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DESTINY Breast11

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

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On behalf of the DESTINY-Breast11 investigators

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Declaration of interests

Commercial interests	Nature of relationship
AstraZeneca, Daiichi Sankyo, Gilead, Lilly, Menarini Stemline, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Viatris, and Zuellig Pharma	Honoraria
Exact Sciences, Gilead, Pfizer, Roche, and Sandoz	Consultant/advisor
AstraZeneca	Institutional site contract
Gilead, IQVIA, and Roche	Data safety monitoring board / advisory board
West German Study Group	Ownership interest

Background

- With no new therapies in over a decade,[1] there remains an unmet need for more effective and less toxic neoadjuvant regimens for HER2+ early-stage breast cancer (eBC)
- Pathologic complete response (pCR) is a prognostic factor for event-free survival (EFS) and overall survival in patients with HER2+ eBC[2–4] and provides essential information to support clinical decision-making
  - With existing SOC regimens, 39–64% of patients[1,5–9] have pCR; rates are lower in patients with hormone receptor (HR)–positive disease and those who are high risk (large tumor size, extensive nodal involvement)[5,6]
  - Patients with pCR are eligible for less burdensome subsequent treatments (reduction in extent of surgery and less toxic post-neoadjuvant therapy)[10–12]
- SOC regimens (eg ddAC-THP, TCbHP) have acute (hematological and gastrointestinal) AEs[13,14] and long-term sequelae, including cardiotoxicity,[10,15] secondary leukemia,[10] and neuropathy[5]
- T-DXd has demonstrated improved survival outcomes vs previous SOC in the metastatic setting[16,17]

DESTINY-Breast11 aimed to bring T-DXd to the neoadjuvant setting to determine whether this would improve efficacy and safety for patients with high-risk, HER2+ eBC

AE, adverse event; ddAC, dose-dense doxorubicin + cyclophosphamide; SOC, standard of care; TCbHP, docetaxel + carboplatin + trastuzumab + pertuzumab; THP, paclitaxel + trastuzumab + pertuzumab.
1. Gianni L, et al. *Lancet Oncol.* 2012;13:25–32; 2. Spring LM, et al. *Clin Cancer Res.* 2020;26:2838–2848; 3. Cortazar P, et al. *Lancet.* 2014;384:164–172; 4. Davey MG, et al. *BJS Open.* 2022;6:zrac028; 5. Hurvitz SA, et al. *Lancet Oncol.* 2018;19:115–126; 6. Huober J, et al. *J Clin Oncol.* 2022;40:2946–2956; 7. Schneeweiss A, et al. *Ann Oncol.* 2013;24:2278–2284; 8. Swain SM, et al. *Ann Oncol.* 2018;29:646–653; 9. Masuda N, et al. *Breast Cancer Res Treat.* 2020;180:135–146; 10. Loibl S, et al. *Ann Oncol.* 2024;35:159–182; 11. Denduluri N, et al. *J Clin Oncol.* 2021;39:685–693; 12. Park KH, et al. *ESMO Open.* 2024;9:102974; 13. van Ramshorst MS, et al. *Lancet Oncol.* 2018;19:1630–1640; 14. Hennessy MA, Morris PG. *Ann Palliat Med.* 2020;9:504–509; 15. van der Voort A, et al. *JAMA Oncol.* 2021;7:978–984; 16. Cortés J, et al. *Nat Med.* 2024;30:2208–15; 17. Tolaney S, et al. *J Clin Oncol.* 2025;43:LBA1008

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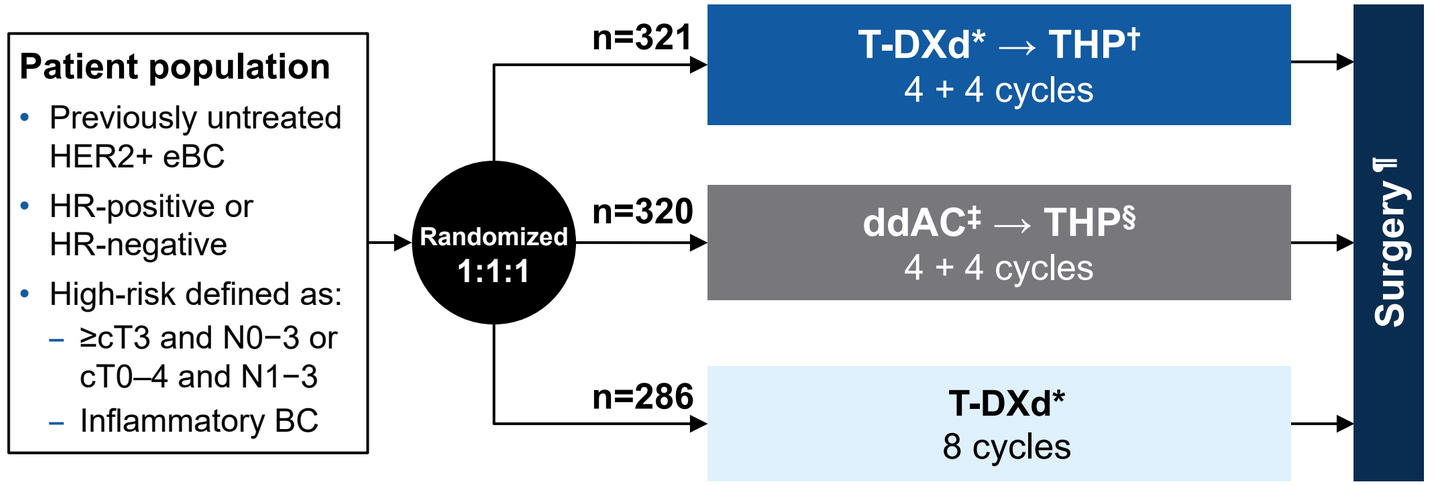
DESTINY-Breast11 study design

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



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

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

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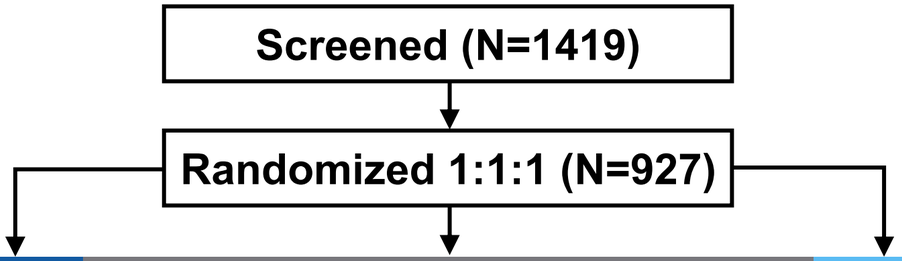
Patient disposition



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

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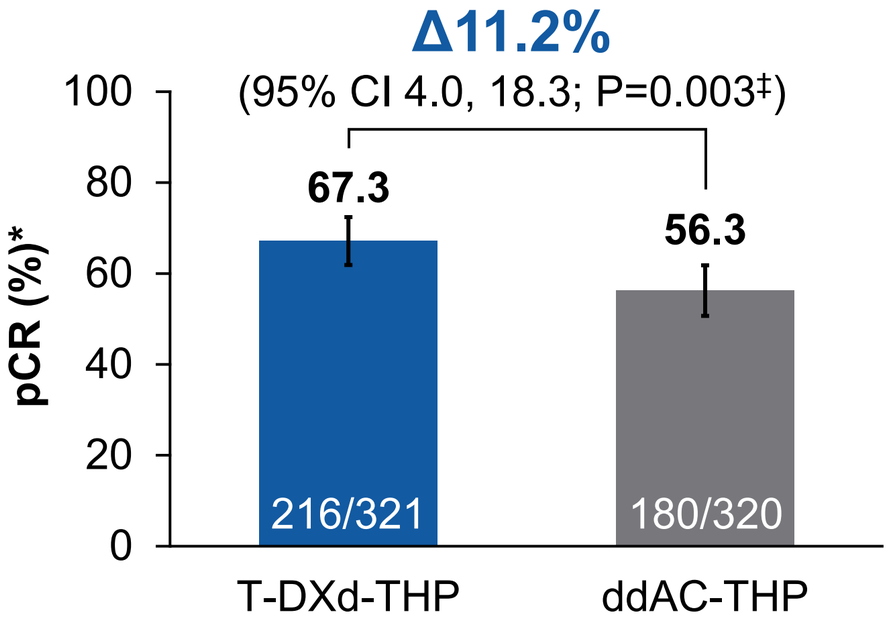
pCR (ypT0/is ypN0): primary endpoint

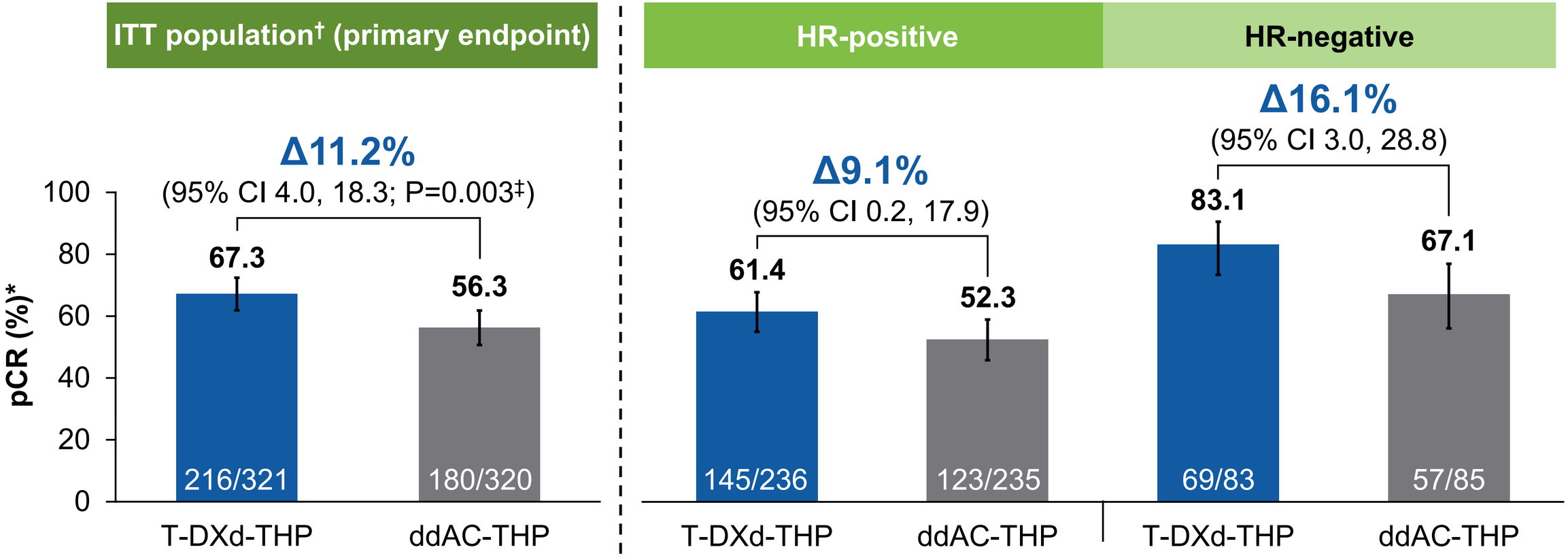
ITT population† (primary endpoint)



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

pCR (ypT0/is ypN0): primary endpoint



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

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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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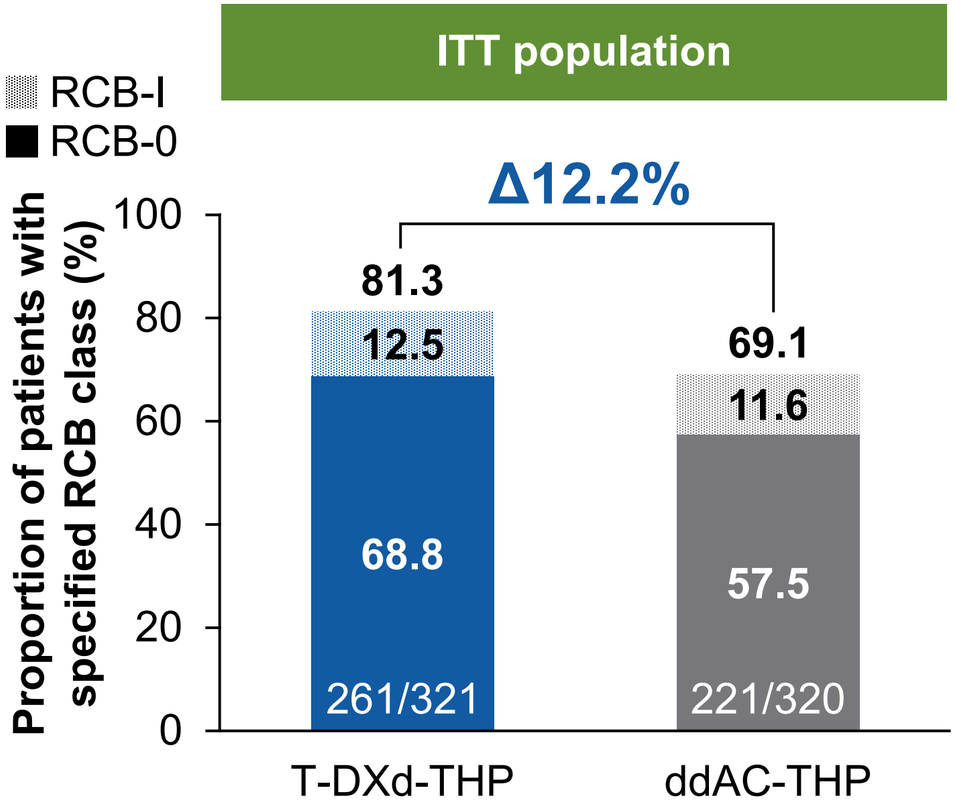
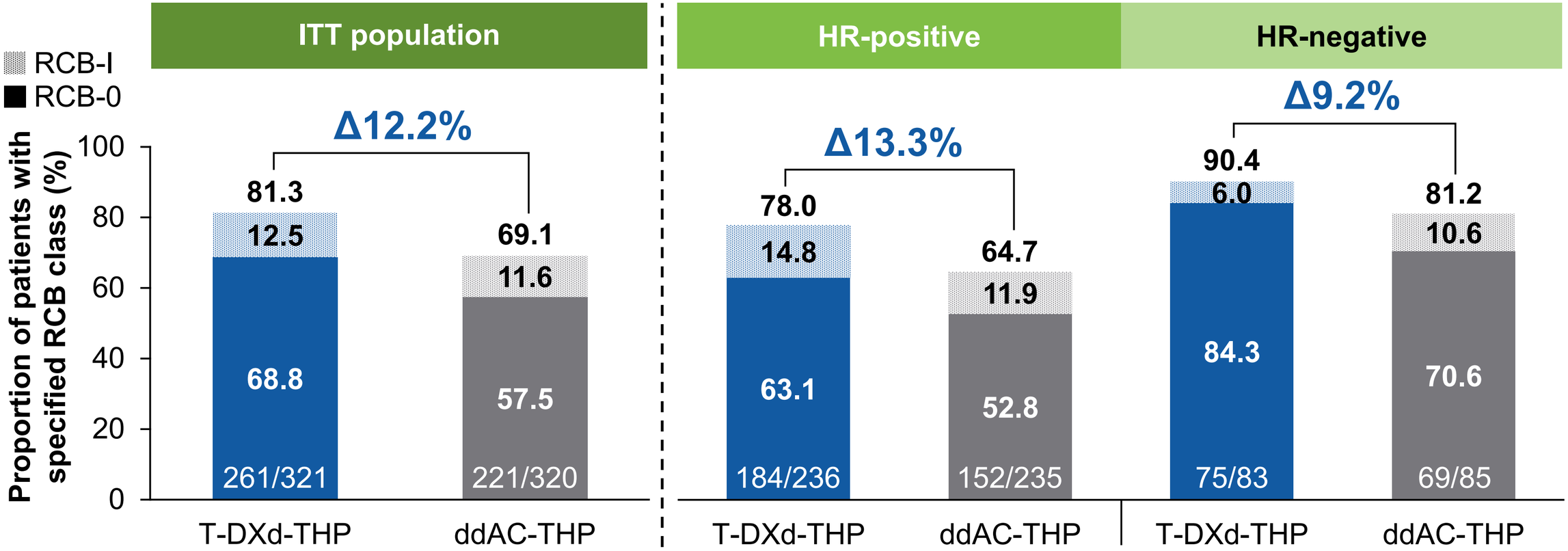
RCB outcomes



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)

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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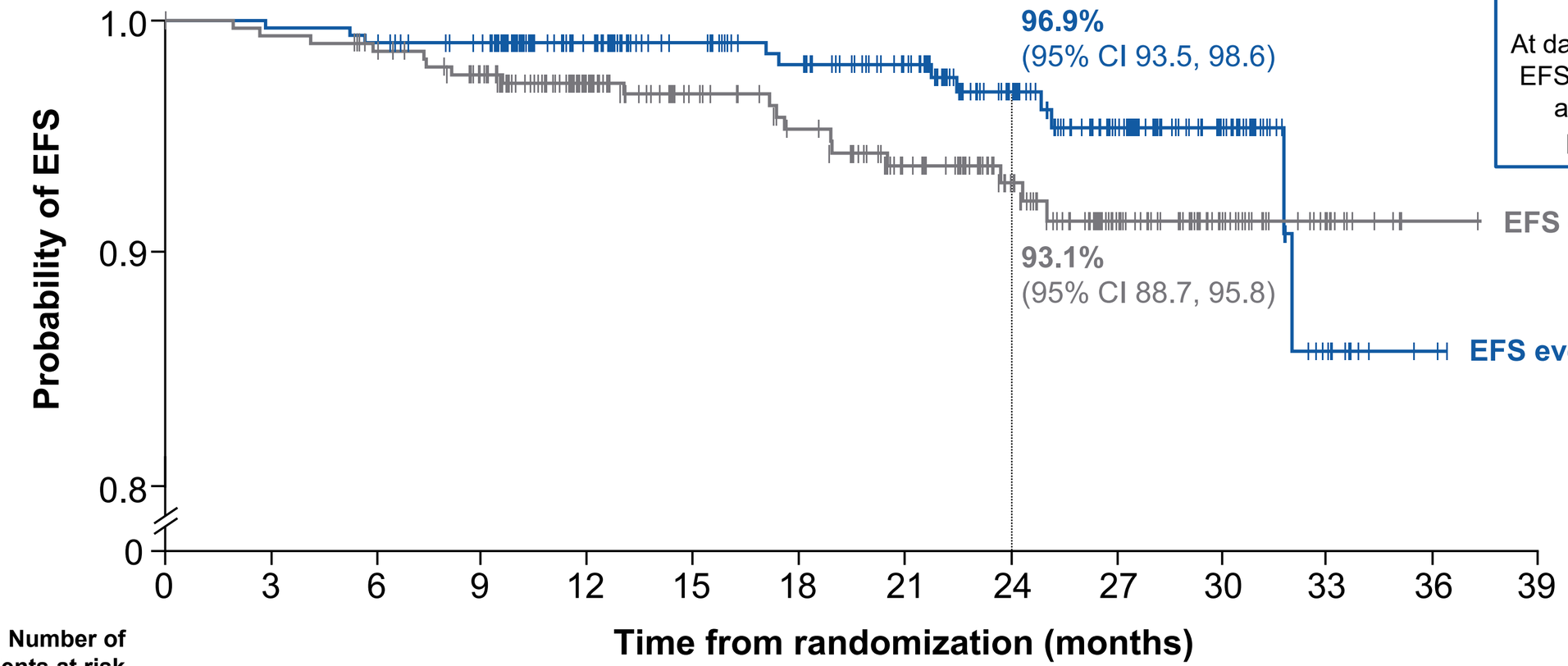
EFS



Hazard ratio

0.56

(95% CI 0.26, 1.17)

At data cutoff (March 12, 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)

Post-neoadjuvant treatments

n (%)	Patients with pCR*		Patients without pCR*	
	T-DXd-THP (n=226)	ddAC-THP (n=190)	T-DXd-THP (n=95)	ddAC-THP (n=130)
Any adjuvant treatment†	224 (99.1)	187 (98.4)	85 (89.5)	107 (82.3)
Any cytotoxic chemotherapy-containing regimen	13 (5.8)	11 (5.8)	10 (10.5)	12 (9.2)
Any T-DM1-containing regimen	4 (1.8)	4 (2.1)	50 (52.6)	74 (56.9)
Any trastuzumab-containing regimen	213 (94.2)	174 (91.6)	37 (38.9)	34 (26.2)

Post-neoadjuvant treatments were generally well balanced between T-DXd-THP and ddAC-THP arms
In both arms, more than half of patients without pCR received post-neoadjuvant T-DM1

Patients may have had at least one anti-cancer therapy and were counted once per therapy. *By local pCR result; †excludes patients who withdrew consent or did not receive surgery; also excludes treatment given in the metastatic setting

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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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)
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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

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)
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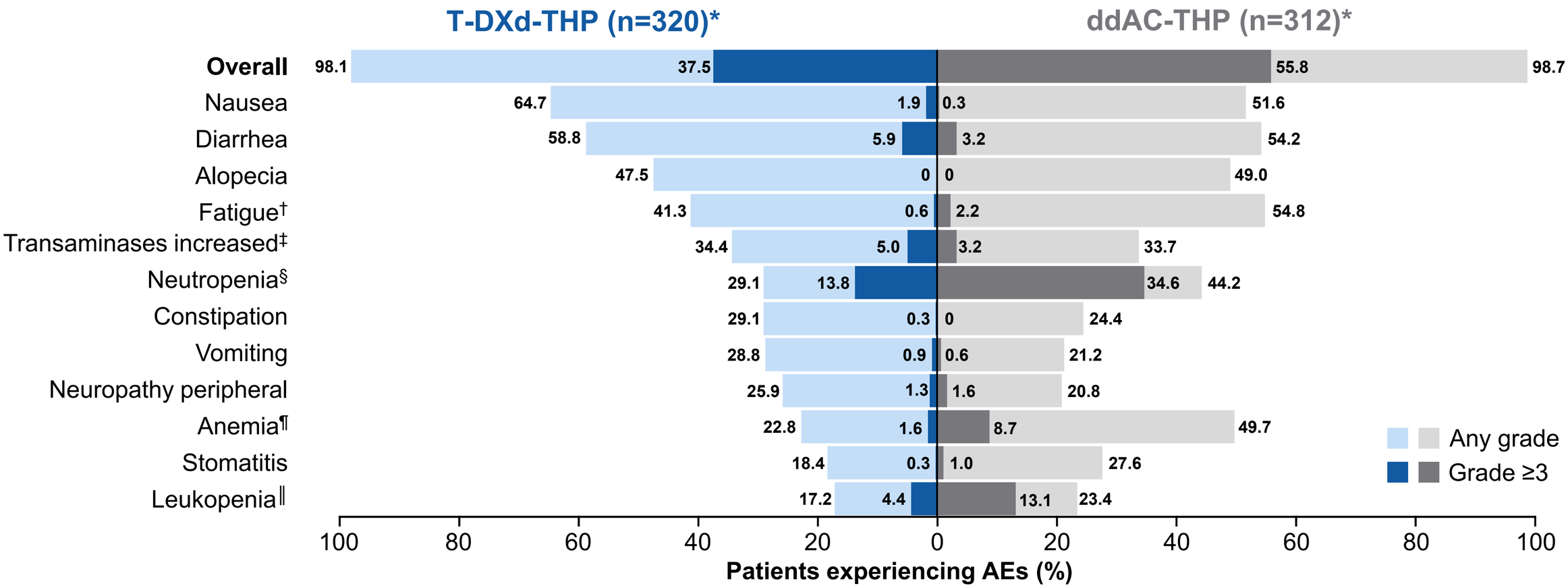
TEAEs in at least 20% of patients in either arm



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

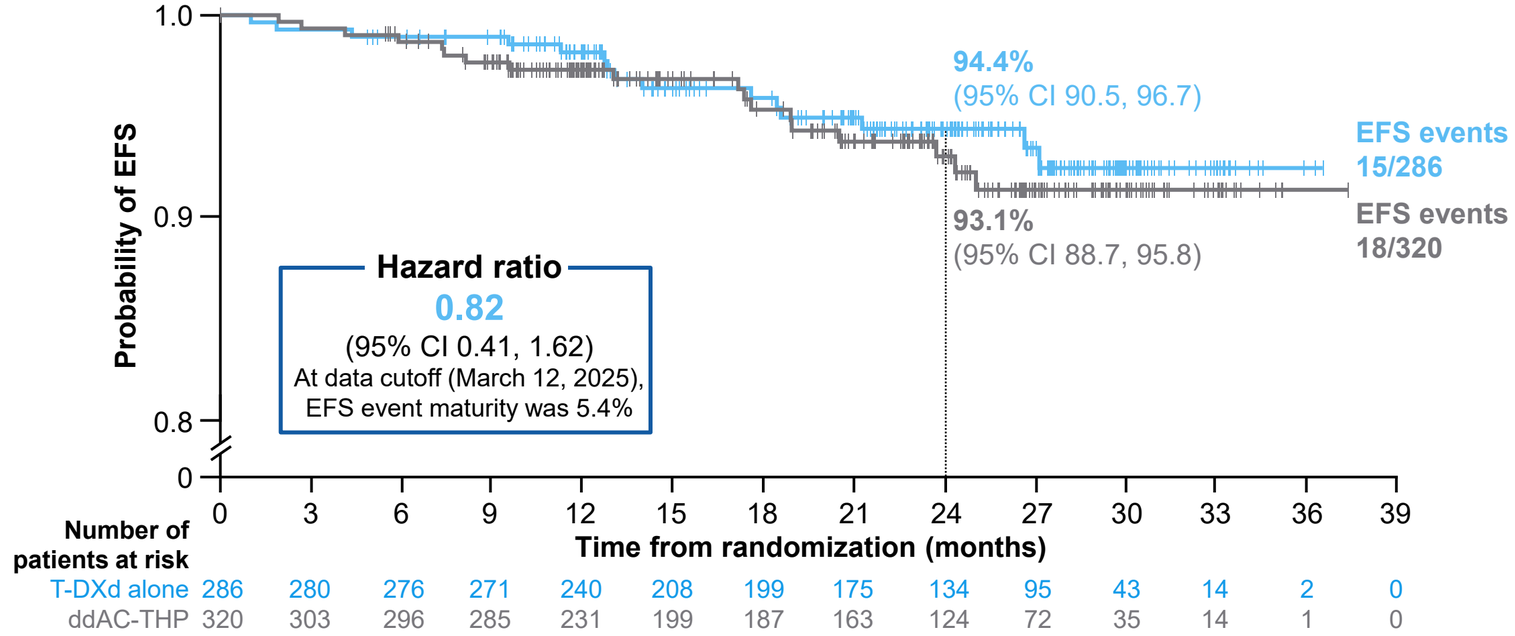
T-DXd alone arm: efficacy summary

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

Nadia Harbeck, MD

T-DXd alone arm: safety summary

n (%)	T-DXd (n=283)*	ddAC-THP (n=312)*
Any AE	276 (97.5)	308 (98.7)
Grade ≥3	64 (22.6)	174 (55.8)
Any serious AE	29 (10.2)	63 (20.2)
AE leading to any dose reduction	19 (6.7)	60 (19.2)
AE leading to any drug interruption	51 (18.0)	170 (54.5)
AE leading to any treatment discontinuation	22 (7.8)	31 (9.9)
Any AE with outcome of death†	1 (0.4)	2 (0.6)
AE of special interest		
Drug-related adjudicated ILD/pneumonitis	14 (4.9)	16 (5.1)
Grade ≥3	0	6 (1.9)
Grade 5	0	1 (0.3)
Left ventricular dysfunction	2 (0.7)	19 (6.1)
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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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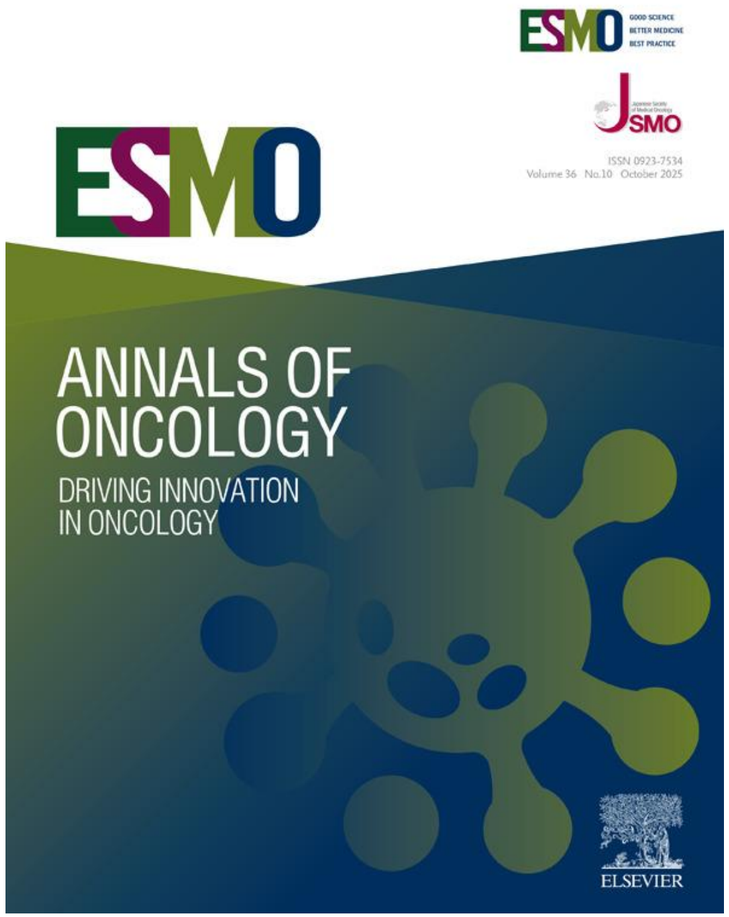


Neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel, trastuzumab, and pertuzumab for high-risk HER2-positive early breast cancer (DESTINY-Breast11): a randomised, open-label, multicentre, phase 3 trial

Annals of Oncology. 2025

Nadia Harbeck, MD

DESTINY-Breast11

BERLIN 2025 ESMO congress

What is the purpose of the DESTINY-Breast11 study?

DESTINY Breast11

Patients diagnosed with early-stage breast cancer often receive treatment before surgery to shrink the tumor (neoadjuvant treatment). However, they may experience unpleasant side effects and there is a chance that tumor cells remain after treatment (residual disease). For some patients, the cancer may return (disease recurrence).

Trastuzumab deruxtecan (T-DXd) is a treatment for patients with breast cancer in which the cancer cells have higher-than-normal levels of the HER2 protein (HER2+). Currently, it may only be used if the cancer has spread from where it started (metastatic or advanced) and has gotten worse despite previous treatment.

DESTINY-Breast11 is a clinical study of adults with HER2+ early-stage breast cancer who received neoadjuvant treatment with T-DXd alone or followed by a commonly used treatment known as THP, compared with an existing neoadjuvant treatment (known as ddAC-THP).

The aim was to find out how well T-DXd, with or without THP, worked compared with ddAC-THP. The main measurement was pathologic complete response (pCR), which means that a laboratory test shows no cancer in the breast or lymph node tissue that is removed during surgery. Patients with a pCR are more likely to survive, less likely to have their cancer come back, and are able to have less-demanding treatments after surgery. Other measurements included how long participants lived before getting worse (event-free survival) and the treatment side effects.

What did the study show?

DESTINY-Breast11 showed that more patients with early breast cancer at a high risk of disease recurrence had a pathologic complete response with fewer side effects when they had neoadjuvant treatment with T-DXd-THP, compared with ddAC-THP.

How was the DESTINY-Breast11 study carried out?

Start of study

Patients included in the study had:

- HER2+ — **HER2+ early-stage breast cancer** that had not been treated
- HR+/− — The tumor could be **hormone receptor-positive or negative**
- High risk of cancer coming back after treatment (**large tumors** and/or cancer in **lymph nodes**, or **inflammatory breast cancer**)

Participants randomly assigned to treatment

- **321** patients were assigned to receive **T-DXd followed by THP** (taxane + trastuzumab + pertuzumab) — 4 + 4 cycles
- **320** patients were assigned to receive **standard ddAC-THP** (dose-dense doxorubicin + cyclophosphamide + THP) — 4 + 4 cycles
- **286** patients were assigned to receive **T-DXd alone*** — 8 cycles

→ Surgery

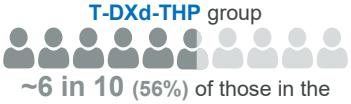
*A group of independent experts who check study data to protect participants and ensure reliable results recommended that no more participants were added to the T-DXd-alone arm partway through the trial

Pathologic complete response (pCR)

The proportion of patients **with no cancer remaining in the breast or lymph nodes** at surgery was:

~7 in 10 (67%) of those in the **T-DXd-THP** group

Difference of **11%**



~6 in 10 (56%) of those in the **ddAC-THP** group

Residual cancer burden (RCB)

The proportion of patients **with no or minimal cancer** remaining following neoadjuvant treatment was:

Event-free survival (EFS)

Two years after treatment started, an initial look showed that the proportion of patients in each group whose cancer had not got worse and stopped them having surgery, or come back, or had died was:

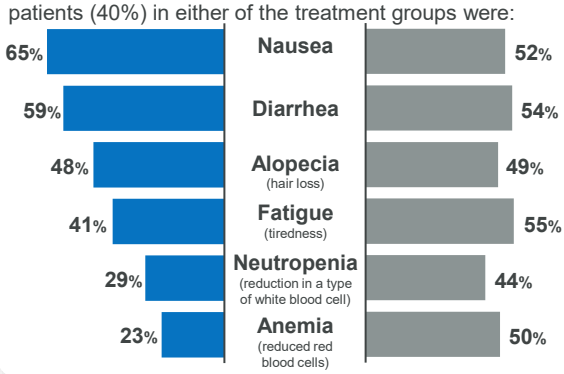
97% of those in the **T-DXd-THP** group

93% of those in the **ddAC-THP** group

Safety

Proportion of patients experiencing side effects that were:

Side effects that were experienced by at least 4 in 10 patients (40%) in either of the treatment groups were:



The number of patients who developed **drug-related interstitial lung disease** (inflammation and/or scarring of the lungs) was **low and similar** across treatment groups

T-DXd-THP: 14 (4%)

ddAC-THP: 16 (5%)

One patient in each group died as a result of interstitial lung disease

Fewer patients developed **left ventricular dysfunction** (reduced ability of the heart to pump blood around the body) with T-DXD-THP than with ddAC-THP

T-DXd-THP: 4 (1%)

ddAC-THP: 19 (6%)

T-DXd alone

- **About 4 in 10 patients (43%)** in the **T-DXd-alone** group had a pCR; this was lower than the **56%** in the **ddAC-THP** group
- Initial results showed that EFS was **94%** in the **T-DXd-alone** group versus **93%** in the **ddAC-THP** group
- The **T-DXd-alone group had fewer severe and serious side effects** and side effects leading to treatment reductions/interruptions than the ddAC-THP group

How do the results of the DESTINY-Breast11 study help to improve the treatment of cancer?

About 7 in 10 patients in the T-DXd-THP group had a pCR, compared with 6 in 10 in the ddAC-THP group. The study results support T-DXd-THP as a more effective and less toxic neoadjuvant treatment compared with ddAC-THP. It may become a treatment option for patients with high-risk, HER2+, early-stage breast cancer, allowing more patients to benefit from improved outcomes and allowing for less-demanding treatments after surgery.

What's next?

The study will continue and results on the longer-term benefit of treatment in each group will be reported in the future

Where can I access more information?

DESTINY-Breast11 ClinicalTrials.gov identifier NCT05113251

This summary is based on an oral presentation by Professor Nadia Harbeck at the 2025 European Society of Medical Oncology (ESMO) Annual Meeting (Presentation ID 291O). This summary, and the results of this study, have not yet been peer reviewed. The authors would like to thank the patients and their families who participated in the DESTINY-Breast11 study, and the investigators, co-investigators, and study staff. Date of summary: October 2025. The DESTINY-Breast11 study was sponsored by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201). This plain language summary was prepared by Jade Murdoch, MChD/BChD, and Stephen Purver, MChem (Helios Medical Communications, part of Helios Global Group), and was funded by AstraZeneca.