



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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Nadia Harbeck

DESTINY-Breast11: Neoadjuvant trastuzumab deruxtecan alone (T-DXd) or followed by paclitaxel + trastuzumab + pertuzumab (T-DXd-THP) vs SOC for high-risk HER2+ early breast cancer (eBC)

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+ eBC²⁻⁴ 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 neuropathy⁵
- 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. *BJO 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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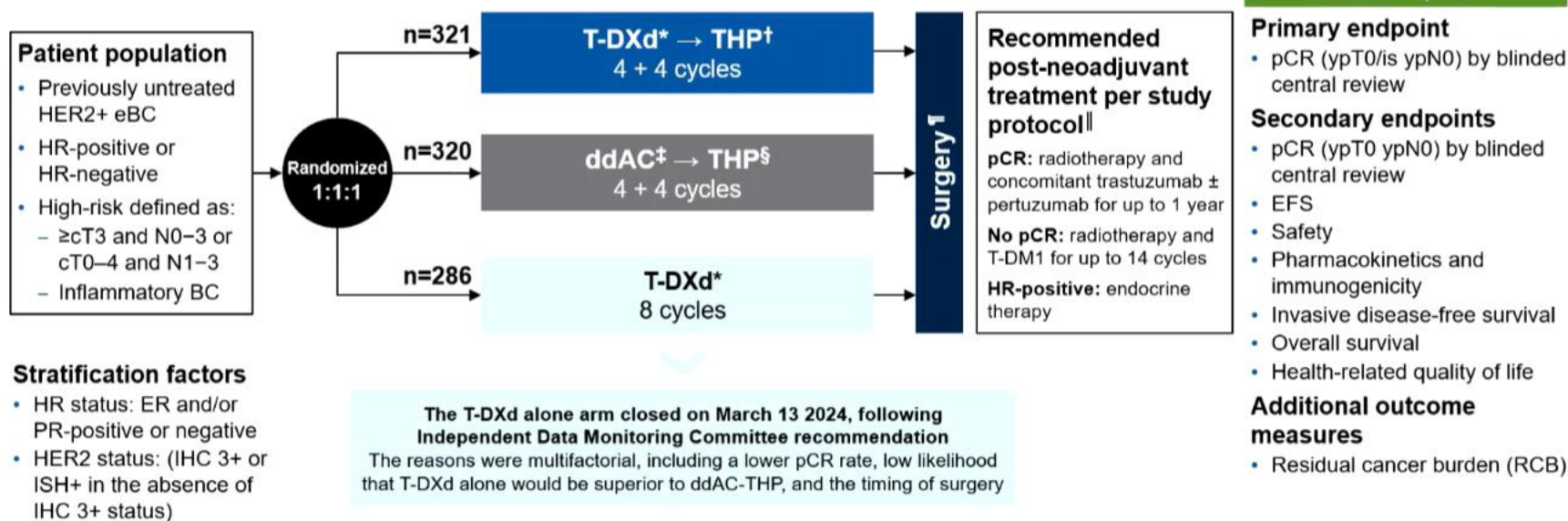


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DESTINY-Breast11 study design

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



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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/m² QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ‡doxorubicin (60 mg/m² Q2W) + cyclophosphamide (600 mg/m² Q2W); §paclitaxel (80 mg/m² 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*	54 (16.9)				43 (13.8)				52 (18.4)
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

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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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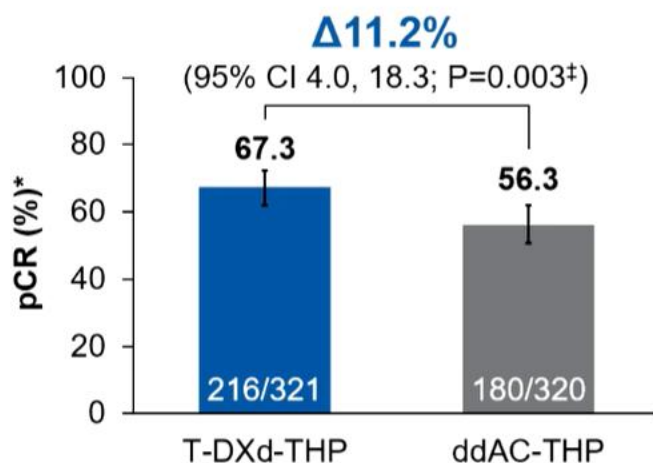


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pCR (ypT0/is ypN0): primary endpoint

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.

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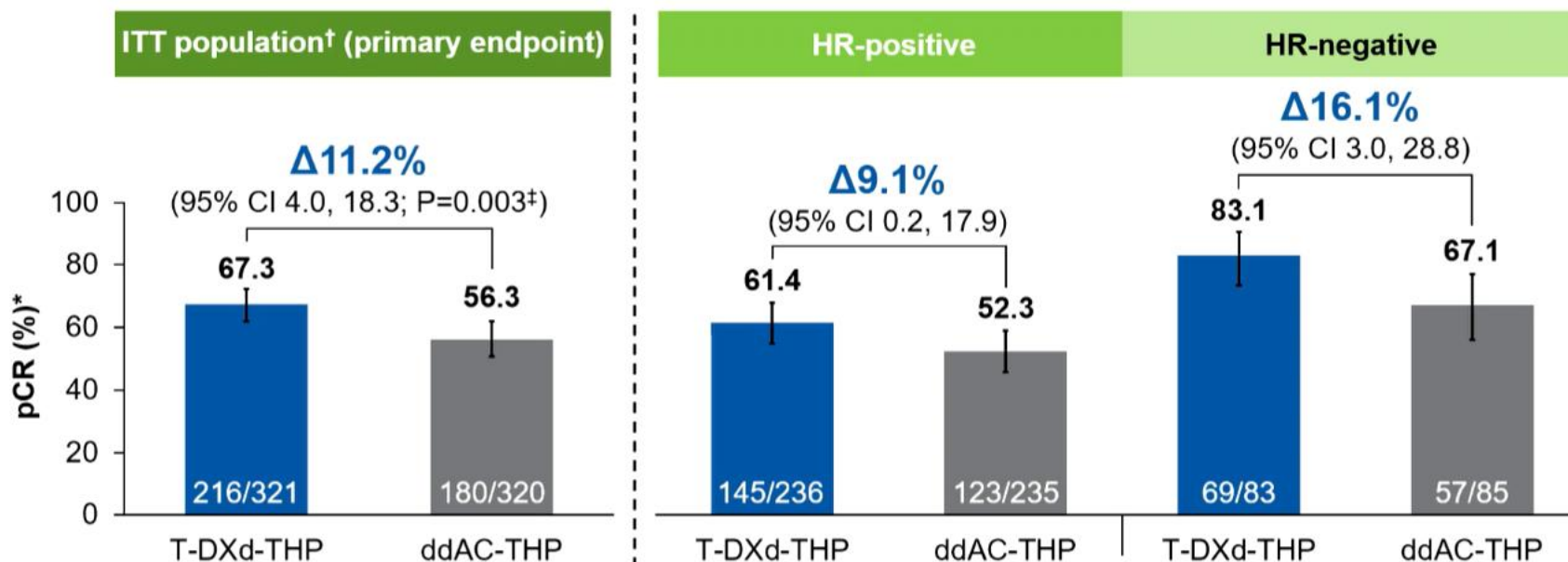
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pCR (ypT0/is ypN0): primary endpoint



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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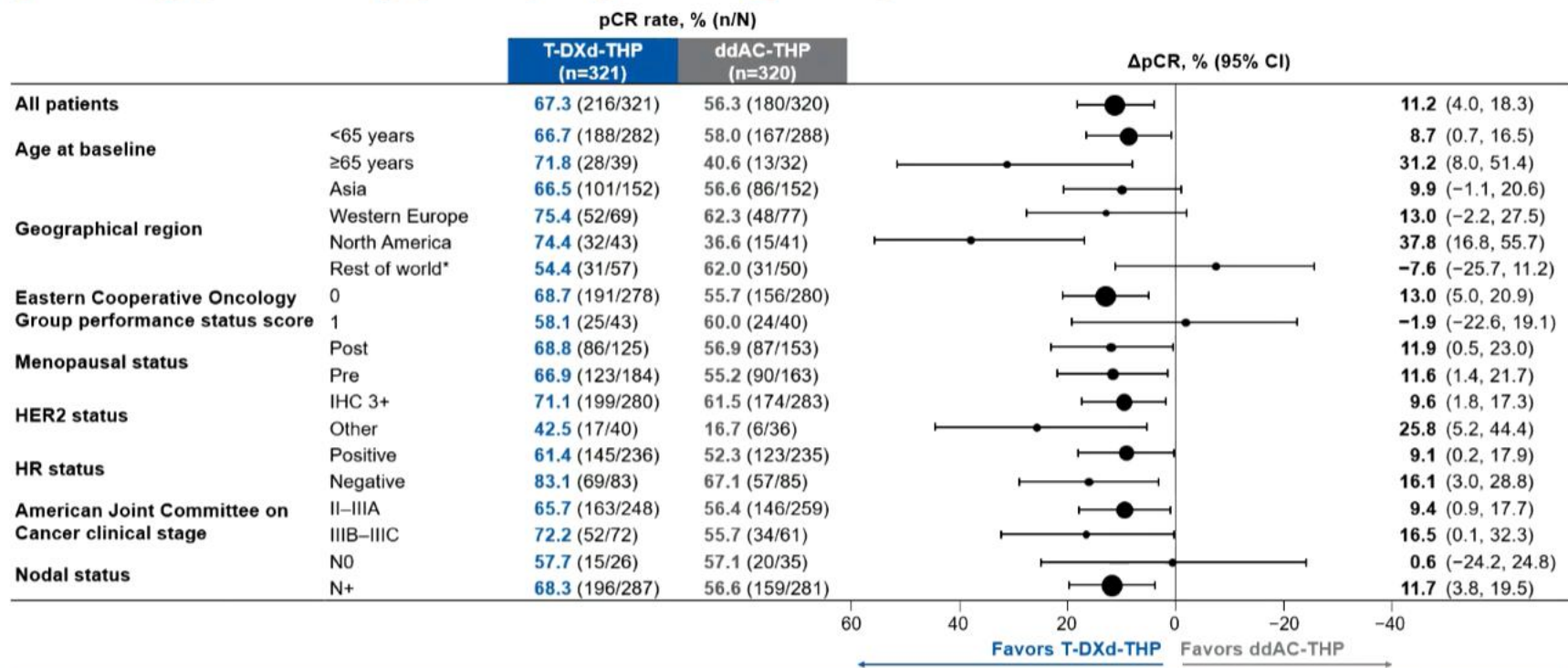
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pCR (ypT0/is ypN0) by subgroups



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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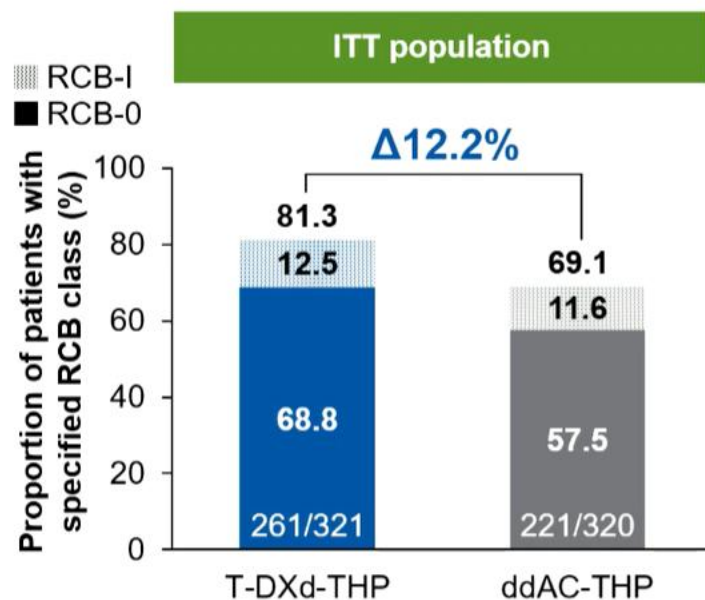
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RCB outcomes



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)

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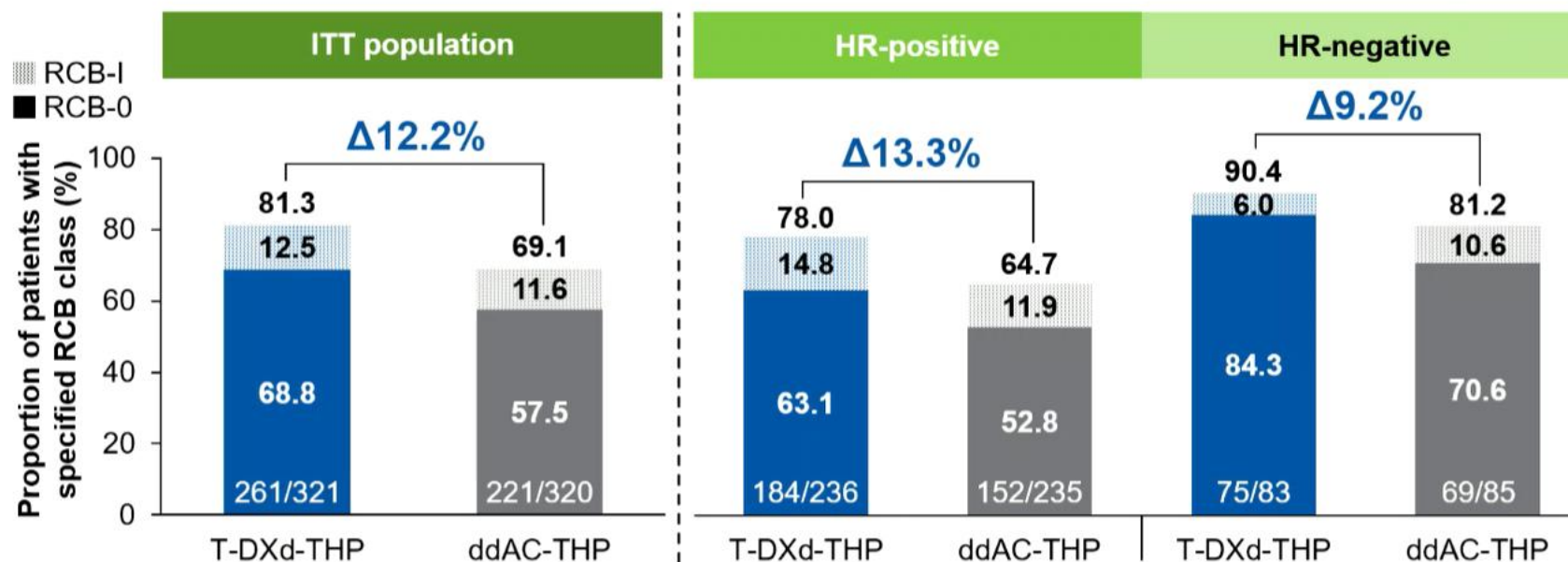
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RCB outcomes



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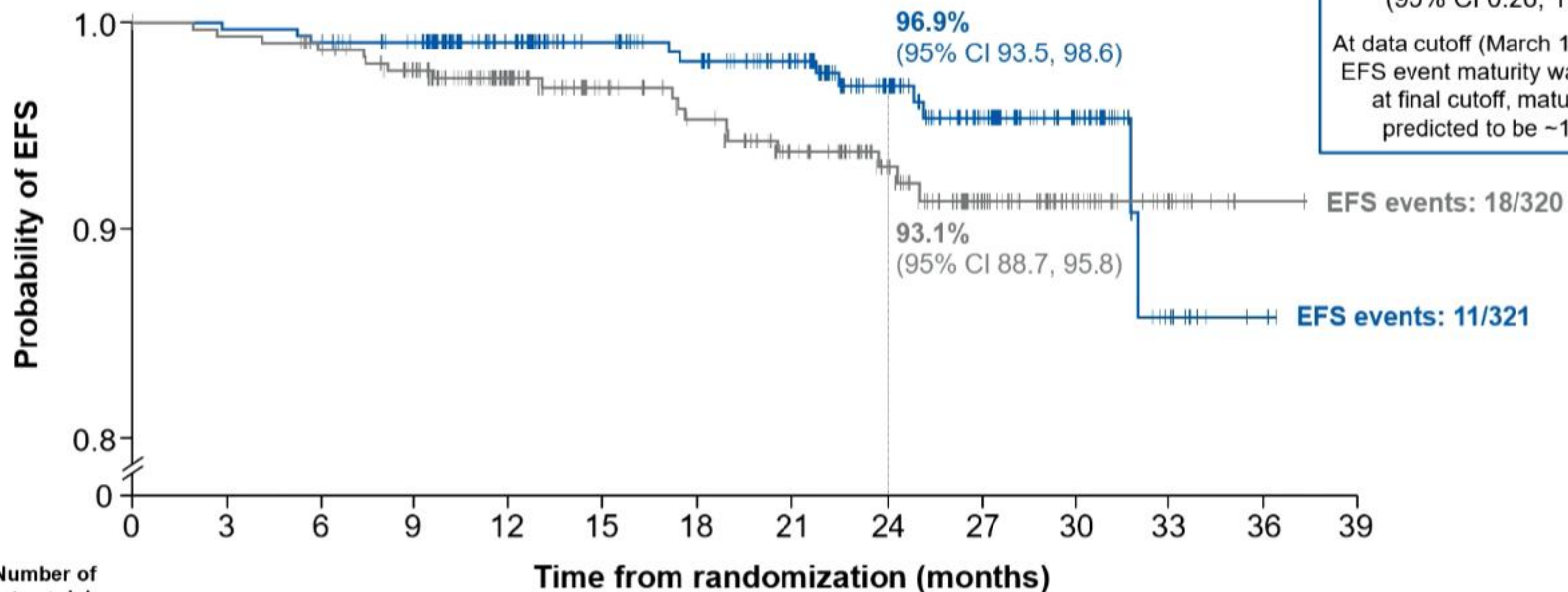
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EFS



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	0	3	6	9	12	15	18	21	24	27	30	33	36	39
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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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

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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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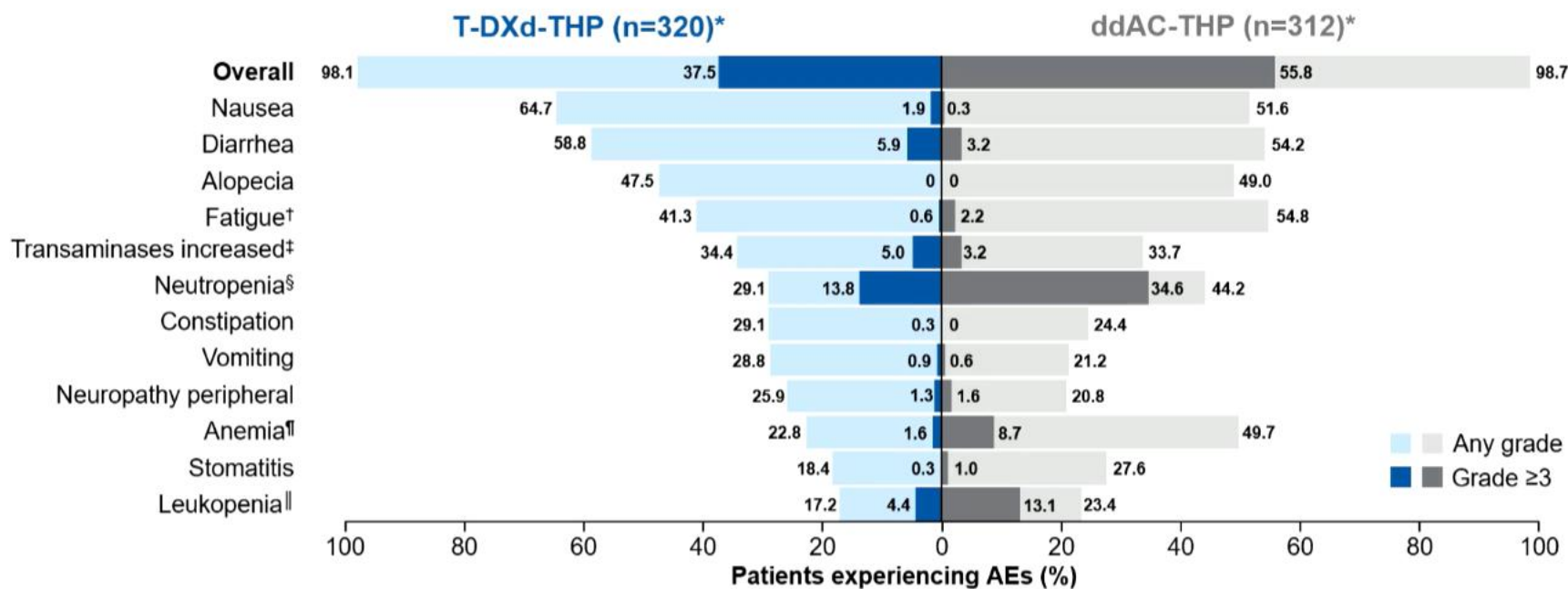
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TEAEs in at least 20% of patients in either arm



**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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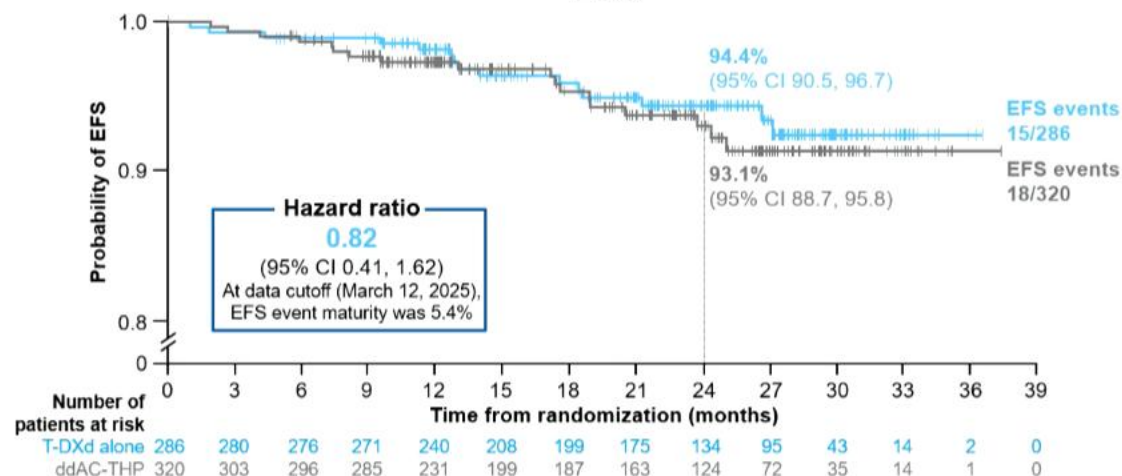
T-DXd alone arm: efficacy summary

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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DESTINY-Breast11: Neoadjuvant trastuzumab deruxtecan alone (T-DXd) or followed by paclitaxel + trastuzumab + pertuzumab (T-DXd-THP) vs SOC for high-risk HER2+ early breast cancer (eBC)

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)
Grade ≥3	0	6 (1.9)
Grade 5	0	0
AE leading to surgical delay‡	18 (6.4)	8 (2.6)

The overall safety profile of T-DXd alone was favorable vs ddAC-THP, with reduced rates of Grade ≥3 AEs, serious AEs, treatment reductions/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 24.0 months (T-DXd) and 21.0 months (ddAC-THP). *Safety analyses included all patients who received at least one dose of any study treatment; †T-DXd alone arm: pulmonary embolism considered by investigator to be unrelated to study treatment (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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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: $\Delta 11.2\%$ (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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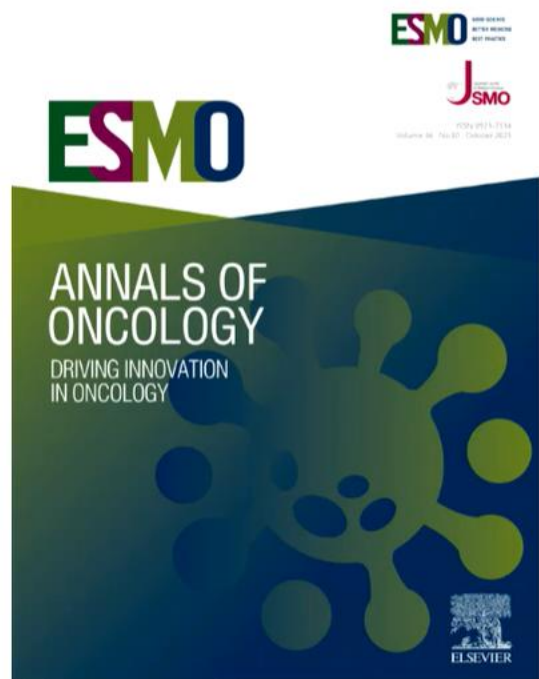
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Neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel, trastuzumab, and pertuzumab for high-risk HER2-positive early breast cancer (DESTINY-Breast11): a randomised, open-label, multicentre, phase 3 trial

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