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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☆

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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 Independent Data Monitoring Committee recommendation. The primary endpoint was pathological complete response (pCR; ypT0/is ypN0; intent-to-treat population). Secondary endpoints included event-free survival (EFS; intent-to-treat population) and safety (safety analysis set).

Results: Between 25 October 2021 and 12 March 2025, 286 (T-DXd), 321 (T-DXd-THP), and 320 (ddAC-THP) female patients were randomised. pCR rates were 43.0% (T-DXd, $n = 123$), 67.3% (T-DXd-THP, $n = 216$), and 56.3% (ddAC-THP, $n = 180$). T-DXd-THP versus ddAC-THP absolute pCR rate difference was 11.2% [95% confidence interval (CI), 4.0% to 18.3%, $P = 0.003$], with benefit in hormone receptor (HR)-positive [61.4% ($n/N = 145/236$) versus 52.3% ($n/N = 123/235$); difference in pCR (ΔpCR) 9.1% (95% CI 0.2% to 17.9%)] and HR-negative [83.1% ($n/N = 69/83$) versus

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67.1% ($n/N = 57/85$); ΔpCR 16.1% (95% CI 3.0% to 28.8%)] subgroups. Median EFS (T-DXd-THP versus ddAC-THP, maturity 4.5%) hazard ratio was 0.56 (95% CI 0.26 to 1.17). Grade ≥3 adverse events (AE; T-DXd, 22.6% ($n = 64$); T-DXd-THP, 37.5% ($n = 120$); ddAC-THP, 55.8% ($n = 174$)], serious AE [T-DXd, 10.2% ($n = 29$); T-DXd-THP, 10.6% ($n = 34$); ddAC-THP, 20.2% ($n = 63$)], and all-grade left-ventricular dysfunction [T-DXd, 0.7% ($n = 2$); T-DXd-THP, 1.3% ($n = 4$); ddAC-THP, 6.1% ($n = 19$)] rates were lower for T-DXd and T-DXd-THP than ddAC-THP. All-grade adjudicated drug-related interstitial lung disease/pneumonitis rates were low and similar across arms [T-DXd, 4.9% ($n = 14$); T-DXd-THP, 4.4% ($n = 14$); ddAC-THP, 5.1% ($n = 16$)]. Three treatment-related deaths occurred [T-DXd-THP, 0.3% ($n = 1$); ddAC-THP, 0.6% ($n = 2$)].
Conclusions: Neoadjuvant T-DXd-THP demonstrated statistically significant and clinically meaningful pCR benefit and improved safety versus ddAC-THP.
Key words: neoadjuvant, early breast cancer, HER2-positive, trastuzumab deruxtecan, pathological complete response

INTRODUCTION

Current standard of care (SOC) for human epidermal growth factor receptor (HER2)-positive early-stage breast cancer, when neoadjuvant treatment is indicated, is dual HER2-targeted therapy with trastuzumab plus pertuzumab administered concurrently or sequentially with polychemotherapy, such as anthracycline-taxane or carboplatin-taxane regimens.[1,2] However, these regimens are associated with a substantial toxicity burden. Anthracyclines carry risks of acute and long-term adverse events (AEs), including febrile neutropenia, cardiotoxicity, and secondary leukaemia[2-4]; and docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) treatment is frequently complicated by neuropathic, haematological, and gastrointestinal AEs.[5,6]

Studies have shown that having a pathological complete response (pCR) is a good prognostic indicator for event-free survival (EFS) at the patient level,[7-9] particularly in HER2-positive disease.[8] Patients who have a pCR after neoadjuvant treatment may have the opportunity to receive less aggressive post-neoadjuvant therapy than those with residual disease.[2,10,11] However, there is a need for new neoadjuvant treatment options because only 39%-64% of patients have a pCR with SOC[5,12-16] and outcomes may be influenced by hormone receptor (HR) status, clinical tumour stage, and nodal stage.[17,18] Approximately 20% of patients with HER2-positive early-stage breast cancer and residual disease after neoadjuvant treatment experience disease recurrence after 3 years[19]; high-risk factors for disease recurrence include node-positive disease and large tumour size (clinical tumour stage ≥cT3) at diagnosis.[17,19] The use of a HER2-directed antibody-drug conjugate (ADC), with a multimodal mechanism of action, may improve survival outcomes for HER2-positive early-stage breast cancer.[20]

Trastuzumab deruxtecan (T-DXd), a HER2-directed ADC with a tetrapeptide-based cleavable linker and topoisomerase I inhibitor payload,[21,22] is approved in the HER2-positive metastatic breast cancer setting.[23,24] In the phase III DESTINY-Breast03 study in HER2-positive metastatic breast cancer, T-DXd versus trastuzumab emtansine (T-DM1) demonstrated a median progression-free survival by investigator assessment of 29.0 months versus 7.2 months, respectively, and a 10-month improvement in overall survival (OS).[25] T-DXd as first-line therapy for HER2-positive metastatic breast cancer was evaluated in a phase III DESTINY-Breast09 interim analysis, in which T-DXd plus pertuzumab showed statistically significant and clinically meaningful improvement in progression-free survival compared with paclitaxel, trastuzumab, plus pertuzumab (THP), and a safety profile consistent with each individual therapy.[26]

DESTINY-Breast11 (NCT05113251) evaluated whether findings with T-DXd in the metastatic setting can translate to early-stage disease. T-DXd alone or followed by THP was compared with dose-dense doxorubicin plus cyclophosphamide (ddAC) followed by THP in patients with high-risk (≥cT3 cN0 or cT0–4 cN1–3), HER2-positive disease. Here, we report the primary pCR analysis. Safety data and selected secondary outcomes [EFS and residual cancer burden (RCB)] are also reported.

METHODS

Study design and participants

We conducted a phase III, open-label, randomised, three-arm study in high-risk, HER2-positive, early-stage breast cancer across 18 countries and 147 sites (hospitals, university hospitals, and medical and oncology centres). The institutional review board or ethics committee at each investigational site approved the trial before initiation. The trial was performed in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations on the conduct of clinical research. This study is registered with ClinicalTrials.gov (NCT05113251) and is active but closed to accrual.

Eligible patients had previously untreated, locally advanced or inflammatory breast cancer with a primary clinical tumour stage of ≥cT3 and cN0–3, or a primary tumour of any size with positive lymph node involvement (any cT and cN1–3). HER2-positive status [immunohistochemistry (IHC) 3+ or *in situ* hybridisation (ISH)+] was determined locally, and confirmed centrally, according to American Society of Clinical Oncology – College of American Pathologists guidelines.[27] Patients were at least 18 years of age and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1. Patient sex (male or female) and race were self-reported. Patients provided written informed consent before participation.

Randomisation and masking

Patients were randomised 1 : 1 : 1 to T-DXd-alone, T-DXd-THP, and ddAC-THP arms. Randomisation was performed centrally using interactive-response technology and was stratified by HR status (oestrogen receptor and/or progesterone receptor-positive versus -negative) and central assessment of HER2-positive status (IHC 3+ versus ISH+ in the absence of IHC 3+ status). The proportion of patients with HR-negative disease was capped at 30% to reflect natural prevalence and to ensure that the study results were clinically meaningful to real-word practice. This study was open-label for personnel at study sites; however, to maintain the integrity of the study, the sponsor did not have access to aggregated efficacy data by each treatment arm prior to data readout for the primary endpoint.

Procedures

Patients were assigned to receive: in the T-DXd-alone arm, T-DXd [5.4 mg/kg once every 3 weeks (Q3W) intravenously (i.v.)] for eight cycles; in the T-DXd-THP arm, T-DXd (5.4 mg/kg Q3W i.v.) for four cycles followed by paclitaxel (80 mg/m^2 once every week [QW] i.v.) concurrent with trastuzumab (6 mg/kg Q3W i.v.) and pertuzumab (840 mg loading dose i.v. followed by 420 mg Q3W i.v.) for four cycles; and in the ddAC-THP arm, doxorubicin [60 mg/m^2 once every 2 weeks (Q2W) i.v.] and cyclophosphamide (600 mg/m^2 Q2W i.v.) for four cycles followed by paclitaxel (80 mg/m^2 QW i.v.) concurrent with trastuzumab (8 mg/kg loading dose i.v. followed by 6 mg/kg Q3W i.v.) and pertuzumab (840 mg loading dose i.v. followed by 420 mg Q3W i.v.) for four cycles. In the event of disease progression, unacceptable toxicity, or withdrawal of consent, neoadjuvant therapy was discontinued. After discontinuation, patients could receive subsequent therapy or surgery at the investigator's discretion.

The recommended window for surgery was 3—6 weeks following administration of the last dose of neoadjuvant study treatment. After surgery, local SOC was administered at the investigator's discretion in all arms; treatments consistent with international treatment guidelines were recommended by the protocol. Radiotherapy[2] and concomitant HER2-directed post-neoadjuvant treatment (trastuzumab with/without pertuzumab for up to 1 year, or T-DM1 for up to 14 cycles,[2,10,11] in patients who did and did not have a pCR, respectively) were recommended per study protocol, and participants with HR-positive tumours were recommended to receive adjuvant endocrine therapy. Because SOC treatment elements were not included in the neoadjuvant phase for participants in the T-DXd-alone arm in contrast to the T-DXd-THP and ddAC-THP arms, patients who did not have a pCR were also recommended per protocol to be considered for treatment with anthracycline- and/or taxane-based chemotherapy in combination with standard HER2-directed therapy.

Despite the study passing the preplanned futility analysis [non-binding stopping boundary of difference in pCR (ΔpCR) less than −15% versus ddAC-THP], enrolment to the T-DXd-alone arm was prematurely closed on 13 March 2024, following the Independent Data Monitoring Committee (IDMC) recommendation. Approximately 95% of the target population had been enrolled (actual/planned enrolment, $n = 286/300$). Reasons for enrolment closure to T-DXd alone were multifactorial, including a lower pCR rate, a low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery. The IDMC recommendation was not based on new safety findings. Patients already receiving T-DXd alone could continue treatment until completion of eight cycles or meeting any discontinuation criteria, or switch to investigator's choice of local SOC. Following cessation of enrolment to T-DXd alone, patients were randomised 1 : 1 to T-DXd-THP and ddAC-THP.

Outcomes

The primary endpoint was pCR rate (ypT0/is ypN0), assessed to evaluate neoadjuvant T-DXd or T-DXd-THP compared with ddAC-THP. Secondary endpoints included pCR rate (ypT0 ypN0), EFS, invasive disease-free survival (iDFS), and OS. pCR rates were assessed by blinded central evaluation following completion of neoadjuvant therapy; details are provided in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.10.019. Additional efficacy measures included distant metastasis-free survival (DMFS) and RCB.[28] Results for iDFS, DMFS, and OS are not reported herein owing to insufficient event numbers.

Safety and tolerability of T-DXd or T-DXd-THP compared with ddAC-THP were evaluated using clinical laboratory data, 12-lead electrocardiograms, echocardiogram or multigated acquisition scans, physical examination, vital signs, and ECOG performance status. AEs were coded using Medical Dictionary for Regulatory Activities v27.1 preferred terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. AEs of special interest were evaluated, including interstitial lung disease (ILD)/pneumonitis and left-ventricular dysfunction rates. High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if new or worsening pulmonary symptoms or radiological abnormality suggestive of ILD/pneumonitis were observed while receiving T-DXd in the T-DXd-alone or T-DXd-THP arms, treatment was interrupted and a full investigation completed. AEs and serious AEs (SAEs; other than ILD/pneumonitis and heart failure) were collected from the time of study entry, throughout treatment, and until the end of the safety follow-up period (40 + 7 days after the discontinuation of all study interventions). For ILD/pneumonitis, safety follow up was continued until resolution of events that occurred between randomisation and the end of the safety follow-up period. Heart failure AEs will be collected and recorded until the end of the study (up to 6 years of follow up). If an event started after the defined safety follow-up period and was considered to be due to a late-onset toxicity to study intervention, it was reported as an AE or SAE as applicable.

Additional endpoints included patient-reported outcomes of physical functioning, tolerability, and quality of life, which will be reported separately.

Statistical analysis

Statistical analyses were performed using SAS software version 9.4. A sample size of 624 patients (208 per treatment arm) was initially selected to detect a 15% improvement in pCR with either investigational regimen compared with an expected 56% pCR for ddAC-THP, with at least 93% power at an overall 5% two-sided alpha level. The sample size was subsequently increased to 900 patients (300 per treatment arm) to increase the precision of the treatment effect estimate on EFS and to characterize the safety profiles of the study treatments better; additional details are provided in the Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2025.10.019.

pCR (ypT0/is ypN0 definition) benefit was estimated as the difference in rates between each investigational treatment and ddAC-THP using the stratified Miettinen and Nurminen's method. To control the family-wise Type I error rate at 5% in terms of the primary pCR analysis, a multiple testing procedure with an alpha-exhaustive recycling strategy[29] was used. pCR was compared between T-DXd and ddAC-THP at a two-sided 2% alpha and between T-DXd-THP and ddAC-THP at a 3% alpha. No changes to the multiple testing procedure were made following enrolment closure to the T-DXd-alone arm. No multiplicity adjustment was made for the EFS analysis. EFS will be analysed again when all patients have been followed for 3 years or have discontinued or withdrawn from the study. Additional details of statistical analyses are in the Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2025.10.019.

pCR outcomes were reported in the intent-to-treat (ITT) population (all randomised patients). Patients who discontinued randomised study treatment and received any subsequent neoadjuvant cancer treatment were considered to have a non-pCR per the prespecified statistical analysis plan regardless of having a pCR or not (unless otherwise stated). Patients who were randomised but did not receive at least one dose of study treatment, did not have a pCR assessment (for example those who did not undergo surgery or were non-starters), or had disease progression or died from any cause prior to surgery were also considered to have a non-pCR. A prespecified supplementary analysis was conducted, in which the primary analysis of pCR was repeated, but patients who discontinued randomised study treatment and received any subsequent anticancer treatment before surgery were not automatically classed as non-pCR responders. EFS events included disease progression that precluded initial surgery, invasive disease recurrence (local, regional, distant, or contralateral), or death from any cause; patients lost to follow up or who withdrew consent were censored at their last evaluable assessment, or at the last time point when they were known to be alive. Safety data are summarised in the safety analysis set (all patients who received at least one dose of any investigational drug). Missing safety data were generally not imputed, although AEs with missing causality were assumed to be related to study drug.

The IDMC periodically reviewed unblinded data to inform recommendations as to continue, amend, or stop the study based on safety or futility findings; data were made available upon request. The study team remained blinded to results of the preplanned futility analysis and *ad hoc* analyses. Potential cases of ILD or pneumonitis were evaluated by an Independent ILD Adjudication Committee, who reviewed relevant data in the clinical database to fully characterise medical history, diagnostic evaluation, treatment, and event outcome.

Role of the funding source

This trial was sponsored by AstraZeneca and designed by AstraZeneca in collaboration with Daiichi Sankyo and the trial steering committee chair. AstraZeneca were responsible for the conduct and analysis of the trial. The authors, steering committee members, and AstraZeneca in collaboration with Daiichi Sankyo were responsible for data interpretation and guided the manuscript development after agreement to publish, with editorial assistance from professional medical writers funded by AstraZeneca. All drafts were reviewed by the authors, who approved the final submitted version and act as guarantors for the completeness and accuracy of the data, and adherence to the trial protocol and statistical analysis plan.

RESULTS

Between 25 October 2021 and 12 March 2025, 927 patients underwent randomisation (ITT population) to T-DXd (before closure; $n = 286$), T-DXd-THP ($n = 321$), and ddAC-THP ($n = 320$) (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.10.019). Demographics and baseline clinical characteristics were balanced among arms (Table 1). Median [interquartile range (IQR)] age was 50 (42−58) years and most patients were Asian (47.9%) or White (44.9%). Overall, 456 patients (49.2%) had American Joint Committee on Cancer clinical stage II disease and 467 patients (50.4%) had stage III disease. In total, 676 patients (72.9%) had HR-positive status at baseline. The proportion of patients with clinical tumour size cT0−2 was 56.2% (521 patients) and cT3−4 was 43.8% (406 patients). Overall, 81 patients (8.7%) had node-negative disease and 822 patients (88.7%) had node-positive disease; the remainder had unknown status.

In the T-DXd, T-DXd-THP, and ddAC-THP arms, respectively, 52 (18.4%), 54 (16.9%), and 43 (13.8%) patients prematurely discontinued any treatment (reasons detailed in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.10.019). Most treatment discontinuations in the T-DXd-THP and ddAC-THP arms were of taxanes. In the T-DXd, T-DXd-THP, and ddAC-THP arms, respectively, 36 (12.6%), 6 (1.9%), and 8 (2.5%) patients switched to receiving local neoadjuvant SOC at the

Table 1. Demographics and baseline clinical characteristics in the ITT population

	T-DXd (n = 286)	T-DXd-THP (n = 321)	ddAC-THP (n = 320)	Total (N = 927)
Age, years, median (IQR)	50 (42-59)	50 (41-58)	50 (42-58)	50 (42-58)
Age group, *n* (%)				
<65 years	252 (88.1)	282 (87.9)	288 (90.0)	822 (88.7)
≥65 years	34 (11.9)	39 (12.1)	32 (10.0)	105 (11.3)
Female sex, *n* (%)	286 (100)	321 (100)	320 (100)	927 (100)
Race, *n* (%)				
Asian	127 (44.4)	160 (49.8)	157 (49.1)	444 (47.9)
White	139 (48.6)	140 (43.6)	137 (42.8)	416 (44.9)
Black or African American	7 (2.4)	5 (1.6)	7 (2.2)	19 (2.0)
American Indian or Alaska Native	2 (0.7)	2 (0.6)	0	4 (0.4)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	1 (0.3)	2 (0.2)
Other	6 (2.1)	9 (2.8)	9 (2.8)	24 (2.6)
Not reported	5 (1.7)	4 (1.2)	9 (2.8)	18 (1.9)
Region, *n* (%)				
Asia	124 (43.4)	152 (47.4)	152 (47.5)	428 (46.2)
Western Europe	66 (23.1)	69 (21.5)	77 (24.1)	212 (22.9)
North America	52 (18.2)	43 (13.4)	41 (12.8)	136 (14.7)
Rest of world[a]	44 (15.4)	57 (17.8)	50 (15.6)	151 (16.3)
ECOG performance status score, *n* (%)				
0	252 (88.1)	278 (86.6)	280 (87.5)	810 (87.4)
1	34 (11.9)	43 (13.4)	40 (12.5)	117 (12.6)
HER2 status, *n* (%)[b]				
IHC 3+	254 (88.8)	280 (87.2)	283 (88.4)	817 (88.1)
ISH+ in the absence of IHC 3+ status	32 (11.2)	40 (12.5)	36 (11.3)	108 (11.7)
Not categorised or missing	0	1 (0.3)	1 (0.3)	2 (0.2)
HR status, *n* (%)[c]				
ER- and/or PR-positive	205 (71.7)	236 (73.5)	235 (73.4)	676 (72.9)
ER- and PR-negative[d]	80 (28.0)	83 (25.9)	85 (26.6)	248 (26.8)
Missing	1 (0.3)	2 (0.6)	0	3 (0.3)
AJCC stage (AJCC staging system, 8th edition), *n* (%)				
Stage I	2 (0.7)	1 (0.3)	1 (0.3)	4 (0.4)
Stage II	131 (45.8)	159 (49.5)	166 (51.9)	456 (49.2)
Stage III	153 (53.5)	161 (50.2)	153 (47.8)	467 (50.4)
Clinical tumour stage, *n* (%)				
cT0–2	157 (54.9)	176 (54.8)	188 (58.8)	521 (56.2)
cT3–4	129 (45.1)	145 (45.2)	132 (41.3)	406 (43.8)
Nodal status, *n* (%)				
N0	20 (7.0)	26 (8.1)	35 (10.9)	81 (8.7)
N+	254 (88.8)	287 (89.4)	281 (87.8)	822 (88.7)
Unknown	12 (4.2)	8 (2.5)	4 (1.3)	24 (2.6)

AJCC, American Joint Committee on Cancer; cT, clinical tumour stage; ddAC, dose-dense doxorubicin + cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; IQR, interquartile range; ISH, *in situ* hybridisation; ITT, intent-to-treat; N, nodal stage; PR, progesterone receptor; T-DXd, trastuzumab deruxtecan; THP, paclitaxel + trastuzumab + pertuzumab.
[a]Rest of world includes Brazil, Bulgaria, Peru, Poland, Russia, and Saudi Arabia.
[b]HER2 status per eCRF data.
[c]HR status per eCRF data.
[d]The 30% cap for patients with HR-negative disease was not reached during the study.

investigator's discretion, and 12 (4.2%), 9 (2.8%), and 20 (6.3%) patients did not undergo surgery (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.10.019). Post-neoadjuvant treatments were generally balanced across arms (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.10.019). T-DM1 use after neoadjuvant treatment by region and pCR status is reported in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.10.019.

pCR rates (ypT0/is ypN0) were 67.3% (n/N = 216/321) in the T-DXd-THP arm and 56.3% (n/N = 180/320) in the ddAC-THP arm, with a ΔpCR of 11.2% [95% confidence interval (CI) 4.0% to 18.3%, P = 0.003], which met the prespecified significance threshold of 0.03 (Figure 1A). The pCR rate in the T-DXd arm was 43.0% (n/N = 123/286) corresponding to a ΔpCR versus ddAC-THP of −13.2% (95% CI −20.8% to −5.4%, P = 0.001) (Figure 1B). In a prespecified supplementary analysis in which patients were not automatically categorised as non-responders if they discontinued study treatment and received subsequent non-study anticancer therapy before surgery, observed pCR rates were 68.9% (n/N = 221/321; T-DXd-THP), 51.4% (n/N = 147/286; T-DXd), and 57.2% (n/N = 183/320; ddAC-THP) [difference T-DXd-THP versus ddAC-THP: 11.8% (95% CI 4.7% to 18.8%); T-DXd versus ddAC-THP: −5.8% (95% CI −13.4% to 1.9%)]. In a sensitivity analysis of patients randomised at least 236 days prior to T-DXd-alone arm closure, pCR findings were 46.3% (n/N = 101/218; T-DXd) and 51.4% [n/N = 112/218; ddAC-THP; difference −4.8% (95% CI −13.9% to 4.2%)].

Improvements in pCR rates by ypT0/is ypN0 were consistent across most prespecified subgroups (Figure 1A-C

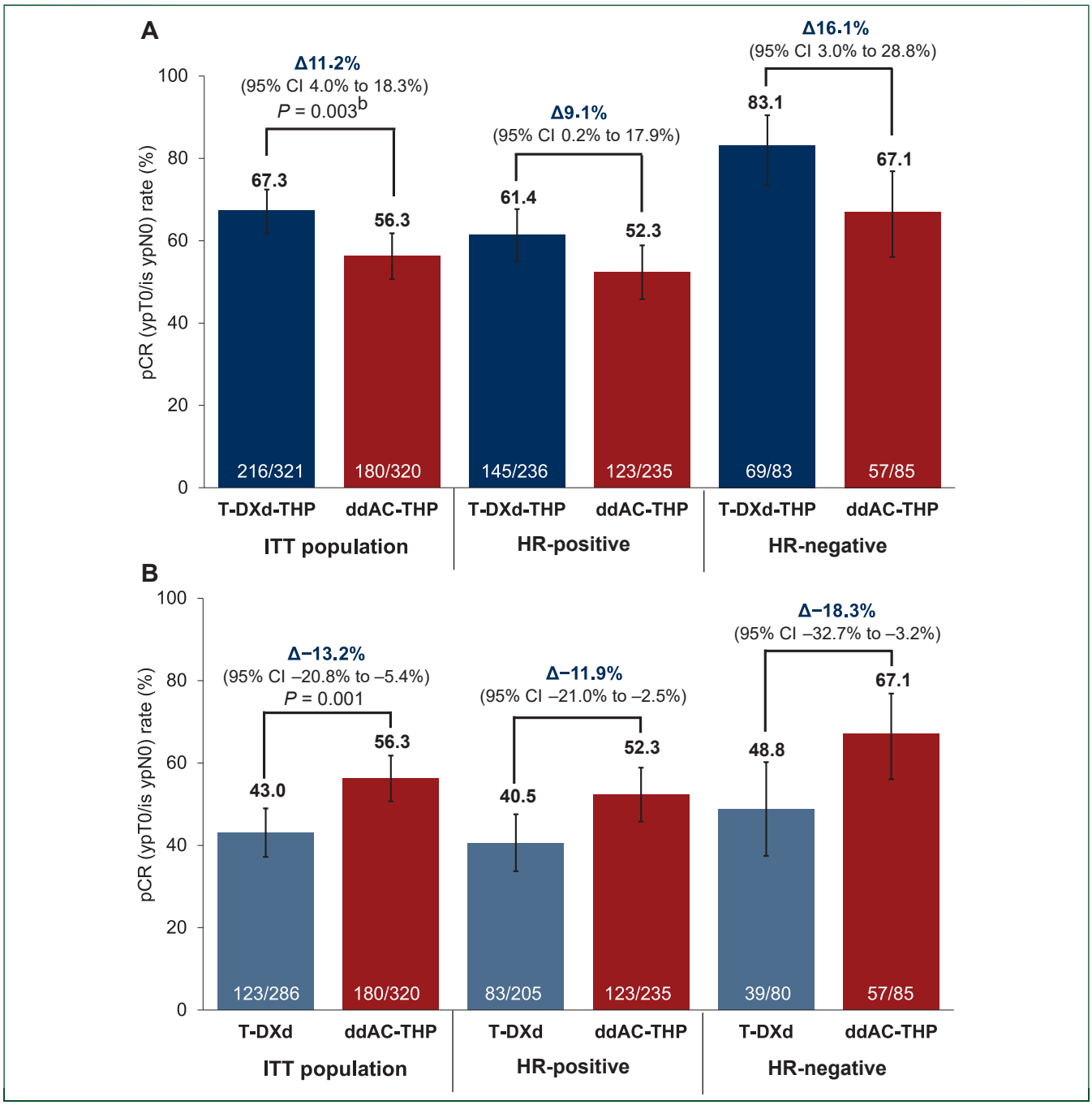

Figure 1. pCR[a] rates by ypT0/is ypN0 in the ITT population (primary endpoint) and HR-positive and HR-negative subgroups for (A) T-DXd-THP versus ddAC-THP arms and (B) T-DXd versus ddAC-THP arms; (C) prespecified subgroup analysis of pCR[a] by ypT0/is ypN0 for T-DXd-THP and ddAC-THP arms; pCR[a] rates by ypT0 ypN0 (secondary endpoint) in the ITT population for (D) T-DXd-THP versus ddAC-THP arms and (E) T-DXd versus ddAC-THP arms. (A-C) pCR by ypT0/is ypN0 was defined as having no evidence on H&E staining of residual invasive disease in the complete resected breast specimen and all sampled regional lymph nodes, assessed by central evaluation on completion of neoadjuvant treatment. (A, B, D, E) Treatment effects were estimated by the difference in pCR rates with 95% CIs, and *P* values for the primary analysis, based on the stratified Miettinen and Nurminen's method, stratified by HR status and HER2 status with strata weighting by sample size (i.e. Mantel—Haenszel weights). (A—E) 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). Patients who had already received T-DXd at time of T-DXd arm enrolment closure either remained on treatment until completion/pre-established discontinuation criteria were met or could immediately switch to local SOC, if appropriate — classified as having a non-pCR. (A, B, C) For each subgroup, the difference in rates and 95% CI was calculated using the unstratified Miettinen and Nurminen's method. (C) Size of circle is proportional to the total sample size in a subgroup. For subgroups with <10 patients in each arm, the pCR difference and 95% CI were presented as NC. Patients with regional lymph nodes of N_X were excluded from subgroup analysis for nodal status. (D, E) pCR by ypT0 ypN0 was defined as having no evidence on H&E staining of residual invasive disease and *in situ* cancer in the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant therapy. AJCC staging system, 8th edition was used.

Δ, difference; AJCC, American Joint Committee on Cancer; CI, confidence interval; cT, clinical tumour stage; ddAC, dose-dense doxorubicin + cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; H&E, haematoxylin and eosin; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ITT, intent-to-treat; N, nodal stage; NC, not calculated; pCR, pathological complete response; PR, progesterone receptor; SOC, standard of care; T-DXd, trastuzumab deruxtecan; THP, paclitaxel + trastuzumab + pertuzumab.

[a]By blinded central review.

[b]Two-sided $P < 0.03$ prespecified boundary.

[c]One patient with AJCC clinical stage IB was included as they were eligible for inclusion based on AJCC prognostic staging.

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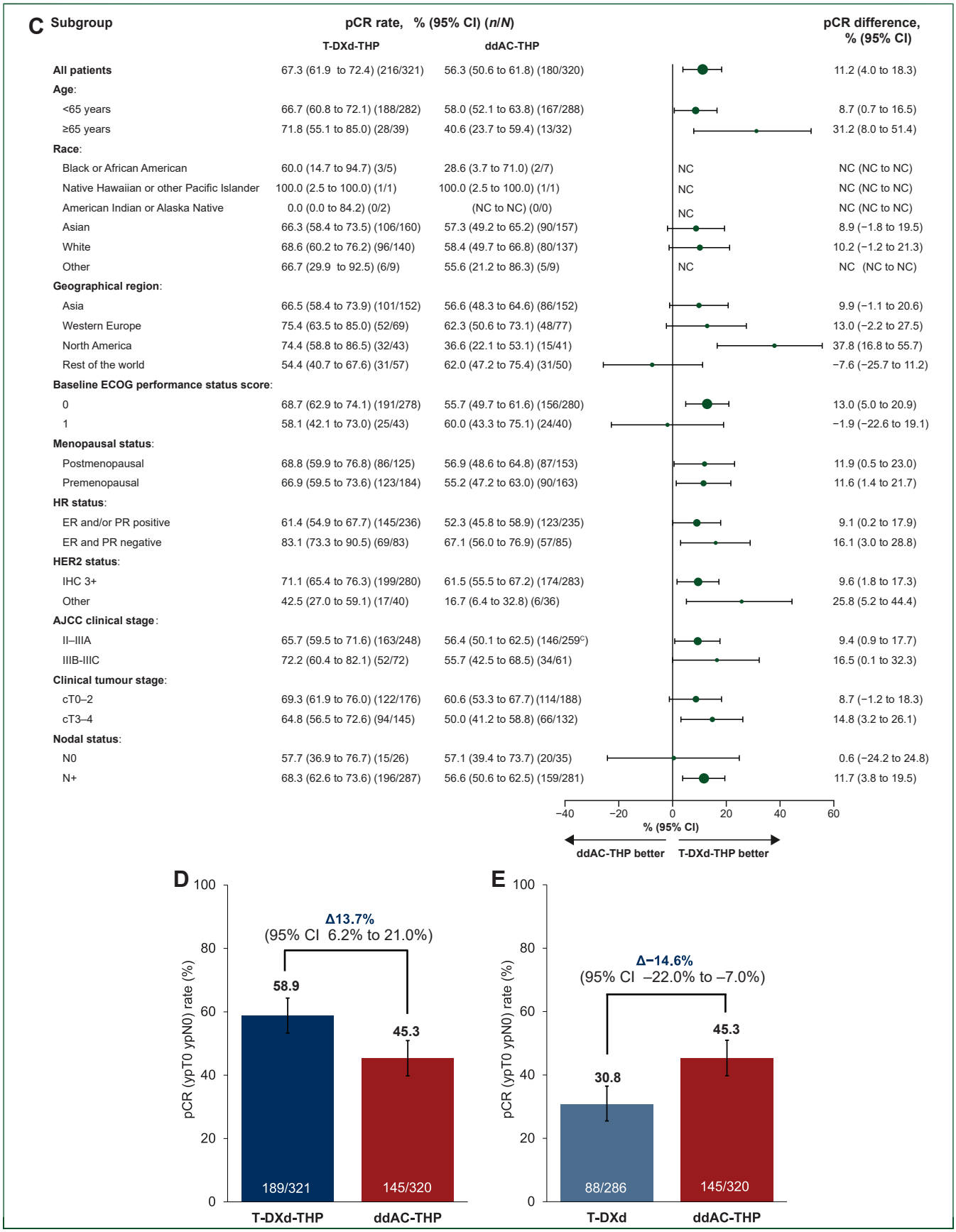

Figure 1. Continued.

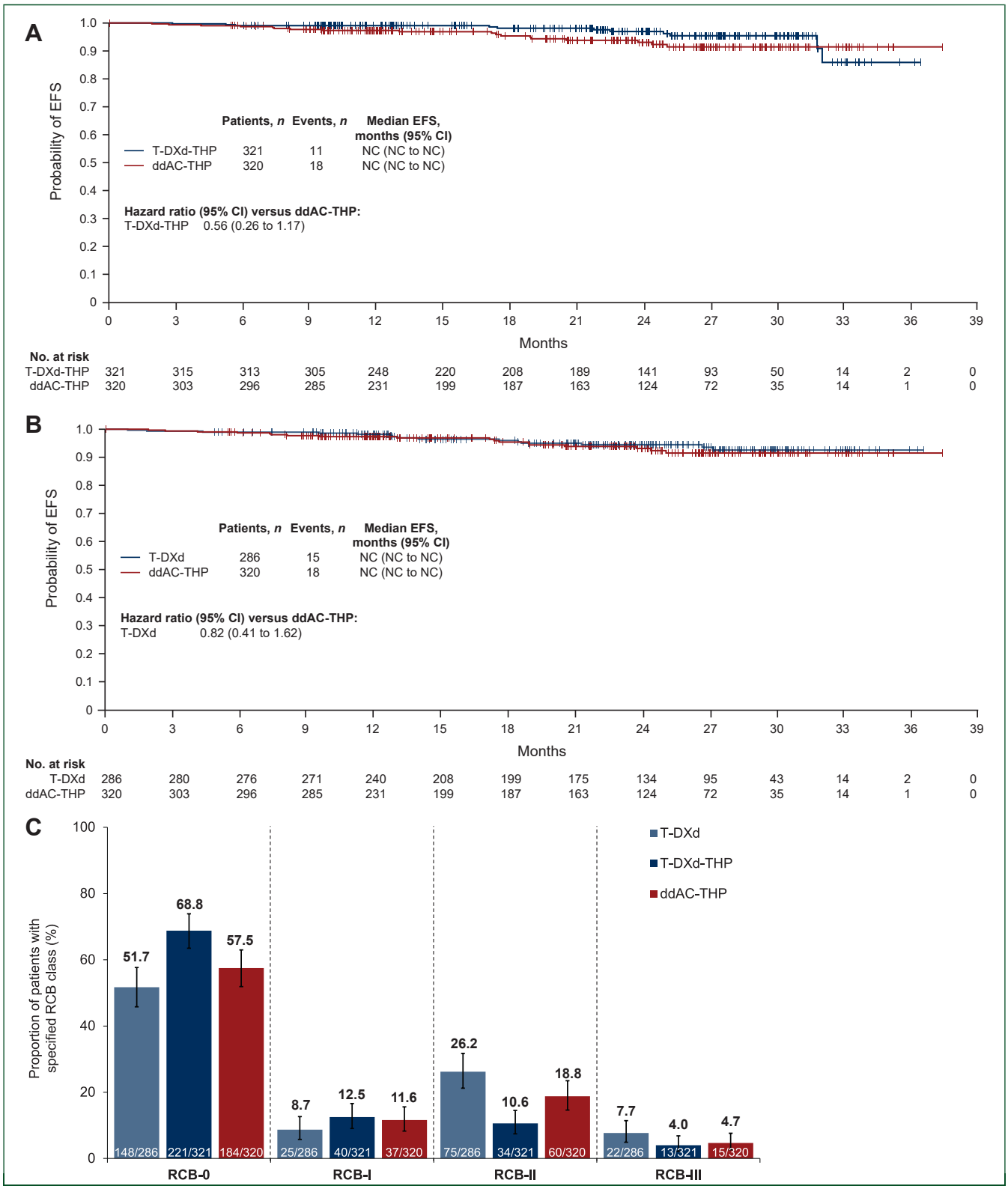

Figure 2. Additional efficacy outcomes in the ITT population: Kaplan–Meier analysis of EFS for (A) T-DXd-THP versus ddAC-THP; (B) T-DXd alone versus ddAC-THP; (C) RCB class of the resected breast or lymph node tissue. (A, B) A vertical line indicates a censored observation. Any patient without an event at the time of analysis was censored at the last recorded date on which they were known to be alive and event-free. If the patient had no evaluable disease assessments at neoadjuvant baseline or post-neoadjuvant baseline, they were censored at randomisation date unless they died in the period prior to surgery, in which case they were treated as having an event at the date of death. Hazard ratios are in relation to ddAC-THP treatment arm. At data cut-off, the event rates were 5.2% in the T-DXd arm, 3.4% in the T-DXd-THP arm, and 5.6% in the ddAC-THP arm. (C) Unlike pCR results, the RCB analysis is based only on the slide read and does not take into account whether a patient received study treatment or any subsequent neoadjuvant treatment; therefore, there may be differences between pCR rate and RCB-0. RCB was categorised based on the residual viable tumour identified by routine H&E staining after mapping of the surgical specimen.[28] The categories were 0, I, II, and III. Sixteen patients (5.6%, T-DXd), 13 patients (4.0%, T-DXd-THP), and 24 patients (7.5%, ddAC-THP) had missing data.

CI, confidence interval; ddAC, dose-dense doxorubicin + cyclophosphamide; EFS, event-free survival; H&E, haematoxylin and eosin; ITT, intent-to-treat; NC, not calculable; pCR, pathological complete response; RCB, residual cancer burden; T-DXd, trastuzumab deruxtecan; THP, paclitaxel + trastuzumab + pertuzumab.

https://doi.org/10.1016/j.annonc.2025.10.019

and Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.10.019). Notably, for T-DXd-THP versus ddAC-THP, pCR rate improvement was observed in HR-positive [61.4% (n/N = 145/236) versus 52.3% (n/N = 123/235); ΔpCR 9.1% (95% CI 0.2% to 17.9%)] and HR-negative [83.1% (n/N = 69/83) versus 67.1% (n/N = 57/85); ΔpCR 16.1% (95% CI 3.0% to 28.8%)] subgroups. Nodal pCR rates (ypN0) are reported in Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.10.019). pCR rates by ypT0 ypN0 (secondary endpoint) are reported in Figure 1D and E and showed improved outcomes with T-DXd-THP versus ddAC-THP.

The median (IQR) duration of follow up was 24.3 (14.3—29.5) months (T-DXd-THP), 24.9 (16.7—29.8) months (T-DXd), and 23.6 (13.4—28.9) months (ddAC-THP). Preliminary EFS data (at 4.5% event maturity) showed fewer events in the T-DXd-THP arm than ddAC-THP arm (hazard ratio 0.56, 95% CI 0.26 to 1.17); median EFS was not reached in any arm (Figure 2A and B). EFS events are described in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.10.019.

T-DXd-THP versus ddAC-THP showed improved RCB-0 [68.8% (n/N = 221/321) versus 57.5% (n/N = 184/320)] and similar RCB-I [12.5% (n/N = 40/321) versus 11.6% (n/N = 37/320)] rates in the resected breast and lymph node tissue (Figure 2C). RCB outcomes by HR status are reported in Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2025.10.019).

Overall, 283 (T-DXd), 320 (T-DXd-THP), and 312 (ddAC-THP) patients were included in the safety analyses. The median number of cycles received for each individual study drug was consistent with the number of planned cycles per study design (four or eight cycles, dependent on treatment allocation; Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.10.019).

The overall incidence of AEs was 97.5% (T-DXd, n = 276), 98.1% (T-DXd-THP, n = 314), and 98.7% (ddAC-THP, n = 308) (Table 2). Grade ≥3 AEs occurred in 22.6% (T-DXd, n = 64), 37.5% (T-DXd-THP, n = 120), and 55.8% (ddAC-THP, n = 174) of patients. All-grade and grade ≥3 haematological AEs, including anaemia, neutropenia, and leukopenia, occurred less frequently in T-DXd and T-DXd-THP arms than in the ddAC-THP arm. All-grade nausea rates were higher in the T-DXd and T-DXd-THP arms than the ddAC-THP arm (Table 3). The most common drug-related AEs are reported in Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2025.10.019. SAEs occurred in 10.2% (T-DXd, n = 29), 10.6% (T-DXd-THP, n = 34), and 20.2% (ddAC-THP, n = 63) of patients. AEs associated with any dose interruptions occurred in 18.0% (T-DXd, n = 51), 37.8% (T-DXd-THP, n = 121), and 54.5% (ddAC-THP; n = 170) of patients. The rate of AEs leading to

Table 2. Overall safety summary in the safety analysis set

	T-DXd (n = 283)	T-DXd-THP (n = 320)	ddAC-THP (n = 312)
Any AE, *n* (%)	276 (97.5)	314 (98.1)	308 (98.7)
Grade 1	71 (25.1)	30 (9.4)	12 (3.8)
Grade 2	141 (49.8)	164 (51.3)	122 (39.1)
Grade ≥3	64 (22.6)	120 (37.5)	174 (55.8)
Possibly treatment-related AE[a], *n* (%)	260 (91.9)	307 (95.9)	301 (96.5)
Grade ≥3	46 (16.3)	101 (31.6)	159 (51.0)
SAE, *n* (%)	29 (10.2)	34 (10.6)	63 (20.2)
Possibly related to treatment[a]	11 (3.9)	23 (7.2)	48 (15.4)
AE leading to discontinuation[b], *n* (%)	22 (7.8)	45 (14.1)	31 (9.9)
AE leading to dose interruption[b], *n* (%)	51 (18.0)	121 (37.8)	170 (54.5)
AE leading to dose reduction[b], *n* (%)	19 (6.7)	58 (18.1)	60 (19.2)
AE leading to surgical delay[c], *n* (%)	18 (6.4)	11 (3.4)	8 (2.6)
Did not undergo surgery due to AE, *n* (%)	0	0	0
AE associated with death, *n* (%)	1 (0.4)	2 (0.6)	2 (0.6)
Possibly related to study treatment[a,d]	0	1 (0.3)	2 (0.6)
Adjudicated drug-related ILD/pneumonitis[e], *n* (%)	14 (4.9)	14 (4.4)	16 (5.1)
Grade ≥3	0	2 (0.6)	6 (1.9)
Left-ventricular dysfunction, *n* (%)	2 (0.7)	4 (1.3)	19 (6.1)
Grade ≥3	0	1 (0.3)	6 (1.9)

Safety analyses included all patients who received at least one dose of any study treatment. Data included AEs with onset or that worsened on or after date of first dose of study treatment and up to and including 47 days after last dose of study treatment prior to the initiation of the first subsequent anticancer therapy. Patients with multiple occurrences in the same category were counted once per category regardless of the number of occurrences.

AE, adverse event; COVID-19, coronavirus disease 2019; ddAC, dose-dense doxorubicin + cyclophosphamide; ILD, interstitial lung disease; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan; THP, paclitaxel + trastuzumab + pertuzumab.

[a]Possibly related AEs were assessed and determined by investigator.

[b]Dose modifications, interruptions, or discontinuations relate to any component of each arm.

[c]A surgical delay was defined as surgery not occurring within 3-6 weeks after the administration of the last cycle of neoadjuvant treatment. AEs leading to surgical delay included: ILD [six patients (2.1%)], pneumonitis [four patients (1.4%)], COVID-19 and nasopharyngitis [two patients (0.7%) each], influenza, pulmonary embolism, blood bilirubin increased, and complication after procedure [one patient (0.4%) each] in the T-DXd arm; ILD [two patients (0.6%)], COVID-19, COVID-19 pneumonia, SARS-CoV-2 test positive, device-related infection, supraventricular tachycardia, pneumonitis, rash erythematous, ejection fraction decreased, and platelet count decreased [one patient (0.3%) each] in the T-DXd-THP arm; and COVID-19, device-related infection, herpes virus infection, herpes zoster, atrial fibrillation, heart failure with reduced ejection fraction, device-related thrombosis, and ejection fraction decreased [one patient (0.3%) each] in the ddAC-THP arm.

[d]Treatment-related AEs with outcome of death were adjudicated pneumonitis (T-DXd-THP), and bacterial encephalitis and adjudicated pneumonitis (ddAC-THP).

[e]Drug-related ILD/pneumonitis cases adjudicated and causality determined by the Independent ILD Adjudication Committee.

Table 3. Most common AEs (in ≥20% of patients) by grouped/preferred term in the safety analysis set

	T-DXd (*N* = 283)		T-DXd-THP (*N* = 320)		ddAC-THP (*N* = 312)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any, *n* (%)	276 (97.5)	64 (22.6)	314 (98.1)	120 (37.5)	308 (98.7)	174 (55.8)
Nausea, *n* (%)	193 (68.2)	3 (1.1)	207 (64.7)	6 (1.9)	161 (51.6)	1 (0.3)
Alopecia, *n* (%)	120 (42.4)	0	152 (47.5)	0	153 (49.0)	0
Fatigue[a], *n* (%)	120 (42.4)	3 (1.1)	132 (41.3)	2 (0.6)	171 (54.8)	7 (2.2)
Constipation, *n* (%)	95 (33.6)	0	93 (29.1)	1 (0.3)	76 (24.4)	0
Vomiting, *n* (%)	88 (31.1)	3 (1.1)	92 (28.8)	3 (0.9)	66 (21.2)	2 (0.6)
Transaminases increased[b], *n* (%)	82 (29.0)	13 (4.6)	110 (34.4)	16 (5.0)	105 (33.7)	10 (3.2)
Diarrhoea, *n* (%)	64 (22.6)	2 (0.7)	188 (58.8)	19 (5.9)	169 (54.2)	10 (3.2)
Neutropenia[c], *n* (%)	61 (21.6)	20 (7.1)	93 (29.1)	44 (13.8)	138 (44.2)	108 (34.6)
Anaemia[d], *n* (%)	43 (15.2)	8 (2.8)	73 (22.8)	5 (1.6)	155 (49.7)	27 (8.7)
Stomatitis, *n* (%)	39 (13.8)	0	59 (18.4)	1 (0.3)	86 (27.6)	3 (1.0)
Leukopenia[e], *n* (%)	29 (10.2)	1 (0.4)	55 (17.2)	14 (4.4)	73 (23.4)	41 (13.1)
Neuropathy peripheral, *n* (%)	11 (3.9)	0	83 (25.9)	4 (1.3)	65 (20.8)	5 (1.6)

Safety analyses included all patients who received at least one dose of any study treatment.
Includes AEs with an onset date or that worsened on or after the date of first dose of study drug and up to and including 47 days after the last dose of study treatment and prior to the initiation of the first subsequent anticancer therapy. Patients with multiple occurrences in the same category were counted once per preferred term regardless of the number of occurrences.
AE, adverse event; ddAC, dose-dense doxorubicin + cyclophosphamide; T-DXd, trastuzumab deruxtecan; THP, paclitaxel + trastuzumab + pertuzumab.
[a]Grouped term: fatigue, asthenia, malaise, and lethargy.
[b]Grouped term: transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hypertransaminasemia, hepatic function abnormal, and liver function test increased.
[c]Grouped term: neutrophil count decreased and neutropenia.
[d]Grouped term: haemoglobin decreased, red blood cell count decreased, and anaemia and haematocrit decreased.
[e]Grouped term: white blood cell count decreased and leukopenia.

any study treatment discontinuation was 7.8% (T-DXd, *n* = 22), 14.1% (T-DXd-THP, *n* = 45), and 9.9% (ddAC-THP, *n* = 31). ILD was the most common AE leading to study treatment discontinuation in the T-DXd arm [*n* = 9 (3.2%)] followed by pneumonitis [*n* = 8 (2.8%)]; neurotoxicity was the most common AE leading to any study treatment discontinuation in the T-DXd-THP arm [*n* = 8 (2.5%)]; and peripheral neuropathy was the most common AE leading to any study treatment discontinuation in the ddAC-THP arm [*n* = 6 (1.9%)]. All neurotoxicity and peripheral neuropathy events leading to study treatment discontinuation were in the T-DXd-THP and ddAC-THP arms, occurred during the last four treatment cycles with THP, and led to the discontinuation of paclitaxel. The rate of AEs leading to dose reduction was 6.7% (T-DXd, *n* = 19), 18.1% (T-DXd-THP, *n* = 58), and 19.2% (ddAC-THP, *n* = 60). AEs resulted in surgical delay for 6.4% (T-DXd, *n* = 18), 3.4% (T-DXd-THP, *n* = 11), and 2.6% (ddAC-THP, *n* = 8) of patients.

Adjudicated drug-related ILD/pneumonitis occurred in 14 patients (T-DXd, 4.9%; grade ≥3, *n* = 0), 14 patients [T-DXd-THP, 4.4%; grade ≥3, *n* = 2 (0.6%)], and 16 patients [ddAC-THP, 5.1%; grade ≥3, *n* = 6 (1.9%)]. Left-ventricular dysfunction occurred in two patients (T-DXd, 0.7%; both grade 2), four patients [T-DXd-THP, 1.3%; grade ≥3, *n* = 1 (0.3%)], and 19 patients [ddAC-THP, 6.1%; grade ≥3, *n* = 6 (1.9%)] (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2025.10.019). No events of cardiac failure occurred in the T-DXd or T-DXd-THP arms; four events (all grade 1–2) occurred in the ddAC-THP arm.

One AE with the outcome of death (grade 5) occurred in the T-DXd arm (pulmonary embolism considered by investigator to be unrelated to study treatment), two occurred in the T-DXd-THP arm (death of unknown cause, drug-related pneumonitis adjudicated by the Independent ILD Adjudication Committee), and two occurred in the ddAC-THP arm (investigator-determined drug-related bacterial encephalitis and drug-related pneumonitis adjudicated by the Independent ILD Adjudication Committee) (Table 2).

DISCUSSION

DESTINY-Breast11 is the first positive global, registrational trial for a new agent in the neoadjuvant HER2-positive early-stage breast cancer setting for over a decade.[16] It begins to address the unmet need for new therapies with improved prognostic outcomes and reduced toxicities compared with existing anthracycline- or carboplatin-based multi-treatment regimens,[2,4-6] and reports a high 67.3% pCR rate with T-DXd-THP in a high-risk, predominantly HR-positive patient population. DESTINY-Breast11 evaluated both T-DXd-THP and T-DXd alone in high-risk, HER2-positive early-stage breast cancer based on the positive efficacy outcomes that were initially demonstrated by DESTINY-Breast01 for T-DXd alone in HER2-positive metastatic breast cancer, and subsequently confirmed by DESTINY-Breast03 and DESTINY-Breast09.[25,26,30]

This study was designed with pCR (ypT0/is ypN0) as its primary efficacy endpoint to provide an early indication of treatment response. In the neoadjuvant setting, pCR allows for an *in vivo* assessment of tumour response to therapy and determines the extent of further therapy, such as surgery and post-neoadjuvant treatment.[1,2] Meta-analyses of neoadjuvant clinical trials have shown pCR to be a prognostic factor for improved EFS at the patient level, particularly in HER2-positive disease,[8] highlighting the value of this endpoint.[7-9] Furthermore, having a pCR

following neoadjuvant therapy allows for a reduced treatment burden for patients, including a reduction in the extent of surgery and less toxic post-neoadjuvant therapy per treatment guidelines, versus those patients who do not have a pCR.[2,10,11]

At the time of the DESTINY-Breast11 study design, ddAC-THP and TCHP were both SOC regimens for HER2-positive early-stage breast cancer across the world,[1,31] with 62% of experts in the 2021 St Gallen Consensus Meeting voting for anthracycline-based regimens as the preferred treatment for node-positive high-risk disease.[31] Cardiac toxicities associated with anthracycline treatment[3] have since led physicians to adopt TCHP as the preferred neoadjuvant SOC in some regions. However, ddAC-THP is still considered to be an effective neoadjuvant regimen in international guidelines,[1,2,11] which was important to reflect in this international study. Although there are no head-to-head trials of TCHP against ddAC-THP, the phase III TRAIN-2 study demonstrated similar pCR rates between TCHP and anthracycline-based regimens (68% and 67%, respectively), albeit using more cycles of therapy than standard and a different anthracycline-containing regimen than the current study.[3] TCHP can also be considered a difficult-to-tolerate regimen owing to neuropathic, haematological, and gastrointestinal AEs.[5] DESTINY-Breast11 was a global study in a high-risk patient population, which was reflected in the decision to use ddAC-THP as the SOC comparator at the time of study design. Use of ddAC-THP also allowed for a similar schedule to T-DXd-THP and direct comparison to understand the relative contributions of ddAC and T-DXd to results when used in sequence with THP.

Neoadjuvant T-DXd followed by THP met the primary endpoint and showed a statistically significant and clinically meaningful (11.2% absolute) improvement in pCR rate (ypT0/is ypN0) compared with ddAC-THP, with improvement observed in HR-positive [61.4 versus 52.3%; ΔpCR 9.1% (95% CI 0.2% to 17.9%)] and HR-negative [83.1% versus 67.1%; ΔpCR 16.1% (95% CI 3.0% to 28.8%)] subgroups, and improved RCB outcomes [RCB-0 + I, 81.3% (T-DXd-THP) versus 69.1% (ddAC-THP)]. T-DXd-THP findings in DESTINY-Breast11 demonstrated a high 67.3% pCR rate despite the high-risk population reported herein. Although differences in study designs and patient populations (for example, HR status, and clinical tumour and nodal stage) limit direct cross-trial comparisons, the T-DXd-THP pCR rate was higher than historical pCR rates (defined by ypT0/is ypN0) from other registrational studies for neoadjuvant SOC in HER2-positive early-stage breast cancer, including anthracycline- and carboplatin-based regimens (39.3% to 62.7%).[5,12,16] These studies also included patient populations at lower risk of disease progression than in this study.[5,12,16] pCR rates can be negatively influenced by a high prevalence of patients with HR-positive disease, with absolute pCR rate differences of 15%—30% previously reported between HR-negative and HR-positive subgroups for ddAC-THP and TCHP[5,12]; therefore, the pCR rate observed for T-DXd-THP in DESTINY-Breast11 is considered particularly notable as the proportion of patients with HR-positive disease (73.5%) was higher than in phase III global studies for ddAC-THP (IMpassion050, 51.3%) and TCHP (KRISTINE, 62.4%).[5,12] Regardless of this, the overall pCR rate for T-DXd-THP in this study (67.3%), as well as for HR-positive (61.4%) and HR-negative (83.1%) subgroups, is robust in its own right.

Preliminary EFS data at 4.5% event maturity showed fewer events in the T-DXd-THP arm than the ddAC-THP arm [hazard ratio 0.56 (95% CI 0.26 to 1.17)]. Although selection of post-neoadjuvant treatment was not mandated and was administered at the investigator's discretion, recommendations were provided by the protocol that aligned with current treatment guidelines[2,10,11]; this was reflected in the data reported. Use of post-neoadjuvant therapy was generally balanced between the T-DXd-THP and ddAC-THP arms, supporting interpretability of EFS findings. T-DM1 is established as the preferred post-neoadjuvant for patients with residual disease, based on results of the KATHERINE study.[2,10,11,20] T-DM1 was recommended by the protocol for patients who did not have a pCR. Although T-DM1 was used in many patients without a pCR (T-DXd-THP, 52.6%; ddAC-THP, 56.9%), use varied by geographic region, and was higher in North America (T-DXd-THP, 70.0%; ddAC-THP, 78.3%) and Western Europe (T-DXd-THP, 80.0%; ddAC-THP, 71.0%) than in other regions, such as Asia (T-DXd-THP, 42.0%; ddAC-THP, 45.8%). For patients who did not receive T-DM1-based post-neoadjuvant treatment, this may have been due to physician's decision, patient preference, or other factors. As per standard clinical practice, and in line with guidelines and the prescribing information for T-DM1, considerations that could influence physician decision include persistent AEs from neoadjuvant treatment, such as peripheral neuropathy, the extent of residual disease at the time of surgery, or loss of HER2 positivity in the residual resected tumour sample.[2,10,11,32,33]

In this study, pCR (ypT0/is ypN0) findings were inferior for T-DXd alone compared with ddAC-THP (43.0% versus 56.3%). Patients who switched to local SOC following IDMC recommendation to close enrolment to T-DXd alone were classified as having a non-pCR, irrespective of their actual response to neoadjuvant therapy, which confounded outcomes. This is supported by the pCR (ypT0/is ypN0) findings in the prespecified supplementary analyses, which classified patients who discontinued study treatment and had a pCR as responders regardless of any subsequent neoadjuvant therapy received (T-DXd alone 51.4% versus ddAC-THP 57.2%); however, the impact of additional, non-study therapy on these data should be considered. In a sensitivity analysis of patients randomised at least 236 days before closure of the T-DXd-alone arm (to account for treatment duration and time to surgery), conducted to exclude patients who discontinued prematurely owing to the arm closure and were unable to undergo pCR evaluation, pCR rates for T-DXd were higher than in the primary analysis (46.3% versus 43.0%). Despite arm closure, T-DXd alone showed reasonable efficacy against a five-agent comparator (ddAC-THP), particularly considering the high-risk patient population. Given that dual versus single

neoadjuvant HER2-directed therapy has previously demonstrated enhanced efficacy benefit,[16] positive outcomes observed in the T-DXd-THP arm may be reflective of dual HER2-blockade combined with early integration of the multimodal action of an ADC.[23,24]

T-DXd alone and T-DXd-THP demonstrated an improved safety profile compared with ddAC-THP, with a similar rate of overall AEs and adjudicated drug-related ILD/pneumonitis, and lower rates of grade ≥3 AEs, SAEs, AEs leading to any drug interruptions, left-ventricular dysfunction, and haematological toxicities; no new safety signals were identified. These results also provide additional evidence on the toxicities associated with anthracycline-based treatment of HER2-positive early-stage breast cancer, with cardiotoxicity a well-known concern.[2] Although rates were low across all treatment arms, drug-related adjudicated ILD/pneumonitis also occurred in 5.1% of patients in the ddAC-THP arm, and resulted in one death; routine scans for ILD/pneumonitis should be therefore be considered, for patients receiving T-DXd-containing and standard care regimens. The T-DXd (any grade ≥3 AE, 22.6%; any SAE, 10.2%) and T-DXd-THP (any grade ≥3 AE, 37.5%; any SAE, 10.6%) arms in this study showed a safety profile that is favourable in the context of the TCHP toxicity profile in the KRISTINE phase III study (any grade ≥3 AE, 64.4%; any SAE, 28.8%).[5]

Although DESTINY-Breast11 was a global study, limitations include under-representation of certain demographic groups, such as Black or African American patients (Table 1 and Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2025.10.019). The proportion of patients who did not receive study treatment was slightly lower in the T-DXd (1.0%) and T-DXd-THP (0.3%) arms than in the ddAC-THP arm (2.5%), and the proportions of patients with American Joint Committee on Cancer stage III disease and cT3—4 were slightly higher in the T-DXd and T-DXd-THP and arms than in the ddAC-THP arm (53.5% and 50.2% versus 47.8%, and 45.1% and 45.2% versus 41.3%, respectively). It should also be acknowledged that patients in the T-DXd arms received more and longer cycles of HER2-directed therapy than those in the ddAC-THP arm, which may have affected relative pCR rates. Efficacy evaluation of T-DXd alone was also limited by early enrolment closure. The DESTINY-Breast05 (NCT04622319) study will deliver insights into long-term outcomes with post-neoadjuvant T-DXd given alone, and other ongoing studies will provide further understanding of the efficacy and safety of neoadjuvant T-DXd alone in early-stage breast cancer, collectively covering patient populations with a broader risk of disease progression than in this study [ARIADNE (NCT05900206), SHAMROCK (NCT05710666), and EXTEND (NCT06548178)]. Furthermore, the aforementioned and other future studies will help to answer questions regarding optimal treatment sequencing in the neoadjuvant and post-neoadjuvant early, as well as metastatic, breast cancer settings should T-DXd become part of earlier treatment regimens. Additionally, biomarkers and genomic tests such as HER2DX may help to inform the best treatment approach for individual patients.[34,35]

In conclusion, neoadjuvant T-DXd-THP demonstrated a statistically significant and clinically meaningful pCR improvement and an improved safety profile compared with ddAC-THP. This study introduces the multimodal action of an ADC early in the treatment pathway, and its results support T-DXd-THP as a more effective and less toxic neoadjuvant regimen than ddAC-THP. T-DXd-THP may become an anthracycline- and carboplatin-free treatment option for high-risk, HER2-positive, early-stage breast cancer.

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DISCLOSURE

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DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Anonymised datasets may be available on request. Requests for access to data may be submitted at https://search.vivli.org/. The request will undergo an internal review process, and if approved, data will be prepared and shared with specified accessors named on the request form for 12 months via Vivli Secure Research Environment.

REFERENCES

1. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. *J Clin Oncol*. 2021;39:1485-1505.
2. Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2024;35:159-182.
3. van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. 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;19:1630-1640.
4. 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;7:978-984.
5. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2018;19:115-126.
6. Hennessy MA, Morris PG. Optimizing anti-HER2 therapy in early breast cancer: updates from the KRISTINE trial. *Ann Palliat Med*. 2020;9:504-509.

7. Davey MG, Browne F, Miller N, Lowery AJ, Kerin MJ. Pathological complete response as a surrogate to improved survival in human epidermal growth factor receptor-2-positive breast cancer: systematic review and meta-analysis. *BJS Open*. 2022;6:zrac028.
8. Spring LM, Fell G, Arfe A, et al. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis. *Clin Cancer Res*. 2020;26:2838-2848.
9. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384:164-172.
10. Denduluri N, Somerfield MR, Chavez-MacGregor M, et al. Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO guideline update. *J Clin Oncol*. 2021;39:685-693.
11. Park KH, Loibl S, Sohn J, et al. Pan-Asian adapted ESMO clinical practice guidelines for the diagnosis, treatment and follow-up of patients with early breast cancer. *ESMO Open*. 2024;9:102974.
12. Huober J, Barrios CH, Niikura N, et al. Atezolizumab with neoadjuvant anti-human epidermal growth factor receptor 2 therapy and chemotherapy in human epidermal growth factor receptor 2-positive early breast cancer: primary results of the randomized phase III IMpassion050 trial. *J Clin Oncol*. 2022;40:2946-2956.
13. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol*. 2013;24:2278-2284.
14. Swain SM, Ewer MS, Viale G, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. *Ann Oncol*. 2018;29:646-653.
15. Masuda N, Ohtani S, Takano T, et al. A randomized, 3-arm, neoadjuvant, phase 2 study comparing docetaxel + carboplatin + trastuzumab + pertuzumab (TCbHP), TCbHP followed by trastuzumab emtansine and pertuzumab (T-DM1 + P), and T-DM1 + P in HER2-positive primary breast cancer. *Breast Cancer Res Treat*. 2020;180:135-146.
16. Gianni L, Pienkowski T, Im Y-H, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13:25-32.
17. Goorts B, van Nijnatten TJA, de Munck L, et al. Clinical tumor stage is the most important predictor of pathological complete response rate after neoadjuvant chemotherapy in breast cancer patients. *Breast Cancer Res Treat*. 2017;163:83-91.
18. Luz P, Lopes-Brás R, de Pinho IS, et al. Predictive factors for pCR and relapse following neoadjuvant dual HER2-blockade in HER2+ breast cancer: an international cohort study. *Clin Transl Oncol*. 2025;27:4160-4169.
19. Mittal A, Tamimi F, Molto C, et al. Three-year disease-free survival in randomized trials of neoadjuvant chemotherapy and HER2-targeted therapy in breast cancer: a meta-analysis. *Crit Rev Oncol Hematol*. 2023;181:103880.
20. Geyer CE, Untch M, Huang C-S, et al. Survival with trastuzumab emtansine in residual HER2-positive breast cancer. *N Engl J Med*. 2025;392:249-257.
21. Nakada T, Sugihara K, Jikoh T, Abe Y, Agatsuma T. The latest research and development into the antibody-drug conjugate, [fam-] trastuzumab deruxtecan (DS-8201a), for HER2 cancer therapy. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185.
22. Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. *Clin Cancer Res*. 2016;22:5097-5108.
23. European Medicines Agency (EMA). ENHERTU: summary of product characteristics. 2025. Available at https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf. Accessed September 19, 2025.
24. US Food and Drug Administration (FDA). ENHERTU (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information (PI). 2025. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761139s032s035lbl.pdf. Accessed September 19, 2025.
25. Cortés J, Hurvitz SA, Im S-A, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY-Breast03 trial. *Nat Med*. 2024;30:2208-2215.
26. Tolaney SM, Jiang Z, Zhang Q, et al. Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for first-line (1L) treatment of patients (pts) with human epidermal growth factor receptor 2−positive (HER2+) advanced/metastatic breast cancer (a/mBC): interim results from DESTINY-Breast09. *J Clin Oncol*. 2025;43:LBA1008.
27. Wolff AC, Hammond ME, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *J Clin Oncol*. 2018;36:2105-2122.
28. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol*. 2007;25:4414-4422.
29. Burman C-F, Sonesson C, Guilbaud O. A recycling framework for the construction of Bonferroni-based multiple tests. *Stat Med*. 2009;28:739-761.
30. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382:610-621.
31. Guo Q, Chen Q. Neoadjuvant chemotherapy choices from population selection to regimen design: the St. Gallen International Expert Consensus Conference 2021. *Transl Breast Cancer Res*. 2021;2:25.
32. European Medicines Agency (EMA). KADCYLA: summary of product characteristics. 2025. Available at https://www.ema.europa.eu/en/documents/product-information/kadcyla-epar-product-information_en.pdf. Accessed September 25, 2025.
33. US Food and Drug Administration. KADCYLA (ado-trastuzumab emtansine):prescribing information. 2025. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125427lbl.pdf. Accessed September 29, 2025.
34. Tung NM, Zhao F, DeMichele A, et al. Predicting pathologic complete response (pCR) from clinicopathologic variables and HER2DX genomic test in stage II/III HER2+ breast cancer treated with taxane, trastuzumab, and pertuzumab (THP): secondary results from the EA1181/CompassHER2 pCR trial. *J Clin Oncol*. 2025;43:501.
35. Tolaney SM, Tung N, Wolff AC, et al. HER2DX genomic test in early-stage HER2-positive breast cancer. *ESMO Open*. 2024;9:103987.