CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125427Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Patricia Cortazar, MD
CDTL Review
Ado-trastuzumab emtansine (KADCYLA™)
BLA 125427

Cross-Discipline Team Leader Review

Date	February 1, 2013
DDOP Clinical Team Leader	Patricia Cortazar, M.D.
BLA	125,427
Applicant	Genentech, Inc
Date of Submission	August 26, 2012
PDUFA Goal Date	Feb 26, 2013
Proprietary Name / Established (USAN) names	KADCYLA/ Ado-trastuzumab emtansine
Dosage forms / Strength	Lyophilized powder in single-use vials containing 100 mg per vial or 160 mg per vial
Proposed Indication(s)	As a single agent for the treatment of patients with HER2-positive metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy
Recommended:	***Approval***

Material Reviewed/Consulted	**Names of discipline reviewers/ Team Leaders**
Regulatory Project Manager	Lisa Skarupa/Alice Kacuba
Medical Officer Reviewers	Laleh Amiri-Kordestan, M.D. (efficacy)/ Patricia Cortazar, M.D. Gideon Blumenthal, M.D. (safety)/ Patricia Cortazar, M.D.
Statistical Review	Qiang Xu/ Shenghui Tang
Pharmacology Toxicology Review	David McGuinn/ Todd R. Palmby
CMC Review/DMA	Linan Ha (Traditional Elements)/Wendy Weinberg
CMC Reviw/ONDQA	Xiao-Hong Chen (drug substance, drug product)/Haripada Sarker Anne Marie Russell (linker)/Haripada Sarker
Microbiology Review (BMAB)	Bo Chi (Drug Substance)/Patricia Hughes Reyes Candau-Chacon (Drug Product)/Patricia Hughes
Clinical Pharmacology	Sarah J. Schrieber / Qi Liu
CDRH	Kevin Lorick/ Rena Philip
DDMAC	Marybeth Toscano/ Karen Rulli
OSI	Lauren Iacono-Connors/Janice Pohlman
OSE/DMEPA Consult	Jibril Abdus-Samad/Todd Bridges

Introduction

Genentech, Inc. submitted an original biologic licensing application (BLA) to support marketing approval of Kadcyla (ado-trastuzumab emtansine) as a single-agent for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy. This document summarizes the reviews and conclusions of each review discipline.

1. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

We recommend the approval of ado-trastuzumab emtansine (KADCYLA™ for injection, Genentech, Inc.) for the following indication:

> "As a single agent for the treatment of patients with HER2-positive metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy"

- Risk Benefit Assessment

The recommendation for regular approval is based on a randomized, multicenter, open-label trial enrolling 991 patients with HER2-positive metastatic breast cancer. Patients must have received prior taxane and trastuzumab-based therapy before trial enrollment. Patients who received these therapies only in the adjuvant setting were required to have disease recurrence during or within six months of completing adjuvant therapy. Breast tumor specimens were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a central laboratory.

Patients were randomly allocated (1:1) to receive ado-trastuzumab emtansine (N=495) by intravenous infusion, 3.6 mg/kg on day 1 every 21-days or lapatinib (N=496), 1250 mg/day orally once daily plus capecitabine, 1000 mg/m^2 orally twice daily for 14 days. Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal.

The co-primary efficacy endpoints of the study were progression-free survival (PFS), based on tumor response assessments by an independent review committee (IRC), and overall survival (OS). A statistically significant improvement in PFS was observed in patients receiving ado-trastuzumab emtansine compared to those receiving lapatinib plus capecitabine [HR=0.65 (95% CI: 0.55, 0.77), $p < 0.0001$]. The median PFS was 9.6 and 6.4 months for patients in the ado-trastuzumab emtansine and lapatinib plus capecitabine arms, respectively. At the time of the second interim OS analysis, a statistically significant improvement in OS was observed in

patients receiving ado-trastuzumab emtansine compared to those receiving lapatinib plus capecitabine [HR=0.68 (95% CI: 0.55, 0.85), p = 0.0006]. This result crossed the pre-specified efficacy stopping boundary (HR = 0.73 or p = 0.0037). The median OS was 30.9 and 25.1 months in the ado-trastuzumab emtansine and the lapatinib plus capecitabine arms, respectively. The effect on progression free survival and overall survival was consistent across relevant subgroups and was supported by evidence of anti-tumor activity with significant improvement in objective tumor responses in the major efficacy study.

Additionally, efficacy results from the pivotal study are further supported by three randomized Phase 2 studies. In Study TDM4450/BO21976, a PFS improvement was observed in patients receiving ado-trastuzumab emtansine compared to those receiving trastuzumab plus docetaxel [HR=0.59 (95% CI: 0.36, 0.97), p =0.035]. The median PFS was 14.2 and 9.2 months for patients in the ado-trastuzumab emtansine and trastuzumab plus docetaxel arms, respectively. In the TDM4374g and TDM4258g (single arm) studies in patients with HER2+ MBC who received prior trastuzumab, the observed ORR were 27% and 38%.

The most common (> 25%) adverse reactions observed in patients receiving ado-trastuzumab emtansine were nausea, fatigue, musculoskeletal pain, thrombocytopenia, increased transaminases, headache, and constipation. The most common adverse events leading to ado-trastuzumab emtansine withdrawal were thrombocytopenia and increased transaminases. The most common (> 2%) NCI – CTCAE (version 3) Grade 3 – 4 adverse reactions were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy and fatigue. Serious hepatobiliary disorders, including at least two fatal cases of severe drug-induced liver injury and associated hepatic encephalopathy, have been reported in clinical trials with ado-trastuzumab emtansine. Other significant adverse reactions reported with ado-trastuzumab emtansine include left ventricular dysfunction, interstitial lung disease, and infusion-associated reactions. Five cases of drug overdose, including a fatal case were reported. To mitigate the risk of medication errors, a distinguished prefix in the nonproprietary name for Kadcyla (ado-trastuzumab emtansine) was required to distinguish the product from Herceptin (trastuzumab).

There were significant CMC concerns related to manufacture of ado-trastuzumab emtansine, both from the small molecule (DM1) and CGMP perspective. The small molecule concern relates to (b) (4) This was identified upon inspection of the (b) (4) drug substance manufacturing facility. CGMP and micro product quality concerns include the lack of a validated test method to measure endotoxin in the final drug product and the inadequate cleaning validation (b) (4) at the drug product facility. (b) (4)

In conclusion, ado-trastuzumab emtansine demonstrates a favorable risk-benefit profile. We are approving this application based on clinical determination that a compelling exigent public health need outweighs the risk. Unfortunately the CMC issues pertaining to the manufacture had delayed the availability of Kadcyla (ado-trastuzumab emtansine) to patients that desperate need anti HER2 therapy. During the review of Pertuzumab, another anti HER2 therapy manufactured by Genentech, the Agency also found multiple CMC issues pertaining to production, which

resulted in the applicant's commitment to undertake several steps to ensure a consistent drug supply and manufacturing process.

Steps to ensure a consistent drug supply and manufacturing process of Kadcyla (ado-trastuzumab emtansine) are outlined in the post-marketing obligations that the company has agreed to undertake (please refer to Section 15 of this review).

2. Background

Ado-trastuzumab emtansine is a HER2-targeted antibody-drug conjugate (ADC) which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex.

The antibody is the humanized anti-HER2 IgG1, trastuzumab. The small molecule cytotoxin, DM1, is a microtubule inhibitor. Upon binding to sub-domain IV of the HER2 receptor, ado-trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites. Binding of DM1 to tubulin disrupts microtubule networks in the cell, which results in cell cycle arrest and apoptotic cell death. In addition, *in vitro* studies have shown that similar to trastuzumab, ado-trastuzumab emtansine inhibits HER2 receptor signaling, mediates antibody-dependent cell-mediated cytotoxicity and inhibits shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2.

Regulatory History

The initial IND application for this product (IND 71072) was submitted by Genentech, Inc in December 2005.

December 19, 2007: The development program in support of ado-trastuzumab emtansine registration was discussed with FDA.

- FDA strongly recommended that a regulatory submission to support T-DM1 approval should be based on results from one or more well-designed, well conducted randomized trials with clinically meaningful and statistically significant study results.
- FDA stated that it is unlikely that the results of single-arm studies alone would support approval.
- FDA cautioned the Sponsor that (b) (4) this determination occurs at the time of BLA review.

June 2, 2010: Genentech submitted a BLA application to support marketing approval of T-DM1 as a single agent for the treatment of patients with HER2-positive metastatic breast cancer who have received both prior trastuzumab and a lapatinib-containing chemotherapy regimen in the metastatic setting. The applicant submitted two phase 2 single arm trials with objective response rate as the primary endpoint (b) (4)

- [redacted] (b) (4)
- FDA also stated that a well-controlled trial is necessary to properly define the safety profile of T-DM1, a new molecular entity. A review of the T-DM1 preclinical and clinical data showed hepatotoxicity, including a Grade 5 event. Attribution of the clinical toxicity after T-DM1 exposure cannot be properly assessed without a control.
- FDA recommended that data from a randomized Phase 3 trial will be necessary to support approval of T-DMl. As discussed at the ODAC meeting held on July 23, 2010, the problems with PFS include interpretation of the clinical significance of a given improvement in PFS, between trial reproducibility, and lack of correlation with OS in metastatic breast cancer trials. If the study is conducted in a less refractory population, OS should be the primary endpoint.
- At the application orientation meeting, FDA stated that [redacted] (b) (4) a final analysis of objective response rate and PFS, with confirmation of clinical benefit based on the final analysis of OS in the same randomized Phase 3 trial. Therefore, FDA strongly recommended that the Phase 3 trial be adequately powered for survival.

October 2010: FDA agreed with the EMILIA trial protocol amendment to incorporate OS as a co-primary endpoint.
May 9, 2012: Fast-track designation was granted.
June 12, 2012: Rolling submission of BLA 125,427 started with the submission of the non-clinical components.
August 24, 2012: The BLA rolling submission was completed with the submission of the clinical and statistical components.

3. CMC

The CMC component of this BLA was reviewed by, the Division of Monoclonal Antibodies, Office of Biotechnology Products (OBP), ONDQA (small molecule drug/linker), and the Biotech Manufacturing Assessment Branch (BMAB). The CMC groups recommend approval of KADCYLA (Ado-trastuzumab emtansine). The data submitted in the BLA application support the conclusion that the manufacture of KADCYLA (Ado-trastuzumab emtansine) is well controlled, and leads to a product that is pure and potent. The conditions used in manufacturing have been sufficiently validated and a consistent product was produced from the multiple production runs presented.

Later in the review, OMPQ was involved [redacted] (b) (4)

Trastuzumab emtansine is produced from two intermediates, the monoclonal antibody trastuzumab and the microtubule inhibitory maytansinoid DM1, which are linked together using a starting material, the heterobifunctional linker SMCC (b) (4)

There were significant CMC concerns related to manufacture of ado-trastuzumab emtansine, both from the small molecule (DM1) and CGMP perspective:

The small molecule concern relates to (b) (4) This was identified upon inspection of the (b) (4) drug substance manufacturing facility and brought back to the Agency as a review issue. Refer to reviews from ONDQA and NDMAB regarding this issue.

Three establishments were inspected in support of the approval of this BLA:

(b) (4)

The final decision on the CGMP status of these establishments is pending by NDMAB (through a TB-EER in DARRTS).

Significant Micro quality and CGMP concerns include:

- endotoxin masking effects and lack of a validated test method to measure endotoxin in final drug product stored in glass vials;
- inadequate cleaning validation (b) (4) at the drug product facility (b) (4) Refer to reviews from BMAB regarding these CGMP issues.

The deficiencies were resolved by the submission of additional data and information from completed studies and through PMCs. (b) (4) concerns associated with market launch lots manufactured at (b) (4) were mitigated with the February 11, 2013 submission of cleaning verification data (b) (4). The total (b) (4) from rinse and swab samples from each of three runs were below the cleaning acceptance criteria (b) (4)

Steps to ensure a consistent drug supply and manufacturing process of Kadcyla (ado-trastuzumab emtansine) are outlined in the post-marketing obligations that the company has agreed to undertake (please refer to Section 15 of this review).

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewer, Dr. McGuinn, and the supervisory reviewers, Drs. Palmby, and Leighton state that there are no outstanding clinical pharmacology issues that preclude approval and that no additional pharmacology/toxicology studies are needed.

Based on the data provided in the BLA, ado-trastuzumab emtansine was assigned a new Established Pharmacologic Class (EPC). The FDA text for the EPC that was determined to be both scientifically accurate and clinically meaningful is "HER2-targeted antibody and microtubule inhibitor conjugate." Including "microtubule inhibitor" is considered an important aspect of the EPC to distinguish toxicities associated with this type of compound compared to those associated with other types of cytotoxic compounds.

The application was supported by pharmacology studies in *in vitro* models and animal safety studies. The *in vitro* studies showed that similar to trastuzumab, ado-trastuzumab emtansine inhibits HER2 receptor signaling, mediates antibody-dependent cell-mediated cytotoxicity and inhibits shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2. In monkeys, treatment with doses of ado-trastuzumab emtansine up to 30 mg/kg (about 7 times the clinical exposure based on AUC) caused dose dependent axonal degeneration in the sciatic nerve with hypertrophy or hyperplasia of the Schwann cells, and axonal degeneration of the dorsal funiculus in the spinal cord. Based on the mechanism of action of the cytotoxic component DM1, there is clinical potential for neurotoxicity.

As documented in Dr. McGuinn's review, based on results from animal toxicity studies, ado-trastuzumab emtansine may impair fertility in humans. In a single-dose toxicity study of ado-trastuzumab emtansine in rats, degeneration of seminiferous tubules with hemorrhage in the testes and hemorrhage and necrosis of the corpus luteum in ovaries, were observed.

The Pharmacology/Toxicology review team recommended pregnancy category D for ado-trastuzumab emtansine. The basis for this recommendation was that preclinical studies with DM1 or ado-trastuzumab emtansine indicated toxic effect to rapidly dividing cells and that DM1 was demonstrated to be genotoxic. In addition, Postmarketing data from trastuzumab show that treatment during pregnancy has resulted in oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death.

(b) (4)

. A more detailed assessment can be found in Dr. Palmby's Supervisory memorandum.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology/biopharmaceutics reviewer (Sarah J. Schrieber) and team leader (Qi Liu) concluded that there are no outstanding clinical pharmacology issues that preclude approval.

The dose and schedule chosen for the major efficacy trial, was based on the results of a Phase 1 dose escalation study (TDM3569g) and 3 phase II studies (TDM4374g, TDM4258g, TDM4450g/BO21976). The maximum tolerated dose (MTD) was determined to be 3.6 mg/kg IV q3w in the phase 1 study.

Based on population pharmacokinetic analysis, following intravenous infusion of ado-trastuzumab emtansine, the clearance was 0.68 L/day and the elimination half-life (t1/2) was approximately 4 days. No accumulation of ado-trastuzumab emtansine was observed after repeated dosing of intravenous infusion every 3 weeks.

Based on population pharmacokinetic analysis (n=671), body weight, sum of longest diameter of target lesions by RECIST, HER2 extracellular domain (ECD) concentrations, AST, albumin, and baseline trastuzumab concentrations were identified as statistically significant covariates for ado-trastuzumab emtansine clearance. However, the magnitude of effect of these covariates on ado-trastuzumab emtansine exposure suggests that, with the exception of body weight, these covariates are unlikely to have a clinically meaningful effect on ado-trastuzumab emtansine exposure. Therefore, the body weight based dose of 3.6 mg/kg every 3 weeks without correction for other covariates was considered appropriate.

The overall incidence of positive anti-therapeutic antibody (ATA) to ado-trastuzumab emtansine was determined to be 5.3% in the studies included in the BLA with the assays used.

Based on the results of the population pharmacokinetic analysis, ado-trastuzumab emtansine exposure in patients with moderate (CLcr 30 - 59 mL/min, n=53) and mild (CLcr 60 - 89 mL/min, n=254) renal impairment were similar to those in patients with to normal renal function (CLcr ≥ 90 mL/min, n=361). Data from only one patient with severe renal impairment (CLcr < 30 mL/min) is available. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited pharmacokinetic data available. No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of ado-trastuzumab emtansine.

The effect of multiple doses of ado-trastuzumab emtansine (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open label, single arm study in 51 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., > 20 ms) were detected in the study.

6. Clinical/Statistical- Efficacy

This BLA is primarily supported by results from a single industry-sponsored study, EMILIA/TDM4370g /BO21977 entitled:

> "A Randomized, Multicenter, Phase III Open-Label Study of the Efficacy and Safety of Trastuzumab-MCC-DM1 vs. Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer Who Have Received Prior Trastuzumab-Based Therapy"

Three additional supportive clinical studies were submitted by the applicant: two single arm Phase 2 studies (TDM4374g TDM4258g) in patients with previously treated HER2+ MBC and one randomized Phase 2 study (TDM4450g) in patients with LABC or no prior MBC treatment.

EMILIA/TDM4370g /BO21977

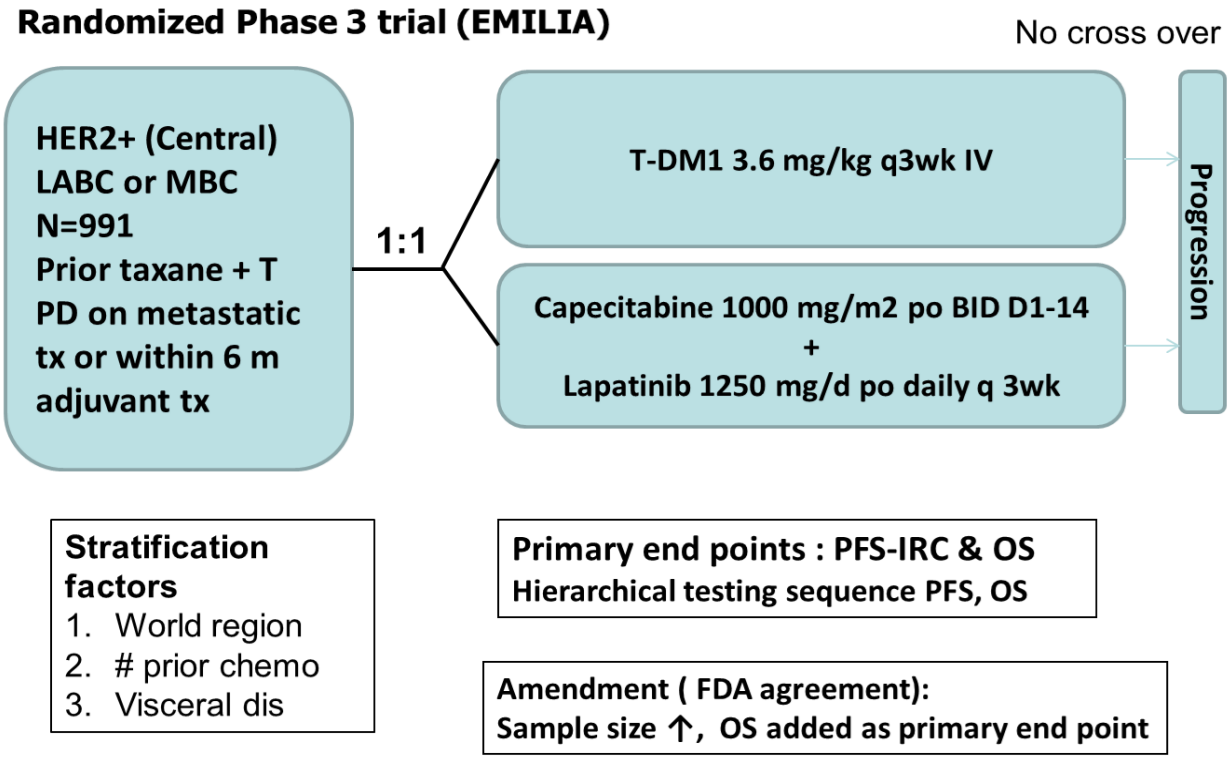
The EMILIA protocol had two major amendments:

- **May 2011:** In response to FDA's advice comments, OS was incorporated as the co-primary endpoint to PFS and the sample size was increased from 580 to 980 to power for OS.
- **June 2012**: In light of the PFS improvement at the time of the final PFS analysis, the sponsor proposed to conduct an additional interim OS analysis when 50% of the planned deaths had occurred. If statistical significance was to be established, then patients in the control arm would be allowed to cross-over to the ado-trastuzumab emtansine arm. The Agency approved the additional interim OS analysis provided that there was appropriate alpha adjustment in the sequential testing plan.

Study Design:

The EMILIA trial was a randomized, multicenter, open-label trial of 991 patients with HER2-positive metastatic breast cancer. Key eligibility criteria included confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease. Breast tumor specimens were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a central laboratory. Patients were eligible if they had prior trastuzumab and a taxane, separately or in combination: as prior therapy for metastatic disease, or as adjuvant therapy with disease recurrence during or within six months of completion. Baseline LVEF was required to be ≥ 50%. Patients were randomly allocated (1:1) to receive lapatinib plus capecitabine or ado-trastuzumab emtansine. Randomization was stratified by world region (United States, Western Europe, other), number of prior chemotherapy regimens for unresectable locally advanced or metastatic disease (0–1, >1) and visceral versus non-visceral disease as determined by the investigators.

Figure 1 EMILIA Study Design (from the clinical review)



Ado-trastuzumab emtansine was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Lapatinib was administered at 1250 mg/day orally once per day of a 21-day cycle and capecitabine was administered at 1000 mg/m^2 orally twice daily on Days 1−14 of a 21-day cycle. Patients were treated with ado-trastuzumab emtansine or lapatinib plus capecitabine until progression of disease, withdrawal of consent, or unacceptable toxicity.

The co-primary efficacy endpoints of the study were progression-free survival (PFS) based on tumor response assessments by an independent review committee (IRC), and overall survival (OS). PFS was defined as the time from the date of randomization to the date of disease progression or death from any cause (whichever occurred earlier). Secondary endpoints included PFS (based on investigator tumor response assessments), objective response rate (ORR), duration of response and time to symptom progression.

Statistical Analysis Plan:
The statistical analysis plan specified a sample size of 980 patients needed to provide 80% power at a 2-sided alpha level of 0.05 to detect a 4.3 month improvement in OS from 17.2 months in the lapatinib plus capecitabine arm to 21.5 months in the ado-trastuzumab emtansine arm (HR=0.8). The trial was sized for approximately 50% of the required deaths at the time of final PFS analysis.

A total of 508 IRF-assessed PFS events were required to detect a 2.1 month improvement in median PFS (from 6.2 months in the control arm to 8.3 months in the ado-trastuzumab emtansine arm) with a hazard ratio of 0.75 at a two-sided significance level of 0.05 with 90% power.

There was no planed interim analysis of PFS. The first interim analysis of OS was planned and conducted at the time of the final PFS analysis. A second interim OS analysis was added when 50% of the planned number of deaths had occurred. A Lan-DeMets alpha-spending function with an O'Brien-Fleming stopping boundary was used for these interim analyses of OS.

EMILIA Efficacy Results:

The trial randomized 991 patients, 495 to the ado-trastuzumab emtansine arm and 496 to the lapatinib plus capecitabine arm, comprising the ITT population.

Baseline demographics and treatment characteristics were balanced between treatment arms. All patients had metastatic disease at study entry. The median age was approximately 53 years (range 24-84 years), 74% were White, 18% were Asian and 5% were Black. All but 5 patients were women. Twenty-seven percent of patients were enrolled in United States, 32% in Europe and 16% in Asia. Tumor prognostic characteristics including hormone receptor status (positive: 55%, negative: 43%), presence of visceral disease (68%) and non-visceral disease only (33%) and the number of metastatic sites (< 3: 61%, ≥ 3: 37%) were similar in the study arms.

The majority of patients (88%) had received prior systemic treatment in the metastatic setting. Twelve percent of patients had prior treatment only in the neoadjuvant or adjuvant setting and had disease relapse within 6 months of treatment. All but one patient received trastuzumab prior to study entry; approximately 85% of patients received prior trastuzumab in the metastatic setting. Over 99% percent of patients had received a taxane, and 61% of patients had received an anthracycline prior to study entry. Overall, patients received a median of three systemic agents in the metastatic setting. Among patients with hormone receptor-positive tumors, 44.4% received prior adjuvant hormonal therapy and 44.8% received hormonal therapy for locally advanced/metastatic disease.

Progression-Free Survival:

The EMILIA trial demonstrated a statistically significant improvement in IRC-assessed PFS in the in the ado-trastuzumab emtansine-treated group compared with the lapatinib plus capecitabine-treated group [hazard ratio (HR) = 0.65, 95% CI: 0.55, 0.77, $p < 0.0001$], and an increase in median PFS of 3.2 months (median PFS of 9.6 months in the ado-trastuzumab emtansine arm-treated group vs. 6.4 months in the lapatinib plus capecitabine group). See Table 1 and Figure 2. The results for investigator-assessed PFS were similar to those observed for IRC-assessed PFS.

Table 1 Summary of Efficacy from EMILIA

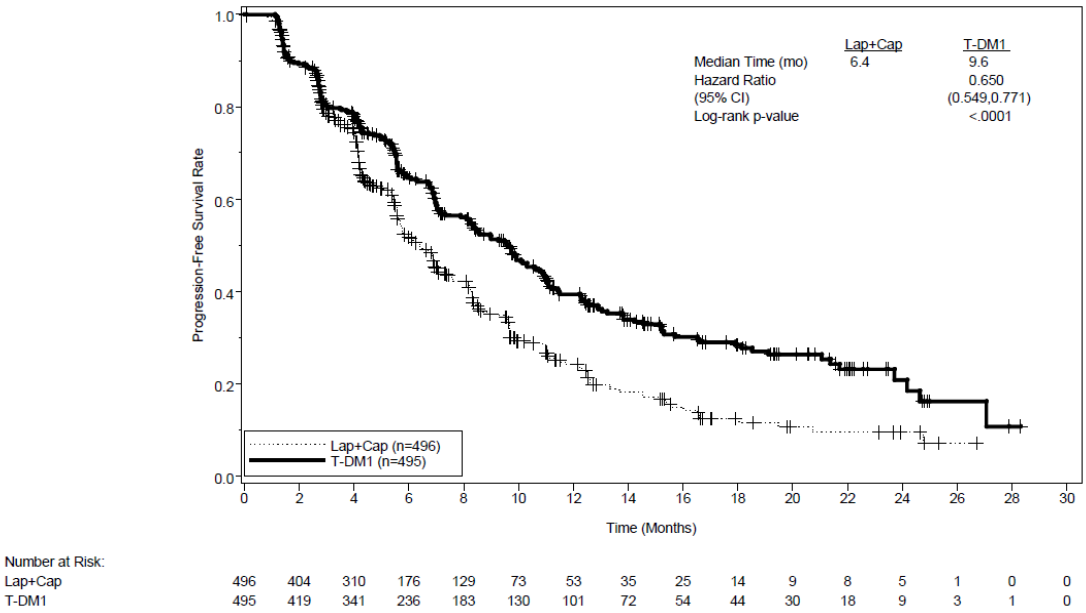
	KADCYLA N= 495	**Lapatinib +Capecitabine N= 496**
Progression-Free Survival (independent review)		
Number (%) of patients with event	265 (53.5%)	304 (61.3%)
Median duration of PFS (months)	9.6	6.4
Hazard Ratio (stratified*)	0.650	
95% CI for Hazard Ratio	(0.549, 0.771)	
p-value (Log-Rank test, stratified*)	<0.0001	
Overall Survival **		
Number (%) of patients who died	149 (30.1%)	182 (36.7%)
Median duration of survival (months)	30.9	25.1
Hazard Ratio (stratified*)	0.682	
95% CI for Hazard Ratio	(0.548, 0.849)	
p-value (Log-Rank test*)	0.0006	
Objective Response Rate (independent review)		
Patients with measurable disease	397	389
Number of patients with OR (%)	173 (43.6%)	120 (30.8%)
Difference (95% CI)	12.7% (6.0, 19.4)	
Duration of Objective Response (months)		
Number of patients with OR	173	120
Median duration (95% CI)	12.6 (8.4, 20.8)	6.5 (5.5, 7.2)

PFS: progression-free survival; OR: objective response

* Stratified by world region (United States, Western Europe, other), number of prior chemotherapeutic regimens for locally advanced or metastatic disease (0-1 vs. >1), and visceral vs. non-visceral disease.

** The second interim analysis for OS was conducted when 331 events were observed and the results are presented in this table.

Figure 2 Kaplan-Meier Curve of IRC-assessed Progression-Free Survival for EMILIA



Number at Risk:

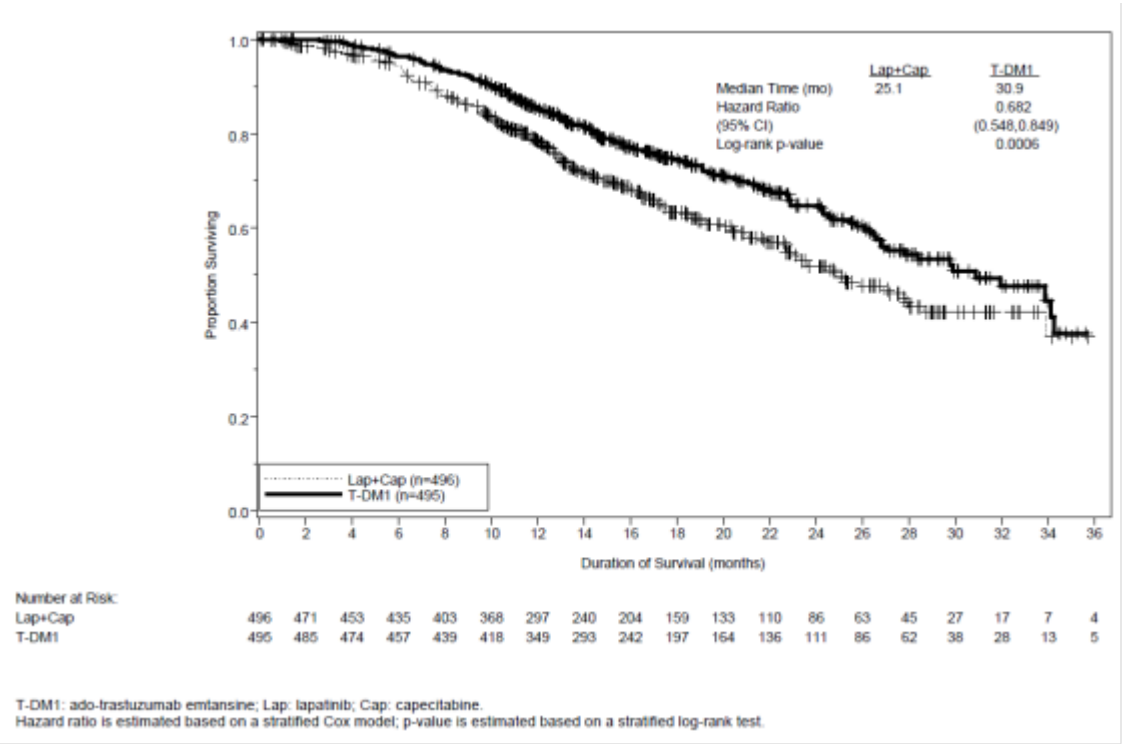
Lap+Cap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

T-DM1: ado-trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine; IRC: independent review committee.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

Overall Survival:

At the time of PFS analysis, 223 patients had died. More deaths occurred in the lapatinib plus capecitabine arm (26%) compared with the ado-trastuzumab emtansine arm (19%), however the results of the first interim OS analysis did not meet the pre-specified stopping boundary for statistical significance. At the time of the second interim OS analysis, 331 events had occurred. The co-primary endpoint of OS was met; OS was significantly improved in patients receiving ado-trastuzumab emtansine (HR = 0.68, 95% CI: 0.55, 0.85, p = 0.0006). This result crossed the pre-specified efficacy stopping boundary (HR = 0.73 or p = 0.0037). The median duration of survival was 30.9 months in the ado-trastuzumab emtansine arm vs. 25.1 months in the lapatinib plus capecitabine arm (See Table 1 and Figure 3).

Figure 3 Kaplan-Meier Curve of Overall Survival for EMILIA



T-DM1: ado-trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

Consistent treatment effect with ado-trastuzumab emtansine in terms of PFS and OS was observed in patient subgroups based on stratification factors, key baseline demographic, disease characteristics, and prior treatments (Figure 4 and Figure 5). In patients ≥ 65 years old (n=138), the hazard ratios for PFS and OS were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively. In patients with non-visceral disease, the hazard ratios for PFS and OS were 0.96 (95% CI: 0.71, 1.3) and 1.05 (95% CI: 0.69, 1.61), respectively.

Figure 4 Forest Plot of PFS for EMILIA Trial (From Dr. Xu Statistical reviewer)

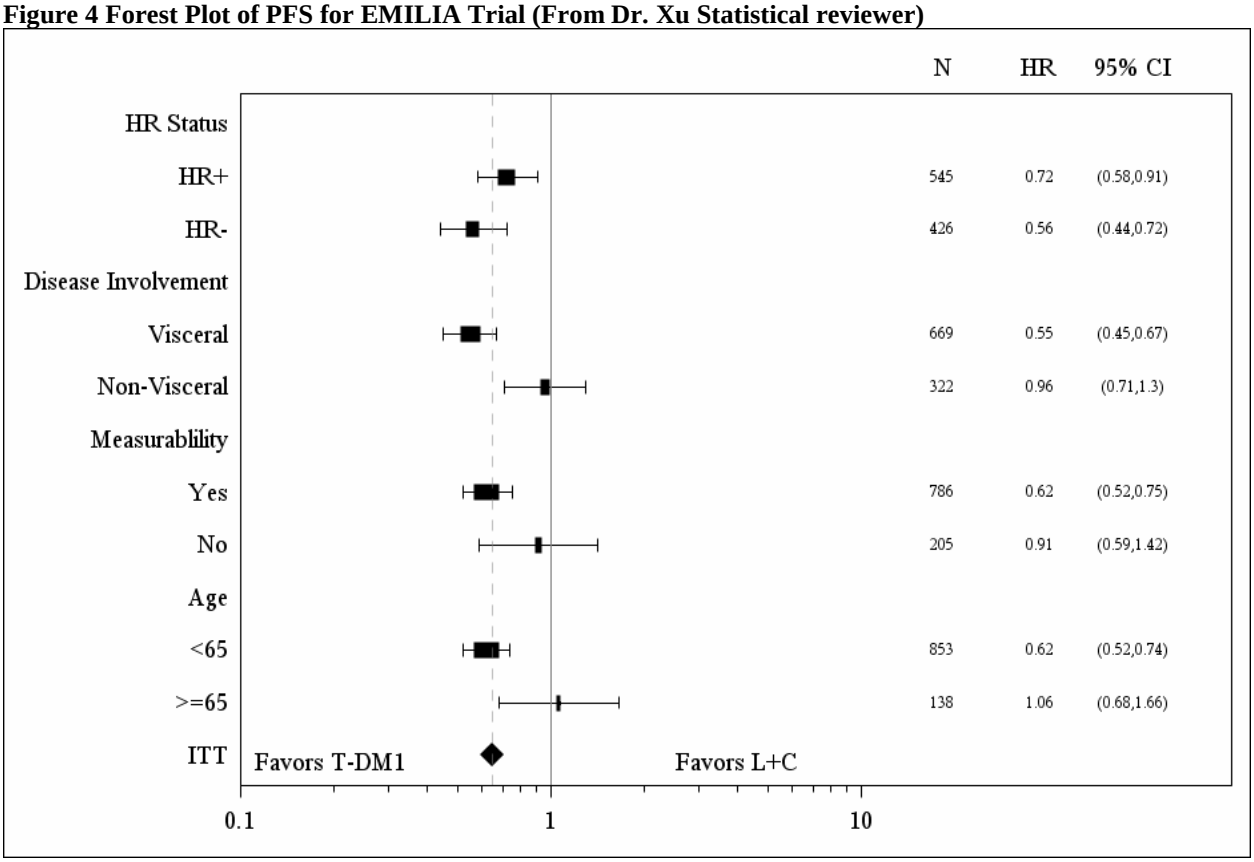
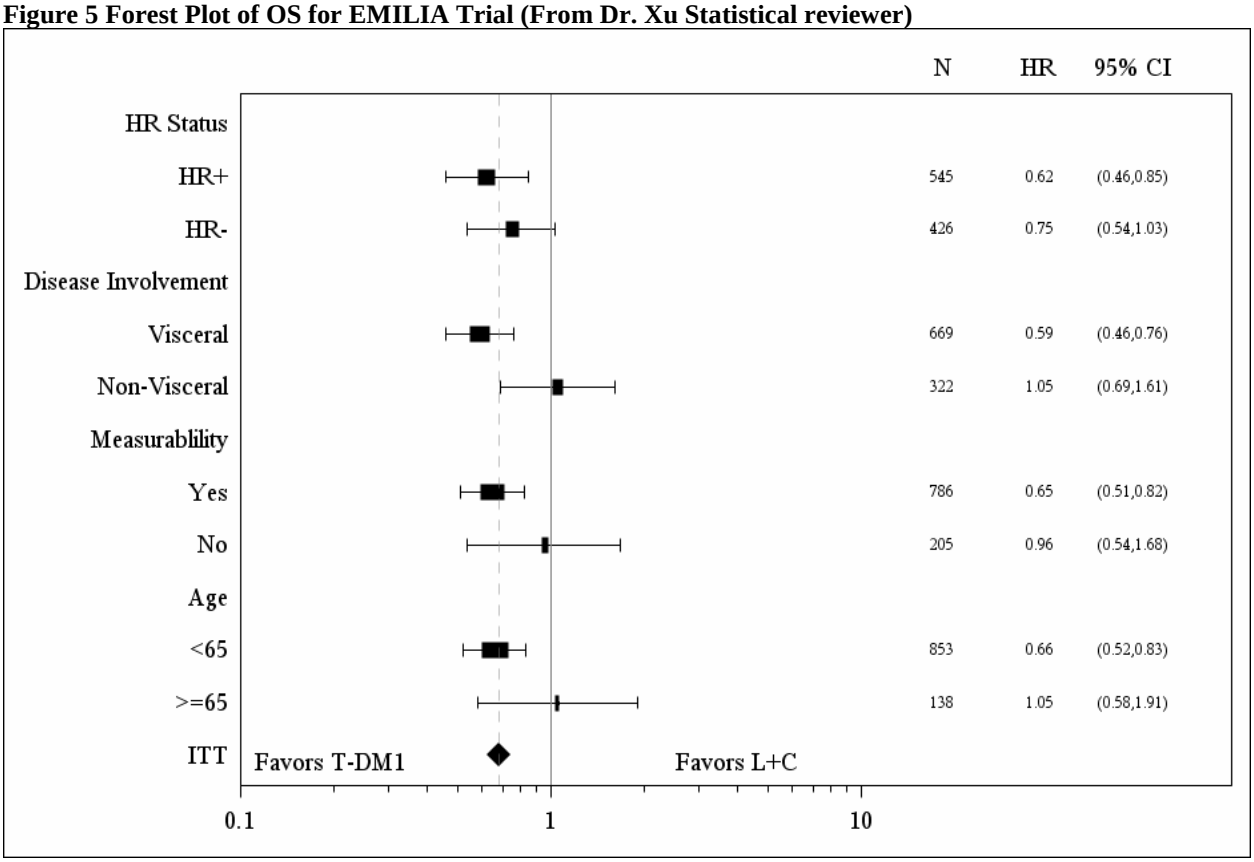


Figure 5 Forest Plot of OS for EMILIA Trial (From Dr. Xu Statistical reviewer)



Several sensitivity analysis conducted by the sponsor as well as the FDA reviewers showed the consistency of the PFS results with the primary PFS analysis.

A GCP compliance deviation related to the conduct of the IRC assessment of disease progression was identified by the FDA during this BLA review. Per the IRC charter, clinical information was to be redacted of all references to specific toxicities that could unblind the treatment. However, the patient profiles provided by the sponsor to the IRC for oncology review contained information on drug specific toxicities, which may have potentially biased the assessments by the oncology reviewer. To examine the impact of this compliance deviation, two additional sensitivity analyses were subsequently conducted in which PFS was derived based on (1) IRC radiologist-assessed progression or death and (2) the earliest progression of either radiology or oncology review or death. The hazard ratios from the stratified Cox regression were consistent with the primary PFS results.

SUPPORTIVE STUDIES

Additionally, efficacy results from the pivotal study are further supported by three Phase 2 studies.

In the **TDM4450/BO21976** randomized Phase 2 study, an improvement in PFS was observed in patients receiving ado-trastuzumab emtansine compared to those receiving trastuzumab plus

docetaxel [HR=0.59 (95% CI: 0.36, 0.97), p =0.035]. The median PFS was 14.2 and 9.2 months for patients in the ado-trastuzumab emtansine and trastuzumab plus docetaxel arms, respectively.

In the **TDM4374g** and **TDM4258g** (single arm) studies in patients with HER2+ MBC who received prior trastuzumab, the observed ORR were 27% and 38%.

7. Safety

The safety database for ado-trastuzumab emtansine was adequate to characterize the safety of this product for the proposed indication. The clinical safety data supporting this BLA is primarily derived from the pivotal phase 3 trial EMILIA (4370g) and 5 additional phase 1 and phase 2 studies. The Applicant submitted safety data from 882 Her2-positive metastatic breast cancer patients exposed to ado-trastuzumab emtansine at a dose of 3.6 mg/kg every 3 weeks. The most common (frequency ≥ 25%) adverse drug reactions (ADRs) seen in patients treated with ado-trastuzumab emtansine were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation. As stated in Dr. Blumenthal's review, the following are the key safety findings from the pivotal EMILIA randomized controlled trial, and from the supportive safety database:

- **Deaths**: There were fewer deaths within 30 days in the ado-trastuzumab emtansine treatment arm compared to the lapatinib plus capecitabine treatment arm (4 versus 18). Of these 4 deaths on ado-trastuzumab emtansine, one was considered drug related (metabolic encephalopathy).

- **Serious Adverse Events (SAE) and Dose Modifications**: There were less SAEs on the ado-trastuzumab emtansine arm compared to the lapatinib + capecitabine arm (15.5% versus 18%). In addition, there were fewer AEs leading to discontinuation (5.9% ado-trastuzumab emtansine, 7.6% lapatinib, 9.4% capecitabine) and AEs leading to dose reduction (15.1% ado-trastuzumab emtansine, 18.9% lapatinib, 38.5% capecitabine) with ado-trastuzumab emtansine.

- **Grade 3 and 4 Adverse Reactions:** There were fewer grade 3-4 adverse reactions on ado-trastuzumab emtansine compared to the lapatinib plus capecitabine arm (41% vs. 57%). Grade 3-4 adverse events more common on ado-trastuzumab emtansine included: thrombocytopenia (particularly in Asian patients), transaminase elevations, and anemia. Grade 3-4 adverse events more common on lapatinib + capecitabine include diarrhea, hand-foot syndrome, vomiting, neutropenia, hypokalemia, fatigue, nausea, and mucosal inflammation.

- **Common Adverse Reactions:** In the EMILIA trial, common adverse events with large differences between ado-trastuzumab emtansine and the control included thrombocytopenia (28% vs. 2%), constipation (25% vs. 10%), headache (27% vs. 14%),

AST increased (22% vs. 9%), epistaxis (20% vs. 8%), dry mouth (16% vs. 5%), myalgia (14% vs. 4%), and pyrexia (18% vs. 8%).

- **Hepatic Toxicity**: In the EMILIA trial, there was a higher incidence of liver enzyme elevation on ado-trastuzumab emtansine, and higher incidence of bilirubin elevations on lapatinib plus capecitabine. In the entire ado-trastuzumab emtansine development program, there have been at least two cases of hepatic failure leading to death possibly related to ado-trastuzumab emtansine. Based on the available data, the potential of ado-trastuzumab emtansine causing rare but serious drug induced liver injury events is high. Therefore, a boxed warning is recommended.

- **Cardiac Toxicity:** Patients with LVEF declines and LV dysfunction w observed in the ado-trastuzumab emtansine development program. The incidence of cardiac toxicity appears to be no greater than that observed in the comparator arms of EMILIA (lapatinib plus capecitabine) and 4450g (trastuzumab plus docetaxel). Since there is no evidence that ado-trastuzumab emtansine is less cardiotoxic than trastuzumab, and trastuzumab carries a boxed warning for cardiomyopathy, a cardiac toxicity boxed warning was placed on the label.

- **Neurologic Toxicity**: In the pivotal EMILIA trial, a higher incidence of grade 3-4 peripheral neuropathy was observed on the ado-trastuzumab emtansine arm compared to the lapatinib plus capecitabine arm (3.1% versus 0.4%), with a lower incidence in the ado-trastuzumab emtansine compared to trastuzumab plus docetaxel (1.4% versus 6.1%) in the randomized phase 2 study). In the EMILIA trial, all but one patient reported resolution of grade 3-4 peripheral neuropathy.

- **Pulmonary Toxicity**: In the EMILIA trial, 6 patients (1.2%) on the ado-trastuzumab emtansine arm developed pneumonitis, all of which were grade 2. Two patients (0.4%) experienced pneumonitis on the lapatinib plus capecitabine arm, both of which were grade 2. Of the six ado-trastuzumab emtansine patients who experienced pneumonitis, four resolved completely, one resolved to grade 1, and one was ongoing at the time of data cut-off.

- **Thrombocytopenia**: In the pivotal study, there was a higher incidence of grade 3-4 thrombocytopenia on the ado-trastuzumab emtansine arm compared to the lapatinib plus capecitabine arm (12.9% vs. 0.2%). The incidence of grade 3-4 thrombocytopenia was particularly high in Asian patients (45.1% vs. 1.3%). The thrombocytopenia was reversible with dose interruption. Six patients treated with ado-trastuzumab emtansine experienced both grade 3-4 bleeding and grade 3-4 thrombocytopenia, but these were not temporally associated. There were no cases of serious bleeding or hemorrhage related to thrombocytopenia in EMILIA.

- **Overdose Potential:** A total of five cases of overdose with ado-trastuzumab emtansine were reported as of November 9, 2012: one serious case and four non-serious. In the fatal case, the patient incorrectly received ado-trastuzumab emtansine at 6 mg/kg and

died approximately 3 weeks following the overdose. It is not possible to exclude the possibility that the death was related to ado-trastuzumab emtansine. The FDA reviewers had concerns about further medication errors, particularly with the proliferation of dropdown menus in chemotherapy ordering systems. Given our concern, as well as concern from the Division of Medication Error Prevention and Analysis (DMEPA) over confusion between trastuzumab and trastuzumab-emtansine, a series of internal meetings (including with DMEPA, DOP-1 and OND Therapeutic Biologics and Biosimilars team) were held on ways to mitigate the risk of medication errors. FDA determined that the use of a distinguishing prefix in the nonproprietary name for Kadcyla (ado-trastuzumab emtansine) will be necessary to distinguish the product from Herceptin (trastuzumab). For further details, see the December 12, 2012 memorandum by Dr Leah A Christl.

8. Advisory Committee Meeting

There were no controversial issues identified by the review team that would have benefitted from an advisory committee discussion.

9. Pediatrics

Ado-trastuzumab emtansine has not been studied in children.

The review for ado-trastuzumab emtansine was conducted by the PeRC PREA Subcommittee on December 12, 2012. The Division presented a full waiver in pediatric patients because the disease/condition does not exist in the pediatric population, which is indicated for the treatment of patients with HER2-positive metastatic breast cancer. The PeRC agreed with the Division to grant a full waiver for this indication.

10. Other Relevant Regulatory Issues

The patent exclusivity has not been determined at the time of this review. This determination will need to be taken to the CDER Exclusivity Board after the BIC discussion. This decision and process will set precedent for biologic reference product exclusivity so there is a need to have agreement from involved parties.

The OSI inspected four of the highest accruing sites, three in South Korea, and one in Canada. The inspectional findings revealed no significant deviations that would preclude the use of the clinical data provided in support of this BLA. An inspection of the CRO revealed that the Applicant provided clinical data for each subject to (b) (4) who could potentially resulted in subject unblinding of the "blind independent medical oncologist reviewer". Sensitivity analysis conducted by the clinical and statistical reviewers showed that this potential unblinding of subjects did not impact the reliability of the study results and the study outcome.

According to the Applicant, the study was conducted in full conformance with the principles of the Declaration of Helsinki or with the laws and regulations of the country where the research was conducted, whichever provided greater protection to the individual. The study adhered to the January 1997 ICH Guideline for Good Clinical Practice. Written informed consent was obtained from each participant in the study. The protocol and subsequent amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB).

There were no financial conflicts of interest identified by any investigator as defined in 21 CFR 54.2(a), (b), and (f).

11. Labeling

Key clinical labeling recommendations included:

Labeling changes to address the potential for hepatotoxicity, cardiotoxicity and embryo-fetal toxicity:

- Add a 'boxed warning':

WARNING: HEPATOTOXICITY, CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- **Do not substitute KADCYLA for or with trastuzumab. (2.1)**
- **Hepatotoxicity, liver failure and death have occurred in KADCYLA-treated patients. Monitor hepatic function prior to initiation and prior to each dose. Institute dose modifications or permanently discontinue as appropriate. (2.2, 5.1)**
- **KADCYLA may lead to reductions in left ventricular ejection fraction (LVEF). Assess LVEF prior to initiation. Monitor and withhold dosing or discontinue as appropriate. (2.2, 5.2)**
- **Can cause fetal harm. Advise women of potential risk to the fetus. (5.3, 8.1, 8.6)**

A prefix prior to trastuzumab-emtansine was added to mitigate against medication errors.

12. Post-Marketing Requirements and Commitments

POSTMARKETING REQUIREMENT UNDER SECTION 505(o) OF THE FD&C ACT:

1. Establish a Pregnancy Registry to collect and analyze information for 10 years on pregnancy complications and birth outcomes in women with breast cancer exposed to ado-trastuzumab-emtansine within 6 months of conception or during pregnancy. Submit yearly interim reports, which may be included in your annual reports, on the cumulative findings and analyses from the Pregnancy Registry. Draft Protocol to be submitted 3/2013.

   This study will be conducted according to the following schedule:

Draft Protocol Submission:	03/2013
Final Protocol Submission:	05/2013
Interim Report #1:	05/2014
Interim Report #2:	05/2015
Interim Report #3:	05/2016
Interim Report #4:	05/2017
Interim Report #5:	05/2018
Interim Report #6:	05/2019
Interim Report #7:	05/2020
Interim Report #8:	05/2021
Interim Report #9:	05/2022
Study Completion:	05/2023
Final Report Submission:	05/2024

   Rationale for required PMR:
   Trastuzumab emtansine may cause embryo-fetal harm. There is an established pregnancy registry for trastuzumab (Herceptin) and pertuzumab (Perjeta).Adding trastuzumab emtansine to the existing registry may provide further information for future patients regarding pregnancy risk. The goal is to determine the incidence of pregnancy occurrences, pregnancy complications, and birth outcomes, including embryo-fetal death, oligohydramnios, and other serious outcomes.

2. Perform a multivariate characterization study to support the implementation (b) (4) of *trans*-succinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) (b) (4) during manufacture of T-DM1.

   This study will be conducted according to the following schedule:

Final Protocol Submission:	03/2013

Patricia Cortazar, MD
CDTL Review
Ado-trastuzumab emtansine (KADCYLA™)
BLA 125427

Study Completion: 05/2013
Final Report Submission: 06/2013

Rationale for required PMR:
Due to the lack of full scale validation data to support the proposed [redacted] *trans*-succinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) [redacted] for the manufacture of trastuzumab emtansine, [redacted]

3. Develop and validate an iCIEF method to use as a drug substance and drug product regulatory method for monitoring the unconjugated antibody content and propose a specification limit for the unconjugated antibody content based on clinical and commercial batch data. Submit the final report as a Prior Approval Supplement.

   This study will be conducted according to the following schedule:

   Final Protocol Submission: 05/2013
   Study Completion: 11/2013
   Final Report Submission: 12/2013

   Rationale for required PMR:
   Due to the lack of free antibody content, the applicant has committed to develop, validate and implement the iCIEF method as a QC method to measure the unconjugated antibody content in lot release testing and propose appropriate acceptance limit for this test. In the interim, Genentech commits to test commercial batches for the unconjugated antibody content using both iCIEF and MS characterization methods.

4. Provide quarterly reports on the status of any [redacted]. These reports should include, at a minimum, a summary of the root cause analyses, associated corrective actions, and disposition of all affected DM1 batches. Also, provide the disposition of any potentially affected finished product batches using these affected DM1 batches. Submit an interim report documenting that the manufacturing processes have been appropriately controlled at the manufacturing facilities according to Genentech's evaluation. The interim report should include a request for follow-up inspection(s). Submit a final report with a statement concerning the follow-up performed on the [redacted] issues during the course of the FDA inspection(s), an update on whether there have been any further instances of [redacted] and a proposal to prevent [redacted] managed by each site's quality system.

   This study will be conducted according to the following schedule:

Quarterly Report #1	05/2013
Quarterly Report #2	08/2013
Quarterly Report #3	11/2013
Quarterly Report #4	02/2014
Interim Report:	04/2014
Quarterly Report #5	05/2014
Quarterly Report #6	08/2014
Quarterly Report #7	11/2014
Quarterly Report #8	02/2015
Final Report Submission:	04/2015

Rationale for required PMR:
The issue of [redacted] has not been permanently resolved. A test and acceptance criterion for [redacted] has been implemented to mitigate the risk for [redacted] of commercial batches. Alleviation of product [redacted] specifications is not a complete solution. [redacted] should not be present. This PMR is to require that the firm performs a complete evaluation of DM-1 and TDM-1 product [redacted] DM-1 and TDM-1 lots from being: (1) used in manufacturing, and (2) distributed in finished products. This PMR ensures that the firm informs FDA in a timely fashion that only products which are of acceptable quality are distributed for use and that observed [redacted] is being investigated.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of increased toxicity in patients with hepatic impairment.

Therefore, based on appropriate scientific data, FDA has determined that the applicant is required to conduct the following:

5. Conduct a clinical trial to evaluate the impact of hepatic impairment on the pharmacokinetics of KADCYLA (ado-trastuzumab emtansine conjugate), total trastuzumab, and DM1-containing catabolites. Based on the results of this trial, update the approved KADCYLA labeling with recommendations for appropriate use of KADCYLA in patients with hepatic impairment and submit it as a Prior Approval Supplement.

   This study will be conducted according to the following schedule:

Final Protocol Submission:	Submitted
Trial Completion:	06/2014
Final Report Submission:	06/2015
Supplement Submission:	06/2015

Rationale for required PMR:

A pre-clinical mass balance study suggested that hepatic elimination is the major elimination pathway of DM1. Therefore, patients with hepatic impairment may have higher exposure of DM1 than that of normal patients, which could cause more toxicity. The applicant is currently conducting trial to assess the effects of normal, mild, and moderate hepatic impairment on the pharmacokinetics of KADCYLA. The impact of hepatic impairment on the pharmacokinetics of KADCYLA (antibody drug conjugate, total antibody, and DM1) should be evaluated. The goal of the clinical trial is to assess the need for a dose reduction or recommend avoidance of KADCYLA for patients with hepatic impairment.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

6. Transfer the methodology for validated dye ingress testing developed by Genentech to (b) (4). Conduct a study to confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method and provide a final report in the 2014 annual report.

   This study will be conducted according to the following schedule:

Study Trial Completion:	02/2013
Final Report:	04/2014

   Rationale for PMC:
   The current dye ingress container closure integrity test used at (b) (4) uses different parameters from those used in the validated method developed by Genentech. However, vials with known breach sizes were tested using both methods and the number of positive control vials was comparable; therefore, the risk of not detecting breached vials with the non-validated method is deemed low. The dye ingress container closure integrity test at (b) (4) will be correlated to microbial ingress.

7. Conduct a study to assess the risk of endotoxin masking (b) (4) using endotoxin spiked ado-trastuzumab emtansine drug product (b) (4) Submit a final report that includes updated specifications as a Prior Approval Supplement.

   This study will be conducted according to the following schedule:

Final Report Submission:	03/2013

   Rationale for PMC:
   Previous studies conducted by the Sponsor suggest endotoxin masking of T-DM1 (b) (4) However, the impact of endotoxin masking in (b) (4) samples is unclear. The sponsor will study endotoxin masking in

[redacted] samples to assess the validity of the standard LAL test in finished drug product. Until those results are available, endotoxin will be tested [redacted] Since there is no endotoxin masking [redacted] under [redacted] conditions, the risk for the introduction of endotoxin [redacted] in the final vials is deemed low. The release test for endotoxin in the finished product may be inadequate. The study will determine the adequacy of the test.

8. If endotoxin masking is observed in the drug product [redacted], develop an alternative method to quantitate endotoxin in the finished ado-trastuzumab emtansine drug product [redacted] using routine production conditions. Submit a final report on any changes in the analytical methods as a Prior Approval Supplement.

   This study will be conducted according to the following schedule:

   Final Protocol Submission: 09/2013
   Final Report Submission: 12/2013

   Rationale for PMC:
   Previous studies conducted by the Sponsor suggest endotoxin masking of T-DM1 [redacted] and the Sponsor will study endotoxin masking in [redacted] samples. If those studies demonstrate that the standard LAL test for endotoxin determination in the finished drug product is not adequate, the sponsor will develop an alternative endotoxin release method for finished product. Until those results are available, endotoxin will be tested [redacted] Since there is no endotoxin masking [redacted] the risk for false endotoxin negatives in the finished product is deemed low.

9. Dedicate [redacted] for ado-trastuzumab emtansine drug product manufacture and submit a final report of the results from sterilization validation and 3 media fill simulations as a Changes Being Effected Supplement (CBE-0).

   This study will be conducted according to the following schedule:

   Final Report Submission: 06/2013

   Rationale for PMC:
   T-DM1 [redacted] will be dedicated to T-DM1. However, sterilization validation and media fill simulations must be conducted [redacted]

   The new [redacted] T-DM1 [redacted]. The sterilization process validation data

and media fill studies will provide sterility assurance for the [redacted] bulk drug product.

10. Conduct cleaning verification [redacted] until use of [redacted] is implemented and report the updated [redacted] procedures in the 2014 Annual Report.

    This study will be conducted according to the following schedule:

Study completion:	06/13
Final Report Submission:	04/14

    Rationale for PMC:
    [redacted] Until the [redacted] is implemented, cleaning verification [redacted] will be conducted [redacted]

    Cleaning verification [redacted] are deemed safe.

11. Conduct endotoxin spiking and recovery studies [redacted] Submit the final report as a Changes Being Effected in 30 days Supplement (CBE-30).

    This study will be conducted according to the following schedule:

Final Report Submission:	05/2013

    Rationale for PMC:
    The study needs to use samples generated from the next trastuzumab emtansine campaign. This is appropriate for a PMC because this PMC does not affect the safety of the product. The risk of endotoxin contamination is mitigated by endotoxin and microbial controls in place during manufacturing. [redacted]

12. Develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ado-trastuzumab emtansine, including procedures for accurate detection of neutralizing antibodies to ado-trastuzumab emtansine in the presence of ado-trastuzumab emtansine levels that are expected to be present in the serum or plasma at the time of patient sampling. The assay final report will be submitted as a Prior Approval Supplement by June, 2015.

    This study will be conducted according to the following schedule:

    Final Report Submission (Assay and Methodology) Date: 06/2015

    Rationale for PMC:
    As stated in the FDA guidance "Assay Development for Immunogenicity Testing of Therapeutic Proteins", the sponsor should address the functional or physiological consequences of product immunogenicity. Therefore, the applicant should develop and validate a neutralizing antibody assay. The potential neutralizing effect of ATA on any positive samples identified to date (including the 44/836 patients identified in the draft label) should be determined. We recommend the applicant expedite the development and validation of the neutralizing antibody assay so samples from planned and ongoing clinical studies can be analyzed.

13. Reassess release and stability specifications for ado-trastuzumab emtansine drug substance and drug product through the end of February, 2015. Submit the final report as a Changes Being Effected-30 Supplement (CBE-30).

    This study will be conducted according to the following schedule:

    Final Report Submission: 05/2014

    Rationale for PMC:
    An assessment of release and stability specifications requires long-term data. This is a standard post-approval assessment that needs to be performed as part of the life cycle approach to manufacturing. An assessment of specifications is part of the normal life-cycle approach to manufacturing. There are generally a limited number of lots available at the time of licensure and reassessment of specifications after further lots have been produced ensures that the specifications have been set appropriately. The validity of the drug substance in-process endotoxin test needs to be evaluated (b) (4) The release test for endotoxin in the finished product may be inadequate. The study will provide an alternative method for endotoxin release in finished product.

14. Provide a material compatibility assessment [redacted] Provide a toxicological risk assessment [redacted] If significant [redacted] are identified during these assessments, initiate action to mitigate the source(s) of risk to product quality.

    This study will be conducted according to the following schedule:

Material Compatibility Assessment Completion:	04/2013
[redacted] Assessment and Toxicological Risk Assessment:	05/2013
Final Report Submission:	06/2013

    Rationale for PMC:
    The issue [redacted] has not been permanently resolved. A test and acceptance criterion [redacted] has been implemented to mitigate the risk for [redacted] commercial batches. Alleviation of product [redacted] specification is not a complete solution. [redacted] This PMC requests that the firm performs a complete evaluation [redacted]

15. Conduct ado-trastuzumab emtansine conjugate exposure-response analyses for progression-free survival, final overall survival, and safety utilizing data from trial BO25734/TDM4997 (TH3RESA). The results of the exposure-response analyses from both TH3RESA and BO21977/TDM4370g (EMILIA) will be used to determine whether a postmarketing trial is needed to optimize the dose in patients with metastatic breast cancer patients who have lower exposure to ado-trastuzumab emtansine conjugate at the approved dose (3.6 mg/kg q3w). Submit a final report of the exposure-response analyses based on TH3RESA and EMILIA.

    This study will be conducted according to the following schedule:

Final Protocol Submission:	Submitted
Study Completion:	06/2016
Final Report Submission:	12/2016

Rationale for PMC:

The exposure-response analyses for trial TDM4370g/BO21977 indicated that patients with lower exposures may benefit from an increase in dose. This is because the exposure-response analysis, after accounting for baseline risk factors, demonstrated that increase in T-DM1 exposure is related with better efficacy in terms of overall survival, progression free survival and objective response rate compared to patients with lower exposure. The exposure-response analysis demonstrated that patients with lower T-DM1 exposure still benefit comparable to the active control treatment.

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/s/

PATRICIA CORTAZAR
02/19/2013