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ORIGINAL ARTICLE

Pooled analysis by best confirmed response to trastuzumab deruxtecan and related biomarkers in patients with HER2-positive metastatic breast cancer from DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03

C. Saura[1]*, J. Cortés[2,3,4,5,6], S. Modi[7], S.-B. Kim[8], E. Hamilton[9], S. A. Hurvitz[10], I. E. Krop[11], G. Curigliano[12,13], H. Iwata[14], S.-A. Im[15], P. Herbolsheimer[16], M. Karnoub[17], A. Boran[17], Y. Kuwahara[17], A. Egorov[17] & F. André[18]

[1]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona; [2]International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona; [3]IOB Madrid, Institute of Oncology, Hospital Beata María Ana, Madrid; [4]Oncology Department, Hospital Universitario Torrejón, Ribera Group, Madrid; [5]Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid; [6]Medical Scientia Innovation Research (MEDSIR), Barcelona, Spain, and Ridgewood, USA; [7]Memorial Sloan Kettering Cancer Center, New York, USA; [8]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [9]Sarah Cannon Research Institute, Nashville; [10]University of Washington and Fred Hutchinson Cancer Center, Seattle; [11]Yale Cancer Center, New Haven, USA; [12]Department of Oncology and Hemato-Oncology, University of Milan, Milan; [13]European Institute of Oncology, IRCCS, Milan, Italy; [14]Nagoya City University Graduate School of Medical Sciences Medical School, Nagoya, Japan; [15]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul National University, Seoul, Republic of Korea; [16]AstraZeneca, Gaithersburg; [17]Daiichi Sankyo Inc., Basking Ridge, USA; [18]Institut Gustave Roussy, Université Paris-Saclay, Villejuif, France

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Background: Objective response rates in the DESTINY-Breast01/02/03 trials, which evaluated trastuzumab deruxtecan (T-DXd) in human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC), were 62%/70%/79%, respectively.

Patients and methods: This exploratory pooled analysis investigated associations between best confirmed response to T-DXd and baseline characteristics/long-term outcomes in patients who received T-DXd 5.4 mg/kg in DESTINY-Breast01/02/03. Endpoints included best confirmed response per (blinded) independent central review [(B)ICR] using RECIST v1.1, progression-free survival (PFS) by (B)ICR, overall survival (OS), safety, and biomarker analyses of expression levels/alterations of genes relevant to HER2-positive mBC or T-DXd activity.

Results: A total of 834 patients who received T-DXd in DESTINY-Breast01/02/03 were assessable for response; 125 (15.0%) experienced complete response (CR), 477 (57.2%) experienced partial response (PR), and 232 (27.8%) were considered non-responders (stable disease/progressive disease). The median number of prior regimens in the metastatic setting was two for patients with CR versus three for patients with PR and non-responders; visceral disease and baseline brain or bone metastases were less frequently observed in patients with CR. The 24-month PFS rates in patients with CR, PR, and no response, respectively, were 77.8%, 46.3%, and 20.6%, and 36-month OS rates were 88.6%, 54.0%, and 35.9%. Rates of serious adverse events, T-DXd discontinuation, and interstitial lung disease/pneumonitis were numerically lower in patients with CR. In exploratory biomarker analyses, responders had tumors with numerically higher *HER2* plasma copy number, lower *ESR1* gene expression and *ESR1* mutation frequency, and lower circulating tumor DNA levels at baseline.

Conclusions: Patients with objective response to T-DXd, particularly those with CR, showed prolonged median PFS and OS. These results support T-DXd use across broad patient groups with HER2-positive mBC, including those with lower disease burden. Patients whose disease does not respond to T-DXd represent an unmet medical need, and research into more effective treatment approaches for these patients is warranted.

Key words: metastatic breast cancer, HER2 positive, trastuzumab deruxtecan, pooled analysis

INTRODUCTION

Approximately 15%-20% of patients with invasive breast cancer (BC) have human epidermal growth factor receptor 2 (HER2)-positive tumors [immunohistochemistry (IHC) 3+/IHC 2+ and *in situ* hybridization (ISH) positive by the American Society of Clinical Oncology/College of American

*Correspondence to: Dr Christina Saura, Head, Breast Cancer Unit, Medical Oncology Service, Vall d'Hebron University Hospital, Paseo de la Vall d'Hebron, 119-129, Barcelona 08035, Spain. Tel: +0034.934893000 (ext 2658)
E-mail: csaura@vhio.net (C. Saura).

Pathologists guidelines].[1] HER2-targeted therapies are associated with improved outcomes in HER2-positive early and metastatic breast cancer (mBC).[2] However, ∼15%-31% of patients with early-stage BC experience disease relapse despite treatment with trastuzumab plus chemotherapy.[2-4] Metastatic recurrence is a major concern given its resistance to therapy and association with the development of brain metastases and poor clinical outcomes.[5]

Clinical practice guidelines recommend a combination of trastuzumab, pertuzumab, and taxane for first-line treatment of HER2-positive mBC[6,7] based on results of the CLEOPATRA study.[8] In the first interim analysis of CLEOPATRA, adding pertuzumab to trastuzumab and docetaxel (pertuzumab group) led to a higher objective response rate (ORR) than trastuzumab and taxane (placebo group) (80.2% versus 69.3%).[9] At final analysis, investigator-assessed median progression-free survival (PFS) was increased by >6 months in the pertuzumab group, to 18.7 months, compared with 12.4 months in the placebo group, and improvements in overall survival (OS) were maintained after a median of >8 years of follow-up (median OS 57.1 months versus 40.8 months).[8]

Trastuzumab deruxtecan (T-DXd), a HER2-directed antibody—drug conjugate with a potent topoisomerase I inhibitor payload designed to deliver an optimal antitumor effect,[10,11] is the recommended second-line therapy for HER2-positive mBC.[6,7,12-18] This is based on primary results from the DESTINY-Breast03 study in patients with HER2-positive unresectable and/or mBC previously treated with trastuzumab and a taxane[14] in which T-DXd provided clinically meaningful improvements in efficacy versus trastuzumab emtansine (T-DM1), with confirmed ORRs (cORRs) by blinded independent central review (BICR) of 79% versus 35%, including complete response (CR) rates of 21% versus 10%, and a median PFS by BICR of 28.8 months versus 6.8 months.[16] In long-term survival analysis, median OS was 52.6 months with T-DXd versus 42.7 months with T-DM1, with a 27% reduction in risk of death [hazard ratio 0.73, 95% confidence interval (CI) 0.56-0.94] with T-DXd.[17] In DESTINY-Breast01, patients with HER2-positive mBC received T-DXd following disease progression on T-DM1.[12] In DESTINY-Breast02, patients with unresectable or metastatic HER2-positive BC were randomly assigned to T-DXd or treatment of physician's choice after disease progression on T-DM1.[13] DESTINY-Breast01 and DESTINY-Breast02 showed cORRs by BICR of 62% and 70% and CR rates of 7% and 14%, respectively, with T-DXd.[13,15]

Interim results from the randomized phase III DESTINY-Breast09 study demonstrated that T-DXd in combination with pertuzumab produced statistically significant and clinically meaningful improvement in PFS compared with a combination regimen of a taxane, trastuzumab, and pertuzumab in first-line treatment of patients with HER2-positive advanced or mBC.[19]

Patients with objective responses to HER2-targeted therapy may have improved long-term outcomes; however, meta-analyses assessing correlations between surrogate endpoints and OS have generated varying results.[8,20-23] An exploratory analysis of CLEOPATRA revealed that an initial CR to treatment with trastuzumab, pertuzumab, and docetaxel was associated with prolonged PFS and OS, with a 60% reduction in risk of death compared with patients who had stable disease (SD).[23] In CLEOPATRA, long-term response in the pertuzumab group was also associated with certain biomarkers, such as *PIK3CA* wild-type tumors, elevated *HER2* messenger RNA (mRNA) and HER2 membrane H score, and low serum HER2 level.[8]

This exploratory, *post hoc* analysis aimed to determine associations between best confirmed tumor response to T-DXd and baseline characteristics/long-term outcomes in patients with HER2-positive mBC and to analyze prespecified biomarker status and levels in a pooled population of patients from DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03.

PATIENTS AND METHODS

Study designs

Data were pooled from the open-label, multicenter, single-arm, phase II DESTINY-Breast01 study and the open-label, multicenter, randomized, phase III DESTINY-Breast02 and DESTINY-Breast03 studies in patients with unresectable or metastatic HER2-positive BC (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.11.007). Baseline brain imaging was mandatory in all three trials. Details of individual study designs are reported.[12-17]

In DESTINY-Breast01, patients received T-DXd 5.4 mg/kg every 3 weeks (q3w) (higher doses in part 1 were excluded from this analysis), with a median duration of follow-up at the 26 March 2021 data cut-off (DCO) of 26.5 months (95% CI 0.7-39.1 months).[15] In DESTINY-Breast02, patients were randomly assigned 2 : 1 to receive T-DXd 5.4 mg/kg q3w or treatment of physician's choice chemotherapy (capecitabine plus either trastuzumab or lapatinib). The median follow-up duration in the T-DXd group of DESTINY-Breast02 at the 30 June 2022 DCO was 21.5 months (interquartile range 15.2-28.4 months).[13] In DESTINY-Breast03, patients were randomly assigned 1 : 1 to receive T-DXd 5.4 mg/kg q3w or T-DM1 3.6 mg/kg q3w.[14] The median follow-up duration in the T-DXd group of DESTINY-Breast03 at the 25 July 2022 DCO was 28.4 months (interquartile range 22.1-32.9 months).[16] In all studies, concomitant endocrine treatment was not permitted for patients with hormone receptor (HR)-positive tumors receiving T-DXd.[12-14]

Ethics approval

All studies were approved by the institutional review board at each site and carried out in adherence to the International Council for Harmonization of Good Clinical Practice, the Declaration of Helsinki, and local regulations on clinical research conduct. All patients provided written informed consent before study participation.

Endpoints

Endpoints for this exploratory pooled analysis included best confirmed response per (B)ICR based on RECIST, version 1.1, duration of response, PFS according to response by (B)ICR, OS, safety [overall and interstitial lung disease (ILD)/pneumonitis], and biomarker status or levels. All analyses were descriptive; no formal statistical testing of efficacy endpoints was undertaken.

Biomarker analyses

Exploratory *post hoc* biomarker analyses were carried out using samples from patients enrolled in the T-DXd arms of DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03 who were assessable for confirmed best response. Tumor tissue for exploratory biomarker analysis was optionally collected as additional tissue slides or remaining block from that submitted for HER2 testing (archival tissue or a newly obtained biopsy if a suitable archival sample was unavailable). RNA sequencing data were generated from available archival baseline tumor tissue samples and used to derive PAM50 subtypes, generated according to published methods.[24]

Expression levels of *HER2*, *HER3*, *EGFR*, *MKI67*, *ESR1*, *PGR*, *SLFN11*, and ABC transporters (*ABCC1*, *ABCB1*, *ABCG2*) were evaluated within each best overall response (BOR) group.

Blood samples used for circulating tumor DNA (ctDNA) analysis were collected at cycle 1, day 1 before T-DXd treatment. Genomic ctDNA analysis focused on the frequency of alterations within each BOR group for the following genes: *PIK3CA*, phosphoinositide 3-kinase (PI3K) pathway, *HER2* (including copy number variations), *EGFR* amplification, *ESR1*, homologous recombination repair (HRR) pathway, *BRCA1/2*, *KRAS/NRAS/HRAS*, and *TOP1* from ctDNA. *HER2* plasma copy number was adjusted for ctDNA tumor fraction according to published methods.[25] The Wilcoxon test was used for comparing continuous biomarker variables across BOR or HER2 IHC groups. Additional biomarker analysis methods are provided in Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.11.007.

RESULTS

Patients

Of 851 patients assigned to T-DXd across the pooled studies, 834 were assessable for response (182 from DESTINY-Breast01, 397 from DESTINY-Breast02, and 255 from DESTINY-Breast03), with 125 (15.0%) achieving a CR, 477 (57.2%) achieving a partial response (PR), and 232 (27.8%) classified as non-responders [SD, $n = 207$ (24.8%)/progressive disease (PD), $n = 25$ (3.0%)]. Patient disposition, including primary reasons for treatment discontinuation, is provided in Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.11.007. As of the DCO dates for DESTINY-Breast01 (26 March 2021), DESTINY-Breast02 (30 June 2022), and DESTINY-Breast03 (25 July 2022), 55.2%, 22.6%, and 8.6% of patients with CR, PR, and no response, respectively, continued to receive T-DXd treatment. Across the studies, the median follow-up duration was 30.5 months (range 4.5-45.6 months) in the CR group, 25.8 months (range 3.1-46.9 months) in the PR group, and 19.2 months (range 1.9-41.8 months) in the non-responder group.

Baseline characteristics by best confirmed response to T-DXd are summarized in Table 1. Patients with a history of recurrent mBC had a similar rate of CR to those with *de novo* disease [18.3% (77/420) and 15.2% (35/230), respectively]. Patients with CR had a median of 2 prior regimens (range 1-11) in the metastatic setting, whereas patients with PR or no response had a median of 3 prior regimens. A higher proportion of patients in the CR group had an Eastern Cooperative Oncology Group performance status of 0 at baseline than 1 or 2. A higher proportion of patients in the PR (55.3%) and non-responder (59.9%) groups had HR-positive status than those in the CR group (42.7%) (Table 1). In patients with HR-positive status, a higher proportion of those in the CR and PR groups had received prior endocrine therapy [74.6% (44/59) and 71.2% (188/264), respectively] than those in the non-responder group [60.4% (84/139)]. A lower proportion of patients in the CR group had visceral disease. Fewer patients with CR had brain or bone metastases [4.0% (5/125) and 9.6% (12/125), respectively] than patients who had PR [18.0% (86/477) and 39.2% (187/477)] and no response [19.8% (46/232) and 39.2% (91/232)]. A similar proportion of patients with fewer than three metastatic sites as those with three or more metastatic sites achieved CR [17.6% (72/408) and 12.5% (53/424)]. Patients in the CR group had numerically smaller measurable baseline tumor size, with a median sum of diameters for target lesions of 31 mm (range 10-136 mm) compared with those in the PR and non-responder groups [52 mm (range 10-252 mm) and 50 mm (range 10-245 mm), respectively]. ctDNA levels at baseline (maximum variant allele frequency), which are representative of tumor burden and ctDNA shedding, were lower in patients with CR than in those in all other response groups (Table 1).

Efficacy

Responses to T-DXd compared with responses to the most recent prior systemic therapy are provided in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.11.007. Patients with CR on T-DXd had a higher response rate to prior systemic therapy than patients with PR and no response [32.8% (41/125) versus 17.6% (84/477) and 22.4% (52/232), respectively], and had received prior systemic therapy for longer (median 11 months versus 6.5 and 6.7 months, respectively).

The median duration of response was not estimable (NE; 95% CI 35.2 months-NE) for patients with CR and 16.9 months (95% CI 14.3-20.7 months) for patients with PR. The median time to best response was 5.7 months (95% CI 1.2-37.7 months) for patients with CR and 1.9 months (95% CI 1.1-21.0 months) for patients with PR. Among patients with CR as their best confirmed response, 22 had CR as their first response and 103 had PR as their first response. For these groups, median

Table 1. Demographics and baseline characteristics

Characteristic	Best confirmed response to T-DXd[a] *N* = 834		
	CR *n* = 125	PR *n* = 477	No response[b] *n* = 232
Age, median (range), years	54.4 (34.2-80.9)	54.1 (22.4-88.3)	55.0 (28.0-96.0)
Sex, female, *n* (%)	124 (99.2)	475 (99.6)	231 (99.6)
Disease history, *n* (%)			
De novo	35 (28.0)	132 (27.7)	63 (27.2)
Recurrent	77 (61.6)	244 (51.2)	99 (42.7)
Missing	13 (10.4)	101 (21.2)	70 (30.2)
Region, *n* (%)			
Asia	58 (46.4)	174 (36.5)	83 (35.8)
Europe	43 (34.4)	147 (30.8)	80 (34.5)
North America	7 (5.6)	66 (13.8)	36 (15.5)
Rest of the world	17 (13.6)	90 (18.9)	33 (14.2)
Time from initial diagnosis of BC to randomization, median (range), months	50.1 (6.0-318.1)	51.6 (1.5-345.8)	54.7 (4.6-431.4)
Prior regimens in the metastatic setting, *n* (%)			
0	0	1 (0.2)	0
1 or 2	66 (52.8)	206 (43.2)	79 (34.1)
3 or 4	45 (36.0)	149 (31.2)	81 (34.9)
≥5	14 (11.2)	121 (25.4)	72 (31.0)
Median (range)	2.0 (1.0-11.0)	3.0 (0.0-16.0)	3.0 (1.0-27.0)
T-DM1	70 (56.0)	327 (68.6)	181 (78.0)
HER2 status (IHC), *n* (%)			
0	1 (0.8)	1 (0.2)	0
1+	0	3 (0.6)	3 (1.3)
2+	16 (12.8)	73 (15.3)	41 (17.7)
3+	108 (86.4)	392 (82.2)	184 (79.3)
Not examined/missing	0	7 (1.5)	3 (1.3)
ECOG PS, *n* (%)			
0	88 (70.4)	276 (57.9)	110 (47.4)
1	37 (29.6)	201 (42.1)	120 (51.7)
2	0	0	2 (0.9)
Hormone receptor (derived), *n* (%)			
Positive[c]	59 (47.2)	264 (55.3)	139 (59.9)
Prior endocrine therapy[c]	44 (74.6)	188 (71.2)	84 (60.4)
Negative	65 (52.0)	211 (44.2)	89 (38.4)
Indeterminate/unknown	1 (0.8)	2 (0.4)	4 (1.7)
Visceral disease, *n* (%)	75 (60.0)	407 (85.3)	186 (80.2)
Baseline brain metastases, *n* (%)	5 (4.0)	86 (18.0)	46 (19.8)
Baseline bone metastases,[d] *n* (%)	12 (9.6)	187 (39.2)	91 (39.2)
RECIST v1.1 target lesion			
<3 metastatic sites, *n* (%)	72 (57.6)	217 (45.5)	119 (51.3)
≥3 metastatic sites, *n* (%)	53 (42.4)	260 (54.5)	111 (47.8)
Missing, *n* (%)	0	0	2 (0.9)
Tumor size (sum of diameters), median (range), mm	31 (10-136)	52 (10-252)	50 (10-245)
ctDNA level, mean maximum VAF (SD)	6.8 (8.6)	14.4 (15.9)	15.8 (18.8)

BC, breast cancer; CR, complete response; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; VAF, variant allele frequency.

[a]Data were pooled for patients who received T-DXd 5.4 mg/kg in DESTINY-Breast01/02/03.

[b]SD or PD.

[c]Endocrine treatment was not given to patients with HR-positive tumors while on T-DXd.

[d]Baseline bone metastases are defined as the presence or absence of a given feature in the population at baseline. The number of patients with exclusively bone metastases is likely to be negligible given the study protocol requirements for measurable disease at screening and the known limitations in measuring bone metastases according to RECIST v1.1.

time to first response of CR was 1.5 months (range 1.2-21.8 months) and to first response of PR was 1.5 months (range 1.0-13.9 months). A swimmer plot for patients in the CR group is shown in Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.11.007.

PFS and OS were longer in patients with CR (median NE for PFS and OS) compared with PR (median PFS 21.8 months; median OS 40.5 months) and longer in patients with PR compared with non-responders (median PFS 8.4 months; median OS 23.6 months) (Figure 1). The 24-month PFS rates were 77.8%, 46.3%, and 20.6% in patients with CR, PR, and no response, respectively, and 36-month OS rates were 88.6%, 54.0%, and 35.9%. Hazard ratios for PFS between response groups were 0.29 (95% CI 0.20-0.43) for CR versus PR and 0.13 (95% CI 0.09-0.20) for CR versus non-responders. Hazard ratios for OS were 0.19 (95% CI 0.10-0.35) for CR versus PR and 0.10 (95% CI 0.05-0.19) for CR versus non-responders. PFS and OS by best response to T-DXd in each individual study are summarized in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.11.007. In pooled data for

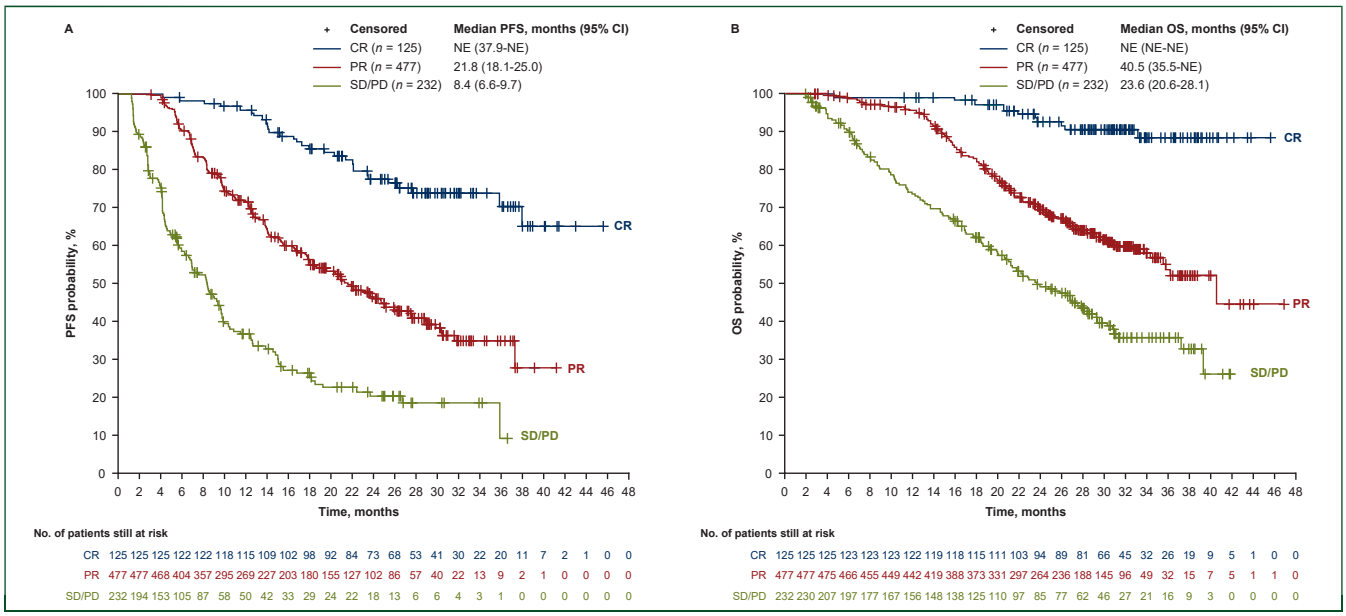

Figure 1. PFS and OS by best response to T-DXd. (A) PFS and (B) OS.
CI, confidence interval; CR, complete response; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.

patients with CR from DESTINY-Breast01 and DESTINY-Breast02, median PFS and OS were not reached, and outcomes were similar to those for patients with CR in DESTINY-Breast03 (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2025.11.007).

Systemic treatment received after T-DXd in the DESTINY-Breast02 and DESTINY-Breast03 studies is summarized in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.11.007; these data were not collected in DESTINY-Breast01. Of patients who discontinued due to adverse events (AEs) in DESTINY-Breast02 or DESTINY-Breast03, 50.0% of patients with CR, 77.3% of patients with PR, and 71.4% of non-responders received subsequent systemic therapy.

Safety

Median treatment duration was 27.4 months (range 4.5-45.1 months) for patients with CR, 14.0 months (range 2.1-39.3 months) for patients with PR, and 6.2 months (range 0.7-40.1 months) for non-responders. The primary reasons for T-DXd discontinuation are provided in Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.11.007; the most common reason for discontinuation was AEs in patients with CR, and PD in patients with PR and no response. A summary of AEs in patients with a best response of CR or PR who discontinued treatment due to AEs is provided in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.11.007.

Rates of any-grade and grade ≥3 drug-related treatment-emergent AEs (TEAEs) were similar regardless of best confirmed response to T-DXd. The proportion of patients with drug-related serious TEAEs, however, was numerically lower for patients with CR (8.0%) than for those with PR (12.4%) or no response (15.5%) (Table 2). Rates of drug-related TEAEs associated with T-DXd discontinuation were also numerically lower for patients with CR (14.4%) than those with PR (17.8%) or no response (16.8%) (Table 2). For patients with CR, the rate of dose reduction (33.6%) was higher than the rate of drug discontinuation (14.4%), whereas the rates of dose reduction and drug discontinuation were similar in patients with PR or no response.

Total patient-years of exposure to T-DXd were 265.71 in the CR group, 643.54 in the PR group, and 180.62 among non-responders (SD + PD). Exposure-adjusted incidence rates (EAIRs) per patient-year for any-grade/grade ≥3 TEAEs were 0.47/0.28 in the CR group, 0.74/0.41 in the PR group, and 1.28/0.71 among non-responders; EAIRs per patient-year for any-grade/grade ≥3 ILD/pneumonitis were 0.04/0.00, 0.11/0.01, and 0.15/0.04, respectively.

Despite longer treatment duration, patients with CR had numerically lower rates of adjudicated drug-related ILD/pneumonitis (8.8% versus 15.1% or 11.6%) and longer median time to first onset of ILD (461 days versus 211 or 125 days) than

Table 2. Overall safety summary

TEAE, *n* (%)	Best confirmed response to T-DXd *N* = 834		
	CR *n* = 125	PR *n* = 477	No response[a] *n* = 232
Any drug-related TEAE	123 (98.4)	470 (98.5)	226 (97.4)
Drug-related grade ≥3 TEAE	62 (49.6)	213 (44.7)	106 (45.7)
Drug-related serious TEAE	10 (8.0)	59 (12.4)	36 (15.5)
Drug-related TEAE associated with drug discontinuation	18 (14.4)	85 (17.8)	39 (16.8)
Drug-related TEAE associated with dose reduction	42 (33.6)	110 (23.1)	48 (20.7)
Drug-related TEAE associated with an outcome of death	0	3 (0.6)	4 (1.7)

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]SD/PD.

Table 3. Adjudicated drug-related ILD/pneumonitis

	Best confirmed response to T-DXd N = 834		
	CR n = 125	PR n = 477	No response[a] n = 232
Adjudicated drug-related ILD/ pneumonitis by worst CTCAE grade,[b] n (%)			
Any grade	11 (8.8)	72 (15.1)	27 (11.6)
Grade 1	5 (4.0)	16 (3.4)	7 (3.0)
Grade 2	5 (4.0)	49 (10.3)	14 (6.0)
Grade 3	1 (0.8)	5 (1.0)	1 (0.4)
Grade 4	0	0	0
Grade 5	0	2 (0.4)	5 (2.2)
Grade ≥3	1 (0.8)	7 (1.5)	6 (2.6)
Time to first adjudicated drug-related ILD onset,[c] median (range), days	461 (41-804)	211 (33-960)	125 (35-457)

CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.
[a]SD/PD.
[b]The outcome of the worst ILD event denominator is based on adjudicated drug-related ILD, and the outcome of the worst ILD event is based on the investigator reported outcome of adjudicated drug-related ILD.
[c]Onset date of first ILD adjudicated as drug-related minus first dose date + 1.

patients with PR or no response (Table 3). There were no grade 4 or 5 ILD/pneumonitis events in the CR group.

Biomarker analyses

Pooled datasets for biomarker analyses are summarized in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.11.007. Baseline demographics and disease characteristics were generally similar to the overall pooled population, categorized by BOR group (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2025.11.007).

HER2-related biomarkers. *HER2* gene expression was similar across BOR groups, although it was higher in tumor samples from patients with HER2 IHC 3+ than IHC 2+ status (Supplementary Figures S5 and S6A, available at https://doi.org/10.1016/j.annonc.2025.11.007). The *HER2*-amp plasma detection rate was 62.4% among all patients and lower (50.9%) in the CR group (Figure 2A), likely due to lower ctDNA shedding/tumor burden as reflected in the lower overall ctDNA levels in the CR group as measured by maximum variant allele frequency (Table 1). Within the *HER2*-amp subgroup, *HER2* plasma copy number (adjusted for ctDNA tumor fraction) was observed to be higher in blood samples from responders (CR and PR) than in those from non-responders and higher in tumor samples from patients with HER2 IHC 3+ than in those from patients with IHC 2+ status (Figure 2A and Supplementary Figure S5B, available at https://doi.org/10.1016/j.annonc.2025.11.007). Together, these results support the observation of a numerically higher proportion of patients with HER2 IHC 3+ status in the CR and PR groups compared with those with HER2 IHC 2+ status (Table 1).

Other biomarkers. In all patients, and more specifically in patients in the HR-positive subgroup, *ESR1* gene expression was lower in baseline tumor samples from responders versus non-responders, with a similar observation for *PGR* gene expression (Figure 2B; Supplementary Figure S6B, available at https://doi.org/10.1016/j.annonc.2025.11.007). In all patients, *ESR1* mutations were not detected in the CR group but were detected in the PR and non-responder groups (Figure 2C) and were primarily in samples from patients with HR-positive disease. For patients with HR-positive BC, there were baseline *ESR1* mutations detected in ctDNA samples from patients in the PR group [16/108 (14.8%)] and in patients from the non-responder group [11/59 (18.6%)] (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2025.11.007). Lower ctDNA tumor fraction could have contributed to the lower frequency of *ESR1* mutations in the CR subgroup (Table 1).

There were no clear differences in mutational frequencies across BOR groups for other genetic alterations analyzed (*PIK3CA*, PI3K pathway, *HER2*, *EGFR* amplification, HRR, *BRCA1/2*, *KRAS/NRAS/HRAS*, *TOP1*) (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2025.11.007).

HER3 (*ERBB3*) expression was higher in the non-responder versus responder groups (Supplementary Figure S6A, available at https://doi.org/10.1016/j.annonc.2025.11.007); however, the difference might be due to the small range of *HER3* expression across the dataset; therefore, this requires further investigation. There were no clear differences in expression levels of other genes analyzed (*EGFR*, *ERBB4*, *MKI67*, *TOP1*, *SLFN11*, and efflux transporter genes) across BOR groups (Supplementary Figures S6A and S7 and Table S8, available at https://doi.org/10.1016/j.annonc.2025.11.007).

PAM50 subtypes. Overall, luminal A was the most common PAM50 subtype, followed by HER2-enriched, and luminal B, with a small number of basal and normal subtypes. The proportion of HER2-enriched subtype was higher in patients with HR-negative tumors than in those with HR-positive tumors. The proportion of HER2-enriched subtype was overall lower and luminal subtype overall higher compared with previous reports in HER2-positive BC.[26-28] Among responders, there was a numerically lower proportion of luminal B subtype and numerically higher proportion of HER2-enriched subtype, especially among patients with HR-negative tumors who achieved PR (Supplementary Figure S8, available at https://doi.org/10.1016/j.annonc.2025.11.007). In all patients, the frequency of responders (PR/CR) versus non-responders (SD/PD) was 35.2% (102/290) versus 25.0% (29/116) for HER2, 41.4% (120/290) versus 48.3% (56/116) for luminal A, and 17.2% (50/290) versus 19.0% (22/116) for luminal B PAM50 subtypes. In patients with HR-positive tumors, the frequency of responders versus non-responders was 22.5% (36/160) versus 15.4% (12/78) for HER2-enriched, 46.9% (75/160) versus 53.8% (42/78) for luminal A, and 27.5% (44/160) versus 25.6% (20/78) for luminal B PAM50 subtypes. In patients with HR-negative tumors, the frequency of responders versus non-responders was 51.6% (66/128) versus

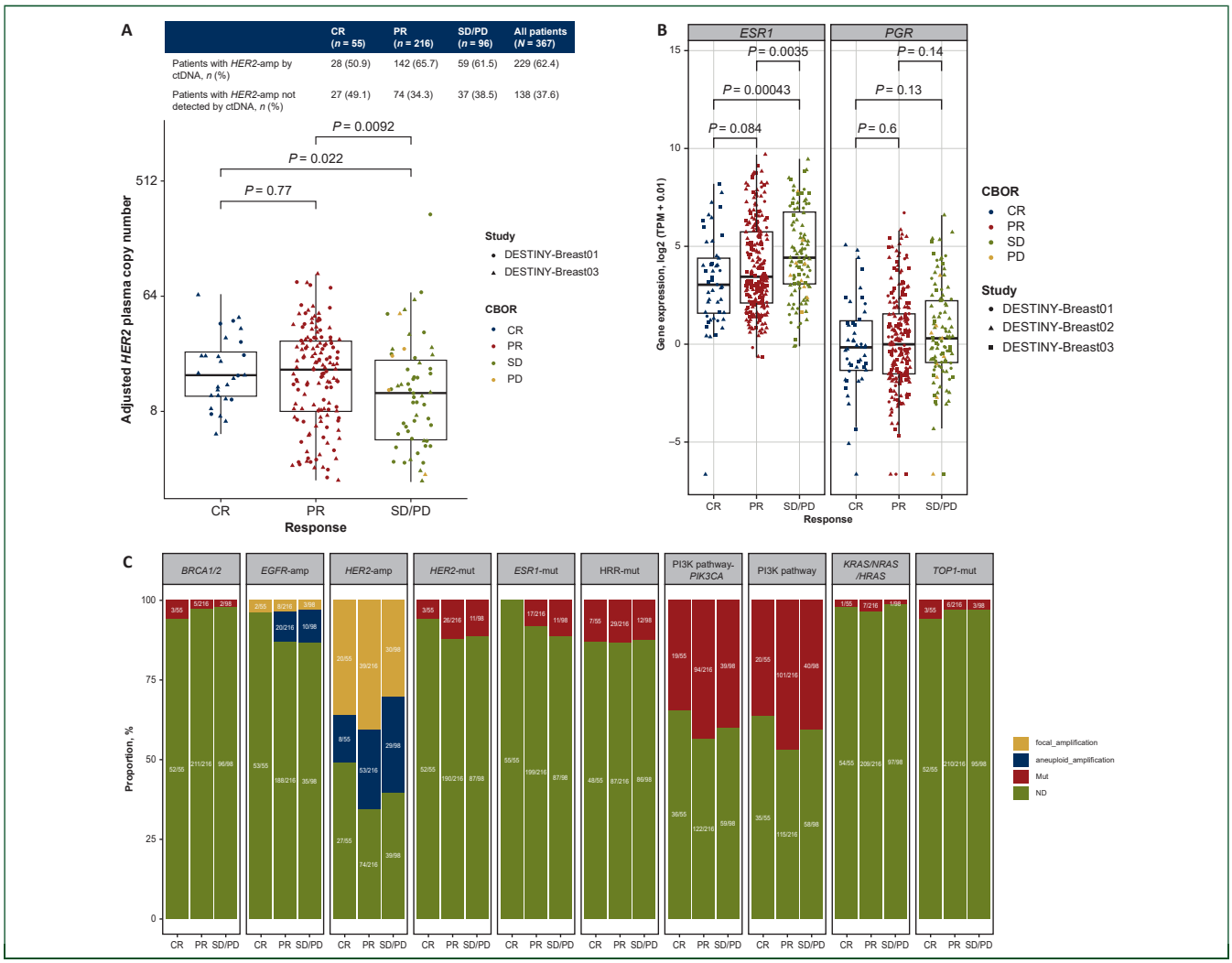

Figure 2. Biomarker analysis by best response to T-DXd. (A) *HER2* plasma copy number by RECIST v1.1 responder groups for patients with detectable *HER2*-amp in baseline ctDNA[a]; (B) baseline *ESR1* and *PGR* gene expression by pooled response groups; (C) genetic alteration frequency for genes of interest by RECIST v1.1 response groups. Patients without detectable *HER2*-amp do not have reported copy number and are not represented in plots. *P* values were determined using the Wilcoxon statistical test.
CBOR, confirmed best overall response; CR, complete response; ctDNA, circulating tumor DNA; HER2, human epidermal growth factor receptor 2; ND, not detectable; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TPM, transcripts per million.
[a]ctDNA was not analyzed in DESTINY-Breast02.

44.4% (16/36) for HER2-enriched, 33.6% (43/128) versus 36.1% (13/36) for luminal A, and 4.7% (6/128) versus 5.6% (2/36) for luminal B PAM50 subtypes.

DISCUSSION

Treatment with T-DXd is associated with durable CR and PR in patients with HER2-positive mBC who have developed disease progression after prior anti-HER2-based therapies.[13,16,17] In this pooled analysis of data from DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03, regardless of T-DXd treatment setting—after T-DM1 (DESTINY-Breast01/DESTINY-Breast02) or trastuzumab plus a taxane (DESTINY-Breast03)—patients who achieved CR on T-DXd had prolonged PFS and OS. However, as demonstrated in individual studies,[13,16,17] the probability of achieving an objective response (particularly CR) was higher when T-DXd was used in an earlier treatment setting. Patients who experienced CR tended to have more favorable baseline characteristics such as better Eastern Cooperative Oncology Group performance status, lower likelihood of visceral disease or brain or bone metastases, and lower metastatic disease burden compared with those with PR or non-responders. The low number of patients with bone metastases who achieved CR was consistent with previous studies and not unexpected given that tumors may continue to be detected in metastatic sites.[29-31]

Safety remained generally manageable, and responders had a lower incidence of serious TEAEs than non-responders in this analysis. Although patients with CR received T-DXd for longer than patients with PR or no response, the CR group had lower EAIRs per patient-year for any-grade/grade $\geq$3 TEAEs, numerically lower rates of discontinuation due to AEs, lower adjudicated, drug-related ILD/pneumonitis rate, no grade 4 or 5 ILD/pneumonitis, and longer median time to first onset of adjudicated, drug-related ILD. The lower rates observed for the CR group might be because patients with PR and non-responders

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were more heavily pre-treated or had more disease symptoms possibly related to treatment.

In pooled baseline biomarker analyses, responders with detectable *HER2* amplifications had higher plasma *HER2* copy number compared with non-responders. Although there was no observable difference in *HER2* gene expression across response groups, a numerically higher proportion of patients with HER2 IHC 3+ status was observed in the CR and PR groups compared with non-responders. Compared with the CR group, the PR and non-responder groups had a numerically higher proportion of patients with HR-positive status, higher *ESR1* gene expression, and fewer *ESR1* mutations. The opposing directional trend of HER2 and *ESR1* expression is consistent with the biology of HR-positive versus HR-negative HER2-positive BC.[28,32,33] The detection of *ESR1* mutations is attributed to prior endocrine therapy exposure and resistance, and, in patients with HR-positive disease, prior endocrine therapy was received by a higher proportion of responder groups (CR, PR) compared with non-responder groups. The CLEOPATRA study included a higher frequency of HER2 IHC 3+ versus 2+ status and higher *HER2* mRNA levels in long-term responder versus non-responder groups,[8] and another study showed that high expression of estrogen receptor (≥30% of tumor cells) predicted reduced probability of tumor response to first-line trastuzumab plus chemotherapy.[32] Overall, response to T-DXd was persistent regardless of HER2 and HR or the presence of genomic alterations or expression levels of genes relevant to HER2-positive BC. Notably, there was no relationship between response to T-DXd and frequency of *PIK3CA* mutations in this study, whereas there were fewer patients with *PIK3CA* mutations in long-term responder groups in CLEOPATRA.[8] There were no clear differences across response groups according to expression levels of *EGFR*, *ERBB4* (*HER4*), *MK167*, *TOP1*, *SLFN11*, and efflux transporter genes in our study. Expression of these biomarkers was not associated with sensitivity or resistance; however, biomarker expression was not measured according to PFS and OS in this analysis.

One limitation of this pooled analysis is heterogeneity across study designs and inclusion criteria of the three trials. The population of DESTINY-Breast01 and DESTINY-Breast02 represents a more advanced disease setting compared with that of DESTINY-Breast03. However, patients who achieved CR with T-DXd treatment demonstrated longer PFS and OS regardless of disease setting. Outcomes in patients with a best confirmed response to T-DXd of CR or PR (responders) were compared with those of a pooled group of patients with either SD or PD as their best response (non-responders). It is acknowledged that SD and PD represent different outcomes. However, due to the low proportion of patients with PD as their best response to T-DXd in DESTINY-Breast01 (1.6%),[15] DESTINY-Breast02 (4.7%),[13] and DESTINY-Breast03 (1.1%),[14] the SD and PD groups were combined for this analysis. Another limitation of the efficacy analyses is that they lacked type I error control (adjustment for multiple testing). Among the limitations of the biomarker analyses (Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.11.007) were the range in sample age, timing, and biopsy location (primary versus metastatic) in the biomarker analyses and the partial availability of ctDNA (gene alteration) and gene expression data for patients with evaluable pooled efficacy. The absence of biomarker analyses from DESTINY-Breast02 also limits the pooled genomic findings.

Conclusions

These results further support the use of T-DXd across broad patient groups with HER2-positive mBC, regardless of tumor burden and baseline disease characteristics. Biomarker analyses suggest that T-DXd is active irrespective of the presence of alterations or expression levels of genes relevant to HER2-positive BC. More effective treatment options are needed for patients who do not experience a response while receiving T-DXd, and T-DXd-based combination therapies are being investigated in earlier lines of therapy.

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DATA SHARING

Anonymized individual participant data on completed studies and applicable supporting clinical trial documents may be available upon request at https://vivli.org/. In cases where clinical study data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo Companies will continue to protect the privacy of company and our clinical study subjects. Details on data sharing criteria and the procedure for requesting access can be found at: https://vivli.org/ourmember/daiichi-sankyo/.

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