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ORIGINAL REPORT

Trastuzumab Emtansine in Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer: An Integrated Safety Analysis

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
The antibody–drug conjugate trastuzumab emtansine (T-DM1) combines the cytotoxic activity of DM1 with the human epidermal growth factor receptor 2 (HER2) –targeted, antitumor properties of trastuzumab. T-DM1 has shown activity in phase I and II single-arm studies in patients with pretreated HER2-positive metastatic breast cancer (MBC) and has demonstrated superior efficacy and improved tolerability versus standard MBC treatments in randomized phase II and III studies. This analysis, combining available data from all single-agent T-DM1 studies to date, was conducted to better define the T-DM1 safety profile.

Patients and Methods
Six studies in patients with HER2-positive MBC who received T-DM1 3.6 mg/kg every 3 weeks and follow-up data from patients in an extension study were analyzed. Analyses included adverse events (AEs) by grade; AEs leading to death, drug discontinuation, or dose reduction; and select AEs.

Results
Among 884 T-DM1–exposed patients, the most commonly reported all-grade AEs were fatigue (46.4%), nausea (43.0%), thrombocytopenia (32.2%), headache (29.4%), and constipation (26.5%). The most common grade 3 to 4 AEs were the laboratory abnormalities of thrombocytopenia (11.9%) and increased AST serum concentration (4.3%). These were manageable and not generally associated with clinical symptoms. There were 12 AE-related deaths. AEs resulted in dose reductions in 17.2% of patients and drug discontinuations in 7.0%.

Conclusion
In this analysis of 884 T-DM1–exposed patients, grade 3 or greater AEs were infrequent and typically asymptomatic and manageable. This favorable safety profile makes T-DM1 treatment suitable for exploration in other breast cancer settings.

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INTRODUCTION

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate (ADC) approved by the US Food and Drug Administration for treatment of human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer (MBC) in patients previously treated with trastuzumab and a taxane.[1] T-DM1 consists of the antimicrotubule agent DM1 (derivative of maytansine) and the HER2-targeted humanized monoclonal antibody trastuzumab, joined with a stable thioether linker.[2] T-DM1 binds the HER2 receptor, is internalized, and undergoes lysosomal degradation, releasing the active cytotoxic DM1 moiety inside HER2-expressing cells, thus greatly reducing systemic exposure. DM1 is a microtubule-destabilizing agent and inhibits tubulin polymerization similar to the vinca alkaloids[3] but with 20-fold more affinity for the tubulin binding site than vinblastine.[3] T-DM1 also exerts antitumor activity through its trastuzumab component. T-DM1 binds to HER2-expressing cells with similar affinity to trastuzumab and, like trastuzumab, mediates antibody-dependent cellular cytotoxicity, inhibits HER2 extracellular domain shedding, and inhibits the phosphatidylinositol 3-kinase signaling pathway.[4]

Data for single-agent T-DM1 administered every 3 weeks to patients with HER2-positive MBC are currently available from phase I to III studies.[5-10] In the phase III study (EMILIA), 991 patients with HER2-positive locally advanced breast cancer or

MBC were randomly assigned to T-DM1 or lapatinib plus capecitabine. T-DM1–treated patients, compared with patients treated with lapatinib plus capecitabine, had prolonged median progression-free survival (9.6 *v* 6.4 months, respectively; hazard ratio, 0.65; $P < .001$) and overall survival (30.9 *v* 25.1 months, respectively; hazard ratio, 0.68; $P < .001$) and fewer grade 3 or greater adverse events (AEs; 41% *v* 57%, respectively). With data now available from 884 patients exposed to single-agent T-DM1 in clinical trials, this integrated safety analysis was conducted to better define its overall safety profile.

PATIENTS AND METHODS

Patient Eligibility

This analysis included all T-DM1 trials of patients with unresectable locally advanced breast cancer or MBC who received T-DM1 3.6 mg/kg every 3 weeks in which the primary end point had been analyzed (ie, six clinical trials [parent studies[5-10]] and an extension study; Appendix Table A1, online only). All studies were approved by institutional review boards and were conducted in accordance with the Declaration of Helsinki. Patients provided written informed consent. Eligibility criteria, designed to enroll patients with adequate left ventricular ejection fraction (LVEF), performance status, and organ function, were consistent across trials (Appendix Table A2, online only).

Study Design

All of the studies assessed AEs, laboratory data, vital signs, physical examination findings, and LVEF on a regular basis according to schedules mandated by the respective protocol. Laboratory assessments typically occurred weekly during the first several treatment cycles and then weekly or every 3 weeks thereafter. Verbatim descriptions of AEs were mapped to Medical Dictionary for Regulatory Activities (MedDRA; MedDRA, McLean, VA) thesaurus terms version 14.1 and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0; the highest grade was reported. Per study protocol, only clinically significant laboratory abnormalities requiring active management (eg, dose modification, more frequent follow-up) were recorded as AEs. A serious AE (SAE) was defined as any AE that resulted in death, was life threatening, resulted in hospitalization or prolonged hospital stay, resulted in persistent or significant disability/incapacity, was considered medically significant, or required intervention to prevent any of these outcomes.

AEs were reported ≤ 30 days after the last dose of study medication or until the early termination visit or initiation of another anticancer therapy, whichever occurred first, with the exception of studies TDM4450g/BO22495, TDM4374g, and TDM4258g, in which SAEs were reported ≤ 90 days after administration of the last treatment. After this period, investigators reported only deaths and SAEs that were considered related to prior study treatment.

Data Analysis

The safety database includes data from 884 patients who received ≥ one dose of T-DM1 in one of the six parent studies. Data from patients who participated in extension study TDM4529g were combined with data from the respective parent study for analysis. The data cutoff date was July 31, 2012.

The integrated safety analysis determined the incidence of all-grade AEs occurring in ≥ 20% of patients; grade 3 to 4 AEs occurring in ≥ 2% of patients; SAEs; AEs leading to death; AEs leading to T-DM1 discontinuation or dose reduction; and selected AEs. Selected AEs were prospectively defined as clinically relevant AEs associated with trastuzumab and/or maytansine (from which DM1 is derived) that have not been identified for T-DM1, AEs reported in T-DM1 toxicology studies, or AEs consistently reported in phase II T-DM1 studies. Selected AEs were hepatotoxicity, thrombocytopenia, peripheral neuropathy, cardiac toxicity (including LVEF decreases), pneumonitis/interstitial lung disease, infusion-related reactions and hypersensitivity, hypokalemia, and vision disorders. Standardized MedDRA Queries were used to group the preferred terms of interest into the selected AE baskets. If no Standardized MedDRA Queries were available, baskets of MedDRA AE Preferred Terms were used. The temporal pattern and clinical events associated with the two most frequently reported grade 3 to 4 AEs (thrombocytopenia and elevated hepatic aminotransferases) were analyzed using cross-tabulation and graphical methods.

Table 1. Patient Demographic and Baseline Clinical Characteristics

Characteristic	T-DM1–Exposed Patients (N = 884) No.	%
Age, years		
Median	53	
Range	25-85	
Age group, years		
< 65	762	86.2
≥ 65	122	13.8
Sex		
Female	880	99.5
Male	4	0.5
Race		
White	692	78.3
Asian	99	11.2
Other	93	10.5
ECOG performance status*		
0	518	58.7
1	353	40.0
2	11	1.2
3	1	0.1
Disease involvement		
Visceral	632	71.5
Nonvisceral	252	28.5
Hormone receptor status		
ER positive and/or PR positive	476	53.8
ER negative and PR negative	378	42.8
Unknown	30	3.4
Previous nonhormonal systemic agents, No.		
Median	5	
Range	0-19	
Type of previous systemic therapy		
Trastuzumab	804	91.0
Taxane	790	89.4
Anthracycline	586	66.3
Hormonal therapy	372	42.1
Lapatinib	215	24.3
Previous nonhormonal systemic therapy for MBC		
Yes	722	81.7
No	162	18.3

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; MBC, metastatic breast cancer; PR, progesterone receptor; T-DM1, trastuzumab emtansine.
*Data available from 883 patients.

RESULTS

Patient Characteristics

The median age of all T-DM1–exposed patients was 53 years. Most patients (98.6%) had an Eastern Cooperative Oncology Group performance status 0 to 1 and visceral disease (71.5%) (Table 1).

T-DM1 Exposure

The median number of doses received was 10, and the median dose-intensity was high (99.7%; Table 2). Eight patients (0.9%) discontinued an infusion prematurely, four because of AEs (grade 2

Table 2. T-DM1 Exposure

T-DM1 Exposure	T-DM1–Exposed Patients (N = 884) No.	%
No. of doses		
Median	10	
Range	1-78	
Average dose, mg/kg*		
Median	3.6	
Range	2.4-6	
Dose-intensity, %†		
Median	99.7	
Range	54.7-200.7	
Treatment duration, months		
Median	6.3	
Range	0-53.4	
Infusion ever interrupted		
Yes	86	9.7
No	798	90.3
Infusion ever prematurely discontinued		
Yes	8	0.9
No	876	99.1
Dose reduced‡		
Yes	134	17.2
Reduced to 3.0 mg/kg	88	65.7
Reduced to 2.4 mg/kg	46	34.3
No	643	82.8
Duration of treatment, years		
> 1	247	27.9
> 2	71	8.0
> 3	17	1.9

Abbreviation: T-DM1, trastuzumab emtansine.
*Data available from 883 patients.
†Dose-intensity is defined as total dose received divided by expected total dose; note the upper limit of the dose-intensity range is greater than 100% as a result of dosing errors. In TDM4450g, two patients randomly assigned to the trastuzumab plus docetaxel group were administered T-DM1 6 mg/kg (the usual dose of trastuzumab) rather than 3.6 mg/kg. In EMILIA, two patients received two doses each within 21 days.
‡Data available for 777 patients. Percentages are derived using 777 as the denominator.

Table 3. Summary of AEs in T-DM1–Exposed Patients

AE (MedDRA Preferred Term)	Toxicity (N = 884) Any Grade No. of Patients	%	Grade 3 No. of Patients	%	Grade 4 No. of Patients	%
All-grade AEs, incidence ≥ 20%						
Fatigue	410	46.4	27	3.1	1	0.1
Nausea	380	43.0	10	1.1	0	0.0
Thrombocytopenia*	285	32.2	84	9.5	21	2.4
Headache	260	29.4	5	0.6	0	0.0
Constipation	234	26.5	5	0.6	0	0.0
Epistaxis	223	25.2	4	0.5	0	0.0
Pyrexia	209	23.6	3	0.3	0	0.0
Increased AST	208	23.5	36	4.1	2	0.2
Decreased appetite	202	22.9	6	0.7	0	0.0
Diarrhea	188	21.3	9	1.0	0	0.0
Vomiting	185	20.9	8	0.9	0	0.0
Cough	181	20.5	1	0.1	0	0.0
Arthralgia	178	20.1	8	0.9	0	0.0
Additional AEs, grade 3 and 4 incidence ≥ 2%						
Hypokalemia*	142	16.1	29	3.3	0	0.0
Increased ALT	139	15.7	27	3.1	0	0.0
Anemia	132	14.9	25	2.8	1	0.1

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; T-DM1, trastuzumab emtansine.
*Baskets of MedDRA AE preferred terms were used. For thrombocytopenia, the preferred terms were thrombocytopenia, platelet count decreased, and platelet disorder. For hypokalemia, the preferred terms were hypokalemia and blood potassium decreased.

hypertension, grade 2 cellulitis due to extravasation, grade 2 hypersensitivity, and grade 1 drug eruption). Dose reductions occurred in 17.2% of patients (Table 2). Most patients (65.7%) who required a dose reduction had the dose reduced one level to 3 mg/kg.

Overview of AEs

The most commonly reported all-grade AEs among T-DM1–exposed patients were fatigue, nausea, thrombocytopenia, headache, and constipation (Table 3). With the exception of fatigue, the most commonly reported grade ≥ 3 AEs were related to laboratory test abnormalities (thrombocytopenia, increased hepatic aminotransferases, hypokalemia, and anemia). Out-of-range laboratory values, including those that qualified as AEs and those that did not, are reported in Appendix Table A3 (online only).

The incidence of grade ≥ 3 AEs was similar among most patient subgroups analyzed (Table 4), but there was a slightly higher incidence in patients age ≥ 65 years compared with those less than 65 years (51.6% *v* 44.0%, respectively). There was also a higher incidence of grade ≥ 3 AEs in Asian patients treated with T-DM1 compared with white patients (63.6% *v* 41.6%, respectively), which was largely driven by the increased rates of grade ≥ 3 thrombocytopenia in Asian patients (see next section).

A total of 62 patients (7.0%) exposed to T-DM1 discontinued treatment because of an AE; the most common of which involved laboratory abnormalities, primarily thrombocytopenia (1.5%), and increased hepatic aminotransferases (0.8% for increased AST, 0.5% for increased ALT). These laboratory abnormalities were also the most frequent reason for dose reductions. SAEs were reported in 175 T-DM1–exposed patients (19.8%). Twelve patients experienced AEs on study or within 30 days of their last T-DM1 treatment that led to death (reported by investigators as hepatic failure, hepatic failure and encephalopathy, hepatic function abnormal, bacterial sepsis, neutropenic sepsis, pneumonia [n = 2], metabolic encephalopathy, respiratory failure [n = 2], interstitial lung disease, and sudden death). Of these events, seven were suspected by the investigator to be caused by T-DM1 treatment (hepatic failure, hepatic failure and encephalopathy [same patient], hepatic function abnormal, bacterial sepsis, neutropenic sepsis, and metabolic encephalopathy).

Selected AEs

All-grade increases in serum AST and ALT occurred in 208 (23.5%) and 139 (15.7%) of T-DM1–exposed patients, respectively. Increases in serum AST were grade 3 in 36 patients (4.1%) and grade 4 in two patients (0.2%). Increases in serum ALT were grade 3 in 27 patients (3.1%); there were no grade 4 increases. All-grade increases in

Table 4. Incidence of Grade ≥ 3 AEs by Patient Subgroup in T-DM1–Exposed Patients

Subgroup	Total No. of Patients (N = 884)	Grade ≥ 3 AE	
		No. of Patients	%
Age, years			
< 65	762	335	44.0
≥ 65	122	63	51.6
≥ 65 to < 75	93	49	52.7
≥ 75	29	14	48.3
Race			
White	692	288	41.6
Asian	99	63	63.6
Other	93	47	50.5
Previous systemic therapy for MBC			
Yes	722	336	46.5
No	162	62	38.3
Previous anthracycline use			
Yes	586	267	45.6
No	298	131	44.0

Abbreviations: AE, adverse event; MBC, metastatic breast cancer; T-DM1, trastuzumab emtansine.

blood bilirubin occurred in 25 patients (2.8%). These increases were grade 3 in three patients (0.3%); there were no grade 4 increases.

The percentage of patients with grade ≥ 3 aminotransferase elevation did not increase over time on study (Figs 1A and 1B). Grade 3 to 4 increases in mean hepatic aminotransferase values were generally transient, usually appeared by the first measurement after dosing (day 8), and generally returned to baseline or the normal range by the next scheduled treatment dose. With appropriate dose modifications (Appendix Table A4, online only), most patients were able to continue T-DM1 treatment. The mean profile and 95% CIs of aminotransferase values in EMILIA are shown in Figures 1C and 1D; most cases of grade 3 ALT increases returned to grade 1 to 2 within one to two treatment cycles (Fig 1E).

There were three cases of biopsy-confirmed nodular regenerative hyperplasia (NRH), a rare liver condition that can lead to noncirrhotic portal hypertension.[11,12] All three patients had clinical or radiographic signs of portal hypertension. NRH was diagnosed after T-DM1 cycle 3, cycle 20, and cycle 37. In one of these patients, NRH resulted in liver failure and death (cycle 37).

All-grade thrombocytopenia was reported for 32.2% of T-DM1–exposed patients. The majority of patients experienced grade 1 or 2 events (20.4%; Fig 2A). Platelet counts over time in patients from EMILIA are shown in Figure 2B. Thrombocytopenia was not fully reversible in all patients, but with appropriate dose modifications (Appendix Table A4), platelet counts recovered sufficiently to allow continued treatment in nearly all patients.

To explore the relationship between thrombocytopenia and hemorrhage, the incidence of thrombocytopenia based on laboratory data and that of hemorrhage were cross-tabulated (Table 5). Of the 128 patients with grade 3 to 4 thrombocytopenia, 56 (43.8%) experienced grade 1 bleeding (primarily epistaxis), five (3.9%) experienced grade 2 bleeding (primarily epistaxis), and six (4.7%) experienced grade 3 to 4 bleeding. Grade 3 to 4 bleeding occurred in 18 patients (2.0%) in the overall population; all bleeding events were grade 3 except one grade 4 GI hemorrhage, and 10 were considered serious. For these 18 patients, the most common types of bleeding were GI tract (n = 7), gynecologic (n = 5), and epistaxis (n = 4). Two patients received concurrent anticoagulants. Grade 3 to 4 bleeding events and grade 3 to 4 thrombocytopenia were temporally concomitant in two patients.

Asian patients from the pooled analysis who were treated with T-DM1 demonstrated a higher incidence of grade 3 to 4 platelet count decrease than non-Asian patients (44.4% *v* 10.6%, respectively; Appendix Table A5, online only). The incidence of grade 3 to 4 platelet count decrease with T-DM1 was higher in Asian patients compared with non-Asian patients, regardless of whether platelet counts were greater or less than the mean for Asian patients at baseline. In contrast, Asian patients and non-Asian patients had a similarly low incidence of grade 3 to 4 hemorrhage, regardless of platelet counts at baseline.

Among T-DM1–exposed patients, the rate of peripheral neuropathy (including all relevant preferred terms) was 29.1%. Most patients (173 of 257 patients; 67.3%) experienced grade 1 events. Grade 3 events were reported in 21 patients (2.4%), and one grade 4 event was reported. Nineteen of the 22 patients had prior treatment with a taxane; five also had prior vinorelbine. Three patients discontinued T-DM1 because of peripheral neuropathy; two events were ongoing at the time of the data cutoff.

Four patients (0.5%) had a postbaseline LVEF less than 40%, and 16 patients (1.8%) had an LVEF decline of ≥ 15 percentage points from baseline to below 50%. A total of four patients (0.45%) discontinued T-DM1 because of cardiac disorders (atrial fibrillation, n = 1; left ventricular dysfunction, n = 1; and decreased ejection fraction, n = 2).

In the current safety analysis, pneumonitis-related AEs (ie, preferred terms pneumonitis, interstitial lung disease, acute respiratory distress syndrome, lung infiltration, organizing pneumonia) were reported rarely among T-DM1–exposed patients (1.1%). Of 10 reported events, one was grade 1, six were grade 2, one was grade 3, one was grade 4, and one was grade 5. The fatal event occurred more than 30 days after the last T-DM1 dose and 14 days after beginning treatment with trastuzumab and protein-bound paclitaxel.

Infusion-related reactions and hypersensitivity events with T-DM1 were reported in 61 patients (6.9%). There was one grade 3 infusion-related reaction that occurred and resolved on day 1 of cycle 1. All other events were grade 1 or 2. Hypersensitivity was reported as an AE in 12 patients (1.4%). Infusion-related reactions and hypersensitivity symptoms generally resolved over the course of several hours to a day.

Hypokalemia was reported in 16.1% of T-DM1–exposed patients. Most events were grade 1 to 2 (113 of 142 patients; 79.6%). Eye disorders were reported for 77 patients (8.7%) and were primarily grade 1 (67 of 77 patients; 87%). These included blurred vision, visual impairment, and reduced visual acuity. No patient discontinued T-DM1 for hypokalemia or visual disorders.

DISCUSSION

In this analysis of 884 patients, T-DM1 was well tolerated, with the most commonly reported grade ≥ 3 AEs being laboratory abnormalities—thrombocytopenia (11.9%) and elevated AST (4.3%). This safety profile is consistent with data from individual

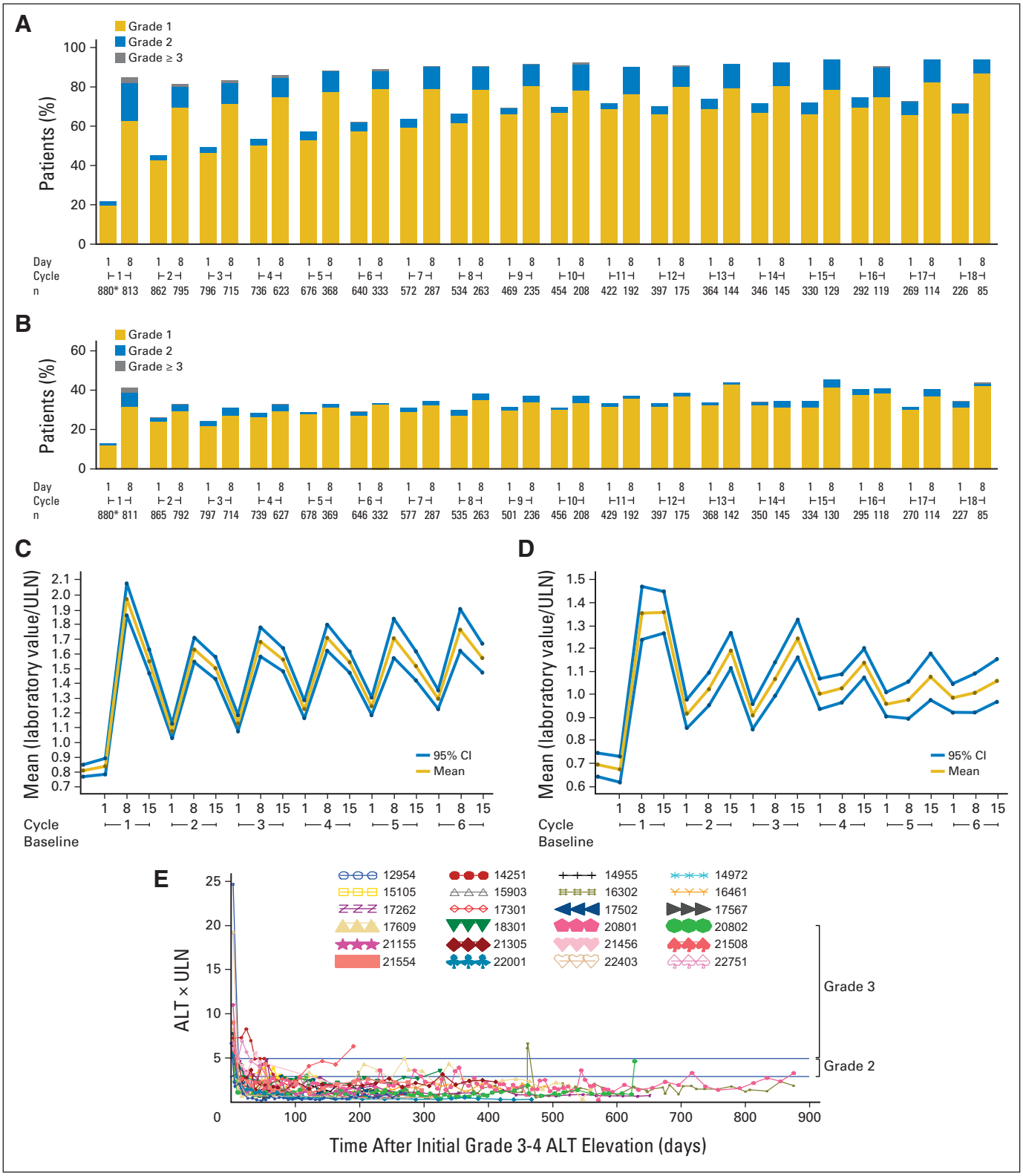

Fig 1. Percentage of patients exposed to trastuzumab emtansine (T-DM1) in each (A) AST National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade category or (B) in each ALT NCI-CTCAE grade category by treatment cycle. Increases in mean (C) AST (U/L) and (D) ALT (U/L) values based on laboratory data over time in patients treated with T-DM1 in the EMILIA study (n = 490). (E) ALT over time in patients after experiencing a grade 3 or 4 ALT elevation while being treated with T-DM1 in EMILIA (n = 23). (*) Four patients had missing data. ULN, upper limit of normal.

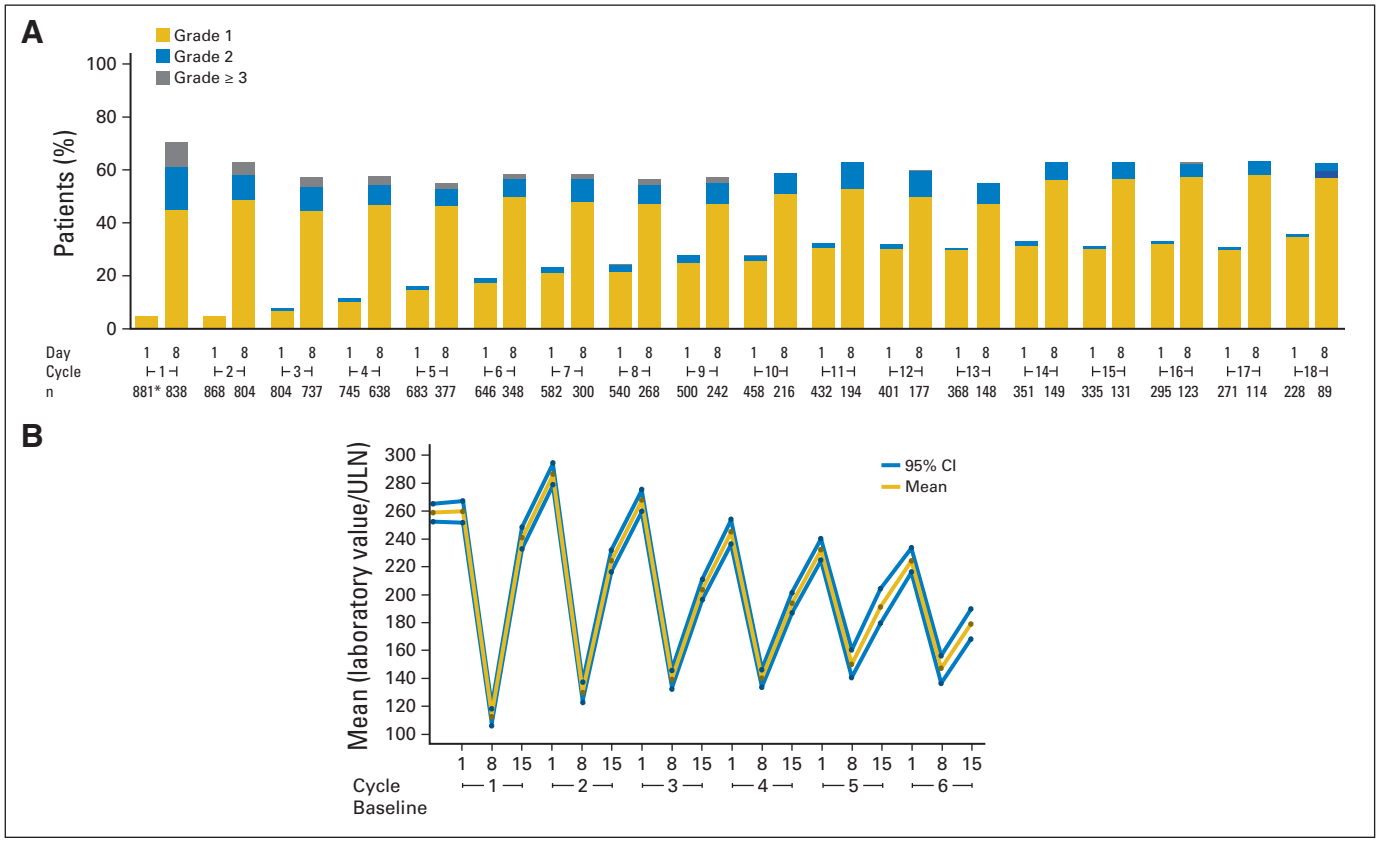

Fig 2. (A) Percentage of patients exposed to trastuzumab emtansine (T-DM1) in each thrombocytopenia National Cancer Institute Common Terminology Criteria for Adverse Events grade category by treatment cycle. Platelet counts are based on laboratory data. (B) Mean platelet count over time in T-DM1 arm of the EMILIA study (n = 490). ULN, upper limit of normal.

studies in patients with previously untreated MBC[10] and in patients with ≥ one prior HER2-targeted therapy regimen for MBC.[5-9,13] The safety profile was also similar across clinically relevant subgroups, except for a greater incidence of grade ≥ 3 AEs among patients older than age 65 years and in Asian patients. In EMILIA, in which comparison with a control group was possible, in patients ≥ age 65 years versus those less than 65 years, an increase in grade ≥ 3 AEs was seen in both the T-DM1 (50.0% *v* 43.7%, respectively) and the lapatinib plus capecitabine (71.2% *v* 57.6%, respectively) arms (data on file, Genentech, South San Francisco, CA). The increase in grade ≥ 3 AEs in Asian patients was primarily a result of an increased incidence of thrombocytopenia.

Table 5. Cross-Tabulation of Platelet Count Based on Laboratory Data and Hemorrhage Grades in T-DM1–Exposed Patients

	Platelet Count Based on Laboratory Data (No. of patients; N = 884)*						
Hemorrhage	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Grade 0	119	269	112	54	7	0	561
Grade 1	20	111	73	44	12	0	260
Grade 2	2	21	17	5	0	0	45
Grade 3	2	4	5	5	1	0	17
Grade 4	0	1†	0	0	0	0	1†
Grade 5	0	0	0	0	0	0	0
Total	143	406	207	108	20	0	884

Abbreviation: T-DM1, trastuzumab emtansine.
*Three patients had missing data.
†This patient had a grade 4 GI hemorrhage on study day 797, 13 days after the most recent T-DM1 dose. The hemorrhage resolved in 1 day and was considered by the investigator to be unrelated to T-DM1.

In this analysis, the majority of thrombocytopenia events were grade 1 to 2. Although most cases of grade ≥ 3 thrombocytopenia were not fully reversible to baseline levels, platelet counts recovered to allow treatment continuation in most patients.

Grade ≥ 3 thrombocytopenia was rarely associated with grade ≥ 3 hemorrhage (occurred in two patients) in this analysis. All T-DM1 clinical trials with completed primary end point analyses at the time of the pooled analysis were included here. Subsequently available safety monitoring data on serious AEs in more than 4,200 T-DM1–exposed patients, however, identified some fatal cases of severe hemorrhage associated with thrombocytopenia; some of the patients had been receiving concurrent anticoagulation therapy. One event, subarachnoid hemorrhage, was deemed related to T-DM1 by the investigator.[13] The fatal bleeding events were independent of patient ethnicity. Patients with thrombocytopenia and patients on anticoagulant treatment should be monitored closely.

The mechanism of thrombocytopenia is unclear; however, recent studies have shown that T-DM1 does not affect mature platelet function. Rather, T-DM1 seems to be internalized by megakaryocyte precursor cells via an Fc receptor–mediated process, after which the DM1 component of T-DM1 impedes the differentiation to mature

megakaryocytes and subsequent platelet formation.[14] An exploratory analysis found a higher incidence of thrombocytopenia among Asian patients. Given the likely role of Fc receptors in T-DM1–mediated thrombocytopenia, this effect may be accounted for by specific Fc polymorphisms found more frequently in Asian patients. Studies are under way to investigate this hypothesis.

Hepatic aminotransferase elevations were generally transient, allowing patients to remain on treatment at the same or a reduced dose. There have been seven biopsy-confirmed cases of a rare but serious liver condition, NRH, among the approximately 5,000 patients exposed to ≥ one cycle of T-DM1 (three in this integrated analysis and four in other single-agent T-DM1 trials; no cases have been reported outside of clinical trials). NRH is characterized by widespread transformation of the hepatic parenchyma into small regenerative nodules with limited fibrosis.[11,12] NRH is generally asymptomatic unless portal hypertension develops, resulting in splenomegaly, esophageal varices, or ascites.[11,12] There is no laboratory finding that is suggestive of NRH, and diagnosis can only be made by biopsy confirmation. All seven patients with biopsy-proven NRH had clinical or radiographic signs of portal hypertension, and six had been exposed to T-DM1 for ≥ 1 year. NRH should be investigated as a possible cause if portal hypertension occurs, and T-DM1 should be permanently discontinued if NRH is diagnosed.

The mechanism of T-DM1–induced elevations in AST and ALT is unclear. Preclinical data showing increases in AST and ALT in HER2-binding and nonbinding species suggest that the effect is not antigen dependent and may be caused by nonspecific effects of DM1.[15] Consistent with this hypothesis, elevations in AST and ALT have been observed with cantuzumab, an ADC comprising an anti-CanAg antibody conjugated to DM1,[16] and also with the parent compound of DM1, maytansine.[17,18]

Other selected AEs were primarily grade 1 to 2 and occurred with relatively low frequency. However, the incidence of infusion-related reactions and cardiac dysfunction could be underestimated because patients with a history of severe infusion reactions and cardiac toxicity secondary to trastuzumab or severe cardiac disease were excluded from enrollment. Patients with early breast cancer, however, also experienced a low rate of cardiac toxicity with T-DM1 in a recent study.[19]

The safety profile of T-DM1 observed in this analysis is consistent with the theoretical concept underlying the design of ADCs—that targeting delivery of chemotherapy to tumor cells and restricting chemotherapy release to the intracellular compartment would reduce systemic toxicity. This decrease in toxicity would also be expected to improve efficacy by allowing higher dose levels, longer treatment duration, and fewer dose reductions than currently available therapies. Indeed, in both randomized studies of T-DM1, patients in the T-DM1 arms had fewer treatment discontinuations of any treatment component as a result of AEs than patients treated with trastuzumab plus docetaxel (7.2% *v* 34.8%, respectively)[10] or with lapatinib plus capecitabine (5.9% with T-DM1 *v* 7.6% with lapatinib *v* 9.4% with capecitabine).[8] Patients in the T-DM1 arm also had fewer dose reductions than patients treated with trastuzumab plus docetaxel (20.3% with T-DM1 *v* 34.8% with docetaxel)[10] or with lapatinib plus capecitabine (16.3% with T-DM1 *v* 53.4% with capecitabine *v* 27.3% with lapatinib).[8] In addition, the favorable safety profile of T-DM1 may translate into an improvement in patient quality of life, as suggested by randomized studies.[8,10]

In summary, T-DM1 seems to offer improved safety and efficacy over two widely used treatments for HER2-positive MBC. T-DM1–associated adverse reactions were generally manageable with appropriate dose modification and supportive care. The safety profile is expected to be similar in patients with first-line MBC or early breast cancer, and clinical trials are under way to evaluate T-DM1 in these settings.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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GLOSSARY TERMS

antibody-dependent cellular cytotoxicity (ADCC): antibody-drug conjugate human epidermal growth factor receptor 2 (HER2) trastuzumab.

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Appendix

Table A1. Patients Included in the T-DM1 Integrated Safety Analysis

Study No. (clinical trial registration number)	Phase	Patient Population	No. of Patients Enrolled or Randomly Assigned to T-DM1	No. of Patients in Safety Analysis
TDM4370g/BO21977/EMILIA (NCT00829166)[8]	III	Patients with HER2-positive unresectable LABC or MBC previously treated with a taxane and trastuzumab, whose disease progressed during or after the most recent treatment for LABC or MBC or within 6 months of completing adjuvant therapy, were randomly assigned to T-DM1 or lapatinib plus capecitabine	495	490*
TDM4450g/ BO21976 (NCT00679341)[10]	II	Patients with HER2-positive unresectable LABC or MBC who had not received previous chemotherapy or trastuzumab for MBC were randomly assigned to T-DM1 or trastuzumab plus docetaxel	67	69† plus 35 control arm patients who crossed over to T-DM1 after progression (total, n = 106)
TDM4374g (NCT00679211)[7]	II	Patients with HER2-positive MBC previously treated with an anthracycline, trastuzumab, taxane, lapatinib, and capecitabine (≥ 2 HER2-directed therapies for MBC)	110	110
TDM4258g (NCT00509769)[6]	II	Patients with HER2-positive unresectable LABC or MBC with progression on an HER2-directed therapy and chemotherapy for MBC	112	112
TDM4688g (NCT00943670)[9]	II	Patients with HER2-positive unresectable LABC or MBC with progression on an HER2-directed therapy and chemotherapy for MBC	51	51
TDM3569g (NCT00932373)[5]	I	Patients with HER2-positive MBC previously treated with a trastuzumab-containing regimen	52	15‡
TDM4529g/BO25430 (NCT00781612)	II	Open-label extension of studies 3569g, 4258g, 4374g, 4688g, and 4450g	43	43§

Abbreviations: HER2, human epidermal growth factor receptor 2; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; T-DM1, trastuzumab emtansine.

*A total of 495 patients were randomly assigned to T-DM1, and 490 patients received at least one dose of T-DM1.

†Safety analysis includes two patients, each of whom mistakenly received a dose of T-DM1, randomly assigned to the control arm.

‡There were 52 patients treated in this dose-ranging phase I trial; the 15 patients who received T-DM1 3.6 mg/kg every 3 weeks are included in this integrated safety analysis.

§For this integrated analysis, data from these patients were combined with the data from the parent study; thus, this number is subsumed within the total number value.

Table A2. Key Safety Inclusion and Exclusion Criteria Across Trials

Criterion	Description
Inclusion criteria	
LVEF	≥ 50% by either ECHO or MUGA
ECOG PS	TDM4370g/BO21977 (EMILIA), TDM4450g/BO22495, TDM4688g, and TDM4529g/BO25430: 0-1 TDM4374g, TDM4258g, and TDM3569g: 0-2
Organ function	ANC > 1500 cells/μL Platelets > 100,000 cells/μL Hemoglobin > 9 g/dL (RBC transfusions allowed) Albumin ≥ 2.5 g/dL Total bilirubin ≤ 1.5 ULN LFTs (AST, ALT, ALP) ≤ 2.5 ULN; patients with bone metastases allowed ALP ≤ 5 ULN Estimated creatinine clearance > 50 mL/min INR and aPTT < 1.5 ULN (unless on therapeutic anticoagulation)
Exclusion criteria	
Related to previous treatment	Grade 3 or 4 peripheral neuropathy (NCI-CTCAE version 3.0)
Cardiopulmonary function	History of symptomatic CHF, history of serious cardiac arrhythmia requiring treatment, history of MI or unstable angina within 6 months of random assignment, current dyspnea at rest as a result of cancer complications, current requirement for continuous oxygen therapy
Previous anthracycline exposure	TDM4450g/BO22495 and TDM4374g: Doxo > 500 mg/m^2; Epi > 900 mg/m^2; Mito > 120 mg/m^2; or Ida > 90 mg/m^2 TDM4258g: Doxo > 360 mg/m^2 or equivalent TDM3569g: Doxo > 360 mg/m^2 or equivalent

Abbreviations: ALP, alkaline phosphatase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; CHF, congestive heart failure; Doxo, doxorubicin; ECHO, echocardiography; ECOG PS, Eastern Cooperative Oncology Group performance status; Epi, epirubicin; Ida, idarubicin; INR, international normalized ratio; LFTs, liver function tests; LVEF, left ventricular ejection fraction; MI, myocardial infarction; Mito, mitoxantrone; MUGA, multiple gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events; ULN, upper limit of normal.

Table A3. Selected Laboratory Data

	Trastuzumab Emtansine		
Parameter	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Increased AST	93.0	4.4	0.2
Increased ALT	74.0	4.9	0.2
Increased bilirubin	18.9	0.9	0
Decreased platelets	84.0	12.2	2.3
Decreased hemoglobin	66.7	3.4	0.6
Decreased potassium	37.9	3.2	0.3

Table A4. Recommended Dose Modification Guidelines by AE

AE and Dose Reduction	Recommended Dose Modification Guidelines by Grade
AE	
Increased hepatic aminotransferases (AST/ALT)	Grade 2 (> 2.5 to ≤ 5× the ULN): treat at the same dose level Grade 3 (> 5 to ≤ 20× the ULN): do not administer T-DM1 until AST/ALT recovers to grade ≤ 2, and then reduce one dose level Grade 4 (> 20× the ULN): discontinue T-DM1
Hyperbilirubinemia	Grade 2 (> 1.5 to ≤ 3× the ULN): do not administer T-DM1 until total bilirubin recovers to grade ≤ 1, and then treat at the same dose level Grade 3 (> 3 to ≤ 10× the ULN): do not administer T-DM1 until total bilirubin recovers to grade ≤ 1, and then reduce one dose level Grade 4 (> 10× the ULN): discontinue T-DM1
Thrombocytopenia	Grade 3 (25,000 to < 50,000/μL): do not administer T-DM1 until platelet count recovers to grade ≤ 1 (≥ 75,000/μL), and then treat at the same dose level Grade 4 (< 25,000/μL): do not administer T-DM1 until platelet count recovers to grade ≤ 1 (≥ 75,000/μL), and then reduce one dose level
Left ventricular dysfunction	Symptomatic CHF: discontinue T-DM1 LVEF < 40%: do not administer T-DM1; repeat LVEF assessment within 3 weeks; if LVEF < 40% is confirmed, discontinue T-DM1 LVEF 40% to ≤ 45% and decrease is ≥ 10 percentage points from baseline: do not administer T-DM1; repeat LVEF assessment within 3 weeks; if LVEF has not recovered to within 10 percentage points from baseline, discontinue T-DM1 LVEF 40% to ≤ 45% and decrease is < 10 percentage points from baseline: continue treatment with T-DM1; repeat LVEF assessment within 3 weeks LVEF > 45%: continue treatment with T-DM1
Dose reduction schedule	
Starting dose	3.6 mg/kg
First dose reduction	3.0 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue T-DM1

Abbreviations: AE, adverse event; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; T-DM1, trastuzumab emtansine; ULN, upper limit of normal.

Table A5. Summary of Thrombocytopenia, Hemorrhage, and Platelet Counts in Asian and Non-Asian Patients

	Asian Patients (n = 99)		Non-Asian Patients (n = 785)	
Factor	No.	%	No.	%
Patients with baseline platelet count available	99		782	
Baseline platelet count, μL				
Mean	240,500		266,800	
SD	68,300		88,000	
Patients with baseline platelet counts ≤ mean*	56	56.6	329	42.1
Patients with baseline platelet counts > mean*	43	43.4	453	57.9
Grade 3 or 4 decrease in platelet count after baseline				
Overall	44	44.4	83	10.6
In patients with baseline platelet count ≤ mean*†	28	50.0	58	17.6
In patients with baseline platelet count > mean*†	16	37.2	25	5.5
All-grade hemorrhage				
Overall	37	37.4	285	36.4
In patients with baseline platelet counts ≤ mean*†	23	41.1	128	38.9
In patients with baseline platelet counts > mean*†	14	32.6	157	34.7
Grade 3 or 4 hemorrhage				
Overall	1	1.0	17	2.2
In patients with baseline platelet counts ≤ mean*†	1	1.8‡	8	2.4
In patients with baseline platelet counts > mean*†	0	0	9	2.0‡

Abbreviation: SD, standard deviation.
*Mean of Asian patients subgroup.
†Percentage based on number of patients with ≤ or > mean baseline platelet counts.
‡There were no grade 4 events.