Original Article

Trastuzumab Emtansine With or Without Pertuzumab Versus Trastuzumab With Taxane for Human Epidermal Growth Factor Receptor 2–Positive Advanced Breast Cancer: Final Results From MARIANNE

Edith A. Perez, MD [iD] [1]; Carlos Barrios, MD[2]; Wolfgang Eiermann, MD[3]; Masakazu Toi, MD, PhD[4]; Young-Hyuck Im, MD, PhD[5]; Pierfranco Conte, MD[6,7]; Miguel Martin, MD[8]; Tadeusz Pienkowski, MD, PhD[9]; Xavier B. Pivot, MD, PhD[10]; Howard A. Burris III, MD[11]; Jennifer A. Petersen, MPH[12]; Sanne De Haas, PhD[13]; Silke Hoersch, MSc[13]; Monika Patre, PhD[13]; and Paul Anthony Ellis, MD[14]

BACKGROUND: In the phase 3 MARIANNE trial, trastuzumab emtansine (T-DM1) with or without pertuzumab showed noninferior progression-free survival and better tolerability than trastuzumab plus a taxane (HT) for the first-line treatment of human epidermal growth factor receptor 2 (HER2)–positive advanced breast cancer. This article reports the final descriptive overall survival (OS) analysis, updated safety data, and additional patient-reported outcomes and biomarker analyses. **METHODS:** OS was assessed in 1095 patients with HER2-positive breast cancer and no prior therapy for advanced disease who had been randomized to HT, T-DM1 plus a placebo (hereafter T-DM1), or T-DM1 plus pertuzumab (T-DM1+pertuzumab). A post hoc exploratory landmark analysis of OS, baseline patient and disease characteristics, and tumor biomarkers in patients with and without an objective tumor response (OR) according to the Response Evaluation Criteria in Solid Tumors within 6.5 months of randomization was conducted. **RESULTS:** The median OS was similar across groups (50.9, 53.7, and 51.8 months for the HT, T-DM1, and T-DM1+pertuzumab groups, respectively). Among patients with an OR, the median OS was longer with T-DM1 (64.4 months) and T-DM1+pertuzumab (not reached) versus HT (56.3 months). No baseline characteristics or biomarkers were strongly associated with OR. The incidence of grade 3 or higher adverse events was greater with HT (55.8%) than T-DM1 (47.1%) or T-DM1+pertuzumab (48.6%). The median time to clinically meaningful deterioration (a 3-point or greater change) in neurotoxicity symptoms was shorter with HT (2.1 months) and T-DM1+pertuzumab (4.2 months) than T-DM1 (6.2 months). Fewer patients reported alopecia and diarrhea and were bothered by treatment side effects in the T-DM1 arm. **CONCLUSIONS:** These results support T-DM1 as a first-line treatment for patients with HER2-positive metastatic breast cancer who are deemed unsuitable for taxane-based therapy. *Cancer* 2019;0:1-11. © *2019 American Cancer Society*.

KEYWORDS: human epidermal growth factor receptor 2 (HER2), metastatic breast cancer, pertuzumab, targeted therapy, trastuzumab emtansine.

INTRODUCTION

The current standard of care for the first-line treatment of human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer (MBC) is a combination regimen comprising the HER2-targeted monoclonal antibodies trastuzumab and pertuzumab plus a taxane.[1-3] The antibody-drug conjugate trastuzumab emtansine (T-DM1), designed to minimize systemic toxicity through selective cytotoxic drug delivery to tumor cells, combines trastuzumab with DM1, a cytotoxic agent that inhibits microtubule polymerization. It has demonstrated safety and efficacy in patients with previously treated HER2-positive MBC[4,5] and is approved for use in this setting. Encouraging safety and efficacy data were observed with T-DM1 in the first-line setting in a randomized phase 2 study, in which T-DM1 significantly prolonged progression-free survival (PFS) in comparison with the standard of care at the time of the study, trastuzumab plus a taxane (HT).[6] The combination of T-DM1 plus pertuzumab (T-DM1+pertuzumab) demonstrated synergistic

cytotoxicity in cell cultures, enhanced antitumor activity in xenograft models, and clinical activity with an acceptable safety profile in a phase 1b/2 study.[7]

MARIANNE was a randomized, phase 3 trial designed to evaluate the safety and efficacy of T-DM1 plus a placebo (hereafter T-DM1) and T-DM1+pertuzumab for the treatment of patients with HER2-positive, progressive or recurrent locally advanced breast cancer or MBC who had not received prior chemotherapy for their metastatic disease versus the standard of care at the time, HT.[8] The primary endpoint was PFS assessed by an independent review. Primary results from MARIANNE demonstrated that T-DM1 and T-DM1+pertuzumab were noninferior, but not superior, to HT (median PFS, 14.1 months with T-DM1, 15.2 months with T-DM1+pertuzumab, and 13.7 months with HT). T-DM1–based treatment was associated with fewer grade 3 or higher adverse events (AEs) and fewer toxicity-related treatment discontinuations than HT. Furthermore, T-DM1–treated patients maintained baseline health-related quality of life longer than their counterparts who received HT. Overall survival (OS) was similar among treatment groups at the time of the primary data analysis, for which the median follow-up time was 35 months; however, median OS had not yet been reached in any treatment arm. This article reports the final descriptive OS analysis; updated safety data; an exploratory analysis of patients responding to T-DM1–containing treatment, including patient characteristics, disease characteristics, and biomarkers involved in the HER2 pathway in these patients; and additional patient-reported outcomes (PROs) from MARIANNE.

MATERIALS AND METHODS

Study Design and Patients

The trial methodology and primary results of this international, 3-arm, phase 3 study have been reported.[8] Briefly, patients were randomly assigned 1:1:1 to HT (control), T-DM1, or T-DM1+pertuzumab and were stratified by world region, prior (and type of) neoadjuvant or adjuvant therapy, and the presence or absence of visceral disease. Key inclusion criteria included HER2-positive (immunohistochemistry score of 3+ and/or in situ hybridization–positive; prospectively and centrally confirmed at Targos Molecular Pathology GmbH, Kassel, Germany) and advanced breast cancer (unresectable, progressive, or recurrent locally advanced or previously untreated metastatic disease); an age ≥18 years; an Eastern Cooperative Oncology Group performance status of 0 or 1; and measurable and/or unmeasurable disease that was evaluable

on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).[9]

In the control arm, patients were assigned to paclitaxel (80 mg/m^2 administered intravenously [iv] weekly) or docetaxel (75 or 100 mg/m^2 administered iv every 3 weeks) according to the investigator's discretion. The taxane was administered for a minimum of 6 cycles until disease progression or unacceptable toxicity. Trastuzumab was administered at standard doses (with docetaxel, 8 mg/kg iv loading dose and 6 mg/kg iv for subsequent cycles; with paclitaxel, 4 mg/kg iv loading dose and 2 mg/kg iv in subsequent weeks). 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 and 420 mg iv every 3 weeks for subsequent cycles).

Secondary endpoints included in this report are OS, defined as the time from randomization to death from any cause; safety, which was monitored throughout the study by the independent data monitoring and cardiac review committees; and the following PRO endpoints: the time to a clinically meaningful deterioration in neurotoxicity symptoms (as measured by the Functional Assessment of Cancer Therapy–Taxane [FACT-Taxane] neurotoxicity subscale[10]), the impact of alopecia (as measured by the Alopecia Patient Assessment scale[11]), and any level of nausea and diarrhea (as measured by 2 items from the Functional Assessment of Cancer Therapy–Colorectal Cancer [FACT-C] scale).[12] The extent to which patients were bothered by treatment side effects as measured by the corresponding item (GP5) of the Functional Assessment of Cancer Therapy–Breast Cancer (FACT-B) scale[13] was assessed post hoc. The PRO assessment schedule is shown in Supporting Table 1. A post hoc exploratory landmark analysis of OS, patient and disease characteristics, and tumor biomarkers in patients with and without an objective tumor response (OR) according to RECIST 1.1 within 6.5 months of randomization was also conducted.

The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice standards and the Declaration of Helsinki and was approved by the relevant institutional review boards or independent ethics committees at each site. All patients provided written informed consent.

Statistical Analyses

Efficacy endpoints were assessed in the intention-to-treat population. Two prespecified interim OS analyses and a final OS analysis were planned with the application of a Lan-DeMets alpha spending function with a Pocock stopping boundary. Median OS was estimated by the

Kaplan-Meier method, and hazard ratios (HRs) and confidence intervals (CIs) were computed with stratified and unstratified Cox proportional hazards regression models. The first OS interim analysis was performed at the time of the primary analysis. The second interim and final analyses were to be performed after minimum follow-up periods of 36 and 48 months, respectively, from the enrollment of the last patient. Because a fixed-sequence hierarchical statistical testing procedure was used and the primary efficacy endpoint did not meet superiority, statistical tests and the associated P values for the OS analyses are considered descriptive.

The post hoc exploratory landmark analysis determined survival by treatment group in patients with an OR by RECIST 1.1[9] at 6.5 months after randomization. This time point was chosen because approximately 3 tumor assessments had been completed by this time, the vast majority of tumor responses had already occurred, and most patients remained in the study. Patients alive at 6.5 months were included in the analysis and were separated into those who had experienced an OR within this time frame and those who had not. All responses after 6.5 months and all deaths before that time were not used in the analysis. Patient and disease characteristics as well as tumor biomarkers involved in the HER2 pathway were descriptively compared by group in patients with and without an OR.

Safety analyses included all patients who received at least 1 dose of the study treatment. AEs were evaluated descriptively.

The PRO results presented here are from additional analyses conducted as part of the primary data analysis of the protocol amendment C population. This protocol amendment was implemented on March 7, 2011, to collect more frequent data. The time to a clinically meaningful deterioration in neurotoxicity symptoms was determined with the Kaplan-Meier method. A deterioration event was defined as the first 3-point or greater decrease in the FACT-Taxane neurotoxicity subscale from cycle 1 on day 1 of treatment.[10] Patients without deterioration were censored at the time of completing the last FACT-Taxane neurotoxicity subscale plus 1 day. The proportion of patients reporting diarrhea (FACT-C, item C5), nausea (FACT-C, item GP2), alopecia (Alopecia Patient Assessment), and bother by side effects of treatment (FACT-B, item GP5) were calculated.

RESULTS

Study Population

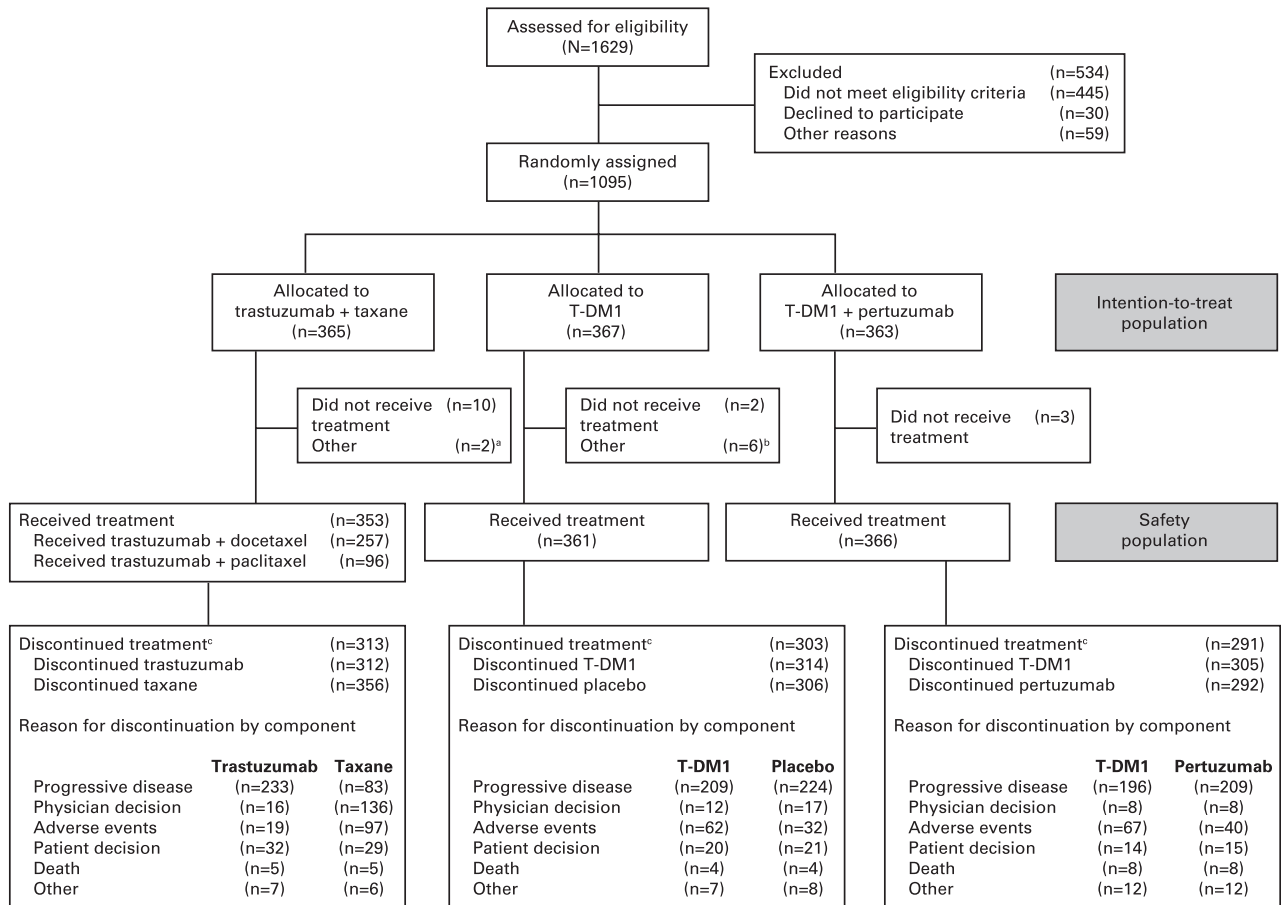As previously reported, the baseline demographic and disease characteristics of the 1095 patients enrolled from 241 study sites in 38 countries from July 2010 to May 2012 were well balanced among treatment groups.[8] In the HT arm (n = 365), 257 patients ultimately received trastuzumab plus docetaxel, and 96 received trastuzumab plus paclitaxel (Fig. 1). In all, 367 and 363 patients were randomized to T-DM1 and T-DM1+pertuzumab, respectively, and 361 and 366 patients ultimately received treatment.

Final OS Results

The median OS had not been reached at the time of the first interim analysis (median duration of follow-up, approximately 35 months), and the 3 Kaplan-Meier curves overlapped.[8] At the cutoff date for the second interim analysis (May 4, 2015) with a median follow-up of approximately 42 months, 409 deaths had occurred (144 in the control arm and 135 and 130 in the T-DM1 and T-DM1+pertuzumab arms, respectively). The median OS was 49.3 months in the HT group but was not reached in either the T-DM1 or T-DM1+pertuzumab group (stratified HR for T-DM1 vs the control group, 0.88; 97.5% CI, 0.67-1.15; stratified HR for T-DM1+pertuzumab vs the control group, 0.81; 97.5% CI, 0.61-1.08).

At the final OS analysis (May 15, 2016; median duration of follow-up, approximately 54 months), 512 deaths had occurred (169 in the control group and 175 and 168 in the T-DM1 and T-DM1+pertuzumab groups, respectively). The median OS was 50.9 months in the HT group, 53.7 months in the T-DM1 group, and 51.8 months in the T-DM1+pertuzumab group (Fig. 2). Compared with the HT group, the stratified HR was 0.93 for T-DM1 (97.5% CI, 0.73-1.20) and 0.86 for T-DM1+pertuzumab (97.5% CI, 0.67-1.11). Subgroup analyses by baseline patient and disease characteristics were consistent with the final OS analysis. Although some numerical differences in HRs were observed, none of the examined subgroups showed a clear benefit with one treatment regimen in comparison with the others (Fig. 3). Approximately 70% of the patients in each treatment arm received at least 1 therapeutic regimen during follow-up (Supporting Table 2). A post hoc exploratory sensitivity analysis of OS that censored patients from the HT group at the time of receipt of nonprotocol T-DM1 or pertuzumab administered for invasive disease progression was consistent with the final OS analysis in the intention-to-treat population. In comparison with the HT group, the stratified HR was 0.92 for T-DM1 (97.5% CI, 0.70-1.19) and 0.87 for T-DM1+pertuzumab (97.5% CI, 0.66-1.13).
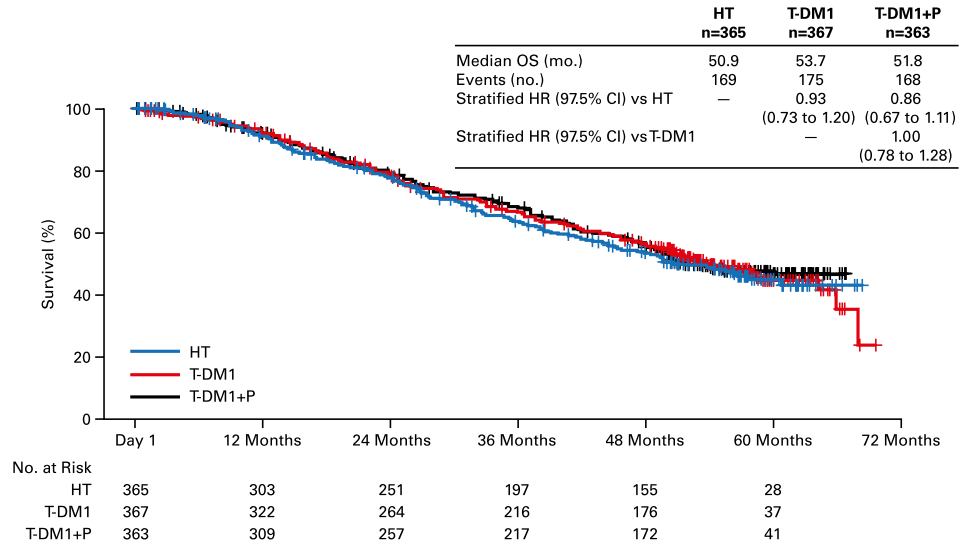
In the primary analysis, 67.9% of the patients in the HT group, 59.7% in the T-DM1 group, and 64.2% in
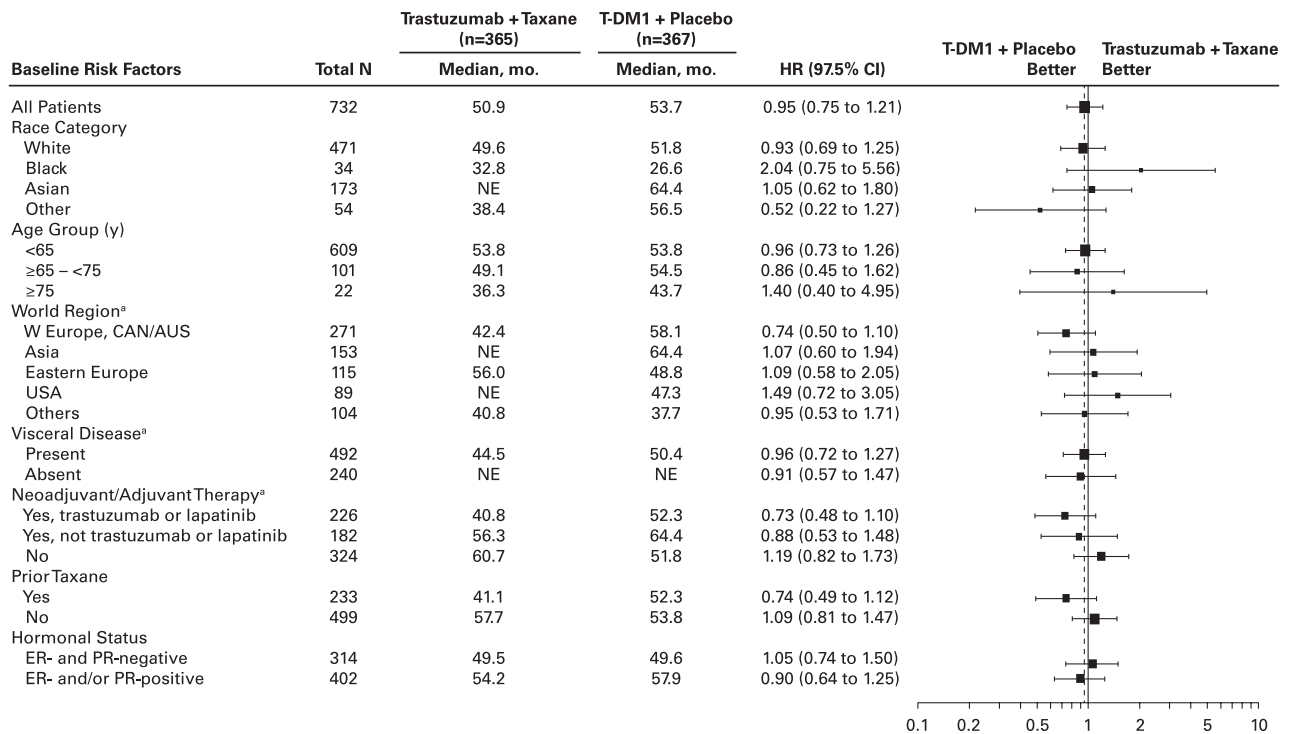
Assessed for eligibility
(N=1629)

Excluded   (n=534)
  Did not meet eligibility criteria (n=445)
  Declined to participate   (n=30)
  Other reasons   (n=59)

Randomly assigned
(n=1095)

Allocated to trastuzumab + taxane (n=365)

Allocated to T-DM1 (n=367)

Allocated to T-DM1 + pertuzumab (n=363)

Intention-to-treat population

Did not receive treatment (n=10)
Other (n=2)[a]

Did not receive treatment (n=2)
Other (n=6)[b]

Did not receive treatment (n=3)

Received treatment (n=353)
  Received trastuzumab + docetaxel (n=257)
  Received trastuzumab + paclitaxel (n=96)

Received treatment (n=361)

Received treatment (n=366)

Safety population

Discontinued treatment[c] (n=313)
  Discontinued trastuzumab (n=312)
  Discontinued taxane (n=356)

Reason for discontinuation by component

	Trastuzumab	Taxane
Progressive disease	(n=83)	(n=233)
Physician decision	(n=16)	(n=136)
Adverse events	(n=19)	(n=97)
Patient decision	(n=32)	(n=29)
Death	(n=5)	(n=5)
Other	(n=7)	(n=6)

Discontinued treatment[c] (n=303)
  Discontinued T-DM1 (n=314)
  Discontinued placebo (n=306)

Reason for discontinuation by component

	T-DM1	Placebo
Progressive disease	(n=209)	(n=224)
Physician decision	(n=12)	(n=17)
Adverse events	(n=62)	(n=32)
Patient decision	(n=20)	(n=21)
Death	(n=4)	(n=4)
Other	(n=7)	(n=8)

Discontinued treatment[c] (n=291)
  Discontinued T-DM1 (n=305)
  Discontinued pertuzumab (n=292)

Reason for discontinuation by component

	T-DM1	Pertuzumab
Progressive disease	(n=196)	(n=209)
Physician decision	(n=8)	(n=8)
Adverse events	(n=67)	(n=40)
Patient decision	(n=14)	(n=15)
Death	(n=8)	(n=8)
Other	(n=12)	(n=12)

Figure 1. Patient flow through the study. [a]Two patients who were randomly assigned to the trastuzumab and taxane arm received 3 cycles of T-DM1 (1 patient received 1 cycle, and 1 patient received 2 cycles). These patients were included in the T-DM1 group for the safety analyses. [b]Six patients who were randomly assigned to T-DM1 received 6 cycles of pertuzumab. These patients were included in the T-DM1 and pertuzumab group for the safety analyses. [c]All components of the treatment regimen were discontinued. The safety analysis population included all patients who received at least 1 dose of the study treatment. T-DM1 indicates trastuzumab emtansine. Perez, E et al: J Clin Oncol 35 (2), 2017: 141-148. Reprinted with permission. © 2017 American Society of Clinical Oncology. All rights reserved.

the T-DM1+pertuzumab group had an OR. The median durations of these responses were numerically longer in the T-DM1 and T-DM1+pertuzumab groups than the HT group (T-DM1, 20.7 months; T-DM1+pertuzumab, 21.2 months; HT, 12.5 months).[8] A post hoc exploratory analysis of OS by tumor response status at 6.5 months after randomization was conducted. At this time point, fewer than 10% of the patients had died or dropped out (HT, 9%; T-DM1, 6%; T-DM1+pertuzumab, 7%), and most tumor responses had occurred (HT, 95%; T-DM1, 96%; T-DM1+pertuzumab, 94%). The median OS was numerically longer for patients with a tumor response within 6.5 months in comparison with patients without a tumor response by that time point, regardless of treatment (Fig. 4). For nonresponders, the median OS was numerically shortest with T-DM1+pertuzumab (41.9 months),

which was followed by T-DM1 (45.7 months) and HT (48.1 months). For responders, the median OS was 64.4 months in the T-DM1 group and 56.3 months in the HT group. The median OS was not yet reached for responders in the T-DM1+pertuzumab group. A comparison of baseline characteristics (Supporting Table 3) and biomarkers (Supporting Table 4) in T-DM1–treated patients with a tumor response by 6.5 months and those without one showed that no baseline characteristics or biomarkers were strongly associated with tumor response by treatment group. However, in both the HT group and the T-DM1 group, patients with above-median HER2 messenger RNA (mRNA) expression had a higher incidence of tumor response, and those with median or lower HER2 mRNA expression were more likely not to have a tumor response. An exploratory subgroup analysis of

	HT n=365	T-DM1 n=367	T-DM1+P n=363
Median OS (mo.)	50.9	53.7	51.8
Events (no.)	169	175	168
Stratified HR (97.5% CI) vs HT	—	0.93 (0.73 to 1.20)	0.86 (0.67 to 1.11)
Stratified HR (97.5% CI) vs T-DM1	—	—	1.00 (0.78 to 1.28)

No. at Risk						
HT	365	303	251	197	155	28
T-DM1	367	322	264	216	176	37
T-DM1+P	363	309	257	217	172	41

Figure 2. Final analysis of OS. Kaplan-Meier estimates of OS at a median follow-up of approximately 54 months are shown. CI indicates confidence interval; HR, hazard ratio; HT, trastuzumab plus a taxane; OS, overall survival; P, pertuzumab; T-DM1, trastuzumab emtansine.

Baseline Risk Factors	Total N	Trastuzumab + Taxane (n=365) Median, mo.	T-DM1 + Placebo (n=367) Median, mo.	HR (97.5% CI)
All Patients	732	50.9	53.7	0.95 (0.75 to 1.21)
Race Category				
White	471	49.6	51.8	0.93 (0.69 to 1.25)
Black	34	32.8	26.6	2.04 (0.75 to 5.56)
Asian	173	NE	64.4	1.05 (0.62 to 1.80)
Other	54	38.4	56.5	0.52 (0.22 to 1.27)
Age Group (y)				
<65	609	53.8	53.8	0.96 (0.73 to 1.26)
≥65 – <75	101	49.1	54.5	0.86 (0.45 to 1.62)
≥75	22	36.3	43.7	1.40 (0.40 to 4.95)
World Region[a]				
W Europe, CAN/AUS	271	42.4	58.1	0.74 (0.50 to 1.10)
Asia	153	NE	64.4	1.07 (0.60 to 1.94)
Eastern Europe	115	56.0	48.8	1.09 (0.58 to 2.05)
USA	89	NE	47.3	1.49 (0.72 to 3.05)
Others	104	40.8	37.7	0.95 (0.53 to 1.71)
Visceral Disease[a]				
Present	492	44.5	50.4	0.96 (0.72 to 1.27)
Absent	240	NE	NE	0.91 (0.57 to 1.47)
Neoadjuvant/Adjuvant Therapy[a]				
Yes, trastuzumab or lapatinib	226	40.8	52.3	0.73 (0.48 to 1.10)
Yes, not trastuzumab or lapatinib	182	56.3	64.4	0.88 (0.53 to 1.48)
No	324	60.7	51.8	1.19 (0.82 to 1.73)
Prior Taxane				
Yes	233	41.1	52.3	0.74 (0.49 to 1.12)
No	499	57.7	53.8	1.09 (0.81 to 1.47)
Hormonal Status				
ER- and PR-negative	314	49.5	49.6	1.05 (0.74 to 1.50)
ER- and/or PR-positive	402	54.2	57.9	0.90 (0.64 to 1.25)

T-DM1 + Placebo Better   Trastuzumab + Taxane Better

0.1   0.2   0.5   1   2   5   10

Figure 3. Subgroup analysis of overall survival. Overall survival by the baseline characteristics of patients treated with T-DM1 versus trastuzumab plus a taxane is shown. The median time to an event was estimated from Kaplan-Meier curves. Unstratified Cox proportional hazards regression was used to estimate the hazard ratio and confidence interval in each covariate subgroup. The vertical, dashed line shows the hazard ratio for all patients. The size of each square is proportional to the sample size of that subgroup. [a]Stratification factor. AUS indicates Australia; CAN, Canada; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; NE, not estimable; PR, progesterone receptor; T-DM1, trastuzumab emtansine; W Europe, Western Europe.
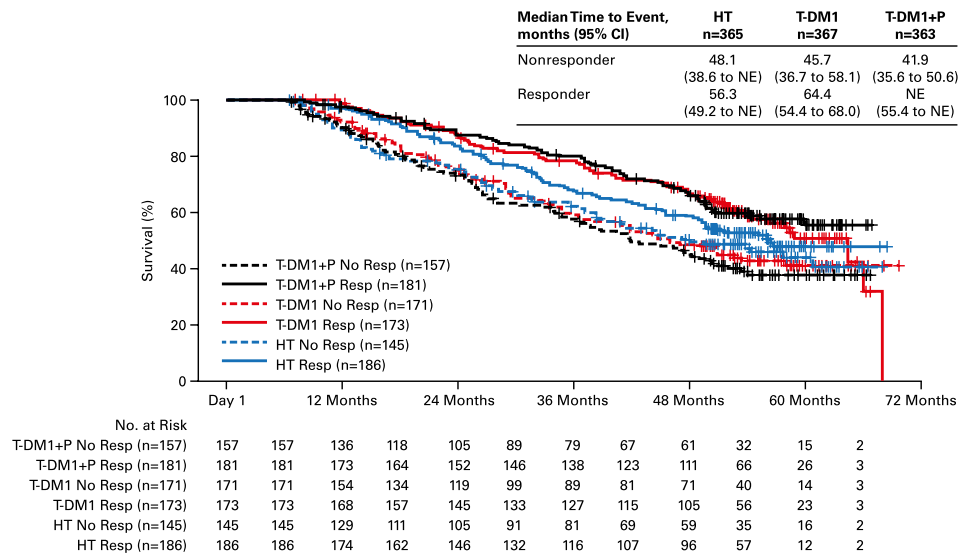
Figure 4. Landmark analysis of overall survival. Kaplan-Meier estimates of survival are shown by treatment group for patients with an objective response to treatment within 6.5 months after randomization (ie, response) and those without an objective response (ie, no response). CI indicates confidence interval; HT, trastuzumab plus a taxane; NE, not estimable because not yet reached; P, pertuzumab; Resp, response; T-DM1, trastuzumab emtansine.

OS was consistent with this. Patients in both treatment groups with greater HER2 gene expression had numerically longer OS (Supporting Fig. 1).

Updated Safety Analysis

The incidence of grade 3 or higher AEs was numerically higher in the control arm (55.8%) than the T-DM1 (47.1%) and T-DM1+pertuzumab arms (48.6%; Table 1). The most commonly reported grade 3 or higher AEs in the HT arm were neutropenia (19.3%), febrile neutropenia (6.5%), and diarrhea (4.2%). In the T-DM1 arm, the most commonly reported grade 3 or higher AEs were increased aspartate aminotransferase (6.9%), thrombocytopenia (6.6%), and anemia (5.0%). In the T-DM1+pertuzumab arm, thrombocytopenia (9.0%), anemia (7.1%), and increased alanine aminotransferase (6.0%) were the most commonly reported grade 3 or higher AEs.

All-grade AEs occurring in more than 20% of the patients in any treatment arm are shown in Table 1. Those that occurred more frequently in the HT arm than the T-DM1–containing arms, with at least a 10–percentage point difference between the T-DM1 or T-DM1+pertuzumab arm and the HT arm, were alopecia (60.1% vs 7.2% with T-DM1 and 9.0% with T-DM1+pertuzumab), diarrhea (49.0% vs 25.5% and 48.6%), peripheral neuropathy (28.0% vs 14.4% and 18.9%), peripheral edema (27.8% vs 10.2% and 9.6%), and neutropenia (22.1% vs 12.2% and 10.1%).

Those that occurred more frequently in the T-DM1 or T-DM1+pertuzumab arm with at least a 10–percentage point difference from the HT arm included nausea (48.2% [T-DM1] and 52.5% [T-DM1+pertuzumab] vs 37.1%), headache (32.1% [T-DM1] and 32.8% [T-DM1+pertuzumab] vs 22.7%), epistaxis (31.3% [T-DM1] and 35.2% [T-DM1+pertuzumab] vs 15.0%), pyrexia (27.4% [T-DM1] and 32.8% [T-DM1+pertuzumab] vs 17.0%), vomiting (22.2% [T-DM1] and 30.6% [T-DM1+pertuzumab] vs 19.5%), and chills (15.2% [T-DM1] and 26.5% [T-DM1+pertuzumab] vs. 4.0%).

A left ventricular ejection fraction <50% with a ≥15–percentage point decrease from the baseline was observed in 17 patients (4.8%) receiving HT, in 4 patients (1.1%) receiving T-DM1, and in 11 patients (3.0%) receiving T-DM1+pertuzumab.

The number of patients who discontinued any treatment component because of AEs was lower in the T-DM1 and T-DM1+pertuzumab arms (T-DM1, 20.8%; T-DM1+pertuzumab, 23.0%; HT, 30.6%). The number of patients who died because of AEs was similar across the treatment arms: 5 patients (1.4%) in the T-DM1 arm, 7 (1.9%) in the T-DM1+pertuzumab arm, and 7 (2.0%) in the HT arm.

Additional PRO Analyses

Patients included in this analysis were randomized after protocol amendment C and had completed PRO measures at

TABLE 1. Adverse Events in the Safety Population

Adverse Event	Trastuzumab + Taxane (n = 353), No. (%)	T-DM1 (n = 361), No. (%)	T-DM1 + Pertuzumab (n = 366), No. (%)
Grade 3 or higher adverse events	197 (55.8)	170 (47.1)	178 (48.6)
Grade 3 or higher adverse events in ≥3% of patients in any treatment group			
Neutropenia	68 (19.3)	16 (4.4)	14 (3.8)
Febrile neutropenia	23 (6.5)	0	0
Diarrhea	15 (4.2)	1 (0.3)	10 (2.7)
Hypertension	11 (3.1)	17 (4.7)	20 (5.5)
Anemia	10 (2.8)	18 (5.0)	26 (7.1)
ALT increase	3 (0.8)	16 (4.4)	22 (6.0)
AST increase	1 (0.3)	25 (6.9)	12 (3.3)
GGT increase	1 (0.3)	12 (3.3)	9 (2.5)
Thrombocytopenia	0	24 (6.6)	33 (9.0)
Any adverse event	348 (98.6)	357 (98.9)	361 (98.6)
All-grade adverse events in >20% of patients in any treatment group			
Alopecia	212 (60.1)	26 (7.2)	33 (9.0)
Diarrhea	173 (49.0)	92 (25.5)	178 (48.6)
Nausea	131 (37.1)	174 (48.2)	192 (52.5)
Fatigue	129 (36.5)	121 (33.5)	130 (35.5)
Peripheral neuropathy	99 (28.0)	52 (14.4)	69 (18.9)
Peripheral edema	98 (27.8)	37 (10.2)	35 (9.6)
Arthralgia	91 (25.8)	84 (23.3)	72 (19.7)
Rash	86 (24.4)	63 (17.5)	89 (24.3)
Myalgia	82 (23.2)	66 (18.3)	61 (16.7)
Headache	80 (22.7)	116 (32.1)	120 (32.8)
Neutropenia	78 (22.1)	44 (12.2)	37 (10.1)
Decreased appetite	76 (21.5)	84 (23.3)	84 (23.0)
Cough	74 (21.0)	72 (19.9)	79 (21.6)
Constipation	72 (20.4)	82 (22.7)	71 (19.4)
Vomiting	69 (19.5)	80 (22.2)	112 (30.6)
Pyrexia	60 (17.0)	99 (27.4)	120 (32.8)
Epistaxis	53 (15.0)	113 (31.3)	129 (35.2)
Chills	14 (4.0)	55 (15.2)	97 (26.5)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; T-DM1, trastuzumab emtansine.

the baseline and at least 1 follow-up visit (T-DM1, n = 171; T-DM1+pertuzumab, n = 154; HT, n = 173). Compliance with questionnaire completion in these patients is shown in Supporting Table 5. Results up to 54 weeks of treatment (cycle 18) are shown; after that point, less than 50% of the patients in the amendment C population were still in the study and completing the PRO measures.

Both the T-DM1 arm and the T-DM1+pertuzumab arm reported longer median times to a clinically meaningful deterioration (increase) in neurotoxicity symptoms (6.2 months with T-DM1 [95% CI, 3.5-10.6 months]; 4.2 months with T-DM1+pertuzumab [95% CI, 2.8-6.2 months]; 2.1 months with HT [95% CI, 1.4-2.8 months]; Fig. 5A). Throughout the study, fewer patients in the T-DM1 arm reported being bothered ("a little bit," "somewhat", "quite a bit", or "very much") by side effects in comparison with patients in the other treatment arms (Fig. 5B and Supporting Fig. 2A). A greater proportion of patients in the HT arm reported being bothered by side effects during the first

6 months of treatment (Fig. 5B); this began to decrease by cycle 12 (9 months) to rates similar to those with T-DM1+pertuzumab (Supporting Fig. 2A). Rates of alopecia were low at the baseline and were similar between treatment arms (T-DM1, 13%; T-DM1+pertuzumab, 13%; HT, 14%). Rates remained relatively unchanged over time in the T-DM1 and T-DM1+pertuzumab arms, whereas the rate of alopecia reached 75% in the HT arm by cycle 2, day 1, and 85% by cycle 3, day 1 (Fig. 5C). Even at 54 weeks, 42% of the patients in the HT arm experienced alopecia (Supporting Fig. 2B). Patient-reported nausea ranged from 17% to 32% in the HT arm, from 12% to 23% in the T-DM1 arm, and from 21% to 36% in the T-DM1+pertuzumab arm throughout the first 54 weeks of treatment, with decreasing frequency in the HT and T-DM1 arms at later time points (Supporting Fig. 2C). The majority of patients in the T-DM1 arm did not experience diarrhea while on treatment (Fig. 5D), and rates in the T-DM1 arm were the lowest of the 3 arms through 54 weeks of treatment (Supporting Fig. 2D).
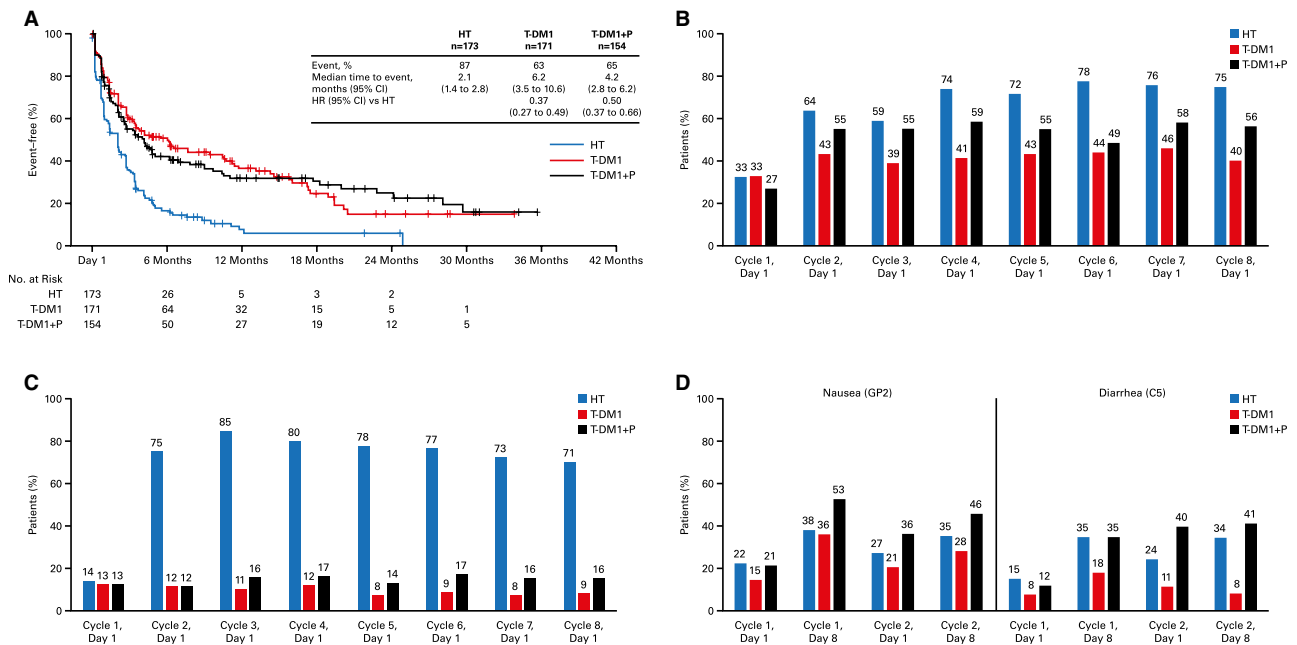
Figure 5. Patient-reported experience of treatment. (A) Time to a clinically meaningful deterioration (increase) in neurotoxicity symptoms. The time to deterioration was defined as the time from the baseline (cycle 1, day 1) to the first 3-point or greater decrease as measured by the FACT-Taxane neurotoxicity subscale. Patients without deterioration were censored (indicated by +) at the time of completing the last FACT-Taxane neurotoxicity subscale plus 1 day. (B) Patients reporting bother ("a little bit," "somewhat," "quite a bit," or "very much") due to treatment side effects (item GP5 of FACT-B). The response options on the FACT-B system are "not at all," "a little bit," "somewhat," "quite a bit," and "very much." Patients were considered to be bothered by side effects if they reported that they were bothered "a little bit," "somewhat," "quite a bit," or "very much." (C) Patients reporting hair loss on the Alopecia Patient Assessment. (D) Patients reporting (*Left*) nausea or (*Right*) diarrhea ("a little bit," "somewhat," "quite a bit," or "very much") on the FACT-C during early treatment. The response options on the FACT-C system are "not at all," "a little bit," "somewhat," "quite a bit," and "very much." Patients were considered to have experienced symptoms if they reported that they had experienced the symptom "a little bit," "somewhat," "quite a bit," or "very much." CI indicates confidence interval; FACT-B, Functional Assessment of Cancer Therapy–Breast Cancer; FACT-C, Functional Assessment of Cancer Therapy–Colorectal Cancer; FACT-Taxane, Functional Assessment of Cancer Therapy–Taxane; HR, hazard ratio; HT, trastuzumab plus a taxane; P, pertuzumab; T-DM1, trastuzumab emtansine.

DISCUSSION

The final MARIANNE results demonstrated similar OS across treatment arms, with all 3 regimens resulting in a median OS longer than 50 months. Notably, the median OS of 50.9 months in the control arm (HT) was longer than that reported in the randomized, phase 3 CLEOPATRA trial for trastuzumab plus docetaxel (40.8 months), although none of the MARIANNE regimens exceeded the median OS of 56.5 months reported in CLEOPATRA for trastuzumab, docetaxel, and pertuzumab.[3] However, it should be noted that approximately 90% of the patients in CLEOPATRA were trastuzumab-naive.[14] In trastuzumab-naive patients in MARIANNE, the median OS ranged from 56.3 to 60.7 months in the HT arm and from 51.8 to 64.4 months in the T-DM1 arm. Nonetheless, the OS results from MARIANNE demonstrate the progress

made in the management of HER2-positive MBC, where median survival times longer than 4 years are now routinely achieved.

An OS subgroup analysis by baseline risk factors did not identify any patients who might do better with T-DM1 over HT or vice versa. Although the forest plots suggested the possibility of a differential effect among black patients and patients 75 years old or older, the patient numbers in these subgroups were too small to draw any conclusions. At the time of the primary analysis, the OR rate was lower in the T-DM1 arms (T-DM1, 59.7%; T-DM1+pertuzumab, 64.2%) than the HT arm (67.9%). However, for patients who had an OR, the median duration of response was numerically longer in the T-DM1 arms (T-DM1, 20.7 months; T-DM1+pertuzumab, 21.2 months) in comparison with the HT arm (12.5 months). The exploratory landmark analysis aimed

to determine whether this longer duration of response in the patients who responded to T-DM1 translated into longer survival. The longer duration of response appeared to result in longer median survival in responding patients, with a median survival of 64.4 months in the T-DM1 group versus 56.3 months in the HT group. An evaluation of baseline and biomarker characteristics did not reveal any clear differences between responders and nonresponders that would allow the identification of tumors likely to respond to T-DM1, nor did this analysis reveal any characteristics associated with a differential response by treatment arm.

The exploratory analysis of OS by HER2 mRNA and protein expression suggested that patients with greater HER2 expression in the T-DM1 arm had longer median OS (Supporting Fig. 1). However, when they were compared with the HT arm, the CIs included 1; thus, no treatment effect was apparent in these subgroups. These data are consistent with a recent analysis of the relationship between HER2 expression and PFS in MARIANNE.[15] In that analysis, greater HER2 mRNA and protein expression was associated with numerically longer PFS in the T-DM1 arm, as was homogeneous HER2 expression (compared with heterogeneous or focal expression). Similarly to the OS analysis, however, this did not result in a differential treatment effect between the T-DM1 and HT arms. These data are consistent with those from the EMILIA study, which showed numerically longer PFS and OS in patients with above-median HER2 mRNA expression,[16] and the TH3RESA study, which showed numerically longer PFS in patients with above-median HER2 mRNA expression.[17] This relationship between HER2 expression and outcomes does not appear, however, to exclusively apply to T-DM1 because high HER2 mRNA expression was a strong prognostic marker in the CLEOPATRA study of pertuzumab, trastuzumab, and docetaxel or a placebo, trastuzumab, and docetaxel for the first-line treatment of HER2-positive MBC.[18] Nonetheless, the aggregate data from all of these studies suggest that T-DM1 may have the most pronounced effects in tumors with high HER2 expression.

The updated safety profiles of T-DM1 and pertuzumab were generally consistent with the primary analysis.[8] There continued to be numerically fewer grade 3 or higher AEs reported with T-DM1 versus HT. The most commonly reported grade 3 or higher AEs in the T-DM1 arm were thrombocytopenia, transaminase elevations, and anemia, whereas neutropenia, febrile neutropenia, and diarrhea were the most common in the HT arm. The post–amendment C PRO analysis was based on a more frequent assessment schedule and included additional patient-experienced measures of neuropathy, diarrhea, alopecia, and nausea. Overall, patients treated with T-DM1 experienced fewer treatment-related side effects with T-DM1 and a longer time to clinically meaningful increases in neurotoxicity. The median time to a clinically meaningful deterioration in neurotoxicity symptoms was numerically shorter in the HT arm (2.1 months) in comparison with the T-DM1 (6.2 months) and T-DM1+pertuzumab arms (4.2 months). Notably, the vast majority of patients treated with T-DM1 or T-DM1+pertuzumab did not report hair loss, which is viewed by women with breast cancer as a distressing side effect of chemotherapy. In contrast, 85% of patients treated with HT reported alopecia by the third treatment cycle, with 42% of the patients in that arm reporting alopecia up to cycle 18 (ie, 54 weeks of study treatment). These data are consistent with recent data showing that 5% to 52% of patients still report partial or complete alopecia at least 18 months after cessation of docetaxel therapy.[19] Patient-reported nausea was generally similar across the treatment arms in the first 10 cycles of treatment but decreased in the HT and T-DM1 arms in later cycles. The majority of patients in the T-DM1 arm did not experience diarrhea while on treatment, and rates in the T-DM1 arm were the lowest of the 3 treatment arms. Fewer patients in the T-DM1 arm reported bother due to side effects of treatment in comparison with patients in the other treatment arms.

In conclusion, the final analysis of MARIANNE supports the use of T-DM1 as a first-line treatment option for certain patients with HER2-positive MBC. Although the control arm of HT has since been superseded by trastuzumab, taxane, and pertuzumab in the first-line setting, the results of MARIANNE nonetheless demonstrate that single-agent T-DM1 has a favorable tolerability profile in comparison with HT, including a lower incidence of grade 3 or higher neutropenia, febrile neutropenia, and diarrhea. In addition, fewer patients on T-DM1 reported bother from side effects of treatment in comparison with the other arms, and they also reported a lower incidence of alopecia and a nearly 3-fold increase in the time to patient-experienced increases in neurotoxicity symptoms. These data provide further support for clinical practice guidelines that recommend first-line T-DM1 as an appropriate choice for patients deemed unsuitable for taxane-based therapy.[1]

CONFLICT OF INTEREST DISCLOSURES

AUTHOR CONTRIBUTIONS

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