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Trastuzumab Emtansine: A Unique Antibody-Drug Conjugate in Development for Human Epidermal Growth Factor Receptor 2–Positive Cancer

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Abstract

Trastuzumab emtansine (T-DM1) is a human epidermal growth factor receptor (HER2)–targeted antibody-drug conjugate, composed of trastuzumab, a stable thioether linker, and the potent cytotoxic agent DM1 (derivative of maytansine), in phase III development for HER2-positive cancer. Extensive analysis of T-DM1 in preclinical studies has shown that T-DM1 combines the distinct mechanisms of action of both DM1 and trastuzumab, and has antitumor activity in trastuzumab- and lapatinib-refractory experimental models. Clinically, T-DM1 has a consistent pharmacokinetics profile and minimal systemic exposure to free DM1, with no evidence of DM1 accumulation following repeated T-DM1 doses. Although a few covariates were shown to affect interindividual variability in T-DM1 exposure and clearance in population-pharmacokinetics analyses, the magnitude of their effect on T-DM1 exposure was not clinically relevant. Phase I and phase II clinical trials of T-DM1 as a single agent and in combination with paclitaxel, docetaxel, and pertuzumab have shown clinical activity and a favorable safety profile in patients with HER2-positive metastatic breast cancer. Two randomized phase III trials of T-DM1 are recruiting patients: EMILIA (NCT00829166) is evaluating T-DM1 compared with lapatinib plus capecitabine, and MARIANNE (NCT01120184) is evaluating T-DM1 plus placebo versus T-DM1 plus pertuzumab versus trastuzumab plus a taxane. Additional combinations of T-DM1 (for example, with GDC-0941) and additional disease settings (early-stage HER2-positive breast cancer) are also under investigation. Data from the phase III trials and other studies of T-DM1–containing agents are eagerly awaited. *Clin Cancer Res; 17(20); 6437–47. ©2011 AACR.*

Introduction

Chemotherapies are limited by systemic toxicity and lack of tumor selectivity, and thus they have a narrow therapeutic index. Antibody-drug conjugates (ADCs) are a therapeutic class comprising a tumor antigen-specific targeting antibody linked to a cytotoxic drug. ADCs may improve the therapeutic index because they are designed to specifically deliver cytotoxic agents to tumor cells and limit collateral damage to normal cells. The concept of ADCs has existed for many years; however, it is only recently that advances in this technology have resulted in clinically useful therapeutic agents. A review of the key challenges in the development of these agents and ADCs currently in clinical development is included in this *CCR Focus* section (1). To date, the only ADC to have received approval from the U.S. Food and Drug Administration (FDA) is gemtuzumab ozogamicin (Mylotarg), which was approved for the treatment of relapsed CD33-positive acute myeloid leukemia in older patients. However, it was recently withdrawn from use because postmarketing studies showed a lack of clinical benefit [reviewed in this *CCR Focus* section by Ricart (2)]. A number of other ADCs, however, are currently in clinical development for hematological malignancies. These include antibodies conjugated to microtubule polymerization inhibitors (3, 4), DNA intercalaters (2), and protein synthesis inhibitors (i.e., protein toxins; ref. 5). Antibody-radionuclide conjugates have also been approved for the treatment of hematologic malignancies (6). Trastuzumab emtansine (T-DM1), a human epidermal growth factor receptor (HER2)–targeted ADC composed of the microtubule polymerization inhibitor DM1 (derivative of maytansine) linked to trastuzumab, is in phase III development for HER2-positive breast cancer. As such, it is the only ADC in late-stage clinical development for a solid tumor.

Breast cancer accounts for ~28% of all new cases of cancer in women (7), and 15% to 25% of these new cases contain gene amplifications or protein overexpression of HER2 (8–10). HER2-positive disease is an aggressive form of breast cancer that typically is associated with a higher risk of distant recurrence with a shorter time to relapse, lower disease-free and overall survival rates, and greater therapeutic resistance compared with HER2-normal disease (8–14). Despite treatment advances, including the humanized anti-HER2 antibody trastuzumab and the dual epidermal growth factor receptor (EGFR)/HER2 tyrosine kinase

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inhibitor lapatinib, HER2-positive breast cancer will eventually progress in most patients, highlighting the need for novel, alternative therapies. In addition, currently available HER2-targeted therapies are rarely given as monotherapy but are generally given in combination with other agents (e.g., chemotherapy or hormonal therapy). Because toxicities associated with chemotherapy can be a significant source of comorbidity for patients with cancer, ADCs are a promising therapeutic approach for this patient population.

Toxicity to normal cells can occur by both target-dependent and target-independent mechanisms. Perhaps the most important consideration for target-independent cytotoxicity in an ADC is the chemical nature of the linker moiety. ADCs containing maytansines were originally designed with linkers that contained disulfide bonds (15, 16). This strategy assumed that once the ADC engaged the cell surface receptor, the complex between the ADC and the receptor would be internalized and trafficked to an endocytic compartment that was sufficiently reducing to release the maytansine. Experimental data disproved this hypothesis when it was shown that the oxidizing potential of endosomes and lysosomes limits the intracellular cleavage of disulfide-containing ADCs (17). These and other observations regarding improved pharmacokinetics and tolerability guided the choice of incorporating a thioether linker containing a cyclohexane carboxylate spacer into the trastuzumab ADC (18). Additional studies indicated that once T-DM1 is internalized, proteolytic digestion of the conjugate occurs, releasing the active metabolite lysine-N^{ε}-4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (MCC)-DM1. Because it is a zwitterion, lysine-N^{ε}-MCC-DM1 does not readily cross the plasma membrane of neighboring normal cells. This likely contributes to the overall safety profile of T-DM1 (19).

The nonclinical activity of T-DM1 was initially assessed in experimental models that were refractory to trastuzumab or lapatinib (18, 20, 21), because trastuzumab and lapatinib are established for the treatment of HER2-postitive metastatic breast cancer (MBC). To date, meaningful antitumor activity has been observed in all of these models. To gain further insight into these findings, we conducted studies to assess the activity of trastuzumab relative to T-DM1. Multiple lines of evidence, including the direct release of adenylate kinase, PARP cleavage, caspase 3/7 activation, and cell cycle analysis, indicate that T-DM1 induces a direct cytotoxic effect against cells that overexpress HER2 (18). The mechanisms of action for trastuzumab include inhibition of the HER3/phosphoinositide 3-kinases (PI3K)/AKT signaling pathway, inhibition of HER2 shedding, and Fcγ receptor–mediated engagement of immune cells, which may result in antibody-dependent cellular cytotoxicity (22). Of importance, T-DM1 retains these same mechanisms of action of unconjugated trastuzumab (20).

Clinical Efficacy of Single-Agent T-DM1

T-DM1 was initially evaluated as a single agent in a dose escalation phase I trial in patients with HER2-positive MBC who previously received a trastuzumab-containing chemotherapy regimen. T-DM1 was given at various doses on a weekly (23) or every 3 weeks schedule (ref. 24; Table 1). The maximum tolerated dose (MTD) was 3.6 mg/kg every 3 weeks, based on the dose-limiting toxicity (DLT) of grade 4 thrombocytopenia at 4.8 mg/kg every 3 weeks. In a group of 15 patients receiving 3.6 mg/kg every 3 weeks, the clinical benefit rate (CBR; objective response rate [ORR] plus stable disease at 6 months) was 73% (ref. 24; Table 1). Interim results for patients receiving weekly T-DM1 showed 9 partial responses (PR; 8 were confirmed) in 15 patients evaluable for response (ORR 53%; ref. 23). On the basis of its clinical activity and dosing convenience, T-DM1 3.6 mg/kg every 3 weeks was selected for further clinical development.

Two large multicenter, single-arm, phase II studies evaluating single-agent T-DM1 3.6 mg/kg every 3 weeks in pretreated patients with locally assessed HER2-positive MBC following progression on previous chemotherapy and HER2-directed therapy have been completed (refs. 25, 26; Table 1). In the first study, the ORR by independent review was 25.9% [95% confidence interval (CI), 18.4–34.4%] and 37.5% by investigator assessment, including 4 complete responses (CR; see Table 1). The median progression-free survival (PFS) was 4.6 months (95% CI, 3.9–8.6 months; ref. 25). In the second study, patients had been previously treated with an anthracycline, a taxane, and capecitabine, as well as lapatinib and trastuzumab with a median of 8.5 agents (range: 5–19) in all settings and 7.0 agents (range: 3–17) for metastatic disease (26). An interim report indicated that the ORR was 34.5% (all PRs; 95% CI, 26.1–43.9%) and the CBR was 48.2% (95% CI, 38.8–57.9%) by independent review. The median PFS was 6.9 months (95% CI, 4.2–8.4 months; Table 1).

To examine the relationship between HER2-positive status and response to T-DM1 (Fig. 1) and identify associated biomarkers, LoRusso and colleagues (28) performed a retrospective analysis using archival tumor tissue from these 2 phase II studies. Confirmed HER2-positive status [immunohistochemistry (IHC) 3+ or fluorescence *in situ* hybridization (FISH)+ by central retesting] was associated with a higher ORR than HER2-normal status (TDM4258g: 33.8% in the 74 confirmed HER2-positive patients vs. 4.8% in the 21 HER2-normal patients; TDM4374g: 40.8% in the 76 confirmed HER2-positive patients vs. 20.0% in the 15 HER2-normal patients). Analysis by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) showed that levels of *HER2* mRNA expression equal to or above the median were also associated with a higher ORR than levels below the median [TDM4258g: 36.0% ($n = 25$) vs. 28.0% ($n = 25$); TDM4374g: 50.0% ($n = 26$) vs. 33.3% ($n = 39$); Table 2]. These results support the specificity of the effect of T-DM1 on HER2-positive MBC. They further suggest that tumor response to T-DM1 may be dependent on HER2 quantity, even among tumors that are already deemed HER2-positive by standard methods. It is important to note, however, that these data are from exploratory

Table 1. Efficacy data from clinical trials of single-agent T-DM1 every 3 weeks in HER2-positive MBC

Trial and reference	Study design and T-DM1 dose	Study population	Patients, *n*	ORR, %	CR, %	CBR[c], %	Median DOR (months)	Median PFS (months)
TDM3569g (24)	Phase I single arm; 0.3–4.8 mg/kg[a]	Previously treated with chemotherapy and progressed on T	24	25.0[b]	0	73	NR	NR
TDM4258g (25)	Phase II single arm; 3.6 mg/kg	Previously treated with chemotherapy and progressed on HER2-targeted therapy	112	37.5 (25.9)	3.6 (0)	NR	9.4 (6.2–NE)	4.6 (4.6)
TDM4374g (26)	Phase II single arm; 3.6 mg/kg	Previously treated with anthracycline, a taxane, and capecitabine, plus lapatinib and T for MBC	110	32.7 (34.5)	4.5 (0)	46.4 (48.2)	NR (7.2)	NR (6.9)
TDM4450g (27)	Phase II randomized; T-DM1 3.6 mg/kg vs. T + D[d]	Recurrent, locally advanced breast cancer or MBC, with no prior chemotherapy for metastatic disease	T-DM1, $n = 67$	47.8	4.5	55.2	NR	NR
			T + D, $n = 70$	41.4	1.4	57.1	NR	NR

Data shown are by investigator assessment, with independent review results in parentheses (where available).
Abbreviations: CBR, clinical benefit rate; CR, complete response; D, docetaxel; DOR, duration of response; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; NE, not estimable; NR, not reported; ORR, objective response rate; PFS, progression-free survival; T, trastuzumab; T-DM1, trastuzumab emtansine.
[a]Efficacy outcomes reported are for patients treated at the MTD (3.6 mg/kg every 3 weeks; $n = 15$).
[b]Confirmed ORR among patients with measurable disease who were treated at the MTD ($n = 9$) was 44%.
[c]Defined as CR, PR, or stable disease $\geq$ 6 months.
[d]Trastuzumab (8 mg/kg loading dose; 6 mg/kg every 3 weeks) + docetaxel (75 or 100 mg/m^2 every 3 weeks).

analyses in a small number of patients; additional studies are necessary to adequately test these hypotheses.

Patients with wild-type PI3K mutation status and normal PTEN expression appeared to achieve a better response in TDM4258g. This association, however, was not observed in patients in TDM4374g (see Table 2). Thus, although no consistent trend in T-DM1 activity was observed in patients with activating PI3K mutations and/or decreased PTEN expression, it should be noted that this analysis was limited because of the exclusive use of archival tissue from the patients' initial diagnoses (28).

A randomized, open-label phase II study (TDM4450g; ref. 29) is investigating single-agent T-DM1 compared with trastuzumab plus docetaxel in the first-line treatment of HER2-positive recurrent, locally advanced breast cancer or MBC (ref. 27; Table 1). Enrollment was completed in December 2009, and safety and ORR data as of April 2, 2010, were included in an interim analysis. Thirteen patients in the T-DM1 arm (19.4%) and 18 patients in the trastuzumab-plus-docetaxel arm (25.7%) had previously received trastuzumab. The ORR by investigator assessment was 47.8% ($n = 32$; 95% CI, 35.4–60.3%) for T-DM1 and 41.4% ($n = 29$; 95% CI, 30.2–53.8%) for trastuzumab plus docetaxel. There were 3 CRs (4.5%) and 1 CR (1.4%), respectively. Final analysis of the primary endpoint, PFS, is eagerly awaited.

Clinical Safety of Single-Agent T-DM1

The most common adverse events (AE) of all grades for T-DM1 seen to date include fatigue (range: 37.5–65.2%), anemia (10.4–29.2%), nausea (25.0–50.9%), and hypokalemia (4.2–24.1%). Among these, the incidence of grade 3 or 4 AEs was <5%, with the exception of grade 3 or 4 hypokalemia in one study (TDM4258g, 8.9%; refs. 24–27; Table 3). T-DM1 also had a favorable safety profile relative to standard-of-care treatment in the first-line setting (27), with fewer grade 3 or 4 AEs (37% with T-DM1 vs. 75% with trastuzumab plus docetaxel). In addition, many of the AEs associated with traditional chemotherapies (e.g., diarrhea, neutropenia, rash, neuropathy, and alopecia) were observed at much lower rates with T-DM1 treatment compared with trastuzumab plus docetaxel (see Table 3; ref. 27).

Thrombocytopenia was one of the most frequently reported grade 3 or 4 laboratory abnormalities across the phase II studies of T-DM1 (range: 7.3–8.0%; refs. 25–27). These reductions in platelet count were generally reversible

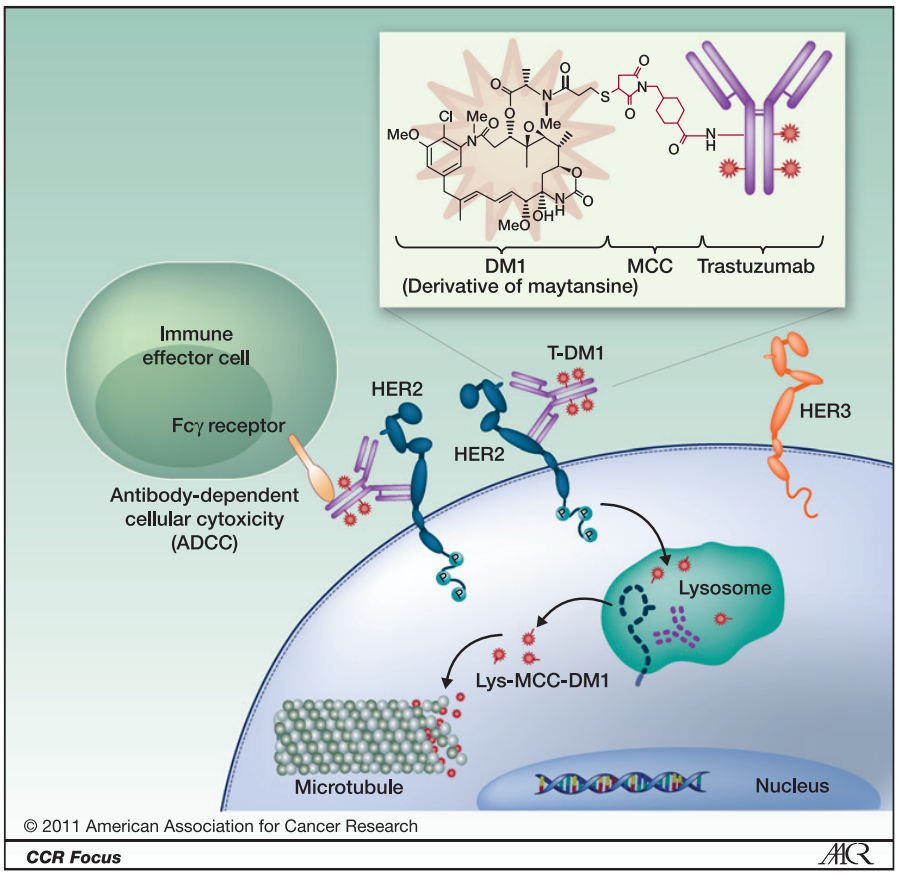

Figure 1. Structure of T-DM1 and mechanisms of action. After T-DM1 binds HER2, the HER2/T-DM1 complex undergoes internalization, followed by lysosomal degradation. This process results in the intracellular release of DM1-containing catabolites that bind to tubulin and prevent microtubule polymerization as well as suppress microtubule dynamic instability. T-DM1 has also been shown to retain mechanisms of action of trastuzumab, including disruption of the HER3/PI3K/AKT signaling pathway and Fcγ receptor–mediated engagement of immune effector cells, which leads to antibody-dependent cellular cytotoxicity.

(24, 30). Thrombocytopenia was observed as early as 1 day after T-DM1 treatment. In most patients, platelet counts reached a nadir by day 8 and recovered by day 18 (24, 30). This pattern persisted even after repeated dosing, and it appears to be distinguishable from immune-mediated thrombocytopenia (24, 30). Thrombocytopenia was not typically associated with clinically meaningful bleeding events. For example, in the first phase II study, 9 patients had grade 3 or 4 thrombocytopenia, but only 1 patient had a concurrent grade 3 bleeding event (i.e., epistaxis;

Table 2. T-DM1 activity in efficacy-evaluable patients by *HER2* qRT-PCR level, PI3K mutation status, and PTEN expression level (28)

	TDM4374g		TDM4258g	
	n	**ORR, % (95% CI)**	***n***	**ORR, % (95% CI)**
***HER2* qRT-PCR level**				
≥Median[a]	26	50.0 (29.9–70.1)	25	36.0 (18.5–56.9)
<Median	39	33.3 (19.7–50.0)	25	28.0 (12.1–47.5)
PI3K mutation[b]				
Wild-type	48	35.4 (22.2–50.0)	42	35.7 (21.6–51.9)
Mutant	11	36.4 (13.5–66.7)	9	22.2 (4.1–55.8)
PTEN by IHC[b]				
Normal	38	36.8 (22.6–53.5)	30	36.7 (20.5–56.0)
Decreased	3	33.3	6	16.7 (0.9–59.8)

[a]Median was based on TDM4258g data.
[b]FISH+ and/or IHC3+.

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