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***Abstract*:** In February 2013, ado-trastuzumab emtansine (T-DM1, Kadcyla®) received regulatory approval in the United States for treatment-refractory human epidermal growth factor receptor 2 (HER2) positive metastatic or locally advanced breast cancer based on results from EMILIA, a large phase III trial that compared standard of care lapatinib plus capecitabine to T-DM1. Several other studies have been reported in the metastatic setting and multiple trials are ongoing or planned in the neoadjuvant, adjuvant and advanced disease settings. Here we provide an updated and comprehensive review of clinical trials evaluating T-DM1, discuss management of toxicity associated with this drug, propose potential mechanisms of resistance and offer practical considerations for the treating oncologist.

Keywords: ado-trastuzumab emtansine, antibody-drug conjugate, breast cancer, T-DM1, HER2

Introduction

Roughly a quarter of all breast cancers are distinguished by amplification of the human epidermal growth factor receptor-2 (*HER2)* gene, leading to overexpression of the HER2 protein on cancer cells. This genetic alteration has been associated with more aggressive disease behavior and worse clinical outcomes [Slamon *et al.* 1987]. Data are now emerging, however, that show the HER2-targeted monoclonal antibody trastuzumab (Herceptin ®, Genentech, San Francisco, CA, USA) has significantly improved outcomes for patients diagnosed with this subtype of cancer [Dawood *et al.* 2010]. While trastuzumab is well tolerated, when given as monotherapy it only leads to tumor shrinkage in about 25% of patients [Vogel *et al.* 2002]. As a result, trastuzumab is typically combined with chemotherapy to increase efficacy, which also increase toxicity. In addition, *de novo* or acquired resistance to trastuzumab eventually occurs in most patients with advanced disease [Nahta *et al.* 2006]. The newer orally bioavailable small molecule tyrosine kinase inhibitor lapatinib (Tykerb® GlaxoSmithKline) that targets both HER2 and epidermal growth factor receptor (EGFR, HER1) offers patients with metastatic HER2+ breast cancer a treatment option after progression on trastuzumab-based therapy. Like trastuzumab, single-agent lapatinib induces a response in the minority of patients [Blackwell *et al.* 2009]. In contrast to trastuzumab, lapatinib is associated with significant toxicity including diarrhea and rash.

Ado-trastuzumab emtansine (T-DM1) is the first antibody-directed chemotherapy approved for a solid malignancy. Preclinical data regarding T-DM1 were published in 2008 and the first clinical trial evaluating it was published in 2010. T-DMI was granted US Food and Drug Administration (FDA) approval in 2013, only 5 years after the first publication. The relatively rapid development of this novel drug reflects both a need and an excitement for targeted therapies that spare normal tissues yet provide improved efficacy compared with traditional cytotoxics.

T-DM1 is an antibody-drug conjugate (ADC) composed of trastuzumab connected *via* a stable thioether linker (SMCC; designated MCC after conjugation) to an average of 3.6 emtansine molecules [Lewis Phillips *et al.* 2008]. Emtansine, also

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called DM1, is a derivative of maytansine that was originally isolated from an Ethiopian plant, *Maytenus ovatus*, and shown to have antitumor activities [Kupchan *et al.* 1972]. It binds tubulin and prevents assembly of microtubules by promoting depolymerization and inhibiting polymerization [Remillard *et al.* 1975) While highly active *in vitro*, 100 times more potent than the vinca alkaloids and 24–270 times more potent than paclitaxel, dose-limiting toxicities including neuropathy, diarrhea and weakness precluded successful clinical development [Cassady *et al.* 2004; Remillard *et al.* 1975]. With the successful development of linker technology that allows a cytotoxic agent to be stably connected to a monoclonal antibody, the potential use of maytansine was resurrected.

In this article, we review early preclinical data relating to T-DM1, provide an updated and comprehensive review of clinical trials that have evaluated or are evaluating T-DM1, discuss management of toxicity associated with this drug, propose potential mechanisms of resistance and offer practical considerations for the treating oncologist.

Preclinical studies and phase I trials

In 2008, Lewis Phillips and colleagues published a series of experiments on the rational design of trastuzumab-MCC-DM1 and its effects on cell lines and mice [Lewis Phillips *et al.* 2008]. They showed minimal antiproliferative effects in breast cancer cell lines lacking overexpression of HER2, while trastuzumab-resistant tumor cells that overexpressed HER2 underwent cell death. Increased linker stability *in vivo* correlated with increased antitumor activity for trastuzumab chemotherapy conjugates in mouse tumor xenograft models. Trastuzumab-MCC-DM1 also demonstrated the best safety profile in mice, with transient elevation of liver enzymes and mild, reversible thrombocytopenia at higher doses. The conjugated molecule is thought to be endocytosed after interacting with HER2 and ultimately fuses with a lysosome where it undergoes proteolytic degradation with release of the active DM1 [Erickson *et al.* 2006]. The primary active metabolite does not seem to cross the plasma membrane thereby minimizing effects on neighboring cells [Xie *et al.* 2004]. The route of T-DM1 clearance in mice is primarily through the gastrointestinal and biliary systems, with none through the renal system [Gupta *et al.* 2012].

The first-in-human study was reported in 2010 by Krop and colleagues (Krop *et al.* 2010a]. T-DM1 was given to 24 patients with HER2+ MBC who had previously received a median of 4 other chemotherapies. Dosing was started at 0.3 mg/kg on an every 3 week cycle and escalated. At 4.8 mg/kg, 2 of the 3 patients experienced grade 4 thrombocytopenia and 3.6 mg/kg was identified as the maximum tolerated dose (MTD). The objective response rate (ORR) in all 24 patients was 21% (5/24 patients). Of 15 patients treated at the MTD, 9 had measurable disease, 4 of whom had a response. The median half-life for T-DM1 was found to be 4.5 days and steady state was achieved by cycle two when given at every 3 week dosing [Girish *et al.* 2012]. A weekly dosing cohort was also evaluated starting at one third of the 3.6 mg/kg every 3 week dosing (i.e. 1.2 mg/kg) [Beeram *et al.* 2012]. The MTD was determined to be 2.4 mg/kg weekly after 2 out of 3 patients at 2.9 mg/kg experienced grade 3 thrombocytopenia and grade 3 elevation of aminotransferase (AST). Of 28 patients treated with the weekly regimen, objective tumor responses were reported in 13 (46.4%) and the clinical benefit rate (CBR) at 6 months was 57%. Similar to the every 3 week schedule, no grade 3 or 4 neuropathy was observed. Overall grade 3 or worse adverse events (AEs), however, were more frequent with weekly dosing (68%) compared with the every 3 week schedule (50%), although patient numbers were small. Larger studies with the weekly schedule are ongoing at this time [Krop *et al.* 2010b].

Previously treated advanced disease

Given the efficacy and proven benefits of trastuzumab combined with chemotherapy in the first-line setting and the lack of nontoxic treatment options for patients after disease progression, the first logical setting to evaluate T-DM1 was in the treatment refractory advanced disease setting. A single arm phase II pilot study of T-DM1 (TDM4258g) enrolled 112 patients whose disease had progressed on prior trastuzumab based therapy [Burris *et al.* 2011]. A confirmatory phase II single-arm study (TDM4374g) evaluated T-DM1 in a more heavily pretreated patient population [Krop *et al.* 2012]. In that study, 110 patients who had already received an anthracycline, capecitabine, taxane, lapatinib and trastuzumab were enrolled [Krop *et al.* 2012]. Both studies demonstrated promising activity for T-DM1, with an ORR of 25.9% and 34.5% respectively. Importantly, T-DM1 was shown to be well tolerated at the every 3 week dosing.

The early phase studies described above led to the landmark EMILIA trial [Verma *et al.* 2012]. In this

study, 991 patients previously treated with trastuzumab and a taxane were randomly assigned to treatment with T-DM1 [3.6 mg/kg intravenously (IV)] or the combination of capecitabine (1000 mg/m^2 orally twice a day, days 1 to 14) plus lapatinib (1250 mg orally daily) with both regimens repeated every 3 weeks. T-DM1 was found to significantly improve progression-free survival (PFS) from 6.4 to 9.6 months (hazard ration [HR] 0.65, 95% confidence interval [CI] 0.55–0.77 $p < 0.001$) and median overall survival (OS) from 25.1 to 30.9 months (HR 0.68, 95% CI 0.55–0.85 $p < 0.001$). A clinically significant improvement in the ORR (31% *versus* 44% $p = 0.0002$) was also observed. Patients with untreated central nervous system (CNS) metastases were excluded from the study. Patients with baseline treated CNS metastases had similarly improved OS compared with the overall intention to treat study population [Krop *et al.* 2013]. Remarkably, the additional efficacy came with a decreased rate of serious AEs. Rates of all grade 3 and 4 AEs were 41% in the T-DM1 arm *versus* 57% in the study arm. Thrombocytopenia was the most common grade 3/4 AE in the T-DM1 arm (13% *versus* 0.2%). The rates of grade 3 or 4 bleeding events were low in both groups (1.4% and 0.8%, respectively). In the recently published patient reported outcomes from EMILIA, time to symptom worsening was also significantly delayed in the T-DM1 arm *versus* the capecitabine-plus-lapatinib arm (7.1 *versus* 4.6 months; $p = 0.0121$) [Welslau *et al.* 2014]. Based on the significant improvements in ORR, PFS, OS and toxicity reported in EMILIA, the FDA granted T-DM1 regulatory approval on 22 February 2013 for HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane.

The recently presented TH3RESA trial went further, comparing T-DM1 with any regimen of the physician's choice in patients who had at least two prior HER2-directed therapies [Krop *et al.* 2014]. A total of 602 patients were randomized 2:1 to T-DM1 *versus* treatment of physician's choice (TPC). Patients in the control arm were allowed to crossover to T-DM1 at progression. More than half the patients had received four prior lines of therapy and nearly one-third had received greater than five prior lines of treatment. Over 80% of patients enrolled in the TPC arm received trastuzumab-containing therapy as their regimen on this study. The median PFS was 6.2 months with T-DM1 *versus* 3.3 months (HR 0.528, $p < 0.001$) with TPC and the first interim median OS was 14.9 months for patients in the TPC arm but was not yet reached for patients treated with T-DM1 (HR 0.552, $p = 0.0034$, efficacy stopping boundary not crossed). The final OS results are expected in 2015. Safety results were similar to EMILIA with more grade 3 and 4 AEs in the control group than in the T-DM1 arm (43.5% *versus* 32.3%, respectively). Rate of cardiac events were low in both groups (EF< 50% in 1.5% of T-DM1 and 1.1% of control). As seen with other studies of T-DM1, there was a higher rate of severe thrombocytopenia (4.7% *versus* 1.6%) and hemorrhage (2.2% *versus* 0.5%) in T-DM1-treated patients. Exploratory subgroup analysis showed that T-DM1 was associated with improved PFS regardless of age, baseline Eastern Cooperative Oncology Group (ECOG) performance status, hormone receptor status, number of prior regimens or sites of disease involvement (visceral *versus* nonvisceral). This study confirmed the findings of EMILIA and showed that T-DM1 is more effective and less toxic than standard of care therapy available for patients previously treated with trastuzumab.

Previously untreated advanced disease

Currently T-DM1 is only approved in previously treated patients with metastatic disease. However, given its impressive activity compared with lapatinib/capecitabine in EMILIA and TPC in TH3RESA, it is logical to evaluate whether T-DM1 is more effective and better tolerated than standard regimens in the first-line setting. Thus far only one study that has evaluated T-DM1 in the upfront setting has been reported. TDM4450 was a phase II open-label trial that enrolled 137 patients with treatment-naïve locally advanced or metastatic HER2 positive breast cancer and randomized them (1:1) to T-DM1 or docetaxel plus trastuzumab [Hurvitz *et al.* 2013]. While the ORR and CBR were similar in the two treatment arms, patients in the T-DM1 arm had a significantly improved PFS (14.2 *versus* 9.2 months; HR, 0.59; $p = 0.035$) and experienced fewer grade 3 or greater AEs compared with the control arm (46% *versus* 91%). The time to a significant decrease in quality of life was also significantly delayed in the T-DM1 arm, from a median of 3.5 months in the docetaxel trastuzumab arm to 7.5 months in the T-DM1 arm (HR, 0.58; $p = 0.022$).

An ongoing phase III study is attempting to address this question definitively [ClinicalTrials.gov identifier: NCT01120184]. In the MARIANNE trial, patients with untreated metastatic or locally advanced HER2-positive breast cancer are randomized to one of three arms: T-DM1 plus placebo;

T-DM1 plus pertuzumab; or trastuzumab plus a taxane. The planned enrollment is 1092 patients with PFS being the primary outcome measure. Enrollment is complete and results are pending. The MARIANNE trial will not be able to address how T-DM1 or T-DM1 plus pertuzumab compare with the new standard front-line regimen of pertuzumab–trastuzumab–taxane. However, it will be able to evaluate how T-DM1 compares with trastuzumab plus a taxane in the front-line setting and will also measure whether there is any added benefit to adding pertuzumab to T-DM1.

T-DM1 in combination with other therapy

T-DM1 does not have the typical AEs of chemotherapy. Therefore there has been interest in combining it with either cytotoxic chemotherapy or traditional anti-HER2 therapies to increase efficacy while maintaining tolerability. In TDM4373, a phase Ib/II single arm trial, T-DM1 was combined with pertuzumab in 67 patients with HER2-positive recurrent locally advanced or metastatic breast cancer in both first-line and previously treated setting [Dieras *et al.* 2010]. Pertuzumab was used at its standard 840 mg loading dose at first cycle followed by 420 mg maintenance dose every 3 weeks thereafter and T-DM1 was dose escalated. The expansion phase dose for T-DM1 was determined to be 3.6 mg/kg every 3 weeks. The combination was tolerable and ORR was 35% (10/28) in previously treated patients and 57.1% in the first-line setting. The MARIANNE trial will be testing this combination in a larger number of patients.

In a safety study, combination of T-DM1 with paclitaxel (TDM4652g) or docetaxel (BP22572) showed no risk of pharmokinetic-based drug interaction, paving the way for larger studies [Lu *et al.* 2011]. In another study, T-DM1 was combined with an oral pan-inhibitor of class I PI3K (GDC-0941) using a 3+3 dose escalation design in 13 patients [Krop *et al.* 2010c]. It appeared to be also well tolerated with some clinical activity. Larger studies are needed to address toxicity with adding chemotherapy or other HER2 blocking agents to T-DM1 as well as confirm level of increased efficacy.

Early disease setting

Few studies have so far examined the role of T-DM1 in the nonmetastatic setting but multiple trials are ongoing. An ongoing single arm phase II trial is evaluating the activity of T-DM1 in the adjuvant or neoadjuvant setting [ClinicalTrials.gov identifier: NCT01196052]. After completion of an anthracycline-based adjuvant/neoadjuvant chemotherapy regimen [doxorubicin–cyclophosphamide (AC) or 5-fluorouracil–epirubicin–cyclophosphamide (FEC)], 153 patients will receive T-DM1 instead of the conventional combination of trastuzumab plus a taxane for 17 cycles. In addition, the safety of T-DM1 with concurrent radiotherapy and in patients who receive concurrent hormonal therapy is a secondary outcome measure in this study and will be measured by the incidence, nature and severity of AEs. In the ATEMPT trial, 500 patients will be randomized to T-DM1 *versus* paclitaxel plus trastuzumab after adjuvant anthracycline based therapy [ClinicalTrials.gov identifier: NCT01853748]. In the KAITLIN trial, 2500 patients will be randomized after adjuvant AC/FEC to either taxane, trastuzumab plus pertuzumab or to T-DM1 plus pertuzumab [ClinicalTrials.gov identifier: NCT01966471]. And lastly in the differently designed phase III trial, (KATHERINE), patients with residual disease after neoadjuvant trastuzumab containing regimens are randomized to continuation of trastuzumab or to T-DM1 [ClinicalTrials.gov identifier: NCT01772472]. This study has a planned enrollment of more than 1400 patients.

The FDA recently approved pertuzumab use in the neoadjuvant setting of HER2 positive breast cancers [Schneeweiss *et al.* 2013]. The KRISTINE trial will examine combination of docetaxel, carboplatin, trastuzumab and pertuzumab (one of the FDA approved neoadjuvant regimens containing pertuzumab) *versus* T-DM1 plus pertuzumab. It will be several years though before we have definitive evidence of the appropriate use of T-DM1 in this setting.

Proposed mechanisms of resistance

As with any therapy, eventual concern is the development of resistance. Understanding mechanisms of resistance to T-DM1 is crucial in designing future trials and combinations that could overcome this resistance. Recently, a novel and so far only mechanism of resistance to T-DM1 was reported through expression of the HER3 ligand, neuregulin β1 [Lewis Phillips *et al.* 2014]. Binding of HER3 by neuregulin leads to heterodimerization of HER2 with HER3 thus strongly activating the PI3K pathway. Lewis Phillips and colleagues showed that the presence of neuregulin can inhibit the cellular response to T-DM1. Interestingly, however, they also showed that combination of pertuzumab, an

inhibitor of HER2-HER3 dimerization, with T-DM1 is not only synergistic in its antitumor activity but can specifically overcome the effects of neuregulin [Lewis Phillips *et al.* 2014]. The clinical relevance of this interesting observation will be tested in trials of T-DM1 with pertuzumab (MARIANNE, KRISTINE, KAITLIN) compared with T-DM1 alone. Other possible mechanisms of resistance include upregulation of drug efflux proteins such as p-glycoprotein (PGP), downregulation of HER2 or expression of the truncated version of HER2 (p95). The extent to which these mechanisms contribute to the development of resistance is unclear at this time.

Practical considerations for clinicians

Administration

The FDA approved starting dosage is 3.6 mg/kg IV every 3 weeks. The weekly regimen has not yet been approved for use. As with trastuzumab, the first infusion is given over 90 minutes and, if tolerated well, subsequent infusions are given over 30 minutes. Infusion reactions can be similarly seen and can be usually managed with acetaminophen and diphenhydramine. No premedication is required as risk of infusion reaction is less than 2% [Verma *et al.* 2012]. Recommended dose reductions for adverse events are to 3 mg/kg IV every 3 weeks and then to 2.4 mg/kg IV every 3 weeks if needed. It is recommended to stop treatment if patient is still having adverse events at the 2.4 mg/kg dose level.

Thrombocytopenia

The most commonly reported grade 3 or 4 AE with T-DM1 is thrombocytopenia. The mechanism underlying thrombocytopenia is not well defined as yet as megakaryocytes lack HER2 cell surface expression and another mechanism for endocytosis appears to exist [Press *et al.* 1990]. In a semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model to evaluate thrombocytopenia, Bender and colleagues showed a slow downward drift in the platelet time profile in some patients receiving repeated doses [Bender *et al.* 2012]. Therefore it is possible that T-DM1 affects a platelet proliferation lineage and new platelets derived from other lineages are less sensitive to T-DM1. This may also explain the nadir of platelets after the first dose and no increased incidence with greater T-DM1 exposure [Bender *et al.* 2012]. The only baseline characteristic to be associated with increased risk of grade 3 thrombocytopenia was platelet count less than 200,000 [Bender *et al.* 2012) A pooled analysis of safety data from five major clinical trials of T-DM1, including EMILIA, confirmed no exposure–safety relationship for thrombocytopenia [Jin *et al.* 2013].

Low platelet count occurred in 28% of patients in the EMILIA trial, with 12.9% being grade 3 or 4 [Verma *et al.* 2012]. The majority of patients were able to continue with dose reductions with only 2% discontinuing the drug as a result of thrombocytopenia. Although the overall incidence of bleeding was higher with T-DM1 (29.8%) than with lapatinib plus capecitabine (15.8%), the rates of grade 3 or 4 bleeding events were low in both groups (1.4% and 0.8%, respectively). The first dose reduction occurred at platelet count less than 25,000 in the EMILIA study.

Transaminitis

The second most commonly reported AE with use of T-DM1 is elevation in liver transaminases. Grade 3 or 4 elevation of AST and alanine aminotransferase (ALT) serum concentrations were seen in 4.3% and 2.9% of patients in the EMILIA trial respectively [Verma *et al.* 2012]. No patients suffered liver injury, although 3 patients (less than 1%) discontinued treatment as a result of grade 3 elevations in AST levels. Similar to thrombocytopenia, transaminitis does not correlate with greater exposure to T-DM1 and typically improves with dose reduction [Jin *et al.* 2013]. In the EMILIA trial, AST of over three times the upper limit of normal or bilirubin of over two times the upper limit of normal resulted in an automatic dose reduction to 3.0 mg/kg. We recommend similar dose reduction in practice.

Other notable adverse events

T-DMI has two black box warnings in addition to possible thrombocytopenia and transaminitis. One is for use in pregnant women. Treatment with trastuzumab, the antibody component of T-DM1, during pregnancy has resulted in oligohydramnios, fatal pulmonary hypoplasia and neonatal death [Zagouri *et al.* 2013]. DM1, the cytotoxic component of the molecule, can also be expected to cause embryo-fetal toxicity based on its mechanism of action on microtubules. Therefore its use is currently contraindicated in pregnancy.

The other black box warning is for cardiac toxicity. The current FDA recommendation is for an

Table 1. Major completed and ongoing clinical trials of ado-trastuzumab emtansine (T-DM1).

Study	Patient population	Phase	Number of patients	Treatment arms*	Results
EMILIA [Verma *et al.* 2012]	Pretreated HER2+ MBC	III	991	T-DM1 *versus* capecitabine + lapatinib	PFS: 9.6 *versus* 6.4 months OS: 30.9 *versus* 25.1 months ORR: 44 *versus* 31%
TH3RESA [Wildiers *et al.* 2013]	Pretreated HER2+ MBC	III	602	T-DM1 *versus* physician's choice	PFS: 6.2 *versus* 3.3 months OS: Not reached *versus* 14.9 months ORR: 31.3% *versus* 8.6%
TDM4450 [Hurvitz *et al.* 2013]	First-line HER2+ MBC	II	137	T-DM1 *versus* trastuzumab + docetaxel	PFS: 14.2 *versus* 9.2 months ORR: 64 *versus* 58%
MARIANNE [ClinicalTrials.gov identifier: NCT01120184]	First-line HER2+ MBC	III	1,092	T-DM1 + placebo *versus* T-DM1 + pertuzumab *versus* trastuzumab + a taxane	Ongoing
TDM4874g [ClinicalTrials.gov identifier: NCT01196052]	Adjuvant/ neoadjuvant	II	153	T-DM1 maintenance for 17 cycles after chemotherapy	Ongoing
KAITLIN [ClinicalTrials.gov identifier: NCT01966471]	Adjuvant	III	2,500	AC/FEC → T-DM1/pertuzumab *versus* AC/FEC → trastuzumab/pertuzumab/ taxane	Ongoing
KATHERINE [ClinicalTrials.gov identifier: NCT01772472]	Residual disease after neoadjuvant therapy	III	1,484 (estimated enrollment)	T-DM1 *versus* trastuzumab maintenance for 14 cycles after surgery	Ongoing
ATEMPT [ClinicalTrials.gov identifier: NCT01853748]	Stage I adjuvant	II	500	T-DM1 x 1 year *versus* paclitaxel/ trastuzumab x 12 weeks followed by trastuzumab maintenance to complete 1 year	Ongoing

AC, doxorubicin–cyclophosphamide; FEC, 5-fluorouracil–epirubicin–cyclophosphamide; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
*T-DM1 given at 3.6 mg/kg IV every 3 weeks in all studies.

echocardiogram prior to and every 3 months during treatment, similar to guidelines for trastuzumab use. Rates of decrease in left ventricular ejection fraction were similar between the T-DM1 and lapatinib/capecitabine groups in the EMILIA trial [Verma *et al.* 2012]. Of 481 patients in the T-DM1 group and 445 in the lapatinib/capecitabine group who could be evaluated, 8 patients (1.7%) and 7 patients (1.6%), respectively, had an ejection fraction that was less than 50% and at least 15 percentage points below the baseline value. Cardiac toxicity rates also appeared to be similar between T-DM1 and trastuzumab arms in the TDM4450 study; however, the numbers were too small to be significant [Hurvitz *et al.* 2013]. Rate of cardiac events was similarly low in both arms of the TH3RESA trial (EF< 50% in 1.5% of T-DM1 and 1.1% of control arms). Cardiac event rates will be further addressed in the MARIANNE trial, where it is being directly compared with a trastuzumab-based regimen.

Conclusion

The available clinical data for T-DM1 demonstrate that antibody-directed chemotherapy is associated with improved efficacy and safety compared with traditional chemotherapy. Trials conducted so far have proven its value in the trastuzumab-pretreated HER2+ metastatic disease setting. Ongoing trials are addressing its role in front-line metastatic disease as well as in the nonmetastatic setting (Table 1). Although this therapy is highly promising, *de novo* and acquired resistance to T-DM1 occurs. Understanding the

mechanism of resistance will be crucial to circumventing it, with one example being combining T-DM1 with pertuzumab to overcome HER3 ligand activation. That said, the innovative nature of this molecule combined with its impressive efficacy and safety data are hopefully just the beginning of a series of ADCs targeted against tumor-specific antigens in multiple cancer types.

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Conflict of interest statement

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References

Beeram, M., Krop, I., Burris, H., Girish, S., Yu, W., Lu, M. *et al.* (2012) A phase 1 study of weekly dosing of trastuzumab emtansine (T-DM1) in patients with advanced human epidermal growth factor 2-positive breast cancer. *Cancer* 118: 5733–5740.

Bender, B., Schaedeli-Stark, F., Koch, R., Joshi, A., Chu, Y., Rugo, H. *et al.* (2012) A population pharmacokinetic/pharmacodynamic model of thrombocytopenia characterizing the effect of trastuzumab emtansine (T-DM1) on platelet counts in patients with HER2-positive metastatic breast cancer. *Cancer Chemother Pharmacol* 70: 591–601.

Blackwell, K., Pegram, M., Tan-Chiu, E., Schwartzberg, L., Arbushites, M., Maltzman, J. *et al.* (2009) Single-agent lapatinib for HER2-overexpressing advanced or metastatic breast cancer that progressed on first- or second-line trastuzumab-containing regimens. *Ann Oncol* 20: 1026–1031.

Burris, H., III, Rugo, H., Vukelja, S., Vogel, C., Borson, R., Limentani, S. *et al.* (2011) Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J Clin Oncol* 29: 398–405.

Cassady, J., Chan, K., Floss, H. and Leistner, E. (2004) Recent developments in the maytansinoid antitumor agents. *Chem Pharm Bull* 52: 1–26.

Dawood, S., Broglio, K., Buzdar, A., Hortobagyi, G. and Giordano, S. (2010) Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. *J Clin Oncol* 28: 92–98.

Dieras, V., Harbeck, N., Albain, K., Burris, H., III, Awada, A., Crivellari, D. *et al.* (2010) A phase Ib/II trial of trastuzumab-DM1 (T-DM1) with pertuzumab for patients with HER2-positive, locally advanced or metastatic breast cancer: interim efficacy and safety results. *Cancer Res* 70(24 Suppl.): abstract P3-14-01.

Erickson, H., Park, P., Widdison, W., Kovtun, Y., Garrett, L., Hoffman, K. *et al.* (2006) Antibody-maytansinoid conjugates are activated in targeted cancer cells by lysosomal degradation and linker-dependent intracellular processing. *Cancer Res* 66: 4426–4433.

Girish, S., Gupta, M., Wang, B., Lu, D., Krop, I., Vogel, C. *et al.* (2012) Clinical pharmacology of trastuzumab emtansine (T-DM1): an antibody-drug conjugate in development for the treatment of HER2-positive cancer. *Cancer Chemother Pharmacol* 69: 1229–1240.

Gupta, M., Lorusso, P., Wang, B., Yi, J., Burris, H., III, Beeram, M. *et al.* (2012) Clinical implications of pathophysiological and demographic covariates on the population pharmacokinetics of trastuzumab emtansine, a HER2-targeted antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer. *J Clin Pharmacol* 52: 691–703.

Hurvitz, S., Dirix, L., Kocsis, J., Bianchi, G., Lu, J., Vinholes, J. *et al.* (2013) Phase II randomized study of trastuzumab emtansine *versus* trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 31: 1157–1163.

Jin, J., Wang, B., Yuying, G., Samant, M., Li, C., Song, C. *et al.* (2013) Exposure–safety relationship of trastuzumab emtansine (T-DM1) in patients with HER2-positive locally advanced or metastatic breast cancer (MBC) *J Clin Oncol* 31(Suppl.): abstract 646.

Krop, I., Beeram, M., Modi, S., Jones, S., Holden, S., Yu, W. *et al.* (2010a) Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. *J Clin Oncol* 28: 2698–2704.

Krop, I., Blackwell, K., Guardino, E., Huober, J., Lu, M., Miles, D. *et al.* (2013) Efficacy and safety of trastuzumab emtansine (T-DM1) *versus* lapatinib plus capecitabine (XL) in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) and central nervous system (CNS) metastases: results from a retrospective exploratory analysis of EMILIA. Poster Presentation, P4-12-27. San Antonio Breast Symposium, December 2013.

Krop, I., LoRusso, P., Miller, K., Modi, S., Yardley, D., Rodriguez, G. *et al.* (2012) A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. *J Clin Oncol* 30: 3234–3241.

Krop, I., Kim, S., González-Martín, A., Lorusso, P., Ferrero, J., Smitt, M. *et al.* (2014) Trastuzumab emtansine *versus* treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol* 15: 689–699.

Krop, I., Modi, S., Elias, A., LoRusso, P., Choi, Y. and Lu, M. (2010b) A dose-escalation study of trastuzumab-DM1 (T-DM1), paclitaxel (T), and pertuzumab (P) in patients with HER2-positive, locally advanced or metastatic breast cancer (MBC) previously treated with a trastuzumab-containing regimen. *Cancer Res* 70(Suppl. 2): abstract P3-14-10.

Krop, I., Wolff, A., Winer, E., Miller, K., Park, B., Ware, J. *et al.* (2010c) A phase Ib study evaluating safety, tolerability, pharmacokinetics (PK), and activity of the phosphoinositide-3 kinase (PI3K) inhibitor GDC-0941 in combination with trastuzumab-MCC-DM1 (T-DM1) in patients with advanced HER2-positive breast cancer. *Cancer Res* 70(24 Suppl): abstract P6-15-02.

Kupchan, S., Komoda, Y., Court, W., Thomas, G., Smith, R., Karim, A. *et al.* (1972) Maytansine, a novel antileukemic ansa macrolide from *Maytenus ovatus*. *J Am Chem Soc* 94: 1354–1356.

Lewis Phillips, G., Fields, C., Li, G., Dowbenko, D., Schaefer, G., Miller, K., Andre, F., Burris, H., III, Albain, K., Harbeck, N. *et al.* (2014) Dual targeting of HER2-positive cancer with trastuzumab emtansine and pertuzumab: critical role for neuregulin blockade in antitumor response to combination therapy. *Clin Cancer Res* 20: 456–468.

Lewis Phillips, G., Li, G., Dugger, D., Crocker, L., Parsons, K., Mai, E. *et al.* (2008) Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody–cytotoxic drug conjugate. *Cancer Res* 68: 9280–9290.

Lu, D., Modi, S., Elias, A., Agarwal, P., Yi, J., Guardino, A. *et al.* (2011) Pharmacokinetics (PK) of trastuzumab emtansine and paclitaxel or docetaxel in patients with HER2–positive MBC previously treated with a trastuzumab-containing regimen. *Cancer Res* 71(24 Suppl.): abstract P1-12-07.

Nahta, R., Yu, D., Hung, M., Hortobagyi, G. and Esteva, F. (2006) Mechanisms of disease: understanding resistance to HER2-targeted therapy in human breast cancer. *Nat Clin Pract Oncol* 3: 269–280.

Press, M., Cordon-Cardo, C. and Slamon, D. (1990) Expression of the HER-2/neu proto-oncogene in normal human adult and fetal tissues. *Oncogene* 5: 953–962.

Remillard, S., Rebhun, L., Howie, G. and Kupchan, S. (1975) Antimitotic activity of the potent tumor inhibitor maytansine. *Science* 189: 1002–1005.

Schneeweiss, A., Chia, S., Hickish, T., Harvey, V., Eniu, A., Hegg, R. *et al.* (2013) Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA) *Ann Oncol* 24: 2278–2284.

Slamon, D., Gary, C., Wong, S., Levin, W., Ullrich, A. and McGuire, W. (1987) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 235: 177–182.

Verma, S., Miles, D., Gianni, L., Krop, I., Welslau, M., Baselga, J. *et al.* (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 367: 1783–1791.

Vogel, C., Cobleigh, M., Tripathy, D., Gutheil, J., Harris, L., Fehrenbacher, L. *et al.* (2002) Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 20: 719–726.

Welslau, M., Diéras, V., Sohn, J., Hurvitz, S., Lalla, D., Fang, L. *et al.* (2014) Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) *versus* capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer. *Cancer* 120: 642–651.

Xie, H., Audette, C., Hoffee, M., Lambert, J. and Blättler, W. (2004) Pharmacokinetics and biodistribution of the antitumor immunoconjugate, cantuzumab mertansine (huC242-DM1), and its two components in mice. *J Pharmacol Exp Ther* 308: 1073–1082.

Zagouri, F., Sergentanis, T., Chrysikos, D., Papadimitriou, C., Dimopoulos, M. and Bartsch, R. (2013) Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat* 137: 349–357.