

Trastuzumab Deruxtecan in Residual HER2-Positive Early Breast Cancer

S. Loibl,^{1,2} Y.H. Park,³ Z. Shao,⁴ C.-S. Huang,⁵ C. Barrios,⁶ J. Abraham,⁷ A. Prat,^{8,9} N. Niikura,¹⁰ S.-A. Im,¹¹ W. Li,¹² H. Li,¹³ Y. Wang,¹⁴ H. Yao,¹⁵ S.-B. Kim,¹⁶ C. Geng,¹⁷ W. Rodriguez Pantigoso,¹⁸ F.J. Ramírez Godínez,¹⁹ C. Song,²⁰ Y. Ching Chang,²¹ A. Antoniazzi,²² S.-C. Chen,²³ Z. Li,²⁴ Z. Nowecki,²⁵ J. Lim,²⁶ E. Mathias,²⁷ Y. Sato,²⁸ W. Lu,²⁹ H. Abdel-Monem,³⁰ M. Untch,³¹ and C.E. Geyer, Jr.,^{32,33} for the DESTINY-Breast05 Trial Investigators*

ABSTRACT

BACKGROUND

Patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer and residual disease after neoadjuvant therapy are at high risk for recurrence.

METHODS

In a phase 3, open-label, international, randomized trial, we investigated postneoadjuvant trastuzumab deruxtecan (T-DXd; 5.4 mg per kilogram of body weight) as compared with trastuzumab emtansine (T-DM1; 3.6 mg per kilogram), the current standard treatment, in patients with HER2-positive breast cancer with residual invasive disease and node-positive disease at surgery or inoperable disease at diagnosis. The primary end point was invasive disease-free survival, and the key secondary end point was disease-free survival (including survival free from noninvasive breast cancers and second primary nonbreast cancers). Other end points included overall survival, distant recurrence-free interval, brain metastasis-free interval, and safety.

RESULTS

A total of 1635 patients were randomly assigned (in a 1:1 ratio) to receive T-DXd (818 patients) or T-DM1 (817 patients). At the data-cutoff date, the median duration of follow-up was approximately 30 months in each group. Invasive-disease events or deaths were reported in 51 patients (6.2%) in the T-DXd group and 102 patients (12.5%) in the T-DM1 group (hazard ratio, 0.47; 95% confidence interval [CI], 0.34 to 0.66; $P < 0.001$); 3-year invasive disease-free survival was 92.4% and 83.7%, respectively. Invasive-disease events, noninvasive-disease events, or deaths were reported in 52 patients (6.4%) in the T-DXd group and 103 patients (12.6%) in the T-DM1 group (hazard ratio, 0.47; 95% CI, 0.34 to 0.66; $P < 0.001$); 3-year disease-free survival was 92.3% and 83.5%, respectively. The most common adverse events were nausea (71.3% of patients), constipation (32.0%), decreased neutrophil count (31.6%), and vomiting (31.0%) with T-DXd and increased liver-enzyme levels (aspartate aminotransferase [50.2%] and alanine aminotransferase [45.3%]) and decreased platelet count (49.8%) with T-DM1. The incidence of adjudicated drug-related interstitial lung disease was higher with T-DXd than with T-DM1 (9.6% vs. 1.6%). Two patients with interstitial lung disease in the T-DXd group died.

CONCLUSIONS

In patients with high-risk, residual invasive HER2-positive breast cancer, postneoadjuvant T-DXd resulted in a significantly higher likelihood of invasive disease-free survival than T-DM1; toxic effects were mainly gastrointestinal and hematologic. An important identified risk of T-DXd is interstitial lung disease, which requires appropriate monitoring and management. (Funded by Daiichi Sankyo and AstraZeneca; DESTINY-Breast05 ClinicalTrials.gov number, NCT04622319.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Sibylle Loibl can be contacted at sibylle.loibl@gbg.de or at GBG Forschungs GmbH, Dornhofstrasse 10, 63263 Neu-Isenburg, Germany.

*A list of investigators in the DESTINY-Breast05 trial is provided in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org).

This article was published on December 10, 2025, and updated on February 18, 2026, at [NEJM.org](https://www.nejm.org).

N Engl J Med 2026;394:845-57.

DOI: 10.1056/NEJMoa2514661

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ANTI-HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2) therapies have improved outcomes in HER2-positive breast cancer.^{1,2} In the KATHERINE trial, postneoadjuvant trastuzumab emtansine (T-DM1) significantly improved invasive disease-free survival and overall survival as compared with trastuzumab among patients with HER2-positive early breast cancer and residual invasive disease after neoadjuvant therapy. Invasive disease or death occurred in 91 patients (12.2%) in the T-DM1 group and 165 patients (22.2%) in the trastuzumab group (hazard ratio, 0.50; 95% confidence interval [CI], 0.39 to 0.64; $P < 0.001$); 3-year invasive disease-free survival was 88.3% and 77.0%, respectively. Death occurred in 89 patients (12.0%) in the T-DM1 group and 126 patients (17.0%) in the trastuzumab group (hazard ratio, 0.66; 95% CI, 0.51 to 0.87; $P = 0.003$); 7-year overall survival was 89.1% and 88.4%, respectively.³⁻⁵ Subgroup analysis of the KATHERINE trial showed that patients in the T-DM1 group who presented with advanced locoregional disease or with positive nodal status after neoadjuvant treatment had 3-year invasive disease-free survival of 76% and 83%, respectively, with 7-year invasive disease-free survival of 67% and 72%; no substantial difference in central nervous system (CNS) recurrence was observed.^{4,6}

Trastuzumab deruxtecan (T-DXd), a HER2-directed antibody-drug conjugate, has significantly improved outcomes and reshaped the treatment landscape for HER2-positive metastatic breast cancer.⁷⁻¹⁰ T-DXd has shown robust efficacy across lines of therapy, including when compared with T-DM1,¹¹⁻¹³ and has shown activity against CNS metastases.^{7,8,14} We hypothesized that T-DXd may offer improved outcomes over T-DM1 in the postneoadjuvant context for patients with early breast cancer at high risk for recurrence. We present the prespecified interim analysis of the DESTINY-Breast05 trial comparing the efficacy and safety of T-DXd with T-DM1 in patients with HER2-positive early breast cancer with residual invasive disease and a high risk of recurrence.

METHODS

TRIAL DESIGN AND TREATMENT

DESTINY-Breast05 is an ongoing phase 3, open-label, international, randomized trial involving patients with centrally confirmed HER2-positive

(immunohistochemical [IHC] score of 3+ or positive on in situ hybridization [ISH] according to 2018 American Society of Clinical Oncology–College of American Pathologists guidelines) primary breast cancer.¹⁵ Eligible patients had residual invasive disease in the breast or axillary lymph nodes after neoadjuvant therapy with high-risk characteristics defined as inoperable disease at presentation (tumor stage T4, nodal stage N0 to N3, and metastasis stage M0 or tumor stage T1 to T3, nodal stage N2 or N3, and metastasis stage M0 before neoadjuvant therapy) or operable disease (tumor stage T1 to T3, nodal stage N0 or N1, and metastasis stage M0) before neoadjuvant therapy with axillary node-positive disease (pathological stage of ypN1 to ypN3) after neoadjuvant therapy. All the patients had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale in which higher scores reflect greater disability); had completed neoadjuvant systemic therapy, including taxane-based chemotherapy and HER2-directed treatment (≥ 9 weeks of trastuzumab [with or without pertuzumab] and ≥ 9 weeks of taxane-based chemotherapy); and had an interval of no more than 12 weeks between the date of the last surgical procedure and randomization.

Key exclusion criteria included a history of noninfectious interstitial lung disease or pneumonitis involving glucocorticoid treatment and current or suspected interstitial lung disease or pneumonitis not ruled out by imaging at screening. Full eligibility criteria are listed in the trial protocol, available with the full text of this article at NEJM.org.

Patients were randomly assigned in a 1:1 ratio to receive either T-DXd (5.4 mg per kilogram of body weight) or T-DM1 (3.6 mg per kilogram) administered intravenously on day 1 of each 21-day cycle, for a total of 14 cycles. Randomization was stratified according to extent of disease status at primary diagnosis before neoadjuvant therapy (operable vs. inoperable), hormone-receptor status (positive vs. negative), pathological nodal status after neoadjuvant therapy (positive [ypN1 to ypN3] vs. negative [ypN0]), and HER2-targeted neoadjuvant therapy (single vs. dual). After early discontinuation of the trial drug before 14 cycles for any reason (except death or loss to follow-up), patients in either group received treatment as clinically indicated by the investigator and could

receive HER2-targeted therapy according to the standard of care to complete up to 14 cycles of HER2-targeted treatment after surgery. Endocrine therapy after surgery was administered according to local standards and at the investigator's discretion in patients with hormone receptor-positive and HER2-positive breast cancer concomitantly with and beyond trial therapy. Among patients who received radiotherapy, trial therapy could be initiated concurrently with radiotherapy or after completion of radiotherapy (sequential).

TRIAL OVERSIGHT

This trial was designed by and conducted as a collaboration among the National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation, the German Breast Group (GBG), the AGO-B Breast Study Group, Solid Tumor Intensification (SOLTI) Breast Cancer Research Group, and Daiichi Sankyo; supported by Daiichi Sankyo, in collaboration with AstraZeneca; and approved by the institutional review board at each participating site. The trial was conducted in adherence with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable local regulations. All the patients provided written informed consent. Data were analyzed and interpreted by the authors and Daiichi Sankyo, who also verified the analyses. The authors reviewed the manuscript and vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. Under the authors' guidance, the manuscript was drafted by medical writers funded by Daiichi Sankyo. AstraZeneca was not involved in trial design or data collection but was involved in data interpretation, manuscript review, and approval of the final submission.

END POINTS

The primary end point, assessed in a time-to-event analysis, was invasive disease-free survival, defined as the time from randomization until the first occurrence of one of the following: recurrence of ipsilateral locoregional invasive breast cancer, distant recurrence, contralateral invasive breast cancer, or death from any cause, excluding second nonbreast primary cancer, consistent with the Standardized Definitions for Efficacy End Points criteria, version 2.0, definition of invasive disease-free survival.¹⁶ The key secondary end

point, assessed in a time-to-event analysis, was disease-free survival, defined as the time between randomization and the date of the first occurrence of an invasive-disease event or death as well as second primary nonbreast cancers or contralateral or ipsilateral ductal carcinoma in situ. Other secondary end points included overall survival, distant recurrence-free interval, brain metastasis-free interval, and safety.

ASSESSMENTS

Assessment of disease status was conducted every 3 months during trial treatment and will be followed for up to 2 years from the time of randomization, then every 6 months from years 3 through 5, and annually from years 6 through 10. All the patients will have long-term follow-up for disease status, occurrence of initial CNS and distant metastases (assessed with the use of magnetic resonance imaging or computed tomography [CT]), vital status, and new anticancer treatments until year 10, death, withdrawal of consent, loss to follow-up, or the end of the trial, whichever comes first.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, and coded according to the *Medical Dictionary for Regulatory Activities*, version 28.0. Specific criteria for managing toxic effects related to T-DXd are provided in the protocol. Investigators managed toxic effects related to T-DM1 according to the local product label. All potential cases of interstitial lung disease or pneumonitis were evaluated by an independent adjudication committee. At screening, all the patients underwent baseline low-dose, non-contrast CT of the chest. For patients who received adjuvant radiotherapy, monitoring for asymptomatic or mildly symptomatic therapy-related interstitial lung disease or pneumonitis included serial low-dose CT of the chest at 6 weeks after the start of trial treatment (before infusion at cycle 3), followed by every 12 weeks during treatment (before infusion at cycles 7 and 11), and at the 40-day follow-up. Patients who received sequential radiotherapy underwent additional low-dose CT of the chest after the completion of radiotherapy before the first trial-drug infusion. Interstitial lung disease or pneumonitis and radiation pneumonitis were managed according to protocol-defined guidelines (see the Supplemen-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Trastuzumab Deruxtecan (N=818)	Trastuzumab Emtansine (N=817)
Age		
Median (range) — yr	50.3 (24–78)	50.6 (21–83)
Distribution — no. (%)		
<65 yr	735 (89.9)	736 (90.1)
≥65 yr	83 (10.1)	81 (9.9)
Female sex — no. (%)	814 (99.5)	814 (99.6)
Race or ethnic group — no. (%)†		
Asian	399 (48.8)	386 (47.2)
White	301 (36.8)	333 (40.8)
Black	22 (2.7)	13 (1.6)
Other	96 (11.7)	85 (10.4)
Geographic region — no. (%)		
Asia	392 (47.9)	380 (46.5)
Europe	222 (27.1)	223 (27.3)
North America and Australia	57 (7.0)	72 (8.8)
Rest of the world‡	147 (18.0)	142 (17.4)
ECOG performance-status score — no. (%)§		
0	656 (80.2)	652 (79.8)
1	162 (19.8)	165 (20.2)
HER2 expression — no. (%)¶		
IHC 3+	676 (82.6)	670 (82.0)
IHC 2+ or ISH-positive	129 (15.8)	133 (16.3)
IHC 2+ and ISH-negative	2 (0.2)	0
IHC 1+ and ISH-positive	11 (1.3)	14 (1.7)
Hormone-receptor status — no. (%)		
Positive	581 (71.0)	583 (71.4)
Negative	237 (29.0)	234 (28.6)
Operative status at disease presentation — no. (%)		
Operable disease**	387 (47.3)	393 (48.1)
Inoperable disease††	431 (52.7)	424 (51.9)
Type of breast surgery — no. (%)		
Mastectomy	590 (72.1)	583 (71.4)
Breast-conserving surgery	228 (27.9)	234 (28.6)
Previous lymph-node surgery — no. (%)		
Axillary-lymph-node dissection or targeted axillary-lymph-node dissection	797 (97.4)	793 (97.1)
Sentinel-node biopsy	19 (2.3)	22 (2.7)
Other	2 (0.2)	2 (0.2)
Pathological nodal status after neoadjuvant therapy — no. (%)		
Positive	660 (80.7)	658 (80.5)
Negative	158 (19.3)	159 (19.5)

Table 1. (Continued.)

Characteristic	Trastuzumab Deruxtecan (N=818)	Trastuzumab Emtansine (N=817)
HER2-targeted neoadjuvant therapy — no. (%)		
Dual	642 (78.5)	646 (79.1)
Trastuzumab and pertuzumab	637 (77.9)	641 (78.5)
Trastuzumab and other HER2-targeted therapy	3 (0.4)	3 (0.4)
Trastuzumab, pertuzumab, and other HER2-targeted therapy	2 (0.2)	2 (0.2)
Single: trastuzumab alone	176 (21.5)	171 (20.9)
Neoadjuvant chemotherapy — no. (%)		
Taxane	818 (100)	817 (100)
Platinum compound	386 (47.2)	392 (48.0)
Anthracycline	423 (51.7)	399 (48.8)
Radiotherapy treatment — no. (%)‡‡		
Adjuvant radiotherapy	764 (93.4)	759 (92.9)
Concurrent	438 (53.5)	480 (58.8)
Sequential	326 (39.9)	279 (34.1)
No radiotherapy	54 (6.6)	58 (7.1)

* Percentages may not total 100 because of rounding. HER2 denotes human epidermal growth factor receptor 2.

† Race and ethnic group were reported by the patients, and this information was collected where permitted by local regulations. “Other” includes Native American, Native Hawaiian or other Pacific Islander, other, and multiple.

‡ This category includes Argentina, Brazil, Chile, Czech Republic, Israel, Mexico, Peru, Poland, Romania, and Russia.

§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

¶ HER2 expression was centrally confirmed according to the score on immunohistochemical (IHC) analysis and the results of in situ hybridization (ISH).

|| Data were collected by an electronic data-capture system.

** Operable disease was defined as tumor stage T1 to T3, nodal stage N0 or N1, and metastasis stage M0.

†† Inoperable disease was defined as tumor stage T4, nodal stage N0 to N3, and metastasis stage M0 or tumor stage T1 to T3, nodal stage N2 or N3, and metastasis stage M0.

‡‡ Among patients who received radiotherapy, trial therapy was initiated concurrently with radiotherapy or after the completion of radiotherapy (sequential).

tary Methods section in the Supplementary Appendix, available at NEJM.org).

STATISTICAL ANALYSIS

A sample size of 1600 patients was planned. Approximately 207 invasive-disease events or deaths were required to provide 80% power to show a significant difference in invasive disease-free survival if the true hazard ratio was 0.675, corresponding to an improvement in 3-year invasive disease-free survival from 83.0% (T-DM1 group) to 88.2% (T-DXd group). A single interim analysis of invasive disease-free survival was planned at approximately 70% of the target events (prespecified efficacy boundary based on the occurrence of 153 invasive-disease events or deaths, $P < 0.0183$). The interim analysis of disease-free survival was

planned to be conducted only if the efficacy boundary for invasive disease-free survival was crossed at the interim analysis. The prespecified efficacy boundary for disease-free survival ($P < 0.0144$) was based on the occurrence of 155 invasive-disease events, noninvasive-disease events, or deaths. In general, missing data or data for patients who withdrew from the trial were not imputed for the purpose of analysis.

Statistical analyses were performed with the use of SAS software, version 9.3 or later (SAS Institute). Efficacy analyses were performed in the full analysis population, which included all the patients who underwent randomization. Safety analyses were performed in the safety analysis population, which included all the patients who received at least one dose of a trial drug. A strati-

Table 2. Efficacy End Points.*

End Point	Trastuzumab Deruxtecan (N=818)	Trastuzumab Emtansine (N=817)
Invasive disease–free survival		
Patients who had invasive disease or who died — no. (%)	51 (6.2)	102 (12.5)
3-Year invasive disease–free survival (95% CI) — %	92.4 (89.7–94.4)	83.7 (80.2–86.7)
Hazard ratio for invasive disease or death (95% CI)	0.47 (0.34–0.66)	
P value	<0.001†	
Disease-free survival		
Patients who had invasive or noninvasive disease or who died — no. (%)‡	52 (6.4)	103 (12.6)
3-Year disease-free survival (95% CI) — %	92.3 (89.5–94.3)	83.5 (79.9–86.4)
Hazard ratio for invasive disease, noninvasive disease, or death (95% CI)	0.47 (0.34–0.66)	
P value	<0.001§	
Distant recurrence–free interval		
Patients who had distant recurrence — no. (%)	42 (5.1)	81 (9.9)
Patients event-free at 3 years (95% CI) — %	93.9 (91.4–95.7)	86.1 (82.5–89.1)
Hazard ratio for distant recurrence (95% CI)	0.49 (0.34–0.71)	
Brain metastasis–free interval		
Patients who had brain metastasis — no. (%)	17 (2.1)	26 (3.2)
Patients event-free at 3 years (95% CI) — %	97.6 (96.2–98.5)	95.8 (93.6–97.2)
Hazard ratio for brain metastasis (95% CI)	0.64 (0.35–1.17)	
Overall survival		
Patients who died — no. (%)	18 (2.2)	29 (3.5)
3-Year survival (95% CI) — %	97.4 (95.8–98.4)	95.7 (93.5–97.2)
Hazard ratio for death (95% CI)	0.61 (0.34–1.10)	

* Hazard ratios and 95% confidence intervals were estimated with the use of a stratified Cox proportional-hazards model, with a stratification factor of operative status at disease presentation. Two-sided P values are based on a stratified log-rank test.

† The P value crossed the efficacy boundary of 0.0183.

‡ Two patients (one in each group) had additional second primary events for disease-free survival.

§ The P value crossed the efficacy boundary of 0.0144.

fied log-rank test was used to compare the distribution of invasive disease–free survival (primary end point) and disease-free survival (key secondary end point) between the two treatment groups. A stratified Cox proportional-hazards model was used to estimate the hazard ratio of each end point and its 95% confidence interval. The estimated percentage of patients who were event-free at 3 years for each end point and the 95% confidence interval were obtained with the use of the Kaplan–Meier method. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypoth-

esis testing. Additional details are provided in the statistical analysis plan, available with the protocol.

RESULTS

PATIENTS

From December 4, 2020, through January 23, 2024, a total of 2067 patients were screened, of whom 1635 were randomly assigned (in a 1:1 ratio) to receive either T-DXd (818 patients) or T-DM1 (817 patients) (Fig. S1 in the Supplementary Appendix). At the data-cutoff date (July 2, 2025), the median

duration of follow-up was 29.9 months (range, 0.3 to 53.4) with T-DXd and 29.7 months (range, 0.1 to 54.4) with T-DM1.

The baseline characteristics of the patients were balanced between treatment groups (Table 1 and Table S1). Most patients were younger than 65 years of age, had hormone receptor–positive cancers, had positive pathological nodal status after neoadjuvant therapy, had received dual anti-HER2 neoadjuvant therapy, had received neoadjuvant anthracycline or platinum-based chemotherapy, and had received adjuvant radiotherapy. Nearly half the trial patients were Asian, and Black patients were underrepresented.

EFFICACY

At the interim analysis data-cutoff date (July 2, 2025), 153 invasive-disease events or deaths had been reported — 51 (6.2%) in the T-DXd group and 102 (12.5%) in the T-DM1 group (hazard ratio, 0.47; 95% CI, 0.34 to 0.66; $P < 0.001$); 3-year invasive disease–free survival was 92.4% (95% CI, 89.7 to 94.4) with T-DXd and 83.7% (95% CI, 80.2 to 86.7) with T-DM1 (Table 2 and Fig. 1A). Most first invasive-disease events were distant recurrences (42 of 818 patients [5.1%] with T-DXd and 77 of 817 patients [9.4%] with T-DM1). CNS recurrences as a component of invasive-disease events were reported in fewer patients in the T-DXd group than in the T-DM1 group (17 of 818 patients [2.1%] vs. 25 of 817 patients [3.1%]). Local invasive recurrences and contralateral invasive breast cancer were infrequent with T-DXd. Deaths without report of a previous invasive-disease event were balanced between groups (7 [0.9%] with T-DXd and 8 [1.0%] with T-DM1) (Table S2).

The analysis of prespecified subgroups is shown in Figure 2. T-DXd appeared to be more effective than T-DM1 across prespecified subgroups.

Invasive-disease events, noninvasive-disease events, or deaths were reported in 52 patients (6.4%) in the T-DXd group and 103 patients (12.6%) in the T-DM1 group (hazard ratio, 0.47; 95% CI, 0.34 to 0.66; $P < 0.001$). The 3-year disease-free survival was 92.3% (95% CI, 89.5 to 94.3%) with T-DXd and 83.5% (95% CI, 79.9 to 86.4%) with T-DM1 (Table 2 and Fig. 1B). Data for overall survival were immature (2.9% maturity), with 18 deaths (2.2%) in the T-DXd group and 29 (3.5%) in the T-DM1 group (Table 2 and Fig. S2A). Data for distant recurrence–free interval and brain me-

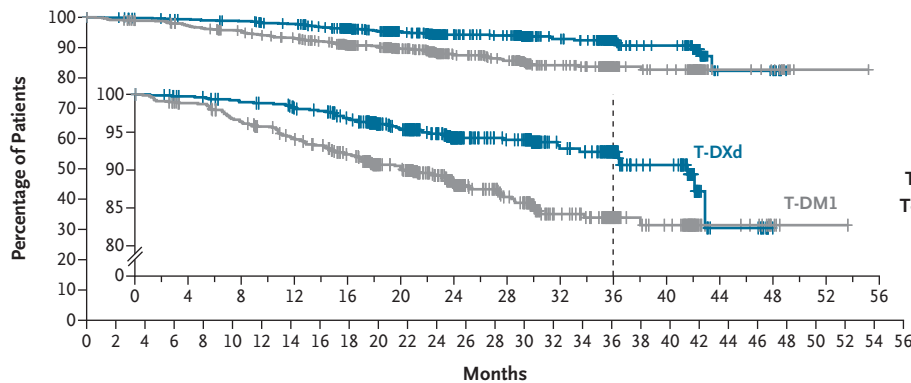
tastasis–free interval are shown in Table 2, Figure 1C, and Figure S2B.

SAFETY

At the data-cutoff date, 583 of 806 patients (72.3%) receiving T-DXd and 611 of 801 patients (76.3%) receiving T-DM1 had completed 14 treatment cycles (Table S3). Adverse events of grade 3 or higher occurred in 408 patients (50.6%) with T-DXd and 416 patients (51.9%) with T-DM1, with serious adverse events occurring in 140 patients (17.4%) and 109 patients (13.6%), respectively (Table S4). The most common adverse events (in ≥ 30 of patients) that occurred with T-DXd were mainly gastrointestinal: nausea (71.3%), constipation (32.0%), decreased neutrophil count (31.6%), and vomiting (31.0%); among patients who received T-DM1, the most common adverse events were increased aspartate aminotransferase level (50.2%), decreased platelet count (49.8%), and increased alanine aminotransferase level (45.3%) (Table 3).

The incidence of adverse events of any grade that were associated with drug discontinuation was 17.9% with T-DXd and 12.9% with T-DM1; drug interruptions occurred in 49.6% and 41.1%, respectively. Drug discontinuation was attributed to drug-related interstitial lung disease or pneumonitis in 10.8% of patients receiving T-DXd and 2.5% of those receiving T-DM1. Adverse events led to dose reductions in 213 patients (26.4%) in the T-DXd group and 213 patients (26.6%) in the T-DM1 group, and the dose reductions were due to nausea in the T-DXd group (6.1%) and thrombocytopenia in the T-DM1 group (3.2%). Drug-related adverse events resulting in dose reduction occurred in 24.1% of the patients who received T-DXd and 25.7% of those who received T-DM1. Adverse events were associated with death in 0.4% of patients (3 of 806) who received T-DXd and 0.6% of patients (5 of 801) who received T-DM1. Causes of death are detailed in Table S4.

Adjudicated drug-related interstitial lung disease occurred in 77 patients (9.6%; deaths [grade 5 events], 0.2% [2 of 806]) with T-DXd and 13 patients (1.6%) with T-DM1 (Table S5). The timing of adjuvant radiotherapy (sequential or concurrent) showed no effect on the incidence of adjudicated drug-related interstitial lung disease (Table S6). The incidence of investigator-reported radiation pneumonitis (grouped term that includes the preferred terms pulmonary radiation injury,

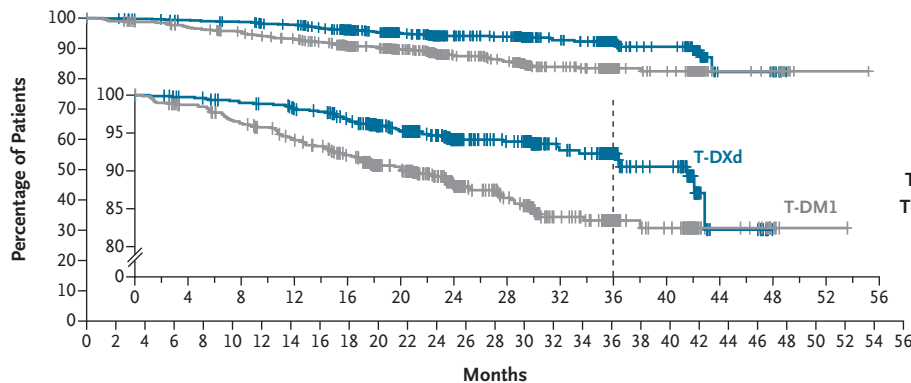
A Invasive Disease-free Survival

Patients with Event	3-Yr Invasive Disease-free Survival (95% CI)	
	no. (%)	percent
T-DXd	51 (6.2)	92.4 (89.7–94.4)
T-DM1	102 (12.5)	83.7 (80.2–86.7)

Hazard ratio for invasive disease or death, 0.47 (95% CI, 0.34–0.66)
P<0.001

No. at Risk

T-DXd	818	788	781	776	771	768	758	753	731	684	634	544	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0	0
T-DM1	817	781	769	760	745	734	719	708	687	632	599	527	417	355	337	233	186	177	120	84	79	38	14	13	4	1	1	0	0

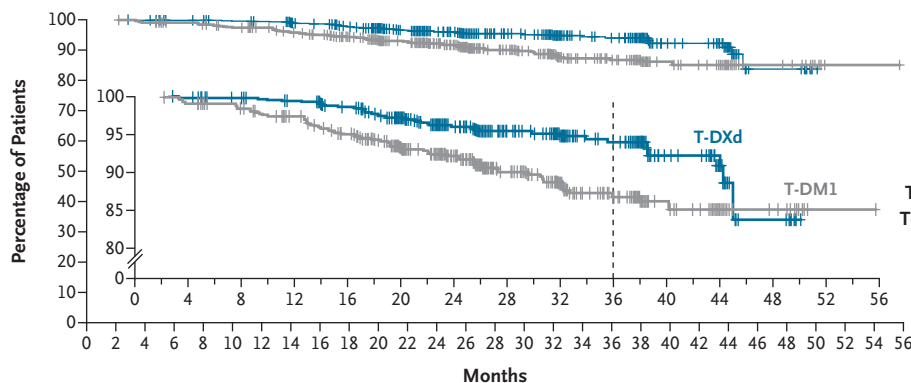
B Disease-free Survival

Patients with Event	3-Yr Disease-free Survival (95% CI)	
	no. (%)	percent
T-DXd	52 (6.4)	92.3 (89.5–94.3)
T-DM1	103 (12.6)	83.5 (79.9–86.4)

Hazard ratio for invasive disease, noninvasive disease, or death, 0.47 (95% CI, 0.34–0.66)
P<0.001

No. at Risk

T-DXd	818	788	781	776	771	768	758	753	731	683	633	543	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0	0
T-DM1	817	779	767	757	743	733	718	707	686	631	598	526	416	354	336	233	186	177	120	84	79	38	14	13	4	1	1	0	0

C Distant Recurrence-free Interval

Patients with Event	Patients Event-free at 3 Yr (95% CI)	
	no. (%)	percent
T-DXd	42 (5.1)	93.9 (91.4–95.7)
T-DM1	81 (9.9)	86.1 (82.5–89.1)

Hazard ratio for distant recurrence, 0.49 (95% CI, 0.34–0.71)

No. at Risk

T-DXd	818	786	778	774	770	767	757	753	731	684	635	545	442	382	372	276	219	213	129	92	90	46	14	14	0	0	0	0	0
T-DM1	817	780	769	761	746	739	724	713	694	639	606	533	424	362	345	240	192	182	121	84	79	38	14	13	4	1	1	0	0

Figure 1 (facing page). Invasive Disease–free Survival, Disease-free Survival, and Distant Recurrence–free Interval with Trastuzumab Deruxtecan (T-DXd) and Trastuzumab Emtansine (T-DM1).

Hazard ratios and 95% confidence intervals were estimated with the use of a stratified Cox proportional-hazards model, with a stratification factor of operative status at disease presentation. Two-sided P values are based on a stratified log-rank test. Tick marks indicate censored data. The insets show the same data on an expanded y axis.

radiation alveolitis, radiation bronchitis, radiation fibrosis–lung, and radiation pneumonitis) was similar in the two groups (31.4% [238 of 757] with T-DXd and 30.5% [229 of 750] with T-DM1); no events of grade 3 or higher were observed. Left ventricular dysfunction occurred in 23 patients (2.9%) in the T-DXd group and 14 patients (1.7%) in the T-DM1 group (Table S7).

DISCUSSION

In this trial, T-DXd resulted in a significantly higher likelihood of invasive disease–free survival than T-DM1 among patients with HER2-positive early breast cancer with residual invasive disease and a high risk of recurrence after neoadjuvant therapy. Invasive-disease events or deaths were reported in 51 patients (6.2%) in the T-DXd group and 102 patients (12.5%) in the T-DM1 group (hazard ratio, 0.47; 95% CI, 0.34 to 0.66; $P < 0.001$; 3-year invasive disease–free survival, 92.4% vs. 83.7%). Although the trial was not powered for subgroup analyses, a benefit with T-DXd was observed across prespecified subgroups. In addition, the efficacy of T-DXd was observed in patients with both an IHC score of 2+ or 1+ and amplification on ISH, findings that support the activity of T-DXd over T-DM1 in this population. Distant recurrences were the predominant invasive-disease events in both groups, with a lower risk of distant recurrence with T-DXd than with T-DM1 (42 patients [5.1%] in the T-DXd group and 81 [9.9%] in the T-DM1 group had an event). CNS recurrences were also less frequent with T-DXd than with T-DM1 (17 [2.1%] vs. 25 [3.1%]). Data for overall survival were 2.9% mature.

By design, the patient population in our trial comprised a high-risk population, with 52% of patients presenting with inoperable disease and

81% being node-positive after neoadjuvant therapy. The KATHERINE trial enrolled patients with less advanced disease — 54% of patients had negative or unknown nodal status at presentation, and 22% had minimal residual invasive disease.^{3,4} The neoadjuvant therapies received by the patients in the DESTINY-Breast05 trial reflect the evolving international standards of care, because 79% of patients had received dual HER2-targeted therapy, a notable increase as compared with 20% in the KATHERINE trial.³ Anthracycline use was 50% in the current trial, as compared with 77% in the KATHERINE trial.³ These characteristics are associated with the changing treatment landscape and were balanced across the trial groups.

The percentage of patients who completed 14 treatment cycles was similar in the two groups, and the overall safety profiles of T-DXd and T-DM1 were consistent with the known safety profile of each agent, with no new safety signals observed. Adverse events of grade 3 or higher occurred in 50.6% of patients in the T-DXd group and 51.9% of those in the T-DM1 group. The most common adverse events reported with T-DXd were gastrointestinal or hematologic in nature. The trial protocol recommended premedication with a combination of two or three antiemetic prophylaxis agents, and antiemetic guidelines were revised during the trial to reclassify T-DXd as highly emetogenic and to recommend a three- or four-drug antiemetic prophylactic regimen.^{17–20} Interstitial lung disease, which remains an important identified adverse event associated with T-DXd, resulted in the death of two patients, highlighting the need for appropriate identification, monitoring, and management.

In the DESTINY-Breast05 trial, patients who received adjuvant radiotherapy underwent serial low-dose CT of the chest, facilitating detection of asymptomatic or minimally symptomatic interstitial lung disease and enabling comprehensive characterization of the risk of interstitial lung disease and radiation pneumonitis with both T-DXd and T-DM1. The incidence of adjudicated drug-related interstitial lung disease was 9.6% with T-DXd and 1.6% with T-DM1 (mostly grade 1 or 2); overall, most patients had recovered. Interstitial lung disease is a known adverse event associated with T-DXd treatment, with management guidelines for appropriate monitoring and timely

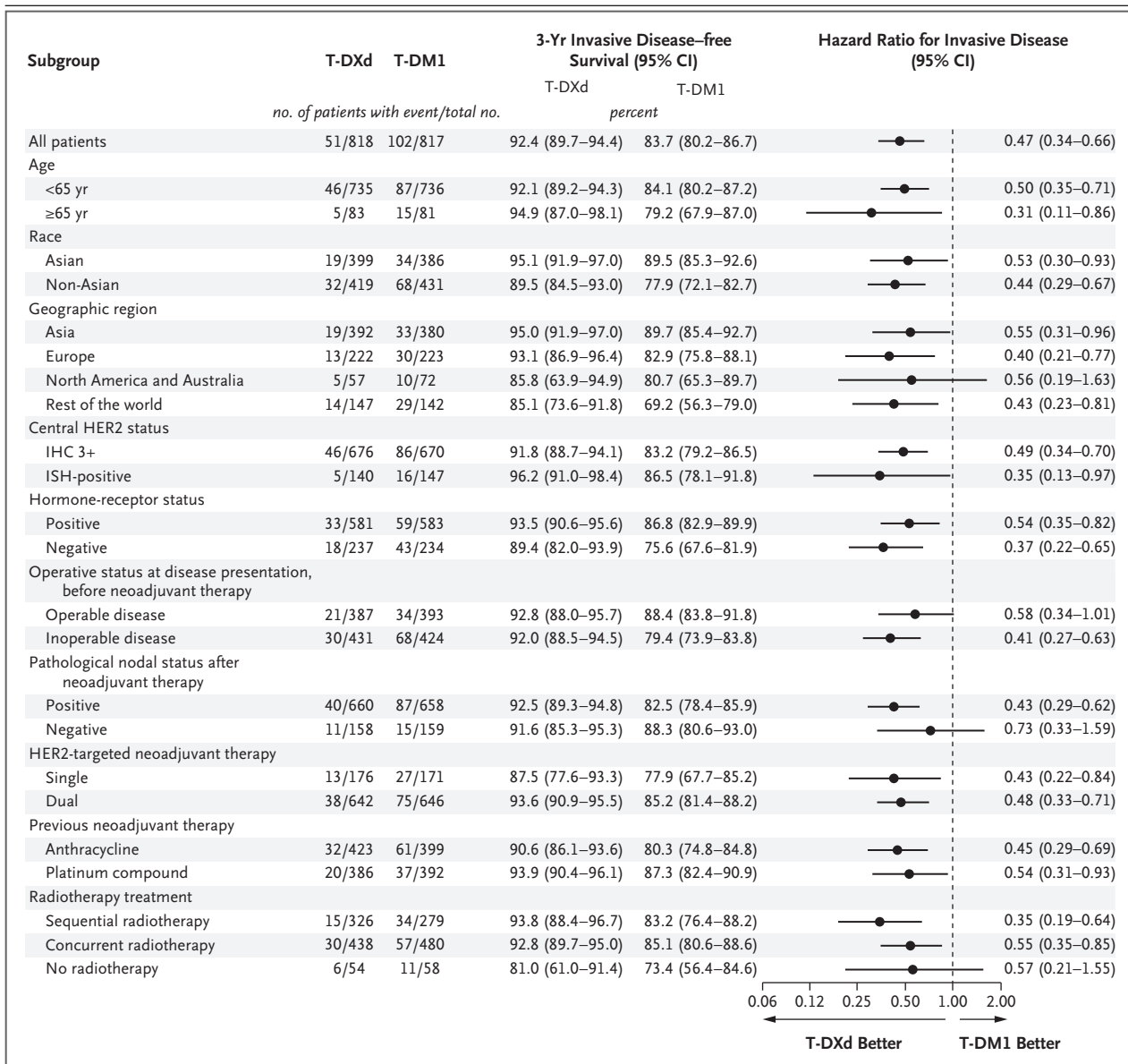


Figure 2. Subgroup Analysis According to Baseline Demographic and Clinical Characteristics.

Hazard ratios and 95% confidence intervals were estimated with the use of an unstratified Cox proportional-hazards model. Central human epidermal growth factor receptor 2 (HER2) status and previous neoadjuvant therapy were not prespecified subgroups. Race was reported by the patients, and this information was collected where permitted by local regulations. Operable disease was defined as tumor stage T1 to T3, nodal stage N0 or N1, and metastasis stage M0. Inoperable disease was defined as tumor stage T4, nodal stage N0 to N3, and metastasis stage M0 or tumor stage T1 to T3, nodal stage N2 or N3, and metastasis stage M0. Positive pathological nodal status was defined as a pathological stage of ypN1 to ypN3, and negative pathological nodal status was defined as a pathological stage of ypN0. IHC denotes immunohistochemical, and ISH in situ hybridization.

intervention. Of note, the timing of adjuvant radiotherapy had no effect on the incidence of adjudicated drug-related interstitial lung disease. Nevertheless, the occurrence of seven cases of grade

3 interstitial lung disease and two deaths related to interstitial lung disease underscores the importance of adherence to risk-mitigation strategies when using T-DXd as a curative-intent treatment.

Table 3. Most Common Adverse Events (≥15% of Patients in Either Group) and Adjudicated Drug-Related Interstitial Lung Disease.*

Adverse Event	Trastuzumab Deruxtecan (N = 806)					Trastuzumab Entansine (N = 801)						
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	number of patients (percent)					
Nausea†	575 (71.3)	315 (39.1)	224 (27.8)	36 (4.5)	0	0	235 (29.3)	190 (23.7)	44 (5.5)	1 (0.1)	0	0
Constipation	258 (32.0)	196 (24.3)	62 (7.7)	0	0	0	130 (16.2)	104 (13.0)	25 (3.1)	1 (0.1)	0	0
Neutrophil count decreased	255 (31.6)	39 (4.8)	91 (11.3)	111 (13.8)	14 (1.7)	0	115 (14.4)	42 (5.2)	50 (6.2)	23 (2.9)	0	0
Vomiting†	250 (31.0)	153 (19.0)	88 (10.9)	9 (1.1)	0	0	72 (9.0)	55 (6.9)	16 (2.0)	1 (0.1)	0	0
White-cell count decreased	239 (29.7)	34 (4.2)	124 (15.4)	78 (9.7)	3 (0.4)	0	104 (13.0)	36 (4.5)	58 (7.2)	10 (1.2)	0	0
Fatigue	238 (29.5)	143 (17.7)	74 (9.2)	21 (2.6)	0	0	162 (20.2)	130 (16.2)	28 (3.5)	4 (0.5)	0	0
Radiation pneumo-nitis	232 (28.8)	195 (24.2)	37 (4.6)	0	0	0	216 (27.0)	167 (20.8)	49 (6.1)	0	0	0
Anemia	228 (28.3)	122 (15.1)	84 (10.4)	22 (2.7)	0	0	136 (17.0)	73 (9.1)	46 (5.7)	16 (2.0)	1 (0.1)	0
AST increased	206 (25.6)	181 (22.5)	19 (2.4)	6 (0.7)	0	0	402 (50.2)	271 (33.8)	105 (13.1)	26 (3.2)	0	0
ALT increased	191 (23.7)	151 (18.7)	33 (4.1)	7 (0.9)	0	0	363 (45.3)	239 (29.8)	94 (11.7)	30 (3.7)	0	0
Diarrhea	187 (23.2)	125 (15.5)	52 (6.5)	10 (1.2)	0	0	69 (8.6)	49 (6.1)	17 (2.1)	3 (0.4)	0	0
Platelet count de-creased	171 (21.2)	74 (9.2)	43 (5.3)	35 (4.3)	19 (2.4)	0	399 (49.8)	85 (10.6)	107 (13.4)	147 (18.4)	60 (7.5)	0
Decreased appetite	161 (20.0)	117 (14.5)	37 (4.6)	7 (0.9)	0	0	80 (10.0)	72 (9.0)	8 (1.0)	0	0	0
Asthenia	153 (19.0)	99 (12.3)	38 (4.7)	16 (2.0)	0	0	113 (14.1)	82 (10.2)	27 (3.4)	4 (0.5)	0	0
Radiation skin injury	152 (18.9)	87 (10.8)	53 (6.6)	12 (1.5)	0	0	137 (17.1)	86 (10.7)	48 (6.0)	3 (0.4)	0	0
Covid-19	139 (17.2)	81 (10.0)	54 (6.7)	4 (0.5)	0	0	157 (19.6)‡	103 (12.9)	49 (6.1)	3 (0.4)	0	0
Neutropenia	138 (17.1)	14 (1.7)	58 (7.2)	60 (7.4)	6 (0.7)	0	49 (6.1)	12 (1.5)	24 (3.0)	12 (1.5)	1 (0.1)	0
Headache	127 (15.8)	99 (12.3)	26 (3.2)	2 (0.2)	0	0	166 (20.7)	140 (17.5)	25 (3.1)	1 (0.1)	0	0
Alopecia	125 (15.5)	93 (11.5)	32 (4.0)	0	0	0	10 (1.2)	9 (1.1)	1 (0.1)	0	0	0
Arthralgia	83 (10.3)	64 (7.9)	19 (2.4)	0	0	0	164 (20.5)	131 (16.4)	31 (3.9)	2 (0.2)	0	0
Thrombocytopenia	48 (6.0)	34 (4.2)	7 (0.9)	6 (0.7)	1 (0.1)	0	148 (18.5)	37 (4.6)	60 (7.5)	41 (5.1)	10 (1.2)	0
Interstitial lung disease	77 (9.6)	16 (2.0)	52 (6.5)	7 (0.9)	0	2 (0.2)	13 (1.6)	8 (1.0)	5 (0.6)	0	0	0

* The table includes data on all the patients who received at least one dose of trial treatment. Shown are adverse events that emerged or worsened after the initiation of trial treatment until 47 days after the last dose of trial treatment. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and Covid-19 coronavirus disease 2019.

† Prophylactic antiemetics were recommended but not mandatory.

‡ Two patients (0.2%) had missing data regarding grade.

The incidence of investigator-reported radiation pneumonitis was similar in the two groups (all grade 1 or 2 events), with a numerically higher incidence among patients who received sequential radiotherapy than among those who received concurrent radiotherapy. T-DXd was interrupted in the event of grade 2 radiation pneumonitis, and glucocorticoid treatment was recommended. Given the overlapping clinical and radiographic features of radiation-induced pneumonitis and drug-related interstitial lung disease, careful multidisciplinary evaluation of pulmonary events and serial low-dose CT of the chest are essential for early detection and management in early breast cancer.²¹

Alongside the DESTINY-Breast05 trial, efforts to optimize postneoadjuvant therapy for patients with HER2-positive early breast cancer and residual disease are ongoing. The CompassHER2 RD trial (ClinicalTrials.gov number, NCT04457596) is evaluating whether the addition of tucatinib to T-DM1 can further improve outcomes, and the ASTEFANIA trial (NCT04873362) is investigating immunotherapy escalation with atezolizumab plus T-DM1.

Limitations of our trial include the open-label design and short follow-up. At the time of this analysis, data for the brain metastasis-free interval and overall survival were immature. In addition, translational studies are ongoing to assess correlations between biomarker status and the efficacy of T-DXd as compared with T-DM1. The underrepresentation of Black patients impairs extrapolation to that population.

These interim results from the DESTINY-Breast05 trial show the superior clinical benefit of postneoadjuvant T-DXd as compared with T-DM1 in patients with HER2-positive early breast cancer with residual invasive disease and a high risk of recurrence. The safety profile of T-DXd continues to require careful monitoring and selected preventative interventions to ameliorate the severity of adverse events.

Supported by Daiichi Sankyo, in collaboration with AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

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.

We thank the patients and their families for their participation and the trial site staff for their contributions; Jaci Dudley, Pharm.D., Jennifer Petschauer, Pharm.D., Hemali Upadhyaya, Pharm.D., Michael Jan, M.D., Ph.D., M.P.H., Cecilia Orbegoso Aguilar, M.D., Julie Jeanes, Pharm.D., Pia Herbolzheimer, M.D., Ph.D., Benjamin Friedmann, Ph.D., and Sophie Davies, B.Sc., for assistance with data interpretation and scientific review. Medical writing support, under the direction of the authors, was provided by Caylin Bosch, Ph.D., Selene Jarrett, Ph.D., Jennifer Lau, Ph.D., and Toinette Labuschagné, M.Sc., ISMPP C.M.P.P., of ApotheCom in accordance with Good Publication Practice guidelines (<http://www.ismpp.org/gpp-2022>).

AUTHOR INFORMATION

Sibylle Loibl, M.D.,^{1,2} Yeon Hee Park, M.D., Ph.D.,³ Zhiming Shao, M.D.,⁴ Chiun-Sheng Huang, M.D., Ph.D., M.P.H.,⁵ Carlos Barrios, M.D.,⁶ Jame Abraham, M.D.,⁷ Aleix Prat, M.D., Ph.D.,^{8,9} Naoki Nii-kura, M.D., Ph.D.,¹⁰ Seock-Ah Im, M.D., Ph.D.,¹¹ Wei Li, M.D.,¹² Huiping Li, Ph.D.,¹³ Yongsheng Wang, M.D.,¹⁴ Herui Yao, M.D.,¹⁵ Sung-Bae Kim, M.D., Ph.D.,¹⁶ Cui-zhi Geng, M.D., Ph.D.,¹⁷ Wulbert Rodriguez Pantigoso, M.D.,¹⁸ Francisco Javier Ramirez Godínez, M.D.,¹⁹ Chuangui Song, Ph.D.,²⁰ Yuan Ching Chang, M.D., Ph.D.,²¹ Augusto Antoniazzi, M.D.,²² Shin-Cheh Chen, M.D.,²³ Zhigao Li, M.D., Ph.D.,²⁴ Zbigniew Nowecki, M.D.,²⁵ Joline Lim, Ph.D.,²⁶ Elton Mathias, M.D.,²⁷ Yuta Sato, M.Sc.,²⁸ Wenjing Lu, Ph.D.,²⁹ Hanan Abdel-Monem, M.D.,³⁰ Michael Untch, M.D.,³¹ and Charles E. Geyer, Jr., M.D.^{32,33}

¹German Breast Group, Neu-Isenburg, Germany; ²Goethe University Frankfurt, Frankfurt am Main, Germany; ³Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; ⁴Fudan University Cancer Hospital, Shanghai; ⁵National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei; ⁶Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil; ⁷Cleveland Clinic, Cleveland; ⁸Hospital Clínic de Barcelona, Barcelona; ⁹Department of Medicine, University of Barcelona, Barcelona; ¹⁰Tokai University School of Medicine, Isehara, Japan; ¹¹Seoul National University Hospital, Seoul, South Korea; ¹²First Hospital of Jilin University, Changchun, China; ¹³Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing; ¹⁴Cancer Hospital of Shandong First Medical University, Jinan, China; ¹⁵Sun Yat-Sen Memorial Hospital, Guangzhou, China; ¹⁶Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; ¹⁷Fourth Hospital of Hebei Medical University, Shijiazhuang, China; ¹⁸Instituto Peruano de Oncología y Radioterapia, Lima, Peru; ¹⁹Hospital Civil de Guadalajara, Guadalajara, Mexico; ²⁰Union Hospital of Fujian Medical University, Fuzhou, China; ²¹MacKay Memorial Hospital, Taipei, Taiwan; ²²Fundação Pio XII—Hospital do Câncer de Barretos, São Paulo; ²³Chang Gung Memorial Hospital, Taoyuan City, Taiwan; ²⁴Harbin Medical University Cancer Hospital, Harbin, China; ²⁵Maria Skłodowska-Curie Memorial Cancer Center, Warsaw, Poland; ²⁶National University Cancer Institute, Singapore; ²⁷Daiichi Sankyo, Basking Ridge, NJ; ²⁸Clinical Science, Daiichi Sankyo, Rueil-Malmaison, France; ²⁹Biostatistics and Data Management, Daiichi Sankyo, Basking Ridge, NJ; ³⁰Clinical Science, Daiichi Sankyo, Basking Ridge, NJ; ³¹Health and Medical University, Breast Cancer Center, Helios Hospital Berlin—Buch, Berlin; ³²National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation, Pittsburgh; ³³University of Pittsburgh School of Medicine—UPMC Hillman Cancer Center, Pittsburgh.

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