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ORIGINAL REPORT

Trastuzumab Emtansine With or Without Pertuzumab Versus Trastuzumab Plus Taxane for Human Epidermal Growth Factor Receptor 2–Positive, Advanced Breast Cancer: Primary Results From the Phase III MARIANNE Study

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ABSTRACT

Purpose
Trastuzumab and pertuzumab are human epidermal growth factor receptor 2 (HER2) –targeted monoclonal antibodies, and trastuzumab emtansine (T-DM1) is an antibody–drug conjugate that combines the properties of trastuzumab with the cytotoxic activity of DM1. T-DM1 demonstrated encouraging efficacy and safety in a phase II study of patients with previously untreated HER2-positive metastatic breast cancer. Combination T-DM1 and pertuzumab showed synergistic activity in cell culture models and had an acceptable safety profile in a phase Ib and II study.

Methods
In the MARIANNE study, 1,095 patients with centrally assessed, HER2-positive, advanced breast cancer and no prior therapy for advanced disease were randomly assigned 1:1:1 to control (trastuzumab plus taxane), T-DM1 plus placebo, hereafter T-DM1, or T-DM1 plus pertuzumab at standard doses. Primary end point was progression-free survival (PFS), as assessed by independent review.

Results
T-DM1 and T-DM1 plus pertuzumab showed noninferior PFS compared with trastuzumab plus taxane (median PFS: 13.7 months with trastuzumab plus taxane, 14.1 months with T-DM1, and 15.2 months with T-DM1 plus pertuzumab). Neither experimental arm showed PFS superiority to trastuzumab plus taxane. Response rate was 67.9% in patients who were treated with trastuzumab plus taxane, 59.7% with T-DM1, and 64.2% with T-DM1 plus pertuzumab; median response duration was 12.5 months, 20.7 months, and 21.2 months, respectively. The incidence of grade ≥ 3 adverse events was numerically higher in the control arm (54.1%) versus the T-DM1 arm (45.4%) and T-DM1 plus pertuzumab arm (46.2%). Numerically fewer patients discontinued treatment because of adverse events in the T-DM1 arms, and health-related quality of life was maintained for longer in the T-DM1 arms.

Conclusion
T-DM1 showed noninferior, but not superior, efficacy and better tolerability than did taxane plus trastuzumab for first-line treatment of HER2-positive, advanced breast cancer.

INTRODUCTION

Overexpression of human epidermal growth factor receptor 2 (HER2) occurs in 15% to 20% of breast cancers.[1-3] Addition of the HER2-targeted monoclonal antibody, trastuzumab, to chemotherapy significantly improves survival relative to chemotherapy alone in patients with previously untreated HER2-positive metastatic breast cancer (MBC).[4] Pertuzumab is an HER2-targeted monoclonal antibody that inhibits ligand-dependent signaling by preventing HER2/HER3 dimerization and activates antibody-dependent cell-mediated cytotoxicity.[5,6] Addition of pertuzumab to trastuzumab plus docetaxel further improves survival[7] and is the current standard of care for patients with previously untreated HER2-positive MBC.[8,9]

ASSOCIATED CONTENT

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Data Supplements

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Antibody–drug conjugates aim to minimize toxicity by selectively delivering the cytotoxic agent to tumor cells, thereby minimizing systemic exposure.[10] Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate that combines trastuzumab with DM1, a cytotoxic agent that induces cell death by inhibiting microtubule polymerization. As with trastuzumab, T-DM1 inhibits HER2 signaling, activates antibody-dependent cellular cytotoxicity, and inhibits HER2 shedding.[11,12] T-DM1 has demonstrated superior efficacy and improved tolerability compared with the previous standard of care in two phase III trials in patients with previously treated HER2-positive, advanced breast cancer.[13,14] This led to approval of T-DM1 for treatment of patients with HER2-positive MBC who previously received trastuzumab and a taxane, separately or in combination.[8,9]

The MARIANNE study was designed to assess the efficacy and safety of T-DM1 and T-DM1 plus pertuzumab compared with trastuzumab plus taxane in patients with HER2-positive, advanced breast cancer and no prior therapy for advanced disease. When the study was designed in 2009, taxane in combination with trastuzumab was the most commonly used regimen for these patients. T-DM1 had demonstrated encouraging efficacy and safety in phase II studies of previously treated MBC[15,16] and previously untreated advanced breast cancer.[17] Combination of T-DM1 and pertuzumab had shown synergistic cytotoxic activity in cell culture and enhanced antitumor activity in xenograft models,[18] as well as an acceptable safety profile, with evidence of activity in a phase Ib and II study.[19]

METHODS

Study Design

MARIANNE is an international, three-arm, randomized, phase III study. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice standards and the Declaration of Helsinki. The study was approved by the relevant institutional review boards or independent ethics committees at each site. Patients provided written informed consent.

Patients were randomly assigned 1:1:1 to trastuzumab plus taxane (control), T-DM1 plus placebo, hereafter T-DM1, or T-DM1 plus pertuzumab by using a hierarchical, dynamic random assignment procedure conducted through an interactive voice-response system. Stratification factors were world region, prior neoadjuvant or adjuvant therapy (if yes, then by prior trastuzumab and/or lapatinib therapy), and visceral disease (presence or absence). The study was open label with respect to assignment to control arm versus T-DM1–containing arms, which were blinded with respect to pertuzumab versus placebo.

The primary end point—progression-free survival (PFS)—was assessed by independent review. PFS was defined as the time from random assignment to disease progression or death from any cause. Progression was assessed by using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[20] Secondary end points included overall survival (OS), objective response rate (ORR), duration of response, health-related quality of life (HRQOL) as assessed by using the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) of the Functional Assessment of Cancer Therapy-Breast (FACT-B),[21] and safety. OS was defined as the time from random assignment to death from any cause. Independent data monitoring and cardiac review committees monitored safety.

Study Oversight

The study was designed by the trial steering committee and representatives of the sponsors, F. Hoffmann–La Roche and Genentech. Data were collected by the sponsor and analyzed in collaboration with the authors, who are responsible for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol.

Patients

Eligible patients had HER2-positive (immunohistochemistry 3+ and/or in situ hybridization positive, prospectively and centrally confirmed at Targos Molecular Pathology GmbH [Kassel, Germany]) advanced breast cancer—that is, unresectable, progressive or recurrent locally advanced, or previously untreated MBC. Patients were age $\geq$ 18 years and had an Eastern Cooperative Oncology Group performance status of 0 or 1 and measurable and/or nonmeasurable disease that was evaluable on the basis of RECIST 1.1.[20] Patients were not eligible if they had received prior chemotherapy in the advanced setting; however, prior hormonal treatment of advanced breast cancer was allowed. Additional exclusion criteria included prior neoadjuvant and/or adjuvant vinca alkaloid or taxane chemotherapy less than 6 months before advanced breast cancer diagnosis and left ventricular ejection fraction of $<$ 50% at baseline.

Procedures

Investigators chose the control treatment: docetaxel plus trastuzumab or paclitaxel plus trastuzumab. Docetaxel (75 mg/m^2 or 100 mg/m^2 administered intravenously [IV] every 3 weeks) or paclitaxel (80 mg/m^2 IV weekly) were administered for a minimum of six cycles (18 weeks) until disease progression or unacceptable toxicity. Trastuzumab was administered at standard doses (with docetaxel: 8 mg/kg IV loading dose, 6 mg/kg IV for subsequent cycles; with paclitaxel: 4 mg/kg IV loading dose, 2 mg/kg IV in subsequent weeks). If taxane or trastuzumab were discontinued for toxicity, treatment with the remaining agent was permitted. T-DM1 and pertuzumab were administered at standard doses (T-DM1: 3.6 mg/kg IV every 3 weeks; pertuzumab 840 mg IV loading dose, 420 mg IV every 3 weeks for subsequent cycles). No dose reductions were permitted for trastuzumab or pertuzumab. Criteria for dose adjustments are listed in Appendix Table A1 (online only).

The protocol-defined schedule for tumor assessments, completion of the FACT-B, and safety monitoring is listed in Appendix Table A2 (online only). FACT-B assessment schedule was modified in a protocol amendment (March 7, 2011) to increase data collection frequency to better assess treatment impact.

Statistical Analysis

Efficacy end points were assessed in the intention-to-treat population. Safety analyses included all patients who received at least one dose of study treatment. Assessment of the primary efficacy end point was planned when approximately 678 PFS events by independent review had occurred. A two-sided stratified log-rank test was used to compare PFS between treatment groups. PFS was also descriptively assessed in prespecified subgroups. Two prespecified interim OS analyses and a final OS analysis were planned, applying a Lan-DeMets alpha spending function with Pocock stopping boundary. The first OS interim analysis was performed at the time of PFS analysis. Final analysis of OS is planned to occur at a minimum follow-up of 46 months after the last patient has been enrolled. If the OS analysis in the intention-to-treat population shows statistical significance, eligible patients would be permitted to switch from trastuzumab plus taxane to T-DM1 or T-DM1 plus pertuzumab.

A clinically meaningful difference in HRQOL was defined as a $\geq$ 5-point decrease from baseline FACT-B TOI-PFB score[22]; a sensitivity analysis was conducted to compare overall results with the postamendment population. For analysis of time-to-event end points (PFS, OS, FACT-B), median time to event was estimated by using the Kaplan-Meier method, and hazard ratios (HRs) and CIs were computed by using stratified and unstratified Cox proportional hazards regression models. Adverse events (AEs) were evaluated descriptively.

Statistical analyses were conducted independently to compare each of the T-DM1−containing arms with control. For each comparison, confirmatory hierarchical statistical testing was performed in a prespecified sequential order as long as statistical significance was obtained. Overall α-level of 5% was split, with 2.5% allocated to each comparison (Appendix Fig A1, online only). Confirmatory comparisons between T-DM1−containing arms were to be conducted only if PFS superiority for T-DM1 plus pertuzumab versus control was demonstrated.

The study had 80% power for PFS noninferiority and superiority analyses. Noninferiority was established if the upper limit of the 97.5% CI for HR was below a prespecified noninferiority margin of HR, 1.1765. This noninferiority margin corresponds to a 15% reduction in median PFS, from 11 months assumed for the control arm to 9.35 months for T-DM1–containing arms. Target HR for superiority was 0.75 (33.3% improvement in median PFS from 11 months to 14.7 months) for T-DM1–containing regimens compared with control, and 0.73 for comparison between T-DM1–containing regimens (37% improvement in median PFS from 14.7 months to 20.1 months). PFS superiority was established if the *P* value obtained from the stratified log-rank test was ≤ .025. Further details on sample size considerations are provided in the Appendix.

RESULTS

Study Population

Between July 6, 2010 and May 2, 2012, 1,095 patients from 241 study sites in 38 countries (Fig 1 and Appendix Fig A2, online only) were randomly assigned to trastuzumab plus taxane (n = 365), T-DM1 (n = 367), and T-DM1 plus pertuzumab (n = 363). In the control arm, 257 patients received trastuzumab plus docetaxel and 96 patients received trastuzumab plus paclitaxel. The data cutoff was September 16, 2014. Baseline demographics and disease characteristics were well-balanced between treatment groups (Table 1). Median duration of follow-up was approximately 35 months in all three arms.

Primary End Point

Treatment with T-DM1 and T-DM1 plus pertuzumab showed noninferior PFS compared with trastuzumab plus taxane, but did

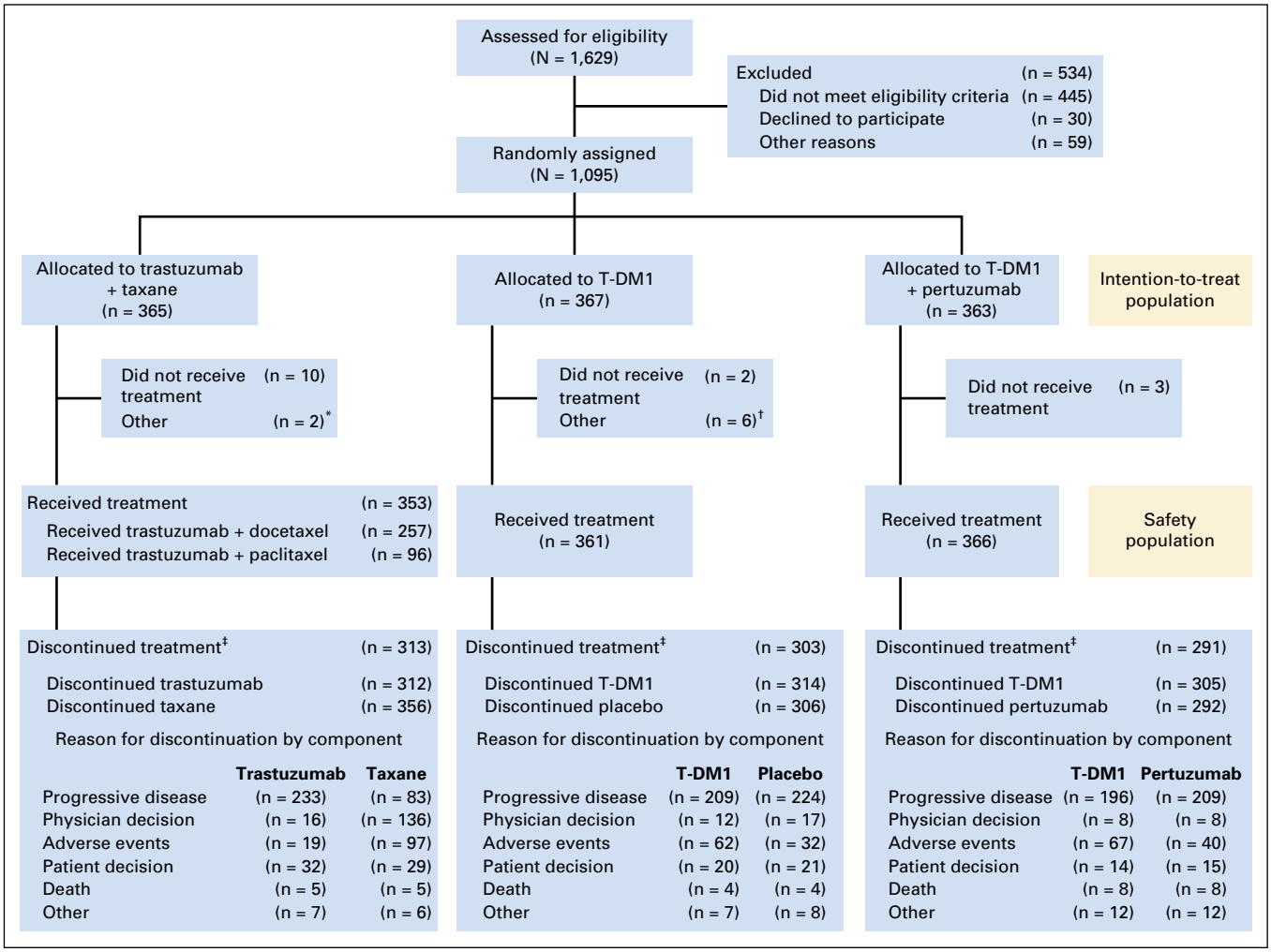


Fig 1. Enrollment, intention-to-treat, and safety populations, treatment discontinuations, and withdrawals. (*)Two patients who were randomly assigned to the trastuzumab plus taxane arm received three cycles of trastuzumab emtansine (T-DM1; one patient received one cycle, one patient two cycles). These patients were included in the T-DM1 group for the safety analyses. (†)Six patients who were randomly assigned to T-DM1 received six cycles of pertuzumab. These patients were included in the T-DM1 plus pertuzumab group for the safety analyses. (‡)Discontinuation of all components of the treatment regimen. The safety analysis population included all patients who received at least one dose of study treatment.

Table 1. Demographic and Baseline Characteristics

Characteristic	Trastuzumab + Taxane (n = 365), No. (%)	T-DM1 (n = 367), No. (%)	T-DM1 + Pertuzumab (n = 363), No. (%)
Age, year			
Median	55	52	52
Range	(22-88)	(27-82)	(27-86)
Race			
White	232 (63.6)	239 (65.1)	233 (64.2)
Black	23 (6.3)	11 (3.0)	10 (2.8)
Asian	89 (24.4)	84 (22.9)	83 (22.9)
Other	21 (5.8)	33 (9.0)	37 (10.2)
World region			
Western Europe, Canada, Australia/Pacific	137 (37.5)	134 (36.5)	137 (37.7)
Asia	76 (20.8)	77 (21.0)	74 (20.4)
Eastern Europe	56 (15.3)	59 (16.1)	56 (15.4)
United States	43 (11.8)	46 (12.5)	42 (11.6)
Other	53 (14.5)	51 (13.9)	54 (14.9)
ECOG PS*			
0	245 (67.1)	239 (65.1)	235 (64.7)
1	119 (32.6)	128 (34.9)	127 (35.0)
ER/PR status†			
ER and/or PR positive	207 (56.7)	195 (53.1)	198 (54.5)
ER and PR negative	154 (42.2)	160 (43.6)	156 (43.0)
Visceral involvement			
Yes	241 (66.0)	251 (68.4)	259 (71.3)
No	124 (34.0)	116 (31.6)	104 (28.7)
Measurable disease			
Yes	287 (78.6)	303 (82.6)	299 (82.4)
No	78 (21.4)	64 (17.4)	64 (17.6)
Prior neoadjuvant/adjuvant therapy			
None	159 (43.6)	165 (45.0)	158 (43.5)
HER2-directed (trastuzumab/lapatinib)	113 (31.0)	113 (30.8)	117 (32.2)
Taxane	120 (32.9)	108 (29.4)	129 (35.5)
Anthracycline	152 (41.6)	162 (44.1)	168 (46.3)
Hormonal	86 (23.6)	85 (23.2)	90 (24.8)
Prior LABC/MBC therapy			
Hormonal	26 (7.1)	21 (5.7)	20 (5.5)
HER2 directed	8 (2.2)	9 (2.5)	8 (2.2)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; PR, progesterone receptor; T-DM1, trastuzumab emtansine.
*ECOG PS = 2 was an exclusion criterion (n = 2).
†Twenty-five patients had unknown ER/PR status.

not show superiority (stratified HR for T-DM1 *v* trastuzumab plus taxane, 0.91; 97.5% CI, 0.73 to 1.13; $P = .31$; stratified HR for T-DM1 plus pertuzumab *v* trastuzumab plus taxane, 0.87; 97.5% CI, 0.69 to 1.08; $P = .14$; [noninferiority margin for the upper boundary of the 97.5% CI was 1.18]; Fig 2A). Median PFS was 13.7 months with trastuzumab plus taxane, 14.1 months with T-DM1, and 15.2 months with T-DM1 plus pertuzumab. Addition of pertuzumab to T-DM1 did not improve PFS (stratified HR for T-DM1 plus pertuzumab *v* T-DM1, 0.91; 97.5% CI, 0.73 to 1.13).

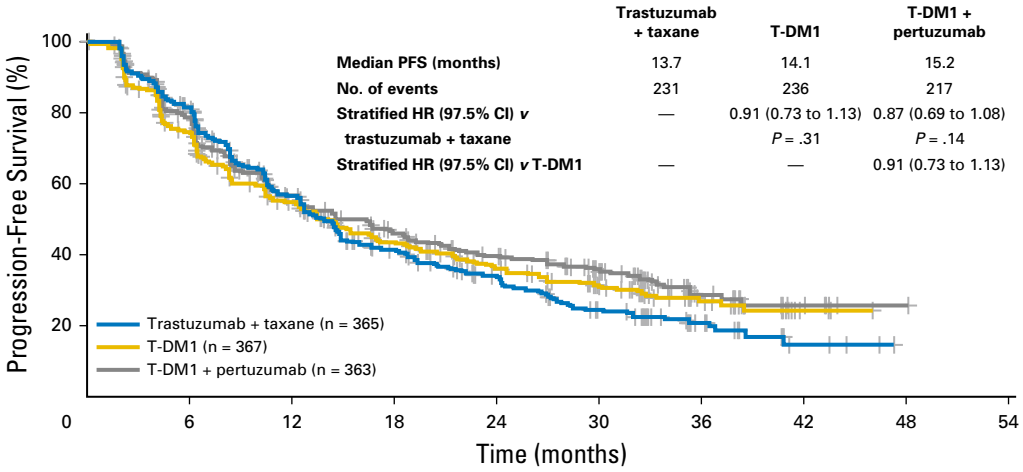
Of 231 PFS events in the trastuzumab plus taxane arm, the earliest contributing event to PFS was death in 31 cases and disease progression in 200 cases. In the T-DM1 arm, 236 PFS events occurred, including 11 deaths and 225 cases of disease progression as the earliest contributing event, and in the T-DM1 plus pertuzumab arm, 217 PFS events occurred, including 23 deaths and 194 cases of disease progression as the earliest contributing event.

PFS was descriptively analyzed in prespecified subgroups and findings were generally consistent with the main analysis conducted in the intention-to-treat population (Fig 2B); however, there was a numerical trend that favored treatment with T-DM1 for patients who had received previous neoadjuvant or adjuvant therapy with trastuzumab or lapatinib (prior treatment: HR, 0.75 [97.5% CI, 0.52 to 1.09]; no prior treatment: HR, 1.12 [97.5% CI, 0.82 to 1.54]) and for patients who had received prior taxane (prior taxane: HR, 0.69 [97.5% CI, 0.48 to 0.99]; no prior taxane: HR, 1.10 [97.5% CI, 0.85 to 1.41]). Similar results were observed for the subgroup analysis of T-DM1 plus pertuzumab versus control (Appendix Fig A2). Subgroup analyses that compared patients who were treated with T-DM1 versus T-DM1 plus pertuzumab showed no notable differences in PFS (Appendix Fig A3, online only). In a post hoc, nonrandomized comparison, median duration of PFS was numerically similar between patients in the control arm who were treated with docetaxel versus paclitaxel (data not shown).

Secondary End Points

In the first interim OS analysis, median OS was not reached in any treatment group (Appendix Fig A4, online only), and the Kaplan-Meier curves were overlapping for the three treatment arms (stratified HRs: T-DM1 *v* trastuzumab plus taxane, 0.86

A



	Trastuzumab + taxane	T-DM1	T-DM1 + pertuzumab
Median PFS (months)	13.7	14.1	15.2
No. of events	231	236	217
Stratified HR (97.5% CI) *v* trastuzumab + taxane	—	0.91 (0.73 to 1.13) *P* = .31	0.87 (0.69 to 1.08) *P* = .14
Stratified HR (97.5% CI) *v* T-DM1	—	—	0.91 (0.73 to 1.13)

No. at risk:									
Trastuzumab + taxane	365	265	163	107	75	50	21	5	
T-DM1	367	257	176	133	104	67	28	3	
T-DM1 + pertuzumab	363	261	177	135	109	75	25	5	1

B

Baseline Risk Factors	Total No.	Trastuzumab + Taxane (n = 365) Median, Mo	T-DM1 (n = 367) Median, Mo	HR (97.5% CI)
All patients	732	13.7	14.1	0.94 (0.76 to 1.16)
World region*				
Asia	153	17.2	11.9	1.16 (0.72 to 1.85)
E. Europe	115	12.4	12.4	1.00 (0.59 to 1.69)
W. Europe, Canada, Australia/Pacific	271	14.0	15.9	0.89 (0.63 to 1.25)
United States	89	12.9	12.6	0.82 (0.45 to 1.49)
Others	104	10.5	14.6	0.75 (0.44 to 1.29)
Neoadjuvant/adjuvant therapy*				
Yes, trastuzumab or lapatanib	226	10.3	15.2	0.75 (0.52 to 1.09)
Yes, not trastuzumab or lapatanib	182	16.5	18.0	0.86 (0.56 to 1.32)
No	324	14.8	12.4	1.12 (0.82 to 1.54)
Visceral involvement*				
Yes	492	12.5	12.4	0.92 (0.72 to 1.18)
No	240	18.1	19.5	0.96 (0.64 to 1.42)
Age group, years				
< 65	609	13.2	13.3	0.96 (0.77 to 1.21)
≥ 65	123	14.6	19.5	0.82 (0.49 to 1.39)
Hormonal status				
ER+ and/or PR+	402	13.7	13.4	0.94 (0.71 to 1.25)
ER- and PR-	314	14.0	13.3	1.00 (0.73 to 1.37)
Prior taxane				
Yes	233	10.8	15.2	0.69 (0.48 to 0.99)
No	499	14.9	12.6	1.10 (0.85 to 1.41)

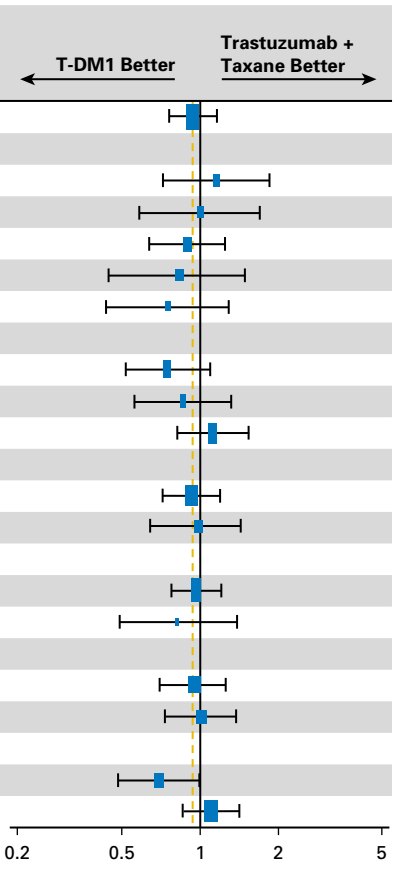


Fig 2. Progression-free survival, as assessed by independent review. (A) Kaplan-Meier estimates of progression-free survival in the intention-to-treat population. Stratified hazard ratios and 97.5% CIs obtained from stratified Cox proportional hazards regression model and *P* values retrieved from stratified log-rank tests are shown. Stratification was according to world region, prior neoadjuvant/adjuvant therapy, and presence of visceral disease. (B) Progression-free survival assessed in prespecified patient subgroups for trastuzumab emtansine (T-DM1) compared with trastuzumab plus taxane. Medians, unstratified hazard ratios, and 97.5% CIs for progression-free survival comparing T-DM1 and trastuzumab plus taxane in prespecified subgroups representing stratification factors and clinically important variables. Vertical dashed line indicates the hazard ratio for all patients. (*)Stratification factor. ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.

[97.5% CI, 0.64 to 1.16]; T-DM1 plus pertuzumab *v* trastuzumab plus taxane, 0.82 [97.5% CI, 0.61 to 1.11]; T-DM1 plus pertuzumab *v* T-DM1, 1.00 [97.5% CI, 0.74 to 1.35]).

ORR analysis included 287 (78.6%), 303 (82.6%), and 299 (82.4%) patients with measurable disease at baseline in the trastuzumab plus taxane, T-DM1, and T-DM1 plus pertuzumab treatment arms, respectively. ORR was 67.9% with trastuzumab plus taxane (195 of 287; 95% CI, 62.3% to 73.3%), 59.7% with T-DM1 (181 of 303; 95% CI, 54.1% to 65.3%), and 64.2% with T-DM1 plus pertuzumab (192 of 299; 95% CI, 58.6% to 69.7%; Appendix Fig A5A, online only). In patients who achieved response, median duration of response was 12.5 months with trastuzumab plus taxane (95% CI, 10.5 to 16.6 months), 20.7 months with T-DM1 (95% CI, 14.8 to 25.0 months), and 21.2 months with T-DM1 plus pertuzumab (95% CI, 15.8 to 29.3 months; Appendix Fig A5B). Additional details on response are available in the Appendix (Appendix Fig A5).

Median time to a clinically meaningful decrease in HRQOL from baseline was 3.6 months with trastuzumab plus taxane, 7.7 months with T-DM1, and 9.0 months with T-DM1 plus pertuzumab (Table 2). Results from the sensitivity analysis were consistent (Appendix Table A3, online only).

Treatment Exposure

In the control arm, the median number of cycles was 7 for docetaxel (range, 1 to 58), 7 for paclitaxel (range, 1 to 42), and 15 for trastuzumab (range, 1 to 69). In the T-DM1 arm, the median number of cycles was 15 (range, 1 to 65) and in the T-DM1-plus-pertuzumab arm, it was 15 (range, 1 to 68) for T-DM1 and 16.5 for pertuzumab (range, 1 to 66). In the control arm, 26.1% and 28.1% of patients who received docetaxel or paclitaxel, respectively, required one dose reduction; one additional patient treated with docetaxel required two dose reductions. In the T-DM1 and T-DM1-plus-pertuzumab arms, 13.6% and 14.8% of patients required a reduction in T-DM1 to 3.0 mg/kg, and an additional 10.5% and 9.0% of patients, respectively, required a second dose reduction to 2.4 mg/kg. Treatment discontinuations as a result of toxicity occurred less often in the T-DM1 arms; 29.7% of patients in the control arm and 18.3% and 19.1% of patients in the T-DM1 and T-DM1-plus-pertuzumab arms, respectively, discontinued any component of their treatment regimen as a result of AEs.

Table 2. Time to Clinically Meaningful Decrease in Health-Related Quality of Life

Time to Event*	Trastuzumab + Taxane (n = 327)	T-DM1 (n = 352)	T-DM1 + Pertuzumab (n = 338)
Median, months	3.6	7.7	9.0
Stratified hazard ratio 95% CI (vs. trastuzumab plus taxane)	—	0.70 (0.57 to 0.86)	0.68 (0.55 to 0.84)

NOTE. Health-Related Quality of Life was measured by the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) of the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire.[21] The analysis included all female patients from the intention-to-treat population who completed the baseline and at least one postbaseline FACT-B assessment.

Abbreviation: T-DM1, trastuzumab emtansine.

*An event was defined as a clinically meaningful decrease in health-related quality of life, which is a ≥ 5-point decrease from baseline in FACT-B TOI-PFB score.[22]

Safety

Incidence of grade ≥ 3 AEs was numerically higher in the control arm (54.1%) than in T-DM1–containing arms (45.4% for T-DM1; 46.2% for T-DM1 plus pertuzumab). The most commonly reported grade ≥ 3 AEs in the trastuzumab plus taxane group were neutropenia (19.8%), febrile neutropenia (6.5%), and diarrhea (4.2%; Table 3). In the T-DM1 arms, the most commonly reported grade ≥ 3 AEs were increased aspartate aminotransferase (6.6%), thrombocytopenia (6.4%), and anemia (4.7%) with T-DM1, and thrombocytopenia (7.9%), anemia (6.0%), and increased alanine aminotransferase (5.2%) with T-DM1 plus pertuzumab. With the exception of an increase in grade ≥ 3 diarrhea (2.5% *v* 0.3% for T-DM1), addition of pertuzumab to T-DM1 did not substantially increase the incidence of high-grade toxicity.

The most commonly reported all-grade AEs that occurred more frequently in the control arm than in T-DM1 arms—with at least a 5-percentage-point difference between arms—were alopecia (59.8% *v* 6.6% with T-DM1 and 9.0% with T-DM1 plus pertuzumab), diarrhea (48.7% *v* 25.2% and 48.1%), and peripheral neuropathy (28.0% *v* 13.3% and 17.8%; Table 3). All-grade AEs that were more frequent in the T-DM1 arm versus control were nausea (47.1% *v* 37.1%), headache (32.1% *v* 22.1%), and epistaxis (31.0% *v* 14.7%). Addition of pertuzumab to T-DM1 generally did not substantially increase the incidence of all-grade toxicities, but it did result in a higher incidence of diarrhea (48.1% *v* 25.2% with T-DM1), as well as vomiting (30.1% *v* 21.6%) and chills (26.8% *v* 15.5%).

A left ventricular ejection fraction of < 50% with a ≥ 15-percentage-point decrease from baseline was observed in 0.8% of patients who were treated with T-DM1 versus 4.5% with trastuzumab plus taxane and 2.5% with T-DM1 plus pertuzumab.

In the safety population, most deaths were attributed to disease progression: 116 (94.3%) of 123 deaths in the control arm, 106 (93.0%) of 114 deaths in the T-DM1 arm, and 106 (91.4%) of 116 deaths in the T-DM1–plus-pertuzumab arm. The number of patients who died as a result of AEs was balanced across treatment arms: 6 (1.7%) in the control arm, 4 (1.1%) in the T-DM1 arm, and 7 (1.9%) in the T-DM1–plus-pertuzumab arm.

DISCUSSION

In this study, T-DM1 and T-DM1 plus pertuzumab demonstrated noninferior PFS compared with trastuzumab plus taxane. Whereas the median PFS observed with T-DM1 (14.1 months) was similar to that observed in a previous phase II study,[17] median PFS of 13.7 months in the trastuzumab plus taxane arm was somewhat longer than expected on the basis of reports of this regimen that were available at the time of study design (median PFS of approximately 9.5 months to 12.5 months).[23-25] However, the median PFS of control arm is consistent with results from more recent studies.[26-28] Addition of pertuzumab to T-DM1 did not improve PFS. Although preclinical data showed synergistic activity for the combination of T-DM1 and pertuzumab,[18] such activity was not

Table 3. Adverse Events in the Safety Population

Adverse Event	Trastuzumab + Taxane (n = 353)	T-DM1 (n = 361)	T-DM1 + Pertuzumab (n = 366)
Grade ≥ 3 adverse events	191 (54.1)	164 (45.4)	169 (46.2)
Grade ≥ 3 adverse events reported in ≥ 3% of patients in any treatment arm			
Neutropenia	70 (19.8)	16 (4.4)	10 (2.7)
Febrile neutropenia	23 (6.5)	0 (0)	0 (0)
Diarrhea	15 (4.2)	1 (0.3)	9 (2.5)
Hypertension	11 (3.1)	16 (4.4)	18 (4.9)
Anemia	10 (2.8)	17 (4.7)	22 (6.0)
ALT increased	3 (0.8)	16 (4.4)	19 (5.2)
AST increased	1 (0.3)	24 (6.6)	11 (3.0)
Thrombocytopenia	0 (0)	23 (6.4)	29 (7.9)
Any adverse event	348 (98.6)	357 (98.9)	361 (98.6)
All-grade adverse events in > 20% of patients in any treatment arm with a > 5-percentage-point difference between trastuzumab + taxane and T-DM1 arms			
Alopecia	211 (59.8)	24 (6.6)	33 (9.0)
Diarrhea	172 (48.7)	91 (25.2)	176 (48.1)
Nausea	131 (37.1)	170 (47.1)	191 (52.2)
Peripheral neuropathy	99 (28.0)	48 (13.3)	65 (17.8)
Peripheral edema	98 (27.8)	34 (9.4)	31 (8.5)
Arthralgia	87 (24.6)	80 (22.2)	69 (18.9)
Rash	86 (24.4)	63 (17.5)	86 (23.5)
Myalgia	82 (23.2)	64 (17.7)	62 (16.9)
Neutropenia	80 (22.7)	41 (11.4)	32 (8.7)
Headache	78 (22.1)	116 (32.1)	118 (32.2)
Peripheral sensory neuropathy	71 (20.1)	47 (13.0)	44 (12.0)
Vomiting	67 (19.0)	78 (21.6)	110 (30.1)
Pyrexia	58 (16.4)	100 (27.7)	118 (32.2)
Epistaxis	52 (14.7)	112 (31.0)	127 (34.7)
Chills	14 (4.0)	56 (15.5)	98 (26.8)

NOTE. Data are given as No. (%). Fifteen patients did not receive any study treatment (10 in trastuzumab + taxane, two in T-DM1, and three in T-DM1 + pertuzumab). Two patients who were randomly assigned to trastuzumab + taxane received at least one cycle of T-DM1 and were included in the T-DM1 arm for safety analyses. Six patients who were randomly assigned to T-DM1 received at least one cycle of pertuzumab and were included in the T-DM1 + pertuzumab arm for safety analyses. The safety analysis population included all patients who received at least one dose of study treatment; safety analyses were based on the treatment that patients actually received.
Abbreviation: T-DM1, trastuzumab emtansine.

substantiated in this trial. Thus, further study that includes ongoing biomarker research may help to better explain this unexpected result.

Whereas T-DM1–containing treatments did not show a statistically significant improvement overall in PFS, data presented here suggest that some patients may derive more relative benefit from T-DM1 than do others. Subgroup analyses showed a numerical trend for an increased relative treatment effect with T-DM1 in patients who had received HER2-directed therapy or taxanes in the early breast cancer setting. This finding is consistent with prior trials in which T-DM1 improved clinical outcomes in patients who previously received treatment with trastuzumab and taxane.[13,14] Moreover, in patients who achieved response, duration of response was numerically longer in T-DM1–treated patients compared with trastuzumab plus taxane–treated patients. Further investigation is necessary to determine whether specific characteristics can define a subgroup of patients with a greater response to T-DM1 in this treatment setting.

Safety profiles of T-DM1 and pertuzumab in this study were consistent with previous reports.[29-31] Treatment with T-DM1 seemed to be more tolerable than that of the control regimen, as there were numerically fewer grade ≥ 3 AEs and fewer treatment discontinuations as a result of AEs observed with T-DM1 versus trastuzumab plus taxane. Of note, incidence of grade ≥ 3 AEs in the control arm (54.1%) was lower than that observed in other trials that used trastuzumab plus docetaxel in the first-line setting (63% to 91%).[17,26] This may be explained, at least in part, by the observation that 27% of patients received paclitaxel instead of docetaxel in the control arm of this study. Nevertheless, T-DM1 also seemd to be more tolerable on the basis of a numerically lower incidence of certain clinically important AEs (febrile neutropenia, neuropathy, diarrhea, and alopecia) versus trastuzumab plus taxane. The most commonly reported high-grade AEs with T-DM1 were laboratory abnormalities, such as transaminase elevation and thrombocytopenia, as previously observed in other T-DM1 studies.[29] T-DM1–treated patients also had a longer time to a clinically meaningful decrease according to the FACT-B TOI-PFB scale, which indicated that they maintained baseline HRQOL longer than did trastuzumab plus taxane–treated patients.

In conclusion, T-DM1–containing regimens demonstrated noninferior—but not superior—PFS compared with treatment with trastuzumab plus taxane. On the basis of the improved tolerability and noninferior PFS observed with T-DM1, it may provide an alternate treatment option to trastuzumab plus taxane in patients HER2-positive MBC. Indeed, the National Comprehensive Cancer Network has included T-DM1 in its breast cancer guidelines as a first-line treatment option for patients with HER2-positive MBC who are considered not suitable for treatment with the preferred regimen, pertuzumab, trastuzumab, and a taxane.[8,32]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Trastuzumab Emtansine With or Without Pertuzumab Versus Trastuzumab Plus Taxane for Human Epidermal Growth Factor Receptor 2–Positive, Advanced Breast Cancer: Primary Results From the Phase III MARIANNE Study

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Sample Size Determination

The study will be powered for superiority, with a target hazard ratio (HR) of 0.75, as well as for noninferiority, with HR, 1.1765 or $\delta = 0.1765$ as the noninferiority margin for comparison between each of the T-DM1–containing treatment arms and the trastuzumab-plus-taxane arm. This margin is equivalent to a 15% reduction in median progression-free survival (PFS). A meta-analysis of trastuzumab trials gives $\delta = 0.194$, assuming a 60% retained effect on the log hazard scale. The chosen δ is therefore comparatively conservative. Comparison of single-agent T-DM1 versus the trastuzumab-plus-taxane control arm and of T-DM1 plus pertuzumab versus the control arm are handled separately. The overall $\alpha = 5\%$ is split so that $\alpha = 2.5\%$ (1.25% one-sided) is spent for each group of comparisons. Depending on the superiority of the primary efficacy end point for the comparison of T-DM1 plus pertuzumab versus the control arm, a formal comparison of T-DM1 plus pertuzumab versus single-agent T-DM1 is planned.

Sample Size Determination for PFS Noninferiority (control arm comparisons: T-DM1 with and without pertuzumab v the control arm)

The following sample size and power considerations are made for an assumed noninferiority situation. Sample size calculations were performed with East 5 software package (Cytel; http://www.cytel.com/) comparing two groups. Assumed study duration timelines are under the alternative hypothesis, that is, treatment effects as specified in each sample size determination section below.

- Assume a median PFS time of 11.0 months for the control arm and an HR of 0.88 or 13.64% improvement in median PFS time to 12.5 months for each of the experimental arms.
- Assume a minimum median PFS as the noninferiority margin of 9.35 months (15% decrease or HR, 1.1765 or $\delta = 0.1765$).
- Assume a recruitment time of approximately 21 months (with ramp-up in the first 6 months) and a study duration time of 35.7 months to required number of events under the alternative hypothesis.
- Define 1.25% one-sided (2.5% two-sided) as the α level and require a power of 80%.
- Request $3 \times 309 = 927$ patients with 670 PFS events (232 events expected for the control arm and 219 events in each of the experimental arms).

Sample Size Determination for PFS Superiority (control arm comparisons: T-DM1 with/without pertuzumab v the control arm)

The following sample size and power considerations are made for an assumed superiority situation:

- Assume a median PFS time of 11.0 months for the control arm and an HR of 0.75 or 33.33% improvement in median PFS time to 14.7 months for each of the experimental arms.
- Assume a recruitment time of approximately 21 months (with ramp-up in the first 6 months) and a study duration time of 33.5 months to the required number of events under the alternative hypothesis.
- Define 1.25% one-sided (2.5% two-sided) as the α level and require a power of 80%.
- Request $3 \times 364 = 1092$ patients with 678 PFS events (248 events expected for the control arm and 215 events in each of the experimental arms).

The required total number of events is higher on the basis of the superiority considerations and drives the total enrollment for the study. Actual occurrence of the total number events—from PFS events on the basis of independent review—will be monitored to get a better estimate of the expected study duration.

Sample Size Determination for PFS Superiority (experimental arm comparisons: single agent T-DM1 v T-DM1 plus pertuzumab)

The following sample size and power considerations are made for an assumed superiority situation. Sample size calculations were performed with East 5 software package (Cytel) comparing two groups:

- Assume a median PFS time of 14.7 months for single-agent T-DM1 and an HR of 0.73 or 36.99% improvement in median PFS time to 20.1 months for T-DM1 plus pertuzumab.
- Assume a recruitment time of approximately 21 months (with ramp-up in the first 6 months) and a study duration time of 33.5 months to the required number of events under the alternative hypothesis.
- Define 1.25% one-sided (2.5% two-sided) as the α level and require a power of 80%.
- Request $2 \times 364 = 728$ patients with 392 PFS events (215 events expected for single-agent T-DM1 and 177 events for T-DM1 plus pertuzuab).

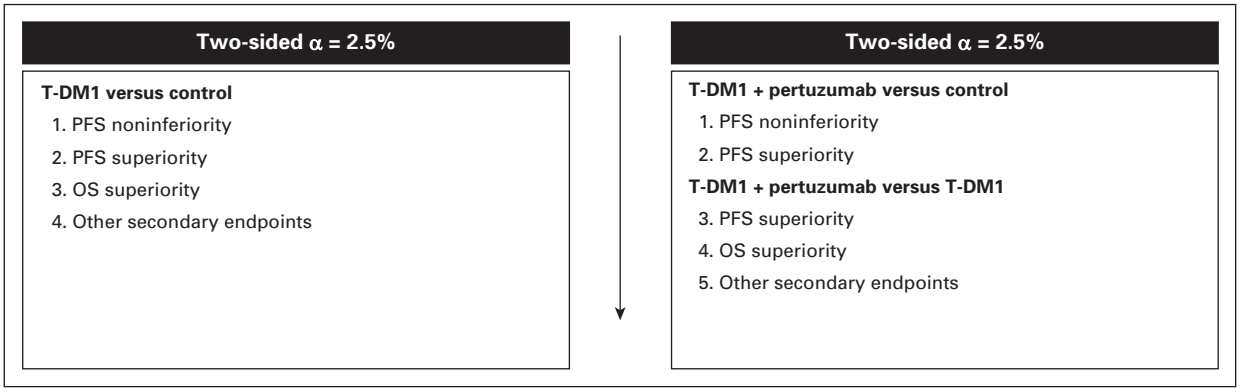


Fig A1. Hierarchical statistical testing sequence. Statistical analyses were conducted independently for trastuzumab emtansine (T-DM1) versus trastuzumab plus taxane (control) and T-DM1 plus pertuzumab versus trastuzumab-plus-taxane (control). Hierarchical statistical testing was performed in a prespecified sequential order with 2.5% α allocated to each sequence. OS, overall survival; PFS, progression-free survival.

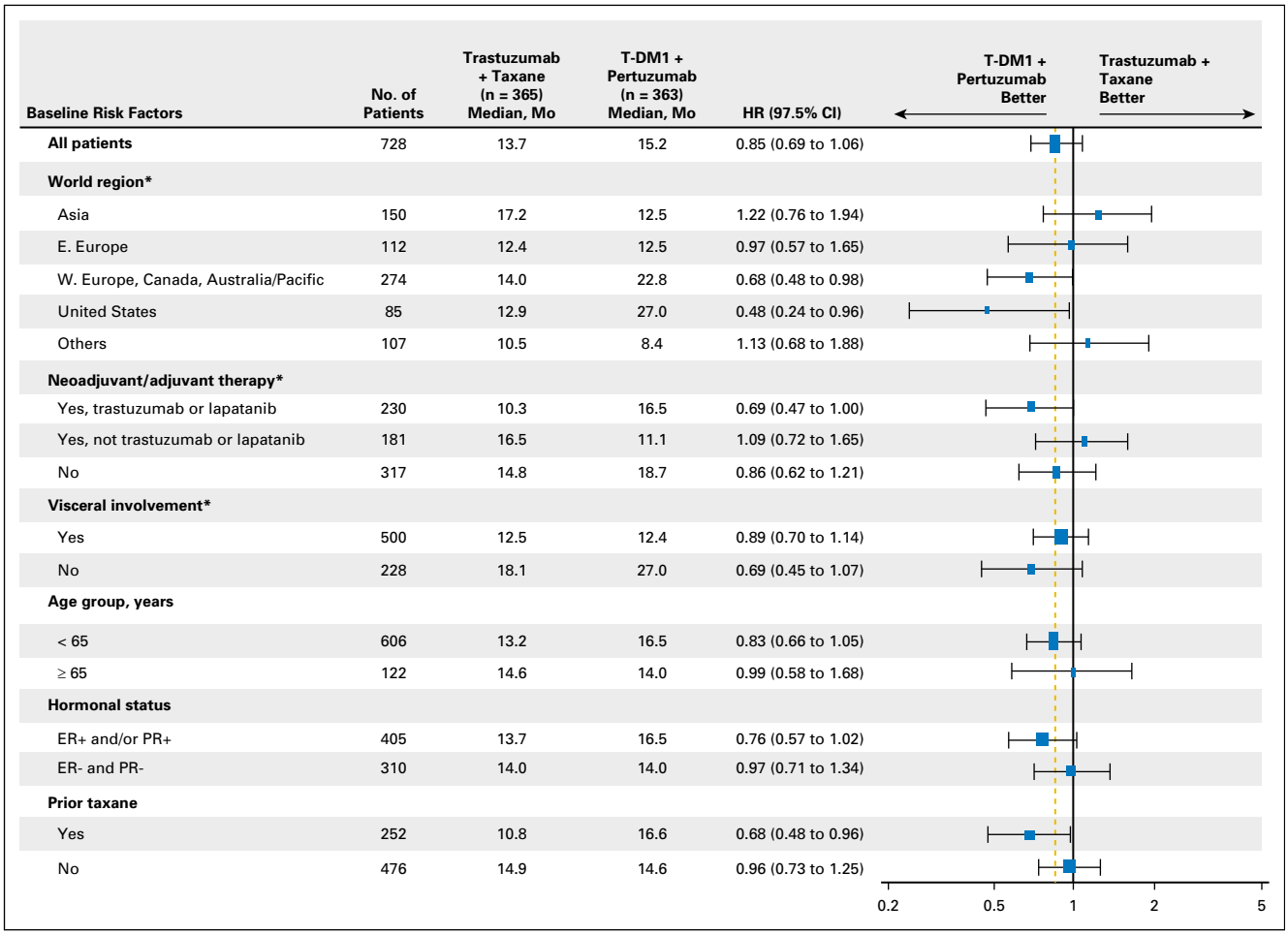


Fig A2. Progression-free survival by independent review assessed in prespecified patient subgroups for trastuzumab emtansine (T-DM1) plus pertuzumab compared with trastuzumab plus taxane. Analysis is based on all patients who were randomly assigned to T-DM1 plus pertuzumab or trastuzumab plus taxane. Hazard ratios (HRs) are unstratified. Vertical dashed line indicates the hazard ratio for all patients. *Stratification factor. ER, estrogen receptor; PR, progesterone receptor.

Baseline Risk Factors	No. of Patients	T-DM1 (n = 367) Median, Mo	T-DM1 + Pertuzumab (n = 363) Median, Mo	HR (97.5% CI)
All patients	730	14.1	15.2	0.91 (0.73 to 1.12)
World region*				
Asia	151	11.9	12.5	1.03 (0.65 to 1.62)
E. Europe	115	12.4	12.5	0.98 (0.59 to 1.65)
W. Europe, Canada, Australia/Pacific	271	15.9	22.8	0.76 (0.53 to 1.10)
United States	88	12.6	27.0	0.58 (0.30 to 1.12)
Others	105	14.6	8.4	1.50 (0.88 to 2.54)
Neoadjuvant/adjuvant therapy*				
Yes, trastuzumab or lapatanib	230	15.2	16.5	0.89 (0.61 to 1.28)
Yes, not trastuzumab or lapatanib	177	18.0	11.1	1.17 (0.76 to 1.81)
No	323	12.4	18.7	0.78 (0.57 to 1.08)
Visceral involvement*				
Yes	510	12.4	12.4	0.96 (0.75 to 1.22)
No	220	19.5	27.0	0.73 (0.47 to 1.13)
Age group, years				
< 65	609	13.3	16.5	0.87 (0.69 to 1.09)
≥ 65	121	19.5	14.0	1.12 (0.66 to 1.91)
Hormonal status				
ER+ and/or PR+	393	13.4	16.5	0.81 (0.61 to 1.09)
ER- and PR-	316	13.3	14.0	1.00 (0.73 to 1.36)
Prior taxane				
Yes	241	15.2	16.6	0.98 (0.68 to 1.42)
No	489	12.6	14.6	0.88 (0.68 to 1.14)

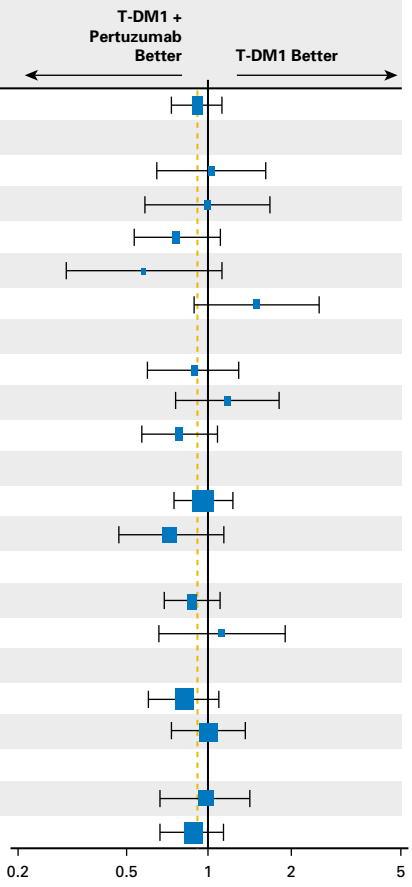


Fig A3. Progression-free survival by independent review assessed in prespecified patient subgroups for trastuzumab emtansine (T-DM1) compared with T-DM1 plus pertuzumab. Analysis is based on all patients who were randomly assigned to T-DM1 or T-DM1 plus pertuzumab. Hazard ratios (HRs) are unstratified. Vertical dashed line indicates the HR for all patients. (*)Stratification factor. ER, estrogen receptor; PR, progesterone receptor.

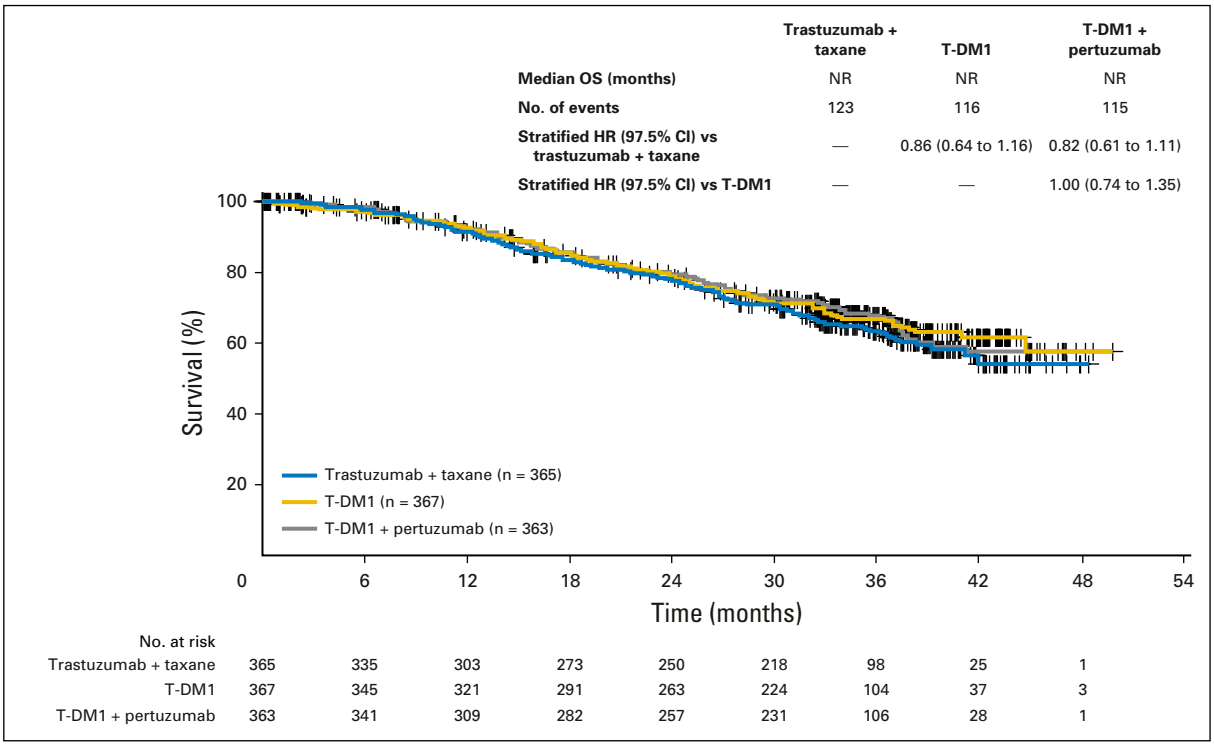
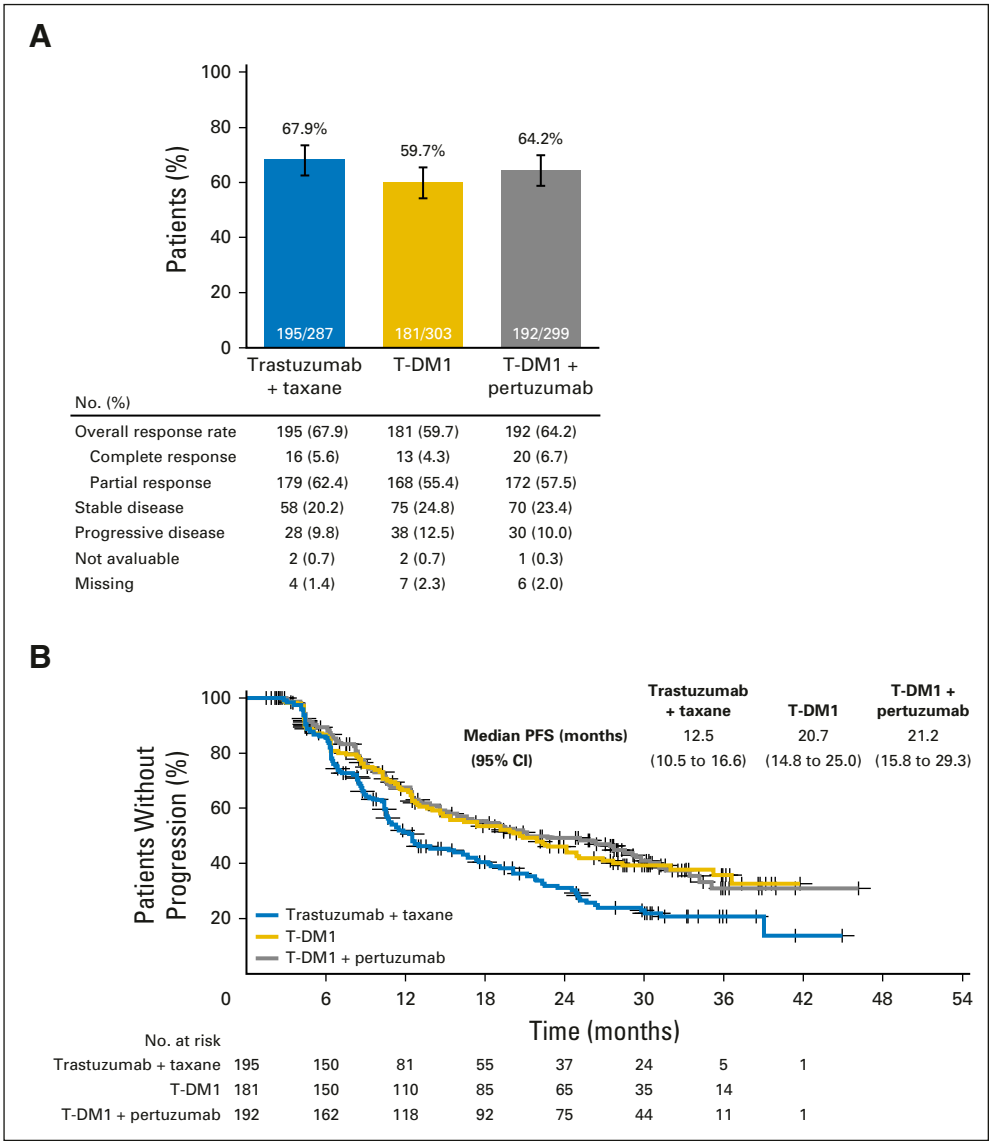


Fig A4. First interim analysis of overall survival. HR, hazard ratio; NR, not reached; OS, overall survival; T-DM1, trastuzumab emtansine.



No. (%)	Trastuzumab + taxane	T-DM1	T-DM1 + pertuzumab
Overall response rate	195 (67.9)	181 (59.7)	192 (64.2)
Complete response	16 (5.6)	13 (4.3)	20 (6.7)
Partial response	179 (62.4)	168 (55.4)	172 (57.5)
Stable disease	58 (20.2)	75 (24.8)	70 (23.4)
Progressive disease	28 (9.8)	38 (12.5)	30 (10.0)
Not avaluable	2 (0.7)	2 (0.7)	1 (0.3)
Missing	4 (1.4)	7 (2.3)	6 (2.0)

Fig A5. (A and B) Objective response (A) and duration of response (B) in patients with measurable disease as assessed by independent review. (A) Objective response rates and 95% CIs (shown as error bars). Percentages shown are based on number of patients with measurable disease at baseline. Complete and partial responses determined by independent review were confirmed by consecutive tumor assessments at least 4 weeks apart on the basis of RECIST 1.1. A best response of stable disease was only made after the patient was on study for a minimum of 6 weeks after random assignment. If the patient was not on study within this minimal time period, any tumor assessment that indicated stable disease before 6 weeks had a best response of not evaluable unless disease progression was identified. (B) Kaplan-Meier estimates of duration of response in patients who were treated with trastuzumab plus taxane (n = 195), trastuzumab emtansine (T-DM1; n = 181), or T-DM1 plus pertuzumab (n = 192). Duration of response was defined as the time from date of initially confirmed partial or complete response by independent review to the date of progressive disease by independent review or death as a result of any cause (whichever occurred first). Only patients with measurable disease at baseline and an objective response were included in this analysis. PFS, progression-free survival.

Table A1. Protocol-Specified Rules for Dose Delays, Dose Reductions, and Dose Discontinuations

Treatment	Dosing
T-DM1	
Starting dose	3.6 mg/kg IV every 3 weeks
Dose delays	If significant related toxicities have not recovered to grade 1 or baseline status, dose could be delayed for up to 42 days after the most recent dose; upon resolution of toxicities, dosing could be either resumed at the same dose level or decreased to one dose level lower
First dose reduction	3.0 mg/kg IV every 3 weeks
Second dose reduction	2.4 mg/kg IV every 3 weeks
Discontinuation	Delays beyond 42 days or toxicities at the 2.4-mg/kg dose level resulted in discontinuation of study treatment
	Patients who discontinued T-DM1 for DM1-related toxicities were allowed to switch to trastuzumab
Pertuzumab	
Starting dose	840 mg IV loading dose for the first 3-week cycle, then 420 mg IV every 3 weeks for subsequent cycles
Dose delays	If significant related toxicities have not recovered to grade 1 or baseline status, dose could be delayed for up to 42 days after the most recent dose
	Pertuzumab dosing was held if the T-DM1 dose was delayed
Dose reduction	No dose reductions were allowed
Discontinuation	If toxicities as a result of pertuzumab required discontinuation, patients could continue with single-agent T-DM1
	Pertuzumab was not administered as a single agent; if T-DM1 was discontinued, pertuzumab was also discontinued
Trastuzumab	
Starting dose	Administered with docetaxel: 8 mg/kg IV loading dose for the first 3-week cycle, followed by 6 mg/kg IV for subsequent cycles
	Administered with paclitaxel: 4 mg/kg IV loading dose for the first week, followed by 2 mg/kg IV in subsequent weeks
Dose delays	Dose delays for up to 42 days after the most recent dose were allowed with both the every 3-week or weekly schedules
	Every 3-week schedule:
	The maintenance dose of 6 mg/kg was to be administered as soon as possible if the dose delay was $\leq$ 4 weeks from last dose (dose delay of $\leq$ 1 week), followed by maintenance dosing every 3 weeks;
	Dosing after a delay $>$ 4 weeks from the last dose started with a loading dose of trastuzumab (8 mg/kg), followed by maintenance dosing every 3 weeks
	Weekly schedule:
	Maintenance dose of 2 mg/kg was to be administered if the dose delay was $<$ 3 weeks from the last administered dose;
	Dosing after a delay $\geq$ 3 weeks from the last administered dose started with the loading dose of trastuzumab (4 mg/kg), followed by weekly maintenance dosing
Dose reduction	No dose reductions were allowed
Discontinuation	Delays beyond 42 days resulted in discontinuation of study treatment
	If trastuzumab dosing was discontinued as a result of toxicity, treatment could continue with the taxane
Docetaxel	
Starting dose	75 mg/m^2 or 100 mg/m^2 IV every 3 weeks
Dose delays	If significant (grade 3 to 4) related toxicity had not recovered to grade $\leq$ 1 or baseline grade, dose could be held
First dose reduction	If starting at 100 mg/m^2, then reduce to 75 mg/m^2
	If starting at 75 mg/m^2, then reduce to 55 mg/m^2
Second dose reduction	For patients who started at 100 mg/m^2, a second dose reduction from 75 mg/m^2 to 55 mg/m^2 was permitted
Discontinuation	Criteria for discontinuation were based on US or national prescribing guidelines
	If docetaxel was discontinued as a result of toxicity, treatment could continue with trastuzumab
Paclitaxel	
Starting dose	80 mg/m^2 IV weekly
Dose delays	If significant (grade 3 to 4) related toxicity had not recovered to grade $\leq$ 1 or baseline grade, dose could be held; dosing could be resumed at 65 mg/m^2
Dose reduction	65 mg/m^2 IV weekly
Discontinuation	Delays beyond 21 days or toxicities at the 65 mg/m^2 dose level resulted in discontinuation of study treatment
	If paclitaxel was discontinued as a result of toxicity, treatment could continue with trastuzumab

Abbreviations: IV, intravenous; T-DM1, trastuzumab emtansine.

Table A2. Schedule of Study Assessments

Assessment	Timing of assessment
Tumor assessment	Performed at baseline and every 9 weeks thereafter for the first 18 months After 18 months, performed every 12 weeks until disease progression or death An additional assessment was required 4 to 6 weeks after disease progression
Cardiac monitoring	Echocardiogram (preferred method) or multigated acquisition scanning: performed at baseline, once on days 15 to 21 of cycle 1 cycle 3, and every third cycle thereafter An additional assessment was performed at least 28 days after the last dose of study drug Electrocardiogram was performed at baseline
Laboratory assessment	For patients on an every 3-week regimen, local laboratory assessments were performed at baseline, on days 1, 8, and 15 of cycles 1 to 3, and on day 1 of all subsequent cycles For patients on a weekly regimen, local laboratory assessments were performed at baseline and on days 1, 8, and 15 of all cycles
FACT-B questionnaire	Before protocol amendment Completed at baseline and every 9 weeks (every third cycle) for 81 weeks After 81 weeks, the questionnaire was completed every 12 weeks (every fourth cycle) until disease progression or death After protocol amendment (March 7, 2011) Completed at baseline, day 1 of each cycle for the first 8 cycles, and then every other cycle until disease progression or death
Adverse event	Monitored continuously and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0*

Abbreviation: FACT-B, Functional Assessment of Cancer Therapy-Breast.
*National Cancer Institute: Common Terminology Criteria for Adverse Events v4.0 (CTCAE). http://ctep.cancer.gov.

Table A3. Sensitivity Analysis of the Time to Clinically Meaningful Decrease in Health-Related Quality of Life

Time to Event*	Trastuzumab + Taxane (n = 173)	T-DM1 (n = 171)	T-DM1 + Pertuzumab (n = 154)
Median, months	3.4	8.0	11.8
Stratified hazard ratio 95% CI (*v* trastuzumab plus taxane)	—	0.69 (0.51 to 0.94)	0.66 (0.48 to 0.92)

NOTE. Health-related quality of life was measured by the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) of the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire.[21] This sensitivity analysis is based on the subset of patients who were randomly assigned after implementation of a protocol amendment (March 7, 2011) that increased the assessment frequency (Appendix Table A2). Sensitivity analysis included all female patients from the intention-to-treat population who were randomly assigned after the signature date for the protocol amendment (March 7, 2011) and who also completed the FACT-B at baseline and at least once postbaseline.
Abbreviation: T-DM1, trastuzumab emtansine.
*An event was defined as a clinically meaningful decrease in health-related quality of life, which is a ≥ 5-point decrease from the baseline in FACT-B TOI-PFB score.[22]