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Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

ABSTRACT

BACKGROUND

Patients who have residual invasive breast cancer after receiving neoadjuvant chemotherapy plus human epidermal growth factor receptor 2 (HER2)–targeted therapy have a worse prognosis than those who have no residual cancer. Trastuzumab emtansine (T-DM1), an antibody–drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor, provides benefit in patients with metastatic breast cancer that was previously treated with chemotherapy plus HER2-targeted therapy.

METHODS

We conducted a phase 3, open-label trial involving patients with HER2-positive early breast cancer who were found to have residual invasive disease in the breast or axilla at surgery after receiving neoadjuvant therapy containing a taxane (with or without anthracycline) and trastuzumab. Patients were randomly assigned to receive adjuvant T-DM1 or trastuzumab for 14 cycles. The primary end point was invasive disease–free survival (defined as freedom from ipsilateral invasive breast tumor recurrence, ipsilateral locoregional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, or death from any cause).

RESULTS

At the interim analysis, among 1486 randomly assigned patients (743 in the T-DM1 group and 743 in the trastuzumab group), invasive disease or death had occurred in 91 patients in the T-DM1 group (12.2%) and 165 patients in the trastuzumab group (22.2%). The estimated percentage of patients who were free of invasive disease at 3 years was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group. Invasive disease–free survival was significantly higher in the T-DM1 group than in the trastuzumab group (hazard ratio for invasive disease or death, 0.50; 95% confidence interval, 0.39 to 0.64; P<0.001). Distant recurrence as the first invasive-disease event occurred in 10.5% of patients in the T-DM1 group and 15.9% of those in the trastuzumab group. The safety data were consistent with the known safety profile of T-DM1, with more adverse events associated with T-DM1 than with trastuzumab alone.

CONCLUSIONS

Among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone. (Funded by F. Hoffmann–La Roche/Genentech; KATHERINE ClinicalTrials.gov number, NCT01772472.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. von Minckwitz at the German Breast Group, GBG Forschungs, Martin-Behaim-Str. 12, 63263 Neu-Isenburg, Germany, or at vonminckwitz@gbg.de.

*A complete list of the KATHERINE Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Among patients with human epidermal growth factor receptor 2 (HER2)–positive early breast cancer who have received neoadjuvant chemotherapy plus HER2-targeted therapy and are then found to have residual invasive disease at surgery, the risk of disease recurrence or death is higher than the risk among patients with a pathological complete response.[1-5] The current standard of postsurgical systemic treatment in patients with hormone-receptor–positive disease is completion of 1 year of HER2-targeted therapy and at least 5 years of adjuvant endocrine therapy, irrespective of pathological findings.[6,7]

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor.[8] T-DM1 retains trastuzumab activity while providing intracellular delivery of DM1 to HER2-overexpressing cells.[9] In two phase 3 trials involving patients with HER2-positive advanced breast cancer who had previously received HER2-targeted therapy including trastuzumab and chemotherapy, T-DM1 showed superior efficacy and a favorable risk–benefit profile as compared with capecitabine plus lapatinib or treatment of the physician's choice.[10-13] T-DM1 is approved for use in patients with HER2-positive metastatic breast cancer who previously received treatment with trastuzumab and a taxane.[14]

Given the activity of T-DM1, we hypothesized that it may provide a benefit for patients in whom residual invasive cancer is detected in the resected breast specimen or axillary nodes at surgery after completion of trastuzumab-based neoadjuvant treatment. A phase 2 trial showed that administration of 17 cycles of T-DM1 after an anthracycline regimen was feasible and was not associated with unacceptable toxic effects in patients with HER2-positive early breast cancer.[15] Here, we report the primary results of the KATHERINE trial, which compared adjuvant T-DM1 with trastuzumab in patients who had HER2-positive early breast cancer and residual invasive cancer at surgery after completion of neoadjuvant chemotherapy plus HER2-targeted therapy.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted a multicenter, randomized, open-label, phase 3 trial. Eligible patients were randomly assigned to receive T-DM1 or trastuzumab as adjuvant therapy (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The trial was designed by a steering committee comprising members of the German Breast Group, the National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation, independent investigators, and the sponsor (F. Hoffmann–La Roche/Genentech) and was conducted under the guidance of an independent data and safety monitoring committee. Investigators at the trial sites entered data into a database that was held and managed by the NSABP Foundation. The prespecified interim analysis was conducted under the auspices of the data and safety monitoring committee, which recommended full analysis and disclosure of the results. The results and recommendation were reviewed and accepted jointly by the sponsor and members of the trial steering committee, who vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol (available at NEJM.org). The first draft of the manuscript was written by the first author and the last author with assistance from a medical writer paid by the sponsor. All the authors contributed to subsequent drafts. The trial was conducted in accordance with the amended Declaration of Helsinki, and the protocol was approved by the institutional review board at each participating center. All the patients provided written informed consent.

PATIENTS

Patients were eligible for participation in the trial if they had histologically confirmed, HER2-positive, nonmetastatic, invasive primary breast cancer (clinical tumor stage T1 to T4, nodal stage N0 to N3, and metastasis stage M0 excluding clinical stage T1aN0 or T1bN0) at presentation and if residual invasive disease was detected pathologically in the surgical specimen of the breast or axillary lymph nodes after completion of taxane-based neoadjuvant chemotherapy administered with trastuzumab. HER2 status was assessed in pretreatment biopsy samples if they were available; if they were not available, a surgical sample was used for assessment. HER2 status was centrally confirmed before trial enrollment (details are provided in the Supplementary Methods section of the Supplementary Appendix). Patients had to have completed at least six

cycles (16 weeks) of a conventional preoperative chemotherapy regimen containing a minimum of 9 weeks of taxane-based therapy and 9 weeks of trastuzumab therapy (slightly shorter treatment durations were permitted for dose-dense regimens). Anthracyclines and alkylating agents were permitted according to local standards, as were additional HER2-targeted agents. (Additional eligibility criteria are provided in the Supplementary Methods section of the Supplementary Appendix.) Exclusion criteria included the following: gross residual disease remaining after mastectomy or positive margins after breast-conserving surgery; progressive disease during neoadjuvant therapy; and cardiopulmonary dysfunction, including heart failure of New York Heart Association (NYHA) class II (mild symptoms and function limitation) or higher or a history of a reduction in the left ventricular ejection fraction to less than 40% with previous therapy.

RANDOMIZATION AND TREATMENT

Within 12 weeks after surgery, patients were randomly assigned in a 1:1 ratio with the use of an interactive voice-response or Web-response system. A permuted-block randomization scheme was used with stratification according to the following: clinical stage at presentation (inoperable breast cancer [tumor stage T4 or nodal stage N2 or N3 and metastasis stage M0] vs. operable breast cancer [tumor stage T1 to T3, nodal stage N0 or N1, and metastasis stage M0]); hormone-receptor status according to local laboratory assessment (estrogen-receptor–positive, progesterone-receptor–positive, or both vs. estrogen-receptor–negative and progesterone-receptor–negative or unknown); preoperative HER2-directed therapy (trastuzumab alone vs. trastuzumab plus an additional HER2-directed agent); and pathological nodal status evaluated after neoadjuvant therapy (node-positive vs. node-negative or not evaluated).

Patients received T-DM1 at a dose of 3.6 mg per kilogram of body weight or trastuzumab at a dose of 6 mg per kilogram intravenously every 3 weeks for 14 cycles. A loading dose of 8 mg of trastuzumab per kilogram was administered if more than 6 weeks had elapsed since the preceding dose of trastuzumab. Patients who discontinued T-DM1 early because of toxic effects could complete 14 cycles of trial treatment with trastuzumab at the discretion of the investigator. Radiation therapy (see the Supplementary Appendix) and endocrine therapy were administered according to institutional standards and the trial protocol.

ASSESSMENTS

Imaging assessment for metastatic disease was not mandatory after patients received neoadjuvant therapy and underwent surgery before randomization. Patients were assessed for toxic effects before each dose of trial therapy was administered and during scheduled follow-up visits. The left ventricular ejection fraction was assessed during the last week of cycle 2; every four cycles thereafter; at trial-drug completion (if an assessment was not performed in the previous 6 weeks); at 3, 6, 12, 18, and 24 months; and annually thereafter to year 5. Clinical assessments for disease recurrence occurred every 3 months from the date of randomization to year 2, then every 6 months to year 5, and annually thereafter to year 10.

STATISTICAL ANALYSIS

The primary end point, invasive disease–free survival, was defined as the time from randomization until the date of the first occurrence of one of the following events (hereafter referred to as invasive-disease events): recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. The standardized definitions for efficacy end points (STEEP criteria) also include second primary nonbreast cancer as an invasive-disease event,[16] so this larger definition of invasive-disease events plus second primary nonbreast cancer was used as a secondary end point. Other secondary end points included disease-free survival (including noninvasive breast cancers), overall survival, distant recurrence–free survival, and safety.

A sample of 1484 patients was planned on the basis of a requirement of 384 invasive-disease events to provide 80% power to detect a hazard ratio of 0.75 with a two-sided significance level of 5% for the primary analysis. This calculation assumed that the percentages of patients who would be free of invasive disease at 3 years would be 70.0% with trastuzumab and 76.5% with T-DM1. A single interim analysis of invasive disease–free survival was planned when approximately 67% of the projected invasive-disease events had occurred, with a P value of 0.0124 for

an efficacy stopping boundary or an observed hazard ratio of less than 0.732. The results of the interim analysis crossed the early stopping boundary for benefit of T-DM1 and are presented here.

The primary analysis was based on the intention-to-treat population. An unstratified log-rank test was used to compare invasive disease–free survival between the two treatment groups, as prespecified in the statistical analysis plan, because the smallest subgroup had fewer than five patients in either group. A Cox proportional-hazards model was used to estimate the hazard ratio and its 95% confidence interval. The percentage of patients who would be free of invasive disease at 3 years in each treatment group was estimated with the Kaplan–Meier method. Data from patients who did not have a documented event were censored at the date the patient was last known to be alive and event-free.

The first interim analysis of overall survival was planned to occur if the interim analysis of invasive disease–free survival crossed the prespecified boundary. The overall type I error is controlled at 0.05 for the overall survival analysis with the use of the Lan–DeMets alpha-spending function with an O'Brien–Fleming boundary. Three additional overall survival analyses are planned: an interim analysis at the time of the final invasive disease–free survival analysis (when approximately 384 events have occurred), an interim analysis when approximately 279 deaths have occurred, and a final analysis when approximately 367 deaths have occurred.

The safety analysis included all the patients who received at least one dose of a trial drug. Cardiac events and potential cases of hepatic dysfunction were adjudicated by an independent clinical-events committee. Cardiac events were defined as death from a cardiac cause or heart failure of NYHA class III or IV, with a decrease in the left ventricular ejection fraction of at least 10 percentage points from baseline to a value of less than 50%. These events were summarized according to treatment group.

RESULTS

PATIENTS

From April 2013 through December 2015, a total of 1486 patients were randomly assigned to receive T-DM1 or trastuzumab (743 patients in each group) at 273 trial sites in 28 countries. The median duration of follow-up in the intention-to-treat population was 41.4 months (range, 0.1 to 62.7) in the T-DM1 group and 40.9 months (range, 0.1 to 62.6) in the trastuzumab group. After randomization, 23 patients in the trastuzumab group and 4 patients in the T-DM1 group did not receive assigned therapy as part of the trial (Fig. S2 in the Supplementary Appendix). The baseline characteristics of the patients were balanced between the two treatment groups (Table 1, and Table S1 in the Supplementary Appendix). Hormone-receptor–positive disease was present in 72.3% of the patients. The majority of the patients (76.9%) had received an anthracycline-containing neoadjuvant chemotherapy regimen, and another HER2-targeted agent in addition to trastuzumab had been administered as a component of neoadjuvant therapy in 19.5% of the patients.

EFFICACY

The early reporting efficacy boundary was crossed at the prespecified interim analysis, which triggered full trial analysis. Invasive disease occurred in 91 patients who received T-DM1 (12.2%) and 165 patients who received trastuzumab (22.2%). Estimated percentages of patients who would be free of invasive disease at 3 years were 88.3% in the T-DM1 group and 77.0% in the trastuzumab group. Invasive disease–free survival, the primary end point, was significantly higher among patients who received T-DM1 than among those who received trastuzumab (hazard ratio, 0.50; 95% confidence interval [CI], 0.39 to 0.64; P<0.001) (Fig. 1). Distant recurrence as the first invasive-disease event occurred in 78 patients who received T-DM1 (10.5%) and 118 patients who received trastuzumab (15.9%) (Table S2 in the Supplementary Appendix). The risk of distant recurrence was lower in the T-DM1 group than in the trastuzumab group (hazard ratio, 0.60; 95% CI, 0.45 to 0.79) (Table S3 in the Supplementary Appendix).

A subgroup analysis of invasive disease–free survival revealed a consistent benefit of T-DM1 across stratification cohorts and other subgroups (Fig. 2), including patients with hormone-receptor–positive or hormone-receptor–negative disease, patients with positive or negative pathological nodal status after neoadjuvant therapy, and patients with either no residual invasive pri-

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

Characteristic	Trastuzumab Group (N=743)	T-DM1 Group (N=743)
Median age (range) — yr	49 (23–80)	49 (24–79)
Race or ethnic group — no. of patients (%)†		
White	531 (71.5)	551 (74.2)
Asian	64 (8.6)	65 (8.7)
Black	19 (2.6)	21 (2.8)
American Indian or Alaska Native‡	50 (6.7)	36 (4.8)
Multiple or unknown	79 (10.6)	70 (9.4)
Clinical stage at presentation — no. of patients (%)		
Inoperable breast cancer§	190 (25.6)	185 (24.9)
Operable breast cancer¶	553 (74.4)	558 (75.1)
Hormone-receptor status — no. of patients (%)		
Estrogen-receptor–negative and progesterone-receptor–negative or status unknown	203 (27.3)	209 (28.1)
Estrogen-receptor–positive, progesterone-receptor–positive, or both	540 (72.7)	534 (71.9)
Previous use of anthracycline — no. of patients (%)	564 (75.9)	579 (77.9)
Neoadjuvant HER2-targeted therapy — no. of patients (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus pertuzumab	139 (18.7)	133 (17.9)
Trastuzumab plus other HER2-targeted therapy‖	8 (1.1)	10 (1.3)

* Additional baseline characteristics are listed in Table S1 in the Supplementary Appendix. Percentages may not total 100 because of rounding. HER2 denotes human epidermal growth factor receptor 2, and T-DM1 trastuzumab emtansine.
† Race or ethnic group was reported by the investigators.
‡ The American Indian category includes North, Central, and South American Indians.
§ Inoperable breast cancer was defined as tumor stage T4, nodal stage Nx, and metastasis stage M0 or tumor stage Tx, nodal stage N2 or N3, and metastasis stage M0.
¶ Operable breast cancer was defined as tumor stage T1 to T3, nodal stage N0 or N1, and metastasis stage M0.
‖ Other HER2-targeted agents were neratinib, dacomitinib, afatinib, and lapatinib.

mary disease or residual primary disease of 1 cm or less in the breast. In an exploratory analysis, benefit was seen in 331 patients with residual invasive disease of 1 cm or less in the breast and negative lymph nodes, with invasive-disease events in 17 patients in the T-DM1 group (10.0%) and 25 patients in the trastuzumab group (15.5%) (hazard ratio, 0.60; 95% CI, 0.33 to 1.12). A benefit of adjuvant T-DM1 relative to adjuvant trastuzumab was observed irrespective of neoadjuvant HER2-targeted therapy. Among patients who received neoadjuvant trastuzumab with chemotherapy, invasive-disease events occurred in 78 patients in the T-DM1 group and 141 patients in the adjuvant trastuzumab group (hazard ratio, 0.49; 95% CI, 0.37 to 0.65). Among patients who received neoadjuvant trastuzumab plus a second HER2-directed therapy with chemotherapy, invasive-disease events occurred in 13 patients in the T-DM1 group and 24 patients in the adjuvant trastuzumab group (hazard ratio, 0.54; 95% CI, 0.27 to 1.06). Pertuzumab was the second therapy in 93.8% of patients who received a second neoadjuvant HER2-directed agent, and in this group, invasive-disease events occurred in 12 patients in the T-DM1 group and 24 patients in the adjuvant trastuzumab group (hazard ratio, 0.50; 95% CI, 0.25 to 1.00) (Table S4 in the Supplementary Appendix).

A total of 98 deaths were reported (42 in the T-DM1 group and 56 in the trastuzumab group), and the overall survival analysis did not cross the early reporting boundary (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.05) (Fig. 1). Of

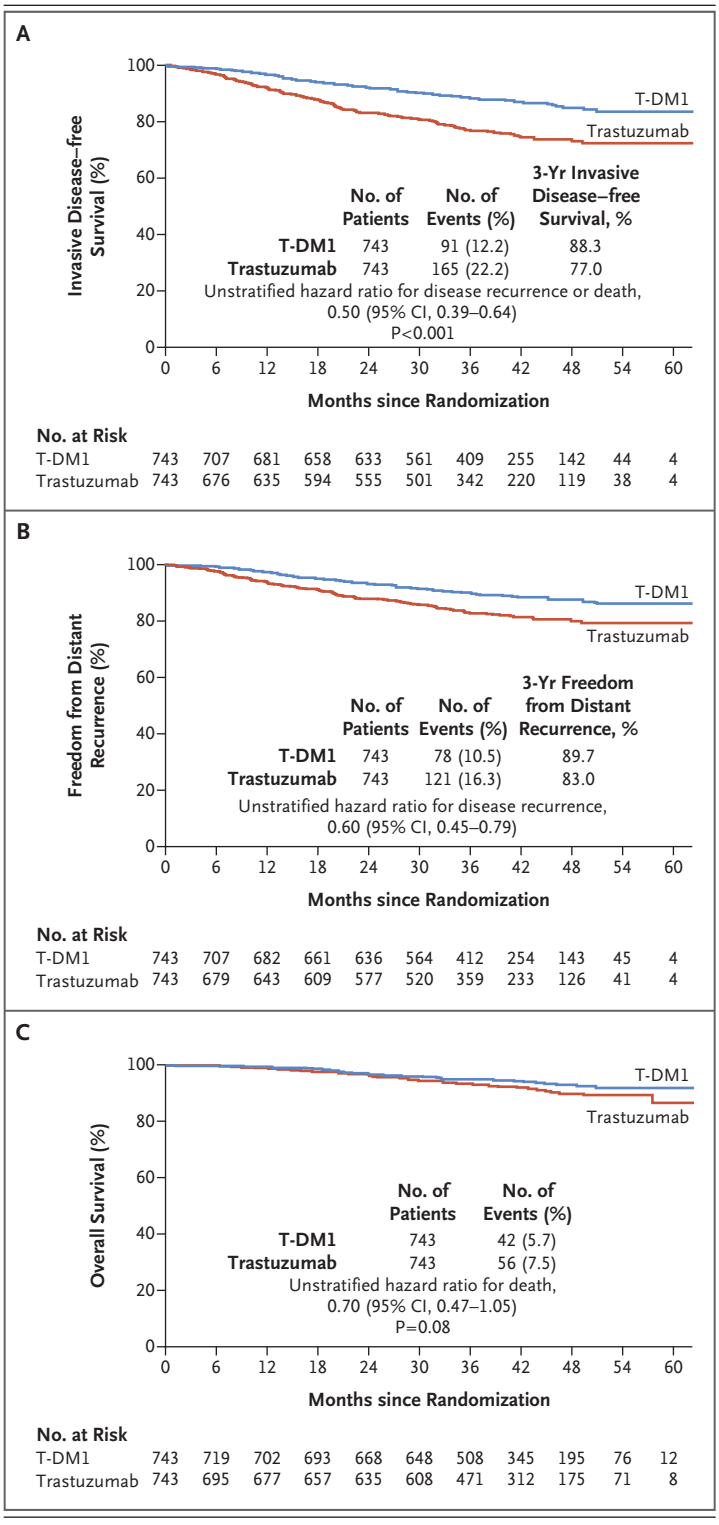

Figure 1. Kaplan–Meier Estimates of Survival in the Interim Analysis.

Invasive disease–free survival (Panel A) was defined as the time from randomization until the date of the first occurrence of one of the following: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. Distant recurrence (Panel B) was defined as evidence of breast cancer in any anatomical site — other than ipsilateral invasive breast tumor or recurrence of locoregional invasive breast cancer — that was either histologically confirmed or clinically diagnosed as recurrent invasive breast cancer. No statistical adjustments were made for multiple comparisons. For overall survival (Panel C), the P value for the boundary for significance in this prespecified interim analysis was less than 0.000032, corresponding to a hazard ratio of less than 0.43. CI denotes confidence interval.

the patients who died, 2 in the T-DM1 group and 3 in the trastuzumab group did not have previous invasive disease.

SAFETY

A total of 1460 patients (740 in the T-DM1 group and 720 in the trastuzumab group) were included in the safety analysis. All 14 cycles of assigned therapy were completed in 71.4% of patients who received T-DM1 and 81.0% of patients who received trastuzumab (Tables S5 and S6 in the Supplementary Appendix). In the T-DM1 group, 77 patients (10.4%) had one dose-level reduction, and 29 (3.9%) had a second dose-level reduction (Table S6 in the Supplementary Appendix). Of the 133 patients who discontinued T-DM1 early, 71 switched to trastuzumab, of whom 63 completed a total of 14 cycles of HER2-targeted treatment.

The most common adverse events of grade 3 or higher were a decreased platelet count (in 5.7% of the patients) and hypertension (in 2.0%) in the T-DM1 group and hypertension (in 1.2%) and radiation-related skin injury (in 1.0%) in the trastuzumab group (Table 2). Serious adverse events occurred in 94 patients who received T-DM1 (12.7%) and 58 patients who received trastuzumab (8.1%). Adverse events leading to discontinuation of the trial drug occurred in 133 patients in the T-DM1 group (18.0%) and 15 patients in the trastuzumab group (2.1%). In the T-DM1 group, the most common adverse events leading to discontinuation of the drug were laboratory abnormalities (decreased platelet count [in 4.2%], elevated blood bilirubin level [in 2.6%], elevated aspartate aminotransferase level [in 1.6%], and elevated alanine aminotransferase level [in 1.5%]), peripheral sensory neuropathy (in 1.5%),

Subgroup	T-DM1	Trastuzumab	Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate	
	no. of patients with an invasive-disease event/total no.			T-DM1 %	Trastuzumab %
All patients	91/743	165/743	0.50 (0.39–0.64)	88.3	77.0
Age group					
<40 yr	20/143	37/153	0.50 (0.29–0.86)	86.5	74.9
40–64 yr	64/542	113/522	0.49 (0.36–0.67)	88.8	77.1
≥65 yr	7/58	15/68	0.55 (0.22–1.34)	87.4	81.1
Clinical stage at presentation					
Inoperable breast cancer	42/185	70/190	0.54 (0.37–0.80)	76.0	60.2
Operable breast cancer	49/558	95/553	0.47 (0.33–0.66)	92.3	82.8
Hormone-receptor status					
Negative (ER-negative and progesterone-receptor–negative or unknown)	38/209	61/203	0.50 (0.33–0.74)	82.1	66.6
Positive (ER-positive, progesterone-receptor–positive, or both)	53/534	104/540	0.48 (0.35–0.67)	90.7	80.7
Preoperative HER2-directed therapy					
Trastuzumab alone	78/600	141/596	0.49 (0.37–0.65)	87.7	75.9
Trastuzumab plus additional HER2-directed agent or agents	13/143	24/147	0.54 (0.27–1.06)	90.9	81.8
Pathological nodal status after preoperative therapy					
Node-positive	62/343	103/346	0.52 (0.38–0.71)	83.0	67.7
Node-negative or NE	29/400	62/397	0.44 (0.28–0.68)	92.8	84.6
Primary tumor stage at definitive surgery					
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	40/331	52/306	0.66 (0.44–1.00)	88.3	83.6
ypT1, ypT1c	14/175	42/184	0.34 (0.19–0.62)	91.9	75.9
ypT2	25/174	44/185	0.50 (0.31–0.82)	88.3	74.3
ypT3	9/51	21/57	0.40 (0.18–0.88)	79.8	61.1
ypT4	3/12	6/11	0.29 (0.07–1.17)	70.0	30.0
Regional lymph-node stage at definitive surgery					
ypN0	28/344	56/335	0.46 (0.30–0.73)	91.9	83.9
ypN1	29/220	50/213	0.49 (0.31–0.78)	88.9	75.8
ypN2	16/86	38/103	0.43 (0.24–0.77)	81.1	58.2
ypN3	17/37	15/30	0.71 (0.35–1.42)	52.0	40.6
ypNX	1/56	6/62	0.17 (0.02–1.38)	98.1	88.7

Figure 2. Subgroup Analysis of Invasive Disease–free Survival.

Five patients with a ypT1 tumor stage had ypT1 disease without further subspecification. The ypT4 category includes all patients with ypT4 and one patient with ypTX. The size of the black squares corresponds to the number of patients. ER denotes estrogen receptor, and HER2 human epidermal growth factor receptor 2.

Table 2. Summary of Adverse Events in the Safety Population.*

Event	Trastuzumab Group (N=720)	T-DM1 Group (N=740)
	no. of patients (%)	
Any adverse event	672 (93.3)	731 (98.8)
Grade ≥3 adverse event	111 (15.4)	190 (25.7)
Adverse event leading to death†	0	1 (0.1)
Serious adverse event	58 (8.1)	94 (12.7)
Adverse event leading to discontinuation of trial drug‡	15 (2.1)	133 (18.0)
Grade ≥3 adverse event that occurred in ≥1% of patients in either group		
Decreased platelet count	2 (0.3)	42 (5.7)
Hypertension	9 (1.2)	15 (2.0)
Radiation-related skin injury	7 (1.0)	10 (1.4)
Peripheral sensory neuropathy	0	10 (1.4)
Decreased neutrophil count	5 (0.7)	9 (1.2)
Hypokalemia	1 (0.1)	9 (1.2)
Fatigue	1 (0.1)	8 (1.1)
Anemia	1 (0.1)	8 (1.1)

* Listed are adverse events with an onset that occurred from the first dose of any trial treatment through 30 days after the final dose of trial treatment and adverse events with an onset in the follow-up period that were determined by the investigators to be related to the trial drug or trial procedure. Patients may have had more than one adverse event.

† One patient with a platelet count of 55,000 per cubic millimeter fell at home and died of an intracranial hemorrhage.

‡ The most common adverse event leading to discontinuation of the trial drug in the trastuzumab group was a decreased ejection fraction in 10 of 720 patients (1.4%). The most common adverse events leading to discontinuation of the trial drug in the T-DM1 group were a decreased platelet count in 31 of 740 patients (4.2%), an increased blood bilirubin level in 19 patients (2.6%), an increased aspartate aminotransferase level in 12 patients (1.6%), an increased alanine aminotransferase level in 11 patients (1.5%), peripheral sensory neuropathy in 11 patients (1.5%), and a decreased ejection fraction in 9 patients (1.2%).

and decreased ejection fraction (in 1.2%). One patient in the T-DM1 group who had a decreased platelet count died from an intracranial hemorrhage that occurred after a fall (Table 2). The percentages of patients with hemorrhage of grade 3 or higher were similar in the T-DM1 group and the trastuzumab group (0.4% and 0.3%).

Adverse events of any grade were more common in the T-DM1 group than in the trastuzumab group (98.8% vs. 93.3%) (Table 3, and Table S7 in the Supplementary Appendix), and 25.7% of the patients had adverse events of grade 3 or higher in the T-DM1 group, as compared with 15.4% in the trastuzumab group. Peripheral sensory neuropathy of any grade was reported in 138 patients who received T-DM1 (18.6%) and 50 patients who received trastuzumab (6.9%); 103 of the 138 cases of sensory neuropathy in the T-DM1 group (74.6%) were reported by the investigators as being resolved at the data cutoff point. Pneumonitis (of any grade) occurred in 19 patients in the T-DM1 group (2.6%) and 6 patients in the trastuzumab group (0.8%). Of the adverse events of any grade, 11 (1.5%) and 5 (0.7%), respectively, were radiation pneumonitis; all cases were resolved at the data cutoff point. Increased aminotransferase levels of any grade occurred more frequently in the T-DM1 group (elevated alanine aminotransferase level in 23.1% of the patients and elevated aspartate aminotransferase level in 28.4%) than in the trastuzumab group (elevated alanine aminotransferase level in 5.7% of the patients and elevated aspartate aminotransferase level in 5.6%) (Table 3). Two adjudicated cases of hepatic nodular regenerative hyperplasia occurred in the T-DM1 group. Adjudicated cardiac events occurred in 4 patients in the trastuzumab group (0.6%) and in 1 patient in the T-DM1 group (0.1%).

DISCUSSION

In this trial, adjuvant treatment with T-DM1 resulted in a 50% lower risk of recurrence of invasive disease or death than adjuvant continuation of trastuzumab among patients with HER2-positive early breast cancer and residual invasive disease after completion of neoadjuvant chemotherapy plus HER2-targeted therapy. As expected, a higher percentage of patients had adverse events in the T-DM1 group than in the trastuzumab group; adverse events of grade 3 or higher occurred in 25.7% of patients in the T-DM1 group and in 15.4% of those in the trastuzumab group. Subgroup analyses showed a consistent benefit, irrespective of hormone-receptor status, the extent of residual disease at surgery, single or dual HER2-targeted therapy in the neoadjuvant regimen, and baseline characteristics of the patients. Distant recurrence was the first invasive-disease event in fewer patients in the T-DM1 group than in the trastuzumab group (10.5% vs. 15.9%). Additional follow-up will be necessary to determine whether there is an effect of adjuvant T-DM1 on overall survival.

Table 3. Adverse Events of Any Grade with an Incidence of at Least 15% in Either Treatment Group in the Safety Population.*

Adverse Event	Trastuzumab Group (N = 720)				T-DM1 Group (N = 740)			
	Any Grade	Grade 1	Grade 2	Grade 3†	Any Grade	Grade 1	Grade 2	Grade 3†
	no. of patients (%)							
Fatigue	243 (33.8)	189 (26.2)	53 (7.4)	1 (0.1)	366 (49.5)	247 (33.4)	111 (15.0)	8 (1.1)
Nausea	94 (13.1)	74 (10.3)	18 (2.5)	2 (0.3)	308 (41.6)	244 (33.0)	60 (8.1)	4 (0.5)
Decreased platelet count†	17 (2.4)	14 (1.9)	1 (0.1)	1 (0.1)	211 (28.5)	105 (14.2)	64 (8.6)	27 (3.6)
Increased aspartate aminotransferase level	40 (5.6)	36 (5.0)	2 (0.3)	2 (0.3)	210 (28.4)	171 (23.1)	35 (4.7)	4 (0.5)
Headache	122 (16.9)	94 (13.1)	27 (3.8)	1 (0.1)	210 (28.4)	165 (22.3)	45 (6.1)	0
Arthralgia	148 (20.6)	114 (15.8)	34 (4.7)	0	192 (25.9)	143 (19.3)	48 (6.5)	1 (0.1)
Radiation-related skin injury	199 (27.6)	121 (16.8)	71 (9.9)	7 (1.0)	188 (25.4)	98 (13.2)	80 (10.8)	10 (1.4
Increased alanine aminotransferase level	41 (5.7)	35 (4.9)	4 (0.6)	2 (0.3)	171 (23.1)	136 (18.4)	32 (4.3)	3 (0.4)
Epistaxis	25 (3.5)	24 (3.3)	1 (0.1)	0	159 (21.5)	143 (19.3)	16 (2.2)	0
Peripheral sensory neuropathy	50 (6.9)	39 (5.4)	11 (1.5)	0	138 (18.6)	90 (12.2)	38 (5.1)	10 (1.4)
Constipation	59 (8.2)	51 (7.1)	8 (1.1)	0	126 (17.0)	105 (14.2)	20 (2.7)	1 (0.1)
Myalgia	80 (11.1)	64 (8.9)	16 (2.2)	0	114 (15.4)	84 (11.4)	27 (3.6)	3 (0.4)
Hot flashes	146 (20.3)	118 (16.4)	26 (3.6)	2 (0.3)	95 (12.8)	82 (11.1)	13 (1.8)	0

* Adverse events of any grade that occurred in at least 10% of the patients in either treatment group are listed in Table S7 in the Supplementary Appendix.
† All listed adverse events are grade 3 except for decreased platelet count, which includes 0.1% of patients in the trastuzumab group and 2.0% of patients in the T-DM1 group who had a grade 4 decreased platelet count.

Patients with HER2-positive early breast cancer who have residual invasive disease after standard neoadjuvant therapies, which include trastuzumab, have a substantially less favorable prognosis than those with a pathological complete response.[3-5] However, pathological complete responses occur in only 40% to 60% of patients,[1,3-5] and a paucity of published data exist to provide guidance on postoperative therapy in patients in whom residual disease is detected in the resected breast specimen or lymph nodes. Since standard adjuvant therapy for HER2-positive breast cancer is 1 year of HER2-targeted therapy, completion of this therapy in patients undergoing neoadjuvant therapy has become an accepted practice, irrespective of pathological response status. In the KATHERINE trial, switching from HER2-directed therapy to single-agent T-DM1 after neoadjuvant chemotherapy with trastuzumab-based neoadjuvant therapy (either single or dual HER2 blockade) improved outcomes in patients with persisting invasive cancer at surgery. It is notable, however, that even with the improved outcomes seen with T-DM1 in these patients, the central nervous system was one of the sites of first recurrence in approximately 5% of patients in both treatment groups (Table S2 in the Supplementary Appendix). Recurrence in the central nervous system in patients with HER2-positive early breast cancer remains a persistent problem for which effective therapies are lacking.

Our trial is the third global, phase 3 trial to show greater improvement in outcomes with additional HER2-targeted therapy than with 1 year of trastuzumab alone in patients with HER2-positive, early breast cancer. The ExteNET trial evaluated 1 year of extended adjuvant therapy with neratinib monotherapy as compared with placebo after completion of 1 year of trastuzumab.[17] In the APHINITY trial, patients were randomly assigned to receive either pertuzumab or placebo added to standard adjuvant chemotherapy plus 1 year of treatment with trastuzumab for resected, operable, HER2-positive breast cancer.[18] The KATHERINE trial focused on higher-risk patients with residual invasive breast cancer after completion of neoadjuvant chemotherapy administered with trastuzumab-containing therapy. Differences in trial designs and patient populations limit the usefulness of comparisons among these studies. For example, patients in the KATHERINE trial had a substantially worse baseline prognosis than those enrolled in the ExteNET and APHINITY trials.

The safety profile of T-DM1 was consistent with that in previous studies; as expected, there were more adverse events with T-DM1 than with adjuvant trastuzumab. Higher-grade or enduring adverse events are of particular importance in the treatment of early breast cancer. All the patients in our trial had received neoadjuvant therapy with a taxane, and patients with preexisting grade 1 neuropathy were allowed to enroll in the trial. Peripheral sensory neuropathy of any grade was reported in 138 patients in the T-DM1 group (18.6%) and in 50 patients in the trastuzumab group (6.9%), and grade 3 peripheral sensory neuropathy was reported in 10 patients in the T-DM1 group (1.4%). By the time of data cutoff, neuropathy had resolved in 103 of 138 patients in the T-DM1 group (74.6%). Despite a higher percentage of patients with thrombocytopenia in the T-DM1 group, the percentages of patients with hemorrhage of grade 3 or higher were similar in the two groups (0.4% in the T-DM1 group and 0.3% in the trastuzumab group). However, 1 patient in the T-DM1 group died of an intracranial hemorrhage associated with a fall and grade 2 thrombocytopenia. Two cases of hepatic nodular regenerative hyperplasia occurred in the T-DM1 group. Radiation pneumonitis occurred in 11 patients in the T-DM1 group (1.5%); this incidence was higher than that in the control group (0.7%). There were fewer cardiac events in the T-DM1 group than in the trastuzumab group, although there were only five events (0.3%) overall.

A potential limitation of the KATHERINE trial was the pragmatic decision to preferentially use the pretreatment core biopsy specimen of the primary tumor to centrally confirm positive HER2-status. The apparent loss of HER2-positive status in patients with residual disease after neoadjuvant therapy has been reported,[19,20] but our trial was not designed to specifically address the activity of T-DM1 in this subgroup. Further analyses to define the rate of HER2 loss in the postsurgical specimens and the activity of T-DM1 in these patients are planned and possible, since paired specimens from more than two thirds of the patients in the trial have been obtained.

In conclusion, in this randomized, phase 3 trial, among patients with HER2-positive early

breast cancer who had residual invasive disease after completion of neoadjuvant therapy with a trastuzumab-containing regimen, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone. The homogeneity of benefit was seen across all subgroups.

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APPENDIX

The authors' full names and academic degrees are as follows: Gunter von Minckwitz, M.D., Chiun-Sheng Huang, M.D., Ph.D., Max S. Mano, M.D., Ph.D., Sibylle Loibl, M.D., Eleftherios P. Mamounas, M.D., Michael Untch, M.D., Ph.D., Norman Wolmark, M.D., Priya Rastogi, M.D., Andreas Schneeweiss, M.D., Andres Redondo, M.D., Ph.D., Hans H. Fischer, M.D., William Jacot, M.D., Ph.D., Alison K. Conlin, M.D., Claudia Arce-Salinas, M.D., Ph.D., Irene L. Wapnir, M.D., Christian Jackisch, M.D., Ph.D., Michael P. DiGiovanna, M.D., Ph.D., Peter A. Fasching, M.D., John P. Crown, M.D., Pia Wülfing, M.D., Zhimin Shao, M.D., Elena Rota Caremoli, M.D., Haiyan Wu, Ph.D., Lisa H. Lam, Pharm.D., David Tesarowski, Ph.D., Melanie Smitt, M.D., Hannah Douthwaite, M.Sc., Stina M. Singel, M.D., Ph.D., and Charles E. Geyer, Jr., M.D.

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