CLINICAL UPDATE · 2025–2026

Antibody-Drug Conjugates in Breast Cancer

What's practice-changing now

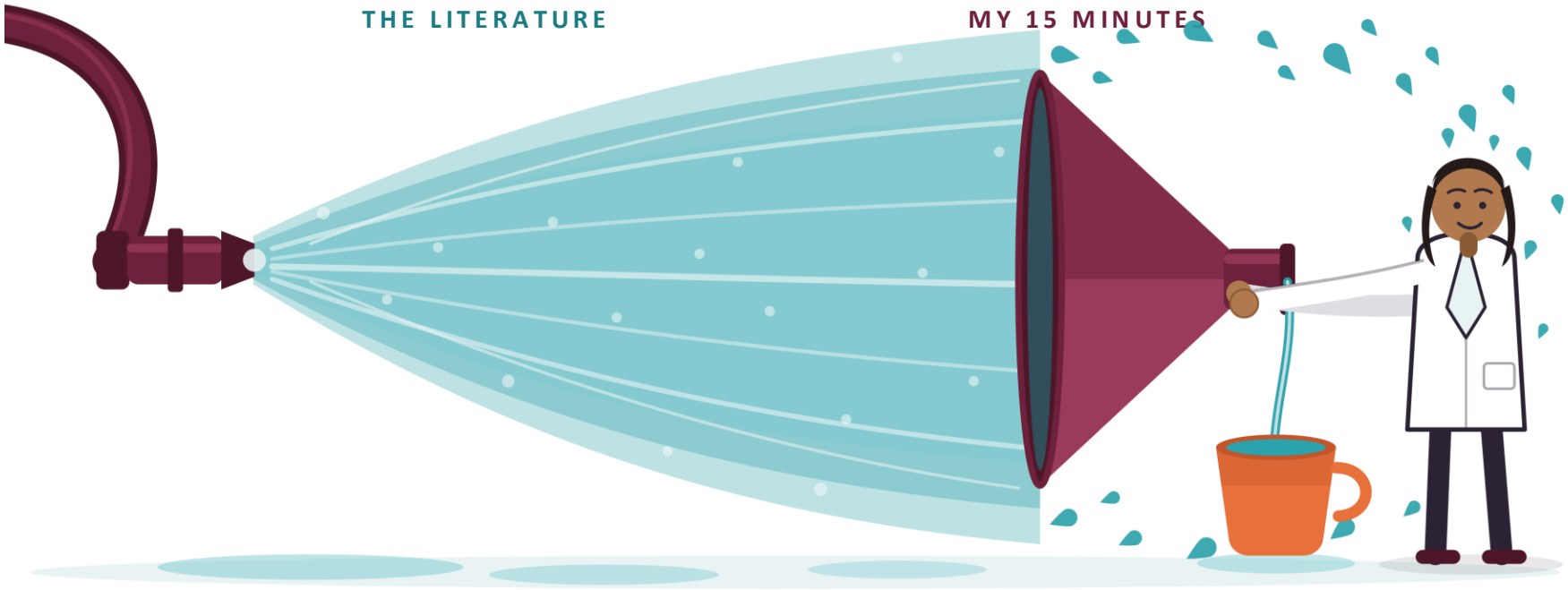
T-DXd · Sacituzumab govitecan · Datopotamab deruxtecan · emerging agents

BEFORE WE DIVE IN

ADCs in breast cancer. In 15 minutes.

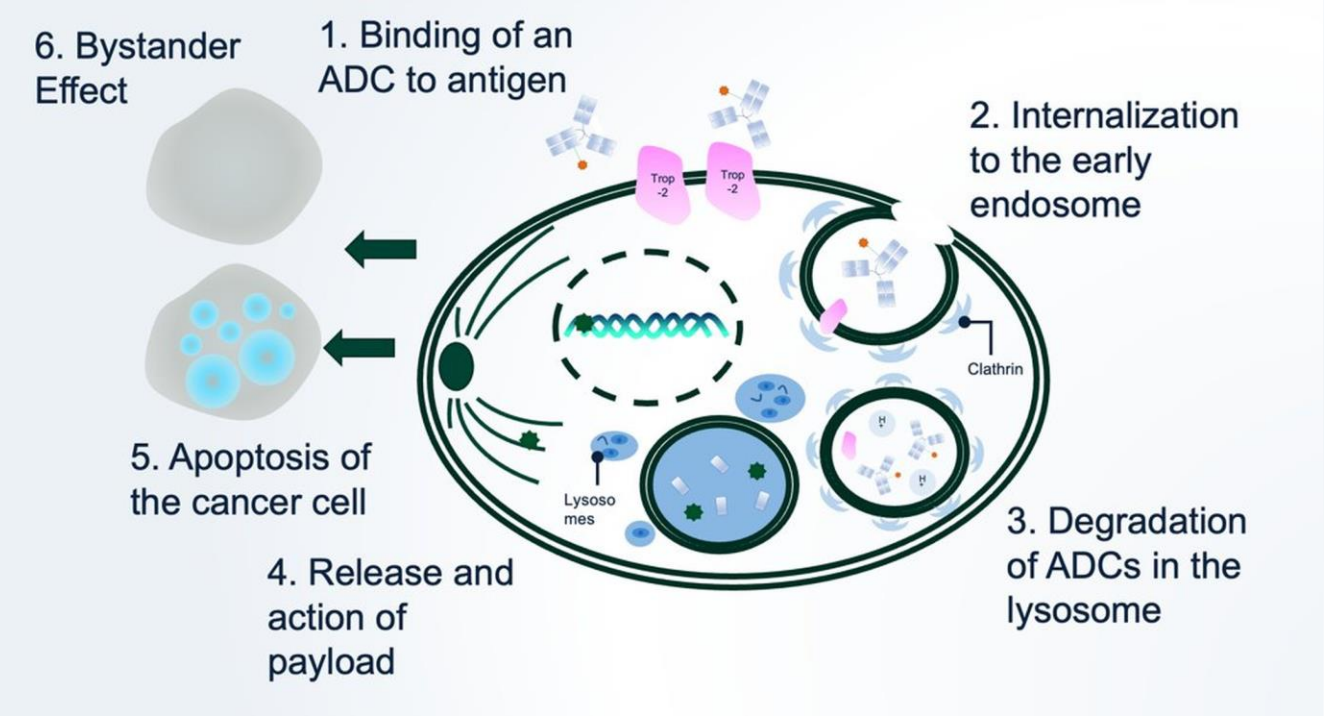
"Aim the funnel — sip only what changes practice."

A year of practice-changing data across three ADCs and a dozen-plus trials —



ADCs: What's the Hype?

Targeted delivery decouples potency from toxicity — the appeal driving ADCs from late-line salvage to front-line, curative-intent care.



Nagayama A, et al. Target Oncol. 2017;12(6):719-739.

Precision over the tumor

Concentrates cytotoxic drug where the antigen lives, sparing normal tissue.

Bystander effect

Membrane-permeable payload diffuses to neighbors — low or heterogeneous antigen still responds.

Wider therapeutic window

Meaningful efficacy at doses conventional chemotherapy could never tolerate.

Activity across subtypes

Spans HER2-positive, -low, -ultralow and TNBC — now moving into early-stage disease.

Three ADCs now anchor the landscape

T-DXd

trastuzumab deruxtecan

TARGET: HER2

Where it lives

HER2+: metastatic breast cancer (front-line and pre-treated) and now early-stage breast cancer

,

Pretreated HER2-low & HER2-ultralow metastatic breast cancer

SG

sacituzumab govitecan

TARGET: TROP-2

Where it lives

Metastatic TNBC (front-line and pre-treated)

Pretreated HR+/HER2-negative metastatic breast cancer

Dato-DXd

datopotamab deruxtecan

TARGET: TROP-2

Where it lives

Metastatic TNBC (front-line)

Pretreated HR+/HER2-negative metastatic breast cancer

Two payloads, two targets — but a shared theme: pushing earlier into the treatment course.

THE BIG PICTURE

Where ADCs sit across the disease course – 2026 snapshot

EARLY-STAGE

curative intent

HER2-positive, residual disease	DESTINY-Breast05
HER2-positive, high-risk locally advanced	DESTINY-Breast11
TNBC, residual after neoadjuvant	ASCENT-05 / TROPION-Breast03

METASTATIC

by subtype

HER2-positive	DESTINY-Breast09 / DESTINY-Breast03
HR+ / HER2-low & ultralow	DESTINY-Breast04 and 06 / TROPiCS-02 / TROPION-Breast01
Triple-negative	ASCENT-04 / ASCENT-03 / TROPION-Breast02 / DESTINY-Breast04

Early Stage HER2+ Breast Cancer

Ms. A

61 year old woman with no pmhx and a new diagnosis of right breast CA

Diagnostic MMG with US: 3.1cm spiculated mass in the upper outer quadrant of the right breast suspicious for malignancy, at least one abnormal appearing LN with cortical thickening

Right breast US guided breast biopsy: IDC, grade 3, ER 55%, PR 10%, HER2 3+

Axillary LN biopsy: +metastatic carcinoma

Staging scans: negative for distant metastatic disease

What would you recommend?

A. Neoadjuvant TCHP x 6 cycles
B. Neoadjuvant THP x 6 cycles
C. Neoadjuvant T-DXd x 4 cycles -> THP x 4 cycles
D. Adjuvant T-DXd x 14 cycles

DESTINY-Breast11 study design

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

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

Randomized 1:1:1

n=321 → **T-DXd* → THP†** 4 + 4 cycles

n=320 → **ddAC‡ → THP§** 4 + 4 cycles

n=286 → **T-DXd*** 8 cycles

→ **Surgery ¶**

Recommended post-neoadjuvant treatment per study protocol‖

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

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

HR-positive: endocrine therapy

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

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

Data cutoff: March 12, 2025

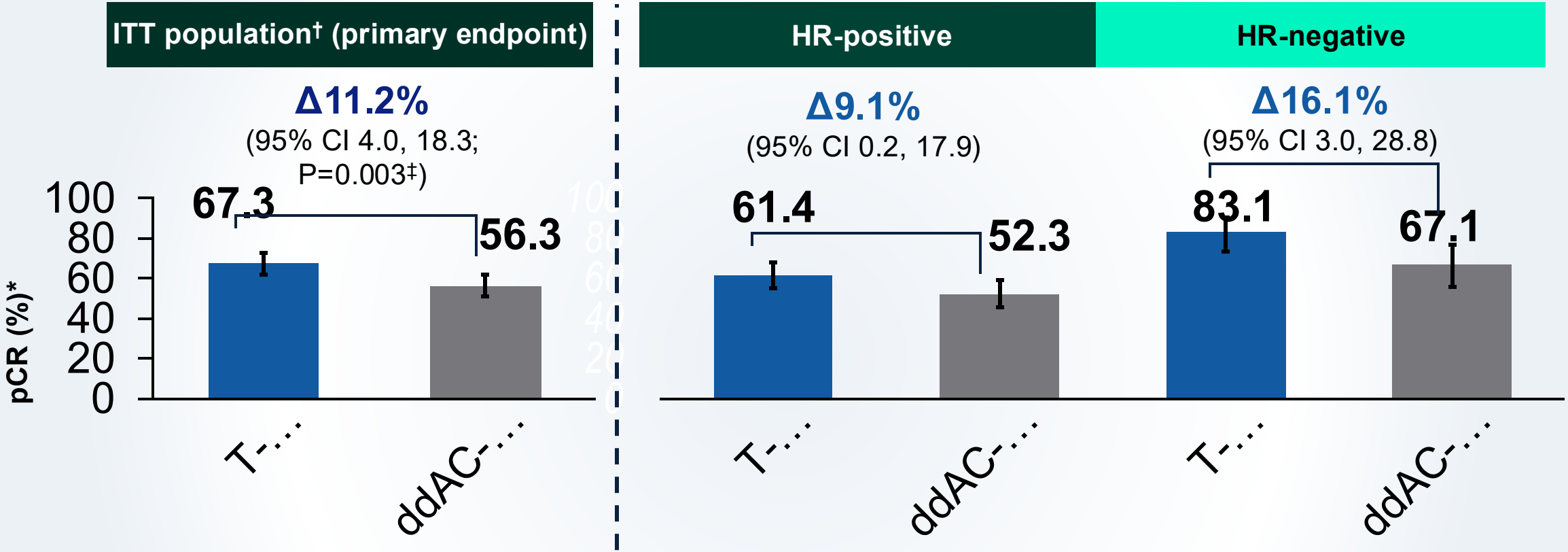
Primary endpoint
- pCR (ypT0/is ypN0) by blinded central review

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

Additional outcome measures
- Residual cancer burden (RCB)

Nadia Harbeck, MD

pCR (ypT0/is ypN0): primary endpoint



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

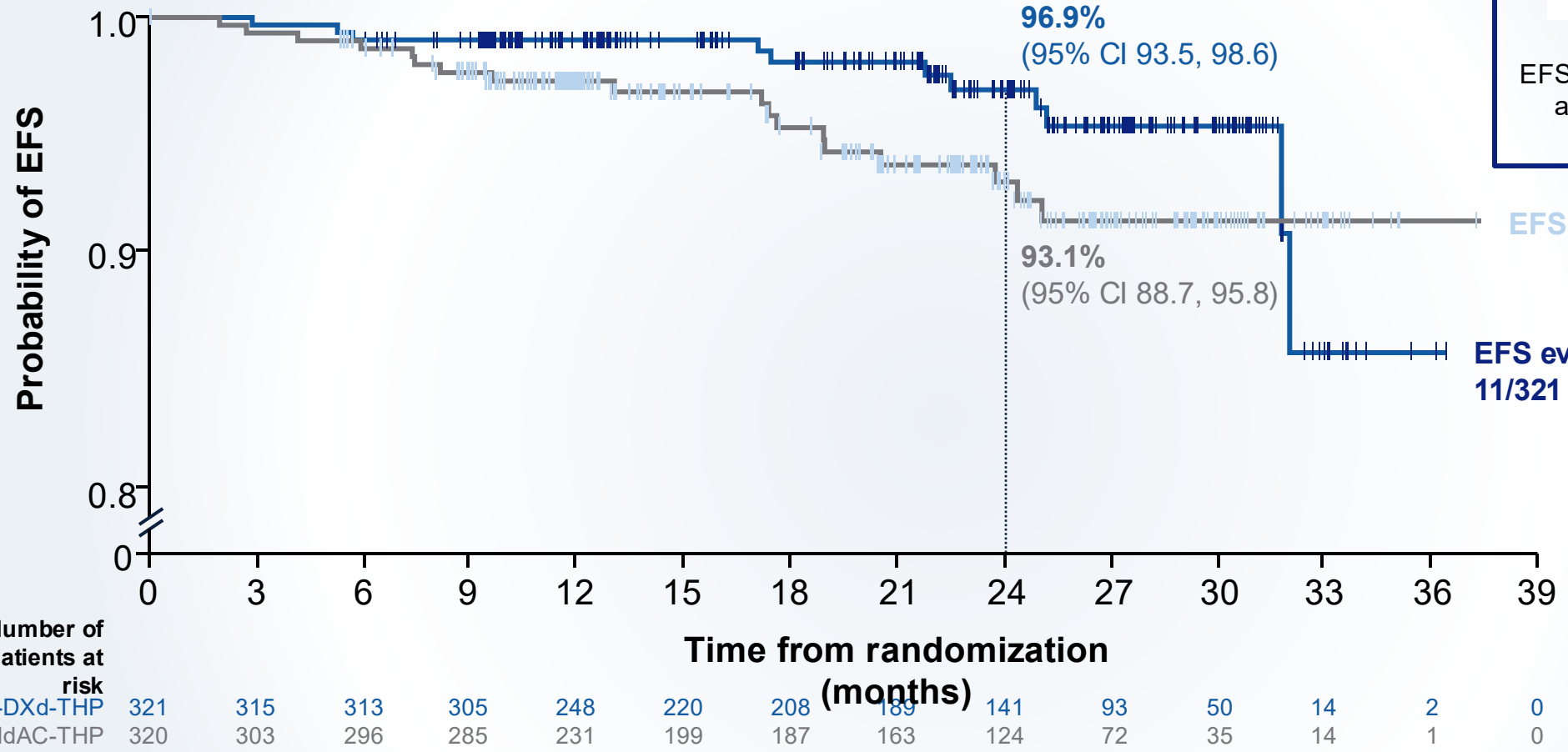
Improvement was observed in both the HR-positive and HR-negative subgroups

For the ITT population, treatment effects were estimated by the difference in pCR with 95% CIs and P-values based on the stratified Miettinen and Nurminen's method, with strata weighting by sample size (ie Mantel–Haenszel weights)

Patients with no valid records regarding pCR status for any reason were considered to be non-responders (including but not limited to withdrawal from the study, progression of disease or death before surgery, lack of surgical specimen, or defined as not evaluable by the central pathologist). Subgroup analyses were unstratified. *By blinded central review; †pCR responders were defined as patients who only received randomized study treatment (at least one dose) and had pCR; ‡two-sided P-value crossed the 0.03 prespecified boundary. ITT, intent-to-treat

Nadia Harbeck, MD

EFS



Hazard ratio
0.56
(95% CI 0.26, 1.17)

2025),
EFS event maturity was 4.5%; at final cutoff, maturity is predicted to be ~10%*

Number of patients at risk														
T-DXd-THP	321	315	313	305	248	220	208	189	141	93	50	14	2	0
ddAC-THP	320	303	296	285	231	199	187	163	124	72	35	14	1	0

An early positive trend in EFS was observed, favoring T-DXd-THP vs ddAC-THP

The median duration of follow up was 24.3 months with T-DXd-THP and 23.6 months with ddAC-THP. *Predicted maturity assumes that the observed EFS hazard ratio continues after data cutoff (March 12, 2025)

Overall safety summary

n (%)	T-DXd-THP (n=320)*	ddAC-THP (n=312)*
Any AE	314 (98.1)	308 (98.7)
Grade ≥3	120 (37.5)	174 (55.8)
Any serious AE	34 (10.6)	63 (20.2)
AE leading to any dose reduction	58 (18.1)	60 (19.2)
AE leading to any drug interruption	121 (37.8)	170 (54.5)
AE leading to any treatment discontinuation	45 (14.1)	31 (9.9)
Any AE with outcome of death†	2 (0.6)	2 (0.6)
AE of special interest		
Drug-related adjudicated ILD/pneumonitis	14 (4.4)	16 (5.1)
Grade ≥3	2 (0.6)	6 (1.9)
Grade 5	1 (0.3)	1 (0.3)
Left ventricular dysfunction	4 (1.3)	19 (6.1)

The overall safety profile of T-DXd-THP was favorable vs ddAC-THP, with reduced rates of Grade ≥3 AEs, serious AEs, treatment interruptions, and left ventricular dysfunction

ILD incidence was low and similar in both arms

High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. Median total treatment duration of whole regimen was 24.1 months (T-DXd-THP), and 21.0 months (ddAC-THP). *Safety analyses included all patients who received at least one dose of any study treatment; †T-DXd-THP arm: death of unknown cause (n=1), drug-related pneumonitis adjudicated by the Independent ILD Adjudication Committee (n=1); ddAC-THP arm: investigator-determined drug-related bacterial encephalitis (n=1), drug-related pneumonitis adjudicated by the ILD Adjudication Committee (n=1); ‡defined as surgery not occurring within 3–6 weeks after the last cycle of neoadjuvant treatment

FDA Approval

May 15, 2026 – Approval of T-DXd -> THP for the neoadjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or III breast cancer.

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

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

Important considerations:

- **Not compared with TCHP in this trial**
  - NeoCARHP TCHP arm (pCR 58.8% in HR+ and 77.8% in HR-); cross-trial comparisons are difficult and fraught; and this trial was predominantly Chinese pts with >70% having stage 2 cancer

- Approved for **T2N0 patients, a group not included in the trial**

- The side effect conversation is slightly different: **ILD**, alopecia
  - Patients require **CT chest at baseline, 6 weeks, and 12 weeks**

Remaining questions

- Who may be consider TCHP or THP for? How does HR status affect decision-making?
- If patients are not ypN0 after DB-11, do we use DB-05?

What would you recommend?

A. Neoadjuvant TCHP x 6 cycles
B. Neoadjuvant THP x 6 cycles
C. **Neoadjuvant T-DXd x 4 cycles -> THP x 4 cycles**
D. Adjuvant T-DXd x 14 cycles

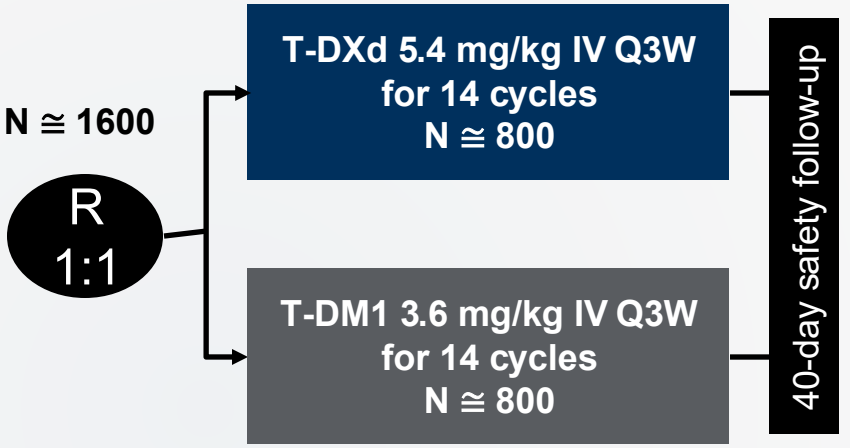
What happens if she does not achieve a pCR?

DESTINY-Breast05 study design

A global, multicenter, randomized, open-label, phase 3 trial (NCT04622319)

Key Eligibility Criteria

- **Residual invasive disease in the breast and/or axillary lymph nodes** after neoadjuvant chemotherapy with HER2-directed therapy (NAT)[a]
- **High-risk defined as presentation prior to NAT with:**
  - **Inoperable eBC (cT4,N0-3,**M0 **or cT1-3,N2-3**,M0**) OR**
  - **Operable eBC (cT1-3,N0-1**,M0**) with axillary node–positive disease (ypN1-3) after NAT**
- **Centrally confirmed HER2+** (IHC 3+ or ISH+) eBC
- ECOG PS 0 or 1



Primary endpoint
- IDFS

Key secondary endpoint
- DFS

Other secondary endpoints
- OS
- DRFI
- BMFI
- Safety

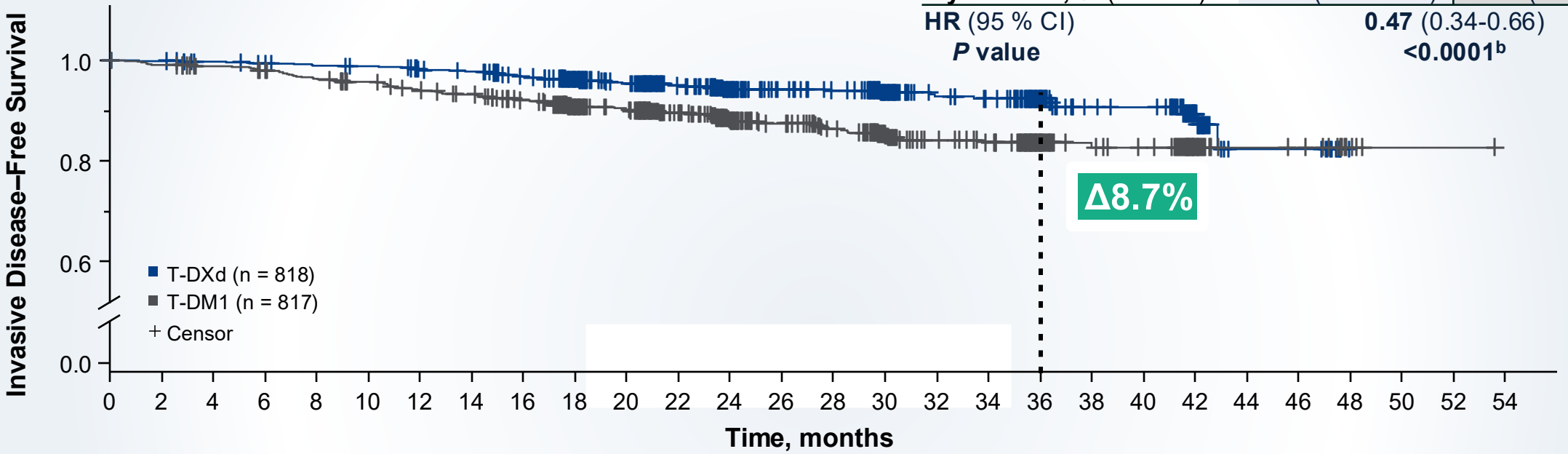
Stratification factors
- Extent of disease at presentation (inoperable, operable)
- HER2-targeted NAT (single, dual)
- Hormone receptor status (positive, negative)
- Post-NAT pathologic nodal status (positive, negative)

- **Concomitant adjuvant ET was allowed per local practices**
- **If administered, RT could be initiated concurrent with study therapy or completed prior to initiation of study therapy (sequential) per investigator**

BMFI, brain metastasis–free interval; CT, computed tomography; eBC, early breast cancer; DCO, data cutoff; DFS, disease-free survival; DRFI, distant recurrence–free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; NAT, neoadjuvant therapy; OS, overall survival; Q3W, every 3 weeks; R, randomization; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]NAT is defined as ≥16 weeks' NAT with ≥9 weeks trastuzumab ± pertuzumab and ≥9 weeks taxane-based chemotherapy.

Primary endpoint: IDFS[a]

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



Number at Risk:

T-DXd	818	788	781	776	771	768	758	753	731	684	634	544	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0
T-DM1	817	781	769	760	745	734	719	708	687	632	599	527	417	355	337	233	186	177	120	84	79	38	14	13	4	1	1	0

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

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

Overall safety summary

TEAEs, n (%)	T-DXd n = 806[a]	T-DM1 n = 801[a]
Any grade	802 (99.5)	788 (98.4)
Grade ≥3	**408 (50.6)**	**416 (51.9)**
Serious	**140 (17.4)**	**109 (13.6)**
Associated with drug discontinuation	**144 (17.9)**	**103 (12.9)**
Drug-related ILD/pneumonitis[b]	**87 (10.8)**	**20 (2.5)**
Associated with drug interruptions	400 (49.6)	329 (41.1)
Associated with dose reductions	**213 (26.4)**	**213 (26.6)**
Associated with deaths	**3 (0.4)**	**5 (0.6)**

- **In the T-DXd arm, causes of death (n = 3) were 2 ILD/pneumonitis[c] and respiratory tract infection (adjudicated as not ILD)**
- **In the T-DM1 arm, causes of death (n = 5) were leiomyosarcoma of the uterus, aneurysm, non-neutropenic sepsis, ovarian cancer, and traumatic pneumothorax**

ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-related adverse event.
[a]All patients who received at least 1 dose of study treatment. [b]Investigator-assessed as drug-related ILD and pneumonitis per preferred term. [c]Investigator assessed and adjudication committee confirmed.

FDA Approval

May 15, 2026 – Approval of adjuvant T-DXd for patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following neoadjuvant treatment with trastuzumab (with or without pertuzumab) and taxane-based treatment.

53% reduction in the risk of invasive disease recurrence or death

3-year IDFS rate
92.4% versus 83.7%
HR 0.47
***P* value <0.0001**

Important considerations:

- **Proactive monitoring for ILD/pneumonitis**: low-dose, non-contrast chest CT scans at baseline, 6 weeks and then every 12 weeks
- **ILD monitoring program for patients treated with RT**
  - All patients had baseline non-contrast, low dose (LD) chest CT during screening
  - All RT patients (concurrent and sequential) had LD chest CT 6 weeks after start of study therapy, then every 12 weeks while on therapy, and at 40-day follow-up
  - Sequential RT patients had additional LD chest CT after completion of RT prior to start of study therapy

Remaining questions

- If patients are not ypN0 after DB-11, do we use DB-05?

Metastatic TNBC

Ms. B

56 year old woman with a new diagnosis of de-novo stage IV TNBC (ER/PR 0%, HER2 1+) with hepatic and osseous metastases

PMH/PSH: HTN

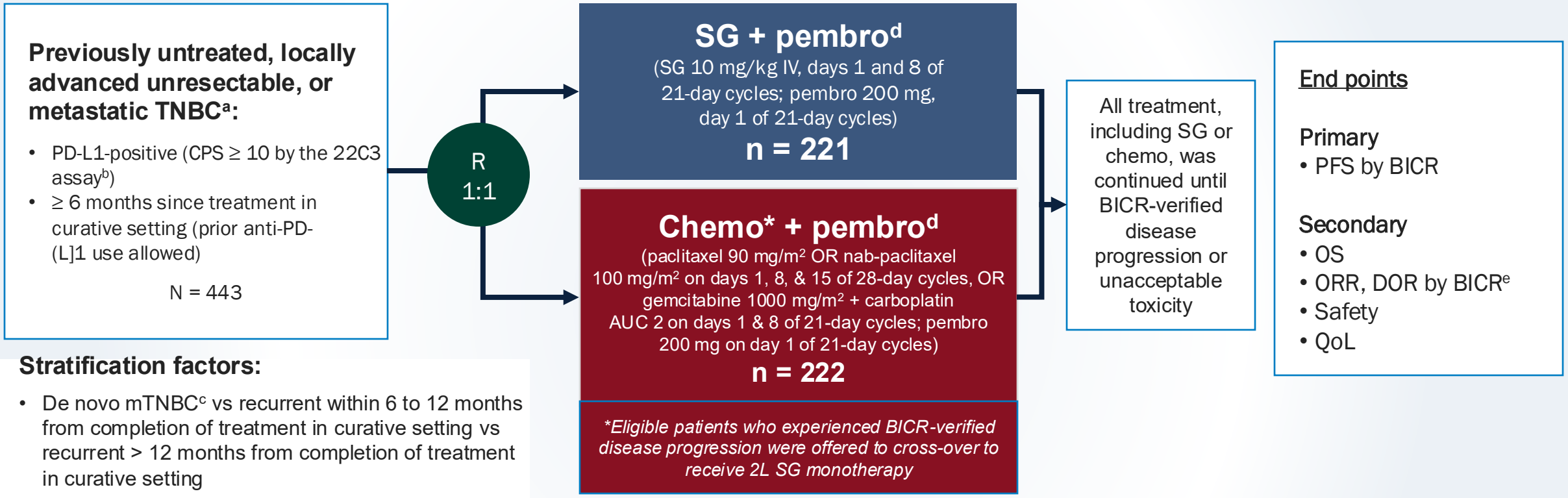
Genetic testing: negative

PD-L1: positive (CPS 12)

What would you recommend?

A. Pembrolizumab + paclitaxel
B. Carboplatin + gemcitabine
C. Sacituzumab govitecan
D. Pembrolizumab + sacituzumab govitecan
E. Datopotamab deruxtecan
F. Durvalumab + datopotamab deruxtecan

ASCENT-04: KEYNOTE-D19 Study Design

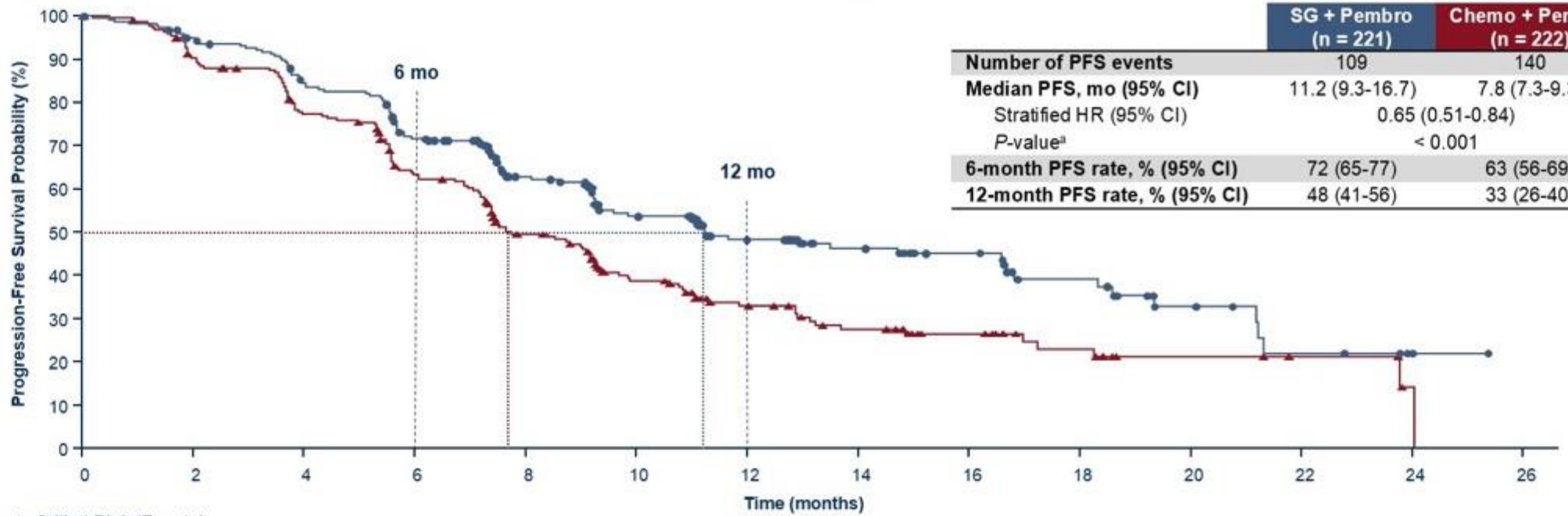


Stratification factors:

- De novo mTNBC[c] vs recurrent within 6 to 12 months from completion of treatment in curative setting vs recurrent > 12 months from completion of treatment in curative setting
- US/Canada/Western Europe vs the rest of the world
- Prior exposure to anti-PD-(L)1 (yes vs no)

ClinicalTrials.gov identifier: NCT05382296.
[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 Pembro was administered for a maximum of 35 cycles. •Per RECIST v1.1.
Tolaney SM, et al; ASCENT-04/KEYNOTE-D19 Clinical Trial Investigators. *N Engl J Med.* 2026;394(4):354-366.

ASCENT-04: 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)

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)

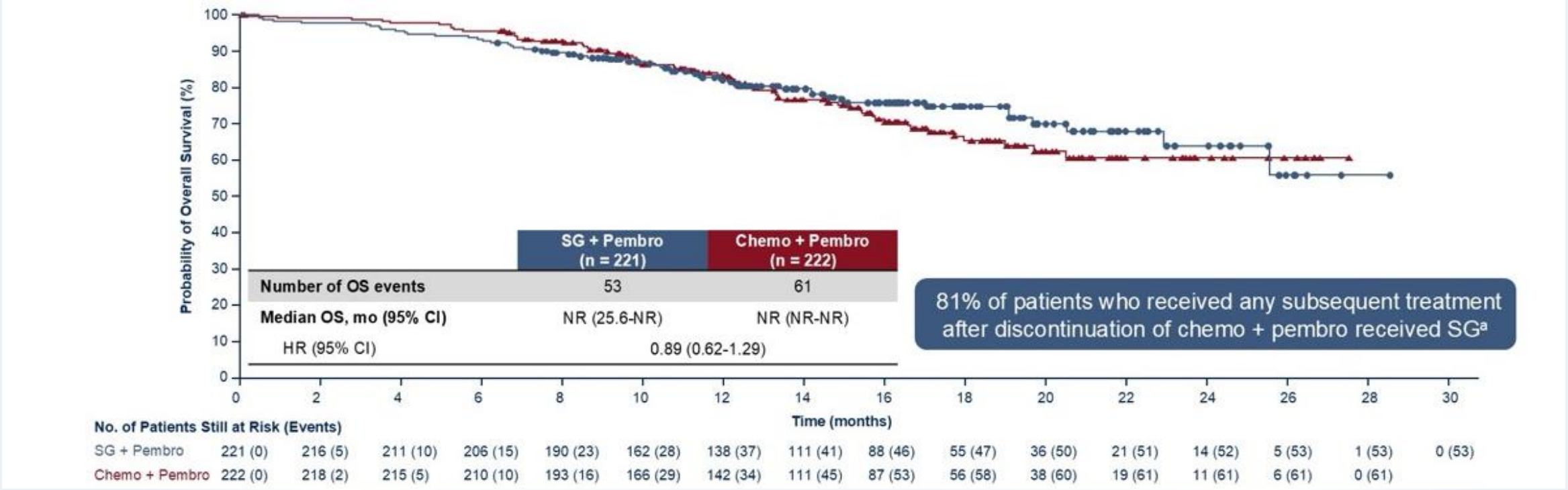
SG + pembro demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo + pembro by BICR analysis, with a 35% reduction in risk of disease progression or death

PFS2 benefit was also seen with frontline SG + pembrolizumab

Data cutott date: March 3. 20251
"Two sided P-value from stratified log-rank test.

Tolaney SM, et al; ASCENT-04/KEYNOTE-D19 Clinical Trial Investigators. *N Engl J Med*. 2026;394(4):354-366.

ASCENT-04: Descriptive Overall Survival at Primary Analysis



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),
*Or the 96 patients who received so monotherapy as subsequent anticancer therapy. 77 received it as part of the protocol-specified crossover after meeting ali crossover eligibility cateria, including BTCR-ventication of disease progression, the remaining 19 patients received subsequent SG monotherapy as commercial supply.

Tolaney SM, et al; ASCENT-04/KEYNOTE-D19 Clinical Trial Investigators. *N Engl J Med.* 2026;394(4):354-366.

ASCENT-04: Adverse Events of Special Interest

	AESI,[a] n (%)	SG + Pembro (n = 221)		Chemo + Pembro (n = 220)	
		Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
SG AESIs	Neutropenia[b]	143 (65)	104 (47)	132 (60)	100 (45)
	Hypersensitivity[b]	43 (19)	4 (2)	51 (23)	5 (2)
	Serious infections secondary to neutropenia[b]	6 (3)	5 (2)	3 (1)	3 (1)
	Diarrhea (Grade 3 or higher)	N/A	22 (10)	N/A	5 (2)
Pembro AESIs	Overall	30 (14)	9 (4)	56 (26)	16 (7)
	Infusion reactions (not immune-mediated)[a]	11 (5)	3 (1)	19 (9)	5 (2)
	Pneumonitis[b]	5 (2)	3 (1)	10 (5)	2 (1)
	Colitis[b]	4 (2)	1 (< 1)	1 (< 1)	1 (< 1)
	Hypothyroidism[b]	4 (2)	0	19 (9)	0
	Hypophysitis[b]	2 (1)	0	2 (1)	0
	Hyperthyroidism[b]	2 (1)	0	5 (2)	0
	Severe skin reactions,[b] including Stevens-Johnson syndrome and toxic epidermal necrolysis	2 (1)	2 (1)	2 (1)	2 (1)
	Hepatitis[b]	1 (< 1)	0	2 (1)	2 (1)
	Adrenal insufficiency[b]	1 (< 1)	0	2 (1)	1 (< 1)
	Pancreatitis[b]	0	0	2 (1)	2 (1)

AESIs were consistent with the known safety profiles of each agent; no new safety concerns were observed and no increased rates of AESIs were observed when combining SG with pembro

AESIs were adverse events determined based on a prespecified list of Medcal Dictionary for Regulatory Activities (MedDRA) terms, which was updated with each new version of MeDRA, Immune mediated adverse events were determined based on a prespecified list of Medica
Dictionary for Regulatory Activities (MedDRA) terms, which was updated with each new version of MedDRA and specified as immune-mediated by the investigator. Data cutoff date: March 3, 2025
'AESIs observed in ≥1% of patients in either group are presented. "Grouped term.

Tolaney SM, et al; ASCENT-04/KEYNOTE-D19 Clinical Trial Investigators. *N Engl J Med.* 2026;394(4):354-366.

What would you recommend?

A. Pembrolizumab + paclitaxel
B. Carboplatin + gemcitabine
C. Sacituzumab govitecan
D. **Pembrolizumab + sacituzumab govitecan**
E. Datopotamab deruxtecan
F. Durvalumab + datopotamab deruxtecan

Ms. B

56 year old woman with a new diagnosis of de-novo stage IV TNBC (ER/PR 0%, HER2 1+) with hepatic and osseous metastases

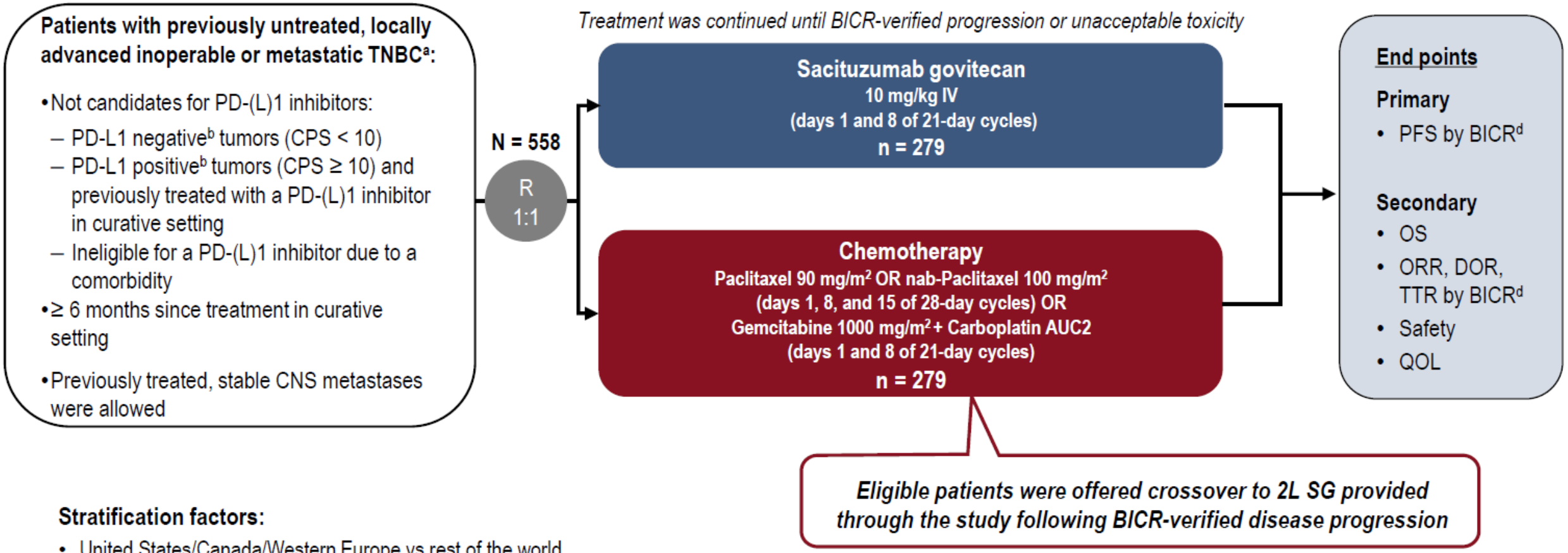
PMH/PSH: HTN

Genetic testing: negative

PD-L1: negative (CPS 0)

ASCENT-03: Sacituzumab Govitecan vs TPS in 1L mTNBC

not expressing PD-L1 or previously treated in the curative setting



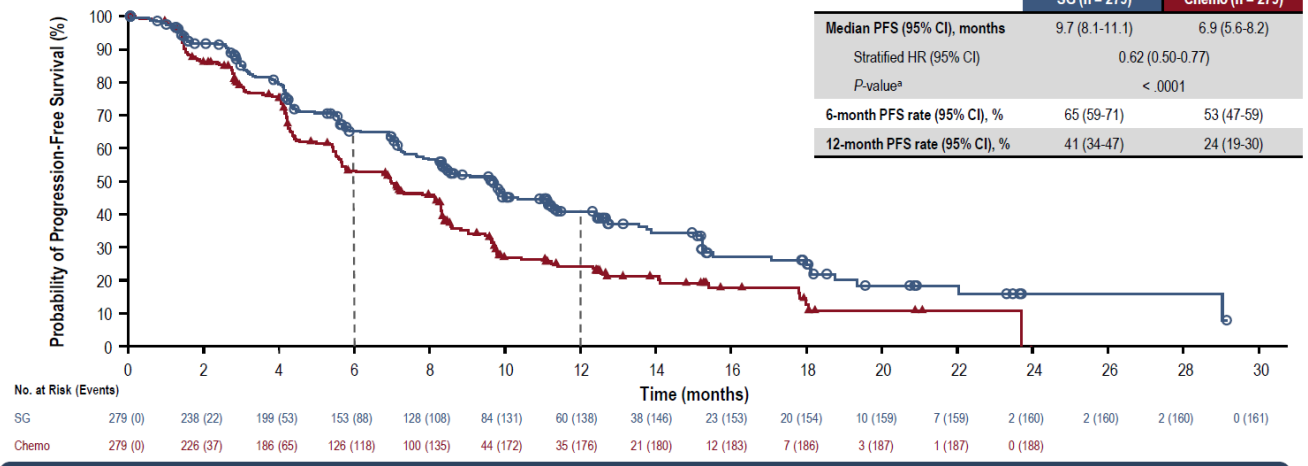
Stratification factors:

- 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

Cortes, J. ESMO 2025

ASCENT-03: Progression-Free & Overall Survival

Progression-Free Survival (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)

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

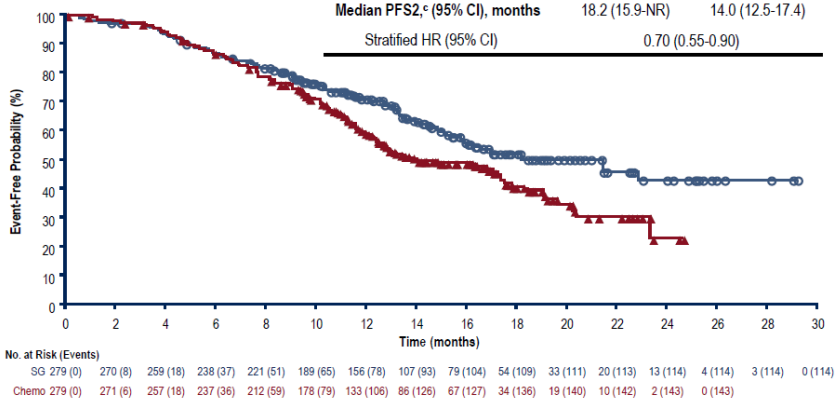
Overall Survival & PFS2

- **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 24-month	 75 (70-80) 46 (36-56)	 73 (67-78) 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

TROPION-Breast02: Dato-DXd vs TPC in 1L mTNBC

not eligible for anti-PD(L)1 therapy

Key inclusion criteria:

- Patients with histologically or cytologically documented locally recurrent inoperable or metastatic TNBC*
- No prior chemotherapy or targeted systemic therapy in the locally recurrent inoperable or metastatic setting
- Immunotherapy not an option†
- ECOG PS 0 or 1
- No minimum DFI‡

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=323)

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

Endpoints

Dual primary:

- OS
- PFS by BICR per RECIST v1.1

Secondary included:

- PFS (investigator-assessed)
- ORR, DoR
- Safety

Randomisation stratified by:

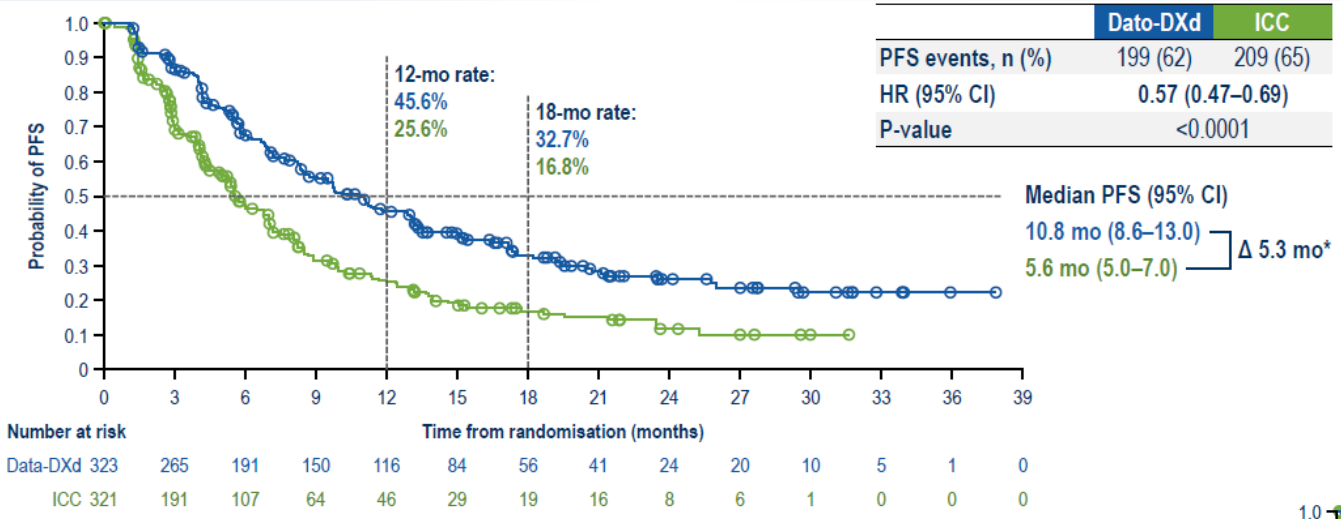
- Geographic region (US/Canada/Europe vs other geographic regions)
- PD-L1 status (high [CPS ≥10] vs low [CPS <10])§
- DFI history (*de novo* vs prior DFI 0–12 months vs prior DFI >12 months)¶

- 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‖

Dent, R. ESMO 2025.

TROPION-Breast02: Progression-Free & Overall Survival

Progression-Free Survival (BICR)

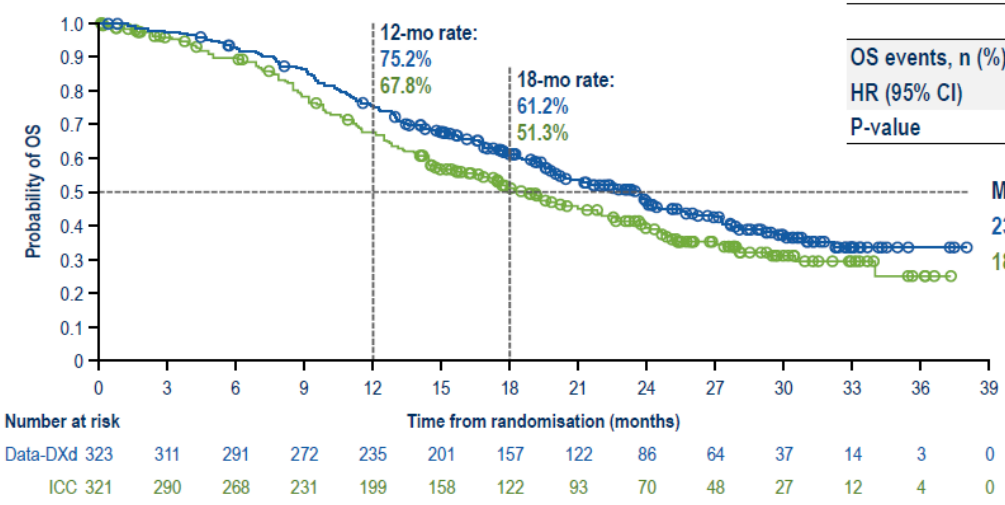


	Dato-DXd	ICC
PFS events, n (%)	199 (62)	209 (65)
HR (95% CI)	0.57 (0.47–0.69)	
P-value	<0.0001	

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%

Overall Survival



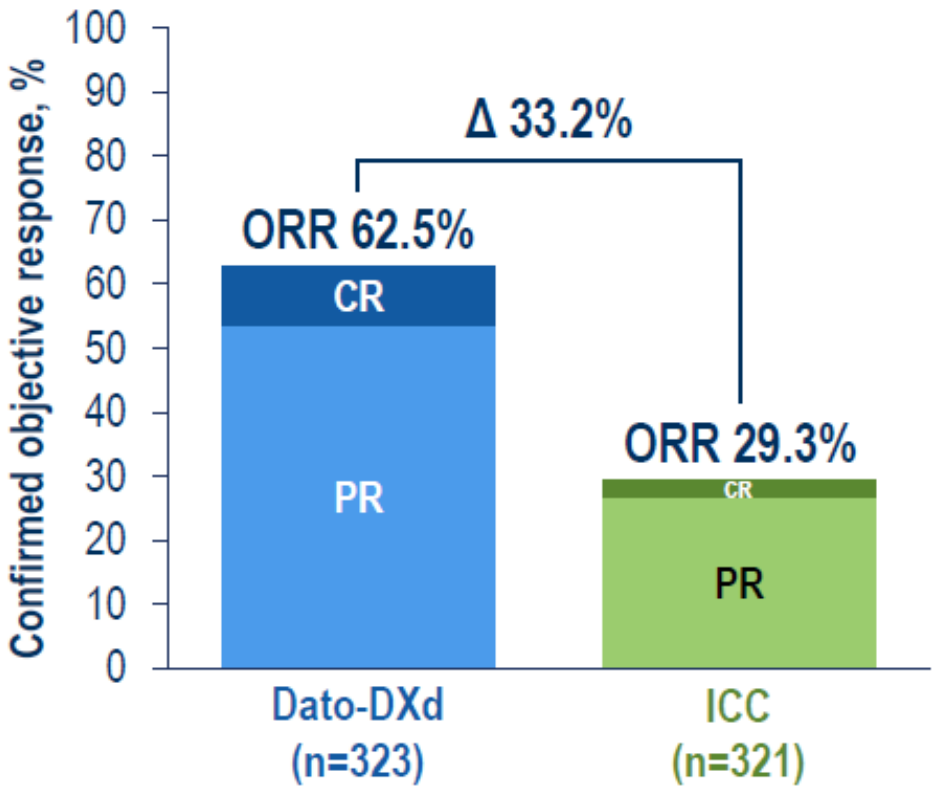
	Dato-DXd	ICC
OS events, n (%)	168 (52)	181 (56)
HR (95% CI)	0.79 (0.64–0.98)	
P-value	0.0291	

Median OS (95% CI)
23.7 mo (19.8–25.6)
18.7 mo (16.0–21.8)
Δ 5.0 mo

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

Dent, R. ESMO 2025.

TROPION-Breast02: 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

TROPION-Breast02: TRAEs for Dato-DXd

AESI category, n (%) Preferred term*	Dato-DXd (n=319)			ICC (n=309)		
	Grade 1	Grade 2	Grade ≥3	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis†	78 (24)	87 (27)	27 (8)	22 (7)	8 (3)	0
Stomatitis	72 (23)	83 (26)	27 (8)	19 (6)	8 (3)	0
Ocular surface events‡§	76 (24)	50 (16)	23 (7)	9 (3)	5 (2)	1 (<1)
Dry eye	51 (16)	21 (7)	4 (1)	6 (2)	3 (1)	0
Keratitis	21 (7)	14 (4)	7 (2)	1 (<1)	0	0
Conjunctivitis	7 (2)	13 (4)	1 (<1)	0	0	0
Adjudicated drug-related ILD/pneumonitis¶	1 (<1)	7 (2)	1 (<1)#	1 (<1)	1 (<1)	0

Treatment-related oral mucositis/stomatitis:

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

Treatment-related ocular surface events:

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

*Details for preferred terms included if reported in ≥20 patients in either arm. †Comprising the preferred terms of aphthous ulcer, mouth ulceration, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis. ‡Comprising the preferred terms of acquired corneal dystrophy, blepharitis, conjunctivitis, corneal disorder, corneal epithelium defect, corneal erosion, corneal exfoliation, corneal lesion, corneal toxicity, dellen, dry eye, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, meibomian gland dysfunction, photophobia, punctate keratitis, ulcerative keratitis, vision blurred, visual acuity reduced, visual impairment, and xerophthalmia. §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. ¶Comprising the preferred terms of interstitial lung disease and pneumonitis. #Grade 5 – this event was characterised by the investigator as grade 3 pneumonitis, with death assessed as related to breast cancer.

Dent R, et al ESMO 2025. Abstract LBA21.

What would you recommend?

A. Pembrolizumab + paclitaxel
B. Carboplatin + gemcitabine
C. Sacituzumab govitecan
D. Pembrolizumab + sacituzumab govitecan
E. Datopotamab deruxtecan
F. Durvalumab + datopotamab deruxtecan

NCCN GUIDELINES – Stage IV TNBC

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

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
See BINV-Q 1 of 15 for Considerations for systemic therapy.		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10[i] regardless of germline *BRCA1/2* PV status[b]	• Chemotherapy (Albumin-bound Paclitaxel, Carboplatin/Gemcitabine, or Paclitaxel) + Pembrolizumab[j] (category 1, preferred) • Sacituzumab govitecan-hziy[k] + Pembrolizumab[j] (category 1, preferred)
	PD-L1 CPS <10[i] or not candidate for PD-1/PD-L1 inhibitor therapy and no germline *BRCA1/2* PV[b]	• Sacituzumab govitecan-hziy[k,l] (category 1, preferred) • Datopotamab deruxtecan-dlnk (category 1, preferred) • Systemic chemotherapy BINV-Q 5 of 15
	PD-L1 CPS <10[i] and germline *BRCA1/2* PV[b]	• PARPi (Olaparib or Talazoparib) (category 1, preferred) • Platinum (Carboplatin or Cisplatin) (category 1, preferred)
Second Line	Germline *BRCA1/2* PV[b]	PARPi (category 1, preferred)
	Any	Sacituzumab govitecan-hziy[k,l] (category 1, preferred)
		Systemic chemotherapy BINV-Q 5 of 15 or targeted agents BINV-Q 7 of 15
	No germline *BRCA1/2* PV[b] and HER2 (*ERBB2*) IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[m] (other recommended)
Third Line and Beyond	Biomarker positive (ie, MSI-H, *NTRK1/2/3* and *RET* gene fusions, TMB-H)	Targeted agents and emerging biomarker options BINV-Q 7 of 15 and BINV-Q 8 of 15
	Any	Systemic chemotherapy BINV-Q 5 of 15

A working map for sequencing

HER2-positive

- Early-stage: adjuvant (DB-05) & neoadjuvant (DB-11) roles emerging
- 1L metastatic: T-DXd–based regimens challenging THP (DB-09)
- Established later-line benefit unchanged (DB-03)

HR+ / HER2-low / ultralow

- Metastatic:
- Post-endocrine, pre-chemo: T-DXd (DB-06)
- Post-endocrine, post-chemo: T-DXd (DB-04)
- Later line: SG (TROPiCS-02 OS) and Dato-DXd (TB-01)

Triple-negative

- 1L, PD-L1+: SG + pembrolizumab (ASCENT-04)
- 1L, IO-ineligible: Dato-DXd (TB-02) or SG (ASCENT-03)
- Later line: SG if not used previously; T-DXd if HER2 low (DB-04)

What's not yet answered

The data are moving fast, but several practice-level questions remain open.

Which ADC after another?	ADC-to-ADC sequencing and optimal order rest largely on retrospective data — prospective guidance is limited.
Do shared payloads drive cross-resistance?	Most approved ADCs carry topoisomerase-I payloads; resistance mechanisms still in question
How much does PFS-without-OS matter?	Weighing agents like Dato-DXd in HR+ disease, where PFS improves but overall survival is neutral or immature.
How long — and can we re-treat?	Optimal treatment duration, planned breaks, and ADC re-challenge after progression are undefined.

ON THE HORIZON

Where the field is heading

New targets & payloads

HER3 (patritumab deruxtecan), B7-H3, etc. and bispecific or dual-payload ADCs aim to broaden the addressable biology beyond HER2 and Trop-2.

Earlier-line & curative intent

Trials are pushing ADCs into adjuvant and neoadjuvant settings and testing de-escalation — reshaping early-stage treatment.

Combinations

ADCs paired with immunotherapy, endocrine agents, or targeted therapy — moving deeper into curative-intent settings.

Biomarkers beyond IHC

Quantitative and spatial HER2 assays plus Trop-2 expression metrics may refine selection as the low/ultralow boundary blurs.