

FDA Approval: Ado-Trastuzumab Emtansine for the Treatment of Patients with HER2-Positive Metastatic Breast Cancer

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Abstract

On February 22, 2013, the FDA licensed ado-trastuzumab emtansine (Kadcyla; Genentech, Inc.) for use as a single agent for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) who previously received trastuzumab and a taxane, separately or in combination. The clinical basis for licensure was a phase III trial in 991 patients with HER2-positive MBC that randomly allocated patients to receive ado-trastuzumab emtansine ($n = 495$) or lapatinib in combination with capecitabine ($n = 496$). The coprimary endpoints were progression-free survival (PFS) based on tumor assessments by an independent review committee and overall survival (OS). Statistically significant improvements in PFS and OS were observed in patients receiving ado-trastuzumab emtansine compared with patients receiving lapatinib plus capecitabine [difference in PFS medians of 3.2 months, HR, 0.65 (95% confidence interval, CI, 0.55–0.77), $P < 0.0001$ and difference in OS medians of 5.8 months, HR, 0.68 (95% CI, 0.55–0.85), $P = 0.0006$]. The most common adverse reactions in patients receiving ado-trastuzumab emtansine were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased aminotransferase levels, and constipation. Other significant adverse reactions included hepatobiliary disorders and left ventricular dysfunction. Given the PFS and OS results, the benefit–risk profile was considered favorable. *Clin Cancer Res*; 20(17); 4436–41. ©2014 AACR.

Introduction

Amplification and overexpression of the human epidermal growth factor receptor 2 (HER2) occurs in approximately 20% of metastatic breast cancer (MBC) and results in activation of the proliferative and prosurvival stimuli associated with HER2 signal transduction through the MAPK and PI3K–Akt pathways. These increased stimuli result in increased tumor growth and a poor prognosis (1–4). Targeting the HER2 receptor with monoclonal antibodies has shown effectiveness as a therapeutic approach. The addition of trastuzumab (Herceptin; Genentech, Inc.), and more recently pertuzumab (Perjeta; Genentech, Inc.) in combination with trastuzumab, to a taxane significantly improved the outcomes of patients with MBC (5, 6). Ado-

trastuzumab emtansine (T-DM1) is an antibody–drug conjugate (ADC) that incorporates the HER2-targeting and therapeutic properties of trastuzumab with the cytotoxic activity of DM1. The FDA review of this Biologics License Application (BLA) is summarized below.

Chemistry and Manufacturing

Ado-trastuzumab emtansine consists of trastuzumab, the thioether linker 4-[N-maleimidomethyl] cyclohexane-1-carboxylate, and the microtubule inhibitor DM1, a maytansine derivative. DM1 is covalently linked to lysine residues on the antibody, and each T-DM1 molecule contains an average of 3.5 DM1 molecules per antibody. Several product quality concerns were identified and resolved during the BLA review and resulted in postmarketing requirements (PMR) and commitments (PMC; ref. 7).

Nonclinical Pharmacology and Toxicology

Ado-trastuzumab emtansine binds to subdomain IV of the HER2 receptor and undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in the intracellular release of DM1-containing cytotoxic catabolites. Binding of DM1 to tubulin disrupts microtubules, resulting in cell-cycle arrest at the G₂–M

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Note: This is a U.S. Government work. There are no restrictions on its use.

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interface and apoptosis. *In vitro*, T-DM1 also inhibits HER2 receptor signaling, mediates antibody-dependent cell-mediated cytotoxicity, and inhibits shedding of the HER2 extracellular domain (8–12).

Monkeys tolerated repeat doses of T-DM1 as high as 30 mg/kg (about 7 times the clinical exposure based on AUC). Even at this high dose, T-DM1 was less toxic to monkeys than the clinical dose was to humans. Thrombocytopenia and anemia occurred in both monkeys and humans but were much less severe in monkeys. Increased aminotransferase levels and centrilobular vacuolization in monkeys predicted the hepatic toxicity observed in patients. Localization to the central lobe suggests that the hepatic toxicity is caused by DM1 as the liver clears it from the blood.

Axonal degeneration in the sciatic nerve with Schwann cell hyperplasia and hypertrophy and axonal degeneration of the dorsal funiculus was observed in the spinal cord in monkeys. The involvement of the Schwann cells suggests that this toxicity may be less reversible than neurotoxicities caused by other cancer drugs.

Although no reproductive and developmental toxicology studies were conducted with T-DM1, both trastuzumab and DM1 are either known or suspected to cause fetal harm or death when administered to a pregnant woman. DM1 was aneugenic or clastogenic in an *in vivo* rat bone marrow micronucleus assay but was not mutagenic in an *in vitro* bacterial reverse mutation assay. Carcinogenicity studies with ado-trastuzumab emtansine were not required or conducted for this indication.

Clinical Pharmacology

The ADC concentration–time profile can be described by a linear two-compartment model with first-order elimination from the central compartment. The C_{max} of the ADC and DM1 occurred close to the end of infusion. The mean binding of DM1 to human plasma proteins *in vitro* was 93%. *In vitro* studies also showed that DM1 is a P-glycoprotein substrate and is metabolized by CYP3A4/5, but does not inhibit or induce major CYP450 enzymes. On the basis of population pharmacokinetic (PK) analyses in patients with breast cancer, the central volume of distribution of T-DM1 was 3.13 L, the clearance was 0.68 L/d, and the elimination half-life was approximately 4 days. T-DM1 accumulation was not observed following multiple dosing, and its PK was not affected by mild to moderate renal impairment.

Exploratory exposure–response (E-R) analyses were conducted for OS, PFS, and objective response rate (ORR; ref. 13). A significant difference in OS was observed for patient groups divided according to quartiles of $C_{min,C1D21}$ (T-DM1 trough concentration on day 21 of cycle 1 predicted by population PK model), with higher exposures associated with longer survival (log-rank test nominal $P < 0.0001$). Furthermore, Cox-proportional hazard analysis indicated that after adjusting for baseline risk factors, higher T-DM1 exposure was associated with longer survival. Similar conclusions were reached when PFS or ORR was used as the response variable. The percentage of patients who received

dose adjustments of T-DM1 was similar across the exposure range and was lower than that of the active control arm. To further understand the E-R relationship with respect to C_{min} and assess the predictability of baseline risk factors, the applicant agreed to a PMC to further explore E-R relationships using additional data from an ongoing phase III trial to assist in determining whether dose-optimization trials will be needed in these patients.

Clinical Trial Design

The clinical support for this BLA was provided mainly by the results of a randomized, multicenter, international, open-label, phase III trial (EMILIA; ref. 14). Three additional phase II trials were supportive (15–17). In the phase III trial, patients with MBC were required to have HER2-positive disease determined at a central laboratory and defined as 3+ by immunohistochemistry or ≥ 2.0 amplification by FISH. A total of 991 patients were randomly allocated (1:1) to T-DM1 or to lapatinib plus capecitabine (LC). T-DM1 was administered at a dose of 3.6 mg/kg i.v. over 30 to 90 minutes on day 1 of a 21-day cycle. Lapatinib, 1,250 mg, was administered orally daily, and capecitabine, 1,000 mg/m², was administered orally twice a day on days 1 to 14 of a 21-day cycle. Patients received study treatment until progression of disease (as assessed by the investigator), unacceptable toxicity, or withdrawal of consent.

The two coprimary endpoints were PFS based on independent review of tumor assessments (IRC-PFS) and OS. PFS was defined as the time from randomization to the first documented IRC-assessed disease progression using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.0) or death from any cause, whichever occurred earlier. The coprimary endpoint, OS, was defined as the time from the date of randomization to the date of death from any cause. Key secondary endpoints included PFS based on investigator assessment, ORR, and duration of response.

The sample size was based on detection of an OS HR of 0.8, and approximately 632 deaths were required to achieve 80% power at a two-sided 5% alpha level. The planned accrual was 980 patients, and the primary efficacy analysis of PFS was to take place when 508 IRC-assessed PFS events had occurred. This provided 90% power to detect a PFS HR of 0.75 with a two-sided alpha of 5%. The two-sided log-rank test, stratified by world region (United States, Western Europe, other), number of prior chemotherapeutic regimens for unresectable, locally advanced, or metastatic disease (0–1 vs. >1), and visceral versus nonvisceral disease was used to compare PFS between the two treatment arms.

Demographics, Disease Characteristics, and Prior Treatment

A total of 991 patients were randomized, 495 to the T-DM1 arm and 496 to the LC arm. Baseline demographics and disease characteristics were balanced between treatment arms. The median age was approximately 53 years (range, 24–84 years), 74% of the patients were white, 18% were Asian, and 5% were black. Twenty-seven percent of the

patients were enrolled in the United States, 32% in Europe, and 16% in Asia. Tumor prognostic characteristics included hormone receptor status (positive, 55%; negative, 43%), presence of visceral disease (68%), nonvisceral disease only (33%), and the number of disease sites (<3, 61%; ≥3, 37%). Eighty-eight percent of patients had received prior treatment for metastatic disease. All but 1 patient had previously received trastuzumab and 85% received it in the metastatic setting. More than 99% of patients had received a taxane and 61% had received an anthracycline before study entry.

Efficacy Results

At the time of the final PFS analysis, 569 IRC-assessed events had occurred. A statistically significant improvement in IRC-PFS was observed in patients receiving T-DM1 compared with patients receiving LC [HR, 0.65 (95% confidence interval, CI, 0.55–0.77), stratified log-rank $P < 0.0001$]. The median PFS durations were 9.6 and 6.4 months in the T-DM1 and LC arms, respectively (Table 1).

A planned interim OS analysis at the time of the final PFS analysis was conducted at 35% of the planned events for the final OS analysis and demonstrated an improvement in OS for patients treated with T-DM1 [HR, 0.62 (95% CI, 0.48–0.81), $P = 0.0005$]. However, the HR and P value for the interim OS analysis did not cross the predefined O'Brien–Fleming stopping boundary. At the time of the second interim OS analysis, a statistically significant improvement in OS was observed in patients receiving T-DM1 compared with those receiving LC [HR, 0.68 (95% CI, 0.55–0.85), $P =$

0.0006]. This result crossed the prespecified efficacy stopping boundary (HR, 0.73 or $P = 0.0037$). The median OS durations were 30.9 and 25.1 months in the T-DM1 and LC arms, respectively (Table 1). These effects on PFS and OS were consistent across relevant subgroups.

Key supportive secondary endpoints included improvements in IRC-assessed ORR [44% (95% CI, 39%–49%) with T-DM1 versus 31% (95% CI, 26%–36%) with LC], duration of response (median duration 12.6 months with T-DM1 and 6.5 months with LC), investigator ORR, and investigator PFS.

Safety Results

The safety database consisted of 884 patients with HER2-positive MBC who received T-DM1 at a dose of 3.6 mg/kg every 3 weeks. The most common (≥25%) adverse drug reactions (ADR) in this population were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased aminotransferase levels, and constipation.

In the phase III trial, the median durations of treatment were 7.6 months for patients treated with T-DM1 and 5.5 months and 5.3 months for patients treated with lapatinib and capecitabine, respectively. Grade 1 to 4 ADRs occurring more frequently (>10%) in the T-DM1 arm than in the LC arm included thrombocytopenia (31.2% vs. 3.3%), constipation (26.5% vs. 11.1%), aminotransferase elevation (28.8% vs. 14.3%), headache (28.2% vs. 14.5%), epistaxis (22.5% vs. 8.4%), arthralgia (19.2% vs. 8.4%), pyrexia (18.6% vs. 8.4%), dry mouth (16.7% vs. 4.9%), and

Table 1. Coprimary endpoint results

	Lapatinib + capecitabine <i>n</i> = 496	T-DM1 <i>n</i> = 495
IRC-PFS (clinical cutoff date, January 14, 2012)		
Number of patients with events (%)	304 (61)	265 (54)
Disease progression	273	237
Death	31	28
Number of censored patients	192	230
Median duration of IRC-PFS (mo; 95% CI)	6.4 (95% CI, 5.7–7.1)	9.6 (95% CI, 8.3–10.6)
HR (95% CI)	0.65 (0.549–0.771)	
<i>P</i> value (stratified log-rank test)	<0.0001	
First interim analysis OS (clinical cutoff date, January 14, 2012)		
Number of patients who died, <i>n</i> (%)	129 (26)	94(19)
Number of censored patients	367	401
Median (mo)	23.3	NE
HR (95% CI)	0.62 (95% CI, 0.48–0.81)	
<i>P</i> value (stratified log-rank)	0.0005	
Second interim analysis OS (clinical cutoff date, July 31, 2012)		
Number of patients who died, <i>n</i> (%)	182 (37)	149 (30)
Median (mo; 95% CI)	25.1 (95% CI, 22.7–28.0)	30.9 (95% CI, 26.8–34.3)
HR (95% CI; stratified Cox regression)	0.682 (0.548–0.849)	
<i>P</i> value (stratified log-rank)	0.0006	
<i>P</i> value (unstratified log-rank test)	0.0012	
O'Brien–Fleming boundary		0.0037

myalgia (14.1% vs. 3.7%). Grade 3 to 4 ADRs occurring more frequently ($\geq 2\%$) in the T-DM1 arm included thrombocytopenia (14.5% vs. 0.4%), aminotransferase elevation (8.0% vs. 2.5%), and peripheral neuropathy (2.2% vs. 0.2%), with all but 1 T-DM1-treated patient having resolution of grade 3 to 4 peripheral neuropathy. The incidence of grade 3 to 4 thrombocytopenia was particularly high in Asian patients treated with T-DM1 (45% vs. 1%). In addition, 1.2% of patients treated with T-DM1 developed pneumonitis, all of which was grade 2 in severity.

Hepatotoxicity was identified by FDA as a safety concern early in the T-DM1 investigational drug development program. Early clinical trials of maytansine in the late 1970s reported frequent elevation of aminotransferase (15–20). In addition, nonclinical studies showed that T-DM1 seemed to induce rises in aminotransferase levels in rats and monkeys, as well as histopathologic changes, including hepatocellular and biliary necrosis. In the phase III trial, there was a higher incidence of liver enzyme elevations in patients on T-DM1, and a higher incidence of bilirubin elevations in patients on LC. Figure 1 plots peak bilirubin versus peak aspartate aminotransferase (AST) in this trial. The plot shows that more patients treated with T-DM1 ($n = 12$) had elevations in both AST and bilirubin as compared with patients treated with LC ($n = 5$). In the

entire T-DM1 development program, there were at least two cases of hepatic failure leading to death possibly related to T-DM1. On the basis of the available data, the potential for T-DM1 to cause rare but serious drug-induced liver injury is high. Therefore, a boxed warning for this risk was included in the product labeling.

Left ventricular ejection fraction (LVEF) declines and left ventricular dysfunction were observed during the T-DM1 development program. However, the incidence of cardiac toxicity seemed to be no greater than that observed in the LC arm of the phase III trial. Because there was no evidence that T-DM1 is less cardiotoxic than trastuzumab, and trastuzumab carries a boxed warning for cardiomyopathy, reduction in LVEF was also included in the boxed warning.

The FDA review revealed five cases of overdose with T-DM1, one serious and four not serious. In the fatal case, the patient incorrectly received T-DM1 at a dose of 6 mg/kg and died approximately 3 weeks later. Given concerns with potential medication errors due to confusion between trastuzumab and ado-trastuzumab emtansine, particularly with drop-down menus in electronic pharmaceutical ordering systems, the FDA determined that the use of a distinguishing prefix in the nonproprietary name would be necessary and the prefix "ado" was selected.

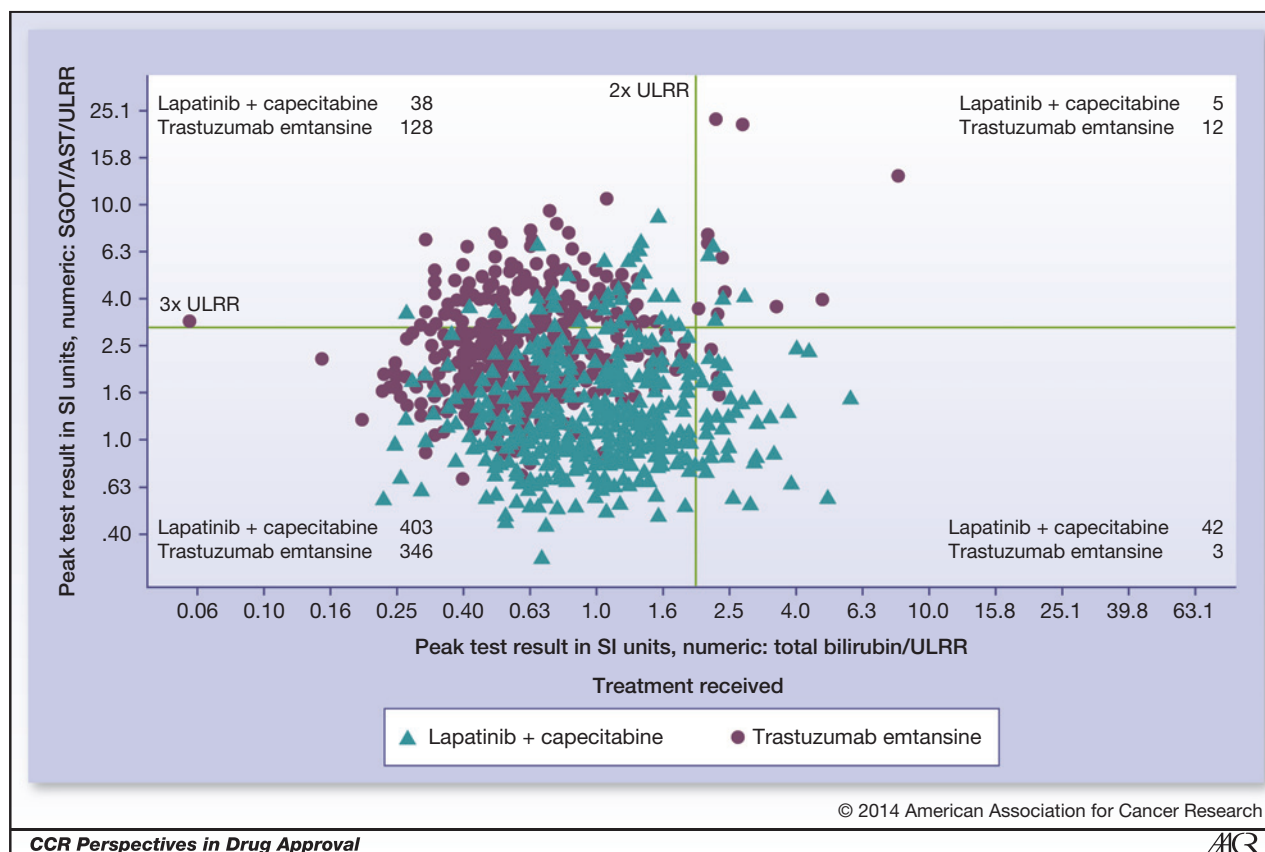


Figure 1. Scatter plot of peak bilirubin versus peak AST by treatment arm in the EMILIA trial. SGOT, serum glutamic oxaloacetic transaminase; ULRR, upper limit of normal reference range.

Table 2. Ongoing studies with T-DM1 in early breast cancer

Clinicaltrials.gov identifier	Study name	Design	Arms	Setting	Primary endpoint
NCT01772472	KATHERINE	2-arm, randomized, open-label, phase III	T-DM1 vs trastuzumab	Adjuvant	IDFS
NCT01196052	N/A	single-arm, open-label, phase II	T-DM1	Neoadjuvant and adjuvant	Safety
NCT01745965	ADAPT	2-arm, randomized, open-label, phase II	T-DM1 vs trastuzumab	Neoadjuvant	pCR
NCT01042379	I-SPY 2	N-arm, randomized open-label, phase II	T-DM1 and pertuzumab versus standard therapy	Neoadjuvant	pCR
NCT01904903	SAFE-HEaRt	open-label, phase II	T-DM1	Any	Cardiac safety

Abbreviations: IDFS, invasive disease-free survival; N/A, not applicable; pCR, pathologic complete response rate.

Discussion

T-DM1 is the first ADC licensed for patients with HER2-positive MBC. In the phase III trial, patients randomly allocated to T-DM1 had statistically significant and clinically meaningful improvements in the coprimary endpoints of PFS and OS. Furthermore, the safety profile of T-DM1 was considered acceptable for the indicated patient population. However, increased hepatic toxicity was observed and led to the addition of hepatotoxicity, liver failure, and death to the boxed warnings section of the prescribing information (21).

The era of targeted therapy in metastatic breast cancer began with the FDA approval of tamoxifen in 1977. In recent years, targeting HER2 has been a successful drug development pathway. Four anti-HER2 therapies have been licensed or approved by the FDA for the treatment of patients with MBC: the monoclonal antibody trastuzumab in 1998, the small molecule tyrosine kinase inhibitor lapatinib in 2007, the monoclonal antibody pertuzumab in 2012, and more recently ado-trastuzumab emtansine in 2013. Unfortunately, not all HER2-positive breast cancers are sensitive to these agents and many patients eventually develop resistance and progress. Recent studies indicate that HER2-positive breast cancer is biologically heterogeneous (22). Promising novel anti-HER2 agents are currently being developed and may ultimately prove to be safe and effective for patients with *de novo* or acquired resistant tumors (23–25). In addition, the safety and efficacy of T-DM1 in patients with early breast cancer are being evaluated in ongoing studies (Table 2).

In conclusion, T-DM1 demonstrated a favorable risk-benefit profile and fulfills an exigent public health need. It is yet another addition to the growing list of personalized therapies and another example of the success of the anti-HER2 drug development strategy.

Disclosure of Potential Conflicts of Interest

Q.C. Xu was an employee of the FDA when this article was first submitted for consideration; she is now an employee of Celgene. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Development of methodology: L. Amiri-Kordestani, R. Pazdur, P. Cortazar
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Skarupa, R. Pazdur

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References

- Yarden Y, Sliwkowski MX. Untangling the cErbB signalling network. *Nat Rev Mol Cell Biol* 2001;2:127–37.
- Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177–82.
- Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. *J Clin Oncol* 2010;28:92–8.
- Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist* 2009;14:320–68.
- Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783–92.
- Swain SM, Kim SB, Cortés J, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2013;14:461–71.
- Department of Health and Human Services. Approval letter [cited 2014 May 7]; p.13. Silver Spring (MD): U.S. Food and Drug Administration; 2011. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000Approv.pdf
- Erickson HK, Park PU, Widdison WC, Kovtun YV, Garrett LM, Hoffman K, et al. Antibody-maytansinoid conjugates are activated in targeted cancer cells by lysosomal degradation and linker-dependent intracellular processing. *Cancer Res* 2006;66:4426–33.
- Erickson HK, Lewis Phillips GD, Leipold DD, Provenzano C, Mai E, Johnson HA, et al. The effect of different linkers on target cell catabolism and pharmacokinetics/pharmacodynamics of trastuzumab maytansinoid conjugates. *Mol Cancer Ther* 2012;11:1133–42.
- Oroudjev E, Lopus M, Wilson L, Audette C, Provenzano C, Erickson H, et al. Maytansinoid-antibody conjugates induce mitotic arrest by suppressing microtubule dynamic instability. *Mol Cancer Ther* 2010;9:2700–13.
- Lewis Phillips GD, Li G, Dugger DL, Crocker LM, Parsons KL, Mai E, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-drug conjugate. *Cancer Res* 2008;68:9280–90.
- Junttila TT, Li G, Parsons K, Lewis Phillips G, Sliwkowski MX. Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib-insensitive breast cancer. *Breast Cancer Res Treat* 2011;128:347–56.
- U.S. Food and Drug Administration. Clinical pharmacology and biopharmaceutics review(s). [cited 2014 May 7]; p. 13. Silver Spring (MD): U.S. Food and Drug Administration; 2011. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000ClinPharmR.pdf.
- Verma S, Miles D, Gianni L, Kropp IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012;367:1783–91.
- Burris HA III, Rugo HS, Vukelja SJ, Vogel CL, Borson RA, Limentani S, et al. 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* 2011;29:398–405.
- Krop IE, LoRusso P, Miller KD, Modi S, Yardley D, Rodriguez G, et al. 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* 2012;30:3234–41.
- Hurvitz SA, Dirix L, Kocsis J, Bianchi GV, Lu J, Vinholes J, et al. 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* 2013;31:1157–63.
- Blum RH, Kahlert T. Maytansine: a phase I study of an ansa macrolide with antitumor activity. *Cancer Treat Rep* 1978;62:435–8.
- Eagan RT, Ingle JN, Rubin J, Frytak S, Moertel CG. Early clinical study of an intermittent schedule for maytansine (NSC-153858): brief communication. *J Natl Cancer Inst* 1978;60:93–6.
- Cabanillas F, Rodriguez V, Hall SW, Burgess MA, Bodey GP, Freireich EJ. Phase I study of maytansine using a 3-day schedule. *Cancer Treat Rep* 1978;62:425–8.
- Labeling [cited 2014 May 7]; p. 21. Reference ID: 3265306. Silver Spring (MD): U.S. Food and Drug Administration; 2011. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125427lbl.pdf.
- Montemurro F, Di Cosimo S, Arpino G. Human epidermal growth factor receptor 2 (HER2)-positive and hormone receptor-positive breast cancer: new insights into molecular interactions and clinical implications. *Ann Oncol* 2013;24:2715–24.
- Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. *Nat Rev Cancer* 2009;9:463–75.
- Tsang RY, Finn RS. Beyond trastuzumab; novel therapeutic strategies in HER2-positive metastatic breast cancer. *Br J Cancer* 2012;106:6–13.
- Stern HM. Improving treatment of HER2-positive cancers: opportunities and challenges. *Sci Transl Med* 2012;4:127rv2.

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