Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods

Patients: Key inclusion and exclusion criteria

All patients were age ≥18 years and had HER2-positive tumors, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, adequate liver/renal function, left ventricular ejection fraction ≥50%, and life expectancy ≥12 weeks.

Patients with mBC were eligible if they had HER2-positive tumors (locally scored as immunohistochemistry [IHC] 3+ or in situ hybridization [ISH]-positive based on ratio of ≥2 copies of the HER2 gene versus number of signals for CEP17) and had received at least one prior treatment for early or metastatic disease (including chemotherapy and trastuzumab, separately or in combination). Eligibility criteria were the same for phase I and II.

Patients with LA/mGC were eligible if they had HER2-positive (IHC 2+, IHC 3+, or ISH-positive, centrally confirmed in the primary tumor or metastatic lesions), inoperable LA/mGC amenable to treatment with T-DM1 plus capecitabine, and had not received prior chemotherapy for advanced or metastatic disease. Prior (neo)adjuvant therapy was allowed if ≥6 months had elapsed between treatment completion and study enrollment.

Patients were excluded if they had previously received T-DM1 or if they received trastuzumab within 21 days, lapatinib within 14 days, hormonal therapy within 14 days, or an investigational therapy within 28 days (or five half-lives) before study drug initiation. Patients were also excluded with: symptomatic brain metastases; history of symptomatic congestive heart failure (CHF) (New York Heart Association Classes II−IV), or myocardial infarction or unstable angina within 6 months prior to study drug initiation; history of left ventricular ejection fraction decrease to <40% or symptomatic CHF with previous trastuzumab treatment.

Collection of baseline demographics data included race, which was self-reported by patients based on categories defined in the case report form.

Procedures: Phase I LA/mGC

Two possible dose levels were identified for the LA/mGC cohort as part of a de-escalation design, starting with the capecitabine MTD from the mBC cohort (700 mg/m^2; dose level −1) (eFigure 1). If dose level −1 was well-tolerated (DLT in ≤1/6 patients), it would be established as the MTD for LA/mGC; if it was not tolerated (DLT in >1/6 patients), dosage would be de-escalated to dose level −2. Capecitabine was given BID (days 1–14 of a 3-week cycle) with T-

DM1 2.4 mg/kg weekly (QW). QW dosing of T-DM1 was used for the phase I LA/mGC cohort to provide higher drug exposure based on studies indicating that 1) trastuzumab exposure is lower in LA/mGC than that observed in breast cancer,[1] and 2) that T-DM1 QW dosing may provide higher cumulative T-DM1 exposure than the Q3W schedule.[2]

Procedures: Phase II mBC

In phase II, patients with mBC were randomized 1:1 to T-DM1 plus capecitabine (at phase I MTD) or T-DM1 alone (3.6 mg/kg Q3W) using an interactive voice response system. Random allocation was generated using permuted blocks with a block size of four (Signant Health [formerly Bracket Global, at the time of study], Plymouth Meeting, PA), and stratified by the number of prior metastatic treatment lines (≤1 or >1; excluding single-agent hormones). Open-label treatment continued until disease progression, unacceptable toxicity, patient withdrawal, death, or at the discretion of the treating physician. Details of treatment administration and criteria for dose adjustments are shown in eTable 1. In case of toxicities requiring capecitabine discontinuation, T-DM1 treatment was continued.

Procedures: Tumor assessments

Tumors were assessed for response via physical examination and computed tomography (CT) or magnetic resonance imaging (MRI) based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 at 9 weeks, and then Q12W until progressive disease/study termination. Patients with isolated brain metastases could continue study treatment if they demonstrated clinical benefit, and a brain CT or MRI was performed in addition to regularly scheduled tumor response assessments.

Procedures: Adverse events

Adverse events (AEs) were coded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version v4.0. All patients were followed for AEs throughout the study and for 28 days following the last infusion of study drug or until the early termination visit, resolution or stabilization of treatment-related AEs, or initiation of another anticancer therapy (whichever occurred first).

Statistical analysis

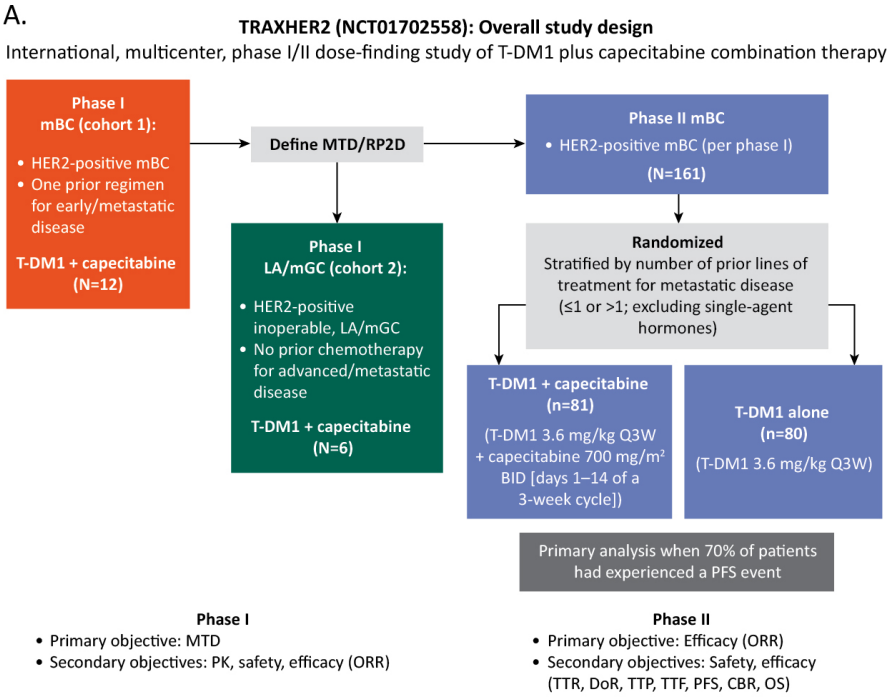
The phase II sample size of 160 patients (80 patients per group) was based on a Fisher's exact test with an alpha level of 5% (one-sided) and power of 70%, and the clinical assumptions of ORRs of 62.5% for T-DM1 plus capecitabine and

43% for T-DM1 alone, with a 15% withdrawal rate. The anticipated ORR was based on prior data indicating that the combination of anti-HER2 agents and capecitabine has a significant efficacy benefit when compared with capecitabine alone.[3,4] Additionally, as preclinical data suggest that the combination of T-DM1 with chemotherapeutic agents has additive activity, the combination of T-DM1 with capecitabine might provide enhanced anti-tumor efficacy in patients with mBC compared with the single agents.[5]

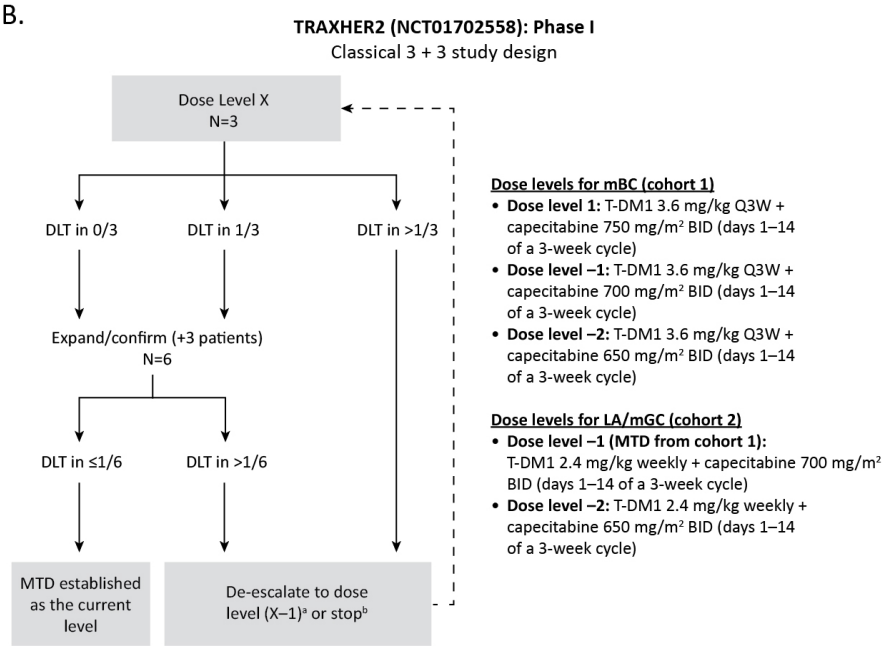
Hazard ratio estimates and 90% confidence intervals for progression-free and overall survival are calculated from a Cox regression model stratified by number of previous lines of treatment.

eFigure 1. TRAXHER2 Study Design

A.

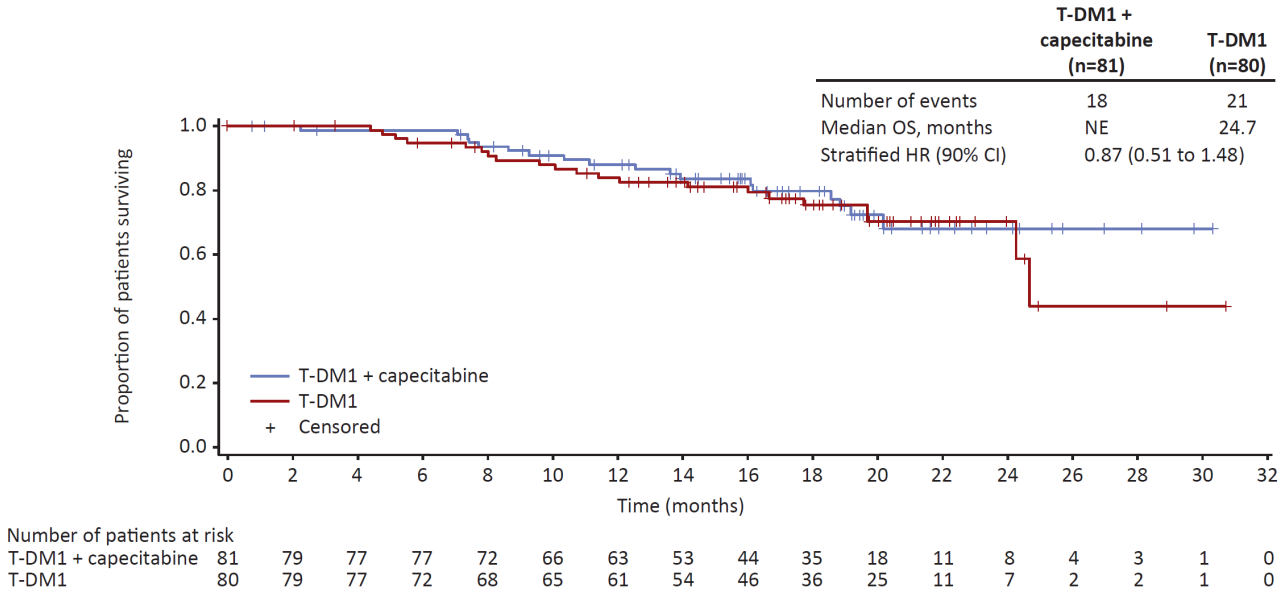


B.



[a]Repeat with the new dose level starting with three patients, until the MTD is established.
[b]If dose level −2 is too toxic (DLT in more than one of six patients), the study will be terminated.
[c]The starting capecitabine dose for cohort 2 was based on the MTD from cohort 1. Dose level −2 was not evaluated in TRAXHER2 because the MTD was established as dose level −1.
Abbreviations: BID,twice daily; CBR, clinical benefit rate; DLT, dose-limiting toxicity; DoR, duration of response; LA, locally advanced; mBC, metastatic breast cancer; mGC, metastatic gastric cancer; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RP2D, recommended phase II dose; T-DM1, trastuzumab emtansine; TTF, time to treatment failure; TTP, time to progression; TTR, time to response.

eFigure 2. Overall Survival in Patients With Metastatic Breast Cancer From Phase II

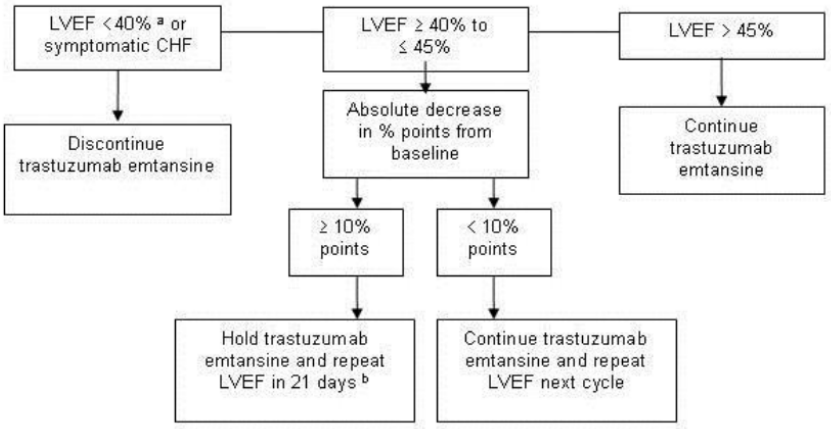


Patients without death were censored at the date of the last tumor assessment. HR estimates and 90% CIs are from a Cox regression model stratified by number of previous lines of treatment.

CI, confidence interval; HR, hazard ratio; T-DM1, trastuzumab emtansine.

eTable 1. Protocol-Specified Administration of T-DM1 and Capecitabine and Rules for Dose Delays, Dose Reductions, and Dose Discontinuations in Phase II

T-DM1		
Administration	*mBC and mGC* The first T-DM1 infusion was administered intravenously over 90 minutes (±10 minutes) and could be slowed/interrupted for patients experiencing infusion-associated symptoms. Patients were observed for ≥90 minutes for fever, chills, or other infusion-associated symptoms. If well tolerated, subsequent doses may have been administered over 30 minutes (±10 minutes) with a 30-minute post-infusion observation period	
Dose delay	If significant T-DM1-related toxicities have not recovered to grade 1 or baseline status, the dose could be delayed for up to 42 days after the most recent dose. Upon resolution of toxicities, dosing could be either resumed at the same dose level or decreased to one dose level lower. No dose re-escalation was allowed Whether toxicities were significant or related was based on the judgment of the investigator in consultation with the Sponsor's Medical Monitor or designee, when appropriate Additional specific criteria were specified for dose delays and reductions related to some specific adverse events (see below)	
Starting dose	*mBC*	*mGC*
	3.6 mg/kg Q3W	2.4 mg/kg QW
First dose reduction	3.0 mg/kg Q3W	2.0 mg/kg QW
Second dose reduction	2.4 mg/kg Q3W	Study treatment discontinuation
Dose discontinuation	Delays beyond 42 days or toxicities at the lowest dosing level resulted in discontinuation of study treatment	
Additional criteria for dose reductions following specific adverse events	*Thrombocytopenia* If platelet counts did not recover to grade ≤1 (≥75,000/mm^3) within 42 days from the last dose received: treatment was discontinued If the platelet count decreased to grade 3 (<50,000/mm^3): T-DM1 could be continued at the same dose level after adequate recovery to grade 1 (≥75,000/mm^3) If platelet count decreased to grade 4 (<25,000/mm^3): First event: T-DM1 could be continued at a reduced dose of 3 mg/kg in subsequent treatment cycles after adequate recovery to a platelet count of grade ≤1 or baseline Patients at the 3 mg/kg dose level could continue T-DM1 at a reduced dose of 2.4 mg/kg in subsequent treatment cycles after adequate recovery Patients at the 2.4 mg/kg dose level who experienced grade 4 thrombocytopenia were discontinued from study treatment *Hepatotoxicity* Regardless of dose level, T-DM1 was permanently discontinued in: Patients with ALT and/or AST >3 × ULN and concurrent increase of total bilirubin to >2 × ULN Patients diagnosed with nodular regenerative hyperplasia Grade 3 elevation of liver function: patients checked twice weekly for transaminases and/or total bilirubin recovery. If no recovery was evident within 42 days from the patient's last dose received, study treatment was discontinued Elevation of total serum bilirubin: T-DM1 dose was modified, as follows: Grade 2 (>1.5 to ≤3 × ULN): T-DM1 was not administered until total bilirubin recovered to grade ≤1; patients were then treated at the same dose level Grade 3 (>3 to ≤10 × ULN): T-DM1 was not administered until total bilirubin recovered to grade ≤1, and then T-DM1 was reduced by one dose level Grade 4 (>10 × ULN): T-DM1 was discontinued Elevation of serum ALT or AST: T-DM1 dose was modified, as follows: Grade 2 (>3 to ≤5 × ULN): Patients were treated at the same dose level Grade 3 (>5 to ≤20 × ULN): T-DM1 was not administered until AST recovered to grade ≤2, and then T-DM1 was reduced by one dose level Grade 4 (>20 × ULN): T-DM1 was discontinued *Neurotoxicity* Patients who experienced grade 3 or 4 peripheral neuropathy that did not resolve to grade 2 within 42 days after the last dose were discontinued from study treatment	

	Cardiotoxicity Delay or discontinuation of T-DM1 related to cardiotoxicity was based on LVEF assessments, as follows[a]:  [a]LVEF could be repeated within 21 days, and T-DM1 was discontinued if LVEF <40% was confirmed. T-DM1 was held while the repeat LVEF was obtained. [b]After a second consecutive confirmatory result, T-DM1 was discontinued if the LVEF was confirmed to be ≥10% points below baseline or if medical management was required to correct the LVEF. *Infusion-related Reactions, Hypersensitivity Reactions* T-DM1 was interrupted in patients with severe infusion-related reactions and permanently discontinued in the event of life-threatening infusion-related reactions T-DM1 infusion was interrupted for patients who developed dyspnea or clinically significant hypotension T-DM1 infusion was slowed to ≤50% or interrupted for patients who experience any other infusion-related symptoms Upon symptom resolution, the infusion could be continued at ≤50% of the rate prior to the reaction and increased in 50% increments every 30 minutes as tolerated. Infusions could be restarted at the full rate during the next cycle Patients with T-DM1 infusion-related temperature elevations to >38.5°C and/or other infusion-related symptoms could be treated symptomatically with acetaminophen and/or diphenhydramine hydrochloride Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress were managed with supportive care, such as oxygen, beta agonists, antihistamines, antipyretics, or corticosteroids at the investigator's discretion Pre-medication with corticosteroids, antihistamines, and antipyretics could be used before subsequent infusions of T-DM1 at the investigator's discretion Patients were monitored until complete resolution of symptoms Patients were discontinued in the event of: A true hypersensitivity reaction A Grade ≥3 hypersensitivity reaction Acute respiratory distress syndrome A severe delayed infusion reaction *Pulmonary toxicity* T-DM1 was permanently discontinued in patients diagnosed with interstitial lung disease or pneumonitis
Capecitabine	
Administration	*mBC and mGC* Capecitabine tablets were given orally and swallowed with water within 30 minutes after a meal, and a minimum interval of 8 hours was allowed between doses Capecitabine was given on days 1–14 of a 3-week cycle, which included a 7-day rest period
Dose delay	*Phase II mBC and mGC* Dose modifications from cycle 2 onwards were made according to the investigators judgment according to the capecitabine Summary of product characteristics (SPC)[6] *Phase II mBC* Dose modifications from cycle 2 onwards were made according to the capecitabine SPC[6]
Dose reduction	Dose modifications from cycle 2 onwards were made according to the investigator's judgment according to the capecitabine SPC[6]

Dose discontinuation	Capecitabine was discontinued according to guidance in the SPC[6] In the case of toxicities requiring discontinuation of capecitabine, patients were permitted to continue single-agent T-DM1

[a]Although an LVEF threshold of 50% was required for eligibility prior to treatment initiation, if a patient with advanced cancer was already receiving T-DM1 or T-DM1 plus capecitabine and benefiting from this treatment, a lower LVEF threshold was deemed to be acceptable in the absence of any clinical concerns.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; QW, weekly; Q3W, every 3 weeks; T-DM1, trastuzumab emtansine; ULN, upper limit of normal.

eTable 2. Patient Demographics and Baseline Characteristics

Characteristic	Phase I mBC[a] T-DM1 n=11	Phase I LA/mGC[a] T-DM1 n=6	Phase II[b]	
			T-DM1 + capecitabine n=81	T-DM1 n=80
Age, median years (range)	54.0 (37–71)	57.5 (53–70)	54.0 (32–79)	52.0 (28–80)
Sex, n (%)				
Male	1 (9.1)	6 (100.0)	1 (1.2)	0
Female	10 (90.9)	0	80 (98.8)	80 (100.0)
Race				
Caucasian	9 (81.8)	6 (100.0)	70 (86.4)	67 (83.8)
Black	0	0	0	2 (2.5)
Asian	0	0	1 (1.2)	1 (1.3)
Other[c]	2 (18.2)	0	10 (12.3)	10 (12.5)
ECOG performance status, n (%)				
0	7 (63.6)	4 (66.7)	55 (67.9)	55 (68.8)
1	4 (36.4)	2 (33.3)	23 (28.4)	23 (28.8)
2	0	0	3 (3.7)	2 (2.5)
Prior metastatic treatment, n (%)				
≤1 lines	7 (63.6)	NA[d]	53 (65.4)	52 (65.0)
>1 lines	4 (36.4)		28 (34.6)	28 (35.0)
Primary site, n (%)				
Body of stomach	NA	2 (33.3)	NA	NA
Gastroesophageal junction		3 (50.0)		
Other		1 (16.7)		
Cancer type, n (%)				
Intestinal	NA	3 (50.0)	NA	NA
Diffuse		2 (33.3)		
Unknown		1 (16.7)		
ER/PR status, n (%)				
Positive	5 (45.5)	NA	53 (65.4)	46 (57.5)
Negative or Unknown	6 (54.5)		28 (34.6)	34 (42.5)
Visceral/non-visceral disease, n (%)				
Visceral	10 (90.9)	NA	65 (80.2)	69 (86.3)
Non-visceral	1 (9.1)		16 (19.8)	11 (13.8)
Brain metastasis, n (%)	NA	NA	9 (11.1)	7 (8.8)

[a]DLT-evaluable population.

[b]ITT population.

[c]Includes patients with a race of "other" or patients for whom race was not applicable, per local regulation.

[d]No patients with LA/mGC received prior metastatic therapy. One patient received prior treatment with anthracyclines plus surgery; one patient received prior radiotherapy; four patients received no prior therapy.

Abbreviations: DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ITT, intention-to-treat; LA/mGC, locally advanced or metastatic gastric cancer; mBC, metastatic breast cancer; NA, not applicable; PR, progesterone receptor; T-DM1, trastuzumab emtansine

eTable 3. Overall Response Rates by HER2 Subgroup From Phase II

	T-DM1 + capecitabine	T-DM1	Treatment comparison
	N (%) [90% CI]	N (%) [90% CI]	Difference [90% CI]
All patients centrally confirmed as HER2-positive[a]	N=53	N=65	
Responders	24 (45.3) [33.5% to 57.4%]	24 (36.9) [26.9% to 47.8%]	8.4% [-6.6 to 23.3%]
Centrally confirmed HER2-positive: IHC 2+[b]	N=11	N=13	
Responders	2 (18.2) [3.3% to 47.0%]	1 (7.7) [0.4% to 31.6%]	10.5% [-12.2% to 33.2%]
Centrally confirmed HER2-positive: IHC 3+[c]	N=40	N=49	
Responders	21 (52.5) [38.5% to 66.2%]	23 (46.9) [34.6% to 59.6%]	5.6% [-11.9% to 23.1%]

[a]IHC 3+ and/or ISH-positive.
[b]IHC 2+ and ISH-positive.
[c]IHC 3+ regardless of ISH status.

Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DM1,trastuzumab emtansine.

eTable 4. Most Common Reasons for Study and Treatment Discontinuation

n (%)	**T-DM1 + capecitabine (N=81)**		**T-DM1 (N=80)**
Primary reason for study discontinuation			
Death	16 (34.0)		20 (47.6)
Withdrew consent	12 (25.5)		4 (9.5)
Lost to follow-up	3 (6.4)		0
Termination by sponsor	0		1 (2.4)
Other	16 (34.0)		17 (40.5)
Primary reason for study treatment discontinuation	T-DM1 discontinuation	Capecitabine discontinuation	T-DM1 discontinuation
Disease progression	49 (60.5)	44 (54.3)	48 (60.0)
Early study termination by sponsor[a]	15 (18.5)	9 (11.1)	13 (16.3)
AE/toxicity	8 (9.9)	21 (25.9)	13 (16.3)
Death	1 (1.2)	0	1 (1.3)
Withdrew consent	1 (1.2)	1 (1.2)	0
Investigator decision	1 (1.2)	2 (2.5)	1 (1.3)
Patient decision	3 (3.7)	1 (1.2)	2 (2.5)
Other	3 (3.7)	3 (3.7)	2 (2.5)

[a]At the end of the study (70% of PFS events), patients still on treatment were able to continue treatment by enrolling into study BO25430 (an open-label, multicenter extension study) or by proceeding to a commercial drug, depending on their country.
Abbreviation: AE, adverse event; PFS, progression-free survival; T-DM1, trastuzumab emtansine.

eTable 5. Safety Results From Phase II[a]

n (%)	T-DM1 + capecitabine (N=82)			T-DM1 (N=78)		
All grade AEs	78 (95.1)			69 (88.5)		
Grade ≥3 AEs	36 (43.9)			32 (41.0)		
Serious AEs	11 (13.4)			10 (12.8)		
AEs leading to discontinuation of study or any study drug	23 (28.0)			12 (15.4)		
All grade AE in ≥15% and grade 3–4 AEs in ≥2 patients of either study arm	**T-DM1 + capecitabine (N=82)**			**T-DM1 (N=78)**		
	All grade	**Grade 3**	**Grade 4**	**All grade**	**Grade 3**	**Grade 4**
Thrombocytopenia[b]	35 (42.7)	8 (9.8)	1 (1.2)	21 (26.9)	2 (2.6)	1 (1.3)
AST increased	27 (32.9)	4 (4.9)	0	31 (39.7)	5 (6.4)	0
GGT increased	8 (9.8)	4 (4.9)	0	16 (20.5)	5 (6.4)	0
Platelet count decreased	12 (14.6)	3 (3.7)	0	13 (16.7)	4 (5.1)	0
PPE[b]	17 (20.7)	4 (4.9)	0	2 (2.6)	0	0
Diarrhea	7 (8.5)	2 (2.4)	0	7 (9.0)	1 (1.3)	0
Asthenia	17 (20.7)	1 (1.2)	0	15 (19.2)	2 (2.6)	0
Fatigue	10 (12.2)	1 (1.2)	0	11 (14.1)	2 (2.6)	0
Hyperglycemia	4 (4.9)	2 (2.4)	0	5 (6.4)	1 (1.3)	0
ALT increased	20 (24.4)	1 (1.2)	0	24 (30.8)	1 (1.3)	0
Vomiting[b]	16 (19.5)	1 (1.2)	0	8 (10.3)	1 (1.3)	0
Blood ALP increased	5 (6.1)	0	0	15 (19.2)	2 (2.6)	0
Device-related infection	0	0	0	3 (3.8)	2 (2.6)	0
Nausea[b]	27 (32.9)	1 (1.2)	0	18 (23.1)	0	0
Pyrexia	13 (15.9)	0	0	15 (19.2)	1 (1.3)	0
Epistaxis[b]	15 (18.3)	0	0	10 (12.8)	0	0
Anemia	9 (11.0)	0	0	13 (16.7)	0	0
Neutropenia[b]	13 (15.9)	0	0	6 (7.7)	0	0

[a]Safety population. Two patients randomized to trastuzumab emtansine (T-DM1) were not included in the safety population for this treatment arm (one patient received capecitabine throughout the study and is included in the combination arm for the safety analysis and one patient was randomized in error and was not treated). All adverse events are listed, regardless of relationship to study drugs.

[b]Incidence was ≥5% higher in patients in the T-DM1 plus capecitabine arm compared with the T-DM1 arm.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; PPE, palmar-plantar erythrodysesthesia syndrome; T-DM1, trastuzumab emtansine.

eTable 6. AEs Leading to Discontinuation From Study or Study Treatment in ≥2 Patients in Either Treatment Arm

n (%)	T-DM1 + capecitabine (N=82)	T-DM1 (N=78)
Thrombocytopenia	5 (6.1)	3 (3.8)
Blood bilirubin increased	2 (2.4)	2 (2.6)
Platelet count decreased	2 (2.4)	1 (1.3)
PPE	2 (2.4)	0
Leukopenia	1 (1.2)	1 (1.3)

Abbreviations: AE, adverse event; PPE, palmar plantar erythrodysesthesia; T-DM1, trastuzumab emtansine.

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