Trastuzumab Emtansine: A Novel Antibody–Drug Conjugate for HER2-Positive Breast Cancer

Ian Krop and Eric P. Winer

Abstract

Trastuzumab emtansine (T-DM1) is a novel HER2-directed antibody–drug conjugate. T-DM1 consists of the potent antimicrotubule agent DM1, linked via a noncleavable linker to the HER2-specific monoclonal antibody trastuzumab. Preclinical studies demonstrate that T-DM1 has dual mechanisms of action: selective delivery of DM1 to the HER2-positive (HER2+) tumor cell combined with trastuzumab’s activation of antibody-dependent cell-mediated cytotoxicity and inhibition of HER2-mediated signal transduction. In phase II studies, T-DM1 was active in patients with trastuzumab- and lapatinib-refractory metastatic breast cancer and led to improved progression-free survival compared with the combination of trastuzumab and docetaxel in the first-line setting. In a recent phase III trial in patients with metastatic breast cancer who previously received trastuzumab and a taxane, T-DM1 resulted in improved progression-free and overall survival compared with capecitabine and lapatinib. T-DM1 is associated with a favorable toxicity profile; reversible thrombocytopenia and hepatic transaminase elevations are the only grade ≥3 adverse event present in 5% or more of patients. Alopecia, peripheral neuropathy, and neutropenia are distinctly uncommon. On the basis of its improved efficacy and toxicity compared with capecitabine/lapatinib, T-DM1 should be considered the standard for patients with HER2+ metastatic breast cancer who have previously progressed on trastuzumab and a taxane. Results from additional randomized studies in metastatic breast cancer are pending, and trials in the (neo)adjuvant setting are being initiated. Clin Cancer Res; 20(1): 15–20. ©2013 AACR.

Introduction

Amplification of the HER2 gene occurs in approximately 20% of primary breast cancers and leads to marked overexpression of the HER2 protein on the cell surface—typically more than 1 million copies per cell—and constitutive activation of HER2 signaling (1, 2). These cancers frequently have a high proliferative rate and are associated with poor clinical outcomes in the absence of systemic therapy. The development of a specific, HER2-targeted therapy, the monoclonal antibody trastuzumab, led to marked improvements in survival for patients with HER2-positive (HER2+) cancers in the adjuvant and advanced disease settings and confirmed the clinical utility of HER2 as a therapeutic target (3, 4). The results with trastuzumab led to the development of other anti-HER2 agents, including the HER1/HER2 kinase inhibitor lapatinib and another HER2-specific monoclonal antibody, pertuzumab, both of which have demonstrated efficacy in patients with advanced HER2+ breast cancer (5, 6). However, none of these agents are uniformly effective. In the metastatic setting, not all cancers respond, and those that do almost inevitably develop resistance. There is clearly a need for additional therapies for HER2+ cancers.

It is noteworthy that while trastuzumab, pertuzumab, and lapatinib are highly targeted drugs, their activity as single agents is relatively modest and in practice all are typically used in combination with conventional chemotherapy. Although this approach leverages the synergy these agents demonstrate when combined with chemotherapy, it also means that patients treated with combination regimens are subject to the toxicities inherent in conventional cytotoxic agents. An approach that potentially avoids the toxicity of targeted therapy/chemotherapy combinations is that of an antibody–drug conjugate (ADC). ADCs consist of a cytotoxic agent linked to a tumor antigen–specific monoclonal antibody. The goal of an ADC is to specifically deliver the cytotoxic agent to tumor cells while minimizing toxicity caused by the cytotoxic agent’s interaction with normal tissues. Such an approach thus has the potential to meaningfully improve the therapeutic index of a cytotoxic agent. In some cases, ADC can also exploit the targeted antitumor effects of the monoclonal antibody, depending on the antibody used.

Trastuzumab emtansine (T-DM1) is a novel ADC developed to treat HER2+ cancers. T-DM1 consists of the cytotoxic agent DM1 (derivative of maytansine) linked to trastuzumab. DM1 is a microtubule polymerization inhibitor that was selected for use in T-DM1 because of its high

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potency. In vitro studies demonstrate that on a molar basis across a range of cancer cell lines, DM1 is 25- to 270-fold more potent than paclitaxel and 180- to 4,000-fold more potent than doxorubicin (7). DM1 is linked to lysine residues of trastuzumab via a nonreducible thioether linker (4-[N-maleimidomethyl] cyclohexane-1-carboxylate, or MCC). On average, there are 3.5 DM1 molecules per trastuzumab antibody. T-DM1 was the first ADC in clinical development to use a noncleavable MCC linker. In vivo studies suggested that this type of linker was associated with less toxicity than the cleavable disulfide linkers that have been used in previous ADC candidates (8), presumably because the greater stability of the noncleavable linker minimized the amount of free DM1 released into the circulation.

Once T-DM1 binds to the extracellular domain of HER2, the complex is internalized into the cell, where the antibody is degraded by proteases, releasing the active metabolite, lysine-N\text{-}MCC-DM1, into the cytoplasm (Fig. 1; ref. 9). Because this metabolite is a charged molecule, it is relatively membrane impermeable, reducing the possibility that the DM1 could enter a neighboring cell, thus further limiting the potential for nonspecific toxicity.

In addition to its ability to deliver DM1 selectively to tumor cells, T-DM1 retains the effector functions of trastuzumab, including inhibition of HER2-mediated signal transduction and activation of antibody-dependent cell-mediated cytotoxicity (ADCC; ref. 7). In preclinical efficacy studies, T-DM1 induces a cell-cycle arrest and apoptosis in HER2\textsuperscript{+} cancer cells but has little effect on HER2-negative cells (8). T-DM1 demonstrates activity in both trastuzumab- and lapatinib-resistant HER2\textsuperscript{+} cancer models (7).

**Clinical Efficacy**

T-DM1 was initially evaluated as a single agent in a phase I dose-escalation study in patients with trastuzumab-refractory HER2\textsuperscript{+} advanced breast cancer. Both weekly and every-3-week schedules were tested. In the every-3-week schedule, the dose-limiting toxicity (DLT) was transient thrombocytopenia at 4.8 mg/kg and the maximum-tolerated dose (MTD) was 3.6 mg/kg (10). In the 9 patients with measurable disease treated at the MTD, the objective response rate (ORR) was 44% (10). In the weekly schedule, the MTD was 2.4 mg/kg and the ORR in the 15 response-evaluable patients treated at the MTD was 40% (11). Although both schedules were clearly active, the every-3-week schedule was used in almost all subsequent studies, largely because of the convenience for patients of less frequent dosing.

T-DM1 monotherapy was further evaluated in two single-arm phase II studies. The first included 112 patients whose cancer had progressed on at least one line of trastuzumab-based therapy. In this study, the ORR was 26% (12). Interestingly, the ORR was similar in the subset of patients who had received prior lapatinib in addition to trastuzumab (24%; ref. 12), suggesting that resistance to lapatinib did not compromise the efficacy of T-DM1. To more definitively address that question, the second phase II study enrolled a uniformly defined population who had previously received

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**Figure 1.** Mechanism of action of T-DM1. T-DM1 binds to the extracellular domain of HER2, followed by internalization of the HER2/T-DM1 complex into lysosomes. The complex is then proteolytically degraded, releasing lysine-MCC-DM1 into the cytoplasm, where it inhibits microtubule polymerization. T-DM1 also retains effector functions of trastuzumab, including Fc\textgamma
 receptor-mediated activation of ADCC and inhibition of HER2-mediated signal transduction, which may contribute to the efficacy of T-DM1. Adapted with permission from LoRusso et al. (26).
all commonly used therapies for HER2+ cancer (trastuzumab, lapatinib, taxane, anthracycline, and capecitabine). Patients also were required to have progressed on at least two HER2-directed agents in the metastatic setting. In this study of 110 patients, in which the median number of agents received in the metastatic setting was seven, the ORR was 35% and the progression-free survival (PFS) duration was 6.9 months, confirming that single-agent T-DM1 did have substantial activity even in patients whose cancer had progressed on multiple other HER2-targeted agents (13).

T-DM1 has recently been evaluated in several randomized studies. The largest reported to date is EMILIA, a phase III international registration study in patients with locally advanced or metastatic, centrally confirmed HER2+ breast cancer. Participants had previously received a taxane and trastuzumab and had progressed on their most recent treatment in the metastatic or locally advanced setting or within 6 months of completion of adjuvant trastuzumab for early-stage disease. The primary endpoints of the study were PFS and overall survival (OS). A total of 991 patients were randomized 1:1 to T-DM1 (3.6 mg/kg every 3 weeks) or docetaxel (75 or 100 mg/m²) with trastuzumab. Median PFS (the primary endpoint of the study) was significantly longer in those patients receiving TDM1 compared with those on docetaxel/trastuzumab (14.2 vs. 9.2 months; HR, 0.59; 95% CI, 0.36–0.97; P = 0.035; ref. 15). A quality-of-life analysis using the Trial Outcome Index—Physical/Functional/Breast (TOI–PFB) subset of the FACT-B instrument also favored T-DM1 (15).

In addition to EMILIA, two randomized phase III studies involving T-DM1 have completed enrollment and are awaiting analysis. The MARIANNE study is seeking to confirm the benefit of T-DM1 in the first-line setting seen in TDM4450g. In MARIANNE, patients were randomized to a taxane combined with trastuzumab, T-DM1 monotherapy, or T-DM1 combined with pertuzumab. The TH3RESA study is evaluating the role of T-DM1 in patients who have received prior trastuzumab, lapatinib, and chemotherapy. The goal is to validate the observations from the prior single-arm studies indicating that T-DM1 is effective even in cancers that have progressed on multiple prior HER2-directed agents. In TH3RESA, patients were randomized 2:1 to either single-agent T-DM1 or a treatment of physician’s choice. The available clinical efficacy data on single-agent T-DM1 are summarized in Table 1.

### Safety of T-DM1

In general, T-DM1 has been well tolerated with a relatively low rate of clinically significant adverse events across the clinical studies. In a pooled analysis of toxicity data from 882 patients treated on seven clinical trials with single-agent T-DM1, the most commonly reported adverse events were lymphopenia (74%), neutropenia (68%), palmar-plantar erythrodysesthesia (66%), and fatigue (47%). The incidence of grade 3 or 4 hematologic toxicities was generally low, except for lymphopenia (20%) and neutropenia (11%).

### Table 1. Efficacy of single-agent T-DM1 in phase II and III clinical trials of patients with HER2+ advanced breast cancer

<table>
<thead>
<tr>
<th>Study type</th>
<th>TDM4258g (12)</th>
<th>TDM4374g (13)</th>
<th>TDM4450g (15)</th>
<th>EMILIA (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient #</td>
<td>112</td>
<td>110</td>
<td>67</td>
<td>495</td>
</tr>
<tr>
<td>Population</td>
<td>Prior T</td>
<td>Prior T, L, chemo</td>
<td>No prior Tx for MBC</td>
<td>Prior T + taxane</td>
</tr>
<tr>
<td>Treatment</td>
<td>T-DM1</td>
<td>T-DM1</td>
<td>Docetaxel/T</td>
<td>T-DM1</td>
</tr>
<tr>
<td>Median PFS</td>
<td>4.6 mo</td>
<td>6.9 mo</td>
<td>14.2 mo</td>
<td>9.2 mo</td>
</tr>
<tr>
<td>Median OS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>30.9 mo</td>
</tr>
<tr>
<td>ORR</td>
<td>25.9%</td>
<td>34.5%</td>
<td>64.2%</td>
<td>58.0%</td>
</tr>
<tr>
<td>DOR</td>
<td>NE</td>
<td>7.2 mo</td>
<td>NE</td>
<td>9.5 mo</td>
</tr>
<tr>
<td>ORR (confirmed HER2+)</td>
<td>33.8%</td>
<td>41.3%</td>
<td>NR</td>
<td>NA*</td>
</tr>
</tbody>
</table>

*All patients on EMILIA had centrally confirmed HER2+ cancers.

NOTE: T-DM1 was given at a dosage of 3.6 mg/kg every 3 weeks in all studies. Abbreviations: Cape, capecitabine; Chemo, chemotherapy (prior anthracycline, taxane, and capectabine required for TDM4374g); DOR, duration of response; L, lapatinib; MBC, metastatic breast cancer; NA, not applicable; NE, not estimable; NR, not reported; T, trastuzumab; Tx, therapy.
Thrombocytopenia is the most common grade ≥3 adverse event observed in patients treated with single-agent T-DM1 (Table 2). T-DM1–associated thrombocytopenia is usually rapidly reversible: Platelet counts can begin to decline within 24 hours of dosing, typically reach a nadir around day 8, and recover by day 15 (10). In approximately 20% of patients, platelet counts do not completely recover to baseline after repeated dosing (16). However, with appropriate dose modifications, those patients typically can continue T-DM1 therapy. Importantly, T-DM1–induced thrombocytopenia is generally not associated with clinically significant bleeding events. In the 882 patients in the pooled safety database, the rate of grade ≥3 hemorrhage was 1.7% (14 grade 3 events and 1 grade 4 event) and there was no temporal association between grade ≥3 hemorrhage and grade ≥3 thrombocytopenia (16). Similarly, in patients receiving T-DM1 in the EMILIA study, the rate of grade ≥3 hemorrhage was low (1.4%) and comparable with that of patients receiving capecitabine/lapatinib (0.8%; ref. 14).

T-DM1 can induce hepatic toxicity. This typically manifests as transient and asymptomatic transaminase elevations; the rate of grade ≥3 elevations is low (≤5%) and does not tend to increase with repeated dosing (16). With appropriate dose modifications, most patients who developed significant transaminase elevations were able to continue T-DM1 treatment. In addition to transaminase elevations, there have been rare cases of biopsy-confirmed nodular regenerative hyperplasia (NRH) seen in patients treated with single-agent T-DM1 (3 cases in the 882-patient safety database; ref. 16). NRH is a rare liver disorder that can lead to noncirrhotic portal hypertension (17). Liver biopsy is the only method to diagnose NRH, and thus biopsy should be considered in any patient receiving T-DM1 who develops signs and/or symptoms of portal hypertension. If the diagnosis of NRH is confirmed, T-DM1 should be discontinued (18).

Because trastuzumab has well-described cardiac toxicity, there has been careful assessment of cardiac function in patients on the clinical studies of T-DM1; typical assessment of left ventricular ejection fraction (LVEF) occurred at least every 12 weeks. In the pooled safety analysis of 882 patients, cardiac adverse events were infrequent (13 events/1.5%), and all but two of the events were grade 1/2 (16). It should be noted that 91% of the patients in this pooled analysis had received prior trastuzumab-based therapy, and thus this population was likely enriched for patients who were less prone to trastuzumab-mediated cardiac toxicity. However, a recent pilot study in which 143 previously untreated patients with early-stage HER2+ breast cancer received an anthracycline followed by approximately 1 year of T-DM1 in the (neo)adjuvant setting demonstrated no prespecified cardiac events (NYHA class III/IV congestive heart failure or cardiac death) and only 4 patients (0.5%) had asymptomatic declines in LVEF to less than 50% (none of which were to <45%; ref. 19).

Pharmacokinetics

In a pooled pharmacokinetic analysis of 288 patients treated on one of four clinical trials with single-agent T-DM1, the pharmacokinetic profile of T-DM1 was consistent across the studies. The half-life of T-DM1 is approximately 3.5 to 4 days and there is no significant accumulation of T-DM1 when it is given in the standard every-3-week schedule. Importantly, the level of free DM1 in the plasma remains extremely low (typically <5 ng/mL) throughout the treatment cycle, which likely plays a role in the favorable toxicity profile of T-DM1. In this pooled analysis, there was no association between T-DM1 exposure and clinical response. Pretreatment residual levels of trastuzumab also did not seem to influence the pharmacokinetic characteristics or clinical efficacy of T-DM1. Antibodies to T-DM1 were detected in 13 of 286 (4.5%) patients, but there was no association between the presence of antibodies and pharmacokinetic parameters or efficacy, so the clinical significance of these antibodies is unclear.

Table 2. Adverse events in a pooled analysis of 882 patients receiving T-DM1

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>All grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>400 (45.4)</td>
<td>27 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>373 (42.3)</td>
<td>9 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>253 (28.7)</td>
<td>5 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>253 (28.7)</td>
<td>73 (8.3)</td>
<td>17 (1.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>225 (25.5)</td>
<td>5 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>205 (23.2)</td>
<td>4 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>203 (23.0)</td>
<td>35 (4.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>202 (22.9)</td>
<td>2 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>195 (22.1)</td>
<td>5 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>183 (20.7)</td>
<td>7 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>179 (20.3)</td>
<td>8 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>172 (19.5)</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>253 (28.7)</td>
<td>73 (8.3)</td>
<td>17 (1.9)</td>
</tr>
<tr>
<td>Increased AST</td>
<td>203 (23.0)</td>
<td>35 (4.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>400 (45.4)</td>
<td>27 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>127 (14.4)</td>
<td>26 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>134 (15.2)</td>
<td>25 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>121 (13.7)</td>
<td>22 (2.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: Adapted from Diéras et al. (16).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Comparison of T-DM1 with Other Agents

The two salient attributes of T-DM1 are its high level of clinical activity and favorable toxicity profile, and both of these characteristics are demonstrated in comparisons between T-DM1 and other standard regimens for HER2+ cancers. In terms of efficacy, T-DM1 demonstrates clear superiority to capecitabine/lapatinib with advantages in both PFS and OS in patients who previously received trastuzumab. In the first line, phase II data show that T-DM1 is associated with improved PFS compared with docetaxel and trastuzumab with data from a definitive phase III study (MARIANNE) pending. T-DM1 is also the first HER2-targeted agent to demonstrate significant clinical activity in patients whose cancer had progressed on both trastuzumab- and lapatinib-based regimens. At this time, no direct comparisons have been made of T-DM1 with combination anti-HER2 regimens such as trastuzumab/pertuzumab and trastuzumab/lapatinib.

In terms of toxicity, in each of the randomized studies in which T-DM1 was compared with conventional chemotherapy combined with a HER2-targeted agent, TDM4450g and EMILIA, the overall rates of grade ≥3 adverse events were lower in the T-DM1 arm compared with the chemotherapy-containing arm (46.4% vs. 90.9% and 40.8% vs. 57.0%, respectively; refs. 14, 15).

Unanswered Questions about T-DM1

In whom is TDM1 most effective?

As a greater number of HER2-directed therapeutic agents become available, the need to identify biomarkers to predict sensitivity to a given agent increases. Such biomarkers are needed to direct a specific agent to those patients most likely to benefit. This rational selection of therapies has the potential to increase clinical efficacy, decrease the toxicity associated with an ineffective therapy, and reduce costs. Unfortunately, identifying robust and specific predictive biomarkers for these agents has proved challenging. Because phosphoinositide 3-kinase (PI3K) signaling downstream of HER2 plays a major role in mediating the oncogenic function of HER2 (20), it has been hypothesized that activating mutations in the gene for the catalytic subunit of PI3K (PIK3CA) would confer resistance to HER2 inhibitors such as trastuzumab. Indeed, several retrospective studies have demonstrated lower response rates and/or shorter PFS in trastuzumab-treated patients with PIK3CA mutations in their tumor compared with those with wild-type cancers (21, 22). A similar analysis was recently performed on archival tumor tissue from the EMILIA study. Interestingly, in this analysis, patients with PIK3CA mutations assigned to the capecitabine/lapatinib arm had shorter PFS and OS compared with the patients with wild-type cancers on the capecitabine/lapatinib arm (23). In contrast, those patients assigned to the T-DM1 arm had similar PFS and OS regardless of whether or not their tumor had a PIK3CA mutation. Thus, the HR for OS benefit of T-DM1 was 0.26 (95% CI, 0.12–0.55) for patients with PIK3CA mutations and 0.68 (95% CI, 0.40–1.15) for patients with wild-type tumors (23). Although these results suggest that tumors with PIK3CA mutations may be relatively resistant to capecitabine/lapatinib therapy, they do not imply that there is no benefit from capecitabine/lapatinib in the setting of a PIK3CA mutation. This work was exploratory and needs further validation. Moreover, we are urgently in need of other biomarkers that will assist in the identification of patients who are more or less likely to benefit from T-DM1.

What are the mechanisms of resistance to T-DM1?

Although T-DM1 has significant efficacy in both treatment-naive and treatment-refractory metastatic breast cancer, resistance eventually develops in both settings. The molecular mechanisms by which cancer cells avoid the cytotoxic effects of T-DM1 are unknown. The EMILIA data noted above would suggest that PIK3CA mutations are not associated with T-DM1 resistance. An alternative, relatively simple hypothesis for T-DM1 resistance is that cancer cells lose their HER2 expression, thus preventing T-DM1 binding and internalization. Consistent with this hypothesis, there are preclinical models of T-DM1 resistance that do display downregulation of HER2 expression (24). However, there are at least limited data that suggest that patients who develop progressive disease on T-DM1 can still respond to other HER2-targeted therapies (25), suggesting that loss of HER2 expression may not be the major resistance mechanism. Another observation from preclinical models is that cancers may develop resistance to T-DM1 by upregulating expression of drug efflux pumps, such as MDR1, thus reducing their intracellular exposure to DM1 (24). To definitively address the mechanism of T-DM1 resistance, studies will require tumor tissue from patients who have developed progressive disease on T-DM1 and therefore biopsies of such patients need to be included in future studies of T-DM1.

Future Directions

The activity of T-DM1 in patients who are refractory to other HER2-directed agents, together with its favorable safety profile, makes T-DM1 an attractive candidate for use in the early disease setting. On the basis of its unique characteristics, T-DM1 could be a very appealing alternative to standard chemotherapy/trastuzumab regimens, or it could be used in addition to standard chemotherapy regimens to potentially increase efficacy in high-risk populations. At least three phase III trials of T-DM1 in patients with HER2+ early-stage breast cancer have started or will start enrollment in the near future.

Disclosure of Potential Conflicts of Interest

I. Krop has other commercial research support from Genentech and is a consultant/advisory board member of GlaxoSmithKline and Genentech (uncompensated). E.P. Winer has received a commercial research grant from Genentech.
References


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