ORIGINAL ARTICLE

Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer

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ABSTRACT

BACKGROUND

Outcomes in patients with hormone receptor–positive metastatic breast cancer worsen after one or more lines of endocrine-based therapy. Trastuzumab deruxtecan has shown efficacy in patients with metastatic breast cancer with low expression of human epidermal growth factor receptor 2 (HER2) after previous chemotherapy.

METHODS

We conducted a phase 3, multicenter, open-label trial involving patients with hormone receptor–positive metastatic breast cancer with low HER2 expression (a score of 1+ or 2+ on immunohistochemical [IHC] analysis and negative results on in situ hybridization) or ultralow HER2 expression (IHC 0 with membrane staining) who had received one or more lines of endocrine-based therapy and no previous chemotherapy for metastatic breast cancer. Patients were randomly assigned in a 1:1 ratio to receive trastuzumab deruxtecan or the physician's choice of chemotherapy. The primary end point was progression-free survival (according to blinded independent central review) among the patients with HER2-low disease. Secondary end points included progression-free survival among all the patients who had undergone randomization, overall survival, and safety.

RESULTS

Of the 866 patients who underwent randomization, 713 had HER2-low disease, and 153 had HER2-ultralow disease. Among the patients with HER2-low disease, the median progression-free survival was 13.2 months (95% confidence interval [CI], 11.4 to 15.2) in the trastuzumab deruxtecan group and 8.1 months (95% CI, 7.0 to 9.0) in the chemotherapy group (hazard ratio for disease progression or death, 0.62; 95% CI, 0.51 to 0.74; P<0.001); the results were consistent in the exploratory HER2-ultralow population. Data for overall survival were immature. Adverse events of grade 3 or higher occurred in 52.8% of the patients in the trastuzumab deruxtecan group and in 44.4% of those in the chemotherapy group. Adjudicated interstitial lung disease or pneumonitis occurred in 49 patients (11.3%; three events were grade 5 in severity) and in 1 patient (0.2%; grade 2), respectively.

CONCLUSIONS

Among patients with hormone receptor–positive, HER2-low or HER2-ultralow metastatic breast cancer who had received one or more lines of endocrine-based therapy, treatment with trastuzumab deruxtecan resulted in longer progression-free survival than chemotherapy. No new safety signals were identified. (Funded by AstraZeneca and Daiichi Sankyo; DESTINY-Breast06 ClinicalTrials.gov number, NCT04494425.)

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*A list of investigators in the DESTINY-Breast06 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer is the most common subtype of breast cancer, accounting for nearly 70% of all cases.[1] A spectrum of HER2 expression exists among breast cancers that are categorized as "HER2-negative," defined as a score on immunohistochemical (IHC) analysis of 0, 1+, or 2+ and negative results on in situ hybridization (ISH).[2] Cancers with an IHC score of 1+ or 2+ with negative results on ISH are currently defined as "HER2-low." The subdivision of IHC 0 into two categories, defined according to membrane staining that is faint and is seen in 10% of tumor cells or fewer ("HER2-ultralow") or no observable staining, has recently been proposed.[2,3]

Currently, the standard treatment for patients with hormone receptor–positive, HER2-negative metastatic breast cancer is an endocrine therapy–based regimen, usually with a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor as first-line treatment, with suggested consideration of additional targeted therapies in the second line of treatment.[4-6] Despite good outcomes with first-line endocrine therapy plus CDK4/6 inhibitors,[7-9] the most appropriate sequence of therapies after disease progression remains unclear. The benefit of endocrine therapy–based regimens declines after exposure to CDK4/6 inhibitors.[10,11] With respect to progression that occurs after multiple lines of endocrine therapy or rapid progression that occurs with adjuvant or first-line endocrine therapy, conventional single-agent chemotherapy shows limited efficacy in later lines of treatment (median progression-free survival, 6 to 7 months after ≤1 previous chemotherapy regimen).[12-14]

Trastuzumab deruxtecan is an antibody–drug conjugate composed of a humanized immunoglobulin G1 monoclonal antibody that specifically targets HER2, a tetrapeptide-based cleavable linker, and a potent topoisomerase I inhibitor payload.[15,16] In the DESTINY-Breast04 trial, trastuzumab deruxtecan showed statistically significant and clinically meaningful benefits with respect to progression-free survival and overall survival as compared with standard chemotherapy among patients with HER2-low metastatic breast cancer (with hormone receptor–positive or hormone receptor–negative disease).[17] These results led to the approval of trastuzumab deruxtecan for patients with unresectable or metastatic HER2-low tumors who have previously received chemotherapy for metastatic disease or have had disease recurrence during adjuvant chemotherapy or within 6 months after completing adjuvant chemotherapy.[18,19]

Given that additional patients may benefit from HER2-directed treatment in earlier lines,[20] the DESTINY-Breast06 trial sought to evaluate the efficacy and safety of trastuzumab deruxtecan as compared with the physician's choice of chemotherapy (single-agent capecitabine, nanoparticle albumin-bound [nab]–paclitaxel, or paclitaxel) in patients with hormone receptor–positive, HER2-low or HER2-ultralow metastatic breast cancer who had received one or more endocrine-based therapies but no previous chemotherapy for metastatic disease.

METHODS

TRIAL DESIGN AND TREATMENT

We conducted a phase 3, multicenter, open-label, randomized trial involving patients with hormone receptor–positive, HER2-low or HER2-ultralow metastatic breast cancer. The primary efficacy analysis was performed in the HER2-low population, which included the patients with low HER2 expression (IHC 1+ or IHC 2+ and negative results on ISH). The secondary efficacy analysis was performed in the intention-to-treat population, which included all the patients who underwent randomization (patients in the HER2-low population and patients in the prespecified exploratory HER2-ultralow population). Ultralow HER2 expression was defined as IHC 0 with membrane staining (defined here as IHC >0 and <1+). HER2 expression for the HER2-ultralow population was centrally confirmed on the basis of analysis of a specimen obtained after metastatic disease had occurred. Additional information is provided in the Supplementary Methods section and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Patients were eligible if they had had disease progression after receiving at least two previous lines of endocrine-based therapy for metastatic disease. Patients who had received one previous line of endocrine therapy for metastatic disease were also eligible if they had had disease recurrence within 24 months after initiation of adjuvant endocrine therapy or if they had had disease progression within 6 months after initiation of

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first-line endocrine therapy plus a CDK4/6 inhibitor for the treatment of metastatic disease. Eligible patients could not have had chemotherapy for advanced or metastatic disease. Additional details regarding eligibility criteria are available in the Supplementary Methods section in the Supplementary Appendix.

Randomization was performed with the use of interactive-response technology. Patients were randomly assigned in a 1:1 ratio to receive trastuzumab deruxtecan (5.4 mg per kilogram of body weight intravenously) once every 3 weeks or to receive the physician's choice of single-agent chemotherapy (capecitabine, nab-paclitaxel, or paclitaxel) until the occurrence of disease progression (according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1)[21] or unacceptable toxic effects. The chemotherapy regimens were as follows: capecitabine (1250 or 1000 mg per square meter of body-surface area) orally twice daily for 2 weeks, followed by a 1-week rest period, in 3-week cycles; nab-paclitaxel (100 mg per square meter), administered intravenously every week for 3 weeks, followed by a 1-week rest period, in 4-week cycles; and paclitaxel (80 mg per square meter), administered intravenously every week in 3-week cycles. Patients were stratified according to previous CDK4/6 inhibitor use (yes or no), HER2 expression (IHC 1+, IHC 2+ and ISH-negative, or IHC 0 with membrane staining), and previous taxane use (yes or no) for the treatment of nonmetastatic disease.

TRIAL OVERSIGHT

The trial was funded by AstraZeneca and Daiichi Sankyo and was designed by AstraZeneca in collaboration with Daiichi Sankyo and the cochairs of the trial steering committee. The institutional review board or ethics committee at each investigational site approved the trial before initiation. The trial was performed in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations on the conduct of clinical research. An independent data monitoring committee monitored efficacy and patient safety. All the patients provided written informed consent. The authors had full access to the trial data and vouch for the completeness and accuracy of the data and the adherence of the trial to the protocol (available at NEJM.org). The authors, steering committee members, and the trial sponsor (AstraZeneca) and cosponsor (Daiichi Sankyo) guided the manuscript development with editorial assistance from professional medical writers funded by AstraZeneca. The first draft of the manuscript was prepared in accordance with Good Publication Practice guidelines by a professional writer in collaboration with representatives of AstraZeneca and Daiichi Sankyo and the authors. All drafts of the manuscript were reviewed and approved by the authors.

END POINTS

The primary end point was progression-free survival in the HER2-low population as determined by blinded independent central review according to RECIST, version 1.1.[21] Key secondary end points were progression-free survival in the intention-to-treat population according to blinded independent central review and overall survival in the HER2-low and intention-to-treat populations. Other secondary end points included progression-free survival in the HER2-low population according to investigator assessment, objective response and duration of response in the HER2-low and intention-to-treat populations, and safety.

SAFETY

Adverse events that occurred during the treatment period were coded using the preferred terms of the *Medical Dictionary for Regulatory Activities*, version 6.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Potential cases of interstitial lung disease and pneumonitis were evaluated by an independent adjudication committee. Guidelines for the management of pulmonary toxic effects were described previously.[17] Additional details are provided in the Supplementary Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

A stratified log-rank test was used to compare progression-free survival between the treatment groups. We determined that death or disease progression in approximately 456 patients would provide at least 95% power to detect a hazard ratio of 0.55 in the HER2-low population for the comparison of trastuzumab deruxtecan with chemotherapy, at a two-sided alpha level of 5%. To control the family-wise type 1 error rate at 5% in terms of the primary and key secondary end points, a multiple testing procedure with a gatekeeping

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strategy was used. The efficacy analyses included all the patients who had undergone randomization. The hazard ratios and corresponding 95% confidence intervals for progression-free survival and overall survival were estimated with the use of a stratified Cox regression analysis. The analyses in patients with HER2-ultralow expression were exploratory; as such, no formal testing of

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (All Populations).*

Characteristic	HER2-Low Population		Intention-to-Treat Population		HER2-Ultralow Population	
	Trastuzumab Deruxtecan (N=359)	Chemotherapy (N=354)	Trastuzumab Deruxtecan (N=436)	Chemotherapy (N=430)	Trastuzumab Deruxtecan (N=76)	Chemotherapy (N=76)
Median age (range) — yr	58.0 (28–87)	57.0 (32–83)	58.0 (28–87)	57.0 (32–83)	58.0 (33–85)	57.5 (34–82)
Female sex — no. (%)	359 (100.0)	353 (99.7)	436 (100.0)	429 (99.8)	76 (100.0)	76 (100.0)
Race — no. (%)†						
White	194 (54.0)	186 (52.5)	231 (53.0)	230 (53.5)	36 (47.4)	44 (57.9)
Black	1 (0.3)	3 (0.8)	4 (0.9)	3 (0.7)	3 (3.9)	0
Asian	122 (34.0)	127 (35.9)	154 (35.3)	151 (35.1)	32 (42.1)	24 (31.6)
Other	6 (1.7)	10 (2.8)	7 (1.6)	12 (2.8)	1 (1.3)	2 (2.6)
Not reported	35 (9.7)	28 (7.9)	39 (8.9)	34 (7.9)	4 (5.3)	6 (7.9)
ECOG performance-status score — no. (%)‡						
0	207 (57.7)	218 (61.6)	252 (57.8)	257 (59.8)	44 (57.9)	39 (51.3)
1	148 (41.2)	128 (36.2)	178 (40.8)	163 (37.9)	30 (39.5)	35 (46.1)
2	1 (0.3)	0	1 (0.2)	1 (0.2)	0	1 (1.3)
HER2 expression — no. (%)						
IHC 0	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	—	—
IHC 0 with membrane staining	—	—	76 (17.4)	76 (17.7)	76 (100)	76 (100)
IHC 1+	238 (66.3)	234 (66.1)	239 (54.8)	234 (54.4)	—	—
IHC 2+ and ISH-negative	117 (32.6)	118 (33.3)	117 (26.8)	118 (27.4)	—	—
IHC 2+	3 (0.8)	1 (0.3)	3 (0.7)	1 (0.2)	—	—
Primary endocrine resistance — no. (%)§	105 (29.2)	116 (32.8)	128 (29.4)	140 (32.6)	23 (30.3)	24 (31.6)
Stage IV disease at diagnosis — no. (%)	111 (30.9)	104 (29.4)	133 (30.5)	132 (30.7)	22 (28.9)	28 (36.8)
Bone-only disease — no. (%)	11 (3.1)	10 (2.8)	13 (3.0)	13 (3.0)	2 (2.6)	3 (3.9)
Visceral disease — no. (%)	309 (86.1)	299 (84.5)	376 (86.2)	364 (84.7)	66 (86.8)	65 (85.5)
Liver metastasis — no. (%)	243 (67.7)	232 (65.5)	296 (67.9)	283 (65.8)	52 (68.4)	51 (67.1)
Brain or CNS metastasis — no. (%)¶	33 (9.2)	25 (7.1)	37 (8.5)	33 (7.7)	4 (5.3)	8 (10.5)
Median no. of disease sites (range)	3 (1–10)	3 (1–11)	3 (1–10)	3 (1–11)	3 (1–6)	3 (1–8)
Endocrine therapy for metastatic disease						
Median no. of lines (range)	2 (1–4)	2 (1–5)	2 (1–4)	2 (1–5)	2 (1–4)	2 (1–5)
1 line — no./total no. (%)	54/358 (15.1)	67/352 (19.0)	65/435 (14.9)	82/428 (19.2)	11/76 (14.5)	15/76 (19.7)
First-line endocrine therapy with CDK4/6 inhibitor for ≤6 mo — no./total no. (%)	33/358 (9.2)	33/352 (9.4)	37/435 (8.5)	40/428 (9.3)	4/76 (5.3)	7/76 (9.2)
2 lines — no./total no. (%)	242/358 (67.6)	236/352 (67.0)	295/435 (67.8)	288/428 (67.3)	52/76 (68.4)	52/76 (68.4)
≥3 lines — no./total no. (%)	62/358 (17.3)	49/352 (13.9)	75/435 (17.2)	58/428 (13.6)	13/76 (17.1)	9/76 (11.8)

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Table 1. (Continued.)

Characteristic	HER2-Low Population		Intention-to-Treat Population		HER2-Ultralow Population	
	Trastuzumab Deruxtecan (N=359)	Chemotherapy (N=354)	Trastuzumab Deruxtecan (N=436)	Chemotherapy (N=430)	Trastuzumab Deruxtecan (N=76)	Chemotherapy (N=76)
Previous therapies for metastatic disease — no. (%)						
Endocrine monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)	41 (53.9)	40 (52.6)
Any endocrine therapy‖	358 (99.7)	352 (99.4)	435 (99.8)	428 (99.5)	76 (100.0)	76 (100.0)
Endocrine therapy with CDK4/6 inhibitor	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)	69 (90.8)	69 (90.8)
Endocrine therapy with targeted therapy other than CDK4/6 inhibitor**	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)	22 (28.9)	22 (28.9)

* The human epidermal growth factor receptor 2 (HER2)–low population included the patients with low HER2 expression, defined as a score on immunohistochemical (IHC) analysis of 1+ or 2+ and negative results on in situ hybridization (ISH). The intention-to-treat population included all the patients who had undergone randomization. The HER2-ultralow population included the patients with ultralow HER2 expression, defined as IHC 0 with membrane staining. HER2-low and HER2-ultralow status were determined according to central laboratory data. Because of stratification errors, the combined sample size of these two populations did not match the intention-to-treat total. Two patients were randomly assigned in error to the intention-to-treat population (one per treatment group) and were subsequently found to have had HER2 IHC 0 without membrane staining according to central laboratory testing. One patient who was initially listed as having HER2-ultralow expression was reclassified as having HER2-low disease on the basis of an updated biopsy (the specimen used at screening was obtained before metastatic disease had occurred). Therefore, this patient was not included in the HER2-ultralow analysis or the HER2-low primary population but was included in the intention-to-treat population. Chemotherapy was the physician's choice of capecitabine, nanoparticle albumin-bound paclitaxel, or paclitaxel. Percentages may not total 100 because of rounding. CDK4/6 denotes cyclin-dependent kinase 4 and 6.

† Race was reported by the patients.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability. A total of 14 patients in the intention-to-treat population (5 patients in the trastuzumab deruxtecan group and 9 patients in the chemotherapy group) had missing ECOG performance-status scores at baseline but had a score of 0 or 1 recorded within 6 days after randomization.

§ Primary endocrine resistance was defined as relapse that had occurred during the first 2 years of adjuvant endocrine therapy or progressive disease that had occurred during the first 6 months of first-line endocrine therapy for metastatic breast cancer.

¶ Patients with clinically active central nervous system (CNS) metastasis (defined as disease that was untreated, was causing symptoms, or warranted therapy with glucocorticoids or anticonvulsants to control associated symptoms) were excluded.

‖ Any endocrine therapy included both monotherapy and combination therapy.

** Other targeted therapies in the trastuzumab deruxtecan group and chemotherapy group in the intention-to-treat population included mammalian target of rapamycin inhibitors (in 23.9% of the patients in the trastuzumab deruxtecan group and in 23.7% of those in the chemotherapy group), phosphoinositide 3-kinase inhibitors (in 5.5% and 2.8%, respectively), or poly(adenosine diphosphate–ribose) polymerase inhibitors (in 0.7% and 1.2%, respectively).

significance was performed in this population, and the corresponding confidence interval for the hazard ratio was not adjusted for multiplicity. Safety analyses included all the patients who received at least one dose of a trial drug. Additional details are provided in the Supplementary Methods section in the Supplementary Appendix.

RESULTS

PATIENTS

From August 20, 2020, to March 18, 2024, a total of 866 patients across 324 sites underwent randomization; 436 patients were assigned to receive trastuzumab deruxtecan, and 430 patients were assigned to receive chemotherapy (59.8% received capecitabine, 24.4% nab-paclitaxel, and 15.8% paclitaxel) (Fig. S1 in the Supplementary Appendix). A total of 713 patients were included in the HER2-low population and 153 in the HER2-ultralow population. The baseline characteristics were balanced between the trial groups (Table 1 and Table S2). Patients had received a median of 2 previous lines (range, 1 to 5) of endocrine-based therapy for metastatic disease. Most patients in the intention-to-treat population (783 patients [90.4%]) had received a previous CDK4/6 inhibitor for metastatic disease. A total of 584 patients (67.4%) had received endocrine therapy plus a CDK4/6 inhibitor as first-line

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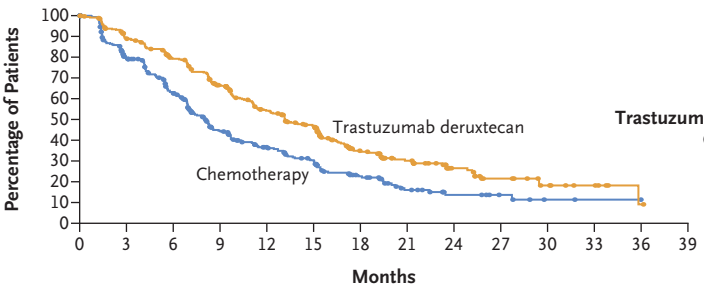
A Progression-free Survival in the HER2-Low Population



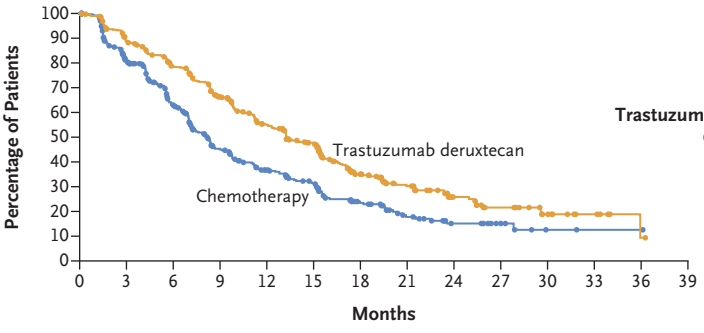
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Trastuzumab Deruxtecan	359	13.2 (11.4–15.2)
Chemotherapy	354	8.1 (7.0–9.0)

Hazard ratio for disease progression or death, 0.62 (95% CI, 0.51–0.74)
P<0.001

No. at Risk

Trastuzumab deruxtecan	359	310	265	213	163	131	72	49	28	17	10	6	1	0
Chemotherapy	354	254	192	118	85	65	37	19	10	6	2	1	1	0

B Progression-free Survival in the Intention-to-Treat Population



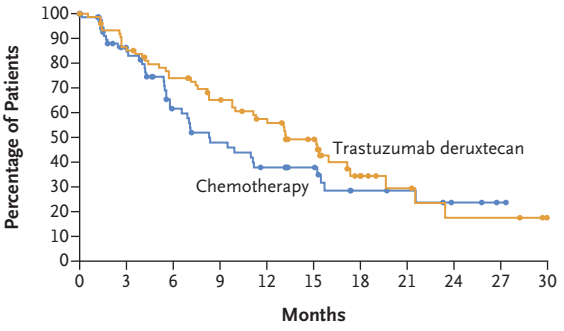
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Trastuzumab Deruxtecan	436	13.2 (12.0–15.2)
Chemotherapy	430	8.1 (7.0–9.0)

Hazard ratio for disease progression or death, 0.63 (95% CI, 0.53–0.75)
P<0.001

No. at Risk

Trastuzumab deruxtecan	436	375	319	258	199	156	82	56	32	21	11	6	1	0
Chemotherapy	430	306	224	142	103	79	44	25	13	7	2	1	1	0

C Progression-free Survival in the HER2-Ultralow Population



	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Trastuzumab Deruxtecan	76	13.2 (9.8–17.3)
Chemotherapy	76	8.3 (5.8–15.2)

Hazard ratio for disease progression or death, 0.78 (95% CI, 0.50–1.21)

No. at Risk

Trastuzumab deruxtecan	76	64	53	44	35	24	9	6	3	3	0
Chemotherapy	76	52	32	24	18	14	7	6	3	1	0

treatment for metastatic disease, and 217 patients (25.1%) had received endocrine therapy plus a CDK4/6 inhibitor as second-line treatment; 636 patients (73.4%) had received fulvestrant as single-agent or combination therapy for metastatic disease. The median duration of follow-up in the intention-to-treat population was 18.2 months (range, 0.0 to 42.9). Among the patients who received treatment, 89 of 434 (20.5%) in the trastuzumab deruxtecan group and 30 of 417 (7.2%) in

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Figure 1 (facing page). Progression-free Survival According to Blinded Independent Central Review (All Populations).

For progression-free survival in the human epidermal growth factor receptor 2 (HER2)–low population (patients with low HER2 expression, defined as a score of 1+ or 2+ on immunohistochemical [IHC] analysis and negative results on in situ hybridization [ISH]), a P value of less than 0.05 is considered to be significant (Panel A). For progression-free survival in the intention-to-treat population (all the patients who had undergone randomization), a P value of less than 0.015 is considered to be significant (Panel B). For progression-free survival in the HER2-ultralow population (patients with ultralow HER2 expression, defined as IHC 0 with membrane staining), statistical significance was not tested, and the corresponding confidence interval for the hazard ratio was not adjusted for multiplicity (Panel C). Chemotherapy was the physician's choice of capecitabine, nanoparticle albumin-bound paclitaxel, or paclitaxel. The circles indicate censored data.

the chemotherapy group were still receiving treatment at the time of data cutoff.

EFFICACY

Progression-free Survival

At the data-cutoff date (March 18, 2024), progression-free survival according to blinded independent central review in the HER2-low population was significantly longer with trastuzumab deruxtecan than with chemotherapy (hazard ratio for disease progression or death, 0.62; 95% confidence interval [CI], 0.51 to 0.74; P<0.001) (Fig. 1A). The median progression-free survival was 13.2 months (95% CI, 11.4 to 15.2) in the trastuzumab deruxtecan group and 8.1 months (95% CI, 7.0 to 9.0) in the chemotherapy group. In the intention-to-treat population, progression-free survival was significantly longer with trastuzumab deruxtecan than with chemotherapy. The median progression-free survival was 13.2 months (95% CI, 12.0 to 15.2) in the trastuzumab deruxtecan group and 8.1 months (95% CI, 7.0 to 9.0) in the chemotherapy group (hazard ratio for disease progression or death, 0.63; 95% CI, 0.53 to 0.75; P<0.001) (Fig. 1B). Efficacy in the prespecified exploratory HER2-ultralow population was similar to that in the HER2-low and intention-to-treat populations. The median progression-free survival was 13.2 months (95% CI, 9.8 to 17.3) in the trastuzumab deruxtecan group and 8.3 months (95% CI, 5.8 to 15.2) in the chemotherapy group (hazard ratio for disease progression or death, 0.78; 95% CI, 0.50 to 1.21) (Fig. 1C). The results according to investigator assessment were similar to those according to blinded independent central review (Fig. S2 and Table S3). Progression-free survival also consistently favored trastuzumab deruxtecan over chemotherapy among patients with a HER2 IHC score of 1+ or a score of IHC 2+ and negative results on ISH, and regardless of previous CDK4/6 inhibitor use, previous taxane use for nonmetastatic disease, and choice of chemotherapy (Fig. 2).

Overall Survival

With respect to the HER2-low population, the overall survival data were 37.9% mature (136 deaths among 359 patients) in the trastuzumab deruxtecan group and 41.2% mature (146 deaths among 354 patients) in the chemotherapy group. At the time of data cutoff, the difference in overall survival between treatment groups in the HER2-low population was not significant (hazard ratio for death, 0.83; 95% CI, 0.66 to 1.05); the estimated 12-month overall survival was 87.6% in the trastuzumab deruxtecan group and 81.7% in the chemotherapy group. Results were consistent in the intention-to-treat and HER2-ultralow populations (Fig. S3). Overall, 20.1% of the patients in the HER2-low population (17.9% in the intention-to-treat population) assigned to chemotherapy received trastuzumab deruxtecan after discontinuation of trial treatment.

Response to Treatment

The confirmed objective response among patients in the HER2-low population was 56.5% (95% CI, 51.2 to 61.7) with trastuzumab deruxtecan and 32.2% (95% CI, 27.4 to 37.3) with chemotherapy (Table 2 and Fig. S4). Complete (confirmed) responses were observed in 9 patients (2.5%) in the trastuzumab deruxtecan group and in none in the chemotherapy group. Among patients in the intention-to-treat population, the confirmed objective response was 57.3% (95% CI, 52.5 to 62.0) with trastuzumab deruxtecan and 31.2% (95% CI, 26.8 to 35.8) with chemotherapy. Results in the HER2-ultralow population were similar to those in the HER2-low and intention-to-treat populations: the confirmed objective response was 61.8% (95% CI, 50.0 to 72.8) with trastuzumab derux-

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Subgroup	Trastuzumab Deruxtecan	Chemotherapy	Median Progression-free Survival (95% CI)		Hazard Ratio for Disease Progression or Death (95% CI)
			Trastuzumab Deruxtecan	Chemotherapy	
	no. of events/no. of patients		*mo*		
Age					
<65 yr	158/252	157/244	13.2 (11.2–15.2)	7.8 (6.9–8.6)	0.59 (0.47–0.74)
≥65 yr	67/107	75/110	13.2 (9.7–17.0)	8.5 (6.9–11.5)	0.68 (0.49–0.95)
HER2 expression					
IHC 1+	157/238	150/234	12.9 (11.0–15.2)	8.2 (7.1–9.8)	0.74 (0.59–0.93)
IHC 2+ and ISH-negative	65/117	80/118	15.2 (12.2–21.4)	7.0 (6.2–8.4)	0.43 (0.31–0.60)
Previous CDK4/6 inhibitor use					
Yes	206/324	212/320	13.1 (11.2–15.2)	7.9 (6.9–8.6)	0.61 (0.51–0.74)
No	19/35	20/34	16.1 (9.7–NE)	11.1 (6.9–20.6)	0.64 (0.34–1.21)
Previous taxane use, adjuvant or neoadjuvant					
Yes	94/151	101/151	12.9 (9.7–14.0)	7.4 (6.3–9.3)	0.64 (0.48–0.85)
No	131/208	131/203	15.0 (11.3–16.5)	8.3 (7.0–9.7)	0.59 (0.46–0.76)
No. of previous lines of endocrine therapy for metastatic disease					
1	27/54	45/67	15.2 (9.7–19.1)	8.0 (5.7–8.5)	0.45 (0.27–0.72)
2	158/242	153/236	13.1 (11.2–15.2)	8.3 (6.9–10.0)	0.69 (0.55–0.86)
≥3	39/62	33/49	12.3 (8.3–18.5)	8.1 (5.4–9.7)	0.53 (0.33–0.86)
Endocrine resistance					
Primary	66/105	83/116	13.1 (10.0–15.2)	6.8 (5.3–8.1)	0.56 (0.40–0.78)
Secondary	159/254	148/236	13.2 (11.3–15.5)	9.0 (7.5–11.1)	0.65 (0.52–0.82)
Physician's choice of chemotherapy					
Capecitabine	131/220	134/208	13.5 (11.4–15.4)	8.5 (7.0–11.4)	0.62 (0.49–0.79)
Taxanes	94/139	98/146	12.9 (9.6–15.4)	7.3 (6.4–8.3)	0.62 (0.46–0.82)
Paclitaxel	38/59	43/56	14.5 (9.6–19.1)	6.3 (5.0–6.9)	0.37 (0.23–0.58)
Nab-paclitaxel	56/80	55/90	12.4 (8.3–15.2)	8.3 (7.1–11.2)	0.82 (0.56–1.20)
Liver metastases					
Yes	163/243	166/232	11.4 (9.8–13.2)	7.0 (6.4–8.1)	0.58 (0.46–0.72)
No	62/116	66/122	17.0 (15.0–19.4)	11.3 (8.2–14.8)	0.66 (0.46–0.93)

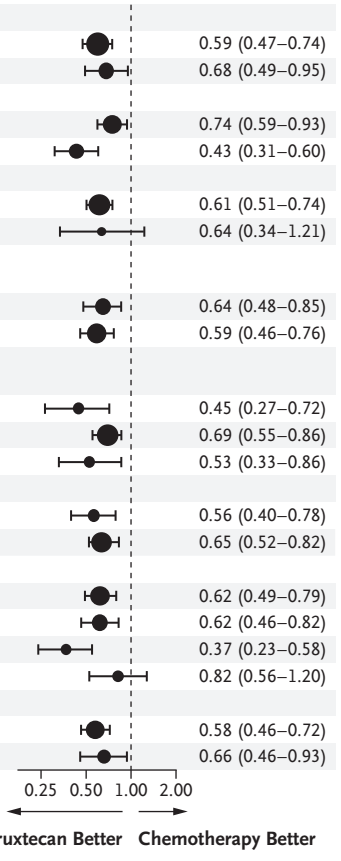

Figure 2. Subgroup Analysis of Progression-free Survival According to Blinded Independent Central Review (HER2-Low Population).

HER2 expression was determined according to central laboratory data (i.e., the result from the most recent evaluable specimen that was obtained before randomization). Primary endocrine resistance was defined as relapse that had occurred during the first 2 years of adjuvant endocrine therapy or progressive disease that had occurred within the first 6 months after first-line endocrine therapy for metastatic breast cancer while the patient was receiving endocrine therapy; secondary (acquired) endocrine resistance was defined as relapse that had occurred while the patient was receiving adjuvant endocrine therapy but after the first 2 years of therapy, or relapse that had occurred within 12 months after completion of adjuvant endocrine therapy, or progressive disease that had occurred more than 6 months after initiation of endocrine therapy for metastatic breast cancer while the patient was receiving endocrine therapy. The physician's choice of chemotherapy (capecitabine, nanoparticle albumin-bound [nab]–paclitaxel, or paclitaxel) was specified before randomization. Grouping of taxanes was performed as a post hoc analysis. The sizes of the circles are proportional to the number of events. CDK4/6 denotes cyclin-dependent kinase 4 and 6, and NE could not be evaluated.

tecan and 26.3% (95% CI, 16.9 to 37.7) with chemotherapy. The median duration of response among the patients in the HER2-low population was 14.1 months in the trastuzumab deruxtecan group and 8.6 months in the chemotherapy group (Table 2). In the intention-to-treat population, the median duration of response was 14.3 months with trastuzumab deruxtecan and 8.6 months with chemotherapy. The results according to investigator assessment were similar to those according to blinded independent central review (Table S3).

SAFETY

In total, 851 patients were included in the safety analysis: 434 in the trastuzumab deruxtecan group and 417 in the chemotherapy group. The median

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duration of treatment was 11.0 months (range, 0.4 to 39.6) and 5.6 months (0.1 to 35.9) in the two groups, respectively.

The incidence of adverse events that occurred during the treatment period was similar in the two groups (98.8% in the trastuzumab deruxtecan group and 95.2% in the chemotherapy group) (Tables S4 and S5). The three most common drug-related adverse events were nausea, fatigue, and alopecia in the trastuzumab deruxtecan group and fatigue, palmar–plantar erythrodysesthesia syndrome, and neutropenia in the chemotherapy group (Table 3). Adverse events of grade 3 or higher occurred in 52.8% of the patients in the trastuzumab deruxtecan group and in 44.4% of those in the chemotherapy group; the three most common adverse events of grade 3 or higher that occurred in both treatment groups were neutropenia, leukopenia, and anemia. Adverse events associated with dose reductions occurred in 24.7% of the patients in the trastuzumab deruxtecan group and in 38.6% of those in the chemotherapy group. Adverse events leading to discontinuation occurred in 14.3% of the patients in the trastuzumab deruxtecan group and in 9.4% of those in the chemotherapy group. Serious adverse events occurred in 20.3% and 16.1%, respectively. Fatal adverse events occurred in 2.5% of the patients in the trastuzumab deruxtecan group and in 1.4% of those in the chemotherapy group; fatal drug-related adverse events occurred in 5 patients (1.2%) who received trastuzumab deruxtecan and in none who received chemotherapy.

Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 49 patients (11.3%) who received trastuzumab deruxtecan, including 7 (1.6%) with a grade 1 event, 36 (8.3%) with a grade 2 event, 3 (0.7%) with a grade 3 event, and 3 (0.7%) with a grade 5 event (Tables S6 and S7). Of these patients, 20 were reported as having recovered, 2 were reported as having recovered with sequelae, and 3 were reported as having recovered at the time of data cutoff. Interstitial lung disease occurred in 1 patient (0.2%) in the chemotherapy group; this was a grade 2 event that resolved after treatment discontinuation. The median time to onset of adjudicated drug-related interstitial lung disease in the trastuzumab deruxtecan group was 141 days (range, 37 to 835).

Left ventricular dysfunction was reported in 35 patients (8.1%) in the trastuzumab deruxtecan group and in 16 patients (3.8%) in the chemotherapy group. In the trastuzumab deruxtecan group, the frequency of left ventricular dysfunction was primarily driven by decreased ejection fraction, which was grade 1 in severity in 1 patient, grade 2 in 31 patients, and grade 3 in 3 patients. Cardiac failure was not reported in any patients in the trastuzumab deruxtecan group but was reported in 3 patients (0.7%) in the chemotherapy group (one event each of grades 2, 3, and 4).

DISCUSSION

In this phase 3, randomized trial, trastuzumab deruxtecan showed a significant benefit with respect to progression-free survival as compared with chemotherapy among patients with hormone receptor–positive, HER2-low metastatic breast cancer, as well as among patients with tumors expressing either HER2-low or HER2-ultralow staining (intention-to-treat population), after one or more lines of endocrine therapy–based regimens. No new safety signals were observed. Interstitial lung disease and left ventricular dysfunction, which have previously been observed with trastuzumab deruxtecan, were reported in a small number of patients.

The DESTINY-Breast04 trial established HER2-low tumors as a targetable clinical entity, with patients deriving a clinical benefit with trastuzumab deruxtecan after receipt of chemotherapy.[17] In this trial, trastuzumab deruxtecan showed efficacy in earlier lines of treatment for metastatic disease following endocrine-based therapies. Trastuzumab deruxtecan therefore represents an additional treatment option between endocrine therapy and standard chemotherapy for patients who have received one or more lines of endocrine therapy for metastatic disease. Treatment with trastuzumab deruxtecan resulted in a median progression-free survival of 13.2 months, approximately 5 months longer than treatment with chemotherapy, among patients in the HER2-low, intention-to-treat, and HER2-ultralow populations. Furthermore, trastuzumab deruxtecan showed a benefit with respect to progression-free survival regardless of HER2 expression status, previous CDK4/6 inhibitor treatment, and previous taxane use for nonmetastatic disease. Superior efficacy with trastuzumab deruxtecan was shown regardless of chemotherapy type among patients who

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Table 2. Antitumor Activity According to Blinded Independent Central Review (All Populations).*

Variable	HER2-Low Population		Intention-to-Treat Population		HER2-Ultralow Population	
	Trastuzumab Deruxtecan (N=359)	Chemotherapy (N=354)	Trastuzumab Deruxtecan (N=436)	Chemotherapy (N=430)	Trastuzumab Deruxtecan (N=76)	Chemotherapy (N=76)
Confirmed objective response (95% CI) — %	56.5 (51.2–61.7)	32.2 (27.4–37.3)	57.3 (52.5–62.0)	31.2 (26.8–35.8)	61.8 (50.0–72.8)	26.3 (16.9–37.7)
Best confirmed response — no. (%)						
Complete response	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Progressive disease	22 (6.1)	43 (12.1)	28 (6.4)	50 (11.6)	6 (7.9)	7 (9.2)
Not evaluable	5 (1.4)	25 (7.1)	6 (1.4)	31 (7.2)	1 (1.3)	6 (7.9)
Median duration of response — mo	14.1	8.6	14.3	8.6	14.3	14.1
Median time to first response — mo	2.6	2.7	2.7	2.7	1.9	2.8
Clinical benefit — no. (%)†	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Disease control — no. (%)‡	328 (91.4)	284 (80.2)	398 (91.3)	346 (80.5)	69 (90.8)	62 (81.6)

* Because of rounding and because patients with no evidence of disease are not included in this table, percentages may not total 100.
† Clinical benefit was a composite of complete response, partial response, and stable disease at week 24 according to blinded independent central review.
‡ Disease control was a composite of complete response, partial response, and stable disease according to blinded independent central review.

were assigned to receive the physician's choice of chemotherapy and despite a longer median progression-free survival with capecitabine and nab-paclitaxel than was shown previously.[13,14] In practice, if trastuzumab deruxtecan is approved for use before chemotherapy in this setting, clinicians will need to use these data to make the appropriate benefit–risk decisions for each individual patient.

The DESTINY-Breast06 trial assessed a HER2-directed therapy in patients with HER2-ultralow tumors (IHC 0 with membrane staining). Taken alongside the results of the DESTINY-Breast04 trial[17] and trials in HER2-positive disease,[22,23] trastuzumab deruxtecan has shown clinical benefit in HER2-expressing metastatic breast cancer across the continuum of expression, from IHC 0 with membrane staining to IHC 3+. Uptake of trastuzumab deruxtecan is thought to be facilitated by very low levels of HER2 and subsequent death of neighboring tumor cells through the bystander effect.[15,16] Our findings are aligned with those of the phase 2 DAISY trial, which showed that a subset of IHC 0 tumors were sensitive to trastuzumab deruxtecan.[20] The most recent guidance from the American Society of Clinical Oncology (ASCO)–College of American Pathologists (CAP) concluded that the current system of HER2 IHC categorization was sufficient to identify patients who would most likely benefit from targeted therapy, on the basis of data available at that time.[2] However, the results of the DESTINY-Breast06 trial indicate that a subgroup of patients currently categorized as having tumors with a IHC score of 0 (with membrane staining) can also benefit from trastuzumab deruxtecan. Indeed, the current data suggest that there is no need to discriminate between HER2-low and HER2-ultralow disease because of the consistent benefit in both populations, albeit with limited patient numbers in the HER2-ultralow population. To enable access for all the patients who may benefit from trastuzumab deruxtecan, pathologists will have to separate the current HER2 IHC 0 category (according to the ASCO-CAP guidelines[2]) into two categories: IHC 0 with membrane staining (HER2-ultralow) and IHC 0 without membrane staining. Although both are captured as part of the HER2 IHC 0 category in the current ASCO-CAP guidelines,[2] differentiating between the two is not yet part of standard clinical practice. Training and education to ensure appropriate identification of HER2-low and HER2-ultralow tumor

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Table 3. Most Common Drug-Related Adverse Events (Safety Population).*

Event	Trastuzumab Deruxtecan (N=434)		Chemotherapy (N=417)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Nausea	286 (65.9)	7 (1.6)	98 (23.5)	1 (0.2)
Fatigue†	203 (46.8)	16 (3.7)	143 (34.3)	6 (1.4)
Alopecia‡	197 (45.4)	0	81 (19.4)	1 (0.2)
Neutropenia§	163 (37.6)	90 (20.7)	115 (27.6)	69 (16.5)
Transaminase increased¶	128 (29.5)	10 (2.3)	49 (11.8)	0
Anemia‖	122 (28.1)	25 (5.8)	81 (19.4)	10 (2.4)
Vomiting	118 (27.2)	6 (1.4)	39 (9.4)	0
Diarrhea	103 (23.7)	8 (1.8)	94 (22.5)	10 (2.4)
Decreased appetite	102 (23.5)	6 (1.4)	39 (9.4)	2 (0.5)
Leukopenia**	101 (23.3)	30 (6.9)	61 (14.6)	23 (5.5)
Palmar–plantar erythrodysesthesia syndrome	2 (0.5)	0	135 (32.4)	28 (6.7)

* Shown are adverse events that emerged or worsened on or after the date of the first dose of a trial drug up to and including 47 days after the last dose of a trial drug or before the initiation of the first subsequent cancer therapy (whichever occurred first); included are adverse events that occurred in at least 20% of the patients and were determined by the investigator to be related to a trial drug. The safety population included all the patients who received at least one dose of a trial drug. Adverse events that occurred during the treatment period were coded using the preferred terms of the *Medical Dictionary for Regulatory Activities*, version 6.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

† This category includes the preferred terms fatigue, asthenia, malaise, and lethargy.

‡ Given that alopecia severity can be classified no higher than grade 2, it is assumed that the one patient with an event that was grade 3 or higher represents a misclassification.

§ This category includes the preferred terms neutrophil count decreased and neutropenia.

¶ This category includes the preferred terms transaminase increased, aspartate aminotransferase increased, alanine aminotransferase increased, γ-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased.

‖ 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.

samples are warranted, as supported by a study that showed improvements in HER2-low scoring after training.[24]

The between-group difference in overall survival was not significant in this first interim analysis (data maturity in the HER2-low population, 39.6%). Because survival after disease progression is long in this patient population, subsequent anticancer therapies are expected to have a substantial effect on overall survival, and indeed, approximately one fifth of all the patients in the chemotherapy group went on to receive trastuzumab deruxtecan. Among other agents, sacituzumab govitecan is now also an effective option for these patients.[25]

Overall, the safety profile of trastuzumab deruxtecan was consistent with that observed in patients with HER2-positive[22,23] and HER2-low[17] metastatic breast cancer, with a longer median duration of treatment than chemotherapy (11.0 months vs. 5.6 months). Although most cases of interstitial lung disease in the trial were mild or moderate in severity, in keeping with previous studies,[17] the adjudication committee concluded that drug-related interstitial lung disease could not be ruled out as a cause of death in three patients in the trastuzumab deruxtecan group. Guidelines for surveillance and management of the toxic effects of interstitial lung disease and pneumonitis were provided in the trial protocol and included guidelines for dose interruptions, reductions, or discontinuations, and prescription of glucocorticoids; however, the administered glucocorticoid dose was lower than recommended in

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the grade 5 cases, and one of three patients with grade 5 adjudicated drug-related interstitial lung disease received a dose of trastuzumab deruxtecan on the day after a scan showed grade 1 interstitial lung disease.

Regarding limitations of the trial, although the patients were largely representative of the overall population with HER2-low and HER2-ultralow metastatic breast cancer in the regions involved in the trial, we acknowledge the underrepresentation of Black patients (Table S8). Another potential limitation is that anthracycline was not available as an option in the chemotherapy group; however, it was not considered to be an appropriate first-line treatment in this setting, and anthracycline-related cardiovascular toxic effects could have limited the duration of treatment. In addition, previous use of phosphoinositide 3-kinase inhibitors and other targeted agents may have been less common than expected and could have been limited by local testing and variable access to such agents in this global trial. The trial was not powered to show statistical significance in the HER2-ultralow population, and it should also be acknowledged that patients with hormone receptor–negative disease were not included, so it remains unclear whether trastuzumab deruxtecan could replace first-line chemotherapy in this population.

The efficacy benefit of trastuzumab deruxtecan over chemotherapy in this trial suggests trastuzumab deruxtecan as a treatment option in patients with hormone receptor–positive, HER2-low and HER2-ultralow metastatic breast cancer who have received one or more lines of endocrine-based therapy but no chemotherapy for metastatic disease, with no new safety signals identified. Interstitial lung disease remains an important safety risk of treatment with trastuzumab deruxtecan.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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