Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial

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Summary

Background An improvement in progression-free survival was shown with trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer in the progression-free survival interim analysis of the DESTINY-Breast03 trial. The aim of DESTINY-Breast03 was to compare the efficacy and safety of trastuzumab deruxtecan versus trastuzumab emtansine.

Methods This open-label, randomised, multicentre, phase 3 trial was done in 169 study centres in North America, Asia, Europe, Australia, and South America. Eligible patients were aged 18 or older, had HER2-positive unresectable or metastatic breast cancer previously treated with trastuzumab and a taxane, had an Eastern Cooperative Oncology Group performance status 0–1, and at least one measurable lesion per Response Evaluation Criteria in Solid Tumours version 1.1. Patients were randomly assigned (1:1) to receive trastuzumab deruxtecan 5·4 mg/kg or trastuzumab emtansine 3·6 mg/kg, both administered by intravenous infusion every 3 weeks. Randomisation was stratified by hormone receptor status, previous treatment with pertuzumab, and history of visceral disease, and was managed through an interactive web-based system. Within each stratum, balanced block randomisation was used with a block size of four. Patients and investigators were not masked to the treatment received. The primary endpoint was progression-free survival by blinded independent central review. The key secondary endpoint was overall survival and this prespecified second overall survival interim analysis reports updated overall survival, efficacy, and safety results. Efficacy analyses were performed using the full analysis set. Safety analyses included all randomly assigned patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT03529110.

Findings Between July 20, 2018, and June 23, 2020, 699 patients were screened for eligibility, 524 of whom were enrolled and randomly assigned to receive trastuzumab deruxtecan (n=261) or trastuzumab emtansine (n=263). Median duration of study follow-up was 28·4 months (IQR 22·1–32·9) with trastuzumab deruxtecan and 26·5 months (14·5–31·3) with trastuzumab emtansine. Median progression-free survival by blinded independent central review was 28·8 months (95% CI 22·4–37·9) with trastuzumab deruxtecan and 6·8 months (5·6–8·2) with trastuzumab emtansine (hazard ratio [HR] 0·33 [95% CI 0·26–0·43]; nominal p<0·0001). Median overall survival was not reached (95% CI 40·5 months–not estimable), with 72 (28%) overall survival events, in the trastuzumab deruxtecan group and was not reached (34·0 months–not estimable), with 97 (37%) overall survival events, in the trastuzumab emtansine group (HR 0·64 [95% CI 0·47–0·87]; p=0·0037). The number of grade 3 or worse treatment-emergent adverse events was similar in patients who received trastuzumab deruxtecan versus trastuzumab emtansine (145 [56%] patients versus 135 [52%] patients). Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 39 (15%) patients treated with trastuzumab deruxtecan and eight (3%) patients treated with trastuzumab emtansine, with no grade 4 or 5 events in either group.

Interpretation Trastuzumab deruxtecan showed a significant improvement in overall survival versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer, as well as the longest reported median progression-free survival, reaffirming trastuzumab deruxtecan as the standard of care in the second-line setting. A manageable safety profile of trastuzumab deruxtecan was confirmed with longer treatment duration.

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Research in context

Evidence before this study

Trastuzumab and pertuzumab, combined with a taxane, is recommended as the standard first-line therapy for patients with advanced or metastatic HER2-positive breast cancer, on the basis of the results of the CLEOPATRA trial. We searched PubMed and relevant congress abstracts for clinical trials evaluating second-line HER2-targeted treatments for patients with HER2-positive metastatic breast cancer published between Oct 20, 2017, and Oct 20, 2022. The search terms included were "HER2-targeted" and "HER2-positive" or "ERBB2-positive" and "breast cancer" or "breast adenocarcinoma" or "breast carcinoma" and "second line" or "pretreated"; the search was restricted to English language publications. Multiple HER2-targeted agents are under investigation in patients with HER2-positive metastatic breast cancer; however, only two agents are approved in Europe and the USA for use in the second-line setting: trastuzumab emtansine and trastuzumab deruxtecan. Trastuzumab emtansine was previously the recommended second-line therapy based on the EMILIA trial. However, the positive results from the interim analysis of progression-free survival in DESTINY-Breast03 resulted in updated guidance for trastuzumab deruxtecan as the preferred second-line therapy, with trastuzumab emtansine as the alternative therapy.

Added value of this study

The second overall survival interim analysis of DESTINY-Breast03 evaluates whether overall survival is improved with trastuzumab deruxtecan versus trastuzumab emtansine and provides updated efficacy and safety results with longer study follow-up. The benefit of trastuzumab deruxtecan was previously demonstrated on the basis of progression-free survival and is now further confirmed by the overall survival results, which are often considered the gold-standard measure of efficacy.

Implications of all the available evidence

This study reaffirms trastuzumab deruxtecan as the standard of care in the second-line setting for patients with HER2-positive metastatic breast cancer and reinforces the established favourable benefit–risk profile of trastuzumab deruxtecan over trastuzumab emtansine.

Introduction

Human epidermal growth factor receptor 2 (HER2, also known as ERBB2) is overexpressed in approximately 15–20% of breast cancers.[1] Standard first-line treatment for patients with HER2-positive metastatic breast cancer includes pertuzumab and trastuzumab in combination with a taxane.[2–4] Preferred second-line treatment is trastuzumab deruxtecan, with trastuzumab emtansine as an alternative option.[4]

Trastuzumab deruxtecan and trastuzumab emtansine are antibody–drug conjugates, and both consist of a humanised anti-HER2 monoclonal antibody linked to a potent cytotoxic payload.[5–7] The payload of trastuzumab emtansine is a microtubule inhibitor conjugated to the antibody via a stable thioether linker.[8] Trastuzumab deruxtecan's payload is a topoisomerase I inhibitor linked via a tetrapeptide-based cleavable linker, which is highly stable in plasma and allows for selective cleavage in cancerous cells.[7,9] This ensures efficient delivery of the potent payload specifically to HER2-expressing cancer cells, thereby reducing off-target toxic effects.[7,10] Trastuzumab deruxtecan has a uniquely high drug-to-antibody ratio of around 8, compared with 3·5 for trastuzumab emtansine.[6,7] The initial US Food and Drug Administration approval of trastuzumab deruxtecan in the third-line setting for HER2-positive metastatic breast cancer was based on the primary results of DESTINY-Breast01, a phase 2, single-group study with a confirmed objective response rate of 61% (95% CI 53·4–68·0) and median progression-free survival of 16·4 months (95% CI 12·7–not reached).[11]

The EMILIA trial was a randomised, open-label, phase 3 trial of trastuzumab emtansine versus capecitabine and lapatinib.[12,13] At the second interim analysis of overall survival, median overall survival was 30·9 months with trastuzumab emtansine versus 25·1 months with capecitabine and lapatinib (hazard ratio [HR] 0·68 [95% CI 0·55–0·85]).[12] DESTINY-Breast03 was a multicentre, open-label, randomised, phase 3 trial of trastuzumab deruxtecan versus trastuzumab emtansine.[14] In the interim analysis of progression-free survival (data cutoff May 21, 2021), trastuzumab deruxtecan showed a statistically significant and clinically meaningful improvement in median progression-free survival versus trastuzumab emtansine; median progression-free survival was not reached (95% CI 18·5 months–not evaluable) with trastuzumab deruxtecan and 6·8 months (5·6–8·2) with trastuzumab emtansine (HR 0·28 [95% CI 0·22–0·37]; p<0·001).[14] The p value did not cross the prespecified threshold of statistical significance, but the HR for death was 0·55 (95% CI 0·36–0·86; p=0·007) for trastuzumab deruxtecan versus trastuzumab emtansine.[14] On the basis of the interim analysis of progression-free survival in DESTINY-Breast03, trastuzumab deruxtecan was approved for patients with unresectable or metastatic HER2-positive breast cancer who have received a previous anti-HER2-based regimen in the metastatic setting and in patients who have developed disease recurrence during or within 6 months of completing therapy in the neoadjuvant or adjuvant setting.[14,15]

Here, we report results from the prespecified second interim analysis of the key secondary outcome of overall survival in DESTINY-Breast03 and present updated efficacy data, including for median progression-free survival, and updated safety data with longer follow-up.

Methods

Study design

DESTINY-Breast03 was an open-label, randomised, multicentre, phase 3 trial that evaluated the efficacy and safety of trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive unresectable or metastatic breast cancer that had progressed during or after treatment with trastuzumab and a taxane.[14] The trial was done at 169 study centres in North America, Asia, Europe, Australia, and South America.

The institutional review board at each study site approved the trial protocol. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the principles of the Declaration of Helsinki, and local regulations regarding the conduct of clinical research. All authors ensured the completeness and accuracy of the data and analyses and the fidelity of the trial to the protocol. Full methods and protocol have been previously published.[14]

Patients

Eligible patients had pathologically documented HER2-positive (centrally confirmed) unresectable or metastatic breast cancer that was previously treated with trastuzumab and a taxane in the advanced or metastatic setting or progressed during or within 6 months after neoadjuvant or adjuvant treatment involving trastuzumab and a taxane.[14] Additional eligibility criteria for inclusion in the study were age 18 years or older, an Eastern Cooperative Oncology Group performance status of 0 or 1, and presence of at least one measurable lesion per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1). Patients were eligible for enrolment in the study if they had clinically inactive or previously treated brain metastases that were no longer symptomatic.[14]

Patients were excluded if they currently had interstitial lung disease or pneumonitis, had a history of interstitial lung disease or pneumonitis that required steroids, or when suspected interstitial lung disease or pneumonitis could not be ruled out by imaging at screening; if they had been previously treated with an anti-HER2 antibody–drug conjugate in the metastatic setting; or if they had uncontrollable or clinically significant cardiovascular disease.[14] Before participating in the trial, all patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either trastuzumab deruxtecan or trastuzumab emtansine. Randomisation was stratified by hormone receptor status (positive or negative), previous treatment with pertuzumab, and history of visceral disease, and was managed through an interactive web-based system. Randomisation details have been previously published.[14] Within each stratum, balanced block randomisation was used with a block size of four and a treatment allocation ratio of 1:1 to trastuzumab deruxtecan and trastuzumab emtansine. An independent biostatistician generated the randomisation schedule. Patients and investigators were not masked to the treatment received as it was not feasible to mask treatment allocations due to different treatment administration protocols and adverse event profiles between trastuzumab deruxtecan and trastuzumab emtansine. Tumour assessments were conducted by blinded independent central review, in which reviewers were masked with respect to the study treatment administered.

Procedures

Patients received either 5·4 mg/kg of trastuzumab deruxtecan or 3·6 mg/kg of trastuzumab emtansine, both administered by intravenous infusion every 3 weeks. Baseline assessments were performed before the first administration of study treatment, and study assessments were collected on day 1 of each 21-day treatment cycle as well as days 8 and 15 of treatment cycle 1. Tumour assessments were performed every 6 weeks (plus or minus 7 days) starting from randomisation and independent of treatment cycle. End-of-treatment assessments occurred within 7 days of the date of study treatment discontinuation. A follow-up visit occurred at 40 days (plus 7 days) after the last administration of study treatment or before starting new anticancer treatment, whichever came first, followed by long-term or survival visits every 3 months (plus or minus 14 days) until death, withdrawal of consent, loss to follow-up, or study closure, whichever came first. Further information on the assessments performed at each visit is available in the study protocol, which is provided in the appendix.[14]

Outcomes

The primary endpoint was progression-free survival, as determined by blinded independent central review. The key secondary endpoint was overall survival. Other secondary efficacy endpoints were objective response rate based on blinded independent central review and investigator assessment, duration of response based on blinded independent central review, and progression-free survival based on investigator assessment. Exploratory efficacy endpoints were clinical benefit rate based on blinded independent central review, best percentage change in the sum of the diameter of measurable tumours based on blinded independent central review, progression-free survival on the next line of therapy based on investigator assessment, and time to response based on blinded independent central review. Exploratory analysis of progression-free survival and overall survival was performed in prespecified subgroups, including hormone receptor status (positive or negative), previous treatment with pertuzumab, presence or absence of visceral disease at baseline, the number of previous lines of systemic therapy not including hormone therapy

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See **Online** for appendix

(fewer than three or three or more), and presence or absence of brain metastases at baseline, if the primary analysis was significant. Overall survival was defined as the time from the date of randomisation to the date of death due to any cause. The objective response rate was the proportion of patients with a best overall response of confirmed complete response or partial response, assessed by blinded independent central review and investigator based on RECIST 1.1. Duration of response was the time from the date of the first documentation of objective response (complete response or partial response) to the date of first objective documentation of progressive disease or death due to any cause.

Safety of trastuzumab deruxtecan versus trastuzumab emtansine was a secondary objective of the study. All adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0, and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Safety parameters included the incidence of treatment-emergent adverse events and serious adverse events. Treatment-emergent adverse events were defined as adverse events that occurred or worsened in severity after initiating the study drug until 47 days after the last dose of the study drug; serious adverse events with an onset or worsening 48 days or more after the last dose of study drug, if considered related to the study treatment, were also deemed to be treatment-emergent adverse events. Serious adverse events were defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalisation or prolonged existing hospitalisation, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was considered an important medical event. Exposure-adjusted incidence rates were summarised for treatment-emergent adverse events, treatment-emergent adverse events grade 3 or worse, and serious treatment-emergent adverse events, and were calculated as the ratio of the number of patients with at least one incidence of the event divided by the sum of the total patient-years of exposure. All potential cases of interstitial lung disease or pneumonitis were identified for adjudication and evaluated by an independent adjudication committee on the basis of the current MedDRA version for the narrow interstitial lung disease Standardized MedDRA Query, selected terms from the broad interstitial lung disease Standardized MedDRA Query, and the preferred terms respiratory failure and acute respiratory failure. Interstitial lung disease or pneumonitis events were treated according to protocol-specified guidelines.

Statistical analysis

A sample size of approximately 500 patients was planned to be randomly assigned in the study. A group sequential design including an interim analysis for progression-free survival using a Haybittle-Peto stopping boundary allowed the study to detect a clinically meaningful progression-free survival benefit for trastuzumab deruxtecan versus trastuzumab emtansine with a two-sided α of 0·05 and a power of approximately 90%. In addition, the study was planned to have approximately 80% power to detect a clinically meaningful overall survival benefit using a three-look group sequential design. Efficacy analyses were performed on the full analysis set, which included all patients randomly assigned; patients were analysed according to the treatments and strata they were assigned at randomisation. Safety analyses were performed on the safety analysis set, which included all randomly assigned patients who received at least one dose of study treatment, either trastuzumab deruxtecan or trastuzumab emtansine.

If there was no death reported for a patient before the data cutoff analysis, overall survival was censored at the last contact date at which the patient was known to be alive. Overall survival was compared between the two treatment groups using a stratified log-rank test. The treatment effect HR and its 95% CIs were estimated using a Cox proportional hazards regression model stratified by the randomisation stratification factors as recorded by the interactive web or voice response system. The median survival time and the two-sided 95% CIs for the median were calculated using the Brookmeyer and Crowley method for each treatment group. The log–log transformation was applied to the survival function and the estimated variance was calculated using Greenwood's formula. Kaplan-Meier estimates of overall survival rates at fixed time points (ie, 3, 6, 9, 12, 18, 24, 36, and 48 months) and their two-sided 95% CIs were provided for each treatment group. A hierarchical testing procedure was used, and the overall survival analysis was performed only if the primary efficacy endpoint of progression-free survival was statistically significant. The efficacy stopping boundaries, with an overall two-sided significance level of 0·05, were constructed using a group sequential design with three-look Lan-DeMets α spending function with O'Brien-Fleming stop boundary for overall survival. The exact p values to declare statistical significance depended on the number of overall survival events that were observed at the time of the analyses. The prespecified second interim analysis of overall survival was planned with 153 events (information fraction of 61%), with a p value boundary to reach statistical significance of 0·008. The p value was recalculated based on the actual overall survival events at the data cutoff.

Progression-free survival analyses were performed using the same approach as described for overall survival. The interim analysis of progression-free survival was performed based on the data cutoff of May 21, 2021, with 245 blinded independent central review events, and was reported previously.[14] The statistical analysis plan was included in the protocol and has been previously published.[14] Because progression-free survival demonstrated statistical significance at the progression-free survival interim analysis, overall survival was compared between trastuzumab deruxtecan and

trastuzumab emtansine for the May 21, 2021, data cutoff, but the p value and α level for the expression was not statistically significant (the p value efficacy boundary was 0·0003 and the actual p value observed was 0·0072).[14] At the second overall survival interim analysis data cutoff of July 25, 2022, 169 overall survival events were observed and the p value boundary for statistical significance was 0·013. Given that the primary endpoint of progression-free survival by blinded independent central review was met at the interim analysis for progression-free survival, no further hypothesis testing on the primary endpoint was required; the p values for progression-free survival and other efficacy endpoints, except for overall survival, at this second interim analysis for overall survival were nominal. Sample size calculation was conducted using EAST version 6.4 software and all statistical analyses were performed using SAS version 9.3 or higher. This study is registered with ClinicalTrials.gov, NCT03529110.

Role of the funding source

Daiichi Sankyo led the study design, data collection, and data analysis. All authors and sponsors assisted in data interpretation, writing of the report, and reviewing the manuscript.

Results

Between July 20, 2018, and June 23, 2020, 699 patients were screened for eligibility, 524 of whom were enrolled and randomly assigned to receive trastuzumab deruxtecan (n=261) or trastuzumab emtansine (n=263; appendix p 14). As of the data cutoff (July 25, 2022), 75 (29%) patients in the trastuzumab deruxtecan group and 18 (7%) patients in the trastuzumab emtansine group remained on treatment. Demographic and baseline characteristics were similar between the two treatment groups (table 1). Median duration of study follow-up was 28·4 months (IQR 22·1–32·9) with trastuzumab deruxtecan and 26·5 months (14·5–31·3) with trastuzumab emtansine.

The primary endpoint, median progression-free survival as assessed by blinded independent central review, was 28·8 months (95% CI 22·4–37·9) with trastuzumab deruxtecan and 6·8 months (5·6–8·2) with trastuzumab emtansine (HR 0·33 [95% CI 0·26–0·43]; nominal p<0·0001; figure 1A). Progression-free survival rate at 12 months was 75·2% (95% CI 69·3–80·2) in the trastuzumab deruxtecan group and 33·9% (27·7–40·2) in the trastuzumab emtansine group. Progression-free survival rate at 24 months was 53·7% (95% CI 46·8–60·1) in the trastuzumab deruxtecan group and 26·4% (20·5–32·6) in the trastuzumab emtansine group.

Median overall survival was not reached (95% CI 40·5 months–not estimable), with 72 (28%) overall survival events, in the trastuzumab deruxtecan group and was not reached (34·0 months–not estimable), with 97 (37%) overall survival events, in the trastuzumab emtansine group (HR 0·64; 95% CI 0·47–0·87);

	Trastuzumab deruxtecan group (n=261)	Trastuzumab emtansine group (n=263)
Age, years	54·3 (47·0–62·8)	54·2 (45·3–63·1)
Sex		
Female	260 (>99%)	262 (>99%)
Male	1 (<1%)	1 (<1%)
Region		
Asia	149 (57%)	160 (61%)
Europe	54 (21%)	50 (19%)
North America	17 (7%)	17 (6%)
Australia and South America	41 (16%)	36 (14%)
Race		
White	71 (27%)	72 (27%)
Black or African American	10 (4%)	9 (3%)
Asian	152 (58%)	162 (62%)
Other*	28 (11%)	20 (8%)
HER2 status by immunohistochemistry†		
3+	234 (90%)	232 (88%)
2+	25 (10%)	30 (11%)
1+	1 (<1%)	0
Not evaluable	1 (<1%)	1 (<1%)
ECOG performance status		
0	154 (59%)	175 (67%)
1	106 (41%)	87 (33%)
Missing	1 (<1%)	1 (<1%)
Positive hormone receptor status	131 (50%)	134 (51%)
Baseline CNS metastases	43 (16%)	39 (15%)
History of visceral disease	184 (70%)	185 (70%)
Any previous systemic cancer therapy‡	260 (>99%)	262 (>99%)
Trastuzumab	260 (>99%)	262 (>99%)
Trastuzumab emtansine	1 (<1%)	0
Pertuzumab	162 (62%)	158 (60%)
Taxane and trastuzumab	260 (>99%)	262 (>99%)
Other anti-HER2 therapy§	42 (16%)	38 (14%)
Anti-HER2 tyrosine kinase inhibitor	42 (16%)	36 (14%)
Other anti-HER2 antibody or antibody–drug conjugate	2 (<1%)	3 (1%)
Hormone therapy	109 (42%)	112 (43%)
Other systemic therapy not hormone or HER2-directed	183 (70%)	177 (67%)
Number of previous lines of therapy	2 (1–3)	2 (1–3)
Previous lines of therapy in the metastatic setting¶		
0	1 (<1%)	1 (<1%)
1	108 (41%)	102 (39%)
2	60 (23%)	64 (24%)
3	44 (17%)	45 (17%)
4	15 (6%)	23 (9%)
≥5	33 (13%)	28 (11%)

Data are median (IQR) or n (%). CNS=central nervous system. ECOG=Eastern Cooperative Oncology Group. HER2=human epidermal growth factor receptor 2. *Includes patients who reported multiple races. †HER2 status as evaluable by central laboratory. ‡Two patients (one in each treatment group) were randomly assigned in error and the previous cancer systemic therapy case report form was not completed. §Includes anti-HER2 tyrosine kinase inhibitor and other anti-HER2 antibody or antibody–drug conjugate. ¶Includes regimens indicated for advanced or metastatic disease or early progression within 6 months of regimen for neoadjuvant or adjuvant (12 months for pertuzumab).

Table 1: **Patient demographics and previous therapies at baseline**

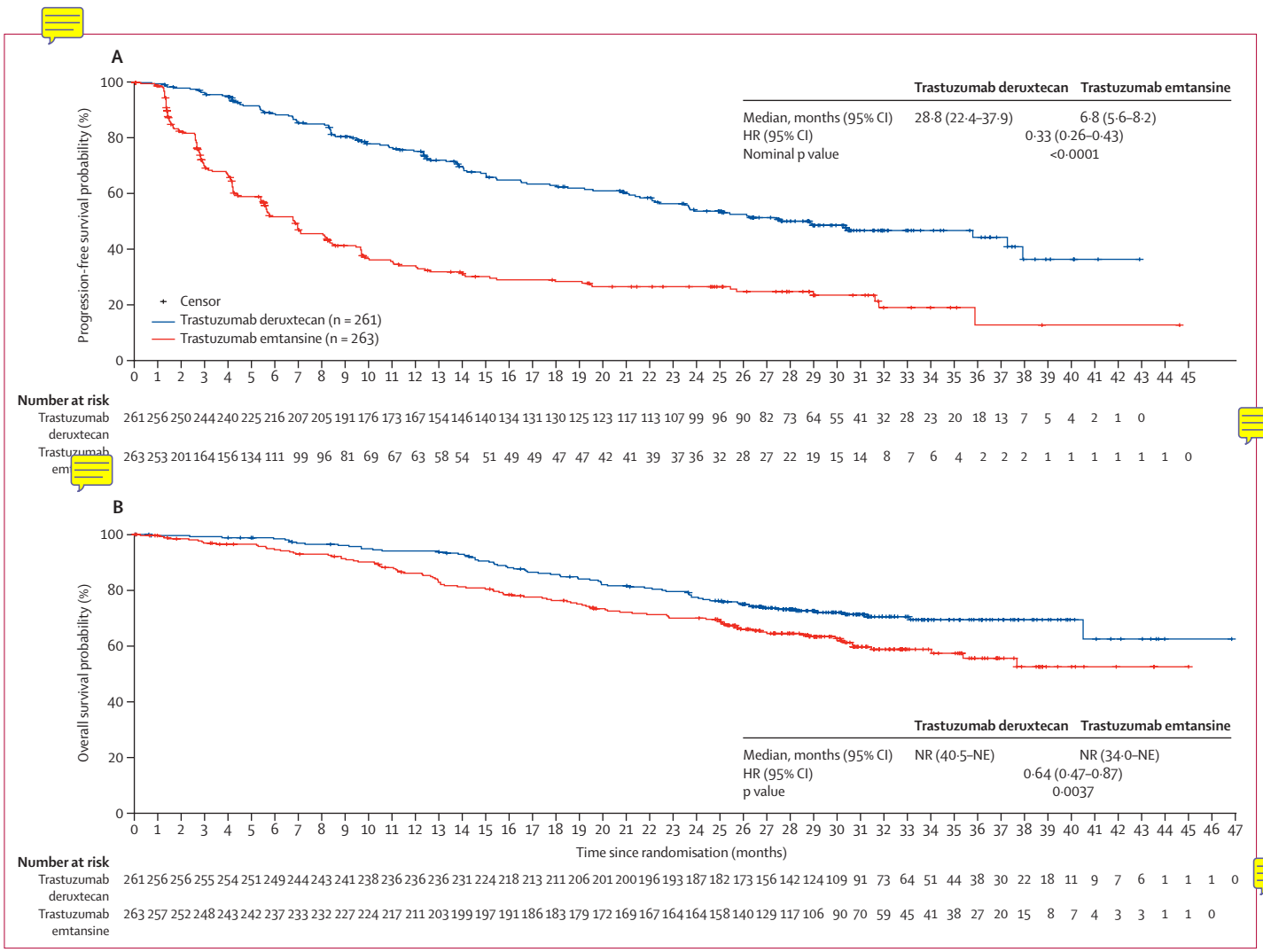

Figure 1: **Kaplan-Meier estimates of progression-free survival and overall survival**
(A) Progression-free survival by blinded independent central review. (B) Overall survival. Crosses indicate where data were censored, number of patients censored are not stated. HR=hazard ratio. NE=not estimable. NR=not reached.

p=0·0037; figure 1B; appendix p 8). Overall survival rate at 12 months was 94·1% (95% CI 90·4–96·4) in the trastuzumab deruxtecan group and 86·0% (81·1–89·8) in the trastuzumab emtansine group. Overall survival rate at 24 months was 77·4% (95% CI 71·7–82·1) in the trastuzumab deruxtecan group and 69·9% (63·7–75·2) in the trastuzumab emtansine group. In the overall survival analysis, 189 (72%) patients in the trastuzumab deruxtecan group and 166 (63%) patients in the trastuzumab emtansine group were censored; 170 (65%) patients in the trastuzumab deruxtecan group and 138 (52%) in the trastuzumab emtansine group were alive at the July 25, 2022 data cutoff. 19 (7%) patients in the trastuzumab deruxtecan group and 28 (11%) in the trastuzumab emtansine group were censored with reason of lost to follow-up; these patients were not known to have died, and the interval between their last contact date and analysis cutoff date was longer than the protocol-defined 3-month interval of survival follow-up plus 2 weeks.

A consistent overall survival benefit in favour of trastuzumab deruxtecan over trastuzumab emtansine was observed across the subgroups analysed (figure 2). A consistent progression-free survival benefit continued to be observed with trastuzumab deruxtecan over trastuzumab emtansine across the subgroups analysed (appendix p 15).

The confirmed objective response rate by blinded independent central review was 79% (205 patients; 95% CI 73·1–83·4) with trastuzumab deruxtecan and 35% (92 patients; 29·2–41·1) with trastuzumab emtansine (figure 3). In the trastuzumab deruxtecan group, 55 (21%) patients had a complete response and 150 (57%) patients had a partial response, compared with 25 (10%) patients with a complete response and 67 (25%) patients with a partial response in the

	Number of events		Median overall survival time, months (95% CI)		Hazard ratio for death (95% CI)
	Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
All patients	**72/261**	**97/263**	**NR (40·5–NE)**	**NR (34·0–NE)**	**0·64 (0·47–0·87)**
Hormone receptor status					
Positive	42/133	51/139	NR (40·5–NE)	37·7 (34·0–NE)	0·76 (0·50–1·14)
Negative	30/126	45/122	NR (NE–NE)	NR (28·5–NE)	0·55 (0·35–0·87)
Previous pertuzumab					
Yes	41/162	50/158	NR (40·5–NE)	NR (37·7–NE)	0·70 (0·46–1·06)
No	31/99	47/105	NR (NE–NE)	31·5 (22·7–NE)	0·59 (0·38–0·93)
Baseline visceral disease					
Yes	64/195	80/189	NR (40·5–NE)	35·4 (29·9–NE)	0·68 (0·49–0·95)
No	8/66	17/74	NR (NE–NE)	NR (NE–NE)	0·44 (0·19–1·02)
Previous lines of systemic therapy*					
<3	44/188	57/191	NR (40·5–NE)	NR (37·7–NE)	0·70 (0·47–1·04)
≥3	28/73	40/72	NR (27·4–NE)	22·8 (16·1–31·5)	0·55 (0·34–0·89)
Baseline brain metastases					
Yes	17/43	22/39	NR (23·8–NE)	25·1 (12·6–NE)	0·54 (0·29–1·03)
No	55/218	75/224	NR (40·5–NE)	NR (37·7–NE)	0·66 (0·47–0·94)

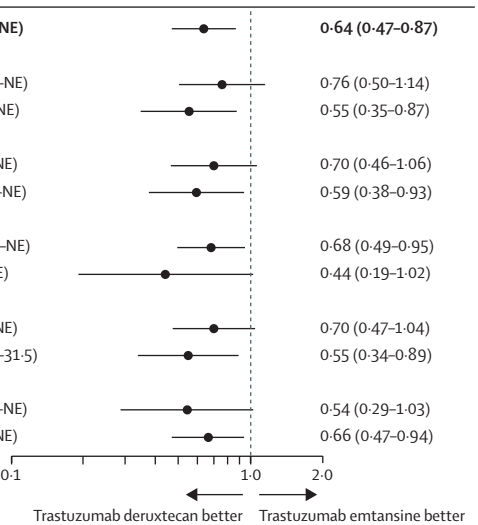

Figure 2: **Subgroup analysis of overall survival.**
NE=not evaluable. NR=not reached. *Previous lines of systemic therapy not including hormone therapy.

trastuzumab emtansine group. The objective response rate by investigator was similar to the objective response rate by blinded independent central review (appendix p 8). The median duration of response by blinded independent central review was 36·6 months (95% CI 22·4–not estimable) with trastuzumab deruxtecan and 23·8 months (12·6–34·7) with trastuzumab emtansine.

Median progression-free survival by investigator assessment was 29·1 months (95% CI 23·7–not estimable) in the trastuzumab deruxtecan group and 7·2 months (6·8–8·3) in the trastuzumab emtansine group (HR 0·30 [95% CI 0·24–0·38]; nominal p<0·0001; appendix pp 8, 16).

The median treatment duration was 18·2 months (IQR 9·0–29·4) with trastuzumab deruxtecan and 6·9 months (2·8–12·3) with trastuzumab emtansine. Safety was assessed in 257 patients in the trastuzumab deruxtecan group and 261 patients in the trastuzumab emtansine group. Any-grade treatment-emergent adverse events occurred in 256 (>99%) patients in the trastuzumab deruxtecan group and 249 (95%) patients in the trastuzumab emtansine group (appendix p 9). Most treatment-emergent adverse events of any grade were gastrointestinal and haematological in nature and included nausea, vomiting, alopecia, constipation, and anaemia (table 2). The numbers of patients with grade 3 or worse treatment-emergent adverse events and serious treatment-emergent adverse events were similar in the trastuzumab deruxtecan group and the trastuzumab emtansine group (grade 3 or worse: 145 [56%] *vs* 135 [52%]; serious: 65 [25%] *vs* 58 [22%]), whereas the exposure-adjusted incidence rates for grade 3 or worse treatment-emergent adverse events and serious treatment-emergent adverse events were lower in patients who received trastuzumab deruxtecan than those who received trastuzumab emtansine (grade 3 or worse: 0·36 *vs* 0·65; serious: 0·16 *vs* 0·28). The most common grade 3 or worse treatment-emergent adverse events in patients who received trastuzumab deruxtecan were neutrophil count decreased, anaemia, and platelet count decreased, whereas the most common grade 3 or worse treatment-emergent adverse events in patients who received trastuzumab emtansine were platelet count decreased, anaemia, aspartate aminotransferase increased, and alanine aminotransferase increased (table 2). The most common treatment-emergent adverse events (in ≥20% of patients) by worst toxicity grade are shown in the appendix (p 10).

Drug-related treatment-emergent adverse events led to discontinuation in 51 (20%) patients in the trastuzumab deruxtecan group and 17 (7%) patients in the trastuzumab emtansine group. The most common drug-related treatment-emergent adverse events that led to discontinuations with trastuzumab deruxtecan were pneumonitis (15 [6%] patients), interstitial lung disease (13 [5%]), and pneumonia (five [2%]), and with trastuzumab emtansine were platelet count decreased (four [2%]), pneumonitis (three [1%]), and thrombocytopenia (three [1%]). Drug-related treatment-emergent adverse events that led to dose reduction occurred in 65 (25%) patients in the trastuzumab

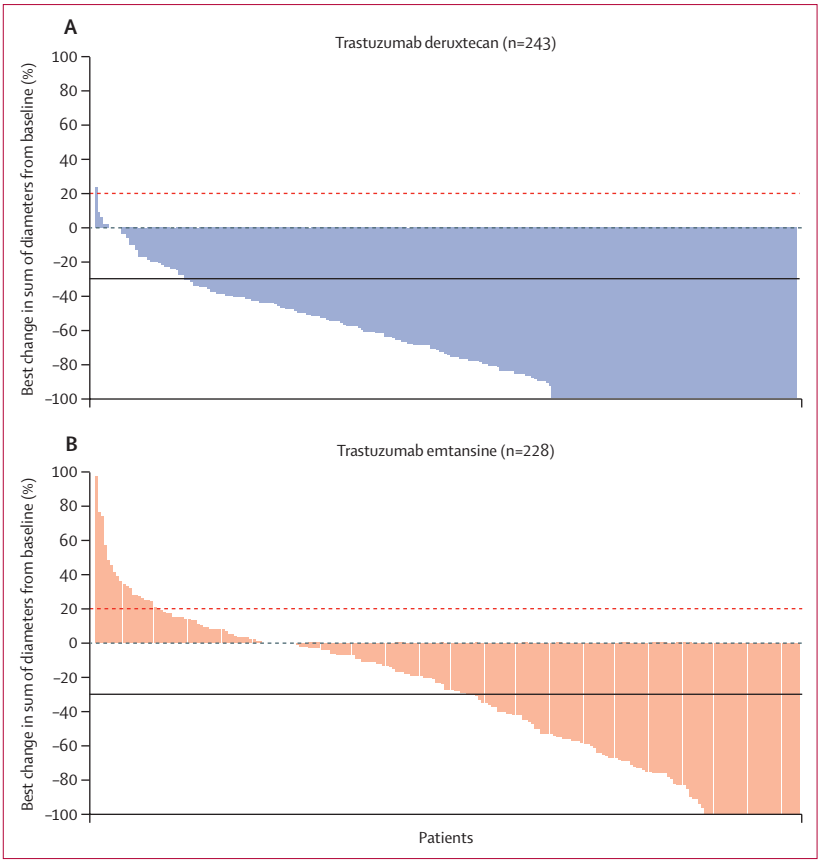

Figure 3: **Antitumour activity of trastuzumab deruxtecan (A) and trastuzumab emtansine (B)**
Baseline was defined as the last measurement taken before the randomisation date. For each patient, the best (minimum) percentage change from baseline in the sum of diameters for all target lesions was represented by a vertical line, plotted in order of greatest percentage increase to greatest percentage decrease. Only patients with measurable disease at baseline and at least one postbaseline assessment were included in the waterfall plots. The red line at 20% indicates progressive disease and the black line at −30% indicates partial response.

	Trastuzumab deruxtecan group (n=257)		Trastuzumab emtansine group (n=261)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system disorders				
Anaemia	95 (37%)	24 (9%)	51 (20%)	17 (7%)
Platelet count decreased*	64 (25%)	20 (8%)	114 (44%)	52 (20%)
White blood cell count decreased	60 (23%)	16 (6%)	16 (6%)	2 (<1%)
Gastrointestinal disorders				
Nausea	198 (77%)	18 (7%)	79 (30%)	1 (<1%)
Vomiting	133 (52%)	4 (2%)	28 (11%)	2 (<1%)
Constipation	96 (37%)	0	51 (20%)	0
Diarrhoea	83 (32%)	3 (1%)	21 (8%)	2 (<1%)
General disorders				
Fatigue	79 (31%)	15 (6%)	53 (20%)	2 (<1%)
Headache	61 (24%)	1 (<1%)	40 (15%)	0
Investigations				
Neutrophil count decreased†	79 (31%)	41 (16%)	30 (11%)	8 (3%)
Aspartate aminotransferase increased	72 (28%)	2 (<1%)	108 (41%)	14 (5%)
Alanine aminotransferase increased	59 (23%)	4 (2%)	83 (32%)	12 (5%)
Metabolism and nutrition disorders				
Decreased appetite	78 (30%)	4 (2%)	46 (18%)	1 (<1%)
Bodyweight decreased	58 (23%)	6 (2%)	23 (9%)	2 (<1%)
Skin and subcutaneous disorders				
Alopecia	102 (40%)	1 (<1%)‡	9 (3%)	0

Data are n (%). *Among the 64 patients in the trastuzumab deruxtecan group and the 114 patients in the trastuzumab emtansine group with platelet count decreased, the worst toxicity grade was grade 1 in 31 (12%) versus 20 (8%), grade 2 in 13 (5%) versus 42 (16%), grade 3 in 18 (7%) versus 45 (17%), grade 4 in two (<1%) versus seven (3%), and grade 5 in zero patients in both groups. †Among the 79 patients in the trastuzumab deruxtecan group and 30 patients in the trastuzumab emtansine group with neutrophil count decreased, the worst toxicity grade was grade 1 in 12 (5%) versus six (2%), grade 2 in 26 (10%) versus 16 (6%), grade 3 in 38 (15%) versus eight (3%), grade 4 in three (1%) versus zero, and grade 5 in zero patients in both groups. ‡Cases of alopecia reported during the study were graded on the basis of the clinical judgement of the investigator. One case of alopecia was categorised as grade 3 by the investigator despite grade 3 alopecia not being recognised by the National Cancer Institute Common Terminology criteria. The event outcome was reported as recovered by the investigator.

Table 2: **Most common any-grade treatment-emergent adverse events in 20% or more of patients by systemic organ class preferred term**

deruxtecan group and 38 (15%) patients in the trastuzumab emtansine group, and drug-related treatment-emergent adverse events that led to drug interruption occurred in 108 (42%) patients in the trastuzumab deruxtecan group and 45 (17%) patients in the trastuzumab emtansine group.

Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 39 (15%) patients treated with trastuzumab deruxtecan and eight (3%) patients treated with trastuzumab emtansine (appendix p 12). In the trastuzumab deruxtecan group, there were 11 (4%) grade 1, 26 (10%) grade 2, two (<1%) grade 3, and no grade 4 or grade 5 adverse events. In the trastuzumab emtansine group, there were four (2%) grade 1, three (1%) grade 2, one (<1%) grade 3, and no grade 4 or grade 5 adverse events. The median time to first onset of adjudicated drug-related interstitial lung disease or pneumonitis events was 8·1 months (IQR 4·2–15·0) in the trastuzumab deruxtecan group and 11·7 months (8·1–15·8) in the trastuzumab emtansine group.

In the exploratory analyses, the clinical benefit rate was 89% (233 patients; 95% CI 84·9–92·8) with trastuzumab deruxtecan and 46% (122 patients; 40·2–52·6) with trastuzumab emtansine. Median progression-free survival on the next line of therapy by investigator assessment was 40·5 months (95% CI 40·5–not estimable) with trastuzumab deruxtecan and 25·7 months (18·5–34·0) with trastuzumab emtansine

(HR 0·47 [95% CI 0·35–0·62). Of the patients who discontinued study treatment, 130 (71%) of 182 patients received anticancer systemic therapies in the trastuzumab deruxtecan group versus 191 (79%) of 243 patients in the trastuzumab emtansine group. The anticancer systemic therapies received in clinical practice after study treatment in the trastuzumab deruxtecan group and trastuzumab emtansine group included trastuzumab (43 [24%] patients *vs* 90 [37%] patients), trastuzumab deruxtecan (three [2%] *vs* 42 [17%]), trastuzumab emtansine (64 [35%] *vs* 24 [10%]), other anti-HER2 therapies (39 [21%] *vs* 88 [36%]), and other systemic therapies (75 [41%] *vs* 147 [60%]; appendix p 13).

Discussion

Trastuzumab deruxtecan showed a statistically significant improvement in overall survival versus trastuzumab emtansine, reducing the risk of death by approximately 36% in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab (with or without pertuzumab) and a taxane. A consistent overall survival benefit was observed across key subgroups analysed, including those with or without baseline brain metastases, previous treatment with pertuzumab, baseline visceral disease, and by hormone receptor status. The median progression-free survival (28·8 months *vs* 6·8 months) and confirmed objective response rate (79% *vs* 35%) observed with trastuzumab deruxtecan versus trastuzumab emtansine were also clinically meaningful and, to our knowledge, represent the longest reported median progression-free survival in this setting.[12,16] Progression-free survival benefit was observed with trastuzumab deruxtecan over trastuzumab emtansine across all subgroups analysed and was consistent with the interim analysis of progression-free survival of DESTINY-Breast03.[14]

Trastuzumab deruxtecan demonstrated a sustained benefit in progression-free survival and overall survival, with continued separation from trastuzumab emtansine in the Kaplan-Meier curves. Overall survival benefits can be challenging to demonstrate in clinical trials due to the long study follow-up required and subsequent treatments received after disease progression that might affect overall survival.[4,17] In the EMILIA trial, the median duration of follow-up was 19·1 months, with a median overall survival of 30·9 months with trastuzumab emtansine, whereas in DESTINY-Breast03, median duration of study follow-up was over 2 years in both treatment groups and the median overall survival was not reached.[12] The longer overall survival observed in both treatment groups of DESTINY-Breast03 might in part be due to the number of newer treatment options that became available after the EMILIA trial; however, cross-trial comparisons should be interpreted with caution given the differences in patient populations.[18]

The median progression-free survival observed in DESTINY-Breast03 with trastuzumab deruxtecan was longer than has been observed in other clinical trials in this setting and was approximately 4 times longer than with trastuzumab emtansine. Despite this study being in a more advanced treatment setting, a substantially longer median progression-free survival was observed with trastuzumab deruxtecan (28·8 months) than previously observed in the first-line setting in the CLEOPATRA and MARIANNE trials (18·5 months with pertuzumab, trastuzumab, and docetaxel and 14·1 months with trastuzumab emtansine); around 90% of patients in the CLEOPATRA trial had not previously been treated with trastuzumab.[2,19] However, given the differences in patient populations analysed and the changing landscape of HER2-positive metastatic breast cancer over time, these historical comparisons should be interpreted with caution. In the real-world second-line setting, median progression-free survival ranged from 8 months to 12 months in patients who received trastuzumab emtansine, lapatinib plus capecitabine, trastuzumab plus chemotherapy, trastuzumab plus endocrine therapy, and other treatments.[20]

The antitumour responses observed with trastuzumab deruxtecan exceeded trastuzumab emtansine and were highly durable, as shown by the higher objective response rate and clinical benefit rate, and longer median duration of response with trastuzumab deruxtecan versus trastuzumab emtansine. The robust responses were further evidenced by the complete response rate, wherein about one in five patients who received trastuzumab deruxtecan had a response; twice as many patients had a complete response with trastuzumab deruxtecan than with trastuzumab emtansine. The objective response rate observed in DESTINY-Breast03 numerically surpassed what was previously observed in phase 2/3 trials with trastuzumab emtansine in the first-line (objective response rate 64%), second-line (43–44%), and third-line (31%) settings.[12,21–23] The median duration of response was also longer than observed in the first-line setting in CLEOPATRA (20·2 months [95% CI 16·0–24·0]).[3] These results further support the clinically significant antitumour activity observed with trastuzumab deruxtecan and suggest that patients can undergo long periods of treatment with sustained disease control.

With longer follow-up, the safety profile of trastuzumab deruxtecan continues to be manageable and was consistent with findings from the interim analysis of progression-free survival in DESTINY-Breast03 and the known safety profile of trastuzumab deruxtecan.[11,14,24] Only six of 524 patients were randomly assigned but not treated, and were excluded from the safety analyses; therefore, the risk of potential bias was low. The majority of treatment-emergent adverse events with trastuzumab deruxtecan were gastrointestinal or haematological in nature. Nausea and vomiting were two of the most frequent treatment-emergent adverse events that occurred with trastuzumab deruxtecan treatment, with incidences similar to those that have been reported previously for trastuzumab

deruxtecan.[11] In the previous safety update analysis of DESTINY-Breast03 (data cutoff Sept 7, 2021), the rates of nausea and vomiting were highest in cycle 1 and lower in subsequent treatment cycles for trastuzumab deruxtecan.[25] Antiemetic prophylaxis recommendations were updated during the trial due to emerging data supporting the moderately emetogenic potential of trastuzumab deruxtecan.[11,26] Proper management of vomiting and nausea is important to improve patients' experience with trastuzumab deruxtecan, and should begin within the first treatment cycle and continue as needed throughout further treatment cycles.[27] Prophylactic antiemetic agents might reduce the rate of nausea and vomiting;[26] however, further investigations of the prevalence and incidence of nausea and vomiting over time are needed.

Drug-related treatment-emergent adverse events that led to drug discontinuation, dose reduction, or drug interruption were also higher in patients who received trastuzumab deruxtecan than trastuzumab emtansine. Optimising the management of adverse events, including nausea and vomiting, and those that led to drug discontinuations, dose reductions, and drug interruptions in patients treated with trastuzumab deruxtecan requires additional investigation. Despite the higher rates of some treatment-emergent adverse events observed with trastuzumab deruxtecan than trastuzumab emtansine, more patients remained on treatment with trastuzumab deruxtecan than trastuzumab emtansine, and the overall safety profile of trastuzumab deruxtecan was manageable.

Alopecia was the third most frequent treatment-emergent adverse event that occurred in patients who received trastuzumab deruxtecan and is a known adverse event with other systemic anticancer therapies. Rates of alopecia were found to be highest in cycle 1 and lower in later cycles for trastuzumab deruxtecan in the DESTINY-Breast03 safety update.[25] Although alopecia might be psychologically and socially impairing,[28] trastuzumab deruxtecan maintained or improved quality of life in DESTINY-Breast03 at the interim analysis of progression-free survival, further supporting the overall benefit of trastuzumab deruxtecan in patients with HER2-positive metastatic breast cancer.[29] However, there remains a need for effective therapies for alopecia induced by antibody–drug conjugates.

The median treatment duration was longer with trastuzumab deruxtecan versus trastuzumab emtansine, yet the overall rates of grade 3 or worse and serious treatment-emergent adverse events were similar between the trastuzumab deruxtecan and trastuzumab emtansine groups. Exposure-adjusted incidence rates were measured to account for differences in treatment duration between trastuzumab deruxtecan and trastuzumab emtansine and were lower in the trastuzumab deruxtecan group than the trastuzumab emtansine group, consistent with the earlier safety update analysis of DESTINY-Breast03.[25] These results reinforce the established favourable benefit–risk profile of trastuzumab deruxtecan over trastuzumab emtansine.

Interstitial lung disease or pneumonitis remains an identified risk in patients treated with trastuzumab deruxtecan. With longer follow-up and increased treatment exposure, the rate of adjudicated drug-related interstitial lung disease or pneumonitis cases with trastuzumab deruxtecan increased from 11% in the interim analysis of progression-free survival (data cutoff May 21, 2021) to 15% in the present second overall survival interim analysis (data cutoff July 25, 2022); however, all new cases were low grade (grade 1 or 2). The overall rates of adjudicated drug-related interstitial lung disease or pneumonitis were similar to other trials in patients with metastatic breast cancer who received trastuzumab deruxtecan, while the rates of grade 3 or worse interstitial lung disease or pneumonitis events were lower.[11,30] Implementation of strict management guidelines for interstitial lung disease or pneumonitis, and the less heavily pretreated patient population in the DESTINY-Breast03 trial, probably contributed to the lower incidence of high grade events observed.[31] Additionally, patients with a history of interstitial lung disease or pneumonitis that required steroids or suspected interstitial lung disease or pneumonitis at trial enrolment were excluded from the study. Interstitial lung disease or pneumonitis management guidelines recommend proactive monitoring of patients for signs and symptoms of the disease and immediate treatment when early symptoms are detected. The guidelines provide detailed information on trastuzumab deruxtecan dose reduction or discontinuation, which are dependent on the grade of interstitial lung disease or pneumonitis observed, and describe the optimal treatment of interstitial lung disease, including steroid dosing, duration, and timing of taper.[31] Overall management and monitoring of interstitial lung disease or pneumonitis are important in patients treated with trastuzumab deruxtecan.

The limitations in this trial include a higher enrolment of patients from Asia versus North America and Europe; however, in a subgroup analysis based on the interim analysis of progression-free survival, efficacy of trastuzumab deruxtecan in patients from Asia was similar to the overall population.[32] The single HR reported for the interim analysis of progression-free survival also has limitations, as the instantaneous HR has built-in selection bias and might change over time; therefore, the average HR depends on the follow-up time.[33] Furthermore, in this second overall survival interim analysis, median overall survival was not reached but future analyses might determine overall survival duration in DESTINY-Breast03.

The clinically meaningful and statistically significant overall survival benefit of trastuzumab deruxtecan versus trastuzumab emtansine and the longest reported median progression-free survival of trastuzumab deruxtecan to date observed in this trial support the use of trastuzumab

deruxtecan as the standard of care for second-line treatment of patients with HER2-positive metastatic breast cancer. Additional studies are underway to determine the efficacy and safety of trastuzumab deruxtecan in patients with HER2-positive metastatic breast cancer in the first-line setting (NCT04538742, DESTINY-Breast07; NCT04784715, DESTINY-Breast09) and in early-stage disease (NCT05113251, DESTINY-Breast11; NCT04622319, DESTINY-Breast05).

Contributors

All authors were involved in the drafting and revision of the manuscript for publication, in the interpretation of the data, and the approval of the final manuscript. S-AI, JWYC, YL, C-SH, JT, BX, and JCa were involved in data collection. S-AI, JWYC, JCa, SAs, AE, BX, GC, AE, and YL were involved in data analysis. SAH and YL accessed and verified the data in the manuscript. JCa, AE, SAs, and YL were involved in the conception or design of the study. SAH, WJ, VG, and JWYC contributed to the investigation of the study. SM, JMP-G, J-SF, JWYC, GC, VP, and SAn contributed to supervision of the study. J-SF contributed to the validation of the study. All authors had full access to all data in the study and provided final approval to submit the manuscript for publication.

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Data sharing

Deidentified individual participant data and applicable supporting clinical trial documents will, absent legal reasons to the contrary, be available upon request at the Vivli website (https://vivli.org). In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, will continue to protect the privacy of our clinical trial participants. Details on data-sharing criteria and the procedure for requesting access can be found at Vivli's Daiichi Sankyo web page (https://vivli.org/ourmember/daiichi-sankyo). For more information, see appendix p 7.

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