CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125427Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
BLA	125427
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)	Single agent for the treatment of patients with HER2+ 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**
Division Director	Robert Justice
Regulatory Project Manager	Lisa Skarupa/Alice Kacuba
Medical Officer Reviewers	Laleh Amiri-Kordestan (efficacy)/ Patricia Cortazar Gideon Blumenthal (safety)/ Patricia Cortazar
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
OPDP	Marybeth Toscano/ Karen Rulli
OSI	Lauren Iacono-Connors/Janice Pohlman
OSE/DMEPA Consult	Jibril Abdus-Samad/Todd Bridges

1. Introduction & Background

On August 26, 2012, Genentech 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+, 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.

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.

This application is primarily supported by a randomized, multicenter, open-label trial enrolling 991 patients with HER2+ 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.

Additionally, efficacy results from the pivotal study are further supported by three randomized Phase 2 studies. See Sections 5 and 6 for clinical efficacy and safety results.

2. CMC

The CMC discipline recommends approval of Kadcyla (ado-trastuzumab emtansine). The data submitted in the BLA support the conclusion that the manufacture of 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 multiple production runs.

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. See reviews from ONDQA and NDMAB.

Significant micro quality and CGMP concerns included:

- 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 facilit (b) (4) See reviews from BMAB.

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 of (b) (4)

Steps to ensure a consistent drug supply and manufacturing process of ado-trastuzumab emtansine are outlined in the post-marketing obligations that the company has agreed to undertake.

3. Nonclinical Pharmacology/Toxicology

There are no outstanding nonclinical issues that preclude approval.

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.

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 nonclinical 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 indicate toxic effects to rapidly dividing cells and DM1 is 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.

4. Clinical Pharmacology/Biopharmaceutics

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 three phase 2 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 PK 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 PK 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 PK 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 $\geq$ 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 PK 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+ metastatic breast cancer. No large changes in the mean QT interval (i.e., > 20 ms) were detected in the study.

5. Clinical Efficacy

This BLA is primarily supported by results from a single 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".

Patients must have received prior taxane and trastuzumab-based therapy prior to enrollment. Patients who received these therapies only in the adjuvant setting were required to have disease recurrence during or within six months of completing this 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 by intravenous infusion, 3.6 mg/kg, on day 1 every 21 days or lapatinib, 1250 mg/day orally once daily, for 21 days plus capecitabine, 1000 mg/m2 orally twice daily, for 14 days. Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal.

The co-primary efficacy endpoints were PFS, based on tumor response assessments by an IRC, and 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]. The median OS was 30.9 and 25.1 months in the ado-trastuzumab emtansine and the lapatinib plus capecitabine arms, respectively.

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	

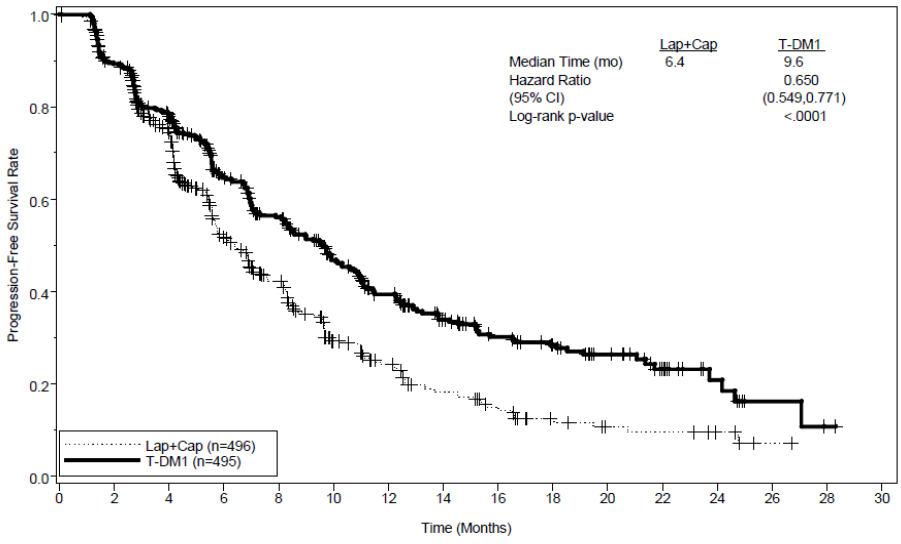
	KADCYLA N= 495	Lapatinib +Capecitabine N= 496
95% CI for Hazard Ratio	(0.549, 0.771)	
p-value (Log-Rank test, stratified*)	<0.0001	
Overall Survival **		
Number (%) of patients who died	149 (30.1%)	182 (36.7%)
Median duration of survival (months)	30.9	25.1
Hazard Ratio (stratified*)	0.682	
95% CI for 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 1 Kaplan-Meier Curve of IRC-assessed Progression-Free Survival for EMILIA

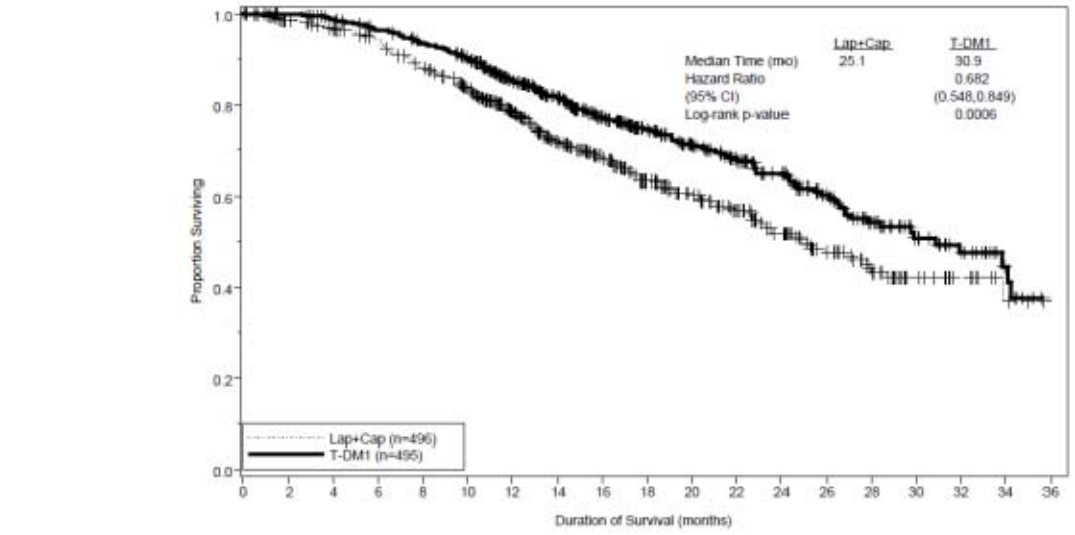


Number at Risk:

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.

Figure 2 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 effects with ado-trastuzumab emtansine in terms of PFS and OS were observed in patient subgroups based on stratification factors, key baseline demographic, disease characteristics, and prior treatments (Figure 3 and Figure 4). 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 3 Forest Plot of PFS for EMILIA Trial (From Dr. Xu Statistical reviewer)

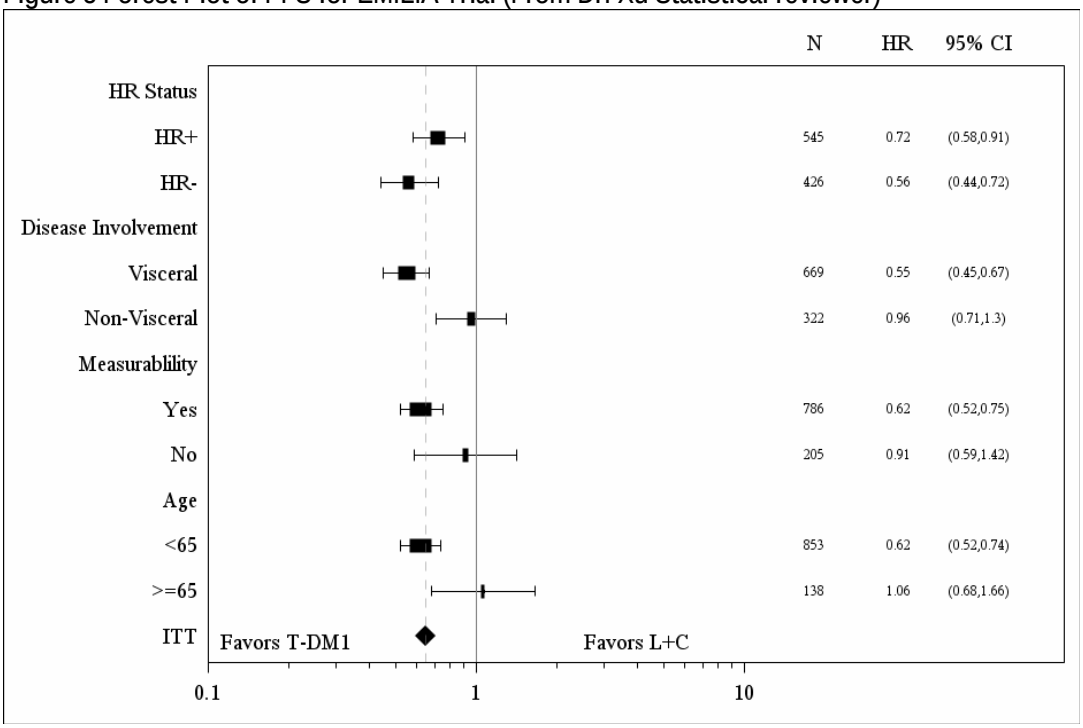
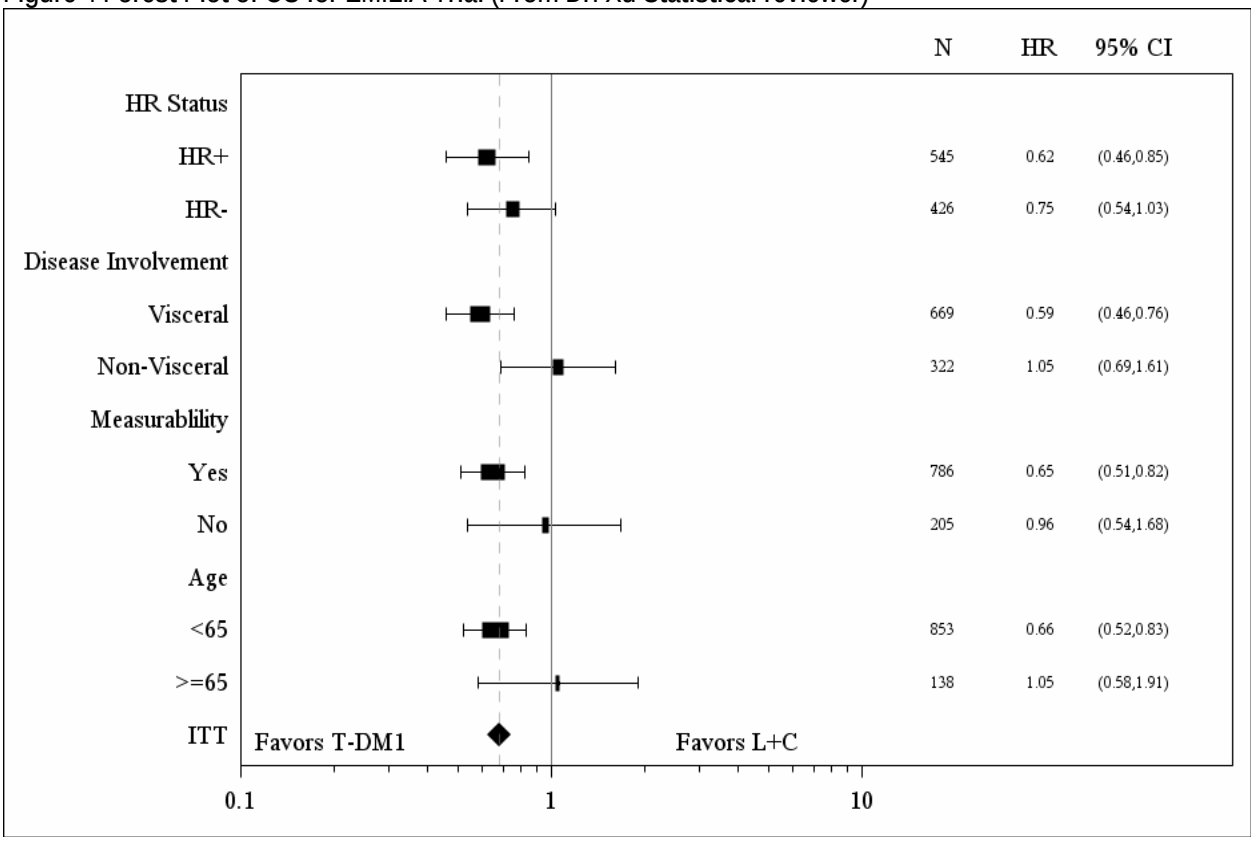


Figure 4 Forest Plot of OS for EMILIA Trial (From Dr. Xu Statistical reviewer)



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

Supportive Studies
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%.

6. 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 five additional phase 1 and phase 2 studies. The Applicant submitted safety data from 882 HER2+ metastatic breast cancer patients exposed to ado-trastuzumab emtansine at a dose of 3.6 mg/kg every 3 weeks.

The most common (> 25%) adverse reactions observed in patients receiving ado-trastuzumab emtansine were nausea, fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, 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%) 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 include left ventricular dysfunction, interstitial lung disease, and infusion-associated reactions.

A BOXED WARNING in product labeling describes the risk of hepatotoxicity, reduction in left ventricular ejection fraction, embryo-fetal toxicity and birth defects, and the need for effective contraception prior to starting ado-trastuzumab emtansine.

7. Advisory Committee Meeting

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

8. Pediatrics

The Division recommended a full waiver in pediatric patients because breast cancer does not exist in the pediatric population. The PeRC agreed with the Division to grant a full waiver for this indication.

9. Labeling

Key safety labeling recommendations which are in a Boxed Warning are: potential for hepatotoxicity, cardiotoxicity and embryo-fetal toxicity.

A prefix ("ado-") prior to trastuzumab-emtansine was added to mitigate against medication errors.

10. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval

- Risk Benefit Assessment

The recommendation for regular approval is based on a randomized, multicenter, open-label trial enrolling 991 patients with HER2+ metastatic breast cancer. 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 PFS and OS 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. Adverse events are identified in Section 6 above and in labeling.

There were significant CMC issues that delayed approval of this BLA for Kadcyla (ado-trastuzumab emtansine). Of note, approval of the Perjeta (pertuzumab) application (approved in 2012) sponsored by Genentech was also delayed by CMC issues. However, the sponsor's responses to CMC issues throughout the review of this BLA for Kadcyla (ado-trastuzumab emtansine) have been satisfactorily resolved to allow

for approval. The sponsor has agreed to several postmarketing obligations to ensure a consistent drug supply and manufacturing process of Kadcyla. See action letter for this postmarketing obligations.

The risk-benefit profile was also determined to be favorable by Drs. Justice, Cortazar, Amiri-Kordestan and Blumenthal. In addition, the review team recommends approval of this BLA, and I concur with their recommendation.

- Recommendation for Post marketing Risk Management Activities

Routine postmarketing surveillance.

- Recommendation for other Post marketing Study Requirements (PMR)/Commitments (PMC)

See action letter for all PMRs/PMCs.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAMY E KIM
02/21/2013

RICHARD PAZDUR
02/21/2013