ORIGINAL ARTICLE

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

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ABSTRACT

BACKGROUND

Trastuzumab emtansine is the current standard treatment for patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer whose disease progresses after treatment with a combination of anti-HER2 antibodies and a taxane.

METHODS

We conducted a phase 3, multicenter, open-label, randomized trial to compare the efficacy and safety of trastuzumab deruxtecan (a HER2 antibody–drug conjugate) with those of trastuzumab emtansine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane. The primary end point was progression-free survival (as determined by blinded independent central review); secondary end points included overall survival, objective response, and safety.

RESULTS

Among 524 randomly assigned patients, the percentage of those who were alive without disease progression at 12 months was 75.8% (95% confidence interval [CI], 69.8 to 80.7) with trastuzumab deruxtecan and 34.1% (95% CI, 27.7 to 40.5) with trastuzumab emtansine (hazard ratio for progression or death from any cause, 0.28; 95% CI, 0.22 to 0.37; P<0.001). The percentage of patients who were alive at 12 months was 94.1% (95% CI, 90.3 to 96.4) with trastuzumab deruxtecan and 85.9% (95% CI, 80.9 to 89.7) with trastuzumab emtansine (hazard ratio for death, 0.55; 95% CI, 0.36 to 0.86; prespecified significance boundary not reached). An overall response (a complete or partial response) occurred in 79.7% (95% CI, 74.3 to 84.4) of the patients who received trastuzumab deruxtecan and in 34.2% (95% CI, 28.5 to 40.3) of those who received trastuzumab emtansine. The incidence of drug-related adverse events of any grade was 98.1% with trastuzumab deruxtecan and 86.6% with trastuzumab emtansine, and the incidence of drug-related adverse events of grade 3 or 4 was 45.1% and 39.8%, respectively. Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 10.5% of the patients in the trastuzumab deruxtecan group and in 1.9% of those in the trastuzumab emtansine group; none of these events were of grade 4 or 5.

CONCLUSIONS

Among patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane, the risk of disease progression or death was lower among those who received trastuzumab deruxtecan than among those who received trastuzumab emtansine. Treatment with trastuzumab deruxtecan was associated with interstitial lung disease and pneumonitis. (Funded by Daiichi Sankyo and AstraZeneca; DESTINY-Breast03 ClinicalTrials.gov number, NCT03529110.)

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*A list of investigators in the DESTINY-Breast03 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Breast cancer is the most commonly diagnosed and deadliest cancer among women worldwide.[1] Approximately 20% of women with breast cancer have tumors that overexpress human epidermal growth factor receptor 2 (HER2).[2] Although HER2-targeted therapies have improved disease outcomes, they are not curative for locally advanced or metastatic disease, and most patients will have disease progression.[3]

The standard treatment for newly diagnosed HER2-positive metastatic breast cancer is pertuzumab and trastuzumab (anti-HER2 antibodies) in combination with a taxane.[4-7] For patients whose disease progresses after this treatment, the standard second-line treatment is trastuzumab emtansine, as indicated by the results of the EMILIA trial,[7,8] in which treatment with trastuzumab emtansine resulted in a median progression-free survival of 9.6 months and a median overall survival of 30.9 months.[8]

Trastuzumab deruxtecan (also known as T-DXd and DS-8201) is an antibody–drug conjugate consisting of a humanized anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor payload through a tetrapeptide-based cleavable linker.[9,10] It is uniquely designed with a high drug-to-antibody ratio of approximately 8 that remains stable, thereby delivering a potent cytotoxic payload that is internalized and selectively cleaved by lysosomal enzymes that are overexpressed in cancer cells — a process that may reduce systemic toxic effects.[9,10] The highly potent payload is therefore released specifically within the HER2-overexpressing tumor cell to induce DNA damage, leading to apoptosis of the target tumor cell and neighboring tumor cells through bystander effect resulting from membrane permeability of the cytotoxic payload.[11]

The phase 2, single-group DESTINY-Breast01 study showed that trastuzumab deruxtecan has durable antitumor activity in heavily pretreated patients with HER2-positive metastatic breast cancer.[12] The results of that study led to the accelerated approval of trastuzumab deruxtecan for the treatment of patients with HER2-positive metastatic breast cancer who have received two or more previous anti-HER2 antibody–based regimens in the context of metastatic disease.[13-15] In that study, 60.9% (95% confidence interval [CI], 53.4 to 68.0) of the patients who received trastuzumab deruxtecan had an overall response (a complete or partial response), and the median progression-free survival was 16.4 months (95% CI, 12.7 to not reached); these results indicated that the efficacy of trastuzumab deruxtecan substantially exceeded that of currently available HER2-directed regimens and provided considerable support for a head-to-head trial comparing trastuzumab deruxtecan with trastuzumab emtansine.[8,12] Here, we report the results of the first interim analysis of the ongoing phase 3 DESTINY-Breast03 trial.

METHODS

TRIAL DESIGN

We conducted DESTINY-Breast03, a phase 3, multicenter, open-label, randomized, active-controlled trial, to evaluate the efficacy and safety of trastuzumab deruxtecan as compared with trastuzumab emtansine in patients with HER2-positive, unresectable or metastatic breast cancer that had progressed during or after treatment with trastuzumab and a taxane in the context of advanced or metastatic disease or that had progressed within 6 months after neoadjuvant or adjuvant treatment involving trastuzumab or a taxane. Patients were randomly assigned in a 1:1 ratio to receive trastuzumab deruxtecan or trastuzumab emtansine. Randomization was performed with the use of an interactive Web-based system and was stratified according to hormone-receptor status (positive or negative), previous treatment with pertuzumab, and history of visceral disease.

Patients with brain metastases were eligible for enrollment if they had clinically stable, previously treated brain metastases. Patients were excluded if they had brain metastases that were symptomatic or required treatment; if they had previously been treated with a HER2 antibody–drug conjugate, including trastuzumab emtansine, in the context of metastatic disease; if they had a history of noninfectious interstitial lung disease for which they had received glucocorticoids; or if they had suspected interstitial lung disease that could not be ruled out by imaging at screening. Additional details regarding the eligibility criteria are provided in the protocol and in the Supplementary Appendix, both of which are available with the full text of this article at NEJM.org. Trastuzumab deruxtecan was administered intravenously every 3 weeks at a dose of 5.4 mg per kilogram of body weight, and trastuzumab emtansine was administered intra-

venously every 3 weeks at a dose of 3.6 mg per kilogram.

TRIAL OVERSIGHT

The trial was funded by Daiichi Sankyo and AstraZeneca and designed by Daiichi Sankyo. The trial protocol was approved by the institutional review board at each site. 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 the patients provided written informed consent before participation. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol. Editorial and medical writing assistance with an earlier version of the manuscript was financially supported by Daiichi Sankyo.

END POINTS

The primary end point was progression-free survival, as determined by blinded independent central review. The key secondary end point was overall survival; other secondary end points included overall response (a complete or partial response, as determined by blinded independent central review and by investigator review), progression-free survival (as determined by investigator review), and safety.

SAFETY

Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 23.0, and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. An independent adjudication committee evaluated all potential cases of interstitial lung disease or pneumonitis; confirmed cases were treated according to protocol-specified guidelines (see the Supplementary Methods and Table S1 in the Supplementary Appendix).

STATISTICAL ANALYSIS

The planned sample was 500 patients. We performed the interim analysis of progression-free survival using the data cutoff date of May 21, 2021, after 245 events of disease progression (as determined by blinded independent central review) or death had occurred; the interim analysis was based on an information fraction of approximately 70%. The independent data and safety monitoring committee recommended that the trial be unblinded on July 30, 2021, after the prespecified efficacy boundary of superiority ($P<0.000204$) had been crossed. A stratified log-rank test with an overall two-sided significance level of 0.05 was used to compare the two treatment groups. If the analysis of the primary end point showed a significant difference between the two groups, overall survival was to be tested. The prespecified boundary for overall survival ($P<0.000265$) was based on the occurrence of 86 deaths. Additional details are provided in the statistical analysis plan, which is included with the protocol.

RESULTS

PATIENTS

Between July 20, 2018, and June 23, 2020, a total of 524 patients with HER2-positive metastatic breast cancer were enrolled at 169 centers in 15 countries. In total, 261 patients were randomly assigned to receive trastuzumab deruxtecan and 263 to receive trastuzumab emtansine (Fig. S1). Demographic and baseline disease characteristics were similar in the two groups and were largely representative of the overall HER2-positive breast cancer population (Table 1 and Table S2). A total of 130 patients (49.8%) in the trastuzumab deruxtecan group and 123 patients (46.8%) in the trastuzumab emtansine group had received one previous line of therapy (not including endocrine therapy) in the context of metastatic disease; 62.1% and 60.1% of the patients, respectively, had received pertuzumab therapy. Stable brain metastases were reported in 62 patients (23.8%) in the trastuzumab deruxtecan group and in 52 patients (19.8%) in the trastuzumab emtansine group. The median duration of follow-up was 16.2 months (range, 0 to 32.7) with trastuzumab deruxtecan and 15.3 months (range, 0 to 31.3) with trastuzumab emtansine.

EFFICACY

Treatment with trastuzumab deruxtecan showed a benefit over trastuzumab emtansine with respect to progression-free survival, as assessed by blinded independent central review. The median progression-free survival was not reached (95% CI, 18.5 to could not be estimated) in the trastuzumab deruxtecan group and was 6.8 months (95% CI, 5.6 to 8.2) in the trastuzumab emtan-

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Trastuzumab Deruxtecan (N=261)	Trastuzumab Emtansine (N=263)
Median age (range) — yr	54.3 (27.9–83.1)	54.2 (20.2–83.0)
Geographic region — no. (%)		
Asia	149 (57.1)	160 (60.8)
North America	17 (6.5)	17 (6.5)
Europe	54 (20.7)	50 (19.0)
Rest of world	41 (15.7)	36 (13.7)
Race — no. (%)†		
White	71 (27.2)	72 (27.4)
Black	10 (3.8)	9 (3.4)
Asian	152 (58.2)	162 (61.6)
Multiple	2 (0.8)	0
Other	26 (10.0)	20 (7.6)
Hispanic or Latinx ethnic group — no. (%)†		
Yes	29 (11.1)	29 (11.0)
No	203 (77.8)	209 (79.5)
Unknown	5 (1.9)	6 (2.3)
Data not collected	24 (9.2)	19 (7.2)
HER2 status — no. (%)‡		
3+	234 (89.7)	232 (88.2)
2+ with HER2 ISH-positive	25 (9.6)	30 (11.4)
1+	1 (0.4)	0
ECOG performance-status score — no. (%)§		
0	154 (59.0)	175 (66.5)
1	106 (40.6)	87 (33.1)
Hormone-receptor status — no. (%)		
Positive	131 (50.2)	134 (51.0)
Negative	130 (49.8)	129 (49.0)
Stable brain metastases — no. (%)¶	62 (23.8)	52 (19.8)
Visceral disease — no. (%)	184 (70.5)	185 (70.3)
Previous treatment for metastatic breast cancer — no. (%)	240 (92.0)	234 (89.0)
Lines of previous therapy in the context of metastatic disease‖		
Median number of lines (range)	1 (0–16)	2 (0–14)
Number of lines — no. (%)		
0	2 (0.8)	3 (1.1)
1	130 (49.8)	123 (46.8)
2	56 (21.5)	65 (24.7)
3	35 (13.4)	35 (13.3)
4	15 (5.7)	19 (7.2)
≥5	23 (8.8)	18 (6.8)
Previous cancer therapy — no. (%)**		
Trastuzumab	260 (99.6)	262 (99.6)
Pertuzumab	162 (62.1)	158 (60.1)

Table 1. (Continued.)

Characteristic	Trastuzumab Deruxtecan (N=261)	Trastuzumab Emtansine (N=263)
Taxane	260 (99.6)	262 (99.6)
Other anti-HER2 antibody	42 (16.1)	38 (14.4)
Anti-HER2 tyrosine kinase inhibitor	42 (16.1)	36 (13.7)
Other anti-HER2 antibody or antibody–drug conjugate	2 (0.8)	3 (1.1)
Hormone therapy	109 (41.8)	112 (42.6)
Other systemic therapy	260 (99.6)	262 (99.6)

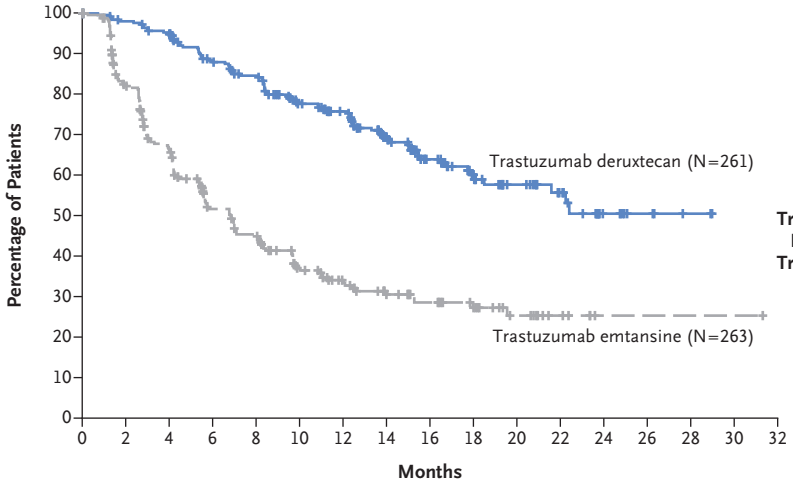
* Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the patient. Available options for race included American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or Other.
‡ Human epidermal growth factor receptor 2 (HER2) status was evaluated by immunohistochemical analysis at a central laboratory. HER2 ISH-positive refers to positive results on in situ hybridization. HER2 status was not able to be evaluated for 1 patient in each treatment group.
§ Eastern Cooperative Oncology Group (ECOG) performance status is scored on a 5-point scale, with higher scores indicating greater disability. The ECOG performance-status score was missing for 1 patient in each treatment group.
¶ Stable brain metastases were defined by a reported history of central nervous system metastases.
‖ Patients who had had rapid progression (i.e., progression that had occurred within 6 months after receipt of neoadjuvant or adjuvant therapy or within 12 months after receipt of a neoadjuvant or adjuvant pertuzumab-containing regimen) were considered to have had one line of previous therapy. Lines of previous therapy did not include endocrine therapy.
** All the patients received at least one previous cancer therapy. One patient who had previously received treatment with trastuzumab emtansine was enrolled in error in the trastuzumab deruxtecan group.

sine group. At 12 months, the percentage of patients who were alive without disease progression, as assessed by blinded independent central review, was 75.8% (95% CI, 69.8 to 80.7) with trastuzumab deruxtecan as compared with 34.1% (95% CI, 27.7 to 40.5) with trastuzumab emtansine; the hazard ratio for disease progression or death from any cause was 0.28 (95% CI, 0.22 to 0.37; P<0.001) (Fig. 1A). Investigator-assessed median progression-free survival was 25.1 months (95% CI, 22.1 to could not be estimated) with trastuzumab deruxtecan as compared with 7.2 months (95% CI, 6.8 to 8.3) with trastuzumab emtansine (hazard ratio, 0.26; 95% CI, 0.20 to 0.35; P<0.001) (Fig. S2). The subgroup analysis showed a benefit in progression-free survival (as assessed by blinded independent central review) with trastuzumab deruxtecan over trastuzumab emtansine across all the subgroups, including the subgroup defined according to the number of lines of previous treatment. The hazard ratio for disease progression or death from any cause was 0.33 among the patients who had received no lines or one line of previous therapy and 0.28 among those who had received two or more lines of previous therapy (Fig. 1B).

At the time of data cutoff for the interim analysis, the percentage of patients who were alive at 12 months was 94.1% (95% CI, 90.3 to 96.4) with trastuzumab deruxtecan and 85.9% (95% CI, 80.9 to 89.7) with trastuzumab emtansine (Fig. 2). The difference between the treatment groups did not reach the prespecified cutoff for significance (P<0.000265) (hazard ratio for death, 0.55; 95% CI, 0.36 to 0.86; P=0.007). A total of 33 of the 261 patients (12.6%) in the trastuzumab deruxtecan group and 53 of the 263 patients (20.2%) in the trastuzumab emtansine group had died as of the date of data cutoff.

An overall response occurred in 79.7% (95% CI, 74.3 to 84.4) of the patients who received trastuzumab deruxtecan as compared with 34.2% (95% CI, 28.5 to 40.3) of those who received trastuzumab emtansine (Fig. 3 and Table S3). A total of 42 patients (16.1%) in the trastuzumab deruxtecan group had a complete response as compared with 23 patients (8.7%) in the trastuzumab emtansine group. Progressive disease was the best overall response in 3 patients (1.1%) in the trastuzumab deruxtecan group and in 46 patients (17.5%) in the trastuzumab emtansine group; the percentage of patients who had disease control (defined as complete response, partial response, or stable disease) was 96.6% in the trastuzumab deruxtecan group and 76.8% in the trastuzumab emtansine group. After completion of the trial treatment, 78 patients in the trastuzumab deruxtecan group and 164 patients in the

A Progression-free Survival



	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

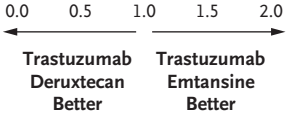
Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

No. at Risk

Trastuzumab deruxtecan	261	250	240	214	200	168	150	112	79	53	36	25	10	5	2	
Trastuzumab emtansine	263	200	155	108	93	65	51	37	29	21	12	6	1	1	1	0

B Progression-free Survival in Prespecified Subgroups

Subgroup	No. of Patients	No. of Events/No. of Patients		Median Progression-free Survival (95% CI)		Hazard Ratio for Disease Progression or Death (95% CI)
				mo		
		Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
All patients		87/261	158/263	NE (18.5–NE)	6.8 (5.6–8.2)	0.28 (0.22–0.37)
Hormone-receptor status						
Positive	272	46/133	84/139	22.4 (17.7–NE)	6.9 (4.2–9.8)	0.32 (0.22–0.46)
Negative	248	41/126	73/122	NE (18.0–NE)	6.8 (5.4–8.3)	0.30 (0.20–0.44)
Previous pertuzumab treatment						
Yes	320	57/162	98/158	NE (18.5–NE)	6.8 (5.4–8.3)	0.30 (0.22–0.43)
No	204	30/99	60/105	NE (16.5–NE)	7.0 (4.2–9.7)	0.30 (0.19–0.47)
Visceral disease						
Yes	384	72/195	123/189	22.2 (16.5–NE)	5.7 (4.2–7.0)	0.28 (0.21–0.38)
No	140	15/66	35/74	NE (NE–NE)	11.3 (6.8–NE)	0.32 (0.17–0.58)
Lines of previous therapy						
0 or 1	258	46/132	75/126	22.4 (17.9–NE)	8.0 (5.7–9.7)	0.33 (0.23–0.48)
≥2	266	41/129	83/137	NE (16.8–NE)	5.6 (4.2–7.1)	0.28 (0.19–0.41)
Stable brain metastases						
Yes	114	31/62	31/52	15.0 (12.6–22.2)	5.7 (2.9–7.1)	0.38 (0.23–0.64)
No	410	56/199	127/211	NE (22.4–NE)	7.0 (5.5–9.7)	0.27 (0.19–0.37)



trastuzumab emtansine group received a new systemic anticancer treatment (Table S4). A total of 43 patients who had received trastuzumab deruxtecan during the trial began treatment with commercially available trastuzumab emtansine after completing the trial treatment, and 30 patients who had received trastuzumab emtansine during the trial began treatment with commercially available trastuzumab deruxtecan after completing the trial treatment.

SAFETY

The median duration of treatment was 14.3 months (range, 0.7 to 29.8) with trastuzumab deruxte-

Figure 1 (facing page). Kaplan–Meier Analysis and Subgroup Analysis of Progression-free Survival.

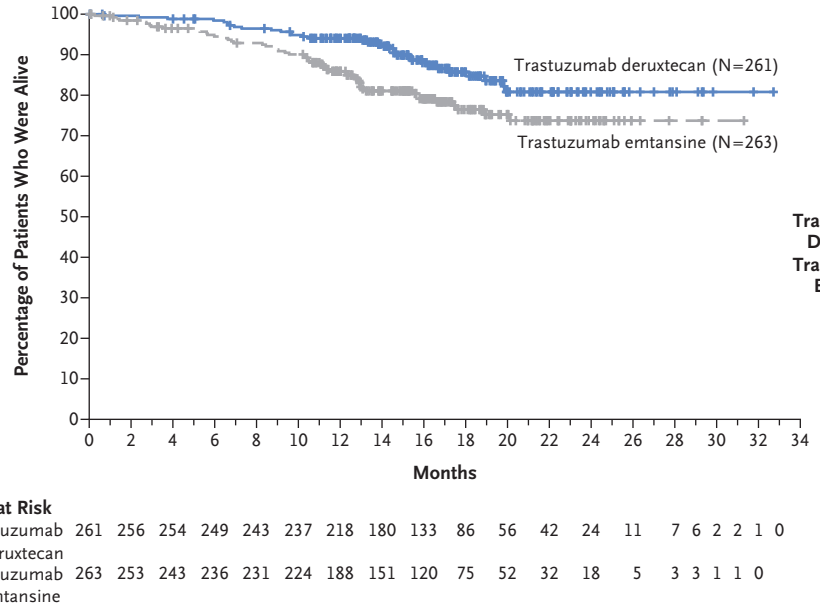
Panel A shows the Kaplan–Meier estimates of progression-free survival, as assessed by blinded independent central review, in the intention-to-treat population (all randomly assigned patients), stratified according to hormone-receptor status, previous treatment with pertuzumab, and history of visceral disease. The median progression-free survival was not reached in the trastuzumab deruxtecan group and was 6.8 months in the trastuzumab emtansine group; the estimated percentage of patients who were alive without progression at 12 months was 75.8% (95% CI, 69.8 to 80.7) and 34.1% (95% CI, 27.7 to 40.5), respectively. The tick marks indicate censored data. Panel B shows hazard ratios and 95% confidence intervals for progression-free survival in subgroups defined according to hormone-receptor status, previous treatment with pertuzumab, baseline visceral disease, lines of previous therapy, and stable brain metastases (as defined by documentation of central nervous system metastases in the patient's medical history). The progression-free survival benefit of trastuzumab deruxtecan over trastuzumab emtansine was consistent across all the subgroups. Patients who had had rapid progression (i.e., progression that had occurred within 6 months after receipt of neoadjuvant or adjuvant therapy or within 12 months after receipt of a neoadjuvant or adjuvant pertuzumab-containing regimen) were considered to have had one line of previous therapy. Lines of previous therapy did not include endocrine therapy. NE denotes could not be estimated, and NR not reached.

can and 6.9 months (range, 0.7 to 25.1) with trastuzumab emtansine. The incidence of adverse events after the start of treatment was similar in the trastuzumab deruxtecan group and the trastuzumab emtansine group (99.6% and 95.4%, respectively) (Table S5). Serious adverse events were reported in 49 of 257 patients (19.1%) in the trastuzumab deruxtecan group and in 47 of 261 patients (18.0%) in the trastuzumab emtansine group. The incidence of adverse events that resulted in the discontinuation of the trial treatment was higher with trastuzumab deruxtecan than with trastuzumab emtansine (13.6% vs. 7.3%). The incidence of adverse events of grade 3 or higher was similar in the two groups (52.1% and 48.3%, respectively).

The incidence of drug-related adverse events of any grade was 98.1% with trastuzumab deruxtecan and 86.6% with trastuzumab emtansine, and the incidence of drug-related adverse events of grade 3 or 4 was 45.1% and 39.8%, respectively. The most common drug-related adverse events of any grade that were reported in the trastuzumab deruxtecan group were nausea (in 72.8% of the patients), fatigue (in 44.7%), and vomiting (in 44.0%); the incidence of each of these events was lower in the trastuzumab emtansine group (27.6%, 29.5%, and 5.7%, respectively) (Table 2). Drug-related alopecia of any grade occurred in 36.2% of the patients in the trastuzumab deruxtecan group and in 2.3% of those in the trastuzumab emtansine group. The most common drug-related adverse events of grade 3 or 4 that occurred after the start of treatment in the trastuzumab deruxtecan group were neutropenia (in 19.1%), thrombocytopenia (in 7.0%), leukopenia (in 6.6%), and nausea (in 6.6%); these events were reported in 3.1%, 24.9%, 0.4%, and 0.4%, respectively, of the patients in the trastuzumab emtansine group. No drug-related adverse events of grade 5 were reported with either treatment.

The independent adjudication committee that evaluated all potential cases of interstitial lung disease or pneumonitis identified drug-related events in 27 patients (10.5%) who received trastuzumab deruxtecan (7 patients had grade 1 events, 18 had grade 2 events, and 2 had grade 3 events) and in 5 patients (1.9%) who received trastuzumab emtansine (4 had grade 1 events and 1 had a grade 2 event) (Table 2). No such events of grade 4 or 5 occurred in either treatment group, and most of the patients recovered by the time of the data cutoff (Table S6). In the trastuzumab deruxtecan group, the median time to onset of interstitial lung disease or pneumonitis was 168 days (range, 33 to 507), and 3 patients had more than one event, as assessed by the adjudication committee (1 patient had two grade 2 events, 1 patient had three grade 2 events, and 1 patient had one grade 1 event and one grade 2 event). Discontinuation of the trial treatment owing to interstitial lung disease or pneumonitis occurred in 21 patients (8.2%) who received trastuzumab deruxtecan and in 3 patients (1.1%) who received trastuzumab emtansine.

A decrease in ejection fraction was reported in 6 patients (2.3%) in the trastuzumab deruxtecan group and in 1 patient (0.4%) in the trastuzumab emtansine group. All the events of ejection fraction decrease were reported as grade 2, and all resolved with no action taken, with the exception of the decrease in 1 patient in the trastuzumab deruxtecan group whose ejection fraction remained compromised. Left ventricular dysfunction (grade 1; resolved with no action taken) was reported in 1 additional patient who received trastuzumab deruxtecan. All the patients



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55 (95% CI, 0.36–0.86)
P=0.007

No. at Risk																	
Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	1	0

Figure 2. First Interim Analysis of Overall Survival.

Shown are Kaplan–Meier estimates of overall survival at 12 months in the intention-to-treat population, stratified according to hormone-receptor status, previous treatment with pertuzumab, and history of visceral disease. At the time of the data cutoff date of May 21, 2021, a total of 86 deaths had occurred; this analysis was performed on the basis of a progression-free survival benefit with trastuzumab deruxtecan. The median overall survival was not reached in either treatment group (hazard ratio, 0.55; 95% CI, 0.36 to 0.86; P=0.007). The percentage of patients who were alive at 12 months was 94.1% (95% CI, 90.3 to 96.4) with trastuzumab deruxtecan and 85.9% (95% CI, 80.9 to 89.7) with trastuzumab emtansine. The tick marks indicate censored data.

who had a decrease in ejection fraction or had left ventricular dysfunction were asymptomatic, with no reported cardiac failure.

DISCUSSION

Among patients with HER2-positive metastatic breast cancer, the risk of disease progression or death was lower among those who received trastuzumab deruxtecan than among those who received trastuzumab emtansine. The duration of progression-free survival, as assessed by blinded independent central review, was significantly longer with trastuzumab deruxtecan than with trastuzumab emtansine. At 12 months, 75.8% of the patients in the trastuzumab deruxtecan group were alive without progression as compared with 34.1% of those in the trastuzumab emtansine group (hazard ratio, 0.28; P<0.001). In addition, the median progression-free survival according to investigator assessment indicated a benefit of approximately 1.5 years. The benefit was consistent across key subgroups, including those based on hormone-receptor status, previous pertuzumab treatment, history of visceral disease, presence or absence of stable brain metastases, and number of lines of previous therapy. Across all the evaluations of progression-free survival (central review, investigator review, and subgroup analysis), the hazard ratios indicate a reduction of approximately 70% in the risk of disease progression or death with trastuzumab deruxtecan as compared with trastuzumab emtansine.

The estimated median progression-free survival of 6.8 months (as assessed by central review) with trastuzumab emtansine in this trial is lower than that reported previously in the EMILIA trial, in which patients were enrolled from 2009 through 2011. In the EMILIA trial, the median progression-free survival was 9.6 months with trastuzumab emtansine and 6.4 months with lapatinib plus capecitabine (hazard ratio for progression or death, 0.65; 95% CI, 0.55 to 0.77; P<0.001), findings that led to the approval of trastuzumab emtansine for the treatment of patients who had previously been treated with trastuzumab and a taxane in the context of

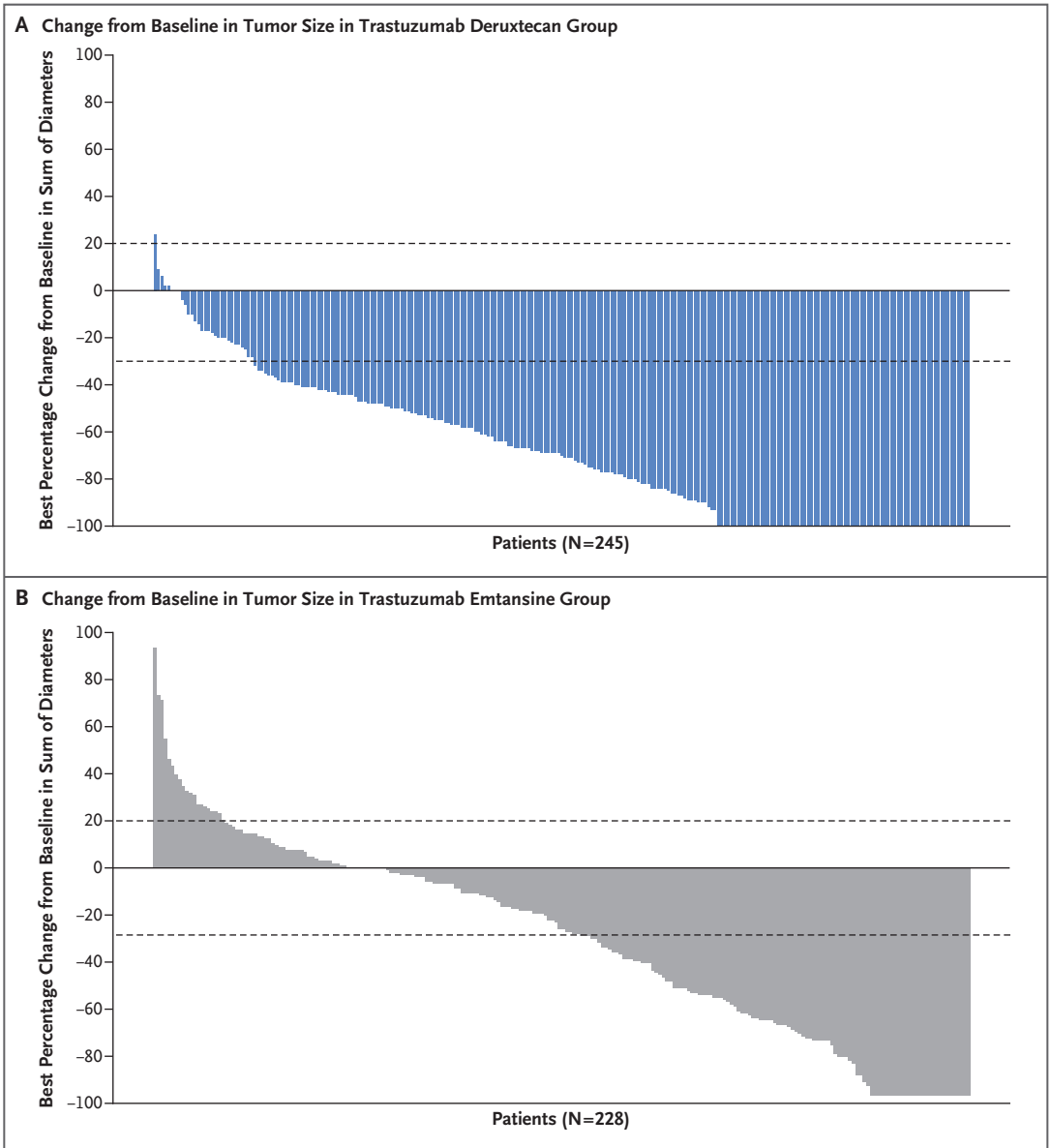


Figure 3. Antitumor Activity.

Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumors in patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review were available: 245 of 261 patients who received trastuzumab deruxtecan (Panel A) and 228 of 263 patients who received trastuzumab emtansine (Panel B). The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression, and the lower dashed line indicates a 30% decrease in tumor size (partial response).

metastatic disease.[8] Differences in the observed efficacy of trastuzumab emtansine between the current trial and the EMILIA trial may result from differences in previous pertuzumab use. Most of the patients in the current trial had previously received pertuzumab treatment. At the time of the EMILIA trial, pertuzumab was an investigational drug.[16] The shorter duration of progression-free survival observed here with trastuzumab emtansine is consistent with that reported in more recent studies that evaluated the efficacy of trastuzumab emtansine after first-line treatment with pertuzumab and trastuzumab in combination with a taxane for metastatic disease, including the KATE2 trial and studies in real-world settings, in which the median progres-

Table 2. Most Common Drug-Related Adverse Events and Adjudicated Drug-Related Interstitial Lung Disease or Pneumonitis.

Event	Trastuzumab Deruxtecan (N=257)		Trastuzumab Emtansine (N=261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Most common drug-related adverse events				
Blood and lymphatic system disorders				
Neutropenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue¶	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
Aspartate aminotransferase increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
Alanine aminotransferase increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia‖	93 (36.2)	1 (0.4)	6 (2.3)	0
Adjudicated drug-related interstitial lung disease or pneumonitis**	27 (10.5)	2 (0.8)	5 (1.9)	0

* This category includes the preferred terms neutrophil count decreased and neutropenia.
† This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased.
‡ This category includes the preferred terms white-cell count decreased and leukopenia.
§ This category includes the preferred terms platelet count decreased and thrombocytopenia.
¶ This category includes the preferred terms fatigue, asthenia, and malaise.
‖ Alopecia of grade 1 occurred in 26.5% of the patients treated with trastuzumab deruxtecan and in 2.3% of the patients treated with trastuzumab emtansine; alopecia of grade 2 occurred in 9.3% of the patients treated with trastuzumab deruxtecan. One case of alopecia in the trastuzumab deruxtecan group was categorized as grade 3 by the investigator despite the fact that alopecia of grade 3 is not included in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0; the outcome of this event was reported by the investigator as resolved.
** Among the 27 patients in the trastuzumab deruxtecan group who had adjudicated drug-related interstitial lung disease or pneumonitis, 7 (2.7%) had grade 1 events, 18 (7.0%) had grade 2 events, and 2 (0.8%) had grade 3 events. Among the 5 patients in the trastuzumab emtansine group, 4 (1.5%) had grade 1 events and 1 (0.4%) had a grade 2 event.

sion-free survival ranged from 3.0 to 6.8 months.[17-20] In this trial, the percentage of patients who were alive without progression did not differ substantially between the subgroup of patients in the trastuzumab emtansine group who had received previous pertuzumab therapy and those who had not received such therapy; however, stratification did not distinguish between the use of pertuzumab as adjuvant therapy and its use as treatment for metastatic disease. In addition, this trial included patients from countries in which trastuzumab emtansine was not yet readily available, a circumstance that led to the inclusion of patients who were receiving later lines of therapy and who still met inclusion criteria. It is notable that, when stratified according to the number of lines

of previous therapy, the median progression-free survival with trastuzumab emtansine was considerably longer among patients who had received no lines or one line of previous therapy than among those who had received two or more lines of previous therapy (8.0 and 5.6 months, respectively).

A trend in overall survival showing a benefit with trastuzumab deruxtecan relative to trastuzumab emtansine is evidenced by an early and sustained separation of the survival curves. The P value did not cross the prespecified threshold of statistical significance; 407 patients are still being followed.

Almost all the patients (96.6%) had disease control with trastuzumab deruxtecan. A complete response was observed in almost twice as many patients in the trastuzumab deruxtecan group as in the trastuzumab emtansine group (16.1% vs. 8.7%). Among the patients who received trastuzumab deruxtecan, only 1.1% had progressive disease as the best overall response as compared with 17.5% who received trastuzumab emtansine. Responses with trastuzumab deruxtecan were usually rapid, with the median time to response corresponding to the first tumor scan scheduled after beginning treatment.

The incidence of adverse events after the start of treatment was similar in the trastuzumab deruxtecan group and the trastuzumab emtansine group (99.6% and 95.4%, respectively). The safety profile of trastuzumab deruxtecan was similar to that observed in the DESTINY-Breast01 trial. However, the incidence of interstitial lung disease and pneumonitis was numerically lower in the current trial than in other clinical trials of trastuzumab deruxtecan,[12,21,22] with no events of grade 4 or 5 reported. This difference in results may be explained by the fact that the patients in this trial received an earlier line of therapy and the fact that there is increased recognition of these adverse events. In the DESTINY-Breast01 trial, the occurrence of interstitial lung disease or pneumonitis was identified as an important risk associated with trastuzumab deruxtecan. As knowledge was evolving that interstitial lung disease and pneumonitis were events of special interest, management guidelines for interstitial lung disease and pneumonitis were incorporated into the DESTINY clinical trial program. Most of the drug-related events of interstitial lung disease or pneumonitis in this trial were of grade 1 or 2, with only two events reported as grade 3.

Management guidelines for interstitial lung disease and pneumonitis recommend monitoring closely for signs and symptoms to identify potential events and actively managing care with dose modification, treatment, and mandatory discontinuation of trastuzumab deruxtecan after the occurrence of any interstitial lung disease or pneumonitis events of grade 2 or higher. Discontinuations of the trial treatment because of interstitial lung disease or pneumonitis accounted for more than half the drug-related discontinuations resulting from adverse events in the trastuzumab deruxtecan group. Aside from interstitial lung disease and pneumonitis, the percentage of patients who discontinued the trial treatment because of an adverse event was similar in the two treatment groups.

These data showed the superiority of trastuzumab deruxtecan over trastuzumab emtansine in reducing the risk of progression or death in patients with HER2-positive metastatic breast cancer who had been previously treated with trastuzumab and a taxane. Treatment with trastuzumab deruxtecan was associated with adjudicated interstitial lung disease and pneumonitis, but the incidence of these events was numerically lower in this trial than in previous trials; careful monitoring is essential in its clinical use. Trastuzumab deruxtecan is an effective new treatment for patients with HER2-positive metastatic breast cancer who have been previously treated with trastuzumab and a taxane, as well as with pertuzumab when available.[23]

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APPENDIX

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