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ORIGINAL REPORT

Phase II Randomized Study of Trastuzumab Emtansine Versus Trastuzumab Plus Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer

Sara A. Hurvitz, Luc Dirix, Judit Kocsis, Giulia V. Bianchi, Janice Lu, Jeferson Vinholes, Ellie Guardino, Chunyan Song, Barbara Tong, Vivian Ng, Yu-Waye Chu, and Edith A. Perez

Sara A. Hurvitz, University of California at Los Angeles Jonsson Comprehensive Cancer Center and Translational Oncology Research International, Los Angeles, CA; Luc Dirix, Sint-Augustinus Hospital, Antwerp, Belgium; Judit Kocsis, Semmelweis University Hospital, Budapest, Hungary; Giulia V. Bianchi, Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy; Janice Lu, State University of New York at Stony Brook, Stony Brook, NY; Jeferson Vinholes, Clinica de Oncologia, Porto Alegre, Brazil; Ellie Guardino, Chunyan Song, Barbara Tong, Vivian Ng, and Yu-Waye Chu, Genentech, South San Francisco, CA; and Edith A. Perez, Mayo Clinic, Jacksonville, FL.

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Clinical trial information: NCT00679341.

Corresponding author: Edith A. Perez, MD, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224; e-mail: perez.edith@mayo.edu.

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ABSTRACT

Purpose
Trastuzumab emtansine (T-DM1), an antibody-drug conjugate composed of the cytotoxic agent DM1 conjugated to trastuzumab via a stable thioether linker, has shown clinical activity in single-arm studies enrolling patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer (MBC) whose disease had progressed on HER2-targeted therapy in the metastatic setting.

Patients and Methods
Patients (N = 137) with HER2-positive MBC or recurrent locally advanced breast cancer were randomly assigned to trastuzumab plus docetaxel (HT; n = 70) or T-DM1 (n = 67) as first-line treatment until disease progression or unacceptable toxicity. Primary end points were investigator-assessed progression-free survival (PFS) and safety. Key secondary end points included overall survival (OS), objective response rate (ORR), duration of objective response, clinical benefit rate, and quality of life.

Results
Median PFS was 9.2 months with HT and 14.2 months with T-DM1 (hazard ratio, 0.59; 95% CI, 0.36 to 0.97); median follow-up was approximately 14 months in both arms. ORR was 58.0% (95% CI, 45.5% to 69.2%) with HT and 64.2% (95% CI, 51.8% to 74.8%) with T-DM1. T-DM1 had a favorable safety profile versus HT, with fewer grade ≥ 3 adverse events (AEs; 46.4% *v* 90.9%), AEs leading to treatment discontinuations (7.2% *v* 40.9%), and serious AEs (20.3% *v* 25.8%). Preliminary OS results were similar between treatment arms; median follow-up was approximately 23 months in both arms.

Conclusion
In this randomized phase II study, first-line treatment with T-DM1 for patients with HER2-positive MBC provided a significant improvement in PFS, with a favorable safety profile, versus HT.

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INTRODUCTION

Overexpression of human epidermal growth factor receptor 2 (HER2) occurs in approximately 20% of breast cancers[1,2] and is associated with increased mortality in early-stage disease, decreased time to relapse, and increased incidence of metastases compared with HER2-normal breast cancer.[3-5] However, patients treated with HER2-targeted therapies have improved clinical outcomes versus those treated with chemotherapy alone. In nonrandomized studies, single-agent trastuzumab has modest activity in the treatment of HER2-positive metastatic breast cancer (MBC).[6-8] Trastuzumab plus taxane–based chemotherapy demonstrated significantly improved overall survival (OS) and progression-free survival (PFS) over chemotherapy alone[9,10] as first-line therapy for HER2-positive MBC, a finding confirmed in other trials of trastuzumab-containing regimens.[11] Nevertheless, MBC will eventually progress in most patients. Moreover, chemotherapy-associated toxicity is a significant source of patient morbidity.[9,10] Severe myelosuppression is frequently observed in patients receiving docetaxel and can be a barrier to adequate treatment for MBC. Even nonserious adverse events (AEs) commonly associated with chemotherapy confer a substantial negative effect on patient quality of life (QOL).[12] Thus, there remains a need for more effective and better-tolerated therapies for HER2-positive MBC.

Trastuzumab emtansine (T-DM1)—composed of cytotoxic microtubule polymerization inhibitor DM1 conjugated to the humanized, monoclonal antibody trastuzumab via a stable thioether linker[13]—is a HER2-targeted antibody-drug conjugate (ADC) in development for the treatment of HER2-positive cancer. T-DM1 is unique among ADCs; it selectively delivers a cytotoxic agent to tumor cells, and the targeting antibody trastuzumab is itself approved to treat MBC.[14,15]

Studies of single-agent T-DM1 at 3.6 mg/kg administered once every 3 weeks in patients previously treated with multiple therapies for HER2-positive MBC demonstrated encouraging efficacy with a tolerable safety profile.[16-18] Investigator-reported objective response rates (ORRs) were 32.7% to 44.0%, and many of the AEs associated with systemic chemotherapies were observed at lower rates relative to historical data.

Preliminary response and tolerability data from TDM4450g [A Study of the Efficacy and Safety of Trastuzumab-MCC-DM1 vs. Trastuzumab (Herceptin) and Docetaxel (Taxotere) in Patients With Metastatic HER2-Positive Breast Cancer Who Have Not Received Prior Chemotherapy for Metastatic Disease] were previously presented.[19,20] Here, we report the primary efficacy and safety results of TDM4450g—which is, to the best of our knowledge, the first direct comparison of T-DM1 with an active HER2-targeted regimen for the first-line treatment of HER2-positive MBC.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ 18 years of age with histologically or cytologically confirmed, HER2-positive, unresectable, locally advanced breast cancer and/or MBC without prior chemotherapy or trastuzumab for metastatic disease. HER2-positivity was defined as immunohistochemistry 3+ (> 10% cell staining) or fluorescent in situ hybridization–positive by local laboratory testing (ratio ≥ 2.0). Other inclusion criteria included measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0,[21] Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and adequate organ function.

Exclusion criteria included less than 6 months from completion of cytotoxic chemotherapy in the neoadjuvant/adjuvant setting until diagnosis of MBC, trastuzumab ≤ 21 days before random assignment, untreated or symptomatic brain metastases, treatment for brain metastases ≤ 60 days before random assignment, cumulative anthracycline dose equivalent to doxorubicin more than 500 mg/m^2, history of significant cardiovascular or other severe uncontrolled systemic disease, and/or grade ≥ 3 peripheral neuropathy.

The protocol was approved by the institutional review boards of all participating institutions and was carried out in accordance with the Declaration of Helsinki, current US Food and Drug Administration Good Clinical Practices, and applicable local laws. Patients provided written informed consent.

Study Design

In this phase II, multicenter, open-label study, patients were randomly assigned 1:1 to either T-DM1 3.6 mg/kg intravenously (IV) once every 3 weeks or trastuzumab 8 mg/kg IV loading dose followed by 6 mg/kg once every 3 weeks and docetaxel 75 or 100 mg/m^2 (HT; per investigator discretion) IV once every 3 weeks. Treatment continued until progressive disease (PD) or unacceptable toxicity. Eligible patients were randomly assigned by using a hierarchical dynamic randomization algorithm to ensure balance between the treatment arms, based on world region (United States/non–United States), prior adjuvant or neoadjuvant trastuzumab therapy (yes/no), and disease-free interval (≤ 24 or > 24 months).

Selected AEs were prespecified in the protocol for dose modifications, delays, or discontinuations of T-DM1 (Appendix Table A1, online only). Although premedication was not used for the initial dose of T-DM1, premedication for docetaxel was allowed according to standard practice guidelines. Trastuzumab dose reductions were not permitted; however, its administration could be delayed to assess or treat prespecified AEs.

Patients randomly assigned to T-DM1 who discontinued T-DM1 for unacceptable DM1-related toxicities were eligible to receive single-agent trastuzumab. For patients in the HT arm, if either trastuzumab or docetaxel was discontinued before PD, the remaining agent could be continued once every 3 weeks. Patients assigned to HT treatment who discontinued treatment because of PD were eligible to cross over to T-DM1 3.6 mg/kg once every 3 weeks.

Primary end points were investigator-assessed PFS and safety. Secondary end points included OS, ORR, duration of response (DOR), clinical benefit rate (CBR), and QOL as measured by the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB),[22,23] a subset of the Functional Assessment of Cancer Therapy-Breast (FACT-B),[22] a summary measurement of physical and functional well-being and breast cancer–specific symptoms.

Assessments

Tumor assessments were conducted at baseline and every 9 weeks from treatment start until PD, death, or study termination, whichever occurred first. All patients with PD were observed for survival approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination. Tumor responses were evaluated per modified RECIST, version 1.0; the modification was defined as a minimum of a 5-mm increase in the sum of the longest diameter in determining PD and a ≥ 20% increase in the sum of the longest diameter of target lesions relative to nadir. Objective response was defined as complete response (CR) or partial response on two consecutive tumor assessments ≥ 4 weeks apart. CBR was defined as a CR or partial response during the study or stable disease sustained for ≥ 6 months after random assignment.

AEs were categorized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0. Complete blood counts were assessed on days 1, 8, and 15 of cycles 1 through 3, and days 1 and 8 of every cycle thereafter. Serum chemistries were assessed on days 1 and 8 of every cycle. Cardiac echocardiogram or multigated acquisition scans were obtained at screening and every 9 weeks thereafter until PD or study termination.

Archival tumor tissue from the initial breast cancer diagnosis was collected and evaluated centrally for HER2 expression (fluorescent in situ hybridization or immunohistochemistry). Patients completed the FACT-B questionnaire on day 1 of all cycles until PD or treatment discontinuation.

Statistical Analysis

The primary efficacy analysis included all randomly assigned patients, and all efficacy and safety analyses were based on clinical data before T-DM1 crossover. PFS was defined as the time from random assignment to the first occurrence of PD or death as a result of any cause within 30 days of the last administered dose of drug. Data were censored at the last tumor assessment date before crossover (or at the date of random assignment plus 1 day, if no assessment was performed after baseline) for patients who did not experience PD or death within 30 days of the last administered dose. The hazard ratio (HR) of PFS comparing T-DM1 with HT and its 95% CIs were estimated from a Cox proportional hazards model, stratified by stratification factors used in random assignment. A stratified two-sided log-rank test measured the difference in PFS between the two arms.

All treated patients were included in the safety analyses on the basis of actual treatment received. Two patients randomly assigned to HT received a single dose of T-DM1 in error and were included in the T-DM1 group for safety analyses.

QOL analyses were performed for patients who had a FACT-B assessment at cycle 1 and at one or more cycles thereafter. The primary analysis evaluated the time to symptom deterioration in the TOI-PFB subset of FACT-B; a decrease of five or more points in the TOI-PFB was considered clinically meaningful.[23]

This study had a hypothesis-generating statistical design. Genentech collected and analyzed the data; all authors had access to the primary data.

RESULTS

The data cutoff for the primary efficacy and safety analysis was November 15, 2010, after 75 PFS events were observed. An updated safety analysis was performed with a data cutoff of August 31, 2011, and is reported here.

Patient Characteristics

Between July 2008 and December 2009, 137 patients were randomly assigned to HT (n = 70) or T-DM1 (n = 67). Baseline characteristics were similar between arms (Table 1). Similar numbers of patients in the HT and T-DM1 arms had previously received treatment with anthracyclines (48.6% and 44.8%, respectively). Prior treatment with neoadjuvant or adjuvant trastuzumab (27.1% and 17.9%, respectively) or taxanes (40.0% and 32.8%, respectively) was fairly well balanced between arms. In the HT arm, most patients (74.2%) initiated docetaxel at a dose of 75 mg/m^2. Thirty-five patients randomly assigned to HT received T-DM1 as second-line treatment as of August 2011.

Treatment

Two patients in the HT arm did not receive treatment (because they withdrew from the trial). All patients in the T-DM1 arm received treatment (Fig 1). Median durations of follow-up were approximately 14 months for the efficacy analysis and approximately 23 months for the updated safety analyses.

Median treatment duration was 8.1 months (range, 1 to 29 months) for trastuzumab, 5.5 months (range, 0 to 22 months) for docetaxel, and 10.4 months (range, 0 to 29 months) for T-DM1; the median number of cycles was 12 (range, two to 43 cycles), eight (one to 31 cycles), and 16 (one to 41 cycles), respectively. Based on prespecified protocol guidelines (Appendix Table A1), the docetaxel dose was reduced in 23 patients (34.8%); the T-DM1 dose was reduced in 14 patients (20.3%). At the August 2011 data cutoff, three patients (4.3%) were continuing HT, four (5.7%) were continuing trastuzumab alone, and 14 (20.9%) were continuing T-DM1. The most common reason for treatment discontinuation in both arms was PD (50 [71.4%] patients in the HT arm and 42 [62.7%] patients in the T-DM1 arm).

Efficacy

In the primary efficacy analysis, T-DM1 provided significant improvement in PFS over HT, with an estimated stratified HR of 0.59 (95% CI, 0.36 to 0.97; $P = .035$). The median PFS was 9.2 months in the HT arm versus 14.2 months in the T-DM1 arm (Fig 2). Similar results were seen in patients confirmed to be HER2-positive per retrospective central testing (9.8 *v* 14.2 months, respectively; HR, 0.53; 95% CI, 0.29 to 0.97; $P = .037$; n = 52 in both arms). Four patients in the HT arm (one each: PD, toxicity, patient withdrew consent, and unknown) and seven patients in the T-DM1 arm (six patients with PD, one physician withdrawal) had a PFS event within the first 2 months.

The ORR in the HT arm was 58.0% (95% CI, 45.5% to 69.2%) with three CRs versus 64.2% (95% CI, 51.8% to 74.8%) with seven CRs in the T-DM1 arm ($P = .458$). Of 40 patients with an objective response to HT, median DOR was 9.5 months (95% CI, 6.6 to 10.6 months: Fig 3). Of 43 patients with an objective response to T-DM1, median DOR was not reached; the twenty-fifth percentile of the DOR was 8.8 months. The CBRs were 81.2% (95% CI, 70.7% to 89.1%) and 74.6% (95% CI, 63.2% to 84.2%; $P = .358$) for HT and T-DM1, respectively.

Table 1. Selected Patient Demographic and Baseline Characteristics

Characteristic	HT (n = 70) No.	HT (n = 70) %	T-DM1 (n = 67) No.	T-DM1 (n = 67) %
Age, years				
Median	52.0		55.0	
Range	33-75		27-82	
World region				
North America		28.6		31.3
Central and South America		28.6		23.9
Europe		42.9		44.8
Race				
White		82.9		77.6
American Indian or Alaskan native		10.0		7.5
Black		4.3		4.5
Other or N/A		2.9		10.4
ECOG PS				
0		63.8*		65.7
1		36.2*		34.3
HER2 status by central laboratory†				
HER2-positive		85.9		85.7
Normal		14.1		14.3
ER/PR status				
ER-positive and/or PR-positive		54.3		49.3
ER-negative and PR-negative		41.4		47.8
ER and PR unknown		4.3		3.0
Stage at initial diagnosis				
I to III		68.1‡		58.2
IV		29.0‡		34.3
Unknown		2.9‡		7.5
No. of distinct sites of involvement				
1-2		49.3		35.8
> 2		50.7		64.2
Lung or liver involvement				
Yes		67.1		71.6
No		31.4		26.9
Unknown		1.4		1.5
Disease-free interval, months				
≤ 24		64.3		59.7
> 24		35.7		40.3
Prior treatment				
Trastuzumab		27.1		17.9
Taxane		40.0		32.8
Anthracycline		48.6		44.8
Total no. of prior chemotherapy agents				
Median	3		3	
Range	1-4		1-6	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HT, trastuzumab plus docetaxel; N/A, not available; PR, progesterone receptor; T-DM1, trastuzumab emtansine.

*ECOG PS data were available for 69 patients in the HT arm.

†Central testing for HER2 status was available for 64 patients in the HT arm and 63 patients in the T-DM1 arm.

‡Data on stage at initial diagnosis were available for 69 patients in the HT arm.

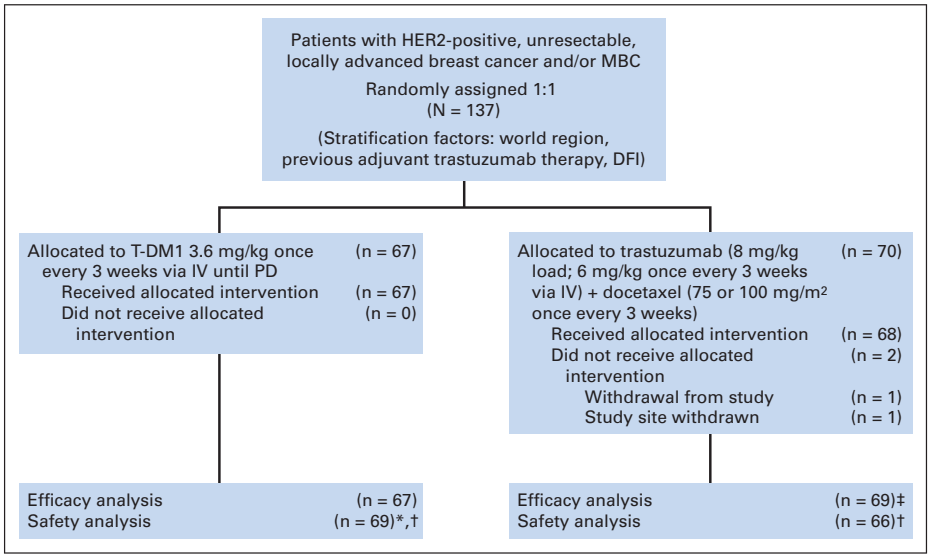

Fig 1. CONSORT diagram. (*) Includes three patients who received at least one dose of trastuzumab alone or trastuzumab plus docetaxel. (†) Two patients mistakenly received a dose of trastuzumab emtansine (T-DM1) and were thus included in the T-DM1 group for the safety analyses. (‡) One patient was not included in the efficacy analysis as a result of study site withdrawal. DFI, disease-free interval; HER2, human epidermal growth factor receptor 2; IV, intravenous; MBC, metastatic breast cancer; PD, progressive disease.

A preliminary OS analysis was performed, with a median follow-up of approximately 23 months in both arms (Appendix Fig A1, online only). With 13 deaths reported in each arm, the stratified HR of death for T-DM1 relative to HT was 1.06 (95% CI, 0.477 to 2.352; $P = .889$).

Safety

Compared with the HT group, the T-DM1 group had fewer grade ≥ 3 AEs (90.9% *v* 46.4%); grade 4 AEs occurred in 57.6% and 5.8% of patients, respectively. Serious AEs (25.8% *v* 20.3%) and AEs leading to treatment discontinuation (40.9% *v* 7.2%) also occurred less frequently with T-DM1. There were no reports of symptomatic congestive heart failure. Three patients per group had decreased left ventricular ejection fractions (LVEF; HT: two grade 2 and one grade 3 event; T-DM1: two grade 1 and one grade 3 event). Two patients in the HT group had postbaseline LVEF ≤ 40% based on local assessment; both had prior anthracycline therapy in the adjuvant setting. One patient in the T-DM1 group had LVEF ≤ 40%. This patient had not received prior anthracycline treatment and did not have a cardiac medical history; no symptoms within the time frame of the LVEF decrease and no medical intervention were reported.

Among patients evaluable for safety, most AEs were grade 1 or 2 in both treatment groups. The most common AEs of any grade (Table 2) in the HT group were alopecia, neutropenia, diarrhea, and fatigue. Consistent with this, more patients in the HT group were treated with colony-stimulating factors (44.3% *v* 6.0% in the T-DM1 group). In the T-DM1 group, the most common AEs were fatigue, nausea, increase in serum AST, pyrexia, and headache.

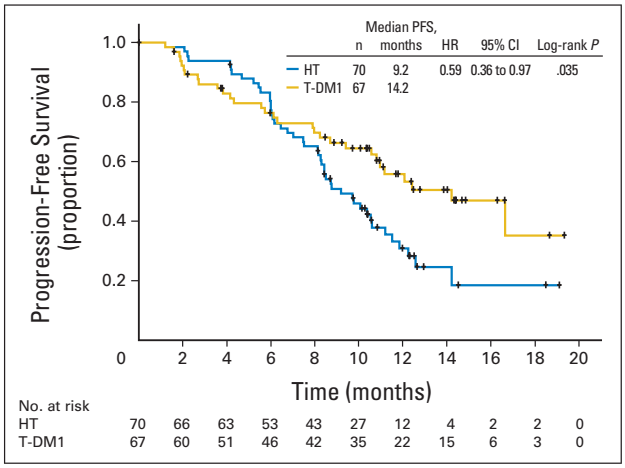

Fig 2. Kaplan-Meier estimates of progression-free survival (PFS) in the overall study population. The median duration of PFS was 14.2 months in the trastuzumab emtansine (T-DM1) arm and 9.2 months in the trastuzumab plus docetaxel (HT) arm, which corresponds to a hazard ratio (HR) for progression of 0.59 ($P = .035$).

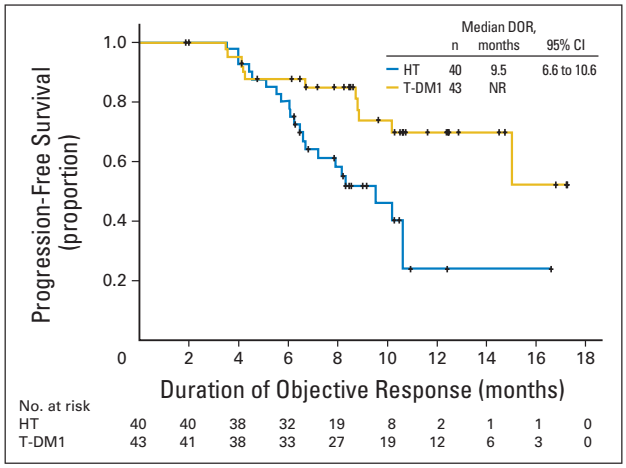

Fig 3. Kaplan-Meier estimates of duration of response (DOR) by investigator. In patients with measurable disease at baseline with an objective response, the median DOR was 9.5 months (95% CI, 6.6 to 10.6 months) in the trastuzumab plus docetaxel (HT) arm (n = 40); in the trastuzumab emtansine (T-DM1) arm (n = 43), the median DOR was not reached (NR).

Table 2. Adverse Events of Any Grade Occurring in ≥ 25% and/or Grade ≥ 3 Occurring in ≥ 5% of Patients in Either Treatment Group

	All Grade				Grade ≥ 3*			
	HT (n = 66)†		T-DM1 (n = 69)†‡		HT (n = 66)†		T-DM1 (n = 69)†‡	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Hematologic								
Neutropenia§	**43**	**65.2**	**11**	**15.9**	**41**	**62.1**	**4**	**5.8**
Thrombocytopenia§	**4**	**6.1**	**19**	**27.5**	2¶	3.0	5¶	7.2
Leukopenia§	17	25.8	7	10.1	**16**	**24.2**	**0**	
Febrile neutropenia	9	13.6	0		9	13.6	0	
Anemia	18	27.3	9	13.0	3	4.5	2	2.9
Nonhematologic								
Alopecia	**44**	**66.7**	**3**	**4.3**	—‖		—‖	
Fatigue	30	45.5	34	49.3	3	4.5	3	4.3
Nausea	29	43.9	34	49.3	0		2	2.9
Diarrhea	**30**	**45.5**	**11**	**15.9**	2	3.0	0	
Peripheral edema	**29**	**43.9**	**7**	**10.1**	4	6.1	0	
Increased AST	**4**	**6.1**	**30**	**43.5**	0		6	8.7
Pyrexia	15	22.7	28	40.6	1	1.5	0	
Headache	**12**	**18.2**	**28**	**40.6**	0		0	
Back pain	21	31.8	19	27.5	3	4.5	1	1.4
Epistaxis	6	9.1	19	27.5	0		0	
Dyspnea	18	27.3	10	14.5	2	3.0	0	
Arthralgia	20	30.3	16	23.2	1	1.5	0	
Cough	14	21.2	18	26.1	0		0	
Vomiting	17	25.8	17	24.6	0		2	2.9
Increased ALT	4	6.1	18	26.1	0		7	10.1
Pneumonia	1	1.5	6	8.7	0		4	5.8

NOTE. Bold indicates those adverse events with ≥ 20% difference in incidence between treatment groups.
Abbreviations: HT, trastuzumab plus docetaxel; MedDRA, Medical Dictionary for Regulatory Activities; T-DM1 trastuzumab emtansine.
*No adverse events listed were grade 5.
†Two patients mistakenly received a dose of T-DM1 and were thus included in the T-DM1 group for safety analyses.
‡Includes three patients who received at least one dose of trastuzumab alone or HT.
§Neutropenia includes events classified as MedDRA-preferred terms "neutropenia" or "neutrophil count decreased"; thrombocytopenia includes events classified as MedDRA-preferred terms "thrombocytopenia," "platelet count decreased," or "heparin-induced thrombocytopenia"; leukopenia includes events classified as MedDRA-preferred terms "leukopenia" or "white blood cell count decreased."
¶All of these events were grade 3.
‖National Cancer Institute Common Terminology Criteria for Adverse Events v.3 categorizes alopecia only as grade 1 or grade 2; there is no grade ≥ 3 for this adverse event.

As of the updated safety data cutoff date, 12 patients in the HT group and 14 patients in the T-DM1 group in the population evaluable for safety died, most commonly because of PD in both groups. Among these patients, one per group had an AE that resulted in death: one cardiopulmonary failure in the HT group and one sudden death in the T-DM1 group. Neither death was attributed to study treatment per investigator assessment.

QOL

The FACT-B completion rate was more than 90%. Mean changes from baseline in FACT-B TOI scores were more favorable in the T-DM1 arm versus the HT arm across all treatment cycles (Fig 4A). The time to a decrease of five or more points in TOI-PFB score was significantly delayed in the T-DM1 arm, from a median of 3.5 months in the HT arm to 7.5 months in the T-DM1 arm (HR, 0.58; 95% CI, 0.36 to 0.92; $P = .022$; Fig 4B).

DISCUSSION

In this study of first-line treatment for HER2-positive MBC, T-DM1 provided a clinically meaningful and statistically significant 41% reduction in the relative risk of PD versus standard treatment. Although the ORRs and CBRs were similar between the two arms, the median PFS was 9.2 months in the HT arm versus 14.2 months in the T-DM1 arm. The ORR and PFS observed in the HT arm are consistent with historical phase II data.[10,24-27] The greater number of PFS events with T-DM1 compared with HT observed in the early part of the Kaplan-Meier PFS curves (Fig 2) could be the result of disproportionate toxicity in the T-DM1 arm, a confounding factor, the existence of HER2-normal metastases, or random chance resulting from the small number of events occurring in this early time period (13 in the HT arm and 15 in T-DM1 arm). This difference is not likely due to greater toxicity with T-DM1 since disease progression was the PFS event for nearly all patients in the T-DM1 arm (six of seven patients) with early PFS events. Disease burden was greater at study entry in the T-DM1 arm compared with the HT arm (Genentech data on file), which could have contributed to the greater number of early PFS events in the T-DM1 arm.

The improvement in PFS observed with T-DM1 in this study was associated with a more durable response, which could result from greater potency related to its unique mechanisms of action, longer treatment duration enabled by its favorable safety and tolerability, or both. Notably, grade 4 AEs were reported for 57.6% of patients

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