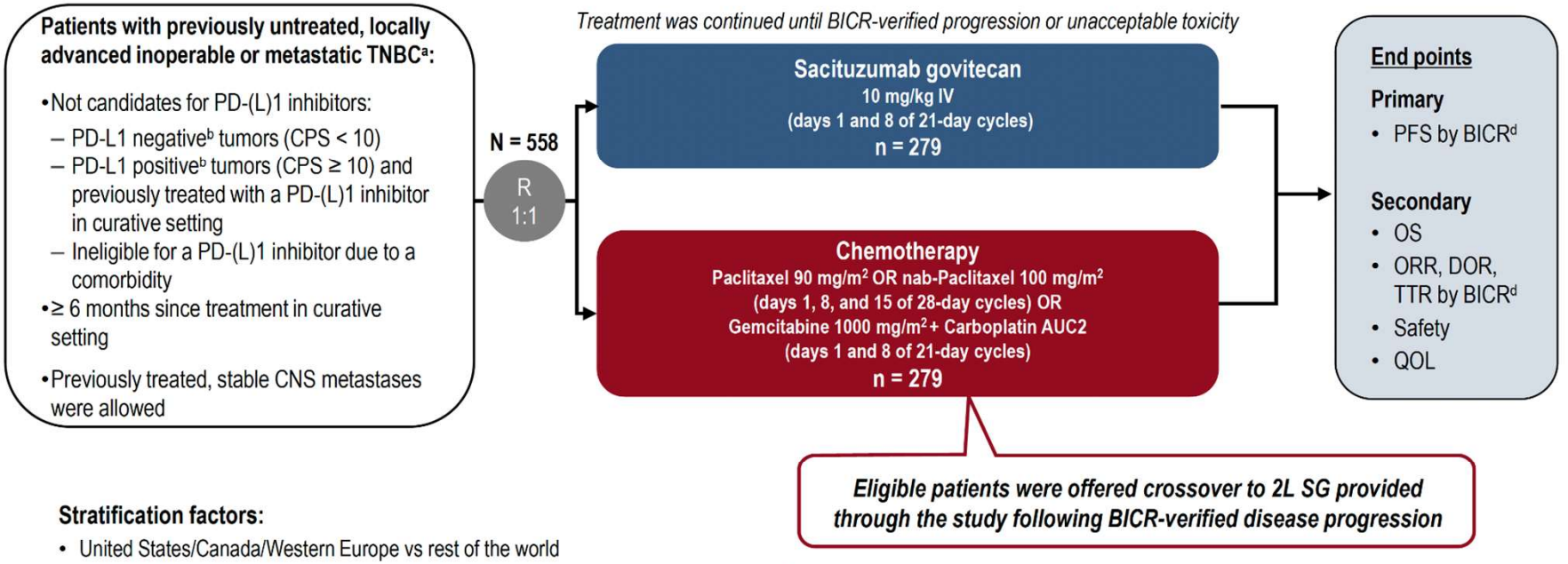
Primary Results From ASCENT-03: A Randomized Phase 3 Study of Sacituzumab Govitecan vs Chemotherapy in Patients With Previously Untreated Metastatic Triple-Negative Breast Cancer Who Are Unable to Receive PD-(L)1 Inhibitors

Javier Cortés[1-5], Aditya Bardia[6], Kevin Punie[7], Carlos Barrios[8], Sara Hurvitz[9], Andreas Schneeweiss[10], Joohyuk Sohn[11], Eriko Tokunaga[12], Adam Brufsky[13], Yeon Hee Park[14], Binghe Xu[15], Roberto Hegg[16], Mafalda Oliveira[17], Alessandra Fabi[18], Natalya Vaksman[19], Theresa Valdez[19], Xinrui Zhang[19], Catherine Lai[19], Sara M Tolaney[20]

[1]International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; [2]IOB Madrid, Institute of Oncology, Hospital Beata María Ana, Madrid, Spain; [3]Oncology Department, Hospital Universitario Torrejón, Ribera Group, Madrid, Spain; [4]Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; [5]Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, NJ, USA; [6]David Geffen School of Medicine, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [7]Ziekenhuis Aan de Stroom, Antwerp, Belgium; [8]Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; [9]Department of Medicine, UW Medicine, Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA USA; [10]Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany; [11]Yonsei Cancer Center, Seoul, Republic of Korea; [12]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [13]Magee-Womens Hospital and the Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [14]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [15]Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [16]University of São Paulo, São Paulo, Brazil; [17]Vall d'Hebron University Hospital, Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [18]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; [19]Gilead Sciences Inc., Foster City, CA, USA; [20]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Sunday, October 19, 2025; 9:15-9:25 am
LBA 20

ASCENT-03: Study Design



Stratification factors:

- United States/Canada/Western Europe vs rest of the world
- De novo mTNBC[c] vs recurrent within 6 to 12 months of treatment vs recurrent after > 12 months from treatment in curative setting

ClinicalTrials.gov identifier: NCT05382299. [a]TNBC status was centrally confirmed and determined according to standard American Society of Clinical Oncology-College of American Pathologists criteria. [b]PD-L1 CPS was centrally confirmed and defined using the PD-L1 IHC 22C3 assay (Dako, Agilent Technologies). [c]Up to 35% de novo mTNBC. [d]Per Response Evaluation Criteria in Solid Tumors version 1.1. **2L**, second line; **AUC**, area under the curve; **BICR**, blinded independent central review; **CNS**, central nervous system; **CPS**, combined positive score; **DOR**, duration of response; **IV**, intravenous; **mTNBC**, metastatic triple-negative breast cancer; **ORR**, objective response rate; **OS**, overall survival; **PD-1**, programmed cell death protein-1; **PD-L1**, programmed cell death ligand 1; **PD-(L)1**, PD-1 or PD-L1; **PFS**, progression-free survival; **QOL**, quality of life; **R**, randomization; **SG**, sacituzumab govitecan; **TNBC**, triple-negative breast cancer; **TTR**, time to response.

Javier Cortés, MD

Demographics and Baseline Characteristics

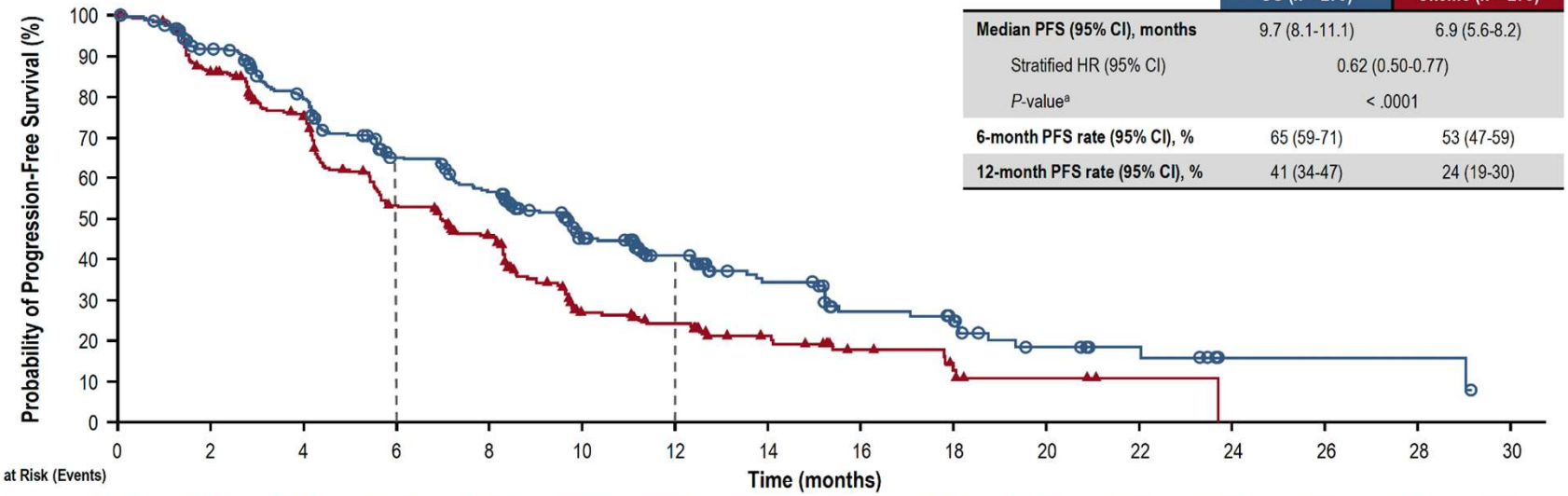
ITT Population	SG (n = 279)	Chemo (n = 279)
Female sex, n (%)	278 (> 99)	277 (99)
Median age, (range) yr	56 (28-84)	54 (23-86)
≥ 65 yr, n (%)	65 (23)	78 (28)
Race or ethnic group,[a] n (%)		
White	178 (64)	178 (64)
Asian	66 (24)	65 (23)
Black	10 (4)	7 (3)
Other/not specified	25 (9)	29 (10)
Geographic region, n (%)		
United States/Canada/Western Europe	89 (32)	89 (32)
Rest of the world[b]	190 (68)	190 (68)
ECOG PS, n (%)		
0	183 (66)	187 (67)
1	96 (34)	92 (33)
Curative treatment-free interval, n (%)		
De novo	87 (31)	88 (32)
Recurrent within 6-12 mo	58 (21)	57 (20)
Recurrent > 12 mo	134 (48)	134 (48)

ITT Population	SG (n = 279)	Chemo (n = 279)
PD-L1 status,[c] n (%)		
Negative	277 (99)	278 (> 99)
Positive	1 (< 1)	1 (< 1)
Metastatic sites, n (%)		
Lung	166 (59)	170 (61)
Liver	81 (29)	72 (26)
Brain	15 (5)	14 (5)
Chemo selected prior to randomization,[d] n (%)		
Taxane	154 (55)	155 (56)
Gemcitabine/carboplatin	125 (45)	124 (44)
Prior (neo)adjuvant therapies, n (%)	185 (66)	191 (68)
Taxanes	162 (58)	162 (58)
Capecitabine	50 (18)	57 (20)
Platinum agents	51 (18)	49 (18)
PD-(L)1 inhibitors	13 (5)	11 (4)

Data cutoff date: April 2, 2025. [a]As reported by the patients; other/not specified includes American Indian or Alaska Native, other races, and not provided/collection not permitted. [b]Rest of the world includes Argentina, Australia, Brazil, Chile, China, Czech Republic, Hong Kong, Hungary, Israel, Japan, Malaysia, Mexico, Poland, Republic of Korea, Romania, Slovakia, South Africa, Taiwan, and Turkey. [c]PD-L1 status assessed using the PD-L1 IHC 22C3 assay (Dako, Agilent Technologies) at time of enrollment; tumors with a combined positive score ≥ 10 were considered PD-L1 positive and tumors with a combined positive score < 10 were considered PD-L1 negative. One patient in the SG group had PD-L1 CPS missing. [d]Actual chemo received was consistent with what was selected prior to randomization; however, 3 patients were randomized but did not receive treatment.
Chemo, chemotherapy; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ITT**, intent to treat; **PD-1**, programmed cell death protein-1; **PD-L1**, programmed cell death ligand 1; **PD-(L)1**, PD-1 or PD-L1; **SG**, sacituzumab govitecan.

Javier Cortés, MD

Progression-Free Survival by BICR



	SG (n = 279)	Chemo (n = 279)
Median PFS (95% CI), months	9.7 (8.1-11.1)	6.9 (5.6-8.2)
Stratified HR (95% CI)	0.62 (0.50-0.77)	
P-value[a]	< .0001	
6-month PFS rate (95% CI), %	65 (59-71)	53 (47-59)
12-month PFS rate (95% CI), %	41 (34-47)	24 (19-30)

No. at Risk (Events)

SG	279 (0)	238 (22)	199 (53)	153 (88)	128 (108)	84 (131)	60 (138)	38 (146)	23 (153)	20 (154)	10 (159)	7 (159)	2 (160)	2 (160)	2 (160)	0 (161)
Chemo	279 (0)	226 (37)	186 (65)	126 (118)	100 (135)	44 (172)	35 (176)	21 (180)	12 (183)	7 (186)	3 (187)	1 (187)	0 (188)			

SG demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo by BICR analysis, with a 38% reduction in risk of disease progression or death

Data cutoff date: April 2, 2025. [a]Two-sided *P*-value from stratified log-rank test.
BICR, blinded independent central review; **chemo**, chemotherapy; **HR**, hazard ratio; **PFS**, progression-free survival; **SG**, sacituzumab govitecan.

Javier Cortés, MD

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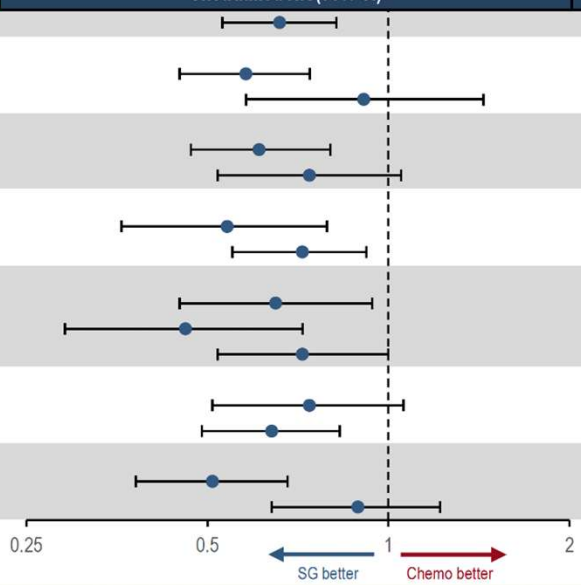
Subgroup Analysis of Progression-free Survival by BICR

	SG		Chemo		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	n	Median PFS, mo (95% CI)	n	Median PFS, mo (95% CI)		
ITT population	279	9.7 (8.1-11.1)	279	6.9 (5.6-8.2)		0.66 (0.53-0.82)
Age group						
< 65 years	214	9.6 (7.6-10.3)	201	5.7 (4.4-7.0)		0.58 (0.45-0.74)
≥ 65 years	65	11.1 (7.3-13.9)	78	9.0 (8.3-10.0)		0.91 (0.58-1.44)
ECOG PS						
0	183	11.2 (9.7-13.5)	187	7.3 (6.0-8.3)		0.61 (0.47-0.80)
1	96	7.1 (5.4-8.5)	92	5.5 (4.2-7.2)		0.74 (0.52-1.05)
Geographic region						
United States/Canada/Western Europe	89	9.9 (7.8-13.9)	89	7.1 (5.4-8.3)		0.54 (0.36-0.79)
Rest of the world	190	9.6 (7.2-11.1)	190	6.9 (5.5-8.3)		0.72 (0.55-0.92)
Disease Status						
De novo	87	8.3 (5.6-12.4)	88	5.5 (4.2-7.3)		0.65 (0.45-0.94)
Recurrent 6-12 mo	58	8.3 (5.6-9.9)	57	5.6 (4.2-6.7)		0.46 (0.29-0.72)
Recurrent > 12 mo	134	11.1 (8.4-13.5)	134	8.4 (7.2-9.8)		0.72 (0.52-1.00)
PD-L1 status						
CPS < 1	102	8.5 (7.2-12.5)	98	8.3 (5.4-9.6)		0.74 (0.51-1.06)
1 ≤ CPS < 10	175	9.8 (7.6-11.3)	180	6.9 (5.5-8.1)		0.64 (0.49-0.83)
Chemo selected prior to randomization						
Taxane	154	11.1 (8.1-12.7)	155	5.7 (4.3-8.1)		0.51 (0.38-0.68)
Gemcitabine/carboplatin	125	8.5 (6.9-9.9)	124	8.1 (5.7-8.3)		0.89 (0.64-1.22)



PFS benefit of SG over chemo was observed across key prespecified subgroups

Data cutoff date: April 2, 2025. **BICR**, blinded independent central review; **chemo**, chemotherapy; **CPS**, combined positive score; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **HR**, hazard ratio; **ITT**, intent-to-treat; **PD-L1**, programmed cell death ligand 1; **PFS**, progression-free survival; **SG**, sacituzumab govitecan.

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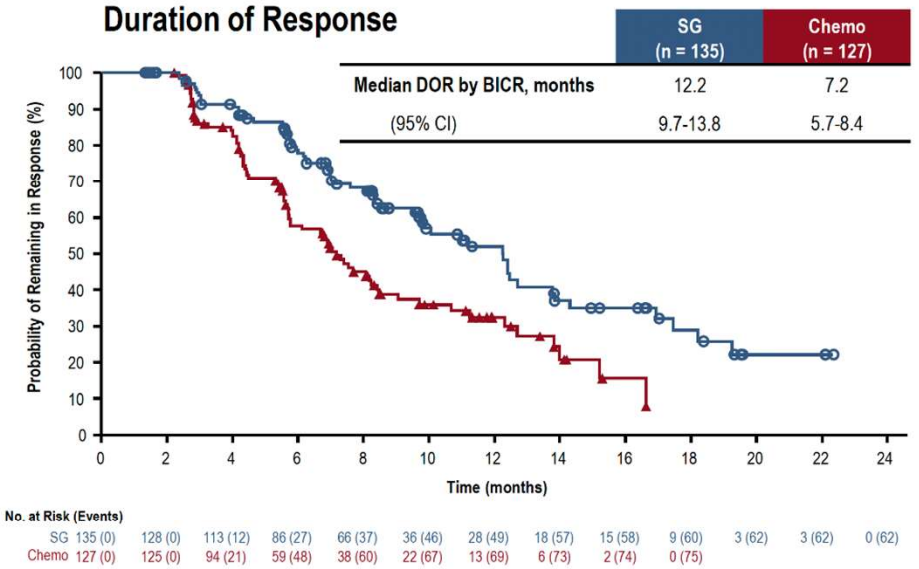
Tumor Response

Variable	SG (n = 279)	Chemo (n = 279)
Objective response rate by BICR[a] (95% CI), %	48 (42-54)	46 (40-52)
Stratified odds ratio (95% CI)	1.1 (0.8-1.6)	
Best overall response by BICR, n (%)		
Complete response	20 (7)	15 (5)
Partial response	115 (41)	112 (40)
Stable disease	113 (41)	101 (36)
Stable disease ≥ 6 months	37 (13)	32 (11)
Progressive disease	14 (5)	36 (13)
Not evaluable	17 (6)	15 (5)
Time to response by BICR,[b] median (range), months	1.6 (0.7-16.7)	1.6 (0.9-6.8)



Objective response rates were similar in both treatment groups; however, duration of response was substantially longer with SG vs chemo

Data cutoff date: April 2, 2025. [a]Objective response rate is defined as the proportion of patients who achieved a best overall response of complete response/partial response. [b]Time to response (months) = (date of first documented confirmed complete or partial response - date of randomization + 1)/30.4375.
Chemo, chemotherapy; **BICR**, blinded independent central review; **DOR**, duration of response; **SG**, sacituzumab govitecan.

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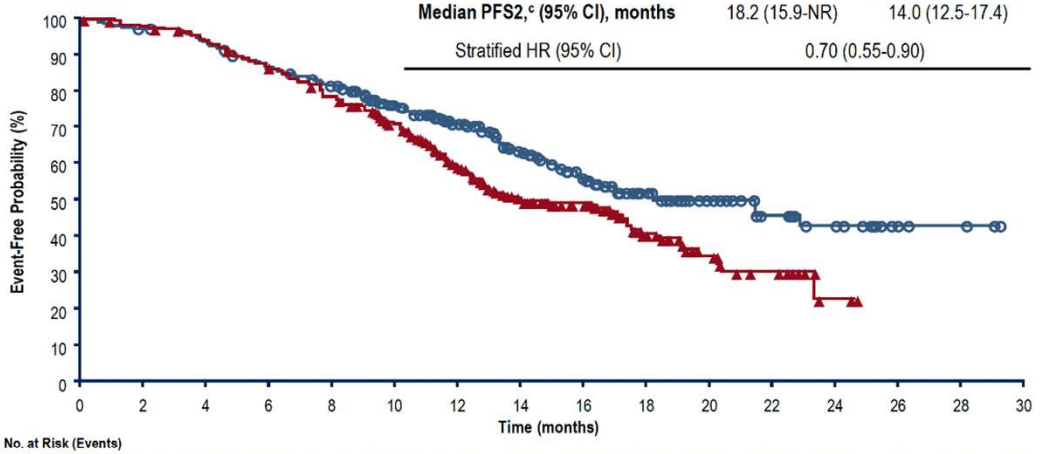
Descriptive Overall Survival and PFS2

- **Overall survival not yet mature[a]**
- Study continues to first formal OS analysis
- Of 179 patients who initiated subsequent treatment after chemo, 147 (82%) received SG

Overall survival	SG (n = 279)	Chemo (n = 279)
Number of events, %	103 (37)	103 (37)
Median (95% CI) , months	21.5 (17.7-NR)	20.2 (18.2-NR)
Stratified HR (95% CI)	0.98 (0.75-1.30)	
OS rate (95% CI), %		
12-month	75 (70-80)	73 (67-78)
24-month	46 (36-56)	42 (29-54)

Progression-Free Survival 2[b]

	SG (n = 279)	Chemo (n = 279)
Median PFS2,[c] (95% CI), months	18.2 (15.9-NR)	14.0 (12.5-17.4)
Stratified HR (95% CI)	0.70 (0.55-0.90)	



At the time of primary analysis, overall survival was immature and PFS2 was longer with SG vs chemo by investigator assessment

Data cutoff date: April 2, 2025. [a]At the time of this analysis, OS data maturity was 37%. [b]PFS2 is defined as the time from date of randomization to the first documented progression on next-line therapy based on investigator assessment of progressive disease or death due to any cause, whichever occurs first. [c]By investigator assessment.
2L, second line; **chemo**, chemotherapy; **HR**, hazard ratio; **NR**, not reached; **OS**, overall survival; **PFS2**, progression-free survival 2; **SG**, sacituzumab govitecan.

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Exposure and Safety Summary

Safety population	SG (n = 275)	Chemo (n = 276)	
Treatment component	**SG**	**Taxane**	**Gemcitabine/ Carboplatin**
All treated patients, n	275	154	122
Median duration of treatment, months (range)	8.3 (< 0.1-28.7)	6.3 (< 0.1-24.2)	5.8 (< 0.1-23.1)

TEAEs, n (%)	SG (n = 275)	Chemo (n = 276)
Any TEAE	273 (99)	269 (97)
Grade ≥ 3 TEAEs	181 (66)	171 (62)
Treatment-related	167 (61)	147 (53)
Treatment-emergent SAE	71 (26)	67 (24)
Treatment-related	46 (17)	37 (13)
TEAEs leading to treatment discontinuation	10 (4)	33 (12)
TEAEs leading to dose interruption	181 (66)	171 (62)
TEAEs leading to dose reduction	101 (37)	124 (45)
TEAEs leading to death	7 (3)	1 (< 1)
Treatment-related	6 (2)	1 (< 1)

All treatment-related deaths with SG were due to infections; 5 infections were secondary to neutropenia. None of the 5 patients, who had risk factors for febrile neutropenia, received prophylaxis with G-CSF

Rates of grade ≥ 3 TEAEs and treatment-emergent SAEs were similar for both groups.
TEAEs leading to dose reduction or treatment discontinuation were lower with SG vs chemo

Data cutoff date: April 2, 2025. TEAEs were defined as any AEs that began or worsened on or after the first dose date of study drug up to 30 days after the last dose date of study drug or the initiation of subsequent anticancer therapy (including crossover treatment), whichever occurs first.
AE, adverse event; **chemo**, chemotherapy; **G-CSF**, granulocyte-colony stimulation factor; **SAE**, serious adverse event; **SG**, sacituzumab govitecan; **TEAE**, treatment-emergent adverse event.

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Patient-Reported Outcomes With Sacituzumab Govitecan vs Chemotherapy in Patients With Previously Untreated Advanced Triple-Negative Breast Cancer Who Are Not Candidates for PD-(L)1 Inhibitors in the Phase 3 ASCENT-03 Study

Kevin Punie[1], Sara M Tolaney[2], Sara A Hurvitz[3], Carlos Barrios[4], Andreas Schneeweiss[5], Joohyuk Sohn[6], Eriko Tokunaga[7], Adam Brufsky[8], Yeon Hee Park[9], Binghe Xu[10], Roberto Hegg[11], Mafalda Oliveira[12], Alessandra Fabi[13], Yuanhui Zhang[14], Hao Wang[14], Yutian Mu[15], Rosemary Delaney[14], Javier Cortés[16-20]

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Wednesday, December 10, 2025, 1:32–1:40 pm - RF6-05

Patient-Reported Outcomes (EORTC QLQ-C30)

Key secondary end points

- Change from baseline in physical functioning at week 25
- Time to first deterioration[a] in fatigue

Exploratory end points

- Change from baseline at week 25 (excluding physical functioning)
- Time to first deterioration (excluding fatigue)[a]
- Time to confirmed deterioration[b]
- Time to first improvement[c]

PRO Assessment Schedule for EORTC QLQ-C30 (All Randomized Patients)

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

Baseline score

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

[a]TTD is defined as the time between randomization and the assessment at which a participant first experienced a worsening exceeding prespecified MWPC from baseline or death. [b]TTCD is defined as meaningful deterioration from baseline confirmed by a next scheduled visit or followed by missing PRO visit or death < 56 days after last PRO assessment or death < 56 days after randomization if baseline/post-baseline assessments were missing. [c]TTI is defined as the time between randomization and the assessment at which a participant first experienced an improvement exceeding prespecified MWPC from baseline. **Chemo**, chemotherapy; **EORTC QLQ-C30**, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; **MWPC**, meaningful within patient change; **PRO**, patient-reported outcome; **SG**, sacituzumab govitecan; **TTCD**, time to confirmed deterioration; **TTD**, time to first deterioration; **TTI**, time to first improvement.

Mean Change From Baseline to Week 25 in Physical Functioning Favored SG vs Chemotherapy

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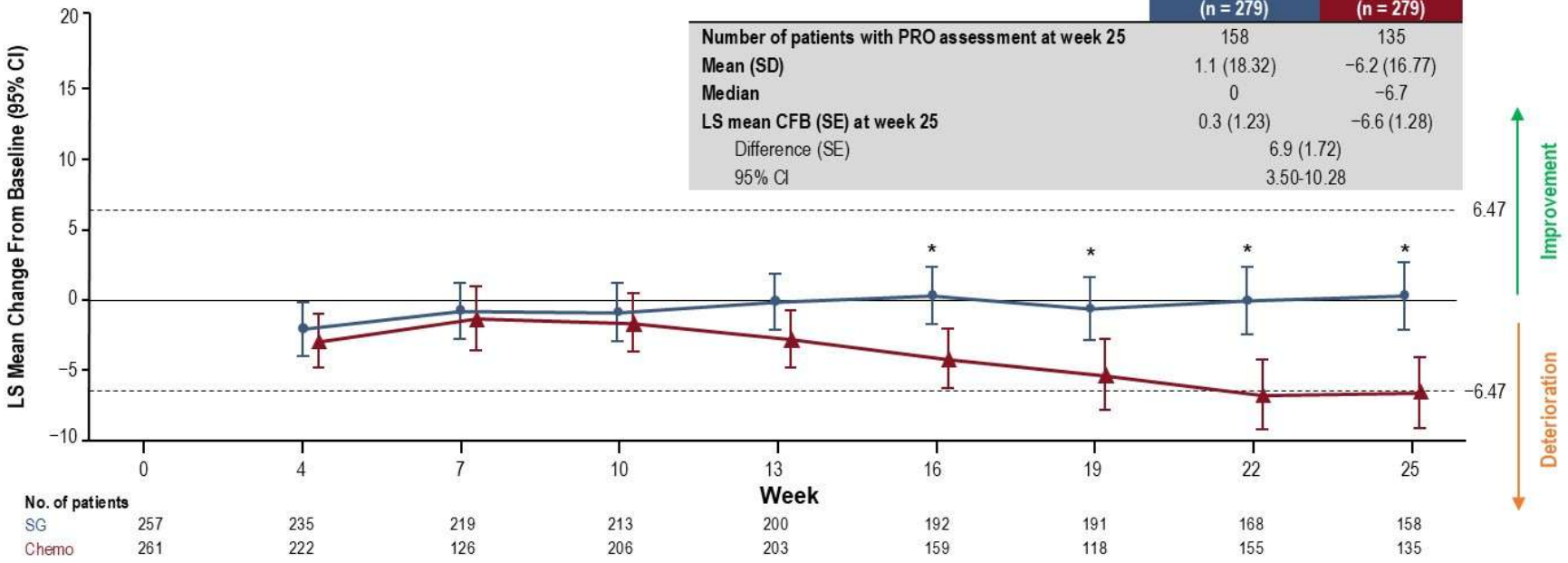
Physical functioning scores were maintained in the SG group; a gradual worsening was observed in the chemotherapy group over time

	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	



No. of patients									
SG	257	235	219	213	200	192	191	168	158
Chemo	261	222	126	206	203	159	118	155	135

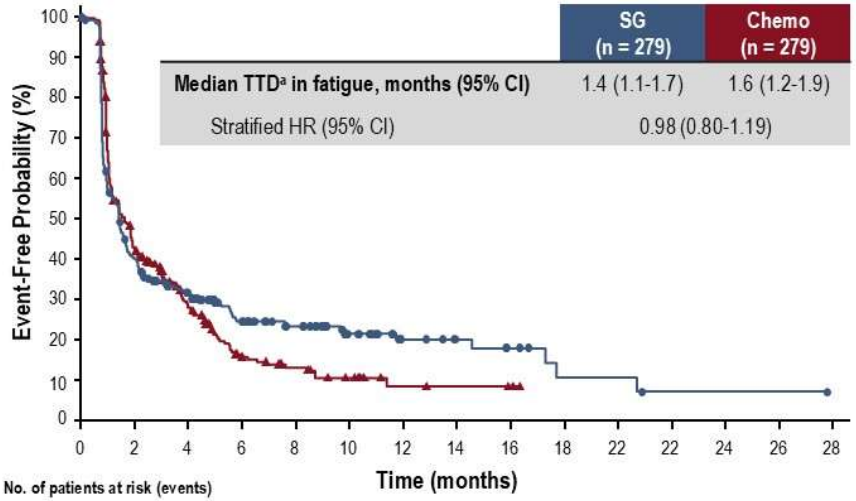
Comparison between treatment arms was analyzed using a mixed-effect model for repeated measure for CFB; an asterisk denote a nominal 2-sided *P*-value < 0.05. MID was defined as 0.3 × SD and corresponded to a change of ±6.47.
CFB, change from baseline; **chemo**, chemotherapy; **CI**, confidence interval; **LS**, least-squares; **MID**, minimum important difference; **MWPC**, meaningful within patient change; **PRO**, patient-reported outcome; **SD**, standard deviation; **SE**, standard error; **SG**, sacituzumab govitecan.

Time to Deterioration in Fatigue Was Similar Between SG and Chemotherapy

Similar results were observed between treatment groups and were consistent over 2 consecutive visits

Key Secondary End Point - TTD

	SG (n = 279)	Chemo (n = 279)
Median TTD[a] in fatigue, months (95% CI)	1.4 (1.1-1.7)	1.6 (1.2-1.9)
Stratified HR (95% CI)	0.98 (0.80-1.19)	

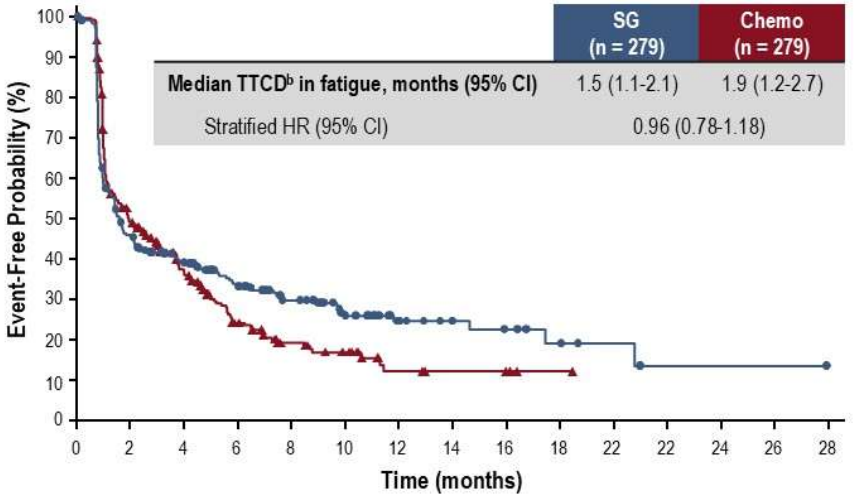


No. of patients at risk (events)

SG	279 (0)	101 (154)	72 (175)	47 (189)	35 (191)	22 (193)	12 (194)	9 (194)	7 (195)	3 (197)	3 (197)	1 (198)	1 (198)	1 (198)	0 (198)
Chemo	279 (0)	104 (144)	60 (175)	26 (200)	17 (204)	10 (207)	4 (208)	3 (208)	2 (208)	0 (208)					

Exploratory End Point - TTCD

	SG (n = 279)	Chemo (n = 279)
Median TTCD[b] in fatigue, months (95% CI)	1.5 (1.1-2.1)	1.9 (1.2-2.7)
Stratified HR (95% CI)	0.96 (0.78-1.18)	



	279 (0)	112 (134)	86 (159)	63 (171)	45 (177)	27 (182)	16 (183)	11 (183)	8 (184)	5 (185)	3 (185)	1 (186)	1 (186)	1 (186)	0 (186)
	279 (0)	116 (131)	75 (159)	39 (184)	23 (192)	15 (195)	6 (198)	4 (198)	3 (198)	1 (198)	0 (198)				

Comparison between treatment arms was analyzed using the stratified Cox regression model. [a]TTD is defined as the time between randomization and the assessment at which a participant first experienced a worsening exceeding prespecified MWPC of ≥10 points from baseline or death. [b]TTCD is defined as meaningful deterioration from baseline confirmed by a next scheduled visit or followed by missing PRO visit or death < 56 days after last PRO assessment or death < 56 days after randomization if baseline/post-baseline assessments were missing. **Chemo**, chemotherapy; **CI**, confidence interval; **HR**, hazard ratio; **MWPC**, meaningful within patient change; **PRO**, patient-reported outcome; **SG**, sacituzumab govitecan; **TTCD**, time to confirmed deterioration; **TTD**, time to first deterioration.

Concluding thoughts

- Progress has been made in triple-negative breast cancer over the last decade
  - Survival after relapse remains far shorter compared to other breast cancer subtypes
- **We will likely see TROP2 ADCs approved in the 1st line setting in metastatic TNBC in 2026, though impact on overall survival is unclear at this time**
  - Datopotomab deruxtecan monotherapy for PD-1 ineligible patients
  - Sacituzumab govitecan monotherapy for PD-1 ineligible patients
  - Sacituzumab govitecan and pembrolizumab for PD-1 eligible patients
- **Clinical development of novel therapeutics in metastatic TNBC remains a top priority**

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