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ORIGINAL REPORT

A Phase II Study of Trastuzumab Emtansine in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer Who Were Previously Treated With Trastuzumab, Lapatinib, an Anthracycline, a Taxane, and Capecitabine

Ian E. Krop, Patricia LoRusso, Kathy D. Miller, Shanu Modi, Denise Yardley, Gladys Rodriguez, Ellie Guardino, Michael Lu, Maoxia Zheng, Sandhya Girish, Lukas Amler, Eric P. Winer, and Hope S. Rugo

Ian E. Krop and Eric P. Winer, Dana-Farber Cancer Institute, Boston, MA; Patricia LoRusso, Karmanos Cancer Institute, Detroit, MI; Kathy D. Miller, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; Shanu Modi, Memorial Sloan-Kettering Cancer Center, New York, NY; Denise Yardley, Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Gladys Rodriguez, South Texas Oncology/Hematology, San Antonio, TX; Ellie Guardino, Michael Lu, Maoxia Zheng, Sandhya Girish, and Lukas Amler, Genentech, South San Francisco, CA; and Hope S. Rugo, University of California, San Francisco Comprehensive Cancer Center, San Francisco, CA.

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Corresponding author: Ian E. Krop, MD, PhD, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston MA 02215; e-mail: ikrop@partners.org.

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ABSTRACT

Purpose
To determine whether the antibody-drug conjugate trastuzumab emtansine (T-DM1), which combines human epidermal growth factor receptor 2 (HER2) –targeted delivery of the potent antimicrotubule agent DM1 with the antitumor activity of trastuzumab, is effective in patients with HER2-positive metastatic breast cancer (MBC) who have previously received all standard HER2-directed therapies.

Patients and Methods
In this single-arm phase II study, T-DM1 3.6 mg/kg was administered intravenously every 3 weeks to patients with HER2-positive MBC who had prior treatment with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. The primary objectives were overall response rate (ORR) by independent review and safety.

Results
Among 110 pretreated patients (median, seven prior agents for MBC; median follow-up, 17.4 months), the ORR was 34.5% (95% CI, 26.1% to 43.9%), clinical benefit rate was 48.2% (95% CI, 38.8% to 57.9%), median progression-free survival (PFS) was 6.9 months (95% CI, 4.2 to 8.4 months), and median duration of response was 7.2 months (95% CI, 4.6 months to not estimable). In patients with confirmed HER2-positive tumors (n = 80 by retrospective central testing), the response rate was 41.3% (95% CI, 30.4% to 52.8%), and median PFS was 7.3 months (95% CI, 4.6 to 12.3 months). Most adverse events were grades 1 to 2; the most frequent grade ≥ 3 events were thrombocytopenia (9.1%), fatigue (4.5%), and cellulitis (3.6%).

Conclusion
T-DM1 is well tolerated and has single-agent activity in patients with HER2-positive MBC who have previously received both approved HER2-directed therapies and multiple chemotherapy agents. T-DM1 may be an effective new treatment for this patient population.

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INTRODUCTION

Amplification of the human epidermal growth factor receptor 2 (*HER2*) gene occurs in approximately 20% to 25% of primary breast cancers.[1,2] Such tumors are considered HER2-positive and are associated with aggressive growth and poor clinical outcomes.[1] Therapies that target the HER2 pathway have greatly improved outcomes for patients with HER2-positive breast cancer.[3-8] Trastuzumab (Herceptin; Genentech, South San Francisco, CA), a humanized monoclonal antibody against the extracellular domain of HER2, is associated with single-agent activity[7] and improved survival when added to chemotherapy[5] in patients with HER2-positive metastatic breast cancer (MBC). The addition of the HER1/HER2 tyrosine kinase inhibitor lapatinib to capecitabine improves time to disease progression.[8] This combination is indicated for patients with HER2-positive advanced cancer or MBC after prior trastuzumab, anthracycline, and taxane therapy. Despite these treatments, disease progression eventually occurs. In clinical practice, anti-HER2 therapies are continued through multiple lines of treatment,[9] given the evidence that HER2 overexpression persists after

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progression.[10-12] However, there is no standard HER2-directed regimen approved for these heavily pretreated patients,[9] and additional HER2-directed therapies are needed.

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate (ADC) designed for treatment of HER2-positive cancer.[13] T-DM1 combines the selective intracellular delivery of DM1, a potent derivative of the antimicrotubule agent maytansine, with the antitumor properties of trastuzumab.[13-17] In T-DM1, trastuzumab and DM1 are covalently linked via a stable thioether linker (*N*-maleimidomethyl)cyclohexane-1-carboxylate, which is thought to limit the exposure of normal tissue to DM1.[18,19] A prior proof-of-concept phase II study (TDM4258g) of single-agent T-DM1 (3.6 mg/kg given every 3 weeks) in 112 patients with HER2-positive MBC who had progressed while receiving HER2-directed therapy, showed antitumor activity.[19] The objective response rate (ORR) by independent assessment was 25.9% (95% CI, 18.4% to 34.4%), and median progression-free survival (PFS) was 4.6 months (95% CI, 3.9 to 8.6 months). Median PFS was higher (8.2 months) among patients with tumors that were HER2-positive by retrospective central testing (n = 74) compared with those found to be HER2-normal (n = 21; 2.6 months). T-DM1 was well tolerated with no dose-limiting cardiotoxicity. Of note, 60% of patients had received prior lapatinib in addition to trastuzumab. The ORR (23.9%) in this subgroup was similar to that in patients who had received trastuzumab alone, suggesting that T-DM1 is effective even in patients who had previously received both of the approved HER2-targeted therapies.

The study described here, TDM4374g, was conducted to confirm that T-DM1 is active in tumors refractory to current therapies. In contrast to TDM4258g, which required only that patients had received and progressed on at least one prior HER2-directed agent and received at least one chemotherapy in the metastatic setting, this study required that all patients had received trastuzumab, lapatinib, a taxane, an anthracycline, and capecitabine. In addition, patients had to have at least two HER2-directed therapy regimens in the metastatic or locally advanced setting and progression on the most recent regimen. Exploratory subgroup analyses are also presented that assess efficacy based on HER2 expression levels and on phosphatidyl inositol-3-kinase (PI3K) mutations, since alterations in the PI3K pathway have been implicated in tumor insensitivity to trastuzumab in HER2-positive MBC.[20-24]

PATIENTS AND METHODS

Patients

Key eligibility criteria included age ≥ 18 years, documented HER2-positive MBC (immunohistochemistry [IHC] 3+ or fluorescent in situ hybridization [FISH] positive by local laboratory criteria), measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.0,[25] Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, and prior treatment with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine in the neoadjuvant, adjuvant, locally advanced, or metastatic setting. Patients also must have had at least two HER2-directed therapy regimens in the metastatic or locally advanced setting and progression on the most recent regimen (see Appendix [online only] for more detail on methods).

Study Design and Objectives

T-DM1 was administered intravenously at 3.6 mg/kg every 3 weeks. The primary objectives were to assess ORR by independent radiologic facility (IRF) review and to evaluate safety and tolerability. Secondary objectives included clinical benefit rate (complete response plus partial response plus stable disease ≥ 6 months), duration of objective response (DOR), PFS, and pharmacokinetic (PK) profile. Correlation of efficacy with biomarkers was an exploratory objective.

All patients provided written informed consent. The study was reviewed and approved by the institutional review board at each site, according to local guidelines.

Assessments and Data Collection

Tumor assessments were conducted every other cycle by investigator and retrospectively by double-reader IRF as needed. Echocardiogram or multigated acquisition scans were obtained at screening and every 6 weeks thereafter until study termination.

Diagnostic and Biomarker Assays

Archival tumor tissue was collected and evaluated by validated assays for HER2 expression (by using FISH, IHC, and quantitative reverse transcriptase polymerase chain reaction [qRT-PCR]) and for mutations in the PI3K catalytic subunit (*PIK3CA*).

Statistics

The planned sample size of 100 patients, calculated by using the exact method for a single proportion, was chosen to ensure ≥ 80% power to reject a null hypothesis of a response rate of ≤ 14% against an alternative of ≥ 25%. Statistical analyses were conducted approximately 15 months after the last patient was enrolled.

Efficacy and safety end points were analyzed in patients who received at least one dose of T-DM1. Objective response was defined as complete or partial response on two consecutive tumor assessments ≥ 4 weeks apart; PFS was defined as time from first day of study treatment to first documented disease progression or death on study (ie, death from any cause within 30 days from last dose of study drug). Median PFS and DOR were calculated by using Kaplan-Meier methods.

RESULTS

Demographics and Patient Characteristics

In all, 110 patients enrolled onto this study and received at least one T-DM1 dose (Table 1). All patients had received prior trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine except for one patient who had received prior ixabepilone instead of a taxane. Patients received a median of 8.5 (range, 5 to 19) prior anticancer agents (excluding hormonal therapies) in all settings, and a median of 7.0 (range, 3 to 17) prior agents (excluding hormonal therapies) for MBC.

Efficacy

Among treated patients, 38 had an objective tumor response (all partial responses) by IRF assessment, corresponding to an ORR of 34.5% (95% CI, 26.1% to 43.9%; Table 2). Median PFS was 6.9 months (95% CI, 4.2 to 8.4 months) by IRF (Table 2 and Fig 1A). ORR in patients with documented progression on prior trastuzumab, lapatinib, and chemotherapy was similar to that of the overall patient population (Table 2). Median DOR was 7.2 months (95% CI, 4.6 months to not estimable [N/E]; Fig 1B). By investigator assessment, the ORR was 32.7% (95% CI, 24.1% to 42.1%), median DOR was 9.7 months (95% CI, 7.1 month to N/E), and median PFS was 5.5 months (95% CI, 4.2 to 7.9 months).

Correlation of Efficacy With Biomarker Expression

HER2 status was centrally reassessed on archival primary tumors in 95 patients; 80 (84.2%) had confirmed HER2-positive disease and 15 (15.8%) had HER2-normal disease, defined as HER2 FISH ratio less than 2.0 and IHC ≤ 2+ (Table 3). By IRF assessment, ORR was 41.3% (95% CI, 30.4% to 52.8%) in patients with confirmed HER2-

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Table 1. Demographics and Baseline Characteristics (N = 110)

Characteristic	No.	%
Age, years		
Median	52.5	
Range	34-77	
Sex		
Male	2	1.8
Female	108	98.2
ECOG performance status		
0	54	49.1
1	53	48.2
2	3	2.7
Baseline LVEF, %		
Median	60	
Range	50-77	
Time from metastatic diagnosis to first study treatment, months		
Median	42.8	
Range	4.6-148.9	
No. of distinct sites of metastases		
1	5	4.5
2	24	21.8
3+	81	73.6
Sites of metastases		
Locoregional	70	63.6
Lung	69	62.7
Bone	57	51.8
Liver	49	44.5
CNS	19	17.3
ER and PR status		
ER-positive and/or PR-positive	55	50.0
ER-negative and PR-negative	51	46.4
Unknown	4	3.6
Prior therapies		
Trastuzumab	110	100
Lapatinib	110	100
Taxane	109	99.1
Capecitabine	110	100
Anthracycline	110	100
Radiotherapy	95	86.4
Hormonal therapy	53	48.2
Other targeted therapy (excluding trastuzumab, lapatinib, and hormonal therapy)	37	33.6
No. of prior anticancer agents in all settings		
Median	8.5	
Range	5-19	
No. of prior anticancer agents for metastatic disease		
Median	7.0	
Range	3-17	
Total duration of prior trastuzumab treatment in the metastatic setting, months		
Median	19.7	
Range	1.8-115.8	
Total duration of prior lapatinib treatment in the metastatic setting, months		
Median	6.8	
Range	0.2-23.3	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; LVEF, left ventricular ejection fraction; PR, progesterone receptor.

Table 2. Responses and Efficacy Assessments by IRF (N = 110)

Assessments	No. of Patients	%	95% CI
Patients with objective response	38	34.5	26.1 to 43.9
Best objective response			
Complete response	0	0.0	
Partial response	38	34.5	
Clinical benefit rate*		48.2	38.8 to 57.9
Duration of objective response, months			
Median	7.2		4.6 to N/E
Progression-free survival, months			
Median	6.9		4.2 to 8.4
Patients who had progressed on trastuzumab plus chemotherapy and lapatinib plus chemotherapy	25/73†		
ORR		34.2	23.5 to 45.4

Abbreviations: IRF, independent radiologic facility; N/E, not estimable; ORR, objective response rate.
*Clinical benefit is defined as objective response plus stable disease at 6 months.
†No. of responders/No. of patients in subgroup.

positive tumors and 20.0% (95% CI, 5.7% to 44.9%) in patients with HER2-normal tumors; median PFS was 7.3 months (95% CI, 4.6 to 12.3 months) and 2.8 months (95% CI, 1.3 months to N/E), respectively (Fig 1C).

Patients with retrospectively confirmed HER2-positive disease and available qRT-PCR data (n = 69) were grouped according to qRT-PCR–determined HER2 expression levels (equal to, greater than, or less than median; Appendix Figure A1, online only). ORR per IRF in patients with at least median HER2 expression (n = 35) was 42.9% (95% CI, 26.3% to 60.6%); median PFS was 8.0 months (95% CI, 5.4 months to N/E; Fig 1D). ORR in patients with less than median HER2 expression (n = 34) was 38.2% (95% CI, 22.2% to 56.4%; Table 3), and median PFS was 6.2 months (95% CI, 3.9 to 12.3 months; Fig 1D). Exploratory analysis was also performed according to HER2 amplification (assessed by FISH): ORR per IRF in patients with at least median HER2/CEP17 [chromosome centromere 17] ratio (n = 36) was 44.4%, and ORR per IRF in patients with less than median HER2/CEP17 ratio (n = 36) was 38.9% (Table 3).

Among patients with centrally reassessed HER2-positive tumors, the ORRs were similar among 49 patients with wild-type PI3KCA and 11 patients with mutant PI3KCA (ORRs, 36.7% and 36.4%, respectively; Table 3).

T-DM1 Exposure and Patient Disposition

As of the data cutoff date (June 21, 2010), patients had received a median of 7.0 doses (range, 1 to 30 doses) of T-DM1 or 19.3 weeks (range, 0.1 to 88.0 weeks) of treatment (Appendix Table A1, online only); 18 patients (16.4%) were still receiving treatment, and 92 (83.6%) had been discontinued from study (Appendix Table A1).

Treatment discontinuations due to adverse events (AEs) occurred in seven patients (Appendix Table A1). Dose reductions were reported for 18 patients, 11 patients reduced their doses to 3.0 mg/kg, and seven reduced their doses to 2.4 mg/kg. The most common reasons for dose reduction were serum transaminase abnormalities and thrombocytopenia.

Six patients developed isolated brain metastases on study and, after receiving local therapy for these lesions, continued T-DM1 treatment per protocol. The median number of cycles received before and after CNS progression were 7.5 (range, 4 to 16) and 4.5 (range, 2 to 8), respectively. Five patients discontinued because of subsequent disease

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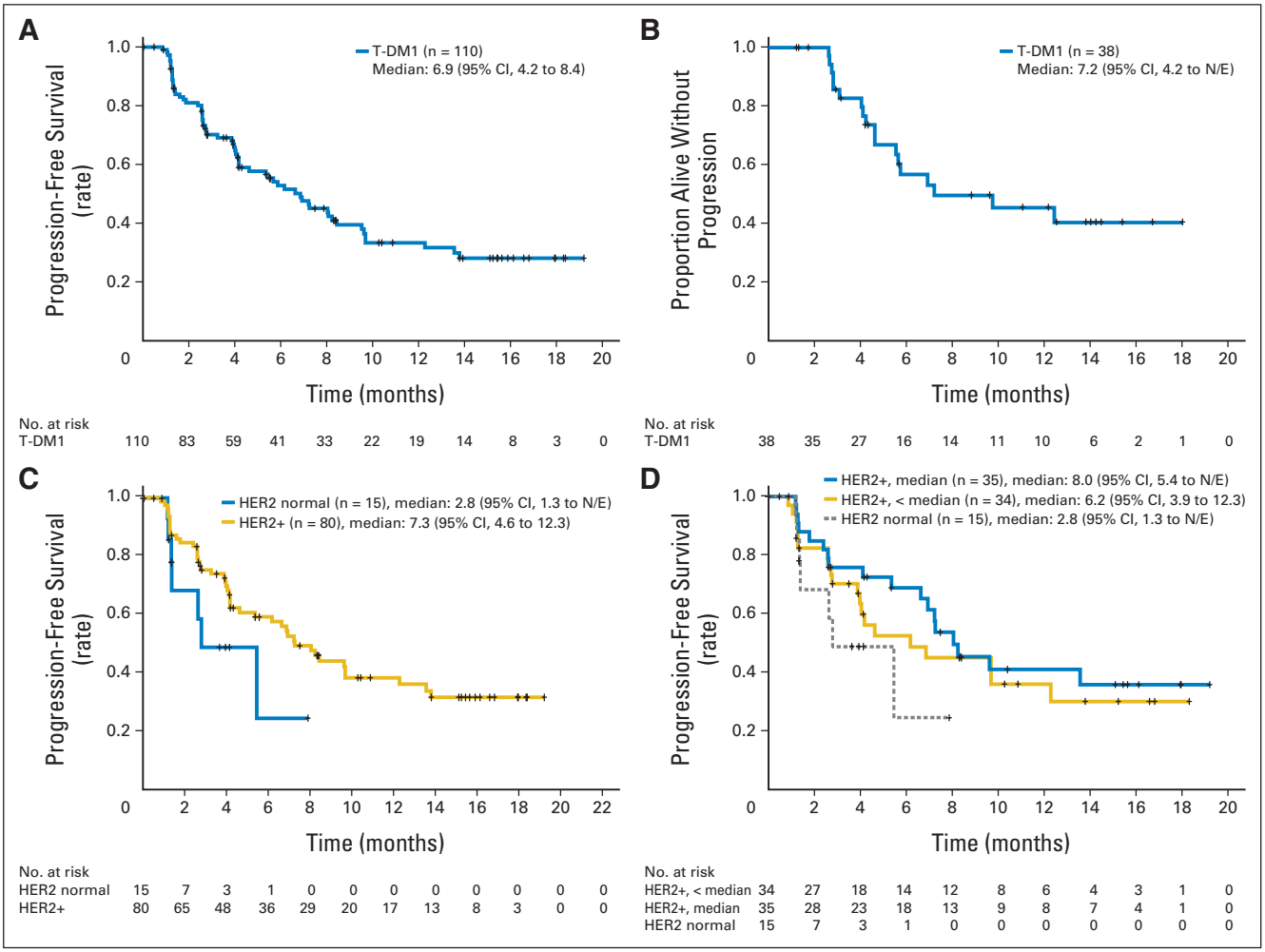

Fig 1. Kaplan-Meier plots. (A) Progression-free survival (PFS) in all treated patients and (B) duration of response. (C) PFS by retrospectively assessed human epidermal growth factor receptor 2 (HER2) status and (D) PFS by quantitative reverse transcriptase polymerase chain reaction HER2 levels in patients with retrospectively confirmed HER2-positive (HER2+) status. NE, not estimable; T-DM1, trastuzumab emtansine.

progression, and one patient discontinued because of investigator decision (patient no longer deriving benefit).

Safety

The most common AEs of any grade were fatigue (61.8%), nausea (37.3%), and thrombocytopenia (38.2%; Table 4). The most common grade ≥ 3 AEs were thrombocytopenia (9.1%), fatigue (4.5%), and cellulitis (3.6%). Fifty-two patients (47.3%) experienced at least one grade 3 AE; six patients experienced at least one grade 4 AE (two with thrombocytopenia, one with spinal cord compression, one with spinal cord compression and abdominal pain, one with sepsis, and one with cellulitis). Three patients experienced grade 5 AEs: one death from pneumonia (in the patient with grade 4 sepsis), one from interstitial lung disease, and one due to abnormal hepatic function in the context of coexisting nonalcoholic fatty liver disease and multiple comorbidities, including contrast-induced renal dysfunction.

Thrombocytopenia, previously identified as a T-DM1 dose-limiting toxicity, was observed in 42 patients (38.2%), including 10 (9.1%) with grade 3 or 4 AEs. Platelet count nadirs typically occurred around day 8 of each treatment cycle, with recovery to grade 1 or lower before the next cycle. Thrombocytopenia infrequently led to T-DM1 discontinuation or dose reduction. Platelet transfusions were infrequent (four patients). Hemorrhagic AEs were generally mild, although one patient (0.9%) experienced grade 3 epistaxis with concurrent grade 2 thrombocytopenia. No patients discontinued T-DM1 because of a hemorrhagic event.

Although overall hepatic toxicities were generally mild, there appeared to be a temporal relationship between T-DM1 dosing and increases in serum transaminases. Common liver function test abnormalities reported as AEs of any grade were increases in serum AST (26.4% of patients) and ALT (13.6%), with increases in total bilirubin (2.7%) observed less frequently. Nine patients (8.2%) experienced some type of grade ≥ 3 hepatic AE (seven patients had grade 3 laboratory abnormalities, one patient had grade 3 hepatotoxicity, and one patient had a grade 5 hepatic event). No left ventricular ejection fraction decline to ≤ 45% or symptomatic congestive heart failure was

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Table 3. Objective Responses by Retrospectively Assessed HER2 Status in Treated Patients With Central HER2 Data (biomarker subgroups, exploratory analyses; n = 95)

Response	No. of Patients	%	95% CI
HER2-positive status	80	84.2	
ORR		41.3	30.4 to 52.8
HER2-normal status	15	15.8	
ORR		20.0	5.7 to 44.9
HER2 qRT-PCR level*†			
At least median	35		
ORR		42.9	26.3 to 60.6
Less than median	34		
ORR		38.2	22.2 to 56.4
HER2/CEP17 ratio†			
At least median	36		
ORR		44.4	27.9 to 61.9
Less than median	36		
ORR		38.9	24.2 to 56.5
PIK3CA mutation status†‡			
Wild-type	49		
ORR		36.7	23.6 to 51.6
Mutant§	11		
ORR		36.4	13.5 to 66.7

Abbreviations: CEP17, chromosome centromere 17; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; *PIK3CA*, phosphatidyl inositol-3-kinase catalytic subunit; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction.

*See Appendix Figure A1 for box plot showing distribution of qRT-PCR values around the median.

†In patients with fluorescent in situ hybridization–positive and/or immunochemistry 3+ tumors and who had measurable disease at baseline determined by an independent radiologic facility.

‡E545K/D, and H1047R hotspot mutations in *PIK3CA* were detected by using the DxS *PIK3CA* mutation test kit (DxS, Manchester, United Kingdom).

§Four H1047R, two E542K, and five E545K/D mutations in patients with confirmed HER2-positive disease.

observed, and no patients discontinued treatment because of cardiotoxicity. Most other reported AEs were mild and manageable, resulting in few drug discontinuations, dose modifications, or dose delays (Appendix Table A1).

PK

The T-DM1 half-life was 3.96 days, with an average maximum concentration (C_{max}) of 79.5 μg/mL and no significant accumulation over the treatment cycles (Appendix Fig A2, online only). Average C_{max} of DM1 was 5.36 ng/mL in cycle 1 and 5.97 ng/mL in cycle 4, suggesting no DM1 accumulation. This PK profile of T-DM1 is similar to that determined in the prior phase I[18] and II[19] studies. Of the 108 evaluable patients, six (5.6%) had an antitherapeutic antibody (ATA) response, and one of these six patients also had an ATA response in their baseline sample before study treatment. There was no observed effect of ATA response on T-DM1 PK.

DISCUSSION

This study assessed whether T-DM1 was efficacious in patients with HER2-positive MBC who had previously received both trastuzumab- and lapatinib-based therapy, in addition to anthracyclines, taxanes, and capecitabine. Eligible patients had received at least two HER2-directed regimens in the advanced disease setting and had progressed on their most recent regimen. The purpose of these stringent eligibility criteria was to select a homogeneous, treatment-refractory population that would best reflect patients with the greatest medical need. To the best of our knowledge, this study is the first to evaluate a new treatment in this carefully defined subset of patients.

Although all patients were heavily pretreated (median of seven prior therapeutic agents for MBC), T-DM1 demonstrated clinical efficacy, with an independently assessed ORR of 34.5% and clinical benefit rate of 48.2%. The ORR was associated with a PFS of 6.9 months and DOR of 7.2 months. Notably, a response rate of 20% (three of 15 patients) was observed in patients with MBC designated as HER2-normal on central laboratory retesting. This observation suggests that HER2 expression below the currently used clinical threshold may be sufficient to confer sensitivity to T-DM1. It is also possible that the HER2 status of the tumor changed over time (ie, the tumor HER2 status at the time of treatment was different from that of the archived tumor sample). Because of the small number of patients in this subset, no definitive conclusions can be drawn, and further study of this issue is needed. Exploratory analyses of other biomarkers to potentially predict responsiveness to T-DM1, including HER2 mRNA level, FISH copy number, and *PIK3CA* mutation status, were also performed in this study. No clear relationship between these markers and clinical outcome was observed, and more work needs to be done to identify patients most likely to respond to this agent.

Several other HER2-directed agents in development have shown promising activity in previously treated patients with HER2-positive MBC. Neratinib,[26] pertuzumab,[27,28] and the HSP-90 inhibitor tanespimycin[29] (the latter two in combination with trastuzumab) have demonstrated ORRs of approximately 25% in phase II studies in patients with HER2-positive MBC who had progressed on trastuzumab-based therapy. However, none of these trials specifically evaluated patients who had previously received both trastuzumab- and lapatinib-based therapy, making it difficult to compare these agents' activities in this clinically relevant population.

The safety profile of T-DM1 in this study was encouraging. Most AEs were grades 1 or 2, and study drug discontinuations were uncommon. No dose-limiting cardiotoxicities were reported; however, all patients had extensive prior anti-HER2 therapy and left ventricular ejection fraction of $\geq$ 50% at entry, so this study cannot fully assess the potential impact of T-DM1 on cardiac function. Thrombocytopenia was the only grade $\geq$ 3 AE present in more than 5% of patients and was associated with significant hemorrhage in only one patient (grade 3 epistaxis). In vitro mechanistic studies with hematopoietic stem cells, megakaryocytes, and platelets suggest that T-DM1 does not have a direct effect on platelet function but can impair megakaryocyte maturation and platelet production.[30] Although further research is underway, these data support the hypothesis that the thrombocytopenia observed in patients following T-DM1 treatment may be explained, at least in part, by impaired platelet production from megakaryocytes in the bone marrow. Alopecia was not observed with T-DM1 therapy, and other toxicities typically associated with chemotherapy (eg, nausea, neuropathy, and neutropenia) were infrequent. Seven patients (6.4%) developed grade 3 increases in serum transaminases, which were successfully managed by holding and/or reducing the dose of T-DM1. A patient who died from hepatic dysfunction had preexisting liver disease and had developed contrast-induced renal failure before manifesting hepatic dysfunction.

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