Southeastern Multidisciplinary Approaches to Cancer Symposium

Early Stage HER2+ Breast Cancer

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Disclosures

I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

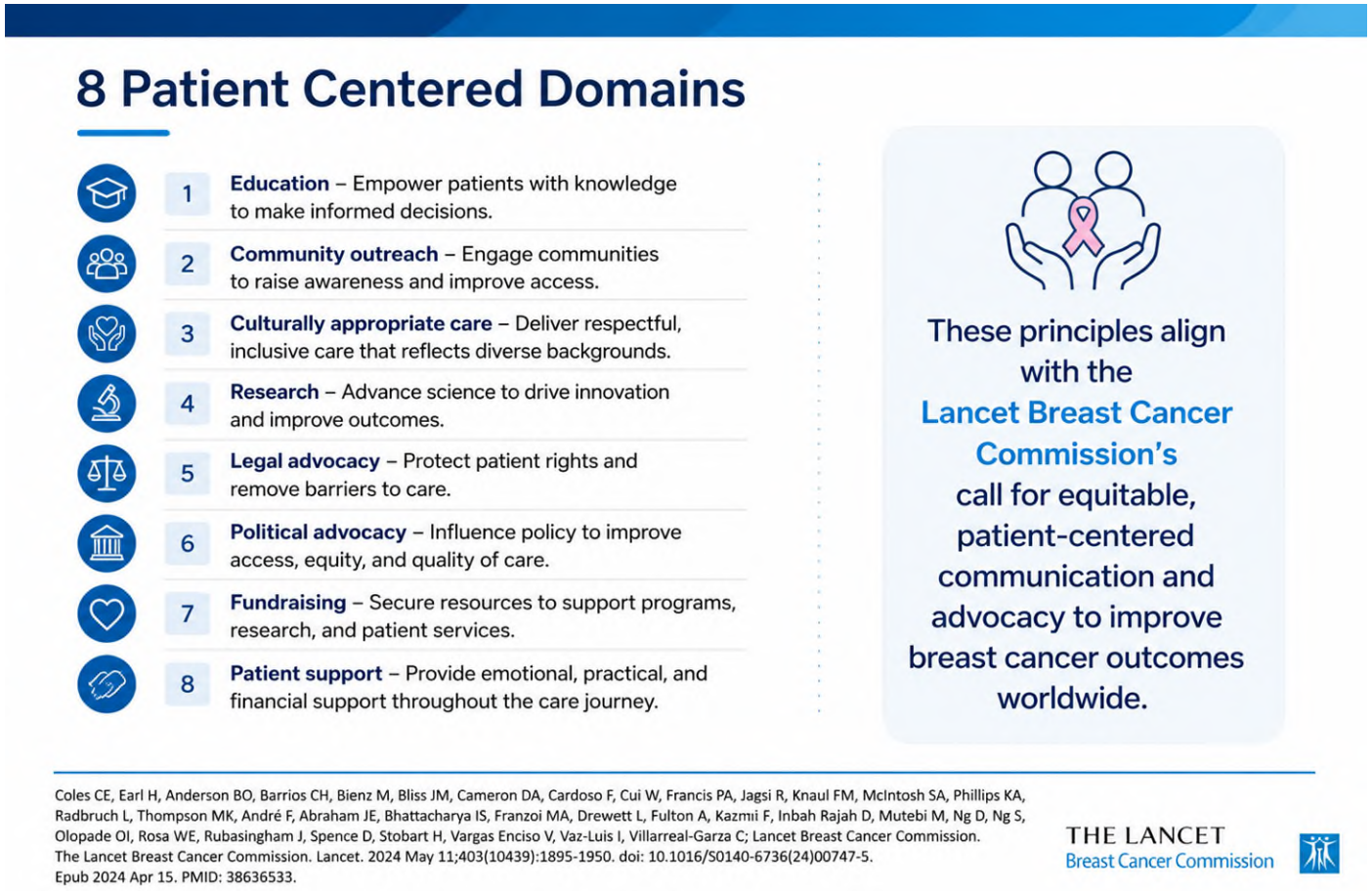
The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- Recognition of cultural, linguistic, and socioeconomic factors that influence understanding of HER2-directed treatment options and clinical trial participation.
- Shared decision-making that incorporates each patient's goals, values, health literacy, and preferences when discussing neoadjuvant and adjuvant treatment strategies. Awareness of implicit bias that may contribute to disparities in timely diagnosis, access to novel HER2-targeted therapies, supportive care, and clinical trial enrollment.

8 Patient Centered Domains



These principles align with the Lancet Breast Cancer Commission's call for equitable, patient-centered communication and advocacy to improve breast cancer outcomes worldwide.

Outline

Evolution of HER2 targeted therapy

Early Stage HER2+ Breast Cancer

Neoadjuvant Trials

Residual Disease Adjuvant Trials

Flamingo Trial

The Evolution of HER2 Testing

1987: identification of HER2 amplification as marker of poor prognostic

1990s: insufficient evidence to recommend HER2 testing (ASCO guidelines)

1998: trastuzumab approval for metastatic disease

2005: Adjuvant trastuzumab demonstrated disease-free and overall survival benefit (HERA trial)

2007-2023: HER2 guidelines updated and refined

Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987;235(4785):177-182.

Slamon DJ, et al. *Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer. N Engl J Med.* 2001;344:783-792.

Early Biomarker Guidelines in Breast Cancer (1990's):

SPECIAL ARTICLE

Clinical Practice Guidelines for the Use of Tumor Markers in Breast and Colorectal Cancer

Adopted on May 17, 1996 by the American Society of Clinical Oncology*

- Recommend testing for **ER and PR** in primary breast cancer to identify patients most likely to benefit from endocrine therapy (***no specific threshold***)
- **Insufficient evidence to recommend HER2 testing – and considered it unlikely to ever be… (was not yet a predictive biomarker)**

(J Clin Oncol. 1996;14:2843-77)

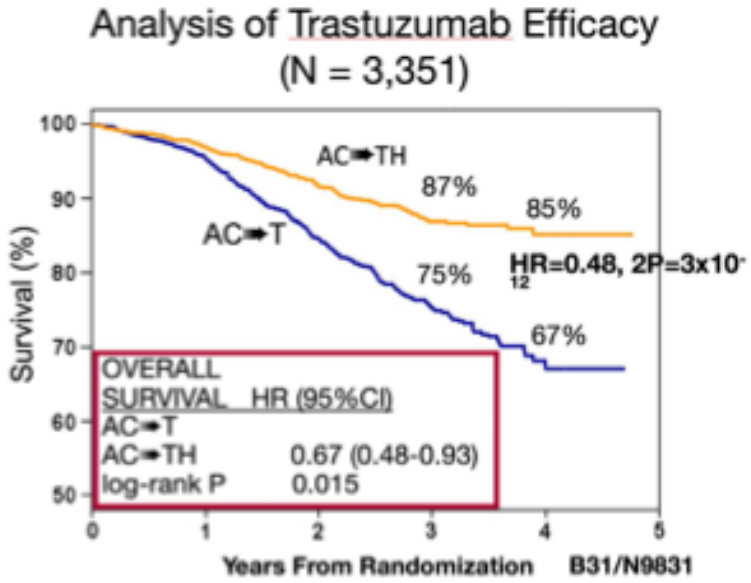
Stanford MEDICINE School of Medicine Department of Pathology

Slide credit to Dr Kimberly Allison

HER2 emerges as a Predictive Biomarker in Early Breast Cancer

2005 ASCO Annual Meeting:

Game-changing adjuvant trastuzumab results in HER2 positive breast cancer presented



4 trials showed reduction in mortality of 33% and recurrence 50%

Trastuzumab Trials Steal Show at ASCO Meeting

Rabiya S. Tuma

JNCI: Journal of the National Cancer Institute, Volume 97, Issue 12, 15 June 2005, Pages 870–871, https://doi.org/10.1093/jnci/97.12.870
Published: 15 June 2005

Edith Perez, MD (HERA trial)

George Sledge, MD (discussant) "I have never seen anything like this in 25 years of breast cancer research."

Stanford MEDICINE School of Medicine
Department of Pathology

Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005 Oct 20;353(16):1673-84. doi: 10.1056/NEJMoa052122. PMID: 16236738.

Slide credit to Dr Kimberly Allison

BCIRG 006

Slamon D, et al. *Adjuvant trastuzumab in HER2-positive breast cancer.* N Engl J Med. 2011;365:1273-1283

BCIRG 006

Adjuvant trastuzumab trial

BCIRG 006

Recruited 3,222 patients from 2001 – 2004

BCIRG 006

Major results published 2005

Published in NEJM 2011

BCIRG 006

Adjuvant TCH vs AC→TH vs AC→T

BCIRG 006

Adjuvant AC → T vs AC → TH vs TCH

BCIRG 006

Adjuvant

a) AC → docetaxel q3 weeks x 4

BCIRG 006

Adjuvant

a) AC → docetaxel q3 weeks x 4

b) AC→ docetaxel + 52 weeks of trastuzumab

BCIRG 006

Adjuvant

a) AC → docetaxel q3 weeks x 4

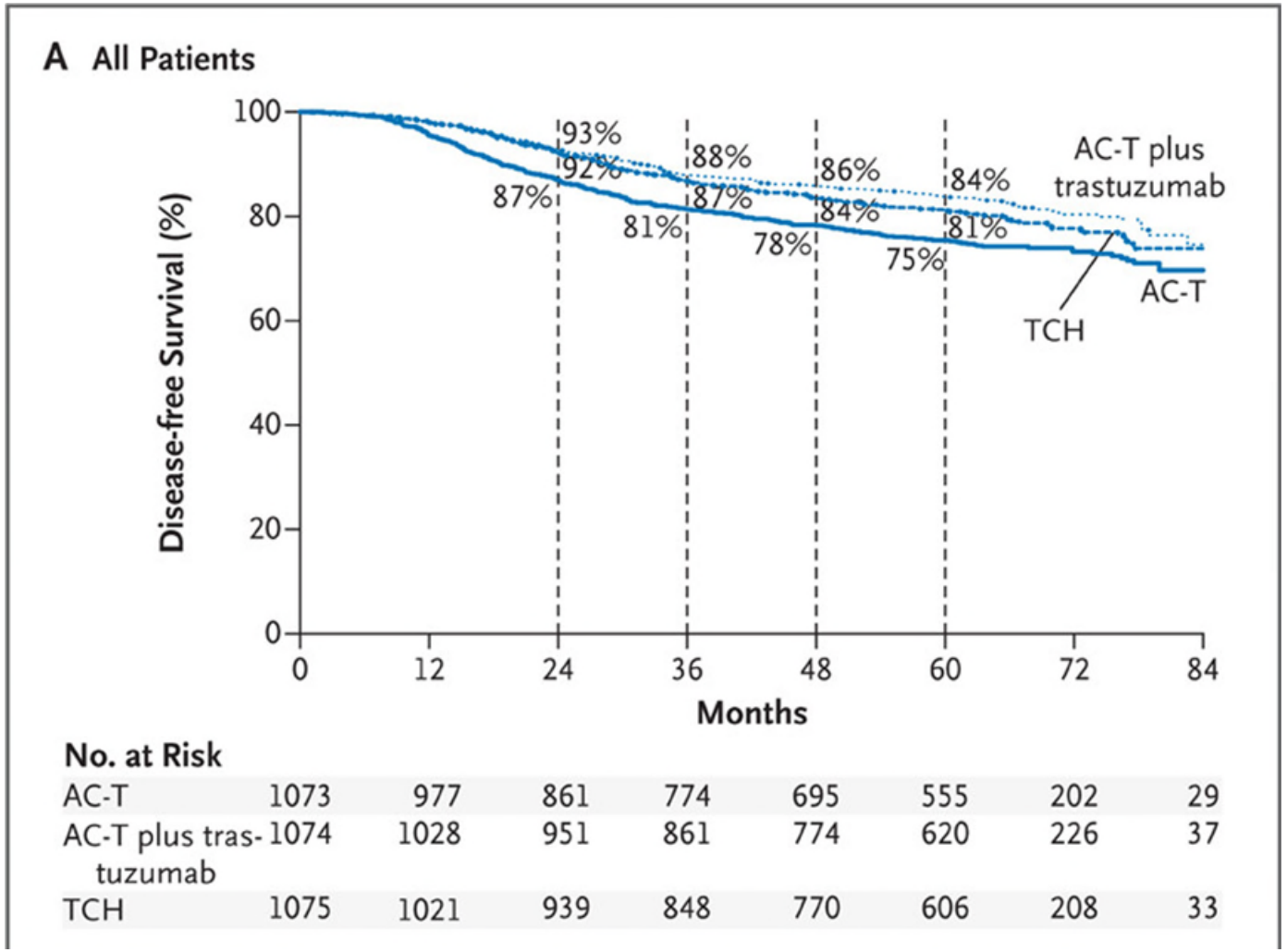
b) AC→ docetaxel + 52 weeks of trastuzumab

c) Docetaxel and carboplatin + 52 weeks of trastuzumab (TCH) q3 weeks x 6

BCIRG 006

Disease-Free Survival Rates at 5 years

- **75% AC-T**
- **84% AC –T + trastuzumab**
- **81% TCH**



No. at Risk								
AC-T	1073	977	861	774	695	555	202	29
AC-T plus trastuzumab	1074	1028	951	861	774	620	226	37
TCH	1075	1021	939	848	770	606	208	33

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BCIRG 006

Overall Survival Rates at 5 years

- **87% AC-T**
- **92% AC-T + trastuzumab**
- **91% TCH**

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BCIRG 006

Lower rates of heart failure & leukemia in TCH

Table 2. Therapeutic Index for Critical Clinical Events.*

Clinical Event	AC-T	AC-T plus Trastuzumab	TCH
		number of events	
Total events	201	146	149
Distant breast-cancer recurrence	188	124	144
Grade 3 or 4 congestive heart failure	7	21	4
Acute leukemia	6	1	1†

* This therapeutic index is a compilation of the numbers of distant breast-cancer recurrences, cases of congestive heart failure, and cases of acute leukemia. AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and trastuzumab.

† This case of acute leukemia developed after the patient received an anthracycline as part of a combination chemotherapy regimen for a diffuse large B-cell lymphoma that occurred after she received treatment with TCH for breast cancer.

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BCIRG 006

Trastuzumab dramatically improved DFS/OS

TCH avoided anthracycline cardiac toxicity

Established TCH as a standard non-anthracycline regimen

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Early Stage HER2+ Breast Cancer

Tumor < 2 cm

Early Stage HER2+ Breast Cancer

Tumor < 2 cm

Axillary Staging Important

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Conclusion

need axillary US

Early Stage HER2+ Breast Cancer

Tumor < 2 cm

De-escalation trials

Early Stage HER2+ Breast Cancer

Tumor < 2 cm

De-escalation trials

- **APT → TH**

Early Stage HER2+ Breast Cancer

Tumor < 2 cm

De-escalation trials

- **APT → TH**
- **ATEMPT → TH vs TDM1**

Early Stage HER2+ Breast Cancer

Tumor < 2 cm

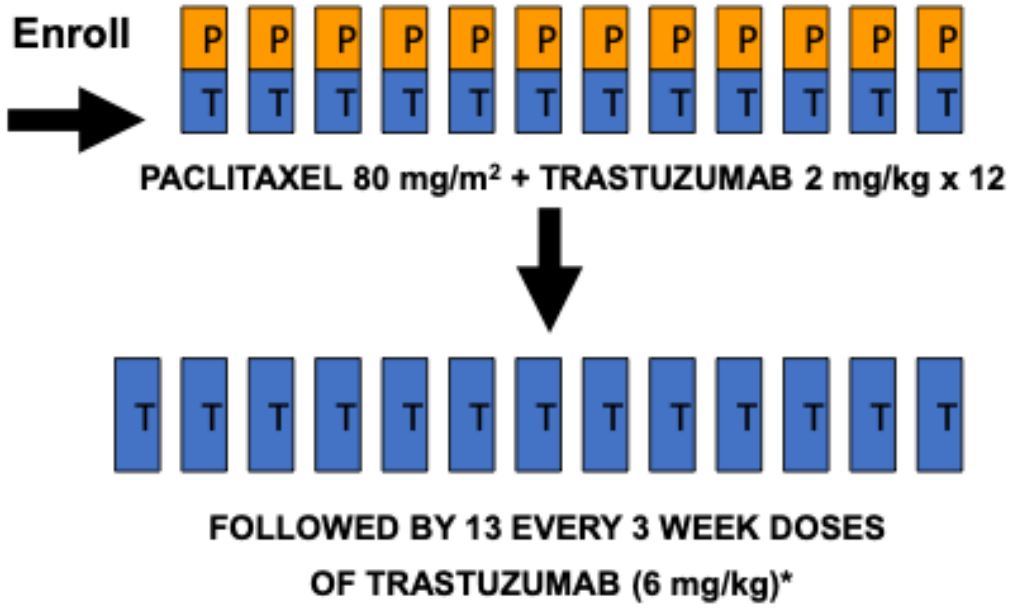
De-escalation trials

- **APT → TH**
- **ATEMPT → TH vs TDM1**
- **ADEPT → (HP .. Omit chemo)**

APT TRIAL: STUDY DESIGN

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

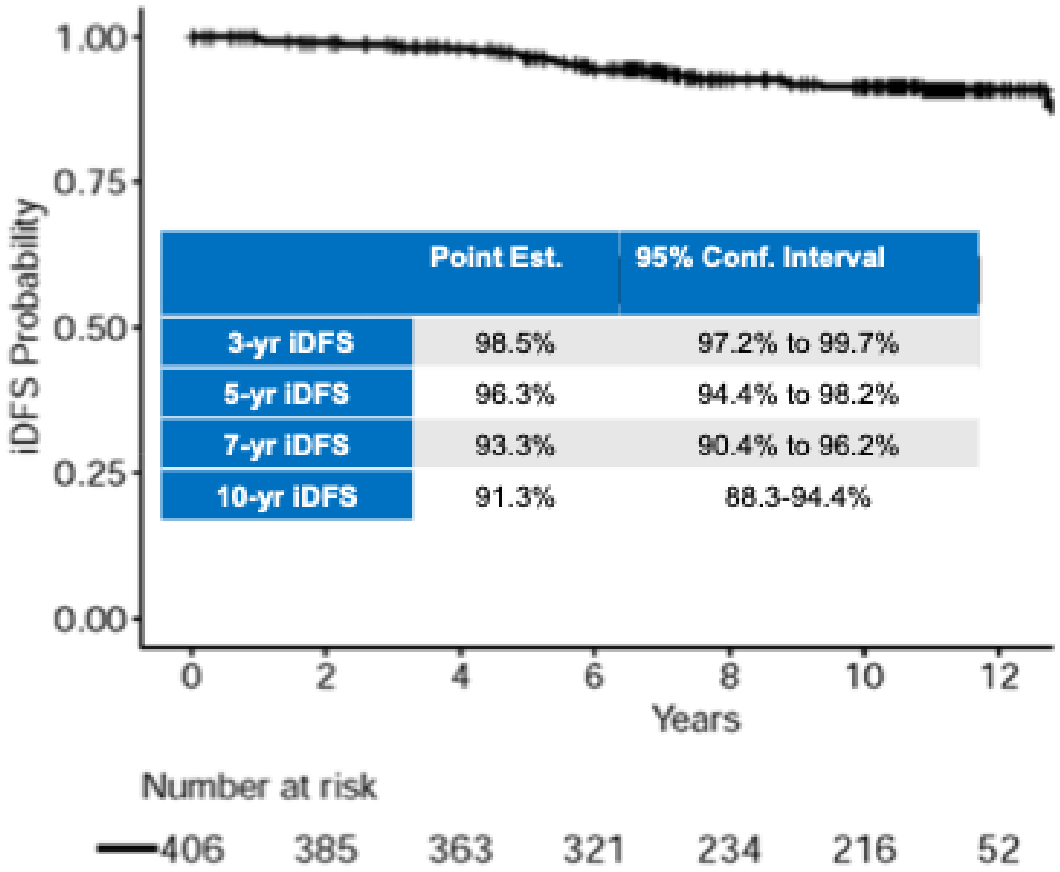
Planned N=400



Tolaney SM et al. *N Engl J Med*. 2015;372(2):134-41.
Tolaney SM et al. *J Clin Oncol*. 2019;37(22):1868-1875.

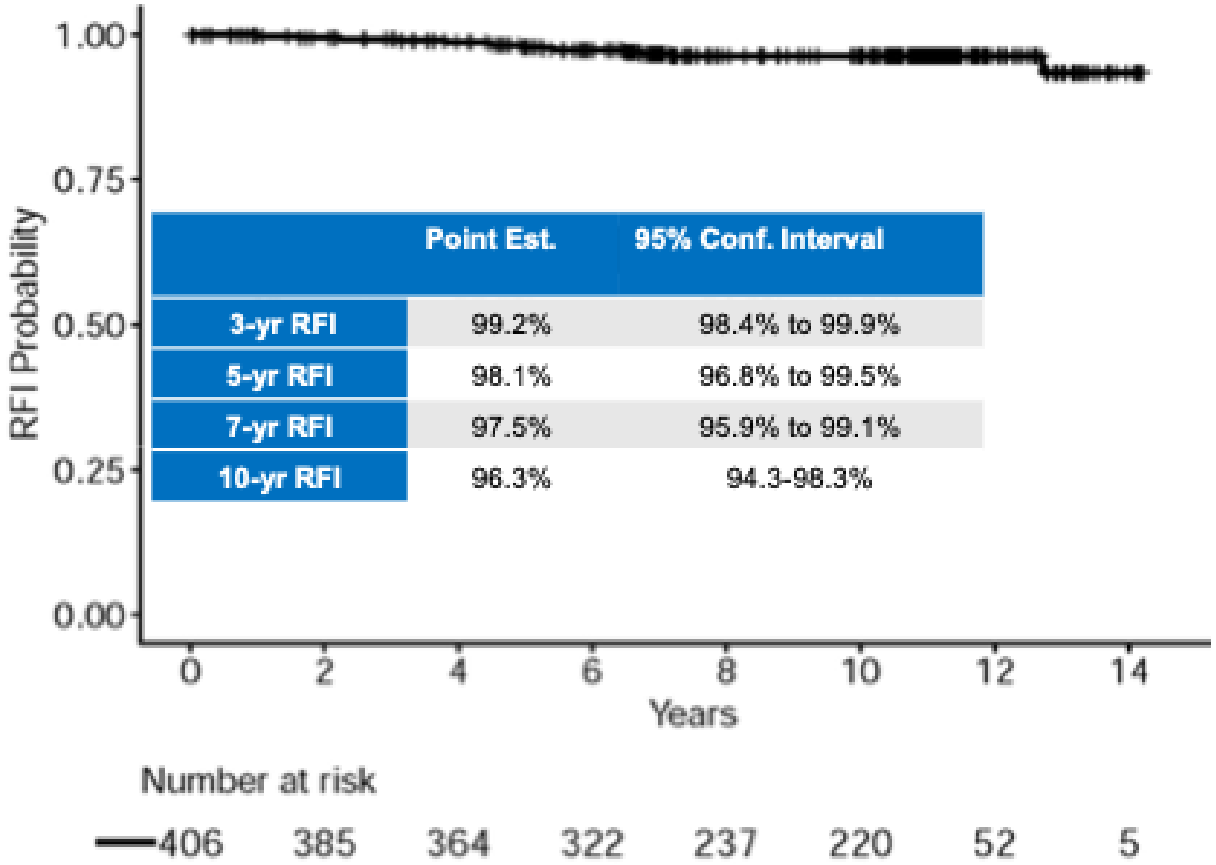
Slide credit: Sara Tolaney

APT: 10-Year RESULTS



	Point Est.	95% Conf. Interval
3-yr iDFS	98.5%	97.2% to 99.7%
5-yr iDFS	96.3%	94.4% to 98.2%
7-yr iDFS	93.3%	90.4% to 96.2%
10-yr iDFS	91.3%	88.3-94.4%

6 Distant Events



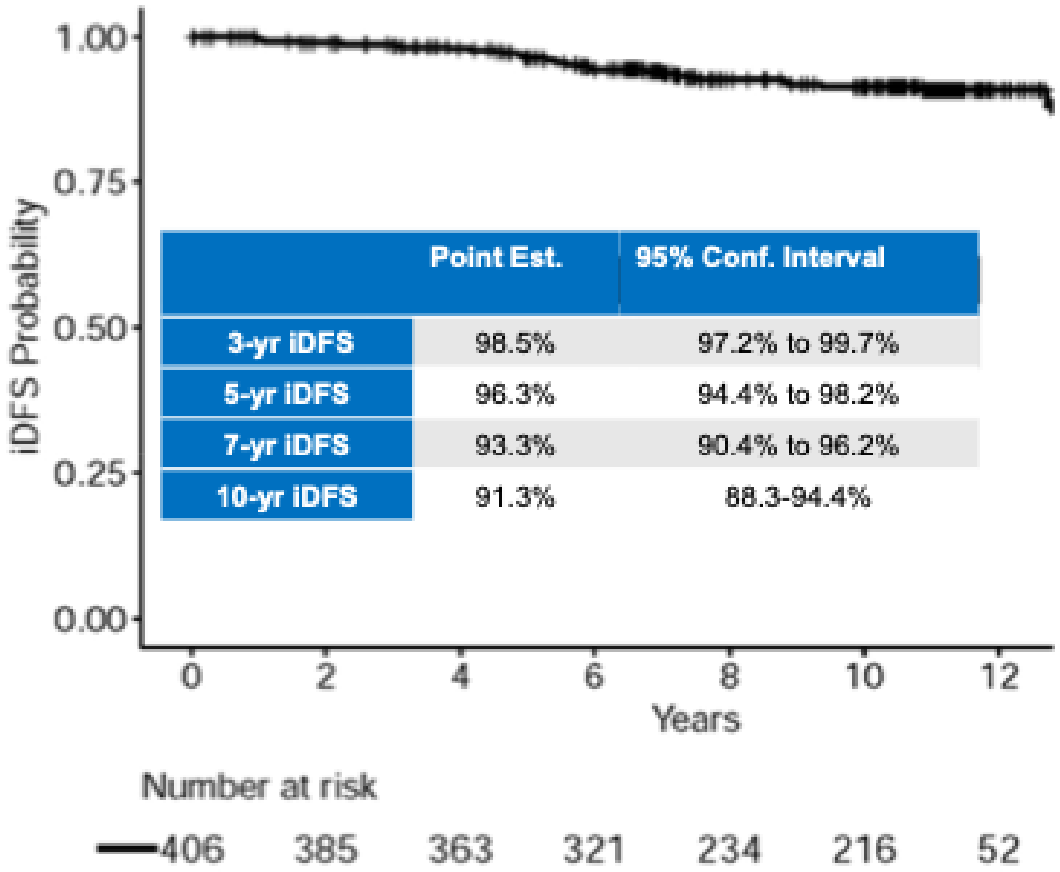
	Point Est.	95% Conf. Interval
3-yr RFI	99.2%	98.4% to 99.9%
5-yr RFI	98.1%	96.8% to 99.5%
7-yr RFI	97.5%	95.9% to 99.1%
10-yr RFI	96.3%	94.3-98.3%

RFI Events=
- **Invasive Local/Regional Recurrence**
- **Distant Recurrence**
- **Death from Breast Cancer**

Tolaney SM et al. SABCS 2022.
Tolaney SM et al. *Lancet Oncol*. 2023;24(3):273-285.

Slide credit: Sara Tolaney

APT: 10-Year RESULTS



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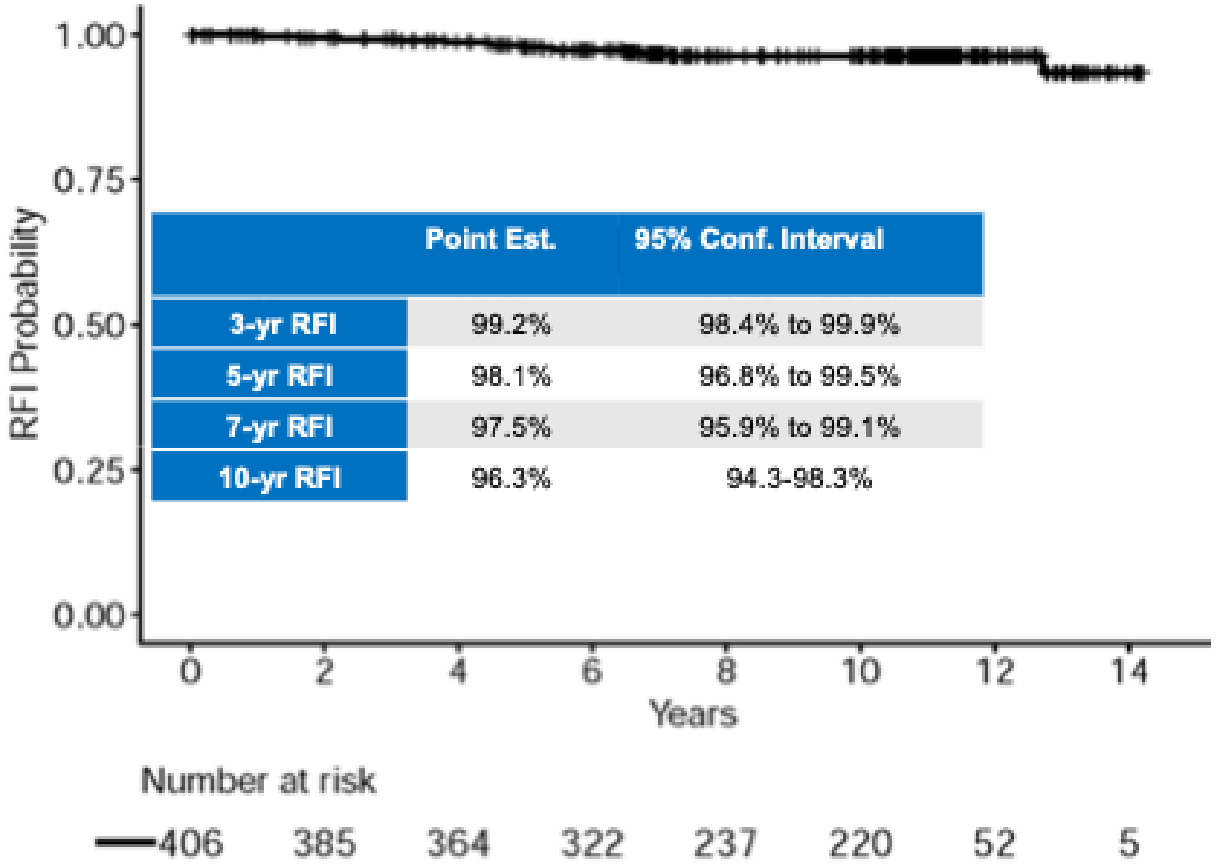
6 Distant Events



	Point Est.	95% Conf. Interval
3-yr RFI	99.2%	98.4% to 99.9%
5-yr RFI	98.1%	96.8% to 99.5%
7-yr RFI	97.5%	95.9% to 99.1%
10-yr RFI	96.3%	94.3-98.3%

RFI Events=
- **Invasive Local/Regional Recurrence**
- **Distant Recurrence**
- **Death from Breast Cancer**

Tolaney SM et al. SABCS 2022.
Tolaney SM et al. *Lancet Oncol*. 2023;24(3):273-285.

Recurrence-free interval (RFI) at 10 years 96.3%

Slide credit: Sara Tolaney

Can TDM1 Replace TH?

ATEMPT (1)

ATEMPT 2.0

Can TDM1 Replace TH?

ATEMPT (1)

ATEMPT 2.0

TDM1 x 1 year vs TH

Can TDM1 Replace TH?

ATEMPT (1)

ATEMPT 2.0

TDM1 x 6 cycles → trastuzumab vs TH

Can TDM1 Replace TH?

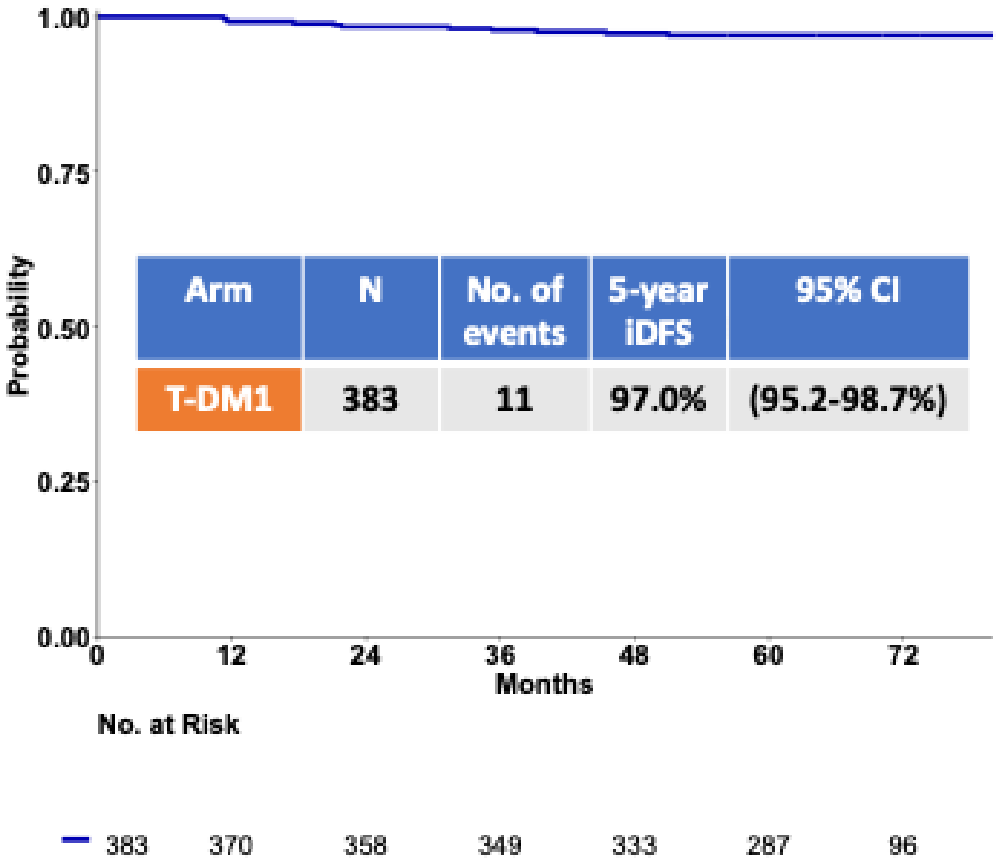
	ATEMPT (1)	ATEMPT 2.0
Population	Stage I HER2+	
Phase	II	
Randomization	**3:1**	
Experimental	**T-DM1 × 1 year**	
Control	**Paclitaxel + trastuzumab (TH)**	
Key question	Can 1 year T-DM1 reduce clinically relevant toxicity while maintaining efficacy?	

Can TDM1 Replace TH?

	ATEMPT (1)	ATEMPT 2.0
Population		Stage I HER2+
Phase		II
Randomization		**3:1**
Experimental		**T-DM1 × 6 cycles → trastuzumab**
Control		**Paclitaxel + trastuzumab (TH)**
Key question		Can **shorter T-DM1 exposure** improve tolerability/QOL while maintaining efficacy?

5-year outcomes with T-DM1: iDFS and RFI

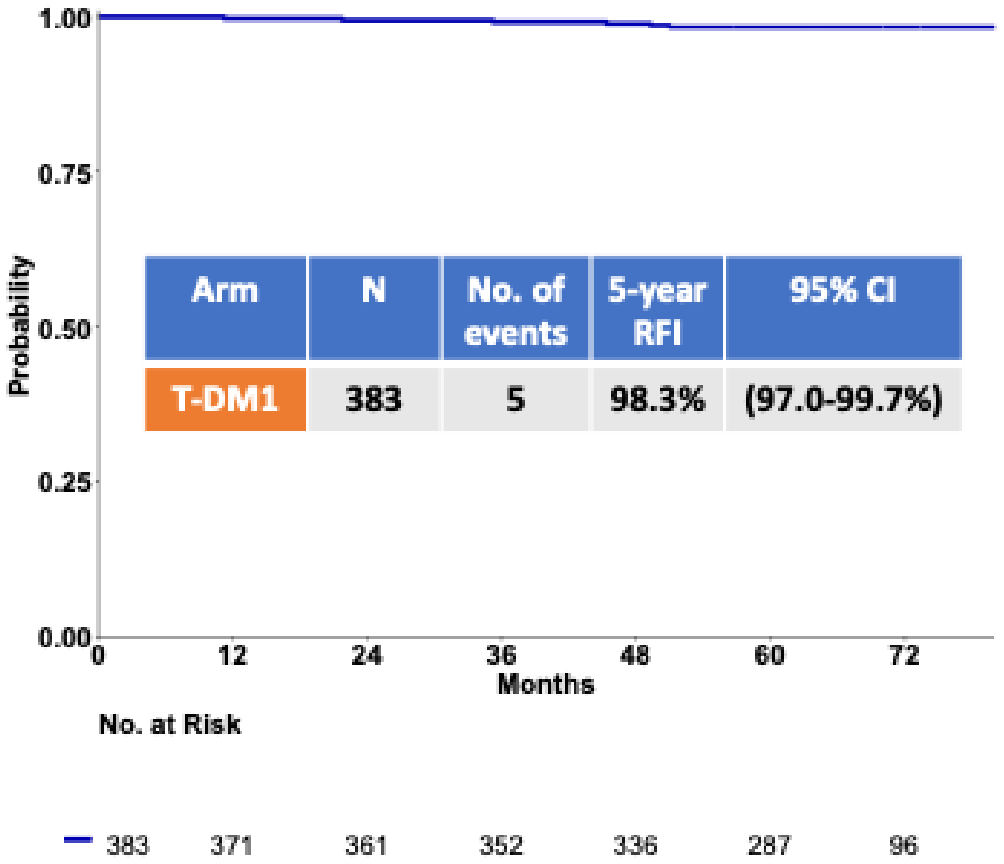
5-year iDFS



Arm	N	No. of events	5-year iDFS	95% CI
T-DM1	383	11	97.0%	(95.2-98.7%)

3 Distant Events

5-year RFI



Arm	N	No. of events	5-year RFI	95% CI
T-DM1	383	5	98.3%	(97.0-99.7%)

Tolaney S et al. SABCS 2022

Slide credit: Sara Tolaney

ATEMPT: CLINICALLY RELEVANT TOXICITY

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥ 2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hematologic toxicity	4 (1%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (2%)
Any toxicity requiring dose delay	106 (28%)	30 (26%)
Any toxicity requiring early discontinuation	67 (17%)	7 (6%)
Total	176 (46%)	53 (46%)

p=0.91

Tolaney S et al. SABCS 2019. GS1-05.

Slide credit: Sara Tolaney

Can TDM1 Replace TH?

ATEMPT (1)

-TDM1 effective, but more early discontinuations

-Not standard of care, but may be an option

Can TDM1 Replace TH?

ATEMPT (2)

-Ongoing, determine if shorter course of TDM1 more tolerated and still preserve efficacy

ADEPT Trial

ADjuvant **E**ndocrine **P**ertuzumab **T**rastuzumab

A Single Arm Phase II Study of ADjuvant Endocrine Therapy, Pertuzumab, and Trastuzumab for Patients With Anatomic Stage I Hormone Receptor-positive, HER2-positive Breast Cancer (ADEPT)

ClinicalTrials.gov ID NCT04569747

Sponsor Dana-Farber Cancer Institute

Information provided by Adrienne G. Waks, Dana-Farber Cancer Institute (Responsible Party)

Last Update Posted 2026-04-02

ADEPT Trial – adjuvant stage I ER+/HER2+

Substitute pertuzumab for taxol + endocrine

ADEPT Trial

Substitute subcutaneous HP (Phesgo) for TH

High Risk HER2+ → Neoadjuvant Chemotherapy

Stage II or III
>2 cm
Lymph node positive

Neoadjuvant Chemotherapy Regimens

Dual HER2 targeted therapy

NEOADJUVANT TRASTUZUMAB / PERTUZUMAB REGIMENS

NeoSphere

4 neoadjuvant cycles q3 weeks → surgery

- **THP: Docetaxel + trastuzumab + pertuzumab**
- **TH: Docetaxel + trastuzumab**
- **HP: Trastuzumab + pertuzumab**
- **TP: Docetaxel + pertuzumab**

TRYPHAENA

6 neoadjuvant cycles; all included HP

- **Arm A: FEC + HP ×3 → docetaxel + HP ×3**
- **Arm B: FEC ×3 → docetaxel + HP ×3**
- **Arm C: TCHP ×6 (docetaxel + carboplatin + HP)**

pCR rates across trials

		Overall	HR-	HR+
Taxane-HP x12 wks	Tax-HP (CompassHER2-pCR)	44%	64%	33%
	THP (DAPHNe)	57%	85%	42%
	THP (WSG-TP-II)	-	-	56%
	DHP (NeoSphere)	39%	-	-
Taxane-HP x18 wks	nab-THP (HELEN006)	66%	86%	53%
	Tax-HP (NeoCARHP)	64%	78%	56%
Taxane-Cb-HP x18 wks	DCbHP (TRYPHAENA)	52%	-	-
	DCbHP (KRISTINE)	56%	73%	44%
	DCbHP (HELEN006)	58%	70%	48%
	Tax-CbHP (NeoCARHP)	66%	78%	59%

Cb: carboplatin; D: docetaxel; T: paclitaxel; Tax: mix of taxanes

Waks AG et al *Nat Rev Clin Oncol* 2025. Gao H-F et al. ASCO 2025. Chen X-C et al. *Lancet Oncol.* 2025.

Neoadjuvant Chemotherapy Regimens

Dual HER2 targeted therapy

TRAIN2
NeoCARHP
COMPASS HER2 PCR
DESTINY-Breast 11

TRAIN 2

438 patients

Untreated stage II-III HER2+

Open-label, randomized phase III neoadjuvant trial across 37 hospitals in Netherlands

van der Voort A, van Ramshorst MS, van Werkhoven ED, et al. Three-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual ERBB2 Blockade in Patients With ERBB2-Positive Breast Cancer: A Secondary Analysis of the TRAIN-2 Randomized, Phase 3 Trial. JAMA Oncol. 2021;7(7):978–984. doi:10.1001/jamaoncol.2021.1371

van Ramshorst MS, van der Voort A, van Werkhoven ED, Mandjes IA, Kemper I, Dezentjé VO, Oving IM, Honkoop AH, Tick LW, van de Wouw AJ, Mandigers CM, van Warmerdam LJ, Wesseling J, Vrancken Peeters MT, Linn SC, Sonke GS; Dutch Breast Cancer Research Group (BOOG). Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018 Dec;19(12):1630-1640. doi: 10.1016/S1470-2045(18)30570-9. Epub 2018 Nov 6. PMID: 30413379.

TRAIN 2

Anthracycline vs non-anthracycline

van der Voort A, van Ramshorst MS, van Werkhoven ED, et al. Three-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual ERBB2 Blockade in Patients With ERBB2-Positive Breast Cancer: A Secondary Analysis of the TRAIN-2 Randomized, Phase 3 Trial. JAMA Oncol. 2021;7(7):978–984. doi:10.1001/jamaoncol.2021.1371

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TRAIN 2

3 cycles FEC + HP → 6 cycles paclitaxel/carboplatin + HP

- FEC: fluorouracil / epirubicin / cyclophosphamide q3 weeks
- Paclitaxel days 1 and 8 + carboplatin AUC 6, day 1, q3 weeks
- Trastuzumab + pertuzumab throughout

9 cycles paclitaxel/carboplatin + HP

- Paclitaxel days 1 and 8
- Carboplatin AUC 6, day 1
- Trastuzumab + pertuzumab
- q3-week cycles

van der Voort A, van Ramshorst MS, van Werkhoven ED, et al. Three-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual ERBB2 Blockade in Patients With ERBB2-Positive Breast Cancer: A Secondary Analysis of the TRAIN-2 Randomized, Phase 3 Trial. JAMA Oncol. 2021;7(7):978–984. doi:10.1001/jamaoncol.2021.1371

van Ramshorst MS, van der Voort A, van Werkhoven ED, Mandjes IA, Kemper I, Dezentjé VO, Oving IM, Honkoop AH, Tick LW, van de Wouw AJ, Mandigers CM, van Warmerdam LJ, Wesseling J, Vrancken Peeters MT, Linn SC, Sonke GS; Dutch Breast Cancer Research Group (BOOG). Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018 Dec;19(12):1630-1640. doi: 10.1016/S1470-2045(18)30570-9. Epub 2018 Nov 6. PMID: 30413379.

TRAIN 2

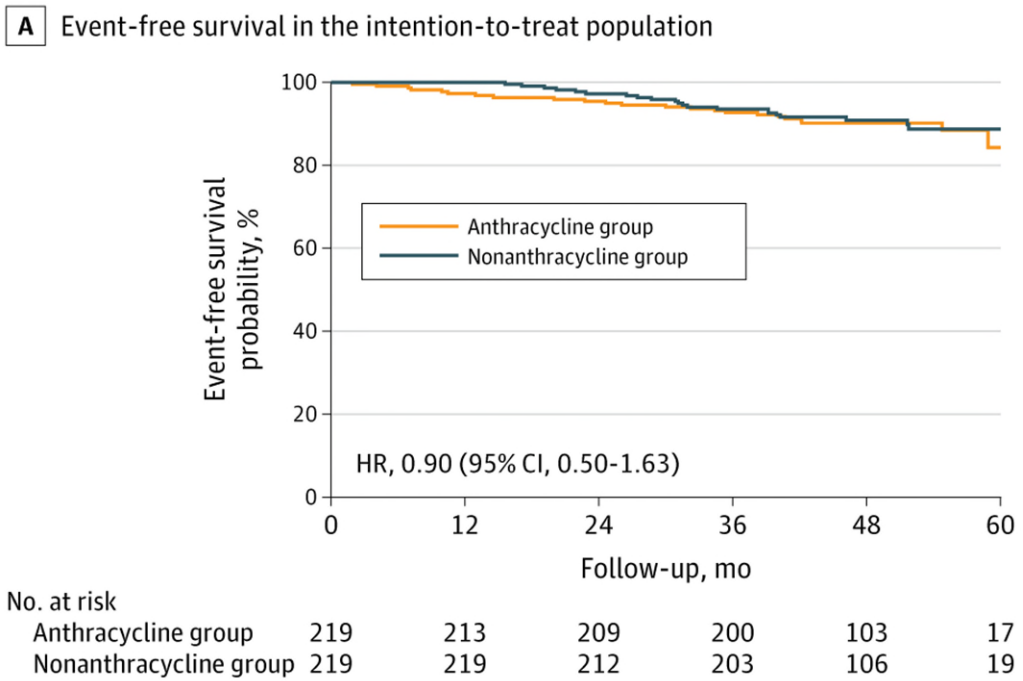
Primary outcome: Pathologic complete response (pCR) in the breast and axilla, ypT0/is ypN0.

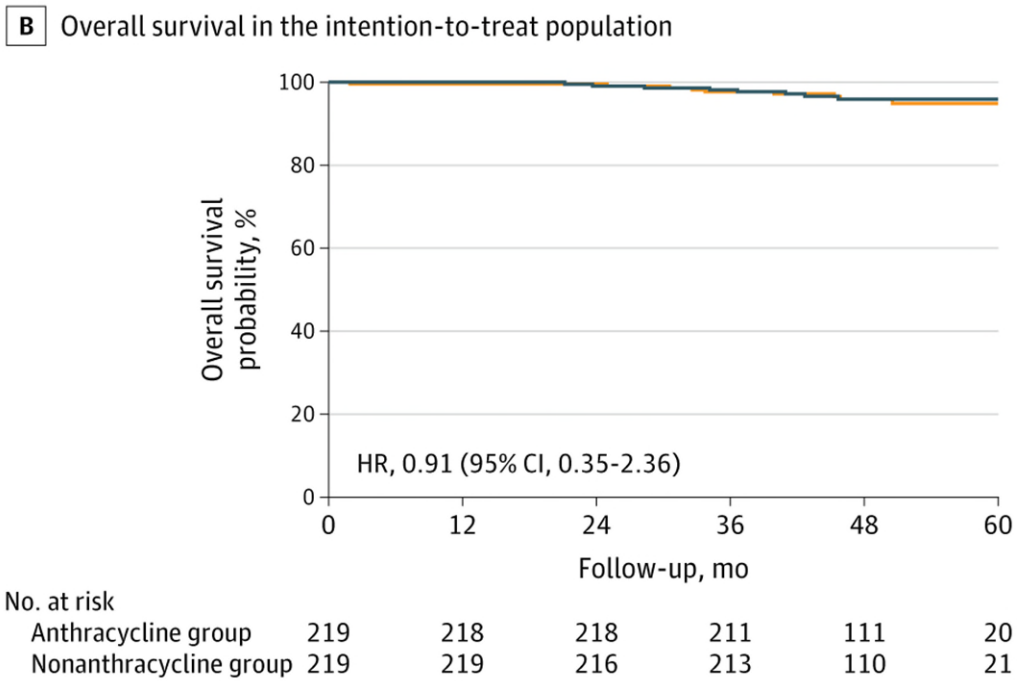
Result: 67% vs 68% pCR with vs without anthracyclines (p = 0.95)

No improvement in pCR from adding anthracyclines to taxane/carboplatin + dual HER2 blockade.

van Ramshorst MS, van der Voort A, van Werkhoven ED, Mandjes IA, Kemper I, Dezentjé VO, Oving IM, Honkoop AH, Tick LW, van de Wouw AJ, Mandigers CM, van Warmerdam LJ, Wesseling J, Vrancken Peeters MT, Linn SC, Sonke GS; Dutch Breast Cancer Research Group (BOOG). Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018 Dec;19(12):1630-1640. doi: 10.1016/S1470-2045(18)30570-9. Epub 2018 Nov 6. PMID: 30413379.

TRAIN-2





3 year overall survival excellent

- 97.7% (FEC → TCHP)
- 98.2% (TCHP)

van der Voort A, van Ramshorst MS, van Werkhoven ED, et al. Three-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual ERBB2 Blockade in Patients With ERBB2-Positive Breast Cancer: A Secondary Analysis of the TRAIN-2 Randomized, Phase 3 Trial. JAMA Oncol. 2021;7(7):978–984. doi:10.1001/jamaoncol.2021.1371

NEOCARHP

Original Reports | Breast Cancer

Check for up

Neoadjuvant Taxane Plus Trastuzumab and Pertuzumab With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: The Randomized Noninferiority Phase III neoCARHP Trial

Hong-Fei Gao, MD[1]; Guo-Lin Ye, MD[2]; Ying Lin, MD, PhD[3]; Qin Huang, MM[4]; Jie Dong, MM[5]; Yin Cao, MM[6]; Yan-Xia Zhao, MD, PhD[7]; Qian-Jun Chen, MD[8]; Shi-Hui Ma, MD[9]; Jie Ouyang, MD, PhD[10]; Jin-Hui Ye, MD[11]; Hua-Wei Yang, MD[12]; Yuan-Qi Zhang, MD[13]; Yong-Cheng Zhang, MD[14]; Gang-Ling Zhang, MM[15]; Wei Li, MD[2]; Yunjian Zhang, MD, PhD[3]; Zhi-Yong Wu, MD[4]; Ying-Yi Lin, MM[16]; Teng Zhu, MD[1]; Liu-Lu Zhang, MD[1]; Ci-Qiu Yang, MD[1]; Mei Yang, MD[1]; Hao Peng, MD[1]; Bo Chen, MD[1]; Yi-Tian Chen, MD[1]; Fei Ji, MD[1]; Min-Yi Cheng, MD[1]; Jie-Qing Li, MD[1]; Zefei Jiang, MD, PhD[17]; and Kun Wang, MD, PhD[1]

DOI https://doi.org/10.1200/JCO-25-02176

ABSTRACT

PURPOSE The neoCARHP aimed to investigate the efficacy and safety of investigator-selected taxane (docetaxel, paclitaxel, or nab-paclitaxel) plus trastuzumab and pertuzumab, with carboplatin (TCbHP) or without carboplatin (THP), in stage II and III human epidermal growth factor receptor 2 (HER2)–positive breast cancer.

METHODS The neoCARHP was a multicenter, randomized, phase III, noninferiority study. Eligible patients were women age 18 years or older with previously untreated, stage II and III, HER2-positive invasive breast cancer. Patients were randomly assigned (1:1) to receive six 3-week cycles of TCbHP or THP. The primary end point was pathologic complete response (pCR) rate in the breast and axilla (ypT0/is ypN0) in the modified intention-to-treat (mITT) population (all randomly assigned patients receiving at least one dose of study treatment). Safety was evaluated in all patients who received any study treatment.

RESULTS Between April 30, 2021, and August 27, 2024, 774 patients were randomly assigned and 766 were included in the mITT population (382 in THP and 384 in TCbHP). pCR was achieved in 245 (64.1% [95% CI, 59.1 to 69.0]) patients in the THP group and 253 (65.9% [60.9-70.6]) in the TCbHP group (absolute dif-

ACCOMPANYING CONTENT

Editorial, p. 1561

Appendix

Data Sharing Statement

Protocol

Accepted December 9, 2025
Published January 23, 2026

J Clin Oncol 44:1587-1596

View Online Article

NEOCARHP

Is carboplatin necessary?

NEOCARHP

Phase III noninferiority neoadjuvant trial

774 patients

2001 – 2004

15 centers in China

NEOCARHP

Stage II–III HER2+

Randomize 1:1

THP × 6 vs TCHP × 6 → Surgery

Primary endpoint: pCR

NEOCARHP

Randomize 1:1 → THP × 6 vs TCbHP × 6 → Surgery

Gao HF, et al. *The Randomized Noninferiority Phase III neoCARHP Trial.* **J Clin Oncol.** Published online January 23, 2026.

NEOCARHP

Regimens

THP — de-escalation	**TCbHP**
Taxane + trastuzumab + pertuzumab	Taxane + carboplatin + trastuzumab + pertuzumab
6 cycles	**6 cycles**
No carboplatin	Carboplatin-containing

NEOCARHP

The taxane was investigator-selected: q3 week docetaxel, paclitaxel, or nab-paclitaxel.

Regimens

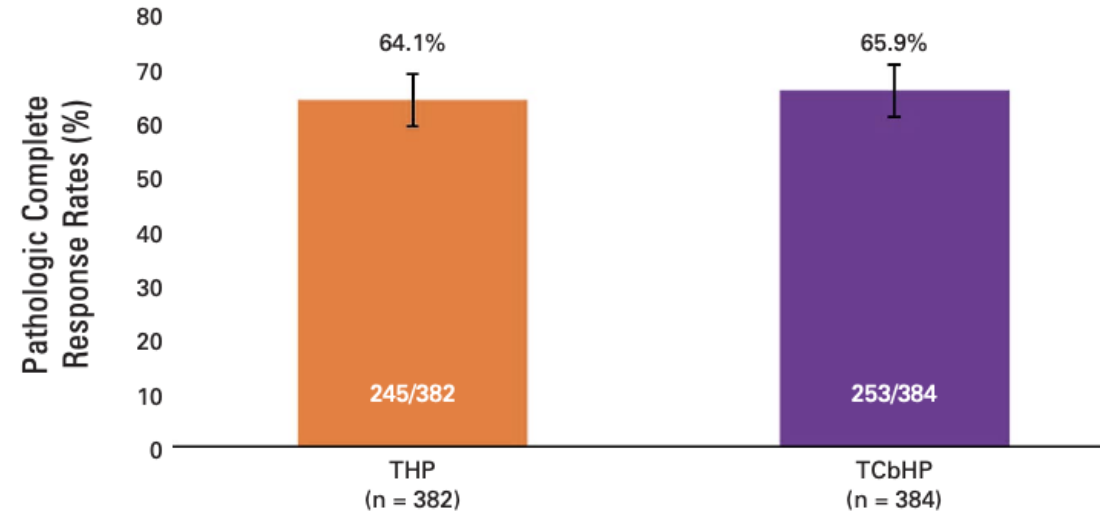
THP — de-escalation	**TCbHP**
Taxane + trastuzumab + pertuzumab	Taxane + carboplatin + trastuzumab + pertuzumab
6 cycles	**6 cycles**
No carboplatin	Carboplatin-containing

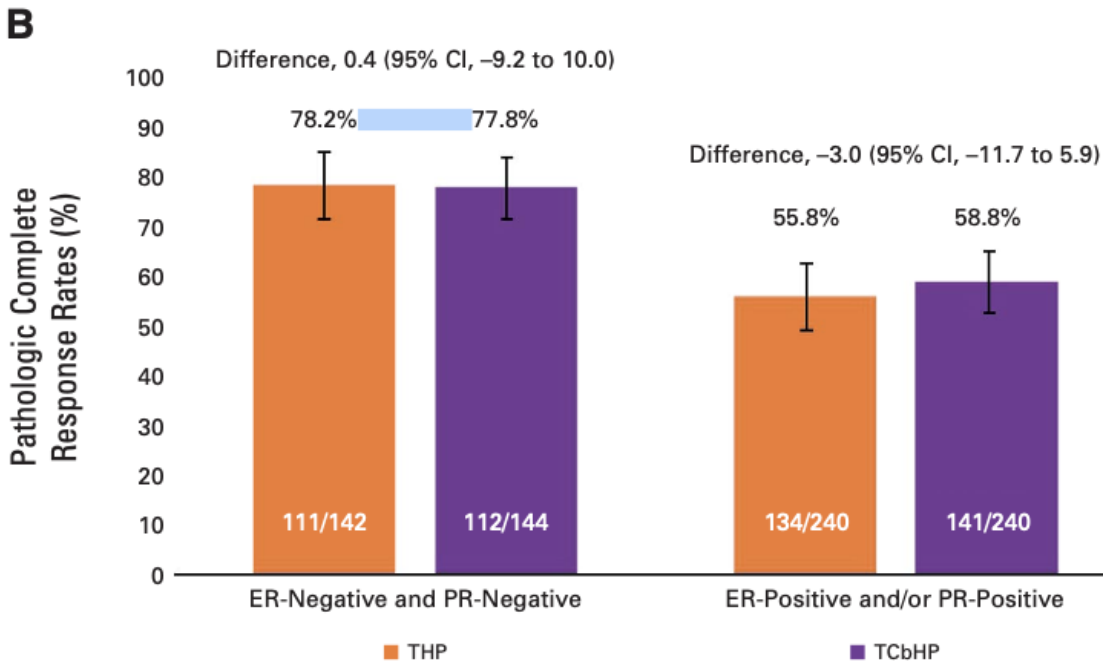
NEOCARHP

Primary endpoint: pCR

NEOCARHP

PCR rate the same





NEOCARHP

Key result: THP achieved a noninferior pCR rate compared with TCbHP, with improved tolerability

NEOCARHP

Key result: THP achieved a noninferior pCR rate compared with TCbHP, with improved tolerability

Supports carbo omission

COMPASSHER2-PCR (EA1181)

Results presented at ASCO 2025

Published as JCO meeting abstract

Tung NM, et al. J Clin Oncol. 2025;43(suppl 16):501.

COMPASSHER2-PCR (EA1181)

Short course of neoadjuvant chemotherapy (4 cycles = 12 weeks)

PCR significantly lower in ER+ (30%)

Paclitaxel > docetaxel

Established usefulness of HER2DX pCR score

Tung NM, et al. J Clin Oncol. 2025;43(suppl 16):501.

COMPASSHER2-PCR (EA1181)

2175 patients enrolled

Tung NM, et al. J Clin Oncol. 2025;43(suppl 16):501.

COMPASSHER2-PCR (EA1181)

Single-arm trial

Stage II/III with HER2+ breast cancer (cT4 or cN3 excluded)

Primary endpoint recurrence-free survival

Secondary endpoint pCR

Tung NM, et al. J Clin Oncol. 2025;43(suppl 16):501.

COMPASSHER2-PCR (EA1181)

Neoadjuvant THP

Tung NM, et al. J Clin Oncol. 2025;43(suppl 16):501.

COMPASSHER2-PCR (EA1181)

Neoadjuvant THP

- **4 cycles of trastuzumab and pertuzumab (HP) w weekly paclitaxel (12 weeks) or docetaxel (q3w x 4) followed by surgery**

Tung NM, et al. J Clin Oncol. 2025;43(suppl 16):501.

COMPASSHER2-PCR (EA1181)

HER2DX pCR score (stratified by ER status) determined using biopsy specimen

Tung NM, et al. J Clin Oncol. 2025;43(suppl 16):501.

COMPASSHER2-PCR (EA1181)

PCR predictors

- No association with clinical stage
- HER2DX pCR score was a significant predictor of pCR regardless ER status
- Lower ER expression and higher grade were associated with higher pCR rates

Tung NM, et al. J Clin Oncol. 2025;43(suppl 16):501.

CompassHER2-pCR Secondary Endpoint: Largest-yet Demonstration of THP pCR Rates

8% stage IIIA

Eligibility: *

Stage II or IIIA HER2+ BC

- cN0 eligible if T ≥ 2 cm*
- cN1-2 eligible, any T1-3
- T4, N3 NOT eligible

*ER+ cT 2-3 cm, cN0 capped at 20% of study population
ER+ defined as ≥1% ER+

REGISTRATION

N=2175

Preoperative Phase

THP x 4 Cycles

paclitaxel

80 mg/m2 qwk x12

OR docetaxel

75 mg/m2 q3 wk x4

COMBINED WITH **trastuzumab** (H) **& pertuzumab** (P) q3 wk x4

SURGERY

ARM A: pCR (no invasive disease)

pCR (ypT0/Tis ypN0) → **Complete 1 year HP** Radiation and endocrine therapy (if appropriate) → **Follow-up for recurrence and survival**

No pCR → **Additional chemo and anti-HER2 therapy per treating physician**

ARM B: no pCR (residual invasive disease)

Primary Objective: determine if 3y RFS >92% in Arm A separately for ER+/HER2+ and ER-/HER2+ cohorts

Tung N et al ASCO 2025

Slide credit Sara Tolaney

COMPASSHER2 TRIALS

Eligibility:
Stage II or IIIA HER2+ BC (T2-3, N0-2)

- cN0 eligible if ≥ 2.0 cm
- cN1-2 eligible ≥ 1.5cm
- ER+ and ER- eligible

REGISTRATION

Preoperative Phase: all patients

THP x 4 Cycles
Paclitaxel qwk x12
OR
Docetaxel q3 wk x4
with
Trastuzumab (H)
& Pertuzumab (P) q3 wk x4

* nab-pacl allowed

SURGERY

pCR (ypT0/Tis ypN0) *40%*

Arm A: pCR (no invasive disease)

EA1181
CompassHER2-pCR

- Complete 1 yr HP
- Radiation and endocrine Rx (if appropriate)

ECOG-ACRIN cancer research group

No pCR *60%*

A011801
CompassHER2-RD

Alliance for Clinical Trials in Oncology

Grp 1: pre-op THP-> AC, Cb/HP x 4
Grp 2: pre-op TCHP, *AC-THP* -> no further chemo

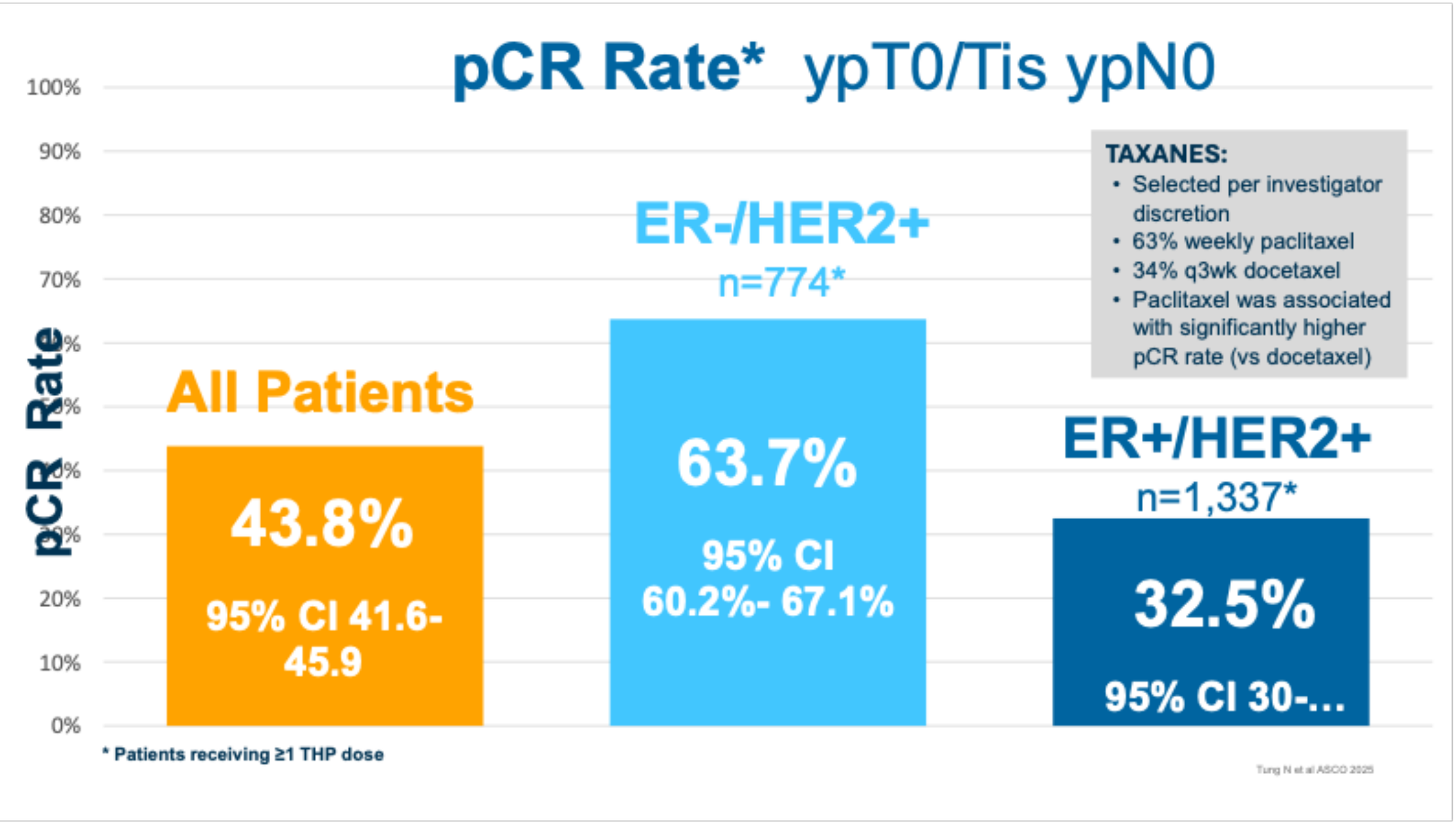
Eligibility
HER2+ RD
ER- & ER+
(ER+ must be N+)
(~30% of A011801 expected to come from EA1181)

Registration

R

T-DM1 x 14 doses

T-DM1/tucatinib x 14 doses



Slide credit Sara Tolaney

COMPASSHER2-PCR

HER2DX Score

All Participants		HER2+/ER-		HER2+/ER+		
	# patients enrolled	pCR rate (95% CI)	# patients enrolled	pCR rate (95% CI)	# patients enrolled	pCR rate (95% CI)
Evaluable Cohort	2141	44% (42-46%)	774	64% (60-67%)	1367	32% (30-35%)
HER2DX Cohort	569	48% (44- 52%)	230	69% (63-75%)	339	34% (29-39%)
HER2DX pCR-high score	182 (32%)	68% (60-74%)	147 (64%)	70% (62-77%)	36 (11%)	58% (41-74%)
HER2DX pCR-medium score	161 (28%)	67% (59- 74%)	70 (30%)	74% (62- 84%)	89 (26%)	61% (50-71%)
HER2DX pCR-low score	226 (40%)	19% (14- 25%)	13 (6%)	31% (9-61%)	214 (63%)	18% (13-24%)
P-value HER2DX score	<0.001		0.010		<0.001	

Tung NM, et al. J Clin Oncol. 2025;43(suppl 16):501.

COMPASSHER2-PCR

HER2DX Score

Relapse risk and PCR risk

- Low
- Medium
- High

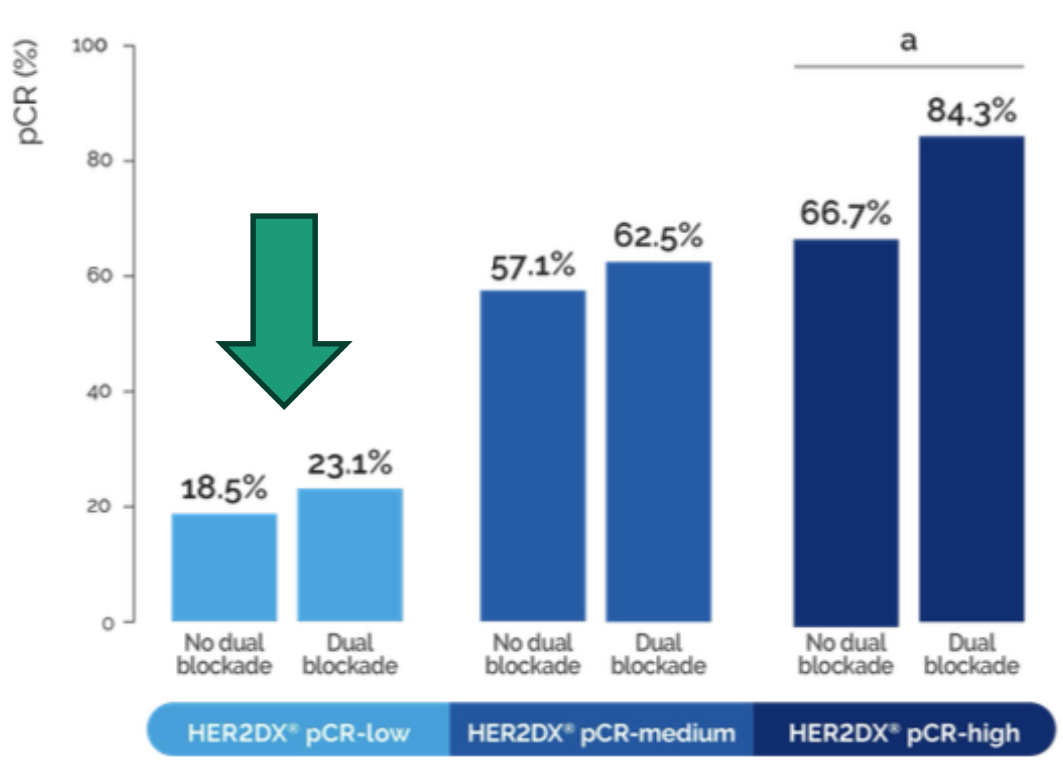
All Participants		HER2+/ER-		HER2+/ER+		
	# patients enrolled	pCR rate (95% CI)	# patients enrolled	pCR rate (95% CI)	# patients enrolled	pCR rate (95% CI)
Evaluable Cohort	2141	44% (42-46%)	774	64% (60-67%)	1367	32% (30-35%)
HER2DX Cohort	569	48% (44- 52%)	230	69% (63-75%)	339	34% (29-39%)
HER2DX pCR-high score	182 (32%)	68% (60-74%)	147 (64%)	70% (62-77%)	36 (11%)	58% (41-74%)
HER2DX pCR-medium score	161 (28%)	67% (59- 74%)	70 (30%)	74% (62- 84%)	89 (26%)	61% (50-71%)
HER2DX pCR-low score	226 (40%)	19% (14- 25%)	13 (6%)	31% (9-61%)	214 (63%)	18% (13-24%)
P-value HER2DX score	<0.001		0.010		<0.001	

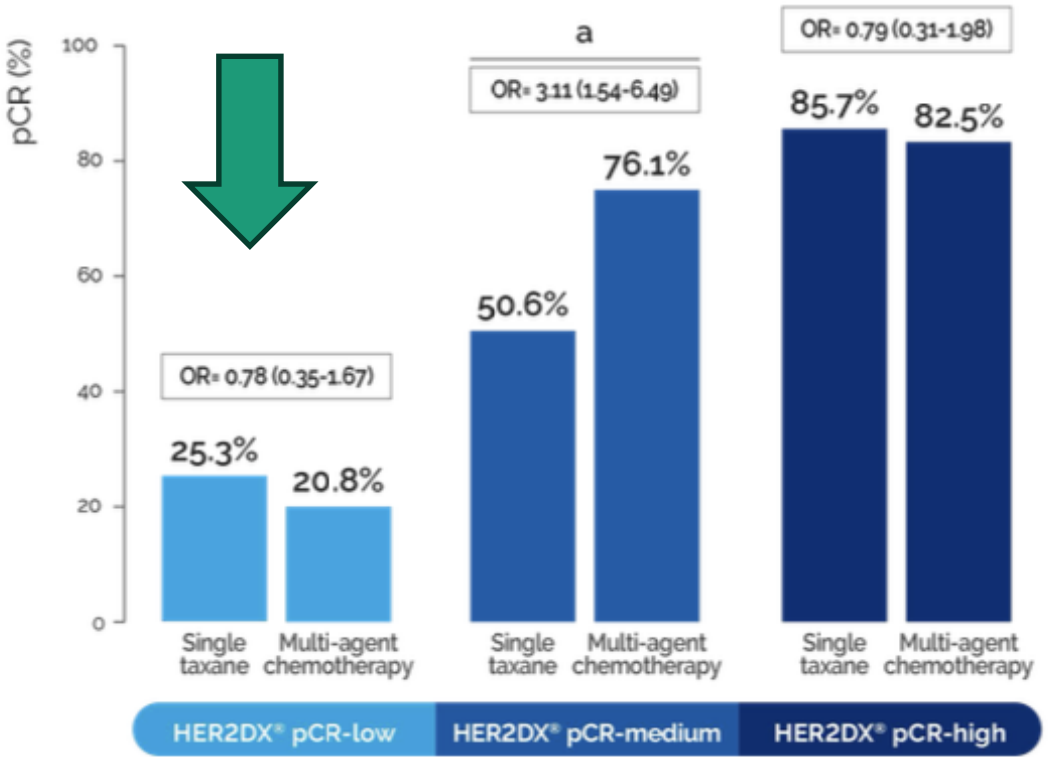
Low PCR

Tung NM, et al. J Clin Oncol. 2025;43(suppl 16):501.

HER2DX Score

pCR-low → pCR rate below 30% regardless of her2 blockade or multiagent chemo; group is highly endocrine sensitive if ER+

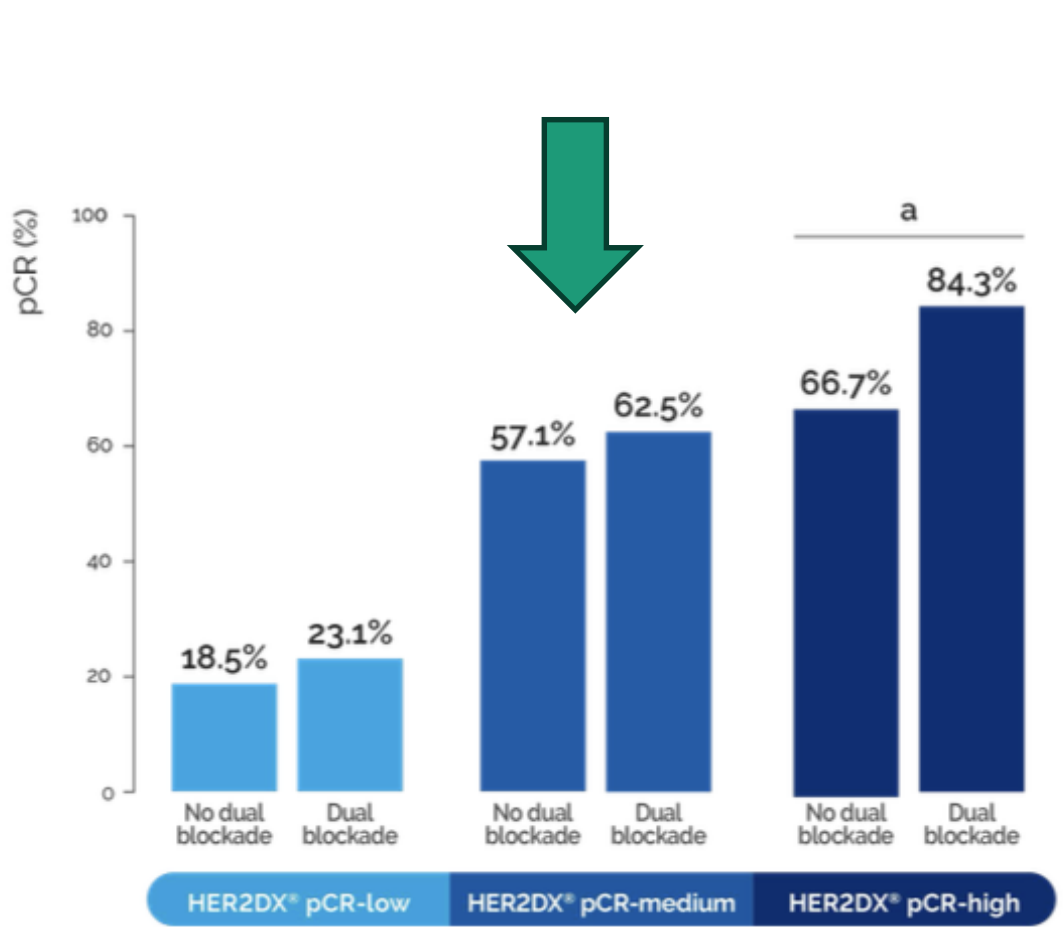


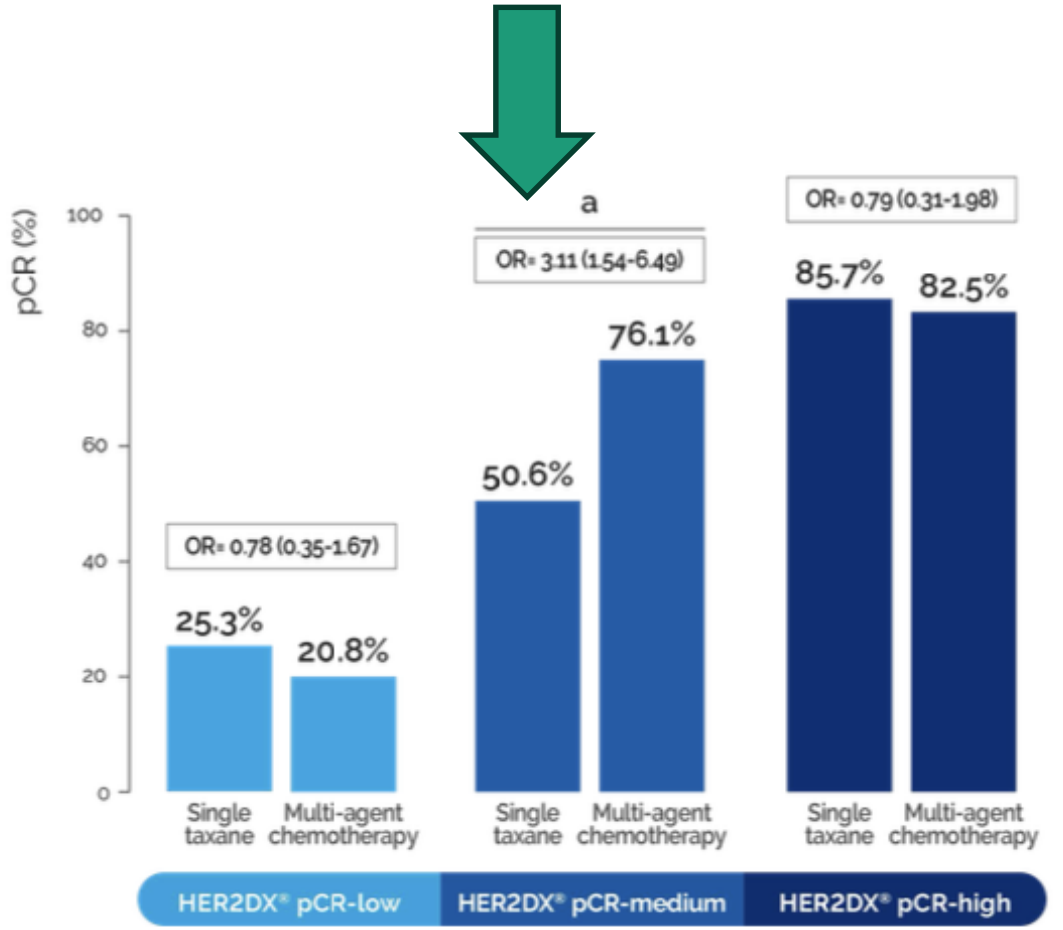


a: Statistically significant

HER2DX Score

pCR-medium → multiagent chemo increases pCR over single taxane w dual HER2 blockade

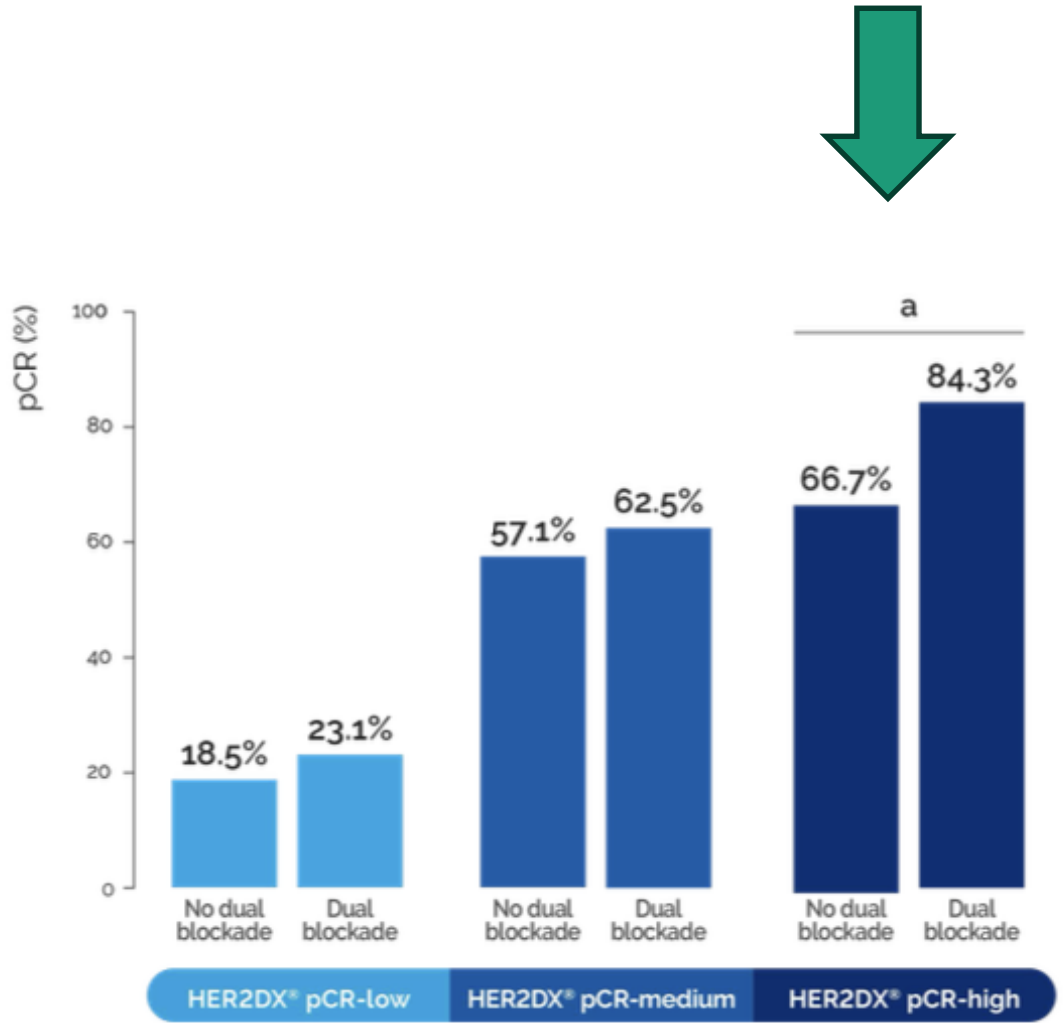


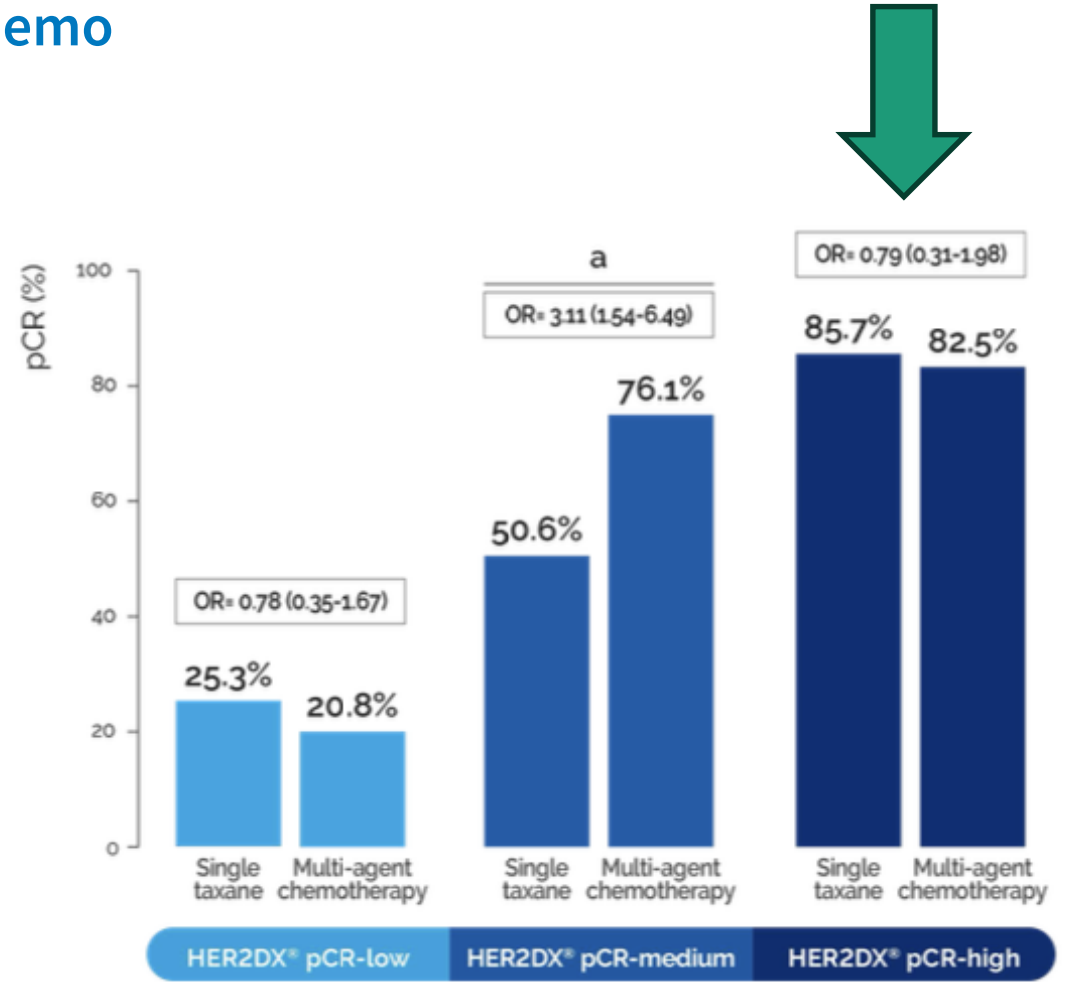


a: Statistically significant

HER2DX Score

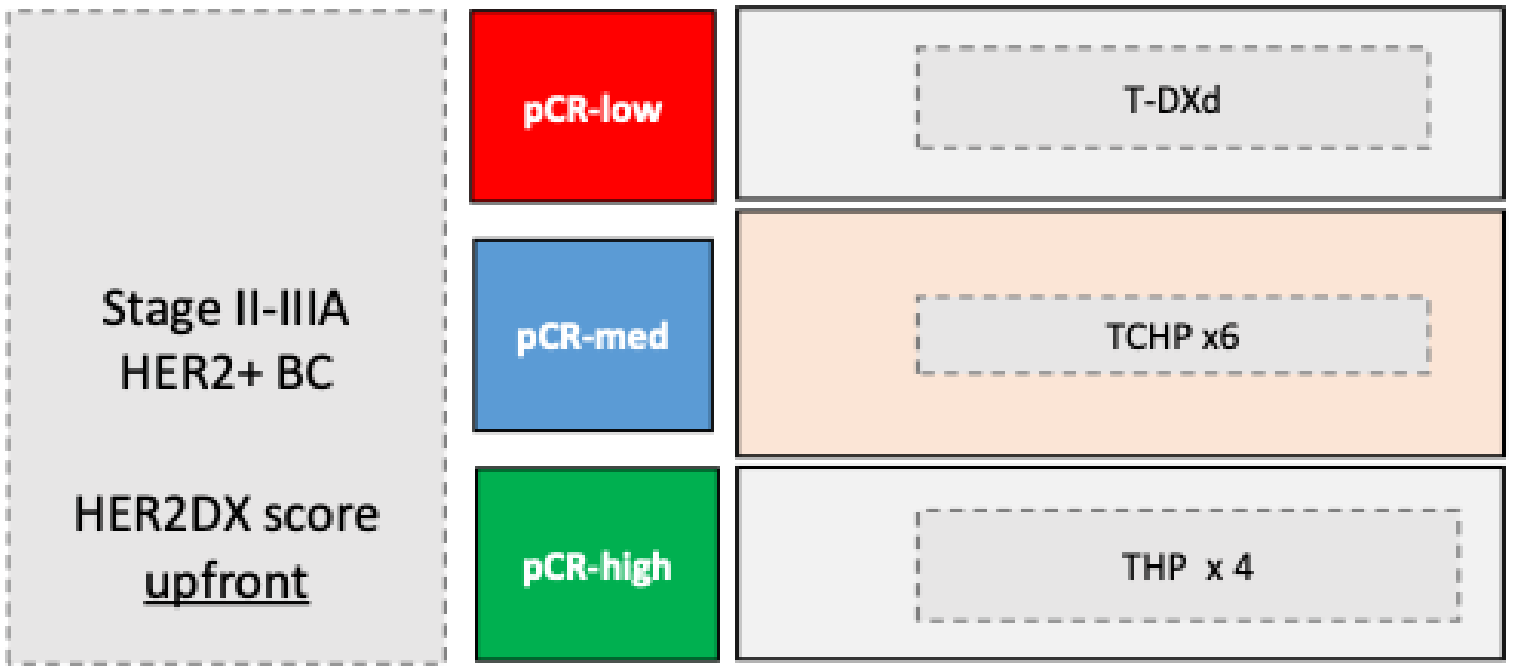
pCR-high → highest pCR >80% w dual HER2 blockade; single taxane same as multiagent chemo





a: Statistically significant

COULD WE EVER GET TO A POINT WHERE WE CAN SELECT THERAPY UPFRONT VIA A BIOMARKER?



Slide credit Sara Tolaney

pCR rates across trials

		Overall	HR-	HR+
Taxane-HP x12 wks	Tax-HP (CompassHER2-pCR)	44%	64%	33%
	THP (DAPHNe)	57%	85%	42%
	THP (WSG-TP-II)	-	-	56%
	DHP (NeoSphere)	39%	-	-
Taxane-HP x18 wks	nab-THP (HELEN006)	66%	86%	53%
	Tax-HP (NeoCARHP)	64%	78%	56%
Taxane-Cb-HP x18 wks	DCbHP (TRYPHAENA)	52%	-	-
	DCbHP (KRISTINE)	56%	73%	44%
	DCbHP (HELEN006)	58%	70%	48%
	Tax-CbHP (NeoCARHP)	66%	78%	59%

Cb: carboplatin; D: docetaxel; T: paclitaxel; Tax: mix of taxanes

Waks AG et al *Nat Rev Clin Oncol* 2025. Gao H-F et al. ASCO 2025. Chen X-C et al. *Lancet Oncol*. 2025.

Slide credit Sara Tolaney

DESTINY-Breast 11

Presented at ESMO

Regimen approved May 15, 2026

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel, trastuzumab, and pertuzumab for high-risk HER2-positive early breast cancer (DESTINY-Breast11): a randomised, open-label, multicentre, phase III trial☆

N. Harbeck[1*], S. Modi[2], L. Pusztai[3], S. Ohno[4], J. Wu[5], S.-B. Kim[6], A. Yoshida[7], A. Fabi[8], X. Cao[9,10], R. Joseph[11], R. Li[12], B. Żurawski[13], S. Escrivá-de-Romaní[14,15], R. Meneguetti[16], A. Supavavej[17], S.-C. Chen[18], Z. Liu[19], C. Kelly[20,21], G. Curigliano[22,23], W. F. Symmans[24], M. Gufran[25], J. Ke[26], A. Konpa[27], P. Herbolsheimer[28] & J.-F. Boileau[29], for the DESTINY-Breast11 Trial Investigators[†]

[1]Breast Center, Department of OB&GYN, LMU University Hospital and CCC Munich, Munich, Germany; [2]Department of Medicine, Breast Medicine Service, Memorial Sloan Kettering Cancer Center, New York; [3]Yale Cancer Center, Yale University School of Medicine, New Haven, USA; [4]Breast Thyroid Surgery, Sagara Hospital, Kagoshima, Japan; [5]Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; [6]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [7]Department of Breast Surgical Oncology, St. Luke's International Hospital, Chuo-ku, Tokyo, Japan; [8]Precision Medicine Unit in Senology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [9]The First Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin; [10]Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin, China; [11]Department of Medical Oncology, Regional Cancer Centre, Thiruvananthapuram, India; [12]Section of Medical Oncology, St Luke's Medical Center, Quezon City, Philippines; [13]Department of Outpatient Chemotherapy, Professor Franciszek Łukaszczyk Oncology Center, Bydgoszcz, Poland; [14]Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona; [15]Breast Cancer Unit, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [16]Clinical Research Center, Instituto de Pesquisa Hapvida Notredame, São Paulo, Brazil; [17]Division of Medical Oncology, Chulabhorn Hospital, Chulabhorn Royal Academy, Bangkok, Thailand; [18]Division of General Surgery, Department of Surgery, Chang Gung Memorial Hospital, Taoyüan, Taiwan, R.O.C.; [19]Department of Breast Disease, Henan Breast Cancer Centre, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; [20]Department of Medical Oncology, Mater Private Hospital, Dublin; [21]Cancer Trials Ireland Breast Group, Dublin, Ireland; [22]European Institute of Oncology, IRCCS, Milan; [23]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; [24]Department of Pathology, University of Texas MD Anderson Cancer Center, Houston, USA; [25]Global Medicines Development, Patient Safety Oncology, AstraZeneca, Luton, UK; [26]Oncology Biometrics, Late-Stage Development, Oncology R&D, AstraZeneca, Waltham, USA; [27]Clinical Development, Late-Stage Oncology, Oncology Research and Development, AstraZeneca, Warsaw, Poland; [28]Clinical Development, Late-Stage Oncology, Oncology Research and Development, AstraZeneca, Gaithersburg, USA; [29]Departments of Surgery and Gerald Bronfman Oncology, Montreal Jewish General Hospital, Segal Cancer Centre, McGill University, Montreal, Canada

Available online 21 October 2025

Background: Neoadjuvant standard-of-care for HER2-positive early-stage breast cancer is trastuzumab + pertuzumab with polychemotherapy; however, existing regimens have high toxicity burdens and suboptimal outcomes. DESTINY-Breast11 assessed efficacy and safety of neoadjuvant trastuzumab deruxtecan (T-DXd) alone or followed by paclitaxel + trastuzumab + pertuzumab (THP) versus dose-dense doxorubicin + cyclophosphamide (ddAC) followed by THP for high-risk (≥cT3cN0 or cT0–4cN1–3) HER2-positive disease.

Patients and methods: This open-label, phase III trial (147 sites, 18 countries) randomised adults 1 : 1 : 1 to T-DXd (×8 cycles), T-DXd-THP (4 + 4 cycles), or ddAC-THP (4 + 4 cycles). T-DXd-alone arm enrolment closed early following the

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1.Harbeck N, Modi S, Pusztai L ...

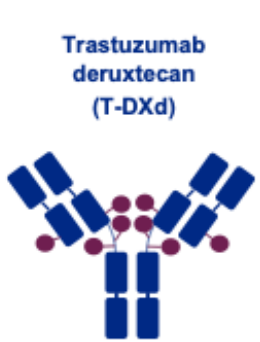
2.Neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel, trastuzumab, and pertuzumab for high-risk HER2-positive early breast cancer (DESTINY-Breast11): a randomised, open-label, multicentre, phase III trial☆

3.Annals of Oncology, 2025; 37, 166-179

Trastuzumab Deruxtecan (T-DXd)

Antibody Drug Conjugate (ADC) with 3 components

1) **Humanized anti-HER2 IgG1 mAb w same amino acid sequence as trastuzumab**
2) **Cleavable Linker that bonds antibody and payload**
3) **Topoisomerase I inhibitor payload (DXd)**
    1) Drug-to-antibody ratio 8:1
    2) Payload can attack neighboring cancer cells through bystander effect



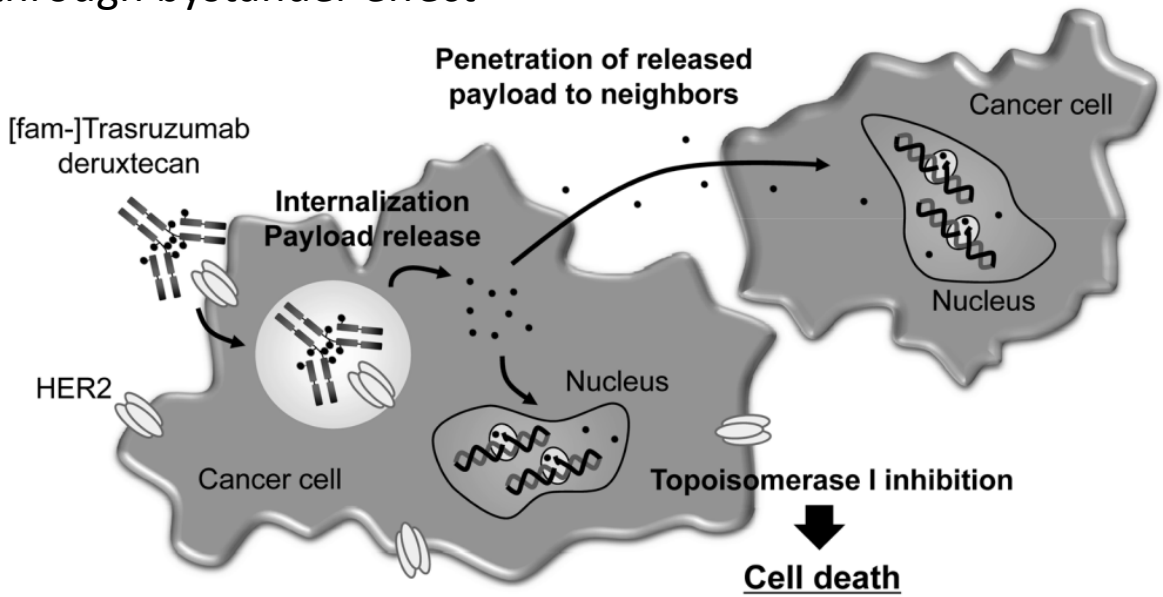


Illustration of the Bystander Effect of [fam-] Trastuzumab Deruxtecan

Nakada T, *Chem Pharm Bull* 2019; Ogitani Y, *Clin Cancer Res* 2016; Trail PA, *Pharmacol Ther* 2018; Ogitani Y, *Cancer Sci* 2016.

BERLIN 2025 ESMO congress

DESTINY Breast11

DESTINY-Breast11: neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel + trastuzumab + pertuzumab vs ddAC-THP for high-risk HER2+ early breast cancer

Nadia Harbeck

Breast Center, Department of OB&GYN and CCC Munich,
LMU University Hospital, Munich, Germany

Co-authors: Shanu Modi, Lajos Pusztai, Shinji Ohno, Jiong Wu, Sung-Bae Kim, Alessandra Fabi, Xuchen Cao, Rona Joseph, Rubi Li, Bogdan Żurawski, Santiago Escrivá-de-Romaní, Shin-Cheh Chen, Catherine Kelly, Giuseppe Curigliano, William Fraser Symmans, Shoubhik Mondal, Shahana Safdar, Pia Herbolsheimer, Jean-François Boileau
On behalf of the DESTINY-Breast11 investigators

Saturday October 18, 2025

Presentation 291O

DESTINY-Breast 11

2021 – 2025

927 patients

Randomized

- **T-DXD x 4 → THP x 4**
- **AC x 4 → THP x 4**
- **T-DXD x 8**

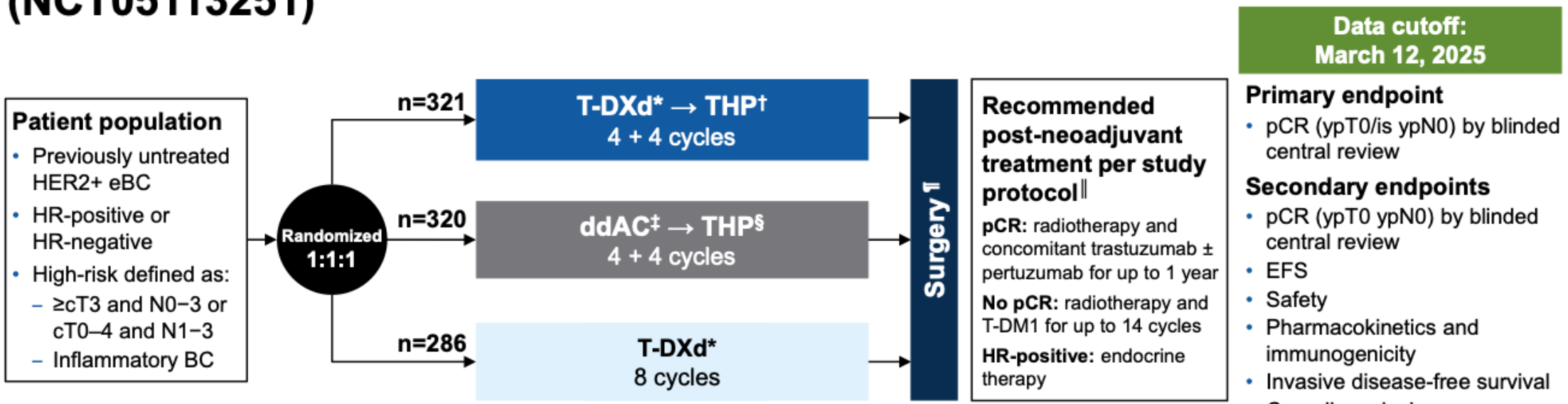
DESTINY-Breast 11

Interstitial Lung Disease (ILD) Monitoring

- **High resolution CT at baseline and q6 weeks until the end of treatment**
-

DESTINY-Breast11 study design

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



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)

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

High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. *5.4 mg/kg Q3W; †paclitaxel (80 mg/m^2 QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ‡doxorubicin (60 mg/m^2 Q2W) + cyclophosphamide (600 mg/m^2 Q2W); §paclitaxel (80 mg/m^2 QW) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ¶the recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment; ‖administered as part of the patient's SOC at the investigator's discretion. cT, clinical tumor stage; ER, estrogen receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH+, in situ hybridization–positive; N, nodal stage; PR, progesterone receptor; QXW, every X weeks; T-DM1, trastuzumab emtansine; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes; ypT0 ypN0, absence of invasive and in-situ cancer in the breast and axillary nodes

Nadia Harbeck, MD

DESTINY-Breast11

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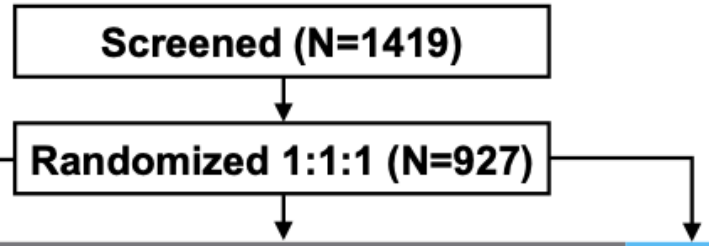
Patient disposition



n (%)	T-DXd-THP (n=321)				ddAC-THP (n=320)				T-DXd (n=286)
Treated	320 (99.7)				312 (97.5)				283 (99.0)
Discontinued study treatment*									
Any	54 (16.9)				43 (13.8)				52 (18.4)
Individual drug	**T-DXd**	**T**	**H**	**P**	**AC**	**T**	**H**	**P**	
	9 (2.8)	45 (14.4)	7 (2.2)	7 (2.2)	9 (2.9)	36 (12.0)	9 (3.0)	11 (3.7)	
Reason for discontinuation*									
AE	4 (1.3)	41 (13.1)	7 (2.2)	7 (2.2)	3 (1.0)	27 (9.0)	4 (1.3)	5 (1.7)	22 (7.8)
Disease progression	0	0	0	0	1 (0.3)	2 (0.7)	2 (0.7)	2 (0.7)	4 (1.4)
Patient decision	3 (0.9)	2 (0.6)	0	0	4 (1.3)	6 (2.0)	2 (0.7)	3 (1.0)	4 (1.4)
Other	2 (0.6)	1 (0.3)	0	0	1 (0.3)	0	0	0	21 (7.4)
Death	0	1 (0.3)	0	0	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.4)
Underwent surgery on trial†	312 (97.2)				300 (93.8)				274 (95.8)

*Percentages are based on the number of patients who started specified treatment; †reasons for not undergoing surgery included patient decision, disease progression, death before surgery, withdrawal of consent before surgery, and patients who were randomized but not treated
AC, doxorubicin + cyclophosphamide; H, trastuzumab; P, pertuzumab; T, paclitaxel

Patient demographics and key baseline characteristics

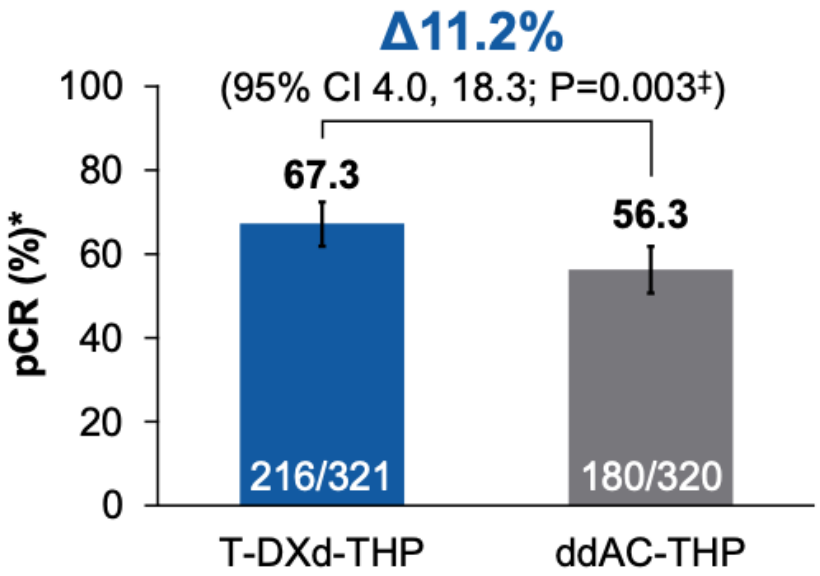
		T-DXd-THP (n=321)	ddAC-THP (n=320)	T-DXd (n=286)
Median (range) age, years		50 (25–82)	50 (23–79)	50 (23–79)
Female, n (%)		321 (100)	320 (100)	286 (100)
Geographical region, n (%)	Asia	152 (47.4)	152 (47.5)	124 (43.4)
	Western Europe	69 (21.5)	77 (24.1)	66 (23.1)
	North America	43 (13.4)	41 (12.8)	52 (18.2)
	Rest of world*	57 (17.8)	50 (15.6)	44 (15.4)
Race, n (%)†	Asian	160 (49.8)	157 (49.1)	127 (44.4)
	White	140 (43.6)	137 (42.8)	139 (48.6)
	Black or African American	5 (1.6)	7 (2.2)	7 (2.4)
	Other	12 (3.7)	10 (3.1)	8 (2.8)
Eastern Cooperative Oncology Group performance status score, n (%)	0	278 (86.6)	280 (87.5)	252 (88.1)
	1	43 (13.4)	40 (12.5)	34 (11.9)
HER2 status, n (%)‡	IHC 3+	280 (87.2)	283 (88.4)	254 (88.8)
	Other	40 (12.5)	36 (11.3)	32 (11.2)
HR status, n (%)§	Positive¶	236 (73.5)	235 (73.4)	205 (71.7)
Clinical tumor stage, n (%)	cT0–2	176 (54.8)	188 (58.8)	157 (54.9)
	cT3–4	145 (45.2)	132 (41.3)	129 (45.1)
Nodal status, n (%)‖	N0	26 (8.1)	35 (10.9)	20 (7.0)
	N+	287 (89.4)	281 (87.8)	254 (88.8)

*Brazil, Bulgaria, Peru, Poland, Russia, and Saudi Arabia; †not reported for four patients (1.2%), nine patients (2.8%) and five patients (1.7%) in the T-DXd-THP, ddAC-THP, and T-DXd alone arms, respectively; ‡centrally confirmed. Not categorized for one patient (0.3%) in the T-DXd-THP arm and missing for one patient (0.3%) in the ddAC-THP arm; §the proportion of patients with HR-negative disease was capped at 30% to reflect natural prevalence. Missing for two patients (0.6%) and one patient (0.3%) in the T-DXd-THP and T-DXd alone arms, respectively; ¶ER and/or PR-positive per electronic case report form data; ‖unknown in eight patients (2.5%), four patients (1.3%), and 12 patients (4.2%) in the T-DXd-THP, ddAC-THP, and T-DXd alone arms, respectively

Nadia Harbeck, MD

pCR (ypT0/is ypN0): primary endpoint

ITT population† (primary endpoint)



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

For the ITT population, treatment effects were estimated by the difference in pCR with 95% confidence intervals (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

DESTINY-Breast11

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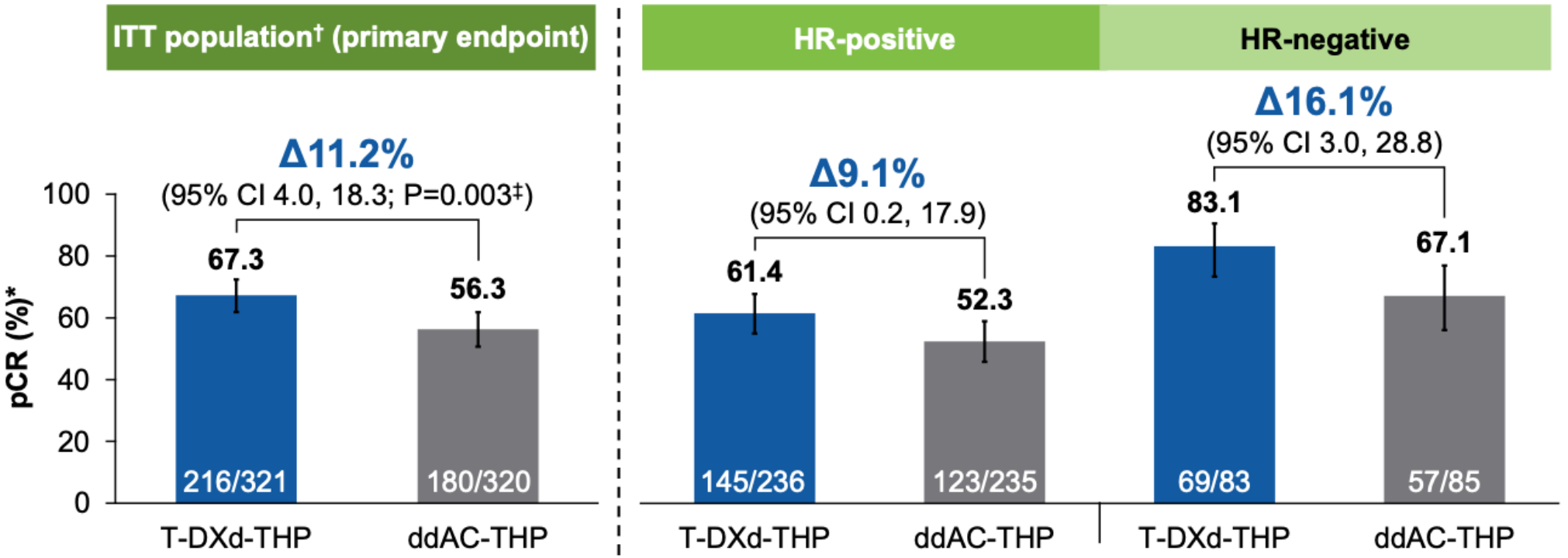
pCR (ypT0/is ypN0): primary endpoint



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

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pCR (ypT0/is ypN0) by subgroups

		pCR rate, % (n/N) T-DXd-THP (n=321)	ddAC-THP (n=320)	ΔpCR, % (95% CI)
All patients		67.3 (216/321)	56.3 (180/320)	**11.2** (4.0, 18.3)
Age at baseline	<65 years	66.7 (188/282)	58.0 (167/288)	**8.7** (0.7, 16.5)
	≥65 years	71.8 (28/39)	40.6 (13/32)	**31.2** (8.0, 51.4)
Geographical region	Asia	66.5 (101/152)	56.6 (86/152)	**9.9** (−1.1, 20.6)
	Western Europe	75.4 (52/69)	62.3 (48/77)	**13.0** (−2.2, 27.5)
	North America	74.4 (32/43)	36.6 (15/41)	**37.8** (16.8, 55.7)
	Rest of world*	54.4 (31/57)	62.0 (31/50)	**−7.6** (−25.7, 11.2)
Eastern Cooperative Oncology Group performance status score	0	68.7 (191/278)	55.7 (156/280)	**13.0** (5.0, 20.9)
	1	58.1 (25/43)	60.0 (24/40)	**−1.9** (−22.6, 19.1)
Menopausal status	Post	68.8 (86/125)	56.9 (87/153)	**11.9** (0.5, 23.0)
	Pre	66.9 (123/184)	55.2 (90/163)	**11.6** (1.4, 21.7)
HER2 status	IHC 3+	71.1 (199/280)	61.5 (174/283)	**9.6** (1.8, 17.3)
	Other	42.5 (17/40)	16.7 (6/36)	**25.8** (5.2, 44.4)
HR status	Positive	61.4 (145/236)	52.3 (123/235)	**9.1** (0.2, 17.9)
	Negative	83.1 (69/83)	67.1 (57/85)	**16.1** (3.0, 28.8)
American Joint Committee on Cancer clinical stage	II–IIIA	65.7 (163/248)	56.4 (146/259)	**9.4** (0.9, 17.7)
	IIIB–IIIC	72.2 (52/72)	55.7 (34/61)	**16.5** (0.1, 32.3)
Nodal status	N0	57.7 (15/26)	57.1 (20/35)	**0.6** (−24.2, 24.8)
	N+	68.3 (196/287)	56.6 (159/281)	**11.7** (3.8, 19.5)

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

Size of circle is proportional to the total sample size in a subgroup. *Brazil, Bulgaria, Peru, Poland, Russia, and Saudi Arabia

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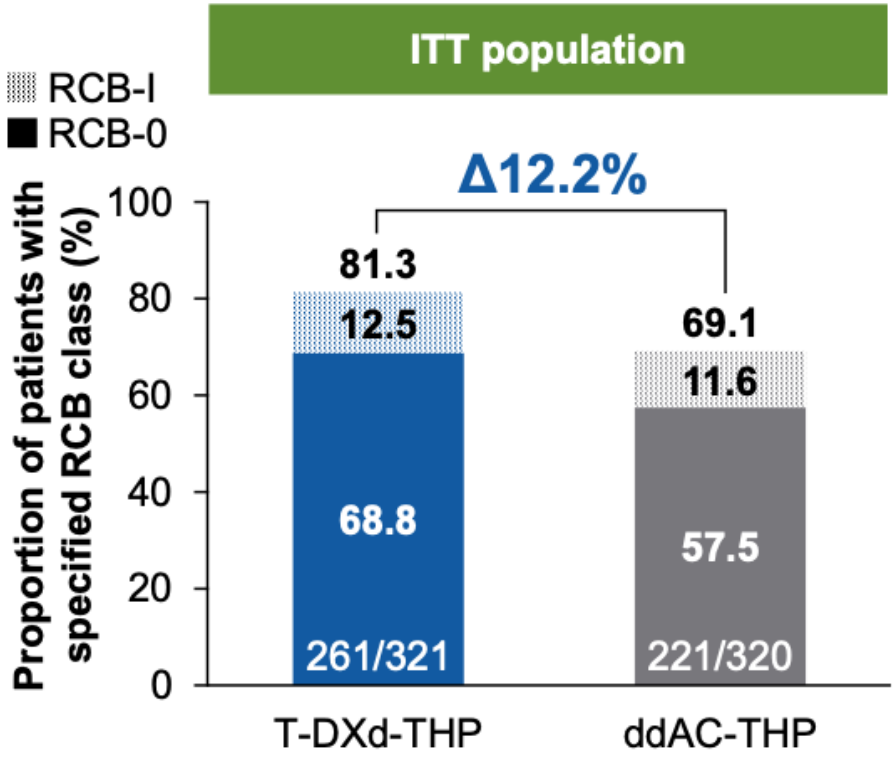
RCB outcomes



RCB-0: pCR: no residual invasive cancer in breast or lymph nodes

RCB-1: minimal residual disease

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

Unlike pCR results, RCB analysis is based on raw data and is not corrected for patients who did not receive study treatment or any bridging/off study neoadjuvant treatment; therefore, there may be differences between pCR and RCB-0. Not reported in 13 patients (4.0%) in the T-DXd-THP arm and 24 patients (7.5%) in the ddAC-THP arm. RCB class was based on central pathologic evaluation of the residual viable tumor (identified on routine hematoxylin and eosin staining after mapping of the surgical specimen)

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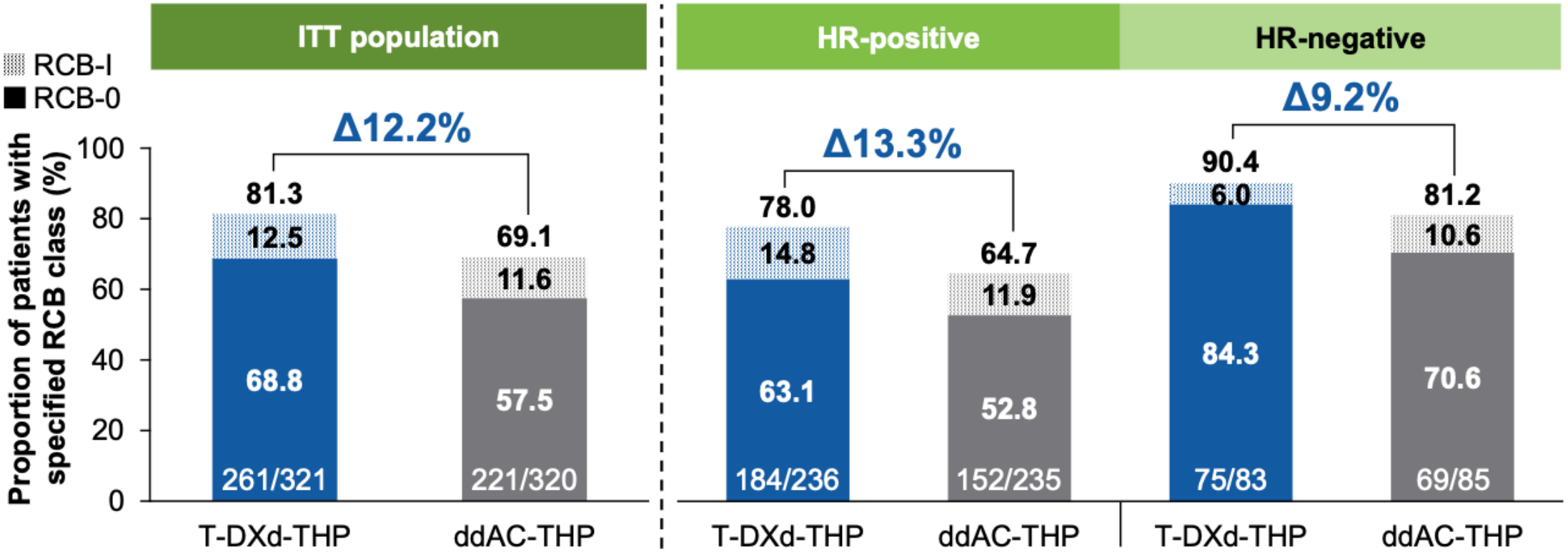
RCB outcomes



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Almost 80% of patients with HR-positive disease had RCB-0+I with T-DXd-THP

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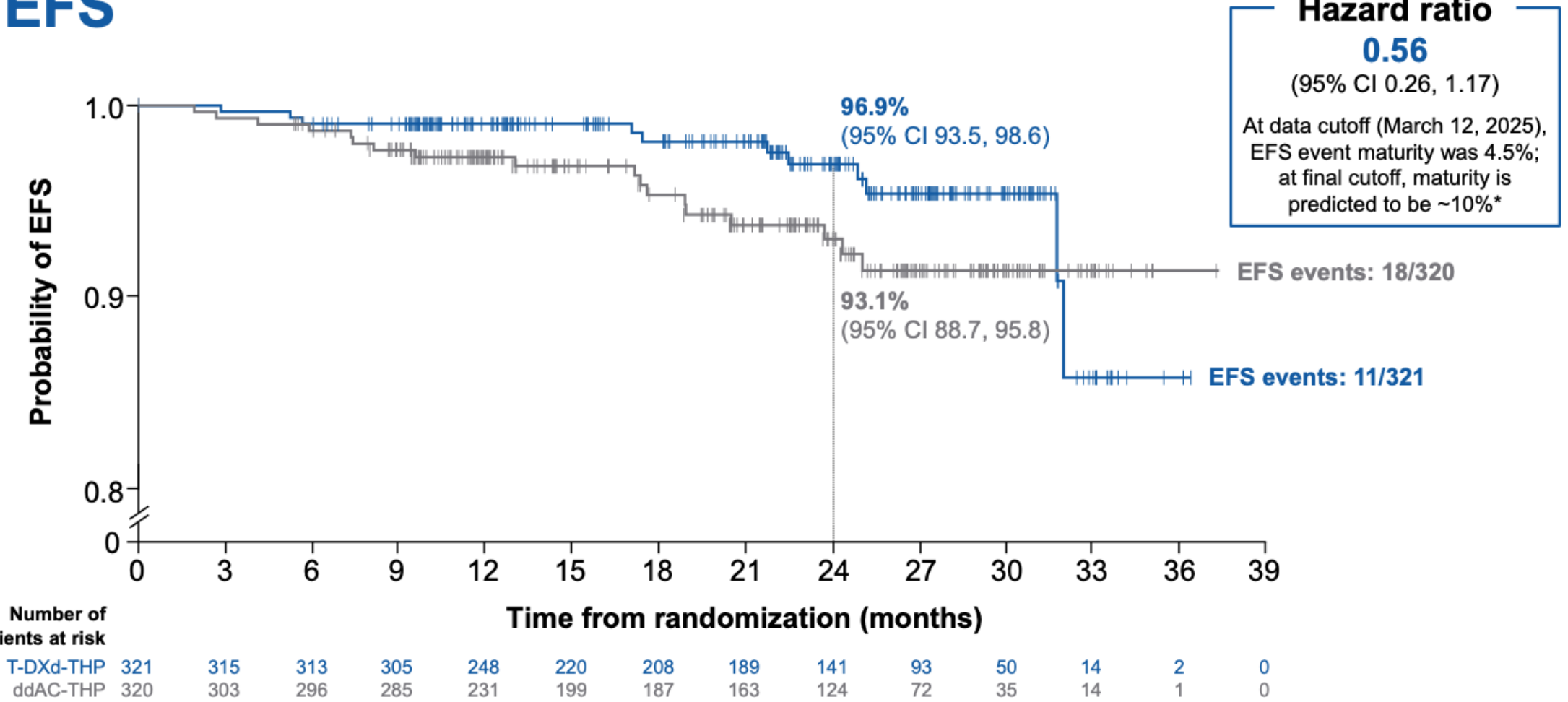
EFS



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)

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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)
Grade ≥3	1 (0.3)	6 (1.9)
Grade 5	0	0
AE leading to surgical delay‡	11 (3.4)	8 (2.6)

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

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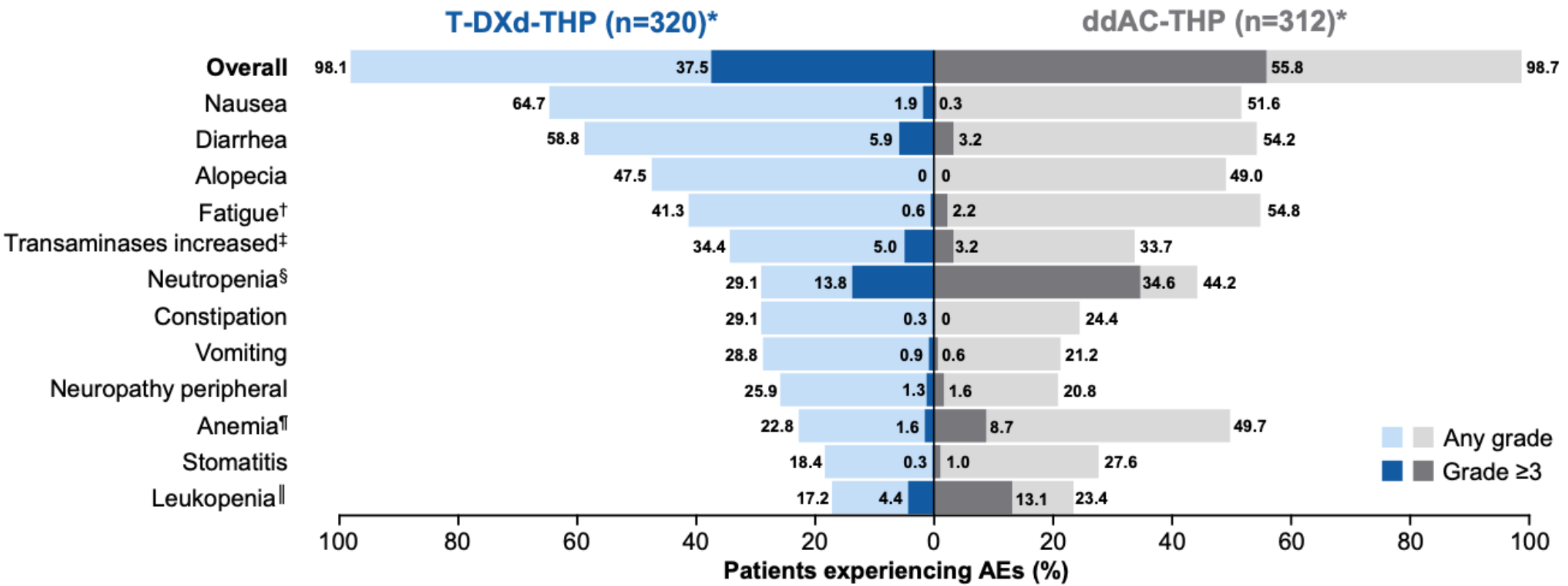
TEAEs in at least 20% of patients in either arm



T-DXd-THP had fewer any-grade and Grade ≥3 hematological and fatigue events than ddAC-THP
Aside from nausea, gastrointestinal toxicity was comparable between arms

*Safety analyses included all patients who received at least one dose of any study treatment; †grouped term: fatigue, asthenia, malaise, and lethargy; ‡grouped term: transaminases increased, aspartate transaminase increased, alanine transaminase increased, gamma-glutamyl transferase increased, liver function test abnormal, hypertransaminasemia, hepatic function abnormal, and liver function test increased; §grouped term: neutrophil count decreased and neutropenia; ¶grouped term: hemoglobin decreased, red blood cell count decreased, and anemia and hematocrit decreased; ‖grouped term: white blood cell count decreased and leukopenia. TEAE, treatment-emergent adverse event

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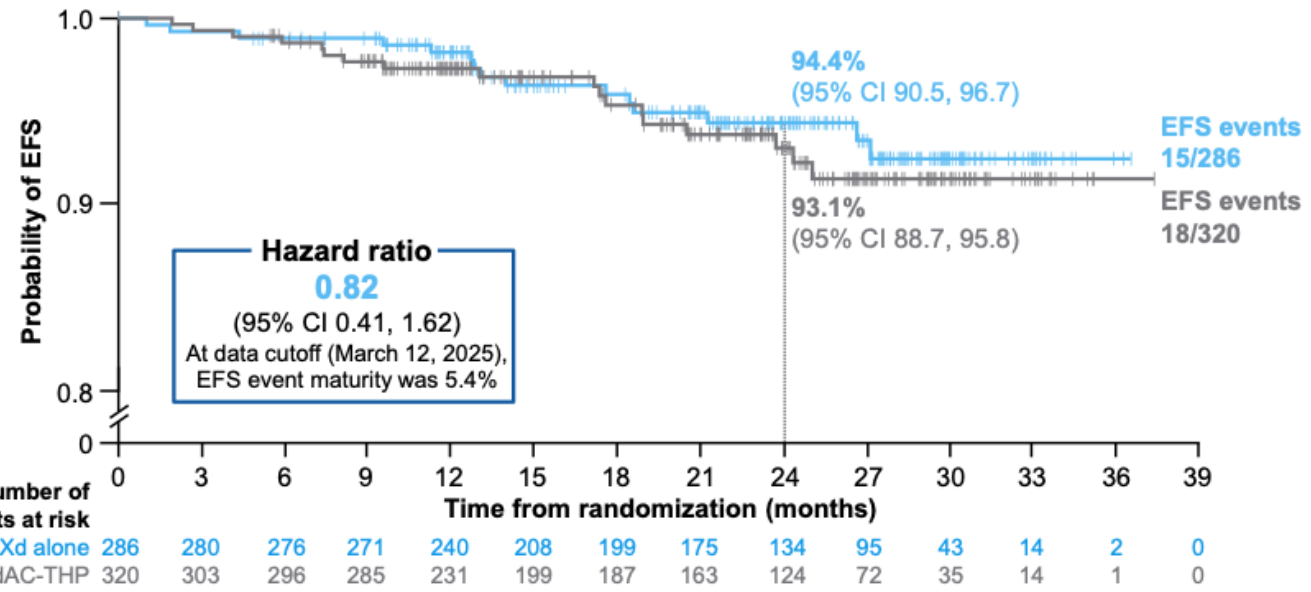
T-DXd alone arm: efficacy summary

On March 13, 2024, the T-DXd alone arm closed following Independent Data Monitoring Committee recommendation.* Patients who were still receiving T-DXd alone could remain on therapy or immediately switch to local SOC

pCR rate

%	T-DXd (n=286)	ddAC-THP (n=320)
Primary analysis Switch to local SOC classified as non-pCR		
pCR†	43.0	56.3
Δ (95% CI)	−13.2 (−20.8, −5.4)	
Prespecified supplementary analysis Switch to local SOC not automatically classified as non-pCR		
pCR†	51.4	57.2
Δ (95% CI)	−5.8 (−13.4, 1.9)	

EFS



T-DXd alone showed inferior but robust pCR compared with the five-agent ddAC-THP
EFS data were similar for T-DXd alone and ddAC-THP

Treatment effects were estimated by the difference in pCR with 95% CIs based on the stratified Miettinen and Nurminen's method, with strata weighting by sample size (ie Mantel–Haenszel weights). Median duration of follow up was 24.9 months (T-DXd) and 23.6 months (ddAC-THP). Analyses are reported in the ITT population. *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; †by blinded central review

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Conclusions

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

pCR rate

67.3%

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

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

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

*Historical pCR rates (defined by ypT0/is ypN0) from other registrational studies for neoadjuvant SOC treatments in HER2+ eBC ranged from 39.3% to 62.7%, and HR-positive prevalence ranged from 46.7% to 62.4%[1–3]

1. Huober J, et al. *J Clin Oncol*. 2022;40:2946–2956; 2. Hurvitz SA, et al. *Lancet Oncol*. 2018;19:115–126; 3. Gianni L, et al. *Lancet Oncol*. 2012;13:25–32

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Adjuvant therapy

KATHERINE TRIAL

DESTINY-Breast 05

KATHERINE Trial – T-DM1

Phase III

1,486 patients

HER2+ early breast cancer with residual disease in breast or axilla after taxane + trastuzumab based neoadjuvant therapy

von Minckwitz G, et al. *N Engl J Med.* 2019;380:617–628.

KATHERINE Trial – T-DM1

Randomized after surgery

T-DM1 3.6 mg/kg IV q3 weeks x 14 cycles

Trastuzumab q3 weeks x 14 cycles

Primary endpoint: invasive disease-free survival (iDFS)

Geyer CE Jr, Untch M, Huang CS, et al. Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer. *N Engl J Med.* **2025;392:249-257.**

von Minckwitz G, et al. *N Engl J Med.* 2019;380:617–628.

KATHERINE Trial – T-DM1

7-year invasive disease–free survival (iDFS)

80.8% with T-DM1

67.1% with trastuzumab

(difference, 13.7 percentage points).

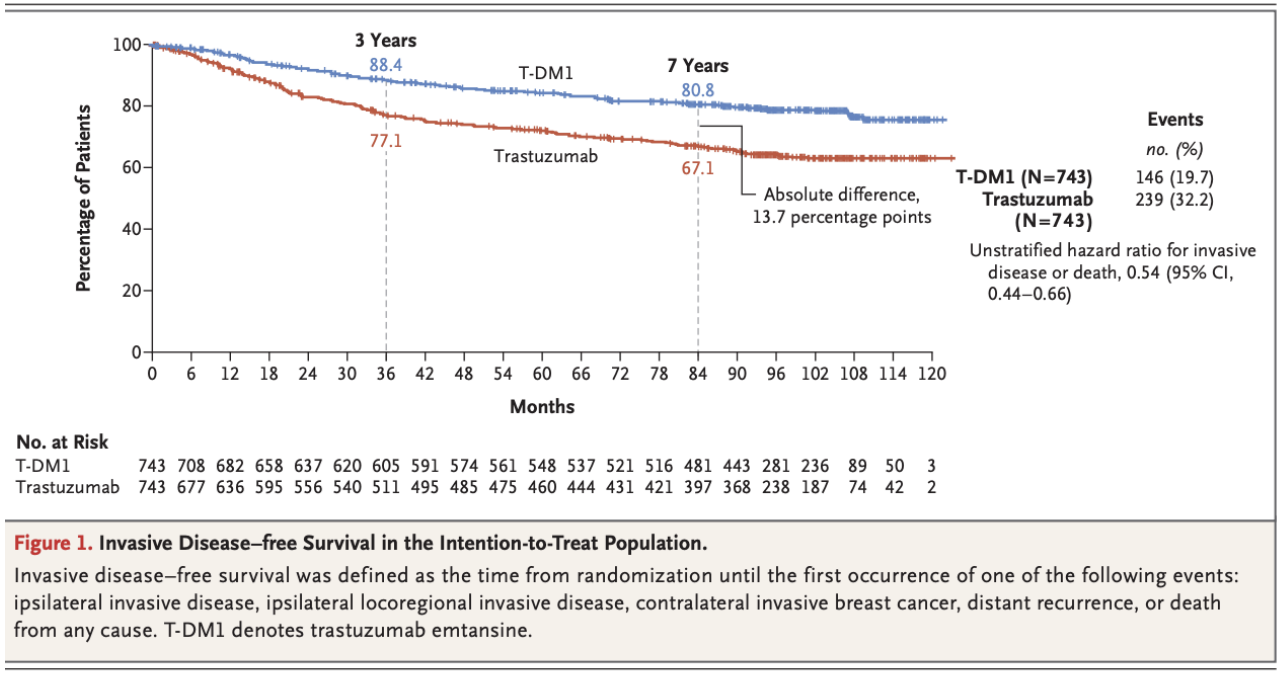

Figure 1. Invasive Disease–free Survival in the Intention-to-Treat Population.

Invasive disease–free survival was defined as the time from randomization until the first occurrence of one of the following events: ipsilateral invasive disease, ipsilateral locoregional invasive disease, contralateral invasive breast cancer, distant recurrence, or death from any cause. T-DM1 denotes trastuzumab emtansine.

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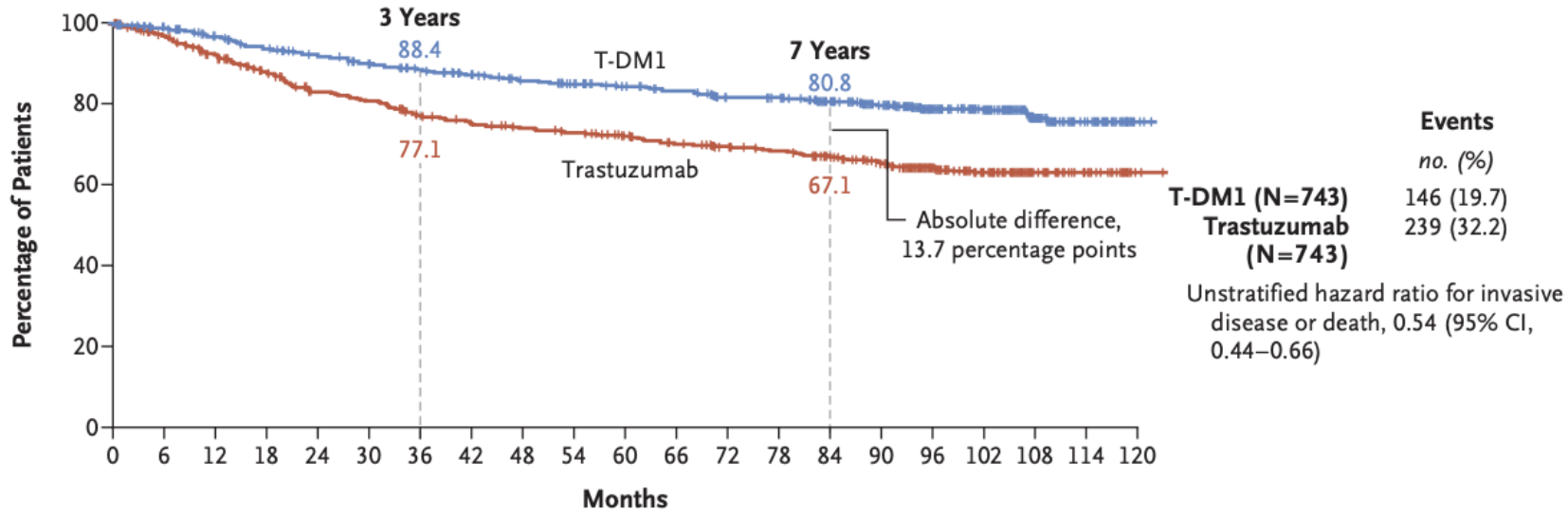
KATHERINE Trial – T-DM1



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von Minckwitz G, et al. *N Engl J Med.* 2019;380:617–628.

KATHERINE Trial – T-DM1

Seven year overall survival

89.1% with T-DM1

84.4% with trastuzumab

(difference, 4.7 percentage points).

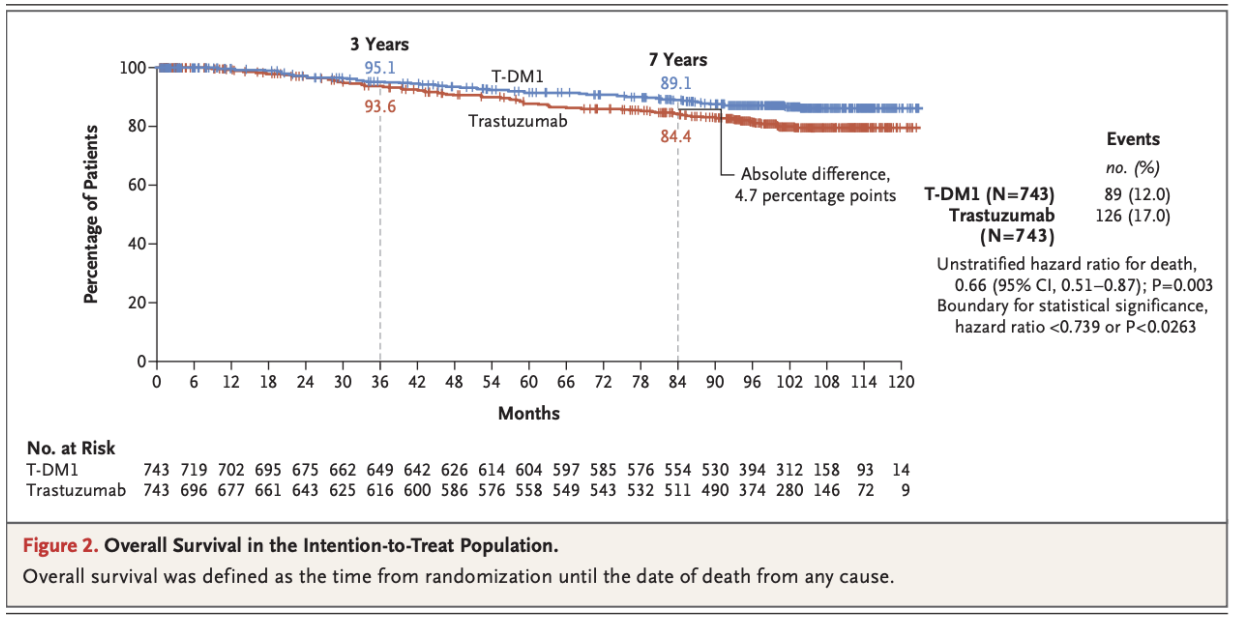

Figure 2. Overall Survival in the Intention-to-Treat Population.
Overall survival was defined as the time from randomization until the date of death from any cause.

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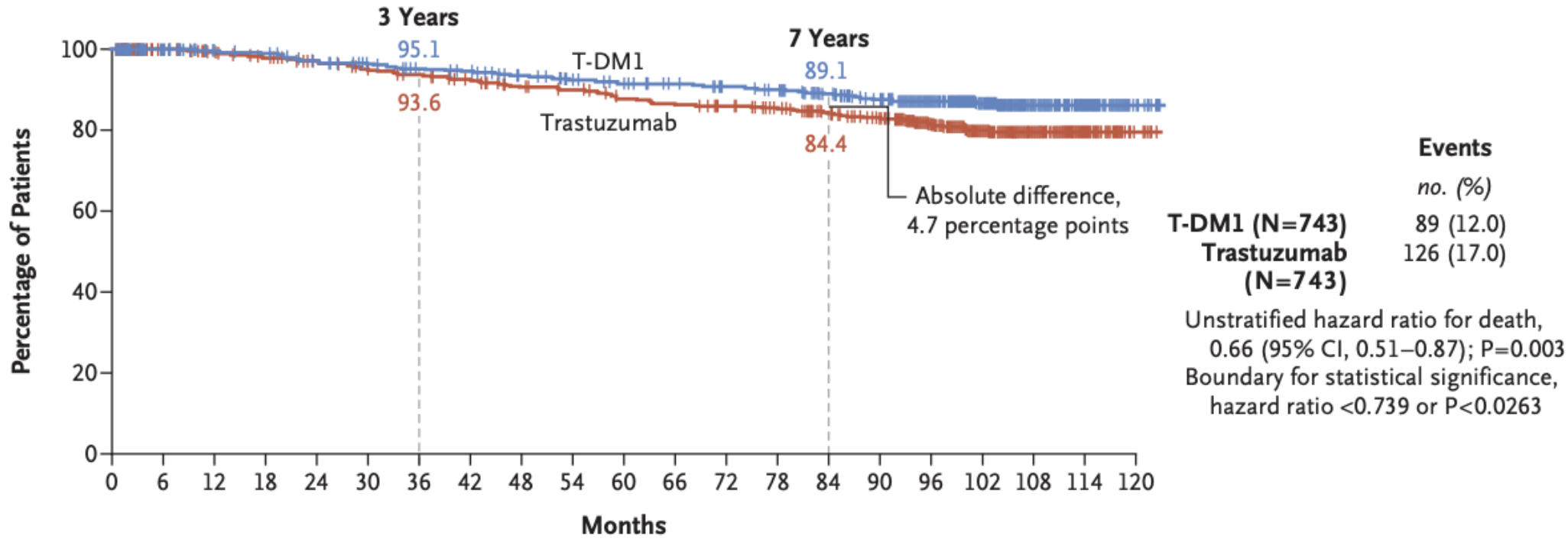
KATHERINE Trial – T-DM1



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DESTINY-Breast 05

Phase III study evaluation adjuvant T-DXd vs T-DM1 in pts w high-risk HER2+ early BC w residual disease after NAT

FDA Approval May 15, 2026

Loibl S, et al. Trastuzumab Deruxtecan in Residual HER2-Positive Early Breast Cancer. *N Engl J Med.* **2025**. doi: **10.1056/NEJMoa2514661**.

DESTINY-Breast 05 FDA Approval

Adjuvant T-DXd approved for adjuvant treatment of HER2+ bc w residual invasive disease after neoadjuvant trastuzumab +/- pertuzumab and taxane therapy

Loibl S, et al. Trastuzumab Deruxtecan in Residual HER2-Positive Early Breast Cancer. *N Engl J Med.* **2025**. doi: **10.1056/NEJMoa2514661**.

DESTINY-Breast 05

1635 patients randomly assigned to

- **T-DXd 5.4 mg/kg IV q3 weeks x 14 vs**
- **T-DM1 3.6 mg/kg IV q3 w x 14**

Primary endpoint invasive disease free survival (IDFS)

DESTINY-Breast 05

Baseline Characteristics[1-2]

		T-DXd n = 818	T-DM1 n = 817
Age, median (range), years		50.3 (24-78)	50.6 (21-83)
Age group, n (%)	< 65 years	735 (89.9)	736 (90.1)
	≥ 65 years	83 (10.1)	81 (9.9)
Female sex, n (%)		814 (99.5)	814 (99.6)
Race, n (%)	White	301 (36.8)	333 (40.8)
	Black or African American	22 (2.7)	13 (1.6)
	Asian	399 (48.8)	386 (47.2)
	Other[a]	96 (11.7)	85 (10.4)
Region, n (%)	Asia	392 (47.9)	380 (46.5)
	Europe	222 (27.1)	223 (27.3)
	North America + Australia	57 (7.0)	72 (8.8)
	Rest of world[b]	147 (18.0)	142 (17.4)
ECOG PS score, n (%)	0	656 (80.2)	652 (79.8)
	1	162 (19.8)	165 (20.2)
HER2 expression,[c] n (%)	IHC 3+	676 (82.6)	670 (82.0)
	IHC 2+ and ISH+	129 (15.8)	133 (16.3)
	IHC 2+ and ISH−	2 (0.2)	0
	IHC 1+ and ISH+	11 (1.3)	14 (1.7)
Hormone receptor status,[d] n (%)	Positive	581 (71.0)	583 (71.4)
	Negative	237 (29.0)	234 (28.6)

DESTINY-Breast 05 vs KATHERINE

DESTINY-BREAST 05: OPTIMIZING OUTCOMES IN HIGH-RISK PATIENTS

DESTINY-BREAST05 vs KATHERINE: BASELINE CHARACTERISTICS

DESTINY-BREAST05			KATHERINE		
ITT Population	T-DXd (n=818)	T-DM1 (n=817)	ITT Population	T-DM1 (n=743)	Trastuzumab (n=743)
Median age (range), years	50.3 (24-78)	50.6 (21-83)	Median age (range), years	49 (24-79)	49 (23-80)
Hormone Receptor status			Hormone Receptor status		
HR+	581 (71.0)	583 (71.4)	HR+	534 (71.9)	540(72.7)
HR-	237 (29.0)	234 (28.6)	HR-	209 (28.1)	203 (27.3)
HER2 IHC					
HER2 3+				573 (77.1)	559 (75.2)
HER2 1+/2+				170 (22.9)	181 (24.3)
				0 (0)	3 (0.4)
Operative Status at Presentation					
Operable				558 (75.1)	554 (74.4)
Inoperable	431 (52.7)	424 (51.9)	Inoperable	185 (24.9)	190 (25.6)
Post-neoadj tx nodal status			Post-neoadj tx nodal status		
Positive	660 (80.7)	658 (80.5)	Positive	343(46.1)	346 (46.6)
Negative	158 (19.3)	159 (19.5)	Negative	400 (53.8)	397(53.4)
Neoadjuvant HER2 Therapy Approach			Neoadjuvant HER2 Therapy Approach		
Single HER2 targeting	176 (21.5)	171 (20.9)	Single HER2 targeting	600 (80.8)	171 (20.9)
Dual HER2 targeting	642 (78.5)	646 (79.1)	Dual HER2 targeting	143 (19.2)	147 (19.8)
Neoadjuvant Anthracycline use	423 (51.7)	399 (48.8)	Neoadjuvant Anthracycline use	579 (77.9)	564 (75.9)

ENROLLED 12/2020-2/2024

Enrolled 4/2013-12/2015

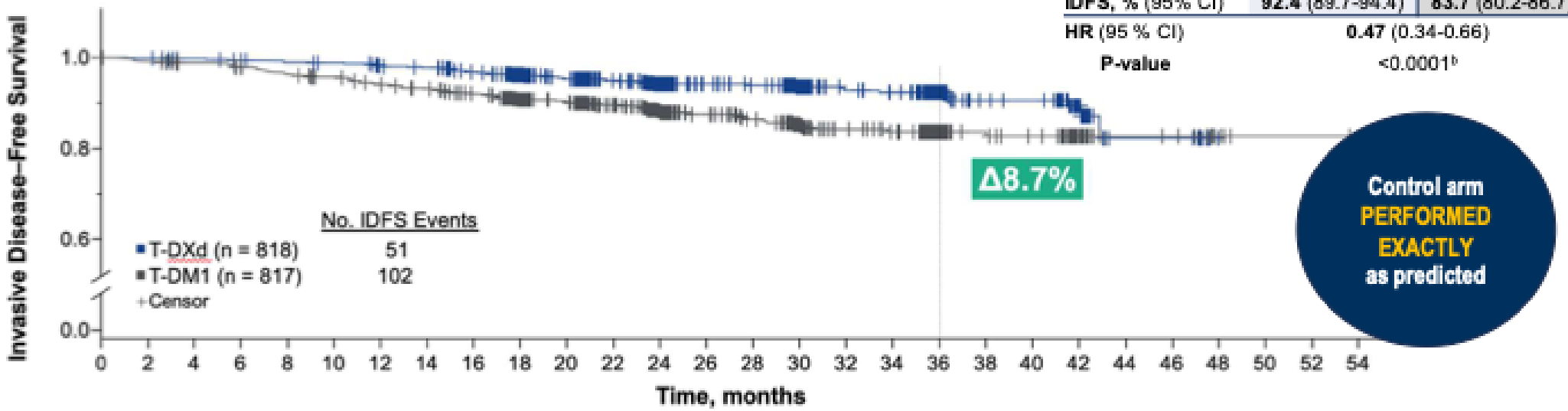
DESTINY-Breast 05

Key result: 3-year iDFS 92.4% with T-DXd vs 83.7% with T-DM1; HR 0.47 (95% CI, 0.34–0.66; *P*<0.001).

DB-05: T-DXd REDUCED RISK OF RECURRENCE BY HALF IN A HIGH-RISK RESIDUAL DISEASE POPULATION

3-year IDFS

	T-DXd n = 818	T-DM1 n = 817
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]	



Control arm PERFORMED EXACTLY as predicted

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.

Geyer CE et al. ESMO 2025

2026 ASCO ANNUAL MEETING

Abstract 516

DESTINY Breast05

Secondary safety analysis of trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in DESTINY-Breast05: Clinical and demographic risk factors of interstitial lung disease and radiation pneumonitis

Michael Untch, Zhiming Shao, Chiun-Sheng Huang, Carlos Barrios, Jame Abraham, Aleix Prat, Naoki Niikura, Sibylle Loibl, Charles Geyer, Cui-Zhi Geng, Francisco Javier Ramirez Godinez, Chuangui Song, Yuan Ching Chang, Augusto Antoniazzi, Shin-Cheh Chen, Elton Mathias, Jennifer Petschauer, Erin Goodman, Michael Jan, Yeon Hee Park
On behalf of the DESTINY-Breast05 investigators

Dr. Michael Untch

Health and Medical University, Breast Cancer Center, Helios Hospital Berlin-Buch, Berlin, Germany

NSABP National Surgical Adjuvant Breast and Bowel Project · GBG German Breast Group · AGO-B Breast Study Group · SOLTI

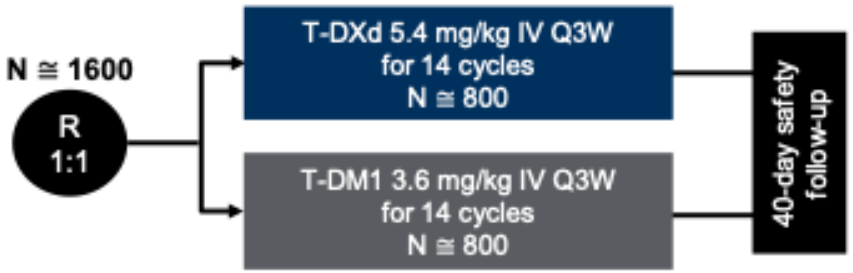
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

DESTINY-Breast05[1]

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 of recurrence**[b]
- **Centrally confirmed HER2+** (IHC 3+ or ISH+) eBC
- ECOG PS 0 or 1



If administered, RT could be initiated concurrent (CC) with study therapy or completed prior to initiation of study therapy (sequential; SEQ) per investigator

Primary endpoint: IDFS

Key secondary endpoint: DFS

Other secondary endpoints: OS, BMFI, Safety, DRFI

DCO: July 2, 2025

Efficacy

T-DXd is approved in the US based on the primary results of DESTINY-Breast05,[2] in which T-DXd demonstrated superior efficacy versus T-DM1 patients with HER2+ eBC with residual invasive disease after NAT and high risk of recurrence (IDFS events hazard ratio, 0.47 [95% CI, 0.34-0.66]; $P < 0.001$) — a population in which RT is broadly used

Safety

In both treatment arms, >72% of patients had completed 14 treatment cycles[c]; treatment had concluded for all patients in the study

Most cases of adjudicated drug-related **ILD were grade 1 or 2**

Rates of investigator-reported **RP**, most of which were **grade 1**, were similar between the T-DXd and T-DM1 arms

Timing of aRT showed no impact on the rates of ILD or RP whether administered SEQ or CC

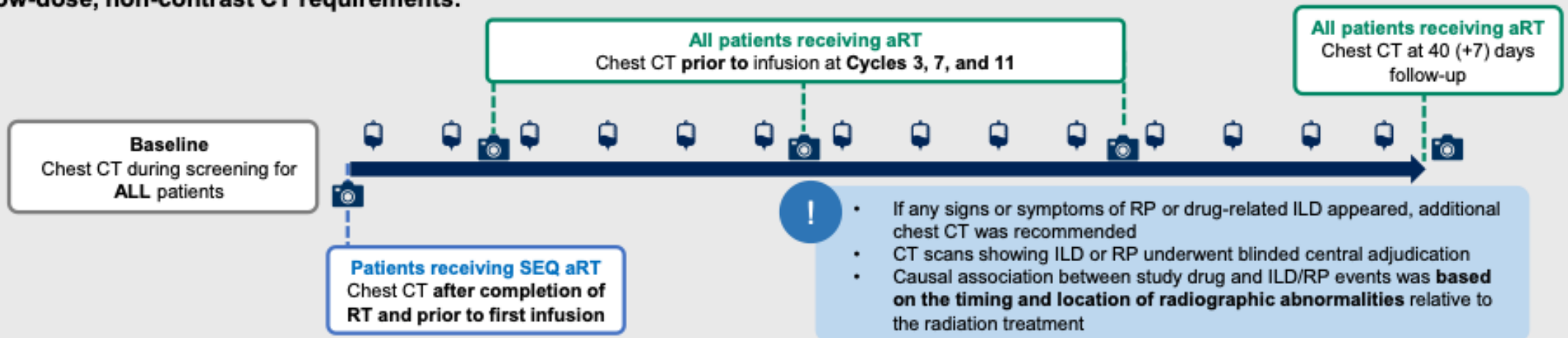
1. Loibl S et al. *New Eng J Med*. 2026;394(9):845-857. 2. Daiichi Sankyo. ENHERTU® Prescribing Information. May 2026.

[a]NAT is defined as ≥16 weeks' NAT, with ≥9 weeks of trastuzumab ± pertuzumab therapy and ≥9 weeks of taxane-based chemotherapy. [b]High risk defined as 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. [c]Median study treatment duration: T-DXd, 9.8 months; T-DM1, 9.7 months.

aRT, adjuvant radiotherapy; BMFI, brain metastasis–free interval; CC, concurrent; CI, confidence interval; DCO, data cutoff; DFS, disease-free survival; DRFI, distant recurrence–free interval; eBC, early breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; 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; RP, radiation pneumonitis; RT, radiotherapy; SEQ, sequential; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; ypN, post-NAT pathologic nodal stage.

Protocol-specific guidance on CT requirements for identifying ILD and RP in patients receiving aRT

Low-dose, non-contrast CT requirements:



Treatment management guidelines:

Grade 1

- **Drug-related ILD: Interrupt** T-DXd for grade 1 and consider steroids; restart T-DXd only after full resolution (grade 0[a])
- **Radiation-related pulmonary toxicity: Maintain** dose for grade 1 cases

Grade 2

- **Drug-related ILD:** Permanently **discontinue** T-DXd and initiate steroids (symptomatic with radiographic abnormalities)
- **Radiation-related pulmonary toxicity: Interrupt** and manage per standard of care (eg, steroids) until recovery to grade ≤1 (asymptomatic)

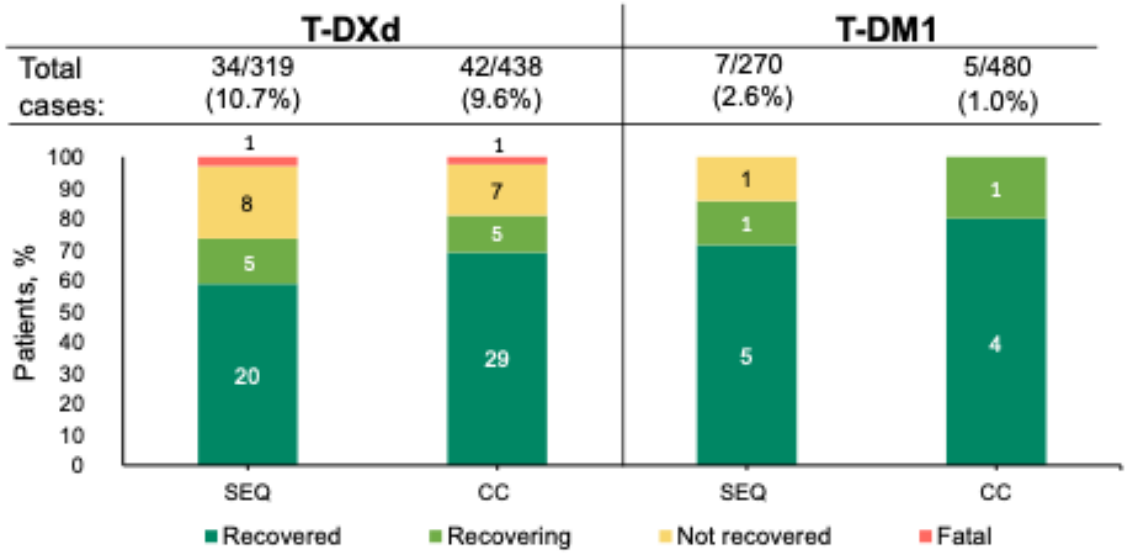
Grade 3-4

Discontinue study treatment and initiate steroids

[a]If resolved in ≤28 days from day of onset, maintain dose. If resolved in >28 days from day of onset, reduce dose 1 level. However, if the event grade 1 ILD/pneumonitis has not resolved within 126 days from the last infusion, T-DXd should be discontinued. aRT, adjuvant radiotherapy; CC, concurrent; CT, computed tomography; ILD, interstitial lung disease; RP, radiation pneumonitis; RT, radiotherapy; SEQ, sequential; T-DXd, trastuzumab deruxtecan

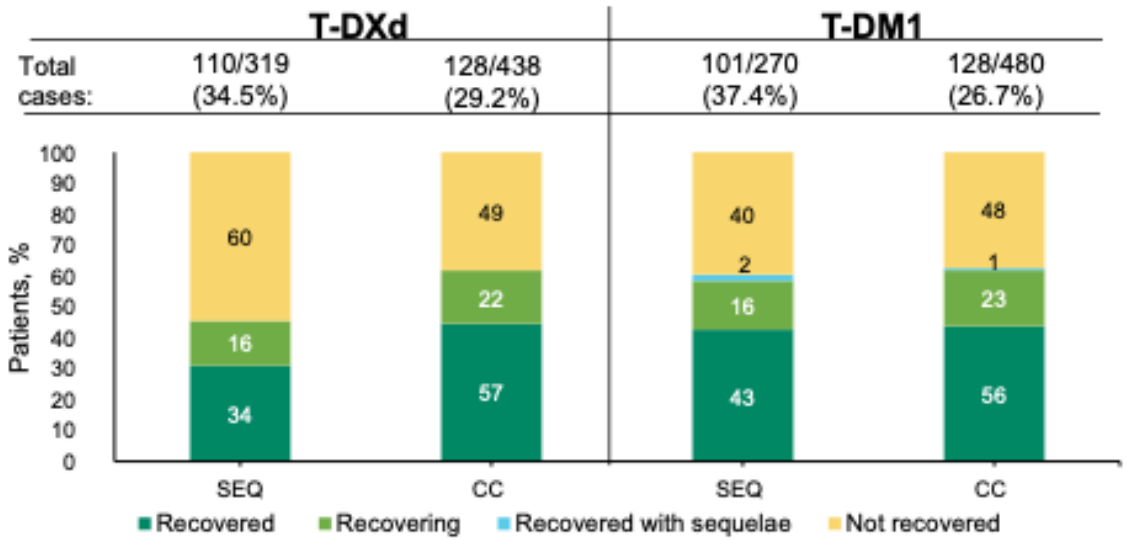
Adjudicated drug-related ILD and investigator-reported RP: outcomes at DCO

Adjudicated drug-related ILD[a]



- **Most ILD** events were **grade 1 or 2; most** patients with **ILD** had **recovered**[c] by DCO (T-DXd, 64.9% [50/77]; T-DM1, 76.9% [10/13]), with **consistent rates across aRT timing**
- Median duration of ILD[d] events in the T-DXd arm was 77.0 days and 67.0 days for SEQ and CC aRT, respectively; in the T-DM1 arm, median durations were 114.0 and 142.0 days, respectively

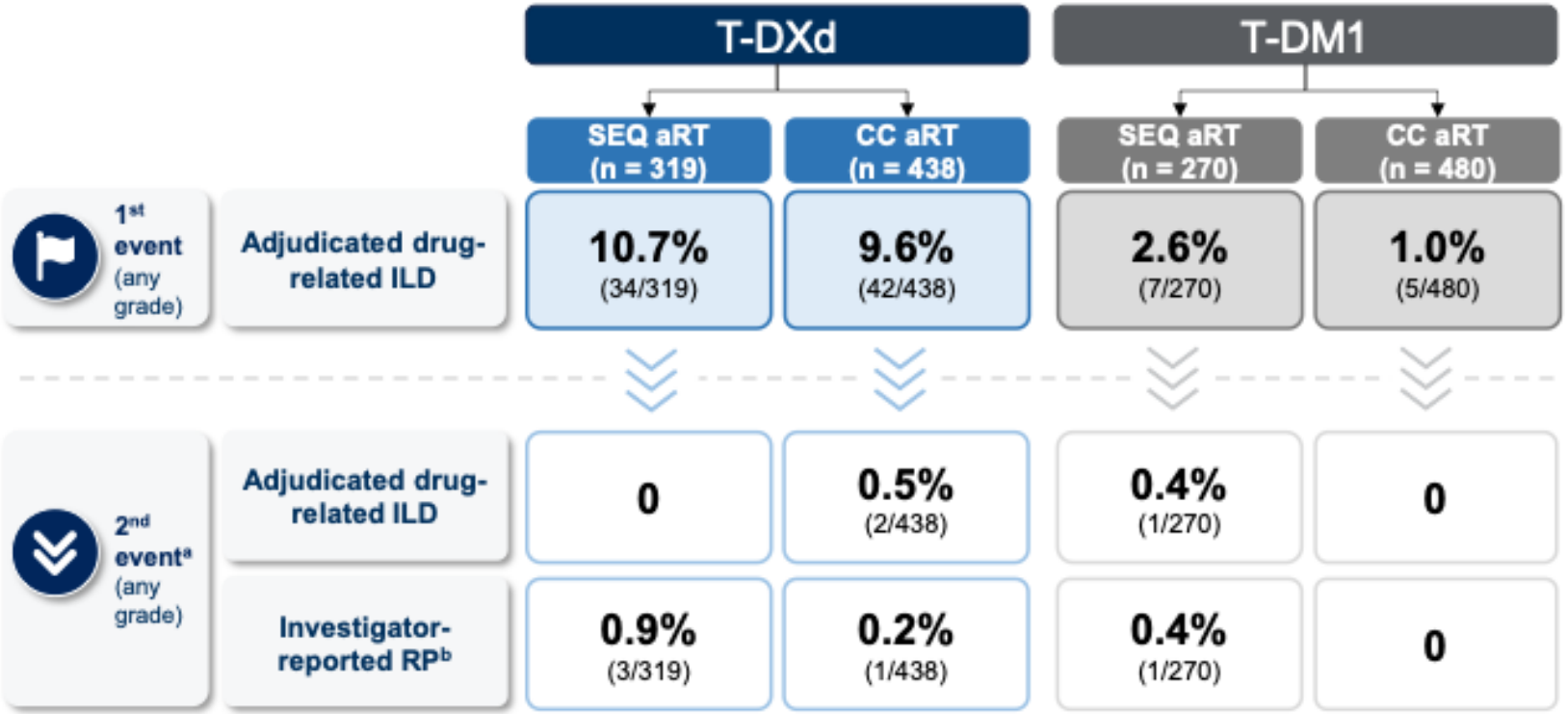
Investigator-reported RP[b]



- Most **RP** events were **grade 1;** 38.2% (91/238) of patients with RP who received T-DXd and 43.2% (99/229) of T-DM1 patients had **recovered**[c]
- Median duration of RP[e] events in the T-DXd arm was 13.5 months and 9.6 months for SEQ and CC aRT, respectively; in the T-DM1 arm, median durations were 10.1 months and 9.8 months, respectively

Stacked bars show percentages of patients; numbers inside bars are counts (n).
[a]The outcome of the worst ILD event denominator is based on the number of patients with adjudicated drug-related ILD events. [b]RP grouped terms include the following MedDRA preferred terms: pulmonary radiation injury, radiation alveolitis, radiation bronchitis, radiation fibrosis - lung, radiation pneumonitis. [c]Recovery/resolution is defined as grade 0 (no radiographic abnormalities). Recovery of RP to grade 0 may take up to 1 year. [d]Duration of first ILD = investigator-reported end date – investigator-reported onset date + 1. End date will be censored for ongoing ILDs. [e]Duration of first investigator-reported RP = investigator-reported end date – investigator-reported onset date + 1. End date will be censored for ongoing events. aRT, adjuvant radiotherapy; CC, concurrent; CT, computed tomography; DCO, data cutoff; ILD, interstitial lung disease; RP, radiation pneumonitis; SEQ, sequential; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Multiple events: adjudicated drug-related ILD as first event

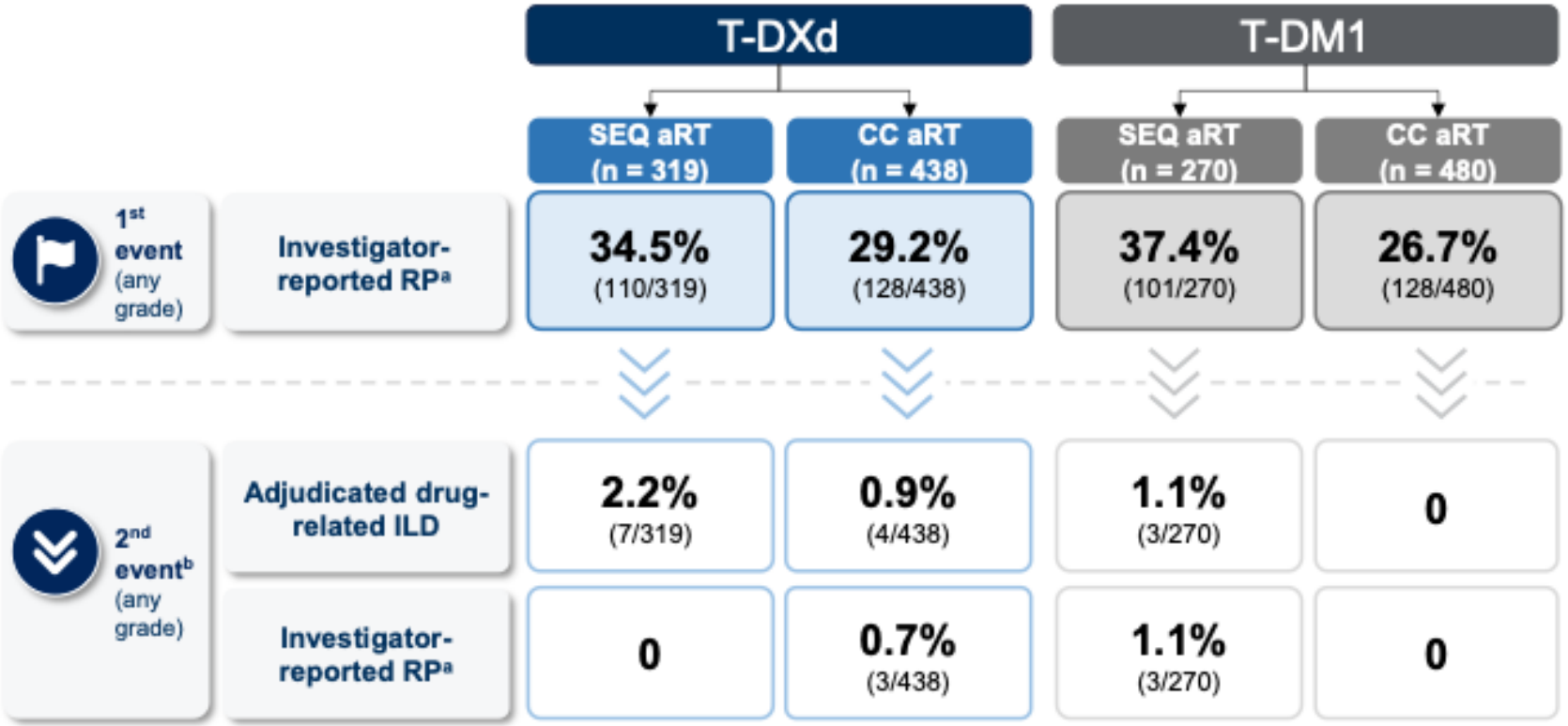


- **Adjudicated drug-related ILD did not increase the risk of subsequent adjudicated drug-related ILD or investigator-reported RP**
- Subsequent adjudicated drug-related ILD and investigator-reported RP events were all low grade (grade 1-2)

[a]Of patients who experienced a second event, adjudicated drug-related ILD occurred in 2 of 42 patients in the T-DXd CC aRT group and 1 of 7 patients in the T-DM1 SEQ aRT group. Investigator-reported RP occurred in 3 of 34 and 1 of 42 patients in the T-DXd SEQ and CC aRT groups, respectively, and 1 of 7 patients in the T-DM1 SEQ aRT group. [b]Grouped term. Includes the MedDRA preferred terms of pulmonary radiation injury, radiation bronchitis, radiation alveolitis, radiation fibrosis – lung, and radiation pneumonitis.

aRT, adjuvant radiotherapy; CC, concurrent; ILD, interstitial lung disease; RP, radiation pneumonitis; SEQ, sequential; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Multiple events: investigator-reported RP as first event



- **Investigator-reported RP did not increase the risk of subsequent adjudicated drug-related ILD or investigator-reported RP**
- Subsequent adjudicated drug-related ILD and investigator-reported RP events were all low grade (grade 1-2)

[a]Grouped term. Includes the MedDRA preferred terms of pulmonary radiation injury, radiation bronchitis, radiation alveolitis, radiation fibrosis – lung, and radiation pneumonitis. [b]Of patients who experienced a second event, adjudicated drug-related ILD occurred in 7 of 110 and 4 of 128 patients in the T-DXd SEQ and CC aRT groups, respectively, and 3 of 101 patients in the T-DM1 SEQ aRT group. Investigator-reported RP occurred in 3 of 128 patients in the T-DXd CC aRT group and 3 of 101 patients in the T-DM1 SEQ aRT group.
aRT, adjuvant radiotherapy; CC, concurrent; ILD, interstitial lung disease; RP, radiation pneumonitis; SEQ, sequential; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Adjudicated drug-related ILD and investigator-reported RP rates were influenced by region (Japan) and baseline renal function in both treatment arms

Japan vs non-Japan

n (%)	T-DXd			T-DM1		
	Japan (n = 87)	Asia (excludes Japan) (n = 301)	Global (excludes Japan) (n = 719)	Japan (n = 60)	Asia (excludes Japan) (n = 315)	Global (excludes Japan) (n = 741)
Adjudicated drug-related ILD	13 (14.9)	25 (8.3)	64 (8.9)	4 (6.7)	4 (1.3)	9 (1.2)
Investigator-reported RP[a]	41 (47.1)	116 (38.5)	197 (27.4)	27 (45.0)	122 (38.7)	202 (27.3)

- In both treatment arms, higher rates of adjudicated drug-related ILD and RP were observed in patients from Japan versus outside Japan and the rest of Asia
  - Patients from Japan who received CC aRT had higher rates of RP compared with those who received SEQ aRT, although sample size was small

Baseline renal function

n (%)	T-DXd (n = 806)			T-DM1 (n = 801)		
	Normal (n = 506)	Mild Impairment (n = 258)	Moderate Impairment (n = 42)	Normal (n = 486)	Mild Impairment (n = 274)	Moderate Impairment (n = 40)
Adjudicated drug-related ILD	49 (9.7)	22 (8.5)	6 (14.3)[b]	5 (1.0)	6 (2.2)	2 (5.0)[c]
Investigator-reported RP[a]	133 (26.3)	95 (36.8)	10 (23.8)	131 (27.0)	86 (31.4)	11 (27.5)

- Across treatment arms, adjudicated drug-related ILD rates were higher in patients with moderate renal impairment versus mild impairment and normal renal function

Normal renal function defined as creatinine clearance ≥90 mL/min; mild impairment defined as creatinine clearance ≥60 and <90 mL/min; moderate impairment defined as creatinine clearance ≥30 and <60 mL/min.
[a]Grouped term. Includes the MedDRA preferred terms of pulmonary radiation injury, radiation bronchitis, radiation alveolitis, radiation fibrosis - lung, and radiation pneumonitis. [b]Among patients with baseline moderate renal impairment who developed adjudicated drug-related ILD in the T-DXd arm, 5 of 6 had grade 2 ILD (all recovered at DCO) and 1 of 6 had grade 3 ILD (not recovered at DCO). [c]Both patients with baseline moderate renal impairment who developed adjudicated drug-related ILD in the T-DM1 arm had grade 2 ILD and had recovered at DCO.
aRT, adjuvant radiotherapy; CC, concurrent; DCO, data cutoff; ILD, interstitial lung disease; RP, radiation pneumonitis; SEQ, sequential; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Dose Modifications for ILD/Pneumonitis Management

See following slide for dose modifications and monitoring for **radiotherapy-related** pneumonitis

Severity	Treatment Modification
Grade 1: **Asymptomatic ILD/Pneumonitis**	**Interrupt T-DXd** until resolved to Grade 0, then: • if resolved in ≤28 days from date of onset, maintain dose • if resolved in >28 days from date of onset, reduce dose one level • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected
Grade ≥2: **Symptomatic ILD/Pneumonitis**	• **Permanently discontinue T-DXd**[a] • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected

Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Advise patients of the risk and to immediately report symptoms.

Dose Modifications and Monitoring for Radiotherapy-Related Toxicity With Post-Neoadjuvant Treatment in DESTINY-Breast05[1,2]

Severity	Treatment Modification
Grade 1: Asymptomatic	• **Maintain** dose and schedule
Grade 2: Symptomatic	• **Interrupt** study treatment until recovered to baseline or Grade ≤ 1 • Manage per SOC (eg, steroids). Relationship to RT should be determined on the basis of timing and location of radiographic abnormalities relative to the radiation treatment
Grade 3 or 4:	• **Discontinue** study treatment
Other Radiation-Related Adverse Events	
Grade 3:	• **Do not administer** study treatment until recovery to **Grade ≤ 1**
Grade 4:	• **Discontinue patient from** study treatment

Monitoring

- Baseline chest CT scan during screening for all patients
- For patients who will receive sequential RT: additional Chest CT after completion of RT and prior to 1st infusion
- For all patients who receive any adjuvant RT: Chest CT at approximately 6 weeks after start of study treatment, approximately every 12 weeks afterwards while on treatment, and at 40 days follow-up

For patients who experience any radiation-related toxicity before first planned infusion, these toxicities should be managed as per SOC or institutional guidelines and continued to receive first infusion as planned as long as the toxicities recover completely or back to baseline prior to starting study treatment

The ENHERTU package insert states: In the adjuvant setting, if drug-induced ILD is suspected, rule out radiotherapy-related pneumonitis. If only radiotherapy-related pneumonitis is suspected, consider interruption of ENHERTU for Grade 2 and permanently discontinue ENHERTU for Grade ≥3[1]

Key takeaway points/conclusions

- Adjudicated drug-related **ILD** cases were mostly **low grade** and **reversible** with treatment management guidelines and at the time of the analysis, had **resolved or were resolving** in 77.9% of T-DXd patients and 92.3% of T-DM1 patients independently of aRT timing
    - In both treatment arms, adjudicated drug-related ILD were influenced by region, particularly patients from Japan, and baseline renal function, consistent with a prior pooled analysis[1]
- RP events were grade 1 or 2 and at the time of the analysis had resolved or were resolving in 54.2% of T-DXd patients and 61.6% of T-DM1 patients; the median duration of RP events was similar in both treatment arms
- Adjudicated drug-related ILD and investigator-reported RP **did not increase the risk or severity** of subsequent adjudicated drug-related ILD or investigator-reported RP, further supporting the feasibility of T-DXd use in the context of aRT

This analysis further establishes the pulmonary safety profile of T-DXd with radiotherapy, complementing its superior efficacy and supporting the adoption of T-DXd as a new post-neoadjuvant standard of care

1. Powell CA et al. *ESMO Open* 2022;7(4):100554.
aRT, adjuvant radiotherapy; ILD, interstitial lung disease; RP, radiation pneumonitis; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

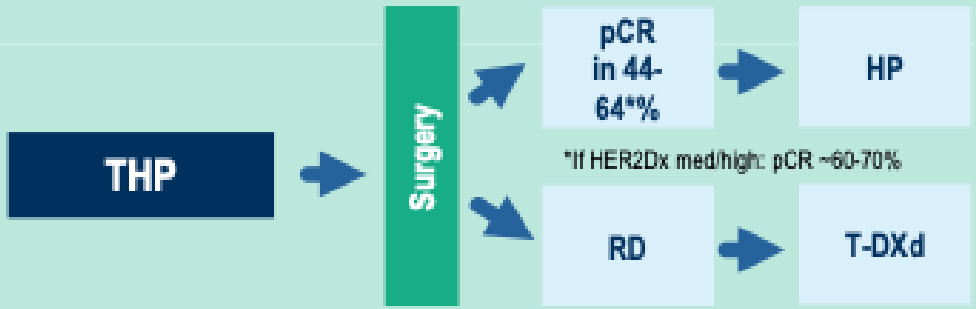
SHOULD WE GIVE T-DXd PREOP OR POST-OP?

Preoperative

1. **Improve** pCR rate→ less axillary surgery
2. **Shorter course** T-DXd (4 cycles) vs 14 cycles
3. **Less toxicity** given just 4 cycles
4. **May result in better** QOL for patients

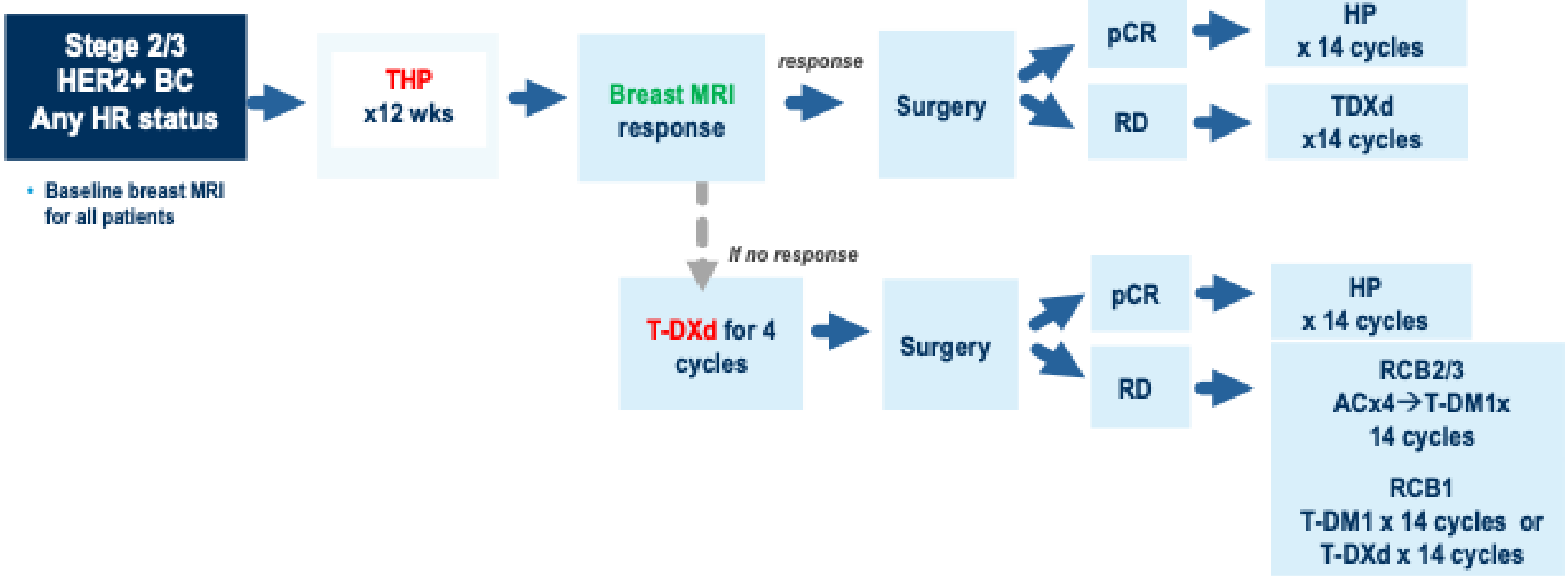
Post-operative

1. Could allow **de-escalated preoperative therapy (THP)**, sparing those patients with pCR T-DXd (but those with RD end up with 14 cycles)



Slide by Sara Tolaney

HOW COULD WE INTEGRATE DB11 AND DB05?



Slide by Sara Tolaney

Slide adapted from Ella Sequist/Ada Weks

HER2 Vaccine Trial Enrolling at City of Hope

Greenwich LifeSciences

Flamingo-01
GLSI-21-01

A Randomized, Multicenter, Placebo-controlled, Phase 3 study to Evaluate the Efficacy and Safety of HER2/neu Peptide GLSI-100 (GP2 + GM-CSF) in HER2/neu Positive Subjects with Residual Disease or High-Risk PCR after both Neoadjuvant and Postoperative Adjuvant Trastuzumab-based Therapy (FLAMINGO-01)

*Adapted from the Site Initiation Visit Slides Version 10 October 7, 2024

- GLSI-100 is co-administration of GP2 and GM-CSF
  - GP2 a biologic nine amino acid peptide of the HER2/neu protein (aa:654-662:IISAVVGIL)
  - Immunoadjuvant recombinant human Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF, rhu GM-CSF, sargramostim, Leukine)
- Amino acid sequence and structure of the GP2 peptide is H-Ile1-Ile-Ser-Ala-Val5- Val-Gly-Ile-Leu9-OH
- GLSI-100 shown to induce a CD8+ T cell response clinical trials along with evidence of intra-antigenic epitope spreading with clonal expansion of GP2-specific CD8+ T cells
- Multiple efficacy and safety studies as adjuvant therapy to prevent the breast cancer recurrence in HER2/neu+ and HLA-A*02 patients

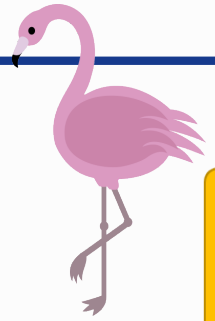
Protocol

- Study Design
  - Prospective, randomized, double-blinded, placebo-controlled Phase 3
- Population
  - HER2/neu expressing breast cancer
  - Extended – adjuvant, post neoadjuvant, surgery, and adjuvant trastuzumab-based (or approved biosimilar) therapy
  - Subjects with stage I, II or III at presentation with residual disease or stage III at presentation with pCR
- Sample size
  - 500 HLA-A*02 subjects randomized to GLSI-100 or placebo control
  - 250 additional subjects, who are non-HLA-A*02 in open-label arm

Schema

HER2/neu positive subjects who are at high risk for disease recurrence and have completed:

- Neoadjuvant systemic treatment consisting of at least 6 cycles of chemotherapy, including at least 9 weeks of anti-HER2 treatment and taxane based chemotherapy. Patients may receive anthracycline as part of neoadjuvant therapy in addition to taxane chemotherapy.
- Surgery.
- At least 90% of planned anti-HER2 treatment post-surgery).



HLA-A*02+

non-HLA-A*02

Randomize

Double-Blinded

GLSI-100 PIS 6 doses once per month → GLSI-100 Booster 5 doses once every 6 months → Survival and Recurrence Follow-Up

Placebo PIS 6 doses once per month → Placebo Booster 5 doses once every 6 months → Survival and Recurrence Follow-Up

Open Label

GLSI-100 PIS 6 doses once per month → GLSI-100 Booster 5 doses once every 6 months → Survival and Recurrence Follow-Up

Inclusion Criteria

Key Eligibility Criteria

- Age >18 years; ECOG 0–2
- HER2-positive early breast cancer (ASCO/CAP criteria)
- Stage I–III with residual invasive disease after neoadjuvant therapy **OR** stage III with pCR
- Completed standard neoadjuvant chemotherapy + HER2-directed therapy, surgery, and ≥90% of planned adjuvant trastuzumab-based therapy
- No clinical or radiographic evidence of active disease
- Enrollment within 1 year of completing adjuvant HER2-directed therapy
- HLA-A*02 positive (except non-HLA-A*02 cohort)
- Adequate organ function and appropriate pregnancy/contraception requirements

Exclusion Criteria

Key Exclusion Criteria

- Stage IV/metastatic or inflammatory breast cancer
- Concurrent chemotherapy, investigational anticancer therapy, or neratinib
- Chronic systemic corticosteroid or immunosuppressive therapy
- Active autoimmune disease or immunodeficiency requiring systemic treatment
- Pregnancy or breastfeeding
- Severe allergy to GM-CSF, yeast-derived products, or study components
- Active serious infection, including TB or active hepatitis B/C
- HIV with detectable viral load
- Other recent/active malignancy (with specified exceptions)
- Medical, psychiatric, cognitive, or social conditions that may impair informed consent or protocol adherence

THANK YOU FOR YOUR ATTENTION

Sarah Friend
sfriend@coh.org