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Trastuzumab emtansine (T-DM1) plus docetaxel with or without pertuzumab in patients with HER2-positive locally advanced or metastatic breast cancer: results from a phase Ib/IIa study†

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Background: Trastuzumab emtansine (T-DM1) exhibited enhanced antitumor activity when combined with docetaxel or pertuzumab in preclinical studies. This phase Ib/IIa study assessed the feasibility of T-DM1 + docetaxel in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) and T-DM1 + docetaxel ± pertuzumab in patients with HER2-positive locally advanced breast cancer (LABC).

Patients and methods: Phase Ib (part 1) explored dose escalation, with T-DM1 + docetaxel administered for greater than or equal to six cycles in patients with MBC. Phase Ib (part 2) began with the maximum tolerated dose (MTD) identified in part 1. Patients with LABC were administered less than or equal to six cycles of T-DM1 + docetaxel or T-DM1 + docetaxel + pertuzumab. Phase IIa explored the MTDs identified in phase Ib.

Results: Administered with T-DM1 (3.6 mg/kg), the docetaxel MTD was 60 mg/m^2 in MBC. In LABC, the MTD was 100 mg/m^2 docetaxel in combination with T-DM1 (3.6 mg/kg), given with granulocyte colony-stimulating factor (G-CSF). Administered with T-DM1 (3.6 mg/kg) + pertuzumab (840 mg, cycle 1; 420 mg, subsequent cycles), the docetaxel MTD in LABC was 75 mg/m^2 with G-CSF support. Neutropenia was the most common grade 3–4 adverse event (AE; MBC, 72% and LABC, 29%). In total, 48% (12/25) of MBC patients and 47% (34/73) of LABC patients experienced AEs requiring dose modification. In MBC (median prior systemic agents = 5), the objective response rate was 80.0% (20/25; 95% confidence interval [CI] 59.3–93.2) and the median progression-free survival was 13.8 months (range, 1.6–33.5). The pathologic complete response (ypT0/is, ypN0) rate in LABC was 60.3% (44/73; 95% CI 48.1–71.5). Pharmacokinetic analyses indicated a low risk of drug–drug interaction between T-DM1 and docetaxel.

Conclusions: T-DM1 combined with docetaxel ± pertuzumab appeared efficacious in MBC or LABC; however, nearly half of patients experienced AEs requiring dose reductions with these T-DM1 combinations.

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Key words: trastuzumab emtansine, ado-trastuzumab emtansine, T-DM1, pertuzumab, docetaxel, breast cancer

introduction

Human epidermal growth factor receptor 2 (HER2) is overexpressed in 15%–20% of breast cancers [1, 2]. Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate comprising the microtubule inhibitor DM1 conjugated to the humanized monoclonal antibody (mAb) trastuzumab via a stable linker [3].

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DM1 is delivered selectively to HER2-overexpressing tumor cells by trastuzumab and triggers apoptosis [3]. Like trastuzumab, T-DM1 prevents HER2 shedding, blocks HER2 signaling, and induces antibody-dependent cell-mediated cytotoxicity [4]. In phase III studies, T-DM1 resulted in significant improvements in progression-free survival (PFS) [5, 6] and overall survival (OS) [5] versus standard therapy in patients with previously treated HER2-positive metastatic breast cancer (MBC).

Pertuzumab is a humanized mAb that binds to a different HER2 domain than trastuzumab [7]. Compared with trastuzumab + docetaxel, trastuzumab + pertuzumab + docetaxel resulted in significant improvements in PFS and OS in patients with previously untreated HER2-positive MBC [8, 9] and pathologic complete response (pCR) rates in patients treated in the neoadjuvant setting [10].

In preclinical studies, T-DM1 exhibited enhanced antitumor activity when combined with docetaxel [11] or pertuzumab [12]. The present phase Ib/IIa study (BP22572/NCT00934856) examined, for the first time, the feasibility, safety, efficacy, and pharmacokinetics of T-DM1 + docetaxel ± pertuzumab in MBC or locally advanced breast cancer (LABC).

methods

patients

Eligible patients were aged ≥18 years and had a life expectancy of ≥12 weeks and an Eastern Cooperative Oncology Group performance status score of 0–1. MBC patients had histologically or cytologically confirmed disease and experienced disease progression within 3 months of enrollment. MBC patients were eligible for phase Ib if they had evaluable (part 1) or measureable (part 2) disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.0 [13] and locally confirmed HER2-positive disease. MBC patients participating in phase IIa had measurable disease per RECIST v1.0 [13] and locally confirmed HER2-positive disease (immunohistochemistry 3+ or fluorescence *in situ* hybridization [FISH]-positive). LABC patients were eligible for phase Ib (part 2) if they had measurable disease, newly diagnosed LABC (clinical stage IIA–IIIC) [14], and centrally confirmed HER2-positive tumors (immunohistochemistry 3+ and/or FISH-positive) and agreed to undergo mastectomy/lumpectomy following neoadjuvant therapy. See supplementary Methods, available at *Annals of Oncology* online for exclusion criteria.

study design and objectives

BP22572 was an open-label, multicenter (supplementary Table S1, available at *Annals of Oncology* online) study (Figure 1). Phase Ib followed a dose-finding design and consisted of two parts. In part 1, MBC patients were assigned consecutively to one of the four regimens under a 3 + 3 dose-escalation design (Figure 1). Each cycle was of 3 weeks' duration. As this was the first study to explore treatment with T-DM1 + docetaxel, patients were initially treated with T-DM1 2.4 mg/kg (dose levels 1–3), which is lower than the approved dose (3.6 mg/kg), to maximize patient safety. Once this dose was found to be tolerable, T-DM1 was escalated to 3.6 mg/kg (dose level 4). When combined with other anti-cancer therapy, docetaxel is typically used at a dose of 75 mg/m^2. Thus, docetaxel 75 mg/m^2 was the starting dose.

Once the MTD was identified, part 2 of phase Ib was activated. Part 2 of phase Ib only enrolled LABC patients. The MTD established in part 1 was used as the starting dose for part 2. The first LABC patients enrolled received T-DM1 + docetaxel (doublet regimen; Figure 1). T-DM1 3.6 mg/kg q3w was combined with one of the three escalating doses of docetaxel: 60 mg/m^2 (dose level 1), 75 mg/m^2 (dose level 2), or 100 mg/m^2 (dose level 3). Both treatments were administered on day 1 of each 3-week cycle. Following a protocol amendment, granulocyte colony-stimulating factor (G-CSF) was added to dose level 3 (dose level 3a). Once the feasibility of the doublet regimen was established, the safety and tolerability of adding pertuzumab (triplet regimen) was explored (Figure 1). T-DM1 3.6 mg/kg q3w was combined with either docetaxel 60 mg/m^2 (dose level 1) or 75 mg/m^2 (dose level 2). Pertuzumab dose was fixed (840 mg during cycle 1 and 420 mg during subsequent cycles). A protocol amendment allowed the concomitant use of G-CSF with dose level 2 (dose level 2a). See supplementary Methods, available at *Annals of Oncology* online for details on dose-limiting toxicities (DLTs). Phase IIa further examined the MTDs established in phase Ib in additional MBC and LABC patients.

T-DM1 + docetaxel was administered to MBC patients for a minimum of six cycles (unless contraindicated by toxicity or disease progression) followed by single-agent T-DM1 until progressive disease, unacceptable/unmanageable toxicity, or withdrawal of consent, whichever occurred first. If toxicity required docetaxel discontinuation, treatment with single-agent T-DM1 was permitted. LABC patients were treated for a maximum of six cycles before surgery (carried out no later than 4 weeks after day 21 of cycle 6). If T-DM1 was discontinued, docetaxel could be continued until the completion of six cycles or unacceptable toxicity. If docetaxel was stopped, T-DM1 ± pertuzumab could be continued, but if T-DM1 was held or discontinued, so was pertuzumab.

The primary objectives of part 1 of phase Ib were to evaluate the safety and tolerability of T-DM1 + docetaxel and to define MTD in MBC. Secondary objectives included PFS, objective response rate (ORR), and pharmacokinetics. The primary objectives of part 2 of phase Ib were to evaluate the safety and tolerability of T-DM1 + docetaxel ± pertuzumab and to determine MTD in LABC. Secondary objectives included pCR (ypT0/is, ypN0) rate, ORR, and pharmacokinetics. Phase IIa further evaluated the safety and efficacy of the MTDs identified in phase Ib. Biomarker analyses were also conducted. The study was conducted according to the established ethical guidelines. All participants provided written informed consent.

assessments

Adverse events (AEs) were graded per National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 [15], and tumor response (MBC patients) was evaluated per RECIST v1.0 [13] at baseline, every 6 weeks for eight cycles, and every 12 weeks thereafter. Survival was assessed every 12 weeks after documented disease progression. Bilateral breast magnetic resonance imaging (carried out at baseline and at the end of cycles 3 and 6) was used to assess preoperative tumor response in LABC patients. Surgical specimens were assessed locally for pCR (ypT0/is, ypN0; absence of invasive neoplastic cells upon microscopic examination of tumor and lymph nodes).

statistical analyses

All patients received at least one dose of study medication and were included in the safety and efficacy analyses. Safety and efficacy were analyzed per intent-to-treat principles. Data are summarized using descriptive statistics; no formal hypothesis testing was conducted. Confidence intervals were calculated using the Clopper–Pearson method. Kaplan–Meier estimates were used to summarize PFS. The biomarker and pharmacokinetic analyses are described in supplementary Material, available at *Annals of Oncology* online . The data cutoff date was 2 May 2013.

results

patients

Twenty-one MBC patients were recruited to part 1 of phase Ib; an additional four patients were recruited to phase IIa (dose level 1, $n = 6$; dose level 2, $n = 6$; dose level 3, $n = 3$; dose level 4,

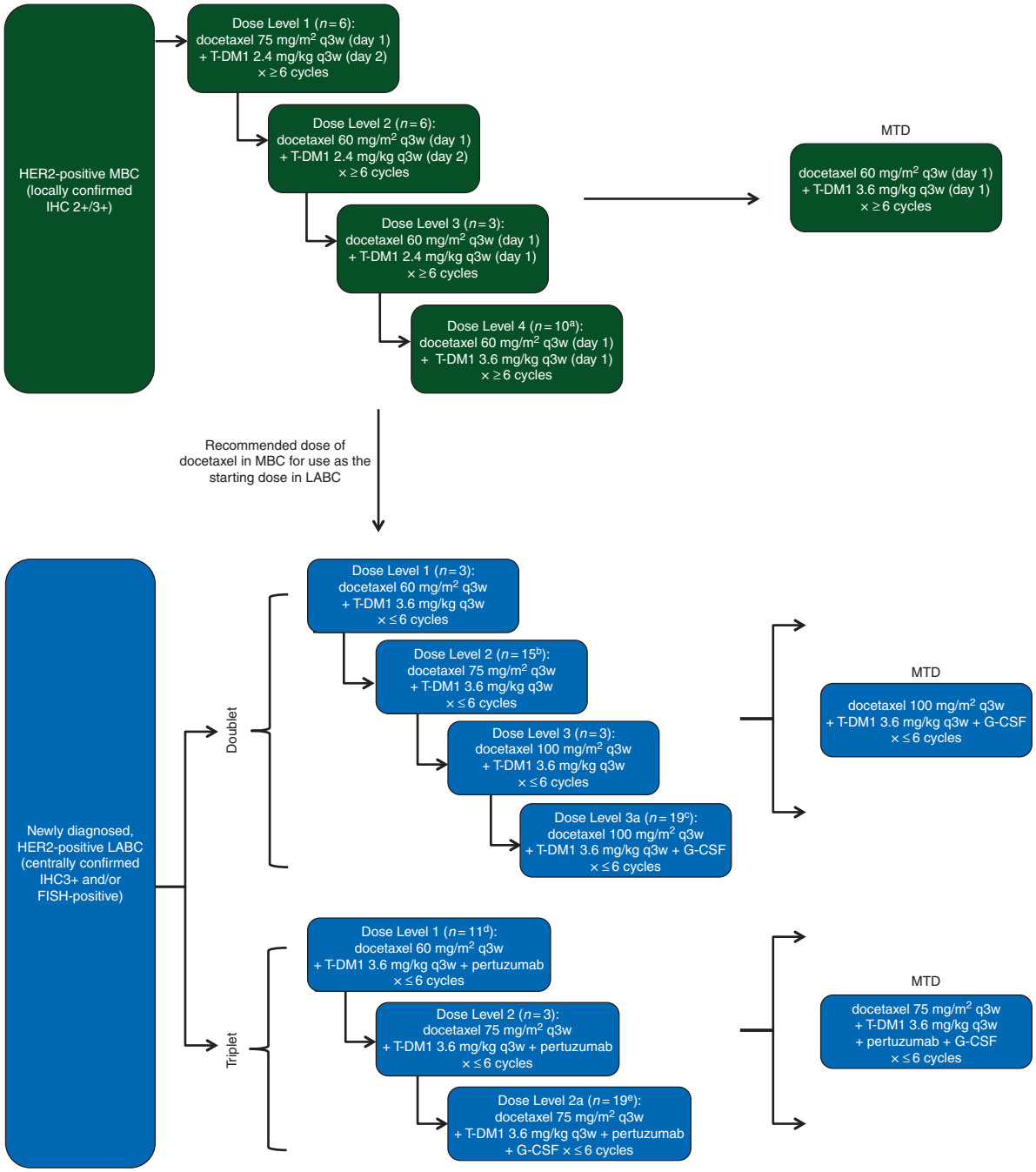

Figure 1. Study design. In part 1, MBC patients were assigned consecutively to one of the four regimens. Each cycle was of 3 weeks' duration. T-DM1 + docetaxel was administered for a protocol-specified minimum of six cycles (unless contraindicated by toxicity or disease progression) followed by single-agent T-DM1 until progressive disease, unacceptable/unmanageable toxicity, or withdrawal of consent, whichever occurred first. If toxicity required docetaxel discontinuation, treatment with single-agent T-DM1 was permitted. In part 2, LABC patients assigned to the doublet regimen received T-DM1 3.6 mg/kg q3w combined with one of three escalating doses of docetaxel: 60 mg/m^2 (dose level 1), 75 mg/m^2 (dose level 2), or 100 mg/m^2 (dose level 3). LABC patients assigned to the triplet regimen received T-DM1 3.6 mg/kg q3w combined with one of the two escalating does of docetaxel (60 mg/m^2 [dose level 1] or 75 mg/m^2 [dose level]) and pertuzumab (840 mg during cycle 1 and 420 mg during subsequent cycles). LABC patients were administered the doublet or triplet regimen for a protocol-specified maximum of six cycles before surgery (carried out no later than 4 weeks after day 21 of cycle 6). If T-DM1 was discontinued, docetaxel could be continued until the completion of six cycles or unacceptable toxicity. If docetaxel was stopped, T-DM1 ± pertuzumab could be continued; however, if T-DM1 was held or discontinued, pertuzumab was, as well. [a]Six patients were recruited to the feasibility phase, and four additional patients were recruited to the extension phase. [b]Three patients were recruited to the feasibility phase, and 12 additional patients were recruited to the extension phase. [c]Three patients were recruited to the feasibility phase, and 19 additional patients were recruited to the extension phase. [d]Three patients were recruited to the feasibility phase, and eight additional patients were recruited to the extension phase. [e]Three patients were recruited to the feasibility phase, and 16 additional patients were recruited to the extension phase. FISH, fluorescence *in situ* hybridization; G-CSF, granulocyte colony-stimulating factor; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; MTD, maximum tolerated dose; q3w, every 3 weeks; T-DM1, trastuzumab emtansine.

$n = 10$). Twenty-one LABC patients were recruited to the feasibility phase, and 52 were recruited to the extension phase. Of 73 LABC patients, 40 received T-DM1 + docetaxel and 33 received T-DM1 + docetaxel + pertuzumab (Figure 1). Baseline characteristics (Table 1) were generally balanced between LABC patients receiving the doublet versus triplet regimens, except a greater proportion assigned to the doublet regimen had stage II disease (70% versus 58%) and hormone-receptor negative disease (52% versus 35%).

treatment exposure

MBC patients received a median of 18 T-DM1 cycles (range, 1–39) and a median of six docetaxel infusions (range, 1–12). In total,

Table 1. Demographics and baseline disease characteristics

Characteristic	MBC ($n = 25$)	LABC ($n = 73$)	
		Doublet ($n = 40$)	Triplet ($n = 33$)
Female, *n* (%)	25 (100)	40 (100)	33 (100)
Race, *n* (%)			
White	22 (88)	31 (78)	28 (85)
Black	1 (4)	3 (8)	1 (3)
Asian	0 (0)	0 (0)	2 (6)
Other	2 (8)	2 (5)	1 (3)
Unknown	0 (0)	4 (10)	1 (3)
Median age, years (range)	47 (33–70)	47 (34–65)	52 (34–76)
Median LVEF, % (range)	63.0 (51.0–78.0)	64.0 (51.0–78.5)	64.5 (50.0–80.0)
ECOG PS, *n* (%)			
0	19 (76)	38 (95)	30 (91)
1	6 (24)	2 (5)	3 (9)
Median time since initial cancer diagnosis, months (range)	50 (13.6–168.5)	1.3 (0.7–3.3)	1.2 (0.6–2.7)
Disease stage at first diagnosis, *n* (%)			
I	3 (12)	0 (0)	0 (0)
IIA	1 (4)	16 (40)	13 (39)
IIB	6 (24)	12 (30)	6 (18)
IIIA	6 (24)	9 (23)	11 (33)
IIIB	5 (20)	2 (5)	2 (6)
IIIC	1 (4)	1 (3)	1 (3)
IV	3 (12)	0 (0)	0 (0)
Prior therapy, *n* (%)			
Taxanes	23 (92)	N/A	N/A
Trastuzumab	23 (92)		
Non-anthracyclines	22 (88)		
Anthracyclines	21 (84)		
Non-trastuzumab biologic	13 (52)		
Hormonal	11 (44)		
Other	4 (16)		
Other investigational therapy	1 (4)		
Median number of prior systemic agents, including hormonal therapy[a], *n* (range)	7 (2–16)	N/A	N/A
(Neo)adjuvant setting	4 (2–13)		
Metastatic setting	5 (1–11)		
Central HER2 status, *n*	25	40	33
IHC2+ and ISH-positive, *n* (%)	2 (8)	2 (5)	3 (9)
IHC3+ and/or ISH-positive, *n* (%)	18 (72)	38 (95)	30 (91)
Unknown	5 (20)	0 (0)	0 (0)
ER/PR status, *n* (%)			
ER-positive and/or PR-positive	12 (48)	24 (60)	15 (45)
ER-negative and PR-negative	13 (52)	14 (35)	17 (52)
Unknown	0 (0)	2 (5)	1 (3)
Median tumor size, mm (range)	N/A	36.0 (14.0–90.0)	33.0 (11.0–100.0)

[a]Multiple occurrences of the same agent used by one individual were counted only once.

ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; ISH, *in situ* hybridization; LABC, locally advanced breast cancer; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; N/A, not applicable; PR, progesterone receptor.

52% (13/25) completed 12 months of treatment. Twenty patients discontinued T-DM1, and five discontinued docetaxel before completing six cycles (supplementary Table S2, available at *Annals of Oncology* online). In the LABC cohort, 83.6% (61/73) of patients completed six treatment cycles (doublet, 90% [36/40]; triplet, 76% [25/33]). LABC patients received a median of six T-DM1 cycles (range, 1–6) and a median of six docetaxel infusions (range, 1–6). Among the 33 patients receiving the triplet regimen, the median number of pertuzumab infusions was six (range, 1–6). Four patients receiving the doublet regimen and eight receiving the triplet regimen discontinued treatment (supplementary Table S2, available at *Annals of Oncology* online).

maximum tolerated dose

metastatic breast cancer. When combined with T-DM1 2.4 mg/kg, four DLTs were reported in two of six patients administered docetaxel 75 mg/m^2 (grade 3 cytolytic hepatitis/elevated hepatic transaminases; grade 4 thrombocytopenia, grade 3 cytolytic hepatitis, and grade 3 febrile neutropenia). On the basis of these DLTs, docetaxel was reduced to 60 mg/m^2 (dose level 2), and one DLT was observed in one of the six patients (grade 3 cytolytic hepatitis). There were no DLTs at dose level 3. For dose level 4, T-DM1 dose was increased to 3.6 mg/kg. One of the six patients administered dose level 4 experienced a DLT (grade 3 increased aspartate aminotransferase [AST]). T-DM1 3.6 mg/kg + docetaxel 60 mg/m^2 was identified as the MTD in MBC.

locally advanced breast cancer. On the basis of the MTD established in MBC, T-DM1 3.6 mg/kg was combined with escalating doses of docetaxel: 60 mg/m^2 ($n = 3$), 75 mg/m^2 ($n = 3$), and 100 mg/m^2 ($n = 3$). No DLTs were observed in patients administered regimens containing docetaxel 60 or 75 mg/m^2. Two of three patients assigned to T-DM1 + docetaxel 100 mg/m^2 experienced a DLT (grade 4 thrombocytopenia and grade 3 mucosal inflammation). In an effort to maintain the dose intensity of docetaxel, primary prophylaxis with G-CSF was instituted. No DLTs were reported in the three patients treated with T-DM1 + docetaxel 100 mg/m^2 + G-CSF. Therefore, the MTD was 100 mg/m^2 docetaxel with T-DM1, given with primary G-CSF.

After the feasibility of T-DM1 + docetaxel was demonstrated in LABC, the use of concomitant pertuzumab was investigated. Six patients were administered T-DM1 + pertuzumab in combination with docetaxel 60 mg/m^2 ($n = 3$) or 75 mg/m^2 ($n = 3$). Two patients in the latter cohort experienced a DLT (grade 3 urinary tract infection and grade 4 thrombocytopenia). Three patients were treated with T-DM1 + docetaxel 75 mg/m^2 + pertuzumab + G-CSF; none experienced a DLT. Therefore, the MTD was 75 mg/m^2 docetaxel in combination with T-DM1 and pertuzumab with G-CSF.

safety

metastatic breast cancer. Among the 25 MBC patients, the most common all-grade AEs were neutropenia (76%), asthenia (72%), thrombocytopenia (64%), and epistaxis (56%); the most common grade ≥3 AEs were neutropenia (72%), and leukopenia (44%; Table 2). Forty-eight percent of patients (12/25) required dose modification due to AEs, most commonly neutropenia (4/25, 16%). Five patients discontinued T-DM1 and/or docetaxel due to AEs (grade 1 thrombocytopenia, $n = 1$; grade 2 thrombocytopenia, $n = 2$; grade 2 paresthesia, $n = 1$; grade 2 increased ALT/grade 3 increased AST, $n = 1$). Safety by dose is summarized in supplementary Table S3, available at *Annals of Oncology* online.

locally advanced breast cancer. Among the 73 LABC patients, the most common all-grade AEs were asthenia (62%), epistaxis (55%), and mucosal inflammation (49%; Table 2). Sixty-four percent of patients had grade ≥3 AEs, most of which were related to laboratory parameters (hematological- and hepatotoxicity-related). The most common grade ≥3 AEs were neutropenia (29%), increased ALT (15%), and thrombocytopenia (12%; Table 2). Five patients had serious AEs related to skin and subcutaneous tissue disorders; four had been receiving the 100-mg/m^2 docetaxel regimen. Of the five serious AEs, two were grade 3 (exfoliative dermatitis and dermatomyositis, $n = 1$ for each) and occurred in patients receiving the 100-mg/m^2 docetaxel regimen; three were grade 1–2 and included melanoderma ($n = 2$) and dermatomyositis ($n = 1$), which occurred in patients receiving the 100-mg/m^2 docetaxel regimen, and skin hyperpigmentation ($n = 1$), which occurred in a patient receiving the 75-mg/m^2 docetaxel regimen. Safety by dose is summarized in supplementary Table S4, available at *Annals of Oncology* online. Safety was generally similar for patients who received ($n = 39$) and did not receive ($n = 34$) primary G-CSF; however, individuals administered G-CSF experienced a numerically lower rate of any-grade and grade ≥3 neutropenia (supplementary Table S5, available at *Annals of Oncology* online).

Forty-seven percent of LABC patients experienced AEs requiring dose modification, most commonly increased ALT (18%), increased AST (10%), neutropenia (8%), and thrombocytopenia (7%); some patients experienced more than one AE leading to dose modification. Fifteen patients (21%) required a dose reduction for T-DM1, and 15 (21%) required a dose reduction for docetaxel. Fourteen percent discontinued treatment due to an AE (the most common was increased ALT).

The safety profiles of the doublet and triplet regimens were generally consistent. The largest differences in the incidence of all-grade AEs were more diarrhea with the triplet versus the doublet (55% versus 30%) regimen and more myalgia (45% versus 24%), constipation (48% versus 33%), and alopecia (50% versus 36%) with the doublet versus the triplet regimen. Grade ≥3 neutropenia was more frequent with the triplet (33%) versus the doublet regimen (25%). More patients in the doublet group required dose modifications (53% versus 39% in the triplet group). Of the 21 LABC patients with dose modifications in the doublet group, 14 had received the regimen containing docetaxel 100 mg/m^2.

efficacy

ORR in MBC was 80.0% (20/25; 95% CI 59.3 − 93.2), with one complete response and 19 partial responses (Table 3). The median PFS was 13.8 months (range, 1.6 − 33.5). Among LABC patients, the pCR (ypT0/is, ypN0) rate was 60.3% (44/73; 95% CI 48.1 − 71.5), with pCR observed in 60.0% (24/40) and 60.6% (20/33) of patients administered the doublet and triplet regimens, respectively (Table 3). pCR rates by patient subgroups are

Table 2. Most common any-grade adverse events (those occurring in >30% of patients in any group) and grade ≥3 adverse events (those occurring in >5% of patients in any group)

All-grade adverse event, *n* (%)	MBC (*n* = 25)	LABC (*n* = 73)		
		Doublet (*n* = 40)	Triplet (*n* = 33)	Total (*n* = 73)
Neutropenia	19 (76)	12 (30)	13 (39)	25 (34)
Asthenia	18 (72)	25 (63)	20 (61)	45 (62)
Thrombocytopenia	16 (64)	10 (25)	8 (24)	18 (25)
Epistaxis	14 (56)	21 (53)	19 (58)	40 (55)
Leukopenia	13 (52)	3 (8)	3 (9)	6 (8)
Alopecia	12 (48)	20 (50)	12 (36)	32 (44)
Stomatitis	12 (48)	4 (10)	5 (15)	9 (12)
Arthralgia	11 (44)	9 (23)	3 (9)	12 (16)
Nausea	11 (44)	16 (40)	16 (48)	32 (44)
Cough	10 (40)	4 (10)	3 (9)	7 (10)
Diarrhea	10 (40)	12 (30)	18 (55)	30 (41)
Back pain	9 (36)	6 (15)	3 (9)	9 (12)
Dysgeusia	9 (36)	19 (48)	13 (39)	32 (44)
Dyspnea	9 (36)	4 (10)	1 (3)	5 (7)
Lymphopenia	9 (36)	3 (8)	4 (12)	7 (10)
Myalgia	9 (36)	18 (45)	8 (24)	26 (36)
Nasopharyngitis	9 (36)	7 (18)	1 (3)	8 (11)
Vomiting	9 (36)	11 (28)	11 (33)	22 (30)
Constipation	8 (32)	19 (48)	11 (33)	30 (41)
Increased lacrimation	8 (32)	15 (38)	16 (48)	31 (42)
Headache	8 (32)	12 (30)	11 (33)	23 (32)
Mucosal inflammation	8 (32)	21 (53)	15 (45)	36 (49)
Peripheral neuropathy	8 (32)	8 (20)	5 (15)	13 (18)
Pyrexia	8 (32)	8 (20)	11 (33)	19 (26)
Dry mouth	7 (28)	14 (35)	10 (30)	24 (33)
Rash	3 (12)	8 (20)	11 (33)	19 (26)
Grade ≥3 adverse event, *n* (%)				
Neutropenia	18 (72)	10 (25)	11 (33)	21 (29)
Leukopenia	11 (44)	1 (3)	0 (0)	1 (1)
Thrombocytopenia	6 (24)	6 (15)	3 (9)	9 (12)
Asthenia	5 (20)	4 (10)	2 (6)	6 (8)
Febrile neutropenia	3 (12)	1 (3)	2 (6)	3 (4)
Lymphopenia	3 (12)	2 (5)	0 (0)	2 (3)
Increased gamma-glutamyltransferase	3 (12)	1 (3)	0 (0)	1 (1)
Anemia	2 (8)	1 (3)	1 (3)	2 (3)
Hepatocellular injury	2 (8)	0 (0)	1 (3)	1 (1)
Increased aspartate aminotransferase	1 (4)	3 (8)	1 (3)	4 (5)
Increased alanine aminotransferase	1 (4)	6 (15)	5 (15)	11 (15)
Diarrhea	0 (0)	0 (0)	2 (6)	2 (3)

LABC, locally advanced breast cancer; MBC, metastatic breast cancer.

summarized in Table 3. pCR rates were numerically higher in patients with estrogen receptor (ER)-negative/progesterone receptor (PR)-negative tumors (74.2%, 23/31) versus ER-positive and/or PR-positive tumors (48.7%, 19/39). Exploratory biomarker analyses are described in supplementary Biomarker Analysis, available at *Annals of Oncology* online.

pharmacokinetics

Pharmacokinetic analyses indicated low levels of plasma DM1, no accumulation, and a low risk of drug–drug interaction between T-DM1 and docetaxel (supplementary Pharmacokinetic Analysis, available at *Annals of Oncology* online).

discussion

This phase Ib/IIa study demonstrated that T-DM1 can be combined with docetaxel ± pertuzumab in patients with HER2-positive MBC or LABC. The types of AEs reported were similar to known risks for T-DM1, docetaxel, or pertuzumab with some exceptions. The most common grade ≥3 AEs in MBC and LABC patients were neutropenia, leukopenia, and thrombocytopenia. However, the incidence of grade ≥3 (15%) increased ALT was higher among LABC patients participating in the present study versus a pooled analysis of 884 MBC patients administered single-agent T-DM1 (3%) [16]; rates of grade ≥3 increased AST were similar (LABC, 5% and MBC, 4%). Relative to the

Table 3. Treatment efficacy

MBC ($n = 25$)		
ORR, *n* (%) [95% CI]	20 (80) [59.3 – 93.2]	
CR, *n* (%) [95% CI]	1 (4) [0.1 – 20.4]	
PR, *n* (%) [95% CI]	19 (76) [54.9 – 90.6]	
SD, *n* (%) [95% CI]	3 (12) [2.5 – 31.2][a]	
PD, *n* (%) [95% CI]	1 (4) [0.1 – 20.4]	
LABC ($n = 73$)		
	Doublet	Triplet
All patients, *n*	40	33
pCR, *n* (%) [95% CI]	24 (60.0) [43.3 – 75.1]	20 (60.6) [42.1 – 77.1]
Patients who completed six treatment cycles, *n*	36	25
pCR, *n* (%)	23 (63.9)	17 (68.0)
Patients who completed less than six treatment cycles, *n*	4	8
pCR, *n* (%)	1 (25.0)	3 (37.5)
Patients with ER-positive and/or PR-positive tumors, *n*	24	15
pCR, *n* (%)	13 (54.2)	6 (40.0)
Patients with ER-negative and PR-negative tumors, *n*	14	17
pCR, *n* (%)	10 (71.4)	13 (76.5)
Patients with tumors ≤5 cm, *n*	32	24
pCR, *n* (%)	20 (62.5)	15 (62.5)
Patients with tumors >5 cm, *n*	8	9
pCR, *n* (%)	4 (50.0)	5 (55.6)

[a]Duration of stable disease was defined as the time from baseline assessment to PD or last assessed stable disease. One patient had PD after 10.6 months of stable disease. The other two patients did not have PD on study. Time from baseline assessment to last on-study stable disease was 14.9 and 26.9 months.
CI, confidence interval; CR, complete response; ER, estrogen receptor; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; ORR, objective response rate; pCR, pathologic complete response; PD, progressive disease; PR, progesterone receptor; SD, standard deviation.

pooled safety data (12%), grade ≥3 thrombocytopenia occurred at increased frequency in the MBC cohort (24%) and similar frequency in the LABC cohort (12%). In the present study, only one patient experienced grade ≥3 hemorrhage (grade 3 epistaxis) versus 2% of patients in the pooled analysis [16]. AEs associated with skin toxicity are a concern with docetaxel [17]; while most of these AEs were low grade, there were more serious AEs related to skin toxicities, particularly with docetaxel 100 mg/m^2, in this study than would be expected with single-agent T-DM1.

It is hypothesized that the increased occurrence and severity of some AEs in the present study were the result of combination therapy exacerbating AEs that occur at relatively lower frequencies when these treatments are used independently. Overall, safety was similar for patients irrespective of whether they received primary G-CSF; although numerically fewer patients receiving G-CSF had grade ≥3 AEs or AEs leading to dose modification, there were too few patients to conclude an absolute need for G-CSF.

Antitumor activity was seen with the use of doublet and triplet regimens in MBC and LABC. In MBC patients who had received a median of five prior systemic therapies in the metastatic setting, an ORR of 80.0% and median PFS of 13.8 months were seen. Among all LABC participants, the pCR (ypT0/is, ypN0) rate was 60.3%. No definitive conclusions about the effect of adding pertuzumab to T-DM1 + docetaxel can be drawn, owing to the nonrandomized and nonstratified nature of the trial and the relatively small sample size. The pharmacokinetic characteristics of T-DM1 2.4–3.6 mg/kg were consistent with historical single-agent data [18], with no evidence of drug–drug interactions with docetaxel.

In summary, this study suggests that T-DM1 can be combined with docetaxel ± pertuzumab. While higher severe/serious AE rates were observed for these combination regimens relative to what has been seen in prior studies with single-agent T-DM1 [16], some of the increase is likely a result of overlapping toxicities. The combination regimens appeared efficacious, with an ORR of 80.0% in MBC and a pCR rate of 60.3% in LABC. The phase III Marianne trial found non-inferiority between T-DM1 and T-DM1 plus pertuzumab compared with trastuzumab plus taxane, and therefore found that the addition of pertuzumab to T-DM1 did not improve PFS in the first-line treatment of HER2-positive MBC [19]. In view of the results from Marianne, the role of pertuzumab in combination with T-DM1 is unclear. Single-agent T-DM1 is well tolerated and the duration of response in those patients whose tumors responded to T-DM1 is notable [19]. The reasons for a lack of response to T-DM1 in some tumors are not clear, but one of the factors playing a role in this could be tumor heterogeneity in HER2 expression. The development of regimens that combine T-DM1 with chemotherapy is a matter of debate. However, a therapeutic regimen of T-DM1 in combination with chemotherapy, as in the current study, could potentially be effective in these types of tumors, albeit with potentially increased toxicity. Additional studies of T-DM1 in combination with chemotherapy and with other therapies are ongoing.

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disclosure

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