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APPLICATION NUMBER:

125427Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125,427
Priority or Standard	Priority
Submit Date(s)	August 26, 2012
PDUFA Goal Date	Feb 26, 2013
Division / Office	DOP1 / OHOP
Reviewer Name(s)	Laleh Amiri-Kordestani, MD (efficacy) Gideon Blumenthal, MD (safety) Patricia Cortazar, MD (CDTL)
Review Completion Date	January 25, 2013
Established Name	Ado-trastuzumab emtansine
(Proposed) Trade Name	KADCYLA™
Therapeutic Class	Antibody-drug conjugate
Applicant	Genentech, Inc.
Formulation(s)	100 mg or 160 mg single-use vial
Dosing Regimen	3.6 mg/kg intravenous infusion every 3 weeks
Indication(s)	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 recurred during or within six months of completing adjuvant therapy.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on review of the clinical data, the clinical review team recommends full approval of biologic license application (BLA) 125,427 ado-trastuzumab emtansine (Kadcyla®, T-DM1) for the following indication:

KADCYLA is a HER2-targeted antibody and microtubule inhibitor conjugate indicated, 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*
- *Recurred during or within six months of completing adjuvant therapy.*

The basis for this recommendation is a favorable benefit-risk profile for ado-trastuzumab emtansine in 991 patients with Her2+ metastatic breast cancer (MBC) who previously received trastuzumab and a taxane in the pivotal randomized, international, multicenter, open-label, Phase 3 study TDM4370g/BO21977 (EMILIA). As compared to the combination lapatinib and capecitabine treatment arm, patients randomized to ado-trastuzumab emtansine had statistically significant improvements in the co-primary endpoints of progression free survival (PFS) [hazard ratio (HR) = 0.65, 95% CI: 0.55, 0.77, $p < 0.0001$, 3.6 month median difference] and overall survival (OS) [HR=0.68, 95% CI: 0.55, 0.85, $p=0.0006$, 5.8 month median difference]. Furthermore, the safety profile of ado-trastuzumab emtansine, when compared to lapatinib plus capecitabine was favorable. There were more deaths, grade 3 and above adverse events, serious adverse events, and discontinuations due to adverse events on the control arm. This single randomized trial demonstrated substantial evidence of safety and efficacy. Full approval is recommended, contingent upon resolution of the manufacturing issues identified by the Division of Monoclonal Antibodies and Office of Compliance.

1.2 Risk Benefit Assessment

Metastatic Breast Cancer (MBC) is a serious and life threatening condition, causing 39,250 deaths in the U.S. in 2011. The HER2/neu receptor is over-expressed in 15-30% of MBC, and is associated with a poor prognosis and an aggressive phenotype.

There is a clear need for new therapies to treat HER2+ MBC to prolong life, substantially delay disease progression, and/or alleviate breast cancer related symptoms.

The ado-trastuzumab emtansine BLA is primarily supported by an international, multicenter, open label, randomized phase 3 study (EMILIA, TDM4370g/BO21977). The pivotal study enrolled a total of 991 patients with HER2+ metastatic breast cancer (MBC) who received prior treatment with trastuzumab and a taxane. Patients were randomized 1:1 to receive ado-trastuzumab emtansine (n=495) or lapatinib plus capecitabine (n=496).

The assessment of benefit is based on the co-primary endpoints of Independent Review Committee (IRC)-assessed Progression Free Survival and Overall Survival. A total of 569 IRC-assessed PFS events occurred with 265 in the ado-trastuzumab emtansine group and 304 in the lapatinib plus capecitabine group. The hazard ratio for IRC-assessed PFS (stratified by world region, number of prior chemotherapies for advanced or metastatic disease, and visceral disease status) was 0.65 (95% CI: 0.55, 0.77; stratified log-rank p-value<0.0001), with a median PFS of 9.6 months (95% CI: 8.3, 10.6) for ado-trastuzumab emtansine and 6.4 months (95% CI: 5.7, 7.1) for lapatinib plus capecitabine. These PFS results are consistent with several sensitivity analyses, including the investigator assessed PFS results, and across several key subgroups.

The first interim OS analysis occurred at the time of the final analysis of PFS. Two hundred twenty-three deaths occurred (35% of the planned total number of deaths) with 94 in the ado-trastuzumab emtansine group and 129 in the lapatinib plus capecitabine group. The hazard ratio for death from stratified analyses was 0.62, with a stratified log-rank p-value of 0.0005, which did not cross the efficacy stopping boundary (significance level of 0.0003).

With FDA concurrence at a May 2012 pre-BLA meeting prior to BLA submission, the Applicant amended the Statistical Analysis Plan to perform a second interim OS analysis. The second OS interim analysis was performed when 52% of the planned number of deaths had occurred (149 in the ado-trastuzumab emtansine arm and 182 in the lapatinib plus capecitabine arm). The stratified hazard ratio was 0.68 (95% CI: 0.55, 0.85; stratified log-rank p-value=0.0006). The Kaplan Meier estimates of median OS was 30.9 months (95% CI: 26.8, 34.3) for ado-trastuzumab emtansine and 25.1 months (95% CI: 22.7, 28.0) for lapatinib plus capecitabine. This analysis crossed the efficacy stopping boundary significance level of 0.0037 and thus was statistically significant.

Other supportive efficacy data from the pivotal EMILIA trial included improved objective response rates with T-DM1 compared to lapatinib + capecitabine (44% versus 31%). Further support of efficacy comes from a randomized phase 2 trial (TDM4450g) submitted to the BLA of T-DM1 versus trastuzumab + docetaxel in 104 patients with no prior MBC treatment, in which a PFS improvement in the T-DM1 treatment arm was observed (HR=0.59, p=0.035, median PFS 14.2 months versus 9.2 months).

Overall, the safety profile of T-DM1 appeared to be acceptable relative to the benefits. In the EMILIA trial, the safety profile was favorable compared to lapatinib plus capecitabine, with fewer deaths, grade 3 and above toxicities, serious adverse events, discontinuation, dose delays and dose reductions for patients receiving KADCYLA. The

most serious adverse events associated with KADCYLA included hepatotoxicity (including cases of liver failure and death), cardiotoxicity (including cases of left ventricular dysfunction), thrombocytopenia, peripheral neuropathy and pneumonitis. There was a case of overdose and death possibly related to receiving T-DM1 rather than trastuzumab and thus a prefix was recommended to be added to “trastuzumab emtansine” to mitigate the risk of medication error (see Overdose section 7.6.4).

In conclusion, ado-trastuzumab emtansine in patients with HER2+ MBC demonstrated a favorable risk-benefit profile, with substantial evidence of safety and efficacy in an adequate and well controlled trial with strong supportive evidence. Full approval is recommended, contingent upon satisfactory resolution of manufacturing issues identified by the Division of Monoclonal Antibodies (see section 4.1, Chemistry Manufacturing and Controls).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS or Medication Guide is required for marketing of ado-trastuzumab emtansine.

1.4 Recommendations for Postmarket Requirements and Commitments

From Division of Monoclonal Antibodies*

PMR1: Perform a multivariate characterization study to support the implementation (b) (4) for the amount of SMCC (b) (4) during manufacture of T-DM1.

Final Protocol submission: MM/DD/YYYY

Study completion: MM/DD/YYYY

Final report submission: MM/DD/YYYY

PMR2: Optimize the assays used for the detection of anti-trastuzumab emtansine antibodies in human serum:

- 1) Provide an assessment of the ATA response to trastuzumab emtansine with a validated ELISA binding assay capable of sensitively detecting ATA responses in the presence of trastuzumab emtansine levels that are expected to be present at the time of patient sampling.
- 2) Develop a validated assay to assess the neutralizing activity of anti-trastuzumab emtansine antibodies.

Final Protocol submission: MM/DD/YYYY

Study completion: MM/DD/YYYY

Final report submission: MM/DD/YYYY

**From Division of Office of Compliance, Office of Manufacturing & Product Quality
Biotech Manufacturing Assessment Branch***

PMC 1: Transfer the methodology for validated dye ingress testing developed by Genentech to (b) (4). Confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method and report changes to the Agency in the next Annual Report.

Final Protocol submission: n.a.

Study completion: 28-Feb-2013

Final report submission: 22-April-2014

PMC 2: Conduct controlled studies to assess the risk of endotoxin masking (b) (4) using endotoxin spiked trastuzumab emtansine drug product (b) (4) and submit results and updated specifications to the Agency by 29-Mar-2013 as a PAS.

Final Protocol submission: n.a.

Study completion: n.a.

Final report submission: 29-March-2013

PMC 3: If endotoxin masking is observed (b) (4) develop an alternative method to quantitate endotoxin (b) (4) using routine production conditions. Any change in the analytical methods should be approved by the Agency before implementation. Submit protocol to the Agency by 30-June-2013 as a PAS.

Final Protocol submission: 30-Jun-2013

Study completion: n.a.

Final report submission: 30-December-2013

PMC 4: Dedicate (b) (4) for trastuzumab emtansine DP manufacture and submit results from sterilization validation and 3 media fill simulations to the Agency by 30-June-2013 as a CBE-0.

Final Protocol submission: n.a.

Clinical Review KADCYLA (ado-trastuzumab emtansine, T-DM1)
Amiri (efficacy) and Blumenthal (safety)
BLA 125,427

Study completion: n.a.

Final report submission: 30-June-2013

PMC 5: Conduct cleaning verification [REDACTED] (b) (4)
[REDACTED] and report the updated [REDACTED] (b) (4) r procedures to the Agency
in the 2014 Annual Report

Final Protocol submission: submitted

Study completion: 28-Feb-2013

Final report submission: 22-April-2014

PMC 6: Conduct endotoxin spiking and recovery studies [REDACTED] (b) (4)
[REDACTED]
[REDACTED] Submit the information and study results in a CBE-30 by May
31, 2013.

Final Protocol submission: n.a.

Study completion: n.a.

Final report submission: 31-May- 2013

From Clinical Pharmacology

PMR Description: Evaluate the impact of hepatic impairment on KADCYLA (xxx-trastuzumab emtansine conjugate, total trastuzumab, and DM1 containing catabolites) pharmacokinetics; consequently update the approved KADCYLA labeling with recommendations for appropriate use of KADCYLA in patients with hepatic impairment.

Final Protocol Amendment submission: June 30, 2013

Study completion: June 30, 2014

Final report submission: June 30, 2015

PMC Description: To conduct xxx-trastuzumab emtansine conjugate exposure-response analyses for progression free survival, final overall survival, and safety endpoints utilizing data from trial BO25734/TDM4997 (TH3RESA). Evaluation of the results of the exposure-response analyses from both TH3RESA and BO21977/TDM4370g (EMILIA) will determine the need, or otherwise, for a postmarketing trial to optimize the dose in metastatic breast cancer patients with lower xxx-trastuzumab emtansine conjugate exposure at the approved dose (3.6 mg/kg q3w).

Final Protocol submission: submitted

Study completion: June 30, 2016

Final report submission: September 30, 2016

From DOP1 Clinical

PMR Pregnancy Registry

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 xxx-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.

Final Protocol submission: May 2013

Study completion: May 2023

Final report submission: May 2024

2 Introduction and Regulatory Background

2.1 Product Information

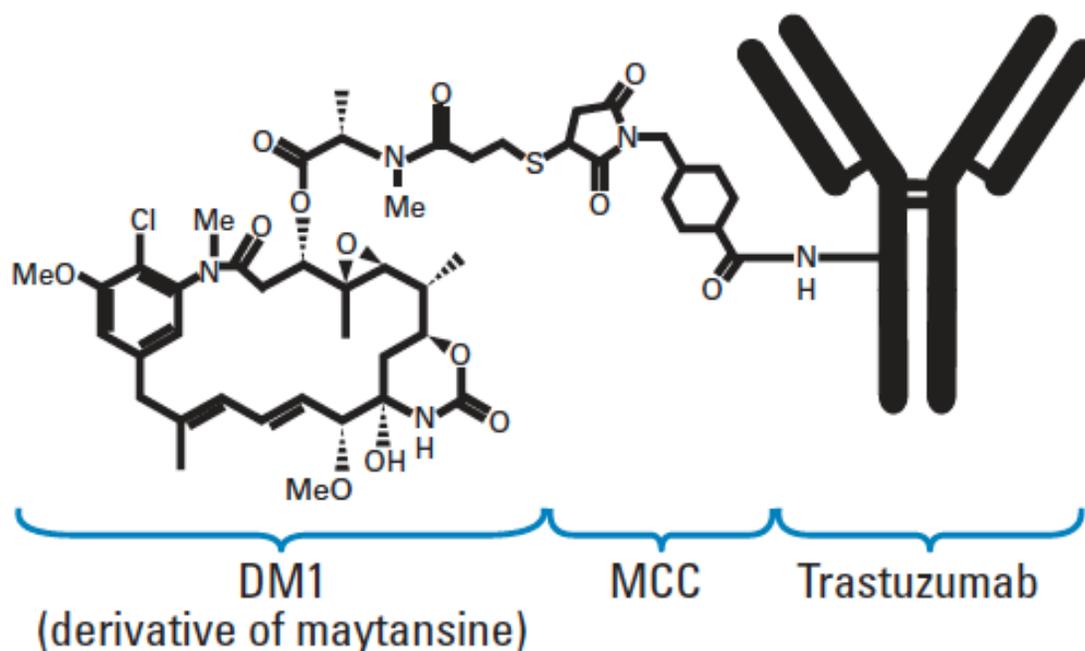
Ado-trastuzumab emtansine is an antibody–drug conjugate. It is composed of the cytotoxic agent DM1 (a thiol-containing maytansinoid anti-microtubule agent) conjugated to trastuzumab via succinimidyl 4-[N-maleimidomethyl]cyclohexane-1-carboxylate, a linker molecule containing lysine side chains. The average drug to antibody ratio is approximately 3.5:1 (Figure 1).

Ado-trastuzumab emtansine binds to HER2 with an affinity similar to that of trastuzumab; which is required for its anti-tumor activity. It is hypothesized that after binding to HER2, ado-trastuzumab emtansine undergoes receptor-mediated internalization, followed by intracellular release of DM1 and subsequent cytotoxicity (Figure 2). DM1 causes apoptosis through inhibition of microtubule assembly, leading to cell cycle arrest at the G2/M phase. Although DM1 has a similar mechanism of action to the vinca alkaloids, it is 20 - 100 times more potent than vincristine, 24 - 270 times more potent than paclitaxel, and two to three times more potent than doxorubicin.¹⁻⁴

In clinical trials, ado-trastuzumab emtansine is provided as a single-use lyophilized formulation in a colorless 20 mL Type I glass vial. Upon receipt of ado-trastuzumab emtansine, vials are refrigerated at 2°C–8°C (36°F–46°F) until use. Vials are stored in the original carton to protect from light, and were not shaken or frozen.

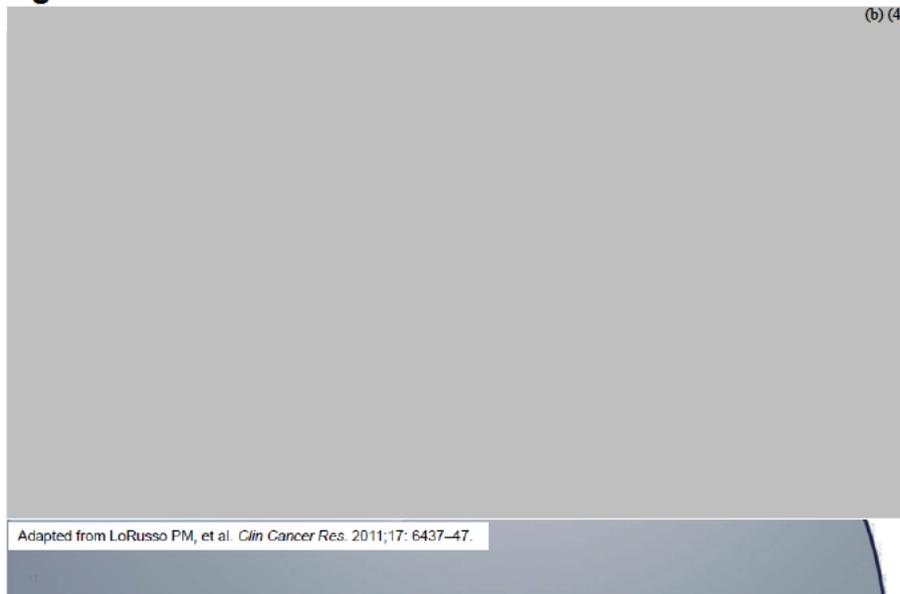
Upon reconstitution, the resulting product contains 20 mg/mL ado-trastuzumab emtansine, 10 mM sodium succinate, pH 5.0, 6% (w/v) (i.e., 60 mg/mL) sucrose, and 0.02% (w/v) polysorbate 20. Use of 0.22 µm in-line PES filters is recommended for the administration of the drug when using (b) (4) sodium chloride as the infusion solution. Each 20 mL vial allows delivery of 160 mg ado-trastuzumab emtansine. The reconstituted product contains no preservative and is intended for single use only.

Figure 1: Ado-trastuzumab emtansine-molecular structure



Source: Burris et al. *J Clin Oncol.* 2011 Feb 1;29(4):398-405.

Figure 2: Ado-trastuzumab emtansine mechanism of action



Source: Applicant briefing document

In a phase I study (TDM3569g), the safety of TDM1 was evaluated. On an every-3-week schedule arm of the study, 24 patients with metastatic breast cancer who had progressed on trastuzumab-based therapy, received T-DM1 at 0.3 mg/kg to 4.8 mg/kg. Thrombocytopenia was dose-limiting at 4.8 mg/kg; the maximum-tolerated dose (MTD) was 3.6 mg/kg. The confirmed response rate in patients with measurable disease at the MTD (n = 9) was 44%. The second arm of the study investigated weekly dosing (1.2 - 2.9 mg/kg). Twenty eight patients were enrolled. Thirteen out of 28 patients had confirmed partial responses.⁵

In two single arm Phase II studies (TDM4374g and TDM4258g), the efficacy and safety of single agent T-DM1 (3.6 mg/kg every 3 weeks) were evaluated. Study TDM4258g was a Phase II open-label, single-arm multicenter trial that enrolled 112 patients who had tumor progression after prior treatment with HER2-directed therapy. ORR by independent assessment was 25.9% (95% CI: 18.4 - 34.4%). In TDM4374g study, 110 patients with HER2-positive MBC who had previous exposure to an anthracycline, a taxane and capecitabine and had two HER2-directed therapies in the metastatic setting were enrolled. The ORR by independent assessment was 34.5% (95% CI: 26.1 - 43.9%), and the median duration of response was 7.2 months (lower limit of 95% CI: 4.6 months, upper limit not reached).⁶

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently three drugs approved in the U.S. for HER2+ metastatic breast cancer (MBC): the monoclonal antibody trastuzumab (Herceptin®, Genentech), the small molecule tyrosine kinase inhibitor lapatinib (Tykerb®, GSK), and the monoclonal antibody pertuzumab (Perjeta®, Genentech). FDA approvals for HER2+ MBC are listed in Table 1.

Table 1: FDA approved anti-HER2 therapies

Drug	Year	Indication	N	Basis for approval
Paclitaxel ± Trastuzumab Chemotherapy (paclitaxel or Adriamycin/ Cyclophosphamide))	1998	1 st line HER2+ MBC	469 (188)	TTP (HR 0.53, median Δ 2.7 m combined; 4.2 m paclitaxel subgroup, 1-year survival rates (79% v 68%; P = .03) later demonstrated OS (HR 0.80; median Δ 4.8 m)
Trastuzumab	1998	HER2+ MBC who have received ≥ 1 chemo regimens	222	ORR (14%) in single arm study
Capecitabine ± Lapatinib	2007	HER2+ MBC after failure of anthracycline, taxane, trastuzumab	399	TTP (IRC HR 0.57, median Δ 8.5 w; INV HR 0.72, median Δ 5.6 w)
Letrozole ± Lapatinib Accelerated Approval	2010	Postmenopausal women w/ HR+, HER2+ MBC for whom hormonal therapy indicated	219	PFS (HR 0.71, median Δ 5 m)
Trastuzumab + Docetaxel ± Pertuzumab / placebo	2012	1 st line HER2+ MBC	808	PFS (HR 0.62, median Δ 6 m); later demonstrated OS (HR 0.66, p=0.0008)

MBC = Metastatic Breast Cancer; HR+ = Hormone Receptor Positive; TTP = Time to Progression; OS = Overall Survival; ORR = Objective Response Rate; IRC = Independent Radiologic Charter; INV = Investigator, m= month, w= week

Source: drugs@fda.com

2.3 Availability of Proposed Active Ingredient in the United States

Ado-trastuzumab emtansine is a new molecular entity and is not currently marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Trastuzumab:

Trastuzumab carries the following Boxed Warnings:

- Cardiomyopathy: Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy.
- Infusion reactions, Pulmonary toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.
- Embryo-Fetal Toxicity: Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death.

In addition, trastuzumab has an associated 'Warnings and Precautions' for exacerbation of chemotherapy-induced neutropenia.

Lapatinib:

Lapatinib carries the following Boxed Warning:

- Hepatotoxicity: Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain.

In addition, lapatinib has associated 'Warnings and Precautions' for decreases in LVEF, diarrhea, interstitial lung disease/pneumonitis, QT prolongation, and fetal harm.

Pertuzumab:

Pertuzumab carries the following Boxed Warning:

- Embryo-Fetal Toxicity: Exposure to Perjeta can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception.

In addition, pertuzumab has associated 'Warnings and Precautions' for LVEF dysfunction, and infusion reactions.



- FDA stated that data from a randomized phase 3 trial will be necessary to support approval of T-DM1. OS is the recommended primary endpoint. (b) (4)



The Agency strongly recommended that the Phase 3 trial be adequately powered for survival.

- FDA 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.
- **October 2010:**
 - FDA: Agreed with EMILIA (TDM4370g/BO21977) protocol amendment to have OS as co-primary endpoint, Sample size increased from 580 to 980 patients
- **May 9, 2012:** Fast-track designation
- **May 30, 2012:** Pre-BLA meeting.
 - FDA stated that EMILIA appears to provide sufficient clinical experience to characterize the benefit-risk of T-DM1 and to form the basis of a BLA submission.
 - FDA stated that an additional OS analysis with appropriate alpha adjustment in the sequential testing plan is acceptable.
- **June 12, 2012:** Submission of Non-clinical components to BLA 125,427
- **July 31, 2012:** Submission of CMC components to BLA 125,427

- **August 24, 2012:** Submission of Clinical Data to BLA 125427, submission completed.

2.6 Other Relevant Background Information

Breast Cancer:

An estimated 226,870 new cases of invasive breast cancer are expected to occur among women in the US during 2012; about 2,190 new cases are expected in men. Excluding cancers of the skin, breast cancer is the most frequently diagnosed cancer in women. An estimated 39,920 breast cancer deaths (39,510 women, 410 men) are expected in 2012. Breast cancer ranks second after lung cancer as a cause of cancer death in women.

Amplification of human epidermal growth factor receptor 2 (HER2) occurs in approximately 20% of breast cancers and is associated with shortened survival.^{7,8} Combining HER2-targeted agents with standard chemotherapy is an effective therapeutic approach for patients with HER2-positive metastatic breast cancer. When combined with chemotherapy, trastuzumab increases the time to progression and overall survival among patients with metastatic disease.⁸ The addition of lapatinib to capecitabine increases the time to progression in patients previously treated with trastuzumab, an anthracycline, and a taxane,⁹ and this combination is a standard option after disease progression with trastuzumab.⁹

With the incorporation of HER2 targeted therapies for adjuvant early breast cancer and for MBC, the prognosis of HER2+ breast cancer has improved. However, new therapies are needed to prolong life, significantly delay disease progression, and/or improve cancer related symptoms.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear to be acceptable.

3.2 Compliance with Good Clinical Practices

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).

The study was conducted at 213 centers in 26 countries. Four clinical sites, chosen on the basis of high enrollment, were inspected for this BLA. Because this is an NME, the applicant and a CRO (Independent Review Committee [IRC] for progression free survival determination) were also inspected.

As shown below in Table 2, one investigator's study data could not be verified. The inspection of Dr. Sunil Verna revealed that the site failed to retain source documentation, "Clinical Trials Worksheets" used to initially record observations/data including target lesion measurements, vital signs, subject weights, ECOG performance status, toxicities/adverse events, concomitant medications, and physician orders at each study visit.

Reviewer Comment: Exclusion of this site data did not change overall study results for primary analyses for PFS and OS based on ITT patients.

Table 2: Site inspections

Name of CI or Applicant/CRO, Location	Site #, and # of Subjects	Inspection Date	Interim Classification
Seock Ah Im, Do-Youn Oh Seoul, Republic of Korea	Site#: 163500 (Roche) S25967(Genentech) Number of Subjects: 36	November 19-23, 2012	NAI
Jungsil Ro Kyunggi-Do, Republic of Korea	Site#: 163502 (Roche) S26016 (Genentech) Number of Subjects: 27	November 12-16, 2012	NAI
Soo Hyeon Lee Seoul, Republic of Korea	Site#: 163504 (Roche) S25968 (Genentech) Number of Subjects: 23	November 26-30, 2012	NAI
Sunil Verna Toronto, Ontario, Canada	Site#: 163026 (Roche) S25585 (Genentech) Number of Subjects Screened/Enrolled: 49/24	October 29- November 2, 2012	OAI
CRO: (b) (4)	Site# Records Reviewed: 163500 (Roche) 163502 (Roche) 163504 (Roche) 163026 (Roche)	(b) (4)	VAI
Applicant: Genentech, Inc. (member of the Roche Group)	Protocol: TDM4370g/BO21977 (EMILIA)	October 16-23, 2012	VAI

Also, a GCP compliance deviation related to the conduct of the IRC assessment of disease progression was identified by the FDA during this BLA review. The IRC in the EMILIA study consisted of blinded radiology review followed by an oncology review which could confirm or over-write the radiology assessment. The radiology review was based only on radiographic scans. The oncology review was based on the results of radiology review as well as the relevant clinical data sent by the applicant.

Per the IRC charter, clinical information was to be redacted of all references to study medication treatment group as well as subject confidential identifiers and investigator site information. Any information about specific toxicities of any study drug was to be removed. However, the patient profiles provided by the sponsor to the IRC for oncology review contained information on drug-specific toxicities, which potentially biased the oncology reviewer.

In order to clarify what was done by the Applicant, and what additional information could be provided by the Applicant to better understand the impact on the primary efficacy endpoint data submitted to the application a teleconference was held between the DOP1 clinical review team and OSI, and the Applicant on October 23, 2012. 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 (see section 6.1.4).

Reviewer Comment: The assessment of the impact of these clinical inspections on study data was performed and overall the sensitivity analysis did not show significant impact on study outcome.

3.3 Financial Disclosures

The applicant received financial disclosure information from 99.0% of principal investigators and sub-investigators on the EMILIA (TDM4370g/BO21977) trial, 91.8 % of principal and sub-investigators on Study TDM4450g/BO21976, 90.5 % of principal and sub-investigators on Study TDM4374g, and 77.6 % of principal investigators and sub-investigators in Study TDM4258g.

Disclosable financial interests were recorded by 5 out of 2134 (0.23%) investigators who responded in Study TDM4370g/BO21977, 3 out of 657 (0.46%) investigators who responded in Study TDM4374g and 7 out of 429 (1.63%) investigators who responded in Study TDM4258g. There were no disclosable financial interests recorded for Study TDM4450g/BO21976. These disclosures are summarized in the following table (Table 3).

Table 3: Summary of Financial Disclosures

Study Protocol	Clinical Site Number	Investigator Name	N	Disclosure
[REDACTED]	[REDACTED]	[REDACTED]	(b) (6)	\$25,000 Honoraria for consulting and advisory boards.
				Owns \$50,000 of Genentech stock.
				Unknown amount of honoraria for advisory boards. Due diligence to obtain payment amount was unsuccessful.
				Honoraria greater than \$25,000.
				\$95,000 Grant for genetic testing research.
				\$286,562 Grant for minority clinical research. Honoraria greater than \$25,000.
				Honoraria greater than \$95,000 for steering committees, investigator meetings, advisory boards, summits, launch meetings and lectures
				Greater than \$25,000 for serving on Data Safety Monitoring Boards for Genentech studies not related to T-DM1
				Honoraria greater than \$95,000 for Steering Committees, investigator meetings, advisory boards, summits, launch meetings and lectures.
				\$450,000 Grant for research. Negotiations for the grant began after the patient was off study at the site.
				(b) (6) \$25,000 per year: Consultancy, meeting, honoraria and advisory boards.
				\$30,000 Consultation, Speaker Bureau
				\$60,000 Honoraria for Speaking
				\$95,000 Genentech Bio-oncology grant to cover genetic testing in under insured patients to develop culturally sensitive genetic education material
				\$286,562 Grant from Genentech to support minority clinical research initiatives

Source: BLA 125,427 Section 1.3.4, financial disclosure

Reviewer Comment: *The financial disclosures do not raise questions about data integrity in the pivotal study. Investigators with significant disclosable interests enrolled a small proportion of the total number of patients such that introduction of bias is unlikely.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The key manufacturing issues that were discussed with Center Director at the meeting held on 1/24/2013 were:

- 1) The investigations (b) (4) potentially attributed to (b) (4) the DM1 manufacturer, were incomplete. Identified (b) (4) (b) (4) remained unidentified. Further, the inspection determined (b) (4) lots of DM1. The investigations have not determined the root cause (b) (4)
- 2) (b) (4) was observed in (b) (4) the DM1 manufacturer. (b) (4)

4.2 Clinical Microbiology

- 1) Genentech has reported endotoxin masking effects for this product (b) (4)
- 2) No cleaning verification data are available for market launch lots and clinical lots (b) (4)

Reviewer Comment: *There are some concerns with the quality oversight of Genentech. These manufacturing issues likely resulted in a delay of BLA approval, which was targeted for 4 months rather than the 6 month Priority review.*

4.3 Preclinical Pharmacology/Toxicology

For full details, please see Pharmacology/Toxicology review by Dr. W. David McGuinn.

4.3.1 Pharmacology:

The activity of trastuzumab emtansine and trastuzumab were investigated in vitro. Binding of trastuzumab emtansine to the extracellular domain of HER2 compared to trastuzumab were approximately equivalent. Data suggests that following internalization of trastuzumab emtansine, DM-1 causes sufficient cell damage to initiate apoptosis in cancer cells. Trastuzumab emtansine caused cytotoxicity, decreased cellular proliferation, and activated effector caspase-3 and -7 in cancer cell lines. These changes were not observed with trastuzumab, which inhibits cellular proliferation, but is not directly cytotoxic. These experiments demonstrated that cell cycle arrest induced by trastuzumab emtansine was predominantly at G2/M, attributed to inhibition of microtubules by DM1. Addition of both trastuzumab emtansine and trastuzumab to a cell line that expresses HER2 and is sensitive to trastuzumab caused a decrease in phosphorylation of AKT. Trastuzumab emtansine had similar activity as trastuzumab in mediating antibody-dependent cell-mediated cytotoxicity (ADCC) when human breast cancer cells were used as target cells and purified peripheral blood mononuclear cells from healthy donors were used as effector cells.

4.3.2 Pharmacokinetics:

Absorption

The elimination of trastuzumab emtansine from the plasma of mouse and rat is biexponential, with a terminal half-life of 0.9-6 days, volume of distribution of 40-50 mL/kg, and plasma clearance that decreases with increasing animal size (10-40 mL/day/kg). The plasma clearance of trastuzumab emtansine was proportional to dose in rodents, but not proportional to dose in the cynomolgus monkey. It ranged from 41.6 mL/day/kg at 0.3 mg/kg to 10.1 mL/day/kg at 30 mg/kg. Clearance of trastuzumab emtansine was approximately 2-2.5 times faster and the half-life was about 50% less than that of total trastuzumab. The volume of distribution was similar for the two drugs and was about equal to plasma volume.

Distribution

In a plasma protein binding study, 92.5% of DM1 bound in human plasma, 91.5% bound in monkey plasma, and 97.1% bound in rat plasma. Binding did not vary with concentration over a range of 20 to 1000 ng/mL in any species.

Metabolism

When human hepatocytes were treated with DM1, the cells maintained their viability during the assay at concentrations up to 1.0 μ M for 48 hours. DM1 did not induce

cytochromes P450 1A2, 2B6 or 3A4 or 5. DM-1, in the presence of NADPH-generating system, inhibited cytochrome P450 1A2, cytochrome P450 2B6, cytochrome P450 2C8, cytochrome P450 2C9, cytochrome P450 2C19, cytochrome P450 2D6 and cytochrome P450 3A4 catalytic activities by less than 50 % at the highest concentration (678 nM; 500 ng/mL) examined. Pre-incubation of DM-1 for 30 min with human liver microsomes, in the presence of NADPH, resulted in inhibition of cytochrome P450 3A4 (midazolam 1'hydroxylase) activity with an IC50 value of 155 nM (114 ng/mL).

Elimination

After rats were treated with a single dose of 10 mg/kg of TDM1 radiolabeled on the DM1 moiety, almost 100% of the radioactivity precipitated when the plasma was treated with acetone. In cannulated rats receiving this dose, 51% of the radiolabel was collected in the bile after seven days, less than 5% was recovered in the feces. Most of the radiolabel in the bile was associated with the acetonitrile extracted fraction, 97% or greater suggesting that the DM1 moiety has been cleaved from the antibody. Consistent with this finding, intact T-DM1 was not present in the bile. In non-cannulated rats, the amount of radioactivity found in the feces, 50%, was comparable to that found in the bile of cannulated rats as one would expect with IV dosing. In these non-cannulated rats, only 8% of the total radioactivity was in the cumulative urine after 168 hours.

4.3.3 General Toxicology:

Monkeys tolerated repeat doses of ado-trastuzumab emtansine as high as 30 mg/kg or about 8 times the clinical dose. Even at this high dose, ado-trastuzumab emtansine was less toxic to monkeys than the lower clinical dose was to humans. Thrombocytopenia was seen in both species but was much less severe in monkeys. Likewise, anemia was also less severe in monkeys. Mononuclear infiltrates in monkeys predicted the pneumonitis seen in humans.

Increased transaminases and centrilobular vacuolization in monkeys predicted the more severe hepatic toxicity seen in cancer patients. There was some evidence of toxicity in the tongue in monkeys that anticipates the stomatitis seen clinically. Diarrhea was also seen in both monkeys and patients. The incidence of peripheral neuropathy in patients is about 21%, this correlated with the axonal degeneration in the sciatic nerve with Schwann cell hyperplasia and hypertrophy and axonal and axonal degeneration of the dorsal funiculus in the spinal cord in monkeys at approximately 7 times the clinical exposure, based on AUC.

In nonclinical toxicity studies, ado-trastuzumab emtansine caused effects that suggest it may impair male and female fertility in humans. Effects in rats that received a single dose of ado-trastuzumab emtansine included degeneration of seminiferous tubules with hemorrhage in the testes associated with increased weights of testes and epididymides in males and signs of hemorrhage and necrosis of the corpus luteum in ovaries in females at approximately 4 times the clinical exposure, based on AUC. In monkeys that received ado-trastuzumab emtansine once every three weeks for 12 weeks at up to 7

times the clinical exposure, based on AUC, there were decreases in the weights of epididymides, prostate, testes, seminal vesicles and uterus. The Applicant attributed some of these changes on the varied sexual maturity of the animals used in this study. Effects on reproductive organs were not unexpected due to the mechanism of action of the small molecule portion, DM1.

4.3.4 Genotoxicity:

DM1 did not cause reverse mutations in the Ames assay. Nevertheless, in an in vivo bone marrow micronucleus assay in rats DM1 did cause a significant increase in the percentage of micronucleated PCE and a significant decrease in the PCE: NCE ratio.

4.3.5 Carcinogenicity

Not required and not submitted.

4.3.6 Reproductive and Developmental Toxicology:

Trastuzumab is a known embryo-fetal toxin in humans, causing oligohydramnios that is potentially fatal. DM1 was negative in an in vitro bacterial reverse mutation (Ames) assay. However, DM1 is a microtubule inhibitor, which caused micronuclei formation in vivo in rat bone marrow cells and is known to be toxic to rapidly dividing cells. Thus, the Applicant did not conduct any new reproductive and developmental toxicity studies with trastuzumab emtansine, relying instead on the results for trastuzumab and the mechanism of action of DM1. Trastuzumab emtansine can likely cause embryo-fetal toxicity and has been labeled accordingly.

The Pharmacology/Toxicology review team recommended pregnancy category D for ado-trastuzumab emtansine.

Based on the known (boxed) clinical risk of oligohydramnios with trastuzumab, the clinical and safety teams recommended a post-marketing registry to collect clinical data on oligohydramnios risk for T-DM1.

4.4 Clinical Pharmacology

For full details, see clinical pharmacology review by Dr. Sara Schrieber.

4.4.1 Mechanism of Action

Trastuzumab emtansine (T-DM1, ado-trastuzumab emtansine) is a HER-2-directed antibody-drug conjugate (ADC) consisting of trastuzumab, a humanized anti-HER2 IgG1 isotype monoclonal antibody, emtansine (DM1), an anti-microtubule agent derived from maytansine, and SMCC, a linker molecule used to conjugate DM1 to trastuzumab. The mechanism of action of T-DM1 consists of a multi-step process. T-DM1 binds to HER2 then undergoes receptor-mediated internalization, which results in the intracellular release of DM1 and subsequently cell death.

4.4.2 Pharmacodynamics

No large changes in the mean QT interval (i.e., >20 ms) were detected at the proposed TDM1 dosing regimen.

4.4.3 Pharmacokinetics

A population PK analysis estimated the TDM1 clearance and terminal elimination half-life as 0.68 L/day and ~4 days, respectively; inter-individual variability of CL is 19.1%. T-DM1 accumulation was not observed following multiple dosing. No dose adjustments are required for significant covariates (sum of longest diameter of target lesions by RECIST, albumin, HER2 ECD concentrations, baseline trastuzumab concentrations, AST, and body weight). Based on the population PK analysis, as well as analysis of Grade 3 or greater adverse drug reactions and dose modifications, dose adjustments are not needed for mild or moderate renal impairment. The influence of hepatic impairment on the PK of T-DM1 or DM1 has not been determined. In vitro studies indicate that DM1, the cytotoxic component of T-DM1, is metabolized mainly by CYP3A4. Concomitant use of strong CYP3A4 inhibitors with T-DM1 should be avoided due to the potential for an increase in DM1 exposure and toxicity.

Exposure-Response (Efficacy and Safety): After accounting for baseline risk factors, the exposure-response analysis demonstrated that increases in T-DM1 exposures are related with improved efficacy (OS, PFS, and objective response rate (ORR)). Exposure-response relationships for safety identified an inverse trend for Grade 3 or worse hepatotoxicity, but no significant exposure-response relationships were identified for thrombocytopenia.

Immunogenicity: With the immunogenicity assays used, the overall incidence of positive anti-therapeutic antibody (ATA) to T-DM1 was determined to be 5.3% in the studies included in the BLA. The presence of T-DM1 in patient serum at the time of ATA sampling can interfere with the ability of this assay to detect anti-KADCYLA antibodies. As a result, data may not accurately reflect the true incidence of anti-T-DM1 antibody development. In addition, neutralizing activity of anti-T-DM1 antibodies has not been assessed.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Data from 7 clinical studies were submitted to the BLA. This included the pivotal phase III study (EMILIA/TDM4370g /BO21977), 3 phase II studies (TDM4374g, TDM4258g, TDM4450g/BO21976), a phase I dose escalation study(TDM3569g), study TDM4688g (QTc study) and TDM4529g/BO25430 (extension study).

Table 4 lists the clinical trials submitted in support of the BLA application. Data from EMILIA (TDM4370g /BO21977) serves as the primary basis for evaluation of efficacy and safety.

Table 4: Key Clinical Studies Submitted

Protocol	Study Design	Disease	N	Primary EP	Status
EMILIA TDM4370g / BO21977	Ph III, randomized T- DM1 vs. Capecitabine + Lapatinib	HER2+ MBC must have received trastuzumab and taxane	991	PFS, OS	Ongoing (enrollment completed)
TDM4374g	Ph II, single arm	Previously treated HER2+ MBC, ≥2 lines of HER2- directed therapy, must have received trastuzumab and lapatinib	110	ORR	Completed
TDM4258g	Ph II, single arm	Previously treated HER2+ MBC progressed on HER2- directed therapy	112	ORR	Completed
TDM4450g	Ph II, randomized T-DM1 vs. trastuzumab+ docetaxel	HER2+ LABC or MBC; no prior MBC treatment	104	PFS	Completed

EP= Endpoint; N= Number; MBC= metastatic breast cancer; PFS= progression free survival; ORR= objective response rate

5.2 Review Strategy

The clinical review is based on the clinical study report for the pivotal study TDM4370g / BO21977 and the supportive studies outlined in 5.1. The efficacy review was conducted by Dr. Laleh Amiri-Kordestani and the safety review by Dr. Gideon Blumenthal. A statistical review was conducted by Dr. Qiang (Casey) Xu. Among the items reviewed were the case report forms, selected narratives, primary data sets for baseline characteristics, efficacy and toxicity submitted by the applicant, study reports for other ado-trastuzumab emtansine clinical trials, research of the FDA data base for regulatory history of the ado-trastuzumab emtansine IND #71072, and a literature review of HER2+ MBC.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Phase 3 EMILIA (TDM4370g/BO21977)

This BLA submission is primarily supported by results from a single industry-sponsored study, EMILIA (U.S. study number 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”

EMILIA Trial Design and treatment plan:

The protocol design was a Phase III, randomized, multicenter, international, two-arm, open-label clinical trial designed to compare the safety and efficacy of T-DM1 with that of capecitabine + lapatinib for HER2-positive MBC. The protocol planned to enroll a total of 980 patients at more than 200 sites worldwide. Eligible patients were to be randomized in a 1:1 ratio to either T-DM1 or lapatinib + capecitabine:

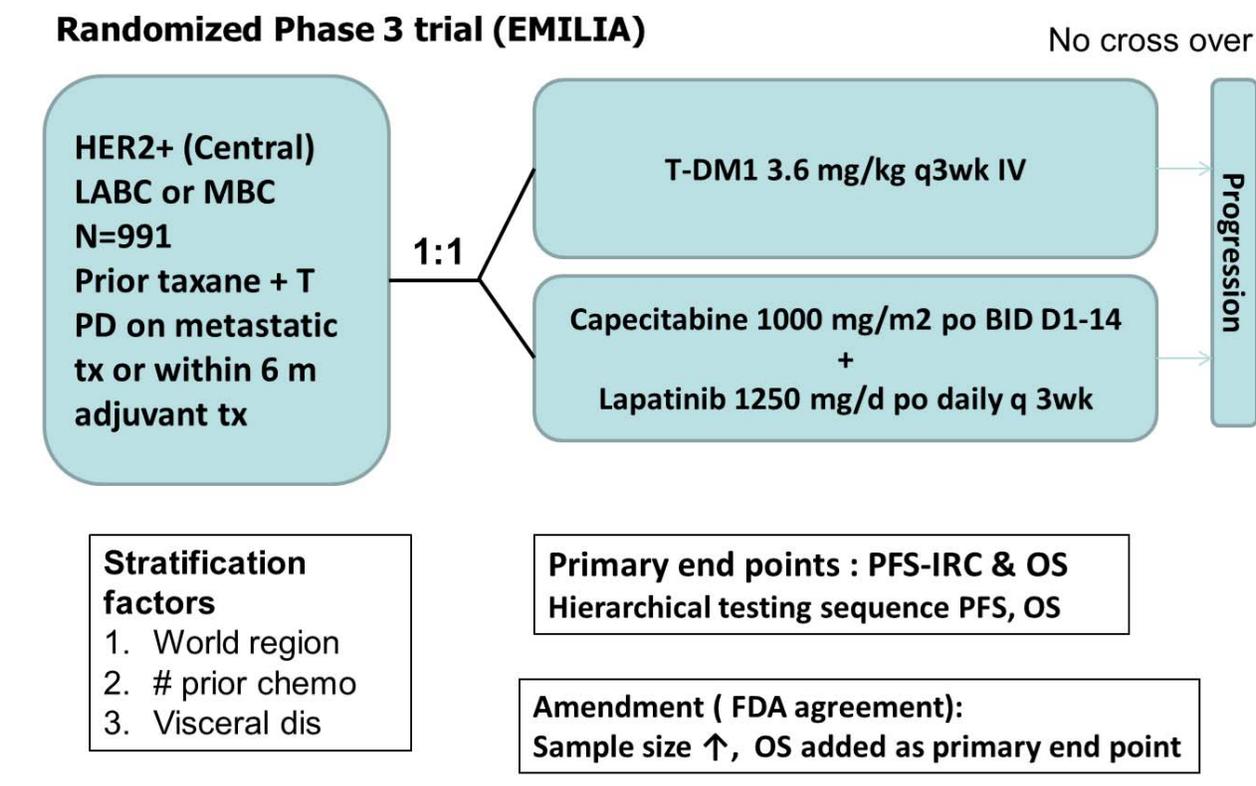
- T-DM1 Arm: T-DM1 3.6 mg/kg intravenously (IV) over 30-90 minutes on Day 1 of a 21-day cycle
- Control Arm (lapatinib + capecitabine): Lapatinib 1250 mg/day orally once per day of a 21-day cycle + capecitabine 1000 mg/m² orally twice daily on Days 1-14 of a 21-day cycle

A hierarchical dynamic randomization scheme was used to ensure an approximately equal sample size for the two treatment arms 1) overall, 2) by world region (United States, Western Europe, other), and 3) within each of the four categories defined by the following two prognostic factors, the number of prior chemotherapeutic regimens for

unresectable, locally advanced or metastatic disease (0–1 vs. > 1), and visceral versus non-visceral disease. Patients with both visceral and non-visceral disease were considered as having visceral disease.

Patients received study treatment until PD (as assessed by the investigator), unmanageable toxicity, or study termination by Genentech and Roche (the Applicants). Assessment of PFS, a co-primary objective of this trial, was based on modified Response Evaluation Criteria in Solid Tumors (RECIST) and was determined by independent review of baseline and follow-up assessments obtained every 6 weeks, regardless of dose delays or dose interruptions. An additional tumor assessment was performed after investigator-documented disease progression. This served to provide the IRC with an additional opportunity to confirm investigator-assessed disease progression in an effort to reduce discordance between investigator and independent assessments of PD.

Figure 3: EMILIA study design



EMILIA TRIAL Eligibility Criteria

Inclusion Criteria:

Disease-Specific Criteria

- Prospective centrally confirmed HER2-positive (i.e., IHC 3 + and/or gene-amplified by FISH, ratio ≥ 2). Both IHC and FISH assays were done; however, only one positive result was required for eligibility. Prior HER2-positive result was also acceptable if they were centrally confirmed from other company sponsored studies (for example, Studies BETH (AVF4285s/BO20906), AVEREL (BO20231), HERA (BO16348), NEOSPHERE (WO20697), MARIANNE (BO22589/TDM4788g), AVANT, HANNAH, PHEREXA, or CLEOPATRA (WO20698/TOC4129g))
- Histologically or cytologically confirmed invasive breast cancer (incurable, locally advanced or metastatic disease)
- Prior treatment for breast cancer were to include both: A taxane, alone or in combination with another agent, and Trastuzumab in the adjuvant, locally advanced, or metastatic setting
- Documented progression of incurable locally advanced or metastatic breast cancer, defined by the investigator was required. (Progression must occur during or after treatment for advanced or metastatic disease or within 6 months of completing adjuvant therapy.)
- Patients with measurable and/or non-measurable disease were included. Patients with CNS-only disease were excluded.

General Criteria

- Age ≥ 18 years
- Cardiac ejection fraction $\geq 50\%$ by either ECHO or MUGA
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function, evidenced by the following laboratory results within 2 weeks prior to randomization:
 - Absolute neutrophil count >1500 cells/mm³
 - Platelet count $>100,000$ cells/mm³
 - Hemoglobin >9.0 g/dL
 - Patients are allowed to be transfused red blood cells to this level.
 - Albumin ≥ 2.5 g/dL
 - Total bilirubin ≤ 1.5 upper limit of normal (ULN)
 - SGOT (AST), SGPT (ALT), and alkaline phosphatase $\leq 2.5X$ ULN with the following exception:
 - Patients with bone metastases: alkaline phosphatase $\leq 5 X$ ULN
 - Creatinine clearance >50 mL/min based on Cockcroft-Gault glomerular filtration rate (GFR) estimation:
 - $(140 - \text{Age}) \times (\text{weight in kg}) \times (0.85 \text{ if female}) / 72 \times \text{serum creatinine}$

- International normalized ratio (INR) and activated partial thromboplastin time (aPTT) <1.5 X ULN (unless on therapeutic coagulation)
- An agreement to use a highly effective, non-hormonal form of contraception was required for women of childbearing potential and men with partners of childbearing potential, Acceptable forms of contraception were two of the following:

Placement of non-hormonal intrauterine device (IUD)
Condom with spermicidal foam/gel/film/cream/suppository
Diaphragm or cervical/vault caps with spermicidal
foam/gel/film/cream/suppository

The above contraception was not a requirement in the case of any of the following:

Patient was surgically sterilized (i.e., who have undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy)
Patient has had no menstrual period for 12 consecutive months, or
Patient truly abstains from sexual activity

Contraception use was to continue for the duration of the study treatment and for at least 6 months after the last dose of study treatment. Periodic abstinence (e.g., calendar ovulation, symptothermal, post-ovulation methods) and withdrawal were not acceptable methods of contraception. Postmenopausal was defined as ≥ 12 months of amenorrhea.

Specific country requirements were followed (e.g., in the United Kingdom, women of childbearing potential and male subjects and their partners of childbearing potential had to use two methods of contraception [one of which must be a barrier method] for the duration of the study).

Exclusion Criteria

Cancer-Related Criteria

- History of treatment with T-DM1
- Prior treatment with lapatinib or capecitabine.
- Peripheral neuropathy of Grade ≥ 3 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0
- History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage 1 uterine cancer, synchronous or previously diagnosed HER2-positive breast cancer, or cancers with a similar outcome as those mentioned above.
- History of receiving any chemotherapy or investigational treatment within 21 days prior to randomization and recovery of treatment-related toxicity consistent with other eligibility criteria

- History of radiation therapy within 14 days of randomization. If the patient had a history of recent radiation therapy, the patient had to have recovered from any resulting acute toxicity (to Grade \leq 1) prior to randomization.
- Brain metastases that were untreated, symptomatic, or required therapy to control symptoms; or any radiation, surgery, or other therapy, including steroids, to control symptoms from brain metastases within 2 months of randomization

Cardiopulmonary Function

- History of symptomatic CHF or ventricular arrhythmia requiring treatment
- History of myocardial infarction or unstable angina within 6 months of Randomization
- Severe dyspnea at rest due to complications of advanced malignancy or current requirement for continuous oxygen therapy

General Criteria

- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
- Pregnancy or lactation
- Current known active infection with HIV, hepatitis B virus, or hepatitis C virus
- Presence of conditions that could affect gastrointestinal absorption:
 - malabsorption syndrome, resection of the small bowel or stomach, and ulcerative colitis
- History of intolerance (such as Grade 3–4 infusion reaction) to trastuzumab
- Known hypersensitivity to 5-fluorouracil or known dihydropyrimidine dehydrogenase deficiency
- Current treatment with sorivudine or its chemically related analogs, such as
 - Brivudine
- Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol (i.e., unable to swallow pills)

Ado-trastuzumab emtansine Formulation and Packaging:

Ado-trastuzumab emtansine was provided as a single-use lyophilized formulation in a colorless 20-mL Type I glass vial closed by means of a (b) (4) stopper and an over seal with a flip-off plastic cap. Upon reconstitution, the resulting product contains 20 mg/mL ado-trastuzumab emtansine, 10 mM sodium succinate, pH 5.0, 6% (w/v) (i.e., 60 mg/mL) sucrose, and 0.02% (w/v) polysorbate 20.

Rationale for Dose Selection:

Ado-trastuzumab emtansine: In phase I Study TDM3569g, the MTD of ado-trastuzumab emtansine administered by IV infusion every 3 weeks was 3.6 mg/kg. DLT consisted of Grade 4 thrombocytopenia in 2 of 3 patients treated at 4.8 mg/kg. Related

Grade ≥ 2 adverse events at 3.6 mg/kg were infrequent and manageable. Patients in the Phase II study, TDM4258g, have shown similar tolerability at the 3.6 mg/kg dose level administered every 3 weeks. Thus, the ado-trastuzumab emtansine dose of 3.6 mg/kg given every 3 weeks was selected by the applicant.

Lapatinib + Capecitabine: Lapatinib 1250 mg/day orally once per day of a 21-day cycle + capecitabine 1000 mg/m² orally twice daily on Days 1–14 of a 21-day cycle. The doses and schedules of both drugs in this study are the same as those in the pivotal study that lead to the approval of Lapatinib + capecitabine in the United States for the treatment of HER2-positive MBC patients who have previously received an anthracycline, a taxane, and trastuzumab.

Ado-trastuzumab emtansine Drug Administration:

T-DM1 was to be administered at a dose of 3.6 mg/kg IV every 21 days until study drug discontinuation. The total dose depended on the patient's weight on Day 1 (or up to 3 days before) of each cycle. The initial dose was to be administered over 90 minutes \pm 10 minutes). Infusions were allowed to be slowed or interrupted for patients experiencing infusion-associated symptoms. Vital signs were to be assessed pre-dose and post-dose. Following the initial dose, patients were observed for at least 90 minutes for fever, chills, or other infusion-associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), subsequent doses of T-DM1 were to be administered over 30 minutes (\pm 10 minutes), with a minimum 30-minute observation period after infusion.

Dose Delay and Modification of ado-trastuzumab emtansine:

If a patient required a dose reduction, dosing was reduced by one dose level, as per Table 5. No dose re-escalation was allowed. If toxicity did not resolve within 42 days from the last dose received, the patient was discontinued from study treatment and was followed for disease progression and survival outcome. When a significant and related toxicity resolved to Grade 1 or baseline, the patient could resume T-DM1, if the delay had not exceeded 42 days from the last received dose.

Table 5: Dose-Reduction for Ado-T-DM1

Dose level	Dose
0	3.6 mg/kg
-1	3.0 mg/kg
-2	2.4 mg/kg
Indication for further dose reduction	Off study

Source: protocol TDM4370g/BO21977

Protocol dose modifications for hematologic toxicities: Patients that received ado-trastuzumab emtansine who experienced a first Grade 4 thrombocytopenia event, after adequate recovery to a platelet count of Grade ≤ 1 or baseline, could continue treatment with ado-trastuzumab emtansine at a dose of 3 mg/kg in subsequent treatment cycles.

Patients at the 3 mg/kg dose level who experienced a Grade 4 thrombocytopenia event, after adequate recovery as defined above, could continue treatment with ado-trastuzumab emtansine at a dose of 2.4 mg/kg in subsequent treatment cycles. Patients who experience a Grade 4 thrombocytopenia event at the 2.4 mg/kg dose level were discontinued from study treatment. A dose delay of up to 42 days from the patient's last dose received was permitted.

Patients who experienced a Grade 3 or 4 hematologic event were checked twice weekly for recovery of counts. If a patient's platelet counts did not recover to baseline or Grade ≤ 1 within 42 days from the patient's last dose received, the patient was discontinued from study treatment. No re-escalation of the ado-trastuzumab emtansine dose was allowed.

Protocol dose modifications for hepatotoxicity: Dose modifications for hepatotoxicity were amended in the protocol. ado-trastuzumab emtansine had to be permanently discontinued in patients with ALT $> 3 \times$ ULN and a subsequent increase of total bilirubin to $> 2 \times$ ULN within 21 day regardless of the dos level.

For patients with AST $> 3 \times$ ULN (without ALT $> 3 \times$ ULN) and a subsequent increase in total bilirubin to $> 2 \times$ ULN within 21 days, treatment with ado-trastuzumab emtansine could be continued with one dose level reduction after recovery of AST to $\leq 2.5 \times$ ULN and total bilirubin to $\leq 1.5 \times$ ULN only after consultation with the Medical Monitor.

Patients receiving ado-trastuzumab emtansine at 3.6 mg/kg who experienced a Grade 3 or 4 transaminase elevation and/or a Grade ≥ 2 total bilirubin elevation could, after adequate recovery to Grade ≤ 2 (transaminase levels) and/or Grade ≤ 1 (total bilirubin level) or baseline, continue treatment with T-DM1 at a dose of 3 mg/kg. Patients at the 3 mg/kg dose level who experienced a Grade 3 or 4 transaminase elevation and/or a Grade ≥ 2 total bilirubin elevation could, after adequate recovery to Grade ≤ 2 (transaminase levels) and/or Grade ≤ 1 (total bilirubin level) or baseline, continue treatment with ado-trastuzumab emtansine at a dose of 2.4 mg/kg. Patients at the 2.4 mg/kg dose level who experienced a Grade 3 or 4 transaminase elevation and/or a Grade ≥ 2 total bilirubin elevation were discontinued from study treatment. A dose delay of up to 42 days from the patient's last received dose was permitted.

Protocol dose modifications for neurotoxicity: Patients receiving ado-trastuzumab emtansine who experienced Grade 3 or 4 peripheral neuropathy that did not resolve to Grade ≤ 2 within 42 days after the last dose received were discontinued from study treatment.

Table 6: EMILIA Schedule of Assessments

D a y	Screening ^a	Cycle 1			Cycles 2–34+			Study Drug Completion Visit	S u r v i v a l
	–30 to –1	1	8 (±3)	15 (±3)	1 (±3)	8 (±3)	15 (± 3)	30 days (±7) after last dose of study drug	
Informed consent	x								
HER2 testing ^d	x								
Medical history and demographics	x								
Complete physical exam	x e								
Limited physical exam		x			x			x	
FACT-B (female patients only)		Day 1 (prior to any study procedures or discussion of test results) of Cycle 1 and every two cycles thereafter until 6 weeks post disease progression						x	
Diarrhea Assessment Scale		Day 1 (prior to any study procedures or discussion of test results) of every cycle						x	
Weight and height ^f	x	x			x			x	
ECOG performance status	x							x	
Concomitant medications	x g	x			x			x	x
Adverse events	x h	x	x	x	x	x	x	x	x
12-lead electrocardiogram ^l	x							x w	
ECHO or MUGA ^j (ECHO preferred)	x	Weeks 6, 12 and every 12 weeks thereafter until discontinuation of study drug						x w	
Tumor assessment ^k	x	Every 6 weeks (± 5 days) regardless of dose delay or early discontinuation until 6 weeks post disease progression							
Bone scan/skeletal X-ray ^l	x	Per clinical indication or to confirm a complete response							
CT or MRI of brain	x	Per clinical indication or to confirm complete response							
Central laboratory tests	See Append								
CBC with platelet and 3-part differential ^{m, n}	x	x	x	x	x	x	x	x	

Clinical Review KADCYLA (ado-trastuzumab emtansine, T-DM1)
Amiri (efficacy) and Blumenthal (safety)
BLA 125,427

Day	Screening ^a	Cycle 1			Cycles 2–34+			Study Drug Completion Visit	Survival Follow-Up ^b
	–30 to –1	1	8 (±3)	15 (±3)	1 (±3)	8 (±3)	15 (±3)	30 days (±7) after last dose of study drug	
Serum chemistries ⁿ	x o	x ^p	x ^q	x ^q	x ^p	x ^q	x ^q	x ^p	
INR and aPTT ^r	x							x	
Serum/urine pregnancy test ^s	x				x				
Laboratory urinalysis ^t	x							x	
Assessment of patient hospitalizations and/or hospital visits		x			x			x	
Evaluation of capecitabine and lapatinib compliance ^u			x	x	x				
Study drug administration/distribution ^v		x			x				

aPTT = activated partial thromboplastin time; CBC = complete blood count; CT = computed tomography; ECHO = echocardiogram;
INR = international normalized ratio; IVRS = interactive voice response system; MRI = magnetic resonance imaging;
MUGA = multiple-gated acquisition.

Notes: Visits are based on a 21-day cycle. If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend that preclude the procedure within the allotted window, the procedure must be performed on the nearest following date.

a Results of screening tests or examinations performed as standard of care prior to obtaining informed consent and within 30 days prior to randomization may be used rather than repeating required tests.

b Only SAEs considered to be related to study medication should be reported. Patients will also be followed for survival, patient-reported outcomes as assessed by the FACT-B, and subsequent anti-cancer therapies (not all concomitant meds) approximately every 3 months starting from the Study Drug Completion Visit until death, loss to follow-up, withdrawal of consent, or study discontinuation by the Sponsor

c Informed consent must be obtained prior to performance of any screening assessments unless the assessments were performed as standard of care prior to obtaining informed consent. Informed consent does not need to be obtained within 30 days of randomization; however, patients who fail screening and are rescreened will need to be reconsented.

d HER2 status must be centrally confirmed any time prior to randomization (result must be IHC 3+ and/or gene amplified by FISH) by the Sponsor-selected central laboratory. IHC, FISH, qRT-PCR will be performed. See Section 4.5.2 for further details.

e Includes assessment of vital signs (blood pressure, pulse, temperature).

f Height at screening only.

g Record concomitant medications used within 14 days prior to randomization and investigational and/or anti-cancer therapies used within 21 days of randomization.

h Prior to initiation of study medication, only serious adverse events considered related to protocol-mandated procedures are collected.

i Electrocardiograms for each patient should be obtained from the same machine whenever possible. One set of all ECG tracings should be printed and kept with the patient's record.

j Because of a potential worldwide Tc-99 shortage, ECHO is preferred; however, the same method used at screening should be used throughout the study. Additional scans may be performed at any point if clinically indicated. Refer to Section 3.4 for further information on cardiac safety surveillance. All ECHO and MUGA scans should be submitted to an IRC for central review within 2 weeks after the visit, if possible.

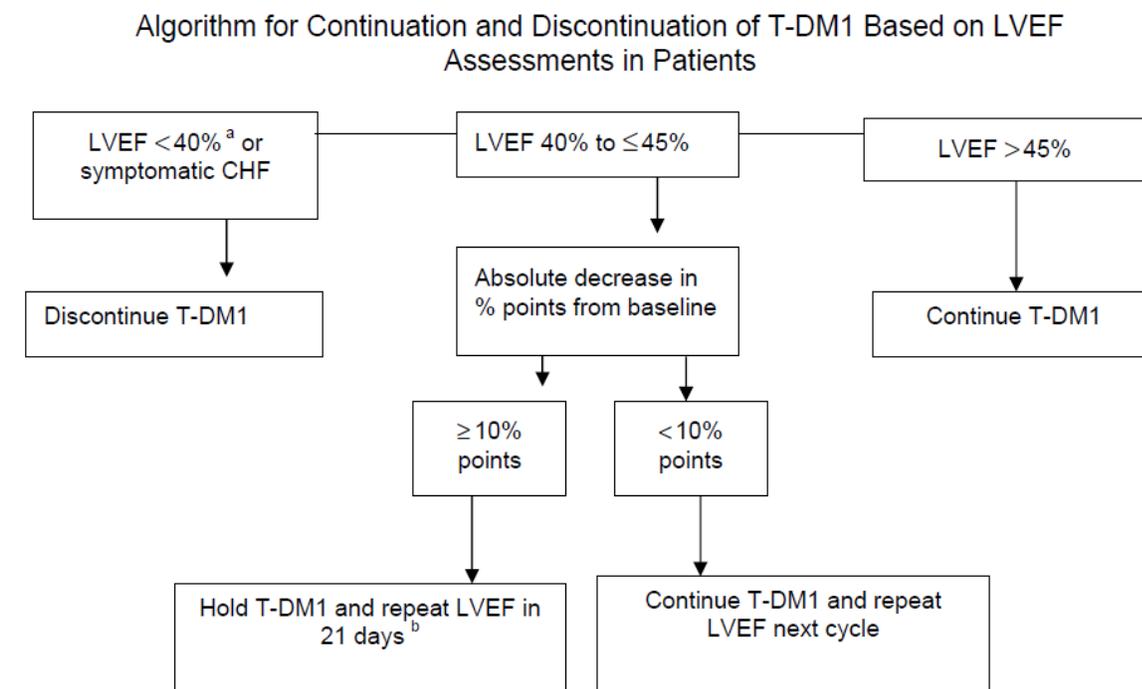
- k Response must be assessed using modified RECIST. Assessments should include an evaluation of all known or suspected sites of disease, whenever possible. The same radiographic procedure used at baseline must be used throughout the study (e.g., the same contrast protocol for CT scans). If the patient cannot undergo CT with contrast, then the chest should be imaged via CT without contrast and the abdomen and pelvis should be imaged using MRI with contrast. See Section 4.5.1 for further details. Technical imaging parameters are defined in Appendix B. All radiographic images should be submitted to the IRC within 2 weeks after the visit, if possible. Patients who are discontinued from study treatment for reasons other than disease progression will continue to undergo tumor assessments approximately every 6 weeks until 6 weeks post disease progression.
- l An isotope bone scan and/or skeletal X-rays will be performed at screening and should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions or for confirmation of complete response.
- m CBC includes hemoglobin, hematocrit, platelet count, red blood cells, white blood cells; 3-part differential includes lymphocytes, monocytes, and granulocytes.
- n Local laboratory assessments performed within 72 hours preceding study drug administration may be used as the Day 1 evaluations (up to 96 hours for Cycle 1, Day 1). Results of these local laboratory assessments must be reviewed (except alkaline phosphatase and lactate dehydrogenase) prior to study drug administration. In the event of a Grade 3 or 4 toxicity (per CTCAE version 3.0), pertinent laboratory assessments should be repeated at the Investigator's discretion until recovery to Grade 2 or less. Refer to Section 4.5 for further details. CBC and serum chemistry are required for Day 8 and 15 for Cycles 1–4. At Day 8 and Day 15 for subsequent cycles, they are optional.
- o Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, and uric acid.
- p Blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase.
- q Aspartate aminotransferase, alanine aminotransferase, and total bilirubin only.
- r Patients on capecitabine who are receiving coumarin-derivative anticoagulant therapy, such as warfarin or phenprocoumon, should have the prothrombin time (PT) or INR monitored weekly.
- s For women of childbearing potential, including premenopausal women who have had a tubal ligation. Screening assessment must be performed on serum within 7 days prior to randomization. Afterward, perform every third cycle on urine. A positive urine test must be confirmed with a serum test.
- t Includes specific gravity, pH, protein, glucose, blood ketones, and bilirubin.
- u Patients randomized to the lapatinib plus capecitabine arm will be assessed for their daily compliance by checking the completion of the patients' diaries, and the information will be entered into the EDC system.
- v Cycle 1, Day 1 must occur within 5 days of randomization. For patients assigned to T-DM1 therapy, T-DM1 should be administered over approximately 90 minutes for the first dose and, in the absence of infusion-related adverse events, over approximately 30 minutes in subsequent doses. Vital signs should be taken before and after the T-DM1 infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first T-DM1 infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions. For patients assigned to the control arm, therapy will be given according to standard prescribing guidelines as described in Section 4.3.2.
- w If the most recent assessments were performed less than 30 days from the Study Drug Completion Visit, these assessments do not need to be repeated.

Ado-T-DM1 Cardiac Monitoring Algorithm:

The algorithm for continuation and discontinuation of T-DM1 t based on LVEF assessments is presented in Figure 4. Ejection fractions were monitored at screening, at 6 and 12 weeks after first dose of study treatment, and every 12 weeks thereafter until the assessment at the Study Drug Completion Visit. Patients with confirmed symptomatic cardiac dysfunction (Grade ≥ 3 left ventricular systolic dysfunction) were discontinued from study treatment. Asymptomatic declines in LVEF were handled as per the algorithm in Figure 4. All ECHO and MUGA scans were collected for potential central review. An independent CRC reviewed all potential cases of left ventricular systolic dysfunction prior to each 6-month DMC review and reported their findings to the DMC. Patients who discontinued for reasons other than disease progression were to

complete the Study Drug Completion Visit approximately 30 days after the last dose of study treatment and were to be followed for survival every 3 months until study closure.

Figure 4: Ado-T-DM1 Cardiac Monitoring Algorithm



CHF = congestive heart failure; LVEF = left ventricular ejection fraction;
T-DM1 = Trastuzumab-MCC-DM1.

Note: LVEF assessment results must be reviewed before the next scheduled T-DM1 infusion.

^a LVEF < 40% can be repeated within 21 days, and T-DM1 should be discontinued if LVEF < 40% is confirmed. T-DM1 should be held while the repeat LVEF is obtained.

^b After a second consecutive confirmatory result, T-DM1 should be discontinued if the LVEF is confirmed and if medical management was not required in order to correct the LVEF.

Source: protocol TDM4370g/BO21977

EMILIA (TDM4370g/BO21977) Study Endpoints

Primary Endpoints:

The EMILIA trial had two co-primary endpoints: PFS and OS.

Progression-Free Survival:

The primary efficacy endpoint of PFS, based on independent review of tumor assessments, is 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 occurs earlier.

Overall Survival:

The co-primary endpoint, OS, is defined as the time from the date of randomization to the date of death from any cause.

Secondary Endpoints:

PFS per Investigator Assessment:

PFS per investigator assessment was defined the same as the primary endpoint, except progression determined by investigator review of tumor assessments using RECIST 1.0, rather than IRC.

Objective Response Rate:

Objective tumor response will be determined per IRC assessment, using RECIST 1.0.

Duration of Objective Response:

Duration of response is defined as the period of time from the date of initial confirmed partial response (PR) or complete response (CR) until the date of progressive disease or death.

Clinical Benefit Rate:

Clinical benefit rate is defined as the proportion of patients who achieve an objective response (CR or PR) or who maintain stable disease (SD) for at least 6 months after randomization.

Time to Treatment Failure (TTF):

TTF is defined as the time from randomization to discontinuation of treatment for any reason, including disease progression or treatment toxicity or death on study from any cause.

Time to symptom progression:

Time to symptom progression (defined as the time from randomization to the first documentation of a ≥ 5 -point decrease from baseline in the scoring of responses) between the two treatment arms was measured by the FACT-B TOI. The FACT-B TOI is a subset of the FACT-B and includes the Physical, Functional and Breast subscales.

EMILIA Statistical Methods:

PFS and OS were the co-primary efficacy endpoints for this study. The date of data cutoff for the final analysis of PFS was when 508 IRC-assessed PFS events occurred. However, the final analysis of PFS was not conducted until the last patient was enrolled. The final analysis of OS was planned to be performed when approximately 632 deaths have occurred.

Sample Size Determination:

The sample size of the study was determined by the analysis of OS. To detect an HR of 0.8 in OS (a 25% improvement in median OS; i.e., from 17.2 months in the control arm to 21.5 months in the treatment arm), approximately 632 deaths were required to achieve 80% power at a two-sided 5% alpha level. A total of 980 patients were required to be enrolled into the study. The primary efficacy analysis of PFS was to take place when 508 IRC-assessed PFS events had occurred. This provided 90% power to detect an HR of 0.75 in PFS (a 33% improvement in median PFS; i.e., from 6.2 months in the control arm to 8.3 months in the treatment arm), with a two-sided alpha of 5%.

Reviewer Comment: In amendment 3 of the protocol, overall survival was changed from a secondary endpoint to a co-primary endpoint to ensure more robust trial results. Further, the sample size was increased from 580 to 980 patients to ensure the study was properly powered to detect a clinically meaningful OS benefit.

Efficacy Analysis Populations:

Intent to Treat: all randomized patients

Other Analysis Populations: For Objective response only patients with measurable disease at baseline included. For duration of response only responders will be included.

Safety Analysis Population: Patients who received at least one dose of study medication, and was based on the treatment they actually received.

Efficacy Analysis

To adjust for multiplicity due to having two primary endpoints, a fixed-sequence hypothesis testing procedure was implemented. The hypothesis test for PFS was conducted at a one-sided alpha of 2.5%. If the PFS was statistically different between the two arms, OS was to be tested at a one-sided alpha of 2.5% to determine if the two arms had significantly different OS.

The co-primary efficacy endpoint of PFS was based on independent review of tumor assessment, defined as the time from randomization to documented IRC-assessed disease progression or death from any cause (whichever occurs earlier).

For the analysis of PFS, data for patients without disease progression or death were censored at the time of the last tumor assessment (or, if no tumor assessment was performed after the baseline visit, at the time of randomization plus 1 day). Data from patients who were lost to follow-up are included in the analysis as censored observations on the last date of tumor assessment that the patient was known to be progression free.

For patients who receive non-protocol therapy (defined as any treatment the patient receives that is intended to treat his or her MBC) prior to documented PD, the primary PFS analysis did not censor patients at the initiation of non-protocol therapy. A sensitivity analysis of PFS censoring patients at the last tumor assessment before the initiation of non-protocol therapy will also be performed.

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 non-visceral disease will be used as the primary analysis to compare PFS between the two treatment arms. The results from the unstratified log-rank test and the stratified and unstratified Wilcoxon test will also be provided.

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. Cox proportional-hazards models, stratified by world region (United States, Western Europe, Other), number of prior chemotherapeutic OS, the co-primary endpoint, is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of randomization plus 1 day. Methods for OS analysis are similar to those described for the PFS endpoint, with the stratified log-rank test being the primary analysis and sensitivity analysis using the unstratified log-rank test and the stratified and unstratified Wilcoxon test. In addition, 1-year and 2-year survival rates and corresponding 95% CIs will be estimated using the Kaplan–Meier approach, as appropriate.

Interim safety analysis:

An independent DMC monitored was accumulating safety data every 6 months. In addition, data on serious adverse events were monitored by the DMC at least once every 3 months. An independent CRC reviewed all potential cases of left ventricular systolic dysfunction prior to each semi-annual DMC review and reported their findings to the DMC until the final PFS analysis.

Sensitivity Analyses:

Several sensitivity analyses were planned (see Table 7 for definition).

Table 7: Sensitivity Analyses

Factor Assessed	Censoring Rules
1) Impact of Non-Protocol Anti-Cancer Therapy	Patients were censored at the last tumor assessment before the initiation of non-protocol anti-cancer therapy.
2) IRC and Investigator Tumor Assessment	PFS was defined as time from randomization to the earliest PFS event based on progression by either the IRC or investigator tumor assessment or death. For patients without a PFS event, PFS was censored on the date of the last IRC tumor assessment with an assessment other than 'unevaluable' or 'unknown', whichever was later. PFS for patients with no post-baseline tumor assessments was censored on the date of randomization plus 1 day.
3) Impact of Missed Tumor Assessments	If a patient had documented IRC-assessed progression after two or more missing or unevaluable assessments, the patient's progression event was recorded as an event at the documented IRC-assessed progression date, after the missing assessments.
4) Impact of Missed Tumor Assessment	If a patient had a documented IRC-assessed progression after one or more missing assessments, the patient's progression event was back-dated to the date of the last non-missing assessment, plus 1 day.
5) Impact of Loss to Follow-Up	Patients who were lost to follow-up for tumor assessment (ie, did not die or have disease progression per investigator but without any tumor assessments for > 84 days [two tumor assessment cycles] prior to data cutoff) were counted as events at the last time they were known to be progression-free.
6) Impact of treatment discontinuation due to toxicity	Patients who discontinued at least one of the study drugs due to adverse events were censored at the last tumor assessment prior to the date of the last drug discontinued due to adverse event.

Source: EMILIA CSR page 75, Table 5

EMILIA Randomization and Blinding:

An interactive Voice Response System used to collect patient screening information and randomize eligible patients in a 1:1 ratio by a hierarchical randomization scheme to one of the two treatment arms (ado-trastuzumab emtansine or lapatinib and capecitabine).

Randomization was stratified by the following criteria:

- World region (United States, Western Europe, Other)
- Prior chemotherapy regimens for unresectable, locally advanced or metastatic disease (0-1, >1)
- Visceral versus non-visceral disease

EMILIA Protocol Amendments

Protocol Version a1, 19 February 2010:

Study was amended to include two interim analyses of the secondary efficacy endpoint overall survival to be conducted, at approximately 125 and 222 deaths at the request of The Data Monitoring Committee. Also because of the potential worldwide Tc99 shortage, the preferred modality to evaluate cardiac function was changed to echocardiogram. Furthermore, skeletal X-rays were recommended to be included at the screening visit.

Protocol Version a2, 13 May 2010:

Prior to the widespread distribution of Amendment 1, in response to regulatory feedback it was determined that an interim analysis at approximately 125 deaths would be premature and it was planned at #222 deaths. Also definition of progression-free survival (PFS), as per U. S. Food and Drug Administration Guidance Document regarding endpoints for Oncology clinical trials was broadened to include all deaths, even those occurring beyond 30 days after the last dose of study treatment. Previously, PFS was defined as the time from randomization to the first occurrence of progression or death on study-that was, within 30 days after the last dose of study treatment.

Protocol Amendment a3 – 4 October 2010:

- Overall survival was changed from a secondary endpoint to a co-primary endpoint to ensure more robust trial results. Further, the sample size was increased from 580 to 980 patients to ensure the study was properly powered to detect a clinically meaningful OS benefit.
- The number of patients in the PK analysis was increased from 80 to 160 patients.
- The frequency of the urine pregnancy test for females of childbearing potential was increased to every three cycles because of the study drugs' potential to cause harm to a fetus.
- The frequency of administration of the FACT-B questionnaire was increased to obtain a more accurate assessment of the changes in symptom burden due to disease progression.

5.3.2 Phase II, randomized study ado-T-DM1 vs. trastuzumab + docetaxel TDM4450g /BO21976

Title: "A Randomized, Multicenter, Phase II Study of the Efficacy and Safety of ado-trastuzumab Emtansine vs. Trastuzumab (Herceptin®) and Docetaxel (Taxotere®) in Patients with Metastatic HER2-Positive Breast Cancer Who Have Not Received Prior Chemotherapy for Metastatic Disease"

Design:

TDM4450g is a Phase II, randomized, multicenter, international, two-arm, open label clinical trial designed to explore the efficacy and safety of ado-trastuzumab emtansine relative to the combination of trastuzumab and docetaxel in patients with HER2-positive, unresectable, locally advanced breast cancer and/or metastatic breast cancer who have not received prior chemotherapy for metastatic disease. Approximately 120 patients were to be enrolled at approximately 100 sites worldwide. Following the determination of eligibility, patients were randomized in a 1:1 ratio to receive one of two treatments:

- Arm A: Ado-trastuzumab emtansine at 3.6 mg/kg intravenous (IV) over 30–90 minutes on Day 1 every 3 weeks
- Arm B: For Cycle 1, on Day 1, trastuzumab at 8 mg/kg IV + docetaxel either 75 mg/m² or 100 mg/m² IV. For subsequent cycles, trastuzumab 6 mg/kg IV on Day 1 every 3 weeks + docetaxel 75–100 mg/m² IV every 3 weeks

A hierarchical dynamic randomization scheme was used to ensure an approximately equal sample size for the two treatment arms (1) overall and (2) within each of the eight permutations (23) of the following 3 categories of variables: world region (U.S., ex-U.S., prior adjuvant trastuzumab therapy (yes, no) and disease-free interval (\leq 24 months or $>$ 24 months). Patients in the trastuzumab + docetaxel arm who discontinued study treatment because of PD were eligible to cross over to ado-trastuzumab emtansine treatment, starting at 3.6 mg/kg, until a second PD event, clinical deterioration, and/or intolerance.

Key inclusion:

This study enrolled patients with HER2-positive (IHC 3+ or FISH-positive, based on local laboratory assay), histologically- or cytologically- confirmed resectable, locally advanced breast cancer and/or metastatic breast cancer, who had not received prior chemotherapy for their metastatic disease. Patients had measurable disease per modified RECIST criteria, with at least one target lesion \geq 2 cm on conventional computed tomography (CT) scan or \geq 1 cm on a spiral CT scan.

Primary Endpoints: PFS based on investigator assessment and safety.

Efficacy:

Efficacy was evaluated through assessment of PFS (the primary endpoint), and the following secondary endpoints: 12-month PFS rate, median PFS, duration of overall survival, survival rate at 12 months, ORR, duration of objective response, and clinical benefit rate (the proportion of patients with CR or PR or SD for \geq 6 months since randomization), per investigator assessment.

The primary efficacy analysis included all randomized patients, following the ITT principle, based on the treatment arm to which patients were randomized.

PFS was defined as the time from randomization to the first occurrence of disease progression, as determined by investigator tumor assessments using modified RECIST or death on study from any cause, whichever occurred earlier. Death on study was defined as death from any cause within 30 days of the last dose of study drug prior to crossover. The first documented PD event prior to crossover on the control arm was included in the analysis of the primary endpoint of PFS.

Safety:

The co-primary objective of this study was to evaluate the safety of ado-trastuzumab emtansine compared with the combination of trastuzumab + docetaxel in this population. Safety was assessed by the incidence, nature, and severity of adverse events (AEs). The safety outcome measures were assessment of the incidence of the following: AEs and SAEs; AEs leading to discontinuation, modification, or interruption of ado-trastuzumab emtansine treatment; AEs leading to trastuzumab discontinuation or interruption; AEs leading to docetaxel discontinuation, modification, or interruption; congestive heart failure (CHF) and symptomatic decline in left ventricular ejection fraction (LVEF); and the cause of death on study.

Statistics:

Primary and secondary efficacy analyses were planned to include all randomized patients following the intent-to-treat (ITT) principle according to the treatment arm to which they were randomized.

The primary PFS analysis was to be performed after 72 PFS events had occurred in the two arms combined. With 72 PFS events, the 95% CI around the estimated hazard ratio (HR) for comparison of the two treatment arms was approximately ($0.63 \times \text{HR}$, $1.59 \times \text{HR}$). For assessment of the primary endpoint, Kaplan–Meier (KM) estimates of the PFS curve and the median PFS and 12-month PFS rate are presented for each treatment arm. The HR of PFS comparing ado-trastuzumab emtansine against the combination of trastuzumab + docetaxel, and its 95% CI were estimated from a Cox proportional hazards model, stratified by world region (U.S., ex-U.S.), prior adjuvant trastuzumab therapy (yes, no), and disease-free interval (≤ 24 months or > 24 months). Unstratified analyses were also performed.

5.3.3 Phase II, single arm study TDM4374g

Title: “A Phase II, Single-Arm, Open-Label Study of Trastuzumab–MCC–DM1 Administered Intravenously to Patients with HER2-Positive Metastatic Breast Cancer”

Design:

This was a Phase II, multi-institutional, single-arm, open-label study of T-DM1 administered at a dose of 3.6 mg/kg by intravenous (IV) infusion every 3 weeks to patients with HER2-positive MBC.

Approximately 100 patients were to be enrolled and treated, and the total enrollment period was expected to span approximately 50 weeks. The analysis of overall response rate was conducted with patient data collected through approximately 26 weeks after the last patient was enrolled in the study. In addition, the final analysis of safety and all secondary and exploratory endpoints was conducted approximately 9 months after the last patient was enrolled in the study.

Tumor responses were categorized as complete response, partial response, stable disease, or progressive disease according to the Response Evaluation Criteria in Solid Tumors (RECIST). Tumor assessments (computed tomography [CT] and/or magnetic resonance imaging [MRI] scans) were performed every 6 weeks irrespective of dose delays, interruptions, or reductions. Bone and brain scans (either CT or MRI) were performed at baseline and when clinically indicated during the study.

Key inclusion:

Patients with HER2-positive documented MBC who had received prior treatment with an anthracycline, trastuzumab, a taxane, lapatinib, and capecitabine in the neoadjuvant, adjuvant, locally advanced, or metastatic setting, with at least two HER2-directed regimens of therapy received in the metastatic or locally advanced setting were eligible for participation in this study.

Primary Endpoints:

- Objective response rate - independent radiologic review
- Safety and tolerability

Secondary Endpoints:

Duration of objective response, clinical benefit rate (complete response, partial response, and stable disease at 6 months, and progression-free survival (PFS), based on independent radiologic review and pharmacokinetics of T-DM1 in this patient population

Statistics:

Objective response was defined as a complete or partial response determined on two consecutive occasions ≥ 4 weeks apart. The objective response rate was the percentage of patients who were determined to have an objective response. The primary analysis population was the treated population; for this analysis, patients without a post-baseline tumor assessment were considered non-responders. An estimate of the objective response rate and the exact 95% confidence interval (CI) using the Blyth–Still–Casella method were provided. Best response as assessed by the IRF was also summarized.

5.3.4 Phase II, single arm study TDM4258g

Title: “A Phase II, Single-Arm, Open-Label Study of Trastuzumab-MCC-DM1 Administered Intravenously to Patients with HER2-Positive Metastatic Breast Cancer Who Have Progressed while Receiving HER2-Directed Therapy”

Design: A multi-institutional, open-label, single-arm, Phase II study

Key inclusion: This trial enrolled patients with HER2-positive MBC who had progressed while receiving HER2-directed therapy. Patients were required to have HER2-positive status, as demonstrated by either 3 + HER2 protein over-expression determined by IHC or HER2 gene amplification determined by FISH.

Trastuzumab-MCC-DM1 dose: T-DM1 was administered by IV infusion at a dose of 3.6 mg/kg every 21 days. The total dose was dependent on the patient’s weight on Day 1 of each cycle. Patients could receive T-DM1 for a maximum of 1 year. Patients continuing to benefit from T-DM1 at the completion of their treatment course were enrolled into an extension study (TDM4529g: An Open-label, Extension Study of T-DM1 in Patients Previously Treated with T-DM1 In a Genentech-Sponsored T-DM1 Study).

Primary Endpoints:

- To assess the objective response rate (by independent radiologic review) associated with T-DM1 3.6 mg/kg IV every 3 weeks in patients with HER2-positive metastatic breast cancer who have progressed while receiving HER2-directed therapy and who have received chemotherapy for metastatic disease
- To characterize the safety and tolerability of this T-DM1 regimen in this patient population

Secondary Endpoints:

- To further characterize the efficacy of this T-DM1 regimen in this patient population, as measured by duration of objective response and progression free survival (PFS), based on independent radiologic review
- To further characterize the efficacy of this T-DM1 regimen in this patient population, as measured by objective response rate, duration of objective response, and PFS, based on investigator assessments
- To characterize the pharmacokinetics of this T-DM1 regimen in this patient population
- To assess the formation of antibodies to T-DM1

Safety: All patients who received any amount of T-DM1 were considered evaluable for safety. All adverse events for all patients were collected for the safety dataset. Safety was assessed by means of summaries of adverse events, deaths, and changes in laboratory test results.

Statistics:

- **Primary Endpoint:** The primary efficacy endpoint of this study was objective response, as assessed by an independent radiologic review using RECIST. Objective response was defined as a complete or partial response determined on two consecutive occasions ≥ 4 weeks apart. An estimate of the objective response rate and 95% confidence intervals (Blythe–Still–Casella) were calculated. The primary analysis population was based on efficacy evaluable patients. In addition, objective response rate was estimated in all treated patients; for this analysis, patients without a post-baseline tumor assessment were considered as non-responders.
- **Secondary Endpoints**
 - Objective Response:** An analysis identical to the primary analysis was performed using investigator assessments of response.
 - Duration of Objective Response:** Duration of objective response was assessed for patients with an objective response. Duration of objective response was defined as the time from the initial documentation of response to documented disease progression or death from any cause on study. Separate analyses of duration of objective response were performed based on IRF and investigator assessments. Duration of response data for patients without disease progression or death was censored at the time of the last tumor assessment.

-Progression-Free Survival: PFS was defined as the time from the first day of treatment to documented disease progression or death from any cause on study, whichever occurred first.

Death on study was defined as death from any cause within 30 days of the last dose of T-DM1.

Separate analyses of PFS were performed based on IRF and investigator assessments.

PFS was estimated for efficacy evaluable patients only. PFS data for patients without disease progression or death was censored at the time of the last tumor assessment.

Kaplan-Meier estimates of median PFS were reported.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Genentech proposed the following indication in their BLA submission:

“KADCYLA is a HER2-targeted antibody drug and microtubule inhibitor conjugate indicated, 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
- Recurred during or within six months of completing adjuvant therapy.”

6.1.1 Methods

This review will focus primarily on the efficacy results of the single randomized controlled trial, TDM4370g/BO21977 (EMILIA). For information on EMILIA study design, see section 5.3.1. For the statistical review, please see Dr. Casey Xu’s review.

In addition to the pivotal study, a review of efficacy data from the randomized phase 2 study TDM4450g /BO21976, and from two single arm phase 2 studies TDM4374g and TDM4258g will be included in sections 6.1.11 and 6.1.12, respectively. For a summary of the study designs of TDM4450g /BO21976, TDM4374g and TDM4258g, see sections 5.3.2, 5.3.3 and 5.3.4.

6.1.2 TDM4450g /BO21976 (EMILIA) Demographics

Table 8 presents the breakdown of enrollment by country. The 5 highest accruing countries were the U.S, South Korea, Canada, France, United Kingdom, Brazil, and Italy; each country recruited more than 50 patients. By region, Western Europe had the highest accrual (317), followed by USA (270), Asia (158) and other (246).

Reviewer Comment: Diverse international representation, including 27% from U.S.

Table 8: TDM4450g /BO21976 Enrollment by country

Country	# Pts	%
USA	270	27.2
South Korea	103	10.4
Canada	73	7.4
France	64	6.5
United Kingdom	56	5.7
Brazil	55	5.5
Italy	52	5.2
Poland	49	4.9
Germany	47	4.7
Spain	39	3.9
Bulgaria	38	3.8
Taiwan	28	2.8
Singapore	22	2.2
Switzerland	14	1.4
Sweden	14	1.4
Russia	12	1.2
Mexico	11	1.1
Portugal	11	1.1
Finland	10	1.0
Bosnia	8	0.8
Slovenia	7	0.7
Hong Kong	3	0.3
Philippines	2	0.2
Denmark	1	0.1
India	1	0.1
New Zealand	1	0.1
Total	991	100

Demographic information including baseline tumor characteristics and prior breast cancer treatments is represented in Tables 9 and 10. There was under-representation

of African Americans (4.2% in Lapatinib + Capecitabine and 5.9% in ado-Trastuzumab emtansine arm.

Almost all patients had metastasis at study entry. Of the 19 patients categorized as having locally recurrent disease at baseline, 7 actually had metastases noted on their baseline disease assessment. Therefore, the number of true locally recurrent patients overall was 1%.

Table 9: TDM4450g /BO21976 Baseline patient demographics

	Lapatinib + Capecitabine (N=496)		Ado-trastuzumab emtansine (N=495)	
Sex				
Female	492	99.2%	494	99.8%
Male	4	0.8%	1	0.2%
Age				
<65 yrs	423	85.3%	430	86.9%
≥65 yrs	73	14.7%	65	13.1%
ECOG				
Missing	8	1.6%	2	0.4%
0	312	62.9%	299	60.4%
1	176	35.5%	194	39.2%
Race				
American Indian or Alaska	7	1.4%	6	1.2%
Asian	86	17.3%	94	19.0%
Black or African American	21	4.2%	29	5.9%
Native Hawaiian/ Other	3	0.6%	1	0.2%
Not Available	5	1.0%	7	1.4%
White	374	75.4%	358	72.3%
Ethnicity				
Hispanic or Latino	57	11.5%	50	10.1%
Not Available	49	9.9%	45	9.1%
Not Hispanic or Latino	390	78.6%	400	80.8%
Region				
Other	200	40.3%	204	41.2%
USA	136	27.4%	134	27.1%
Western Europe	160	32.3%	157	31.7%

Table 10 : TDM4450g /BO21976 Baseline tumor characteristics

	Lapatinib + Capecitabine (N=496)		Ado-trastuzumab emtansine (N=495)	
Visceral				
No	161	32.5%	161	32.5%
Yes	335	67.5%	334	67.5%
Measurable disease at baseline				
No	71	14.3%	64	12.9%
Yes	425	85.7%	431	87.1%
Estrogen receptor				
Negative	240	48.4%	226	45.7%
Positive	248	50.0%	259	52.3%
Unknown	8	1.6%	10	2.0%
Progesterone receptor				
Negative	310	62.5%	281	56.8%
Positive	170	34.3%	199	40.2%
Unknown	16	3.2%	15	3.0%
Stage				
I	43	8.7%	44	8.9%
II	139	28.0%	127	25.7%
III	138	27.8%	155	31.3%
IV	131	26.4%	114	23.0%
Unknown	45	9.1%	55	11.1%
Liver				
No	295	59.5%	282	57.0%
Unknown	6	1.2%	3	0.6%
Yes	195	39.3%	210	42.4%

Reviewer Comment: Overall baseline patient demographics and tumor characteristics were well balanced between treatment arms.

Table 11 : TDM4450g /BO21976 previous therapies

	Lapatinib + Capecitabine (N=496)		Ado-trastuzumab emtansine (N=495)	
Line of therapy by chemotherapy				
1st Line	80	16.1%	79	16.0%
2nd Line	282	56.9%	283	57.2%
3rd Line	134	27.0%	133	26.9%
Line of therapy by chemotherapy or hormonal therapy				
1st Line	65	13.1%	66	13.3%
2nd Line	230	46.4%	235	47.5%
3rd Line	201	40.5%	194	39.2%
Line of therapy by systemic				
1st Line	58	11.7%	60	12.1%
2nd Line	175	35.3%	186	37.6%
3rd Line	263	53.0%	249	50.3%
Reproductive status				
Not applicable	9	1.8%	14	2.8%
Perimenopausal	16	3.2%	22	4.4%
Postmenopausal	204	41.1%	196	39.6%
Premenopausal	229	46.2%	222	44.8%
Unknown	38	7.7%	41	8.3%
Prior trastuzumab treatment in advanced or metastatic setting				
No	77	15.5%	78	15.8%
Yes	419	84.5%	417	84.2%
Prior anthracyclines				
No	194	39.1%	192	38.8%
Yes	302	60.9%	303	61.2%
Prior HER2 therapy				
No	1	0.2%	0	0.0%
Yes	495	99.8%	495	100.0%
Prior radiation				
No	141	28.4%	137	27.7%
Yes	355	71.6%	358	72.3%
Prior systemic therapy				
YES	496	100.0%	495	100.0%
Prior surgery				
No	61	12.3%	50	10.1%
Yes	435	87.7%	445	89.9%
Prior taxanes				
No	2	0.4%	2	0.4%
Yes	494	99.6%	493	99.6%

Reviewer Comment: Overall previous therapies were well balanced between treatment arms.

6.1.3 Subject Disposition

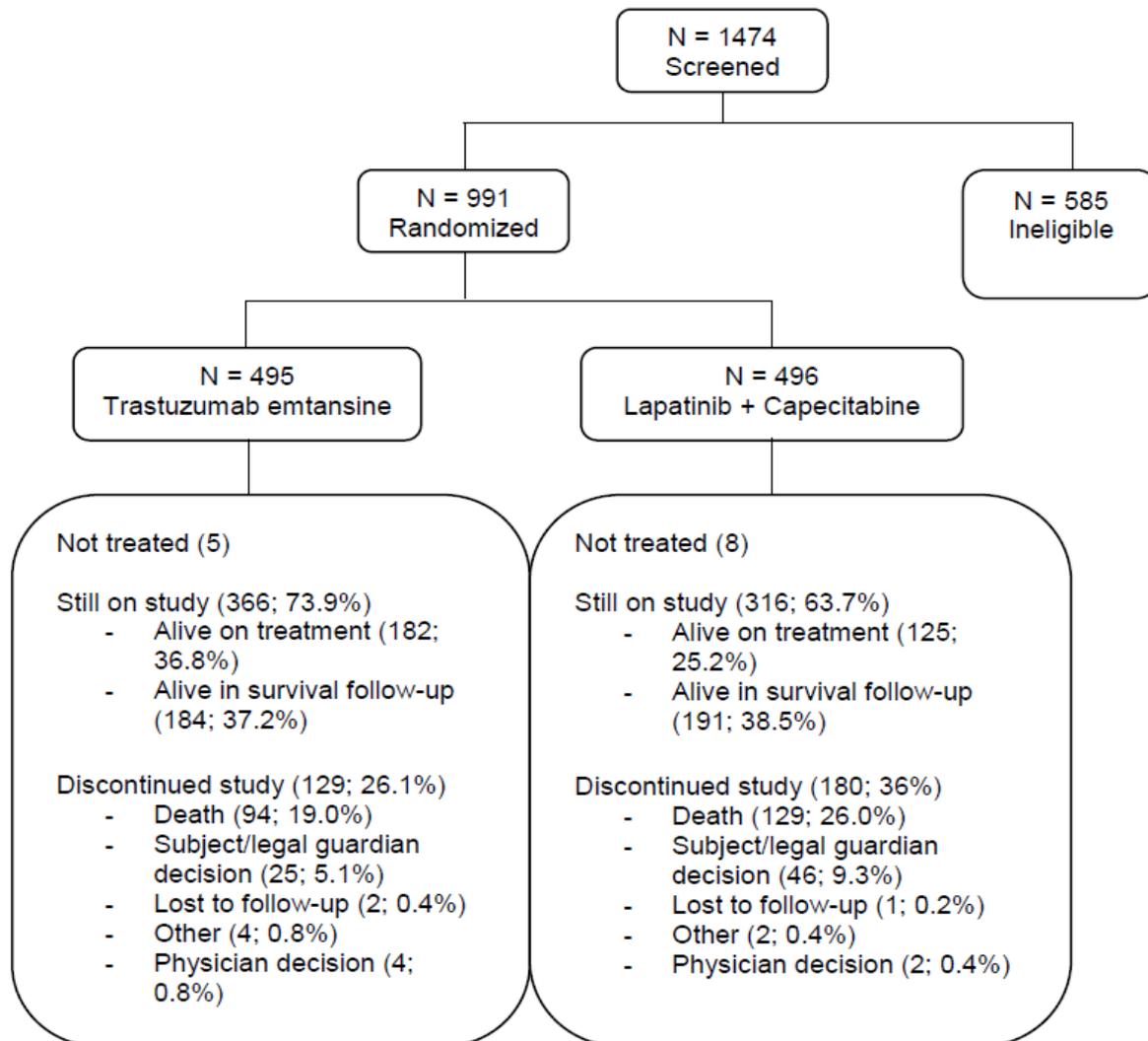
From the first patient visit February 23, 2009 to data cut-off January 14, 2012, a total of 1474 patients were screened, and 991 patients were enrolled from 213 centers in 26 countries. A total of 991 patients were randomized, 496 to the lapatinib plus capecitabine arm and 495 to the ado-trastuzumab emtansine arm, comprising the ITT population (Table 12). The country with the highest enrollment was the US (270 patients). Of the randomized patients, 13 (5 in the ado-trastuzumab emtansine arm and 8 in the lapatinib plus capecitabine arm) did not receive any study treatment.

The median duration of follow-up was similar in both arms: 12.9 months in the ado-trastuzumab emtansine arm and 12.4 months in the lapatinib plus capecitabine arm. The minimum follow-up period was 0 months and the maximum duration of follow-up was approximately 34.7 months in both arms.

Table 12: TDM4450g /BO21976 Patient Disposition (As of July 31, 2012)

	Trastuzumab emtansine (%)	Lapatinib+ Capecitabine (%)
Randomized	495	496
Evaluable for Efficacy	495 (100)	496 (100)
Evaluable for Safety	490 (99.0)	488 (98.4)
Still on Study	308 (62.2)	262 (52.8)
On Treatment	106 (21.4)	55 (11.1)
In Survival Follow-Up	202 (40.8)	207 (41.7)
Discontinued Study		
Death	149 (30.1)	182 (36.7)
Patient Decision	28 (5.7)	48 (9.7)
Physician Decision	4 (0.8)	2 (0.4)
Lost to Follow-Up	3 (0.6)	1 (0.2)
Other	3 (0.6)	1 (0.2)

Figure 5: TDM4450g /BO21976 Patient Disposition



Source : CSR figure 3

6.1.4 Analysis of Primary Endpoint(s)

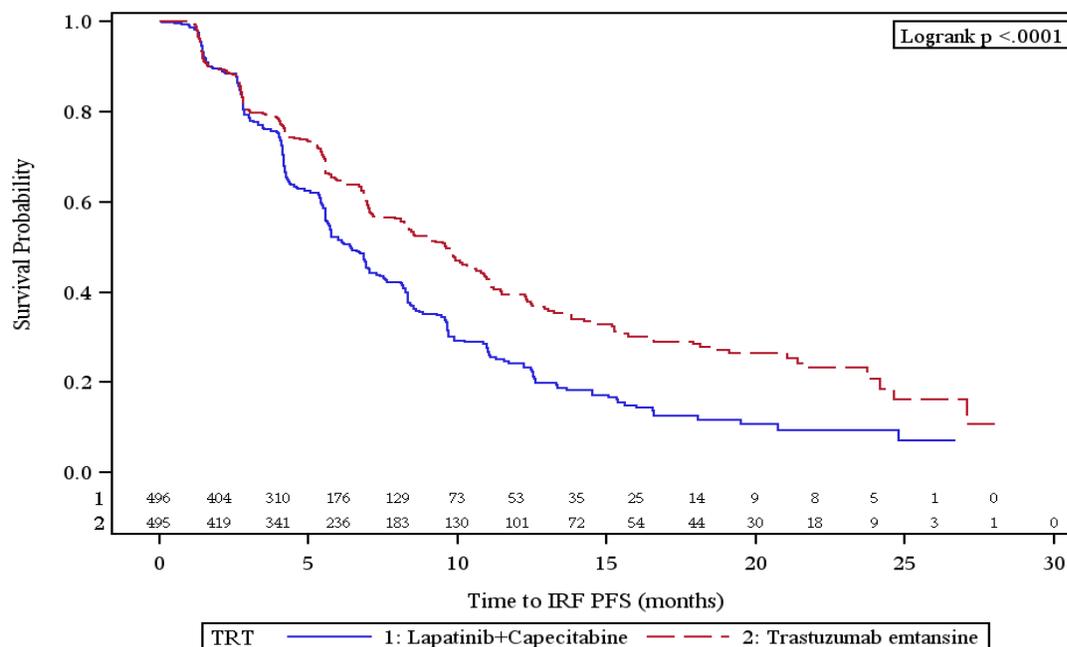
As of the January 14, 2012, 569 IRF-confirmed PFS events had occurred, 304 (61%), (273 progressive diseases + 31 deaths) in the L+C arm and 265 (54%), (237 PDs + 28 deaths) in the TDM1 arm. The randomized trial demonstrated a statistically significant improvement in IRC-assessed PFS in the trastuzumab emtansine -treated group compared with the lapatinib plus capecitabine-treated group [hazard ratio (HR) = 0.65, 95% CI: 0.55, 0.77, stratified log-rank $p < 0.0001$], and an increase in median PFS of 3.2 months (median PFS of 9.6 months in the trastuzumab emtansine -treated group vs. 6.4 months in the lapatinib plus capecitabine group).

Table 13: TDM4450g /BO21976 Primary endpoint: IRC assessed PFS

	L+C N = 496	T-DM1 N = 495
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 PFS (months)	6.4 (95% CI: 5.7, 7.1)	9.6 (95% CI: 8.3, 10.6)
Hazard ratio (95% CI)	0.65 (0.549, 0.771)	
P-value (stratified Log-Rank test)	<0.0001	

Reviewer comment: The magnitude of median PFS difference (3.2 months) is relatively modest and less than the median OS difference (5.8 months), but the hazard ratios are similar (0.65 and 0.68).

Figure 6: TDM4450g /BO21976KM curve IRC-assessed PFS



Sensitivity Analyses:

Several sensitivity analyses were conducted (see Table 7 for definition and Table 14 for results).

Table 14: Results of sensitivity analysis

Sensitivity Analysis	Description	Median PFS L + C	Median PFS T-DM1	HR (95% CI)
#1	Censoring for NPT	6.7	9.5	0.677 (0.566, 0.810)
#2	Earliest IRC/INV event	5.5	6.9	0.713 (0.612, 0.831)
#3	Missing tumor assessment	6.4	9.6	0.643 (0.544, 0.761)
#4	Missing tumor assessment (backdate)	6.0	9.6	0.640 (0.541, 0.758)
#5	Loss to follow up	5.7	8.4	0.629 (0.536, 0.738)
#6	Censoring for treatment discontinuation due to toxicity	6.4	9.8	0.643 (0.539, 0.767)

Source: CSR (Table 23)

Reviewer Comment: All sensitivity analyses are internally consistent, with HRs ranging from 0.53 to 0.81 and median differences ranging from 1.4 months to 3.6 months. This indicates that the results of the study are robust.

Oncology unblinding issues:

A GCP compliance deviation related to the conduct of the IRC assessment of disease progression was identified by the FDA during this BLA review. The IRC in the EMILIA study consisted of blinded radiology review followed by an oncology review which could confirm or over-write the radiology assessment. The radiology review was based only

on radiographic scans. The oncology review was based on the results of radiology review as well as the relevant clinical data sent by the applicant.

Per the IRC charter, clinical information must be redacted of all references to study medication treatment group as well as subject confidential identifiers and investigator site information. Any information about specific toxicities of any study drug must be removed. However, the patient profiles provided by the applicant to the IRC for oncology review contained information on drug-specific toxicities, which might have potentially biased the oncology reviewer.

To examine the impact of this compliance deviation on the primary PFS results, 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 0.65 (95%CI: 0.54, 0.77) and 0.66 (95%CI: 0.56, 0.78), respectively. In inspection of [REDACTED]^{(b)(4)}, partial unblinding of oncologists involved in IRC team was contracted by the applicant (Genentech) to provide independent review of tumor responses was detected at the CRO.

Information on drug-specific toxicities was provided by the applicant to the IRC oncologist, potentially biasing the IRC tumor assessments. Two sensitivity analyses were retrospectively 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 were 0.65 (95%CI: 0.54, 0.77) and 0.66 (95%CI: 0.56, 0.78), respectively, showing consistent results with the primary analyses.

Table 15: Concordance between Radiologists and Oncologists

	L+C N = 496	T-DM1 N = 495
Agree on PFS Status, N (%)	464 (94)	470 (95)
Agree on date, N (%)	434 (88)	428 (86)
Disagree on date, N (%)	30 (6)	42 (9)
Disagree on PFS Status	31 (6)	26 (5)

Reviewer comment: Considering the fact that the radiologists remained completely blinded, the results from the supporting favorable sensitivity analysis and favorable overall survival results, FDA considered that the unblinding of the independent oncologists did not have a negative impact on the study results.

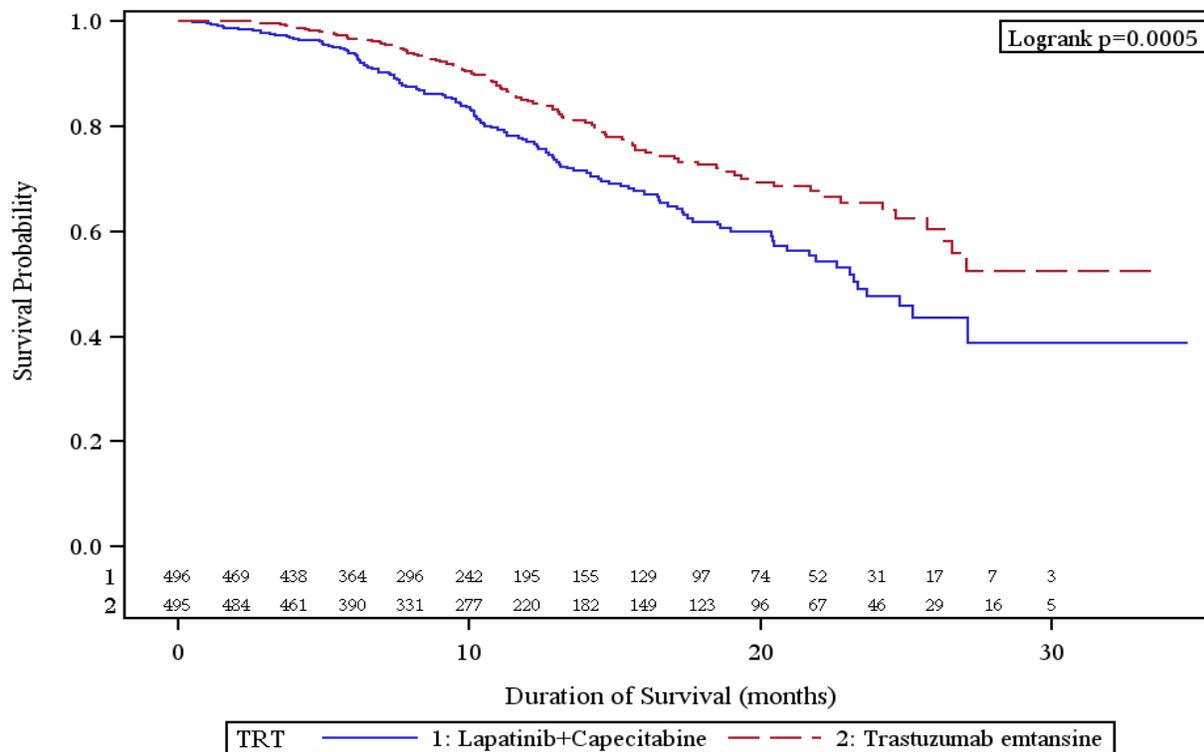
Co-primary endpoint: Overall Survival

At the Jan 14 2012 cut-off, a planned interim OS analysis was performed, comprising 35.3% of the events planned at the final analysis. For this planned interim analysis, 94 patients (19%) died on the T-DM1 arm and 129 patients (26%) died on L + C. This yielded a hazard ratio of 0.63, and a p value of 0.0007, which did not cross the O'Brien Fleming statistical boundary (Table 16).

Table 16: TDM4450g /BO21976 1st interim analysis OS

	L + C N = 496	T-DM1 N = 495
Number of patients who died, N (%)	129 (26)	94(19)
Number of Censored Patients	367	401
Median (months)	23.3	NE
Hazard ratio (95% CI)	0.62 (95% CI: 0.48, 0.81)	
P-value (stratified Log-Rank)	0.0005	

Figure 7: TDM4450g /BO21976 KM curve 1st interim analysis OS



Reviewer Comment: The first interim OS analysis favored the T-DM1 arm which did not meet the pre-specified statistical significance. The pre-specified efficacy stopping boundary of alpha level for this interim analysis was 0.0003.

In the original statistical analysis plan, no further interim analyses of OS were pre-specified. However, in light of the strong clinical benefit observed at the time of the primary PFS analysis, the company planned a second interim analysis for OS (when at least 50% of the target number of 632 events had occurred) to justify allowing patients in the control arm of the study access to ado-trastuzumab emtansine and to obtain an accurate estimate of the true treatment effect of ado-trastuzumab emtansine on OS prior to any confounding effect due to crossover. This analysis was done with prior approval of the agency. The clinical cut-off date for this analysis was 31 July 2012. For this unplanned interim analysis, 149 patients (30%) died on the T-DM1 arm and 189 patients (37%) died on L + C. This yielded a hazard ratio of 0.68, and a p value of 0.0006, which crossed the pre-specified O'Brien Fleming statistical boundary of 0.0037 (Table 17).

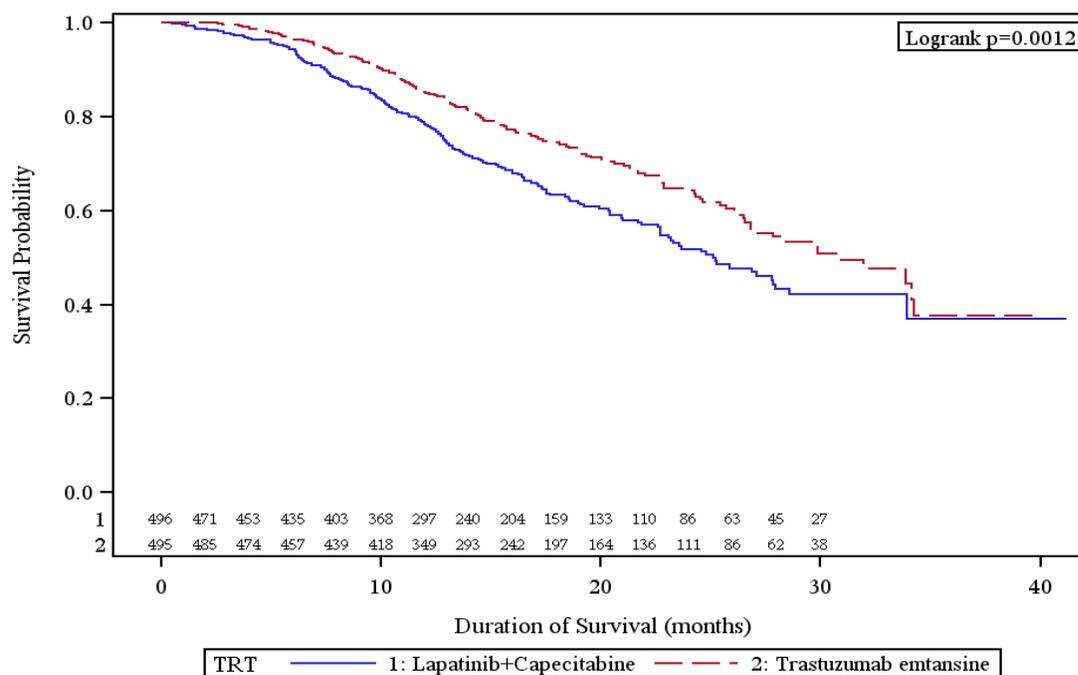
Table 17 :TDM4450g /BO21976 2nd interim analysis OS

	L + C N = 496	T-DM1 N = 495
Number of patients who died, N(%)	182 (37)	149 (30)
Median (months)	25.1 (95% CI: 22.7, 28.0)	30.9 (95% CI: 26.8, 34.3)
Hazard ratio (95% CI) (Stratified Cox Regression)	0.682 (0.548, 0.849)	
P-value (stratified Log-Rank)	0.0006	
p-Value (Unstratified Log-Rank Test)	0.0012	
O'B-F Boundary	0.0037	

Reviewer comments:

The second interim analysis was performed when 52% of the planned number of deaths had occurred. A 32% decrease in the hazard of death in the ado-trastuzumab emtansine group compared to the lapatinib plus capecitabine group is similar to the 35% decrease seen in the hazard of disease progression or death. The 5.8 month improvement in median OS is statistically significant and clinically meaningful.

Figure 8: TDM4450g /BO21976 KM curve 2nd interim analysis OS



6.1.5 Analysis of Secondary Endpoints(s)

PFS based on investigator assessment:

Table 18 summarizes PFS by investigator, and Table 19 highlights the PFS concordance rates between investigator and independent review facility.

Table 18 : TDM4450g /BO21976 Investigator-assessed PFS

	L + C N = 496	T-DM1 N = 495
Progressed or Died, N (%)	335 (68)	287 (58)
Median, Months	5.8 (95%CI: 5.6, 6.9)	9.4 (95%CI: 7.5, 10.8)
Hazard ratio (95% CI)	0.66 (95%CI 0.56, 0.78)	
Stratified log-rank P value	<0.0001	

Reviewer Comment: Investigator PFS has a similar HR as central review, further supporting the robustness of the findings.

Table 19: TDM4450g /BO21976 PFS concordance IRF and Investigator

	L + C N = 496	T-DM1 N = 495
Agree on PFS Status, N (%)	415 (84)	391 (79)
Agree on date, N (%)	225 (45)	209 (42)
Disagree on date, N (%)	190 (38)	182 (37)
Disagree on PFS Status	81 (16)	104 (21)

Reviewer Comment: No evidence of differential discordance between L+ C and T-DM1 treatment arms. The amount of disagreement between IRF and Investigator in the pivotal study is consistent with what has been observed in other phase 3 oncology trials.

Objective Response Rate:

The IRC assessed objective response rate was 30.8% in the L + C arm and 43.6% in the T-DM1 arm (Table 20). The ORR by investigator assessment was 34.8% in the L + C arm and 47.8% in the T-DM1 arm, respectively.

Table 20 : TDM4450g /BO21976 Objective response rate

	L + C N=389	T-DM1 N=397	OR (95% CI)
ORR by IRC (%)	30.8	43.6	12.7 (6.0, 19.4)
Complete Response	0.5	1.0	
Partial Response	30.3	42.6	
ORR by INV (%)	34.8	47.8	13.0 (6.4-19.5)

Reviewer Comment: The difference in the ORR in the two treatment arms further supports the results of the study.

Duration of Response:

The median duration of response was 6.5 months in the L + C arm and 12.6 months on the T-DM1 arm.

6.1.6 Other Endpoints

Diarrhea Assessment Scale (DAS):

As an exploratory analysis, diarrhea was assessed. DAS included 4-item questionnaire that assessed four elements of diarrhea symptoms including frequency, consistency, urgency, and abdominal discomfort. See Table 21 for the results.

Table 21: Percentage of Patients with Diarrhea Over the First 8 Cycles of Treatment

Cycle	≥ 2 stools per day		Loose Stools		Urgency		Abdominal discomfort	
	Lapatinib + Capecitabine	Trastuzumab Emtansine						
Baseline	n=428 31.8%	n=416 31.0%	n=427 44.7%	n=416 43.3%	n=428 32.0%	n=416 32.5%	n=428 23.8%	n=416 27.6%
Cycle 2	n=403 60.5%	n=397 31.7%	n=402 75.1%	n=397 39.5%	n=402 60.2%	n=397 27.5%	n=400 51.0%	n=396 27.3%
Cycle 3	n=393 63.1%	n=400 30.0%	n=392 71.9%	n=399 42.4%	n=393 56.7%	n=400 28.0%	n=393 47.8%	n=400 24.7%
Cycle 4	n=366 61.7%	n=369 31.2%	n=368 73.1%	n=370 36.5%	n=366 56.0%	n=370 22.2%	n=367 48.5%	n=370 22.7%
Cycle 5	n=356 56.2%	n=358 30.7%	n=354 70.6%	n=358 36.6%	n=355 54.6%	n=358 29.1%	n=355 43.1%	n=358 27.4%
Cycle 6	n=314 51.3%	n=340 30.6%	n=314 66.6%	n=341 33.4%	n=313 46.6%	n=340 25.0%	n=312 39.7%	n=341 24.0%
Cycle 7	n=270 52.6%	n=306 26.5%	n=267 67.4%	n=306 35.3%	n=270 51.1%	n=306 28.8%	n=268 42.9%	n=306 22.9%
Cycle 8	n=217 53.9%	n=277 30.0%	n=218 67.0%	n=277 33.2%	n=217 52.1%	n=276 23.9%	n=218 44.0%	n=277 26.4%

Source: CSR, Table 34, page 141

Reviewer comments: These results are consistent with the overall AE results.

6.1.7 Subpopulations

The ado-trastuzumab emtansine arm on almost all the covariates that were pre-specified in the statistical analysis plan was superior to lapatinib + capecitabine arm (Figure 9 and Figure 10).

Figure 9: Forest plot of Progression-Free Survival by baseline risk factors

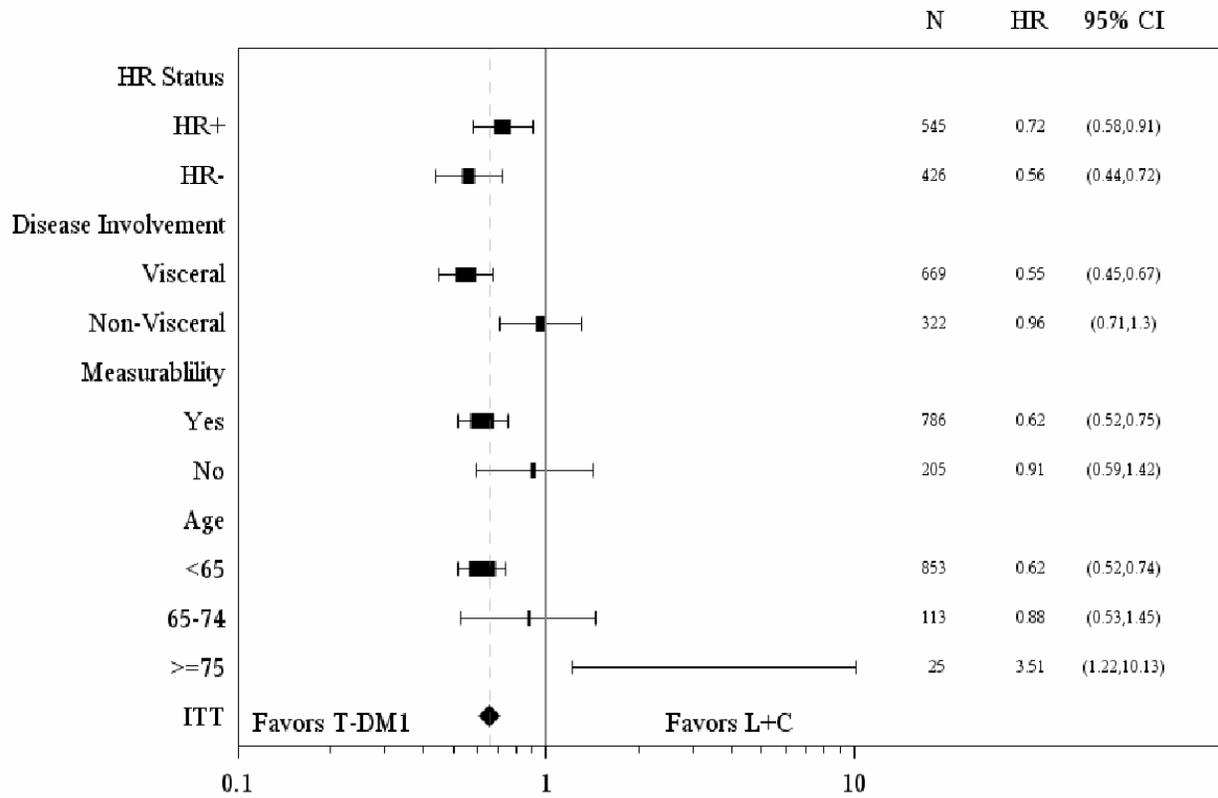
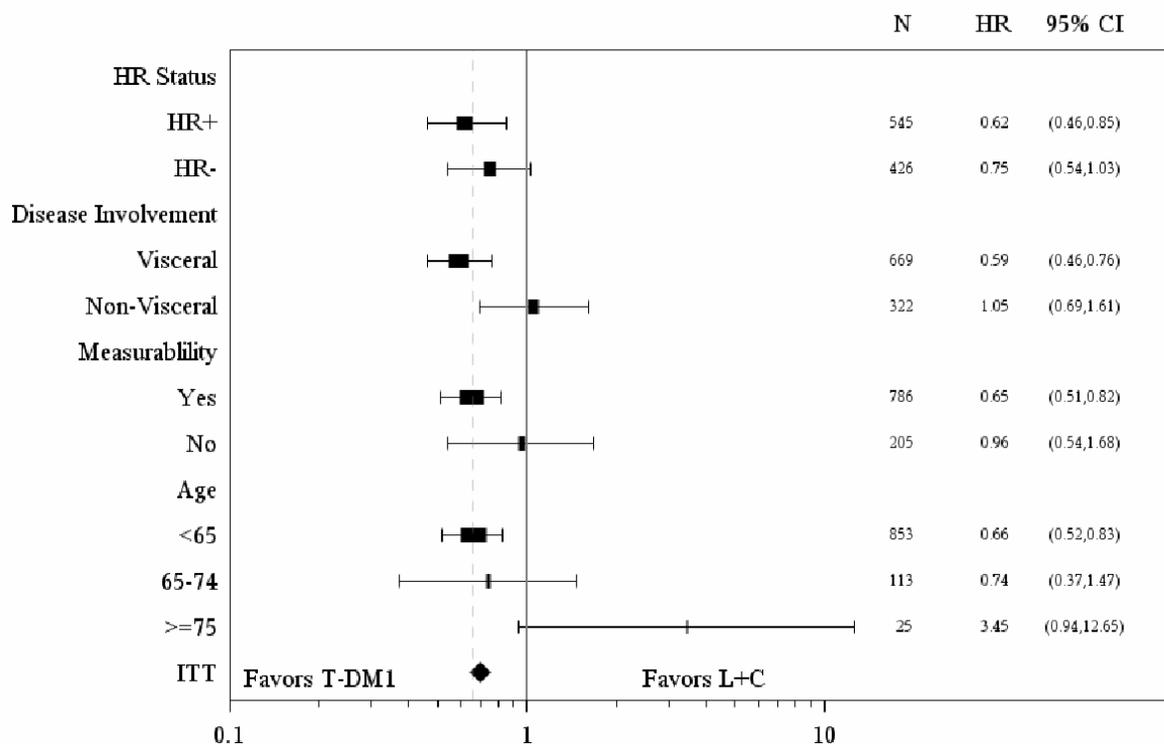


Figure 10: Forest plot of overall survival by baseline risk factors



Reviewer comments:

In the subgroup of patients 75 years of age or older (n=25), the hazard ratios for PFS and OS were 3.51 (95% CI: 1.22, 10.13) and 3.45 (95% CI: 0.94, 12.65), respectively. This subgroup analysis was not pre-specified and the number of patients in this subgroup is too small to draw a conclusion.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Please see Clinical Pharmacology Review by Dr Sara Schreiber.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Preliminary inspectional observations revealed that a Canadian site largely did not retain study source documentation until after October 2011. Therefore, the reliability of the data generated at this site could not be verified because the vast majority of original

source records (Clinical Trials Worksheets) were disposed of after the data were transcribed to “Clinical Trials Progress Notes”, which were retained by the site. The site screened 49 subjects and randomized 24.

To determine the impact on overall study outcome, the subjects enrolled at this site were censored and a sensitivity analysis was conducted.

The sensitivity analysis based on 967 patients (555 PFS events and 322 deaths) showed:

- (1) HR for PFS is 0.66 (95%CI: 0.55, 0.78), Log-rank p-value <0.0001;
- (2) HR of updated OS is 0.69 (95%CI: 0.55, 0.86), Log-rank p-value=0.001.

Reviewer Comment: The sensitivity analysis results support the primary analyses based on ITT patients.

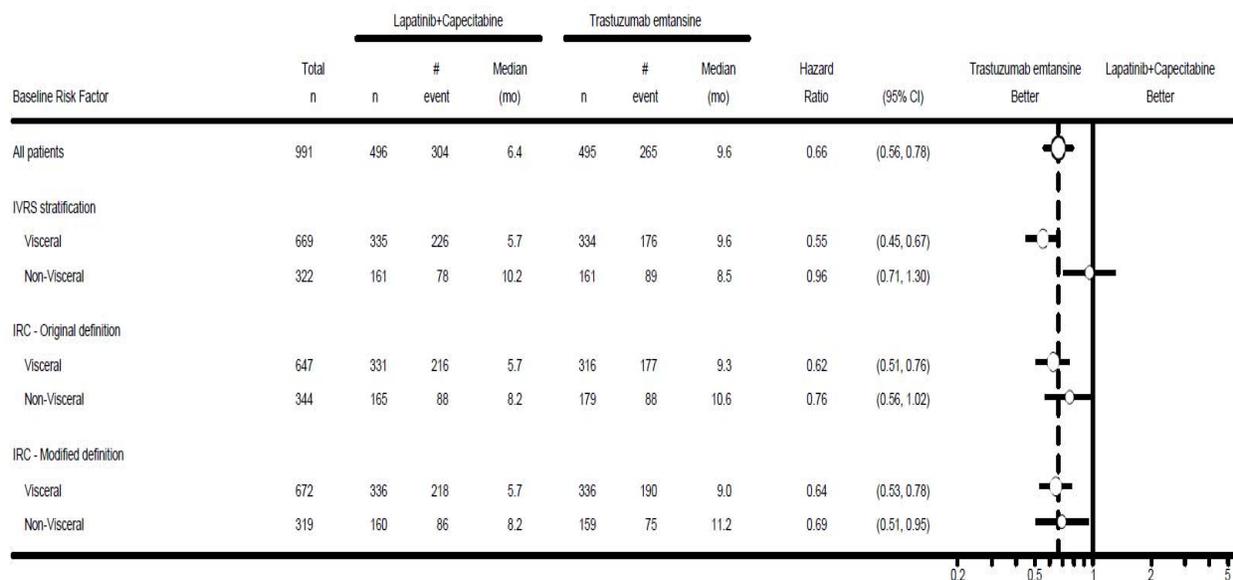
Issue of visceral and non-visceral miss-classification:

During review, FDA noticed that there were some patients with liver and lung involvement that were categorized as non-visceral. Responding to an FDA information request, the Applicant acknowledged this finding and clarified that this classification was based solely on investigator judgment at the time of randomization. Additionally, the Applicant performed analyses to better understand the impact of this apparent misclassification on PFS and OS outcomes. In these analyses, the sites of disease were determined by the radiologist. The following two definitions were used:

- Definition 1: a) Presence of disease in the lungs or liver (either target or nontarget lesions) vs. b) absence of disease in both the lungs and liver
- Definition 2: a) Presence of disease in the lungs or liver or ascites or pleural effusion (either target or non-target lesions) vs. b) absence of disease in all these 4 sites

The unstratified hazard ratios for PFS by IRC were 0.76 (95% CI: 0.56, 1.02) per Definition 1b and 0.69 (95% CI: 0.51, 0.95) per Definition 2b. The unstratified hazard ratios for OS were 0.73 (95% CI: 0.48, 1.12) per Definition 1b and 0.59 (95% CI: 0.37, 0.94) per Definition 2b. Below are the forest plots of these subgroup analyses.

Figure 11: Forest Plot of Progression-Free Survival (IRC Assessment) by Visceral/Non-Visceral Baseline Risk Factor



Source: Datasets (pat, patirf tumorr), applicant figure

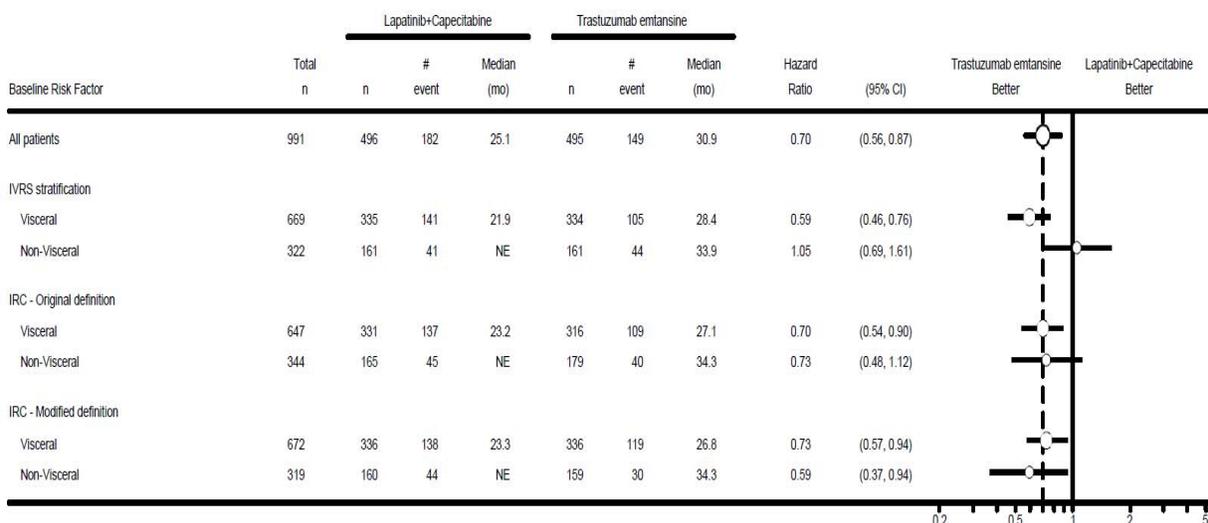
Data cut -off date on January 14 2012, NE = not estimable.

Visceral Original definition (IRC): Subjects with presence of lung or liver disease at baseline as per IRC.

Visceral modified definition (IRC): Subjects with presence of lung or liver or ascites or pleural effusion disease at baseline as per IRC.

Median time to event variable was estimated from Kaplan-Meier curves. Hazard ratio relative to Lapatinib+Capecitabine group and 95% confidence interval (CI) for hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of the circle is proportional to the square root of the total number of subjects. The hazard ratios are from unstratified analysis. Baseline disease measurability and number of disease sites are based on IRC assessment.

Figure 12: Forest Plot of Overall Survival by Visceral/Non-Visceral Baseline Risk Factor



Source: Datasets (pat, patirf tumorr), applicant figure
 Data cut-off date on July 31 2012, NE = not estimable.

Visceral Original definition (IRC): Subjects with presence of lung or liver disease at baseline as per IRC.

Visceral modified definition (IRC): Subjects with presence of lung or liver or ascites or pleural effusion disease at baseline as per IRC. Median time to event variable was estimated from Kaplan-Meier curves. Hazard ratio relative to Lapatinib+Capecitabine group and 95% confidence interval (CI) for hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of the circle is proportional to the square root of the total number of subjects. The hazard ratios are from unstratified analysis. Baseline disease measurability and number of disease sites are based on IRC assessment.

Reviewer Comment: These results are ad hoc and exploratory analysis but it appears that patients with non-visceral disease benefit less than patients with visceral disease at baseline.

6.1.11 Supportive Metastatic Randomized Phase 2 Study Results (TDM4450g /BO21976)

See section 5.3.2 for study design.

Disposition:

The first patient was randomized in the study on 17 September 2008 and the last patient was randomized on 28 December 2009. A total of 137 patients were enrolled and randomized in the study from 65 sites in 14 countries within Europe, North America and South America. Sixty-seven patients were enrolled in the ado-trastuzumab emtansine arm and 70 patients were enrolled in the trastuzumab + docetaxel arm. As of the 31 August 2011 data cut-off date, 14 patients (20.9%) remain on study treatment and 53 (79.1%) had discontinued. The most common reason for discontinuation of ado-trastuzumab emtansine was disease progression (62.7%), with

7.5% of patients discontinuing due to AEs and 4.5% discontinuing due to subject or legal guardian decision.

Demographics:

100% of patients in both arms were female. 82.9% in the trastuzumab + docetaxel arm and 77.6% of ado-trastuzumab emtansine arm were White. The median age was 52 and 55 yr respectively. The majority of patients were ECOG PS 0 at screening (63.8% and 65.7%, respectively). Half of the patients were ER positive.

Efficacy results:

At the time of the clinical cut-off (31 August 2011) for OS and safety analyses, the median duration of follow-up (calculated using a reverse KM method) was 23.0 months in the trastuzumab emtansine arm and 22.8 months in the trastuzumab + docetaxel arm.

The primary efficacy endpoint was PFS as assessed by investigator. Median PFS was 14.2 months in the ado-trastuzumab emtansine arm and 9.2 months in the trastuzumab + docetaxel arm (Hazard Ratio: 0.594, 95% CI 0.364, 0.968, Log-rank P-value 0.0353). Objective response was defined as a complete response or partial response determined on two consecutive assessments \geq 4 weeks. ORR was 64% in the ado-trastuzumab emtansine arm and 58% in the trastuzumab + docetaxel arm.

At the time clinical data cut-off (31 August 2011), 26 deaths (13 in each arm) had been observed. The stratified HR for death in the ado-trastuzumab emtansine arm relative to the trastuzumab + docetaxel arm was 1.06 (95% CI: 0.477, 2.352).

6.1.12 Supportive Metastatic Phase 2 Study Results (TDM4374g)

See section 5.3.3 for study design.

Disposition:

Between 13 August 2008 and 2 April 2009, 110 patients from 44 study sites in the United States were enrolled and treated in the study. As pre-specified in the protocol, analyses of the primary endpoint of objective response rate were based on data collected through approximately 26 weeks after the last patient was enrolled in the study.

Demographics: 98.2% were females. The median age was 52.5 (range 34-77). The majority of patients (97.3%) were ECOG PS 0 or 1 at screening. Half of the patients were ER +.

Efficacy results:

- A confirmed objective response rate of 32.7% (95% CI: 24.1%, 42.1%), as assessed by IRF review
- A confirmed objective response rate of 32.7% (95% CI: 24.1%, 42.1%), as assessed by investigator review
- A median duration of response that was not reached (95% CI: 4.6, NR) by IRF assessment and 9.7 months (95% CI: 6.6, NR) by investigator assessment
- A clinical benefit rate of 48.2% (95% CI: 38.8%, 57.9%) by IRF assessment and 46.4% (95% CI: 37.1%, 56.1%) by investigator assessment
- A median PFS of 6.9 months (95% CI: 4.2, 9.5), as assessed by the IRF and 5.5 months (95% CI: 4.1, 7.5) by investigator review

6.1.13 Supportive Metastatic Phase 2 Study Results (TDM4258g)

See section 5.3.4 for study design.

Results single arm phase 2 TDM4258g in HER2+ MBC who progressed while receiving HER2-directed therapy.

Disposition: Between 20 July 2007 and 31 July 2008, 112 patients from 32 study sites were enrolled and treated in the study. As pre-specified in the protocol, analyses of the primary endpoint of objective response rate were based on data collected through 26 weeks after last patient enrolled in the study on 31 July 2008.

Demographics: 99.1 % of patients were female and 90.2% were White. The median age was 54.5 (range 33 – 82). The majority of patients (92%) were ECOG PS 0 or 1 at screening. Half of the patients were ER +. All patients received trastuzumab prior to enrollment as their last treatment as per inclusion criteria.

Key efficacy results:

- Confirmed objective response rate of 26.9%, as assessed by single-reader IRF review.
- Confirmed objective response rate of 38.9%, as assessed by investigator review.
- The median PFS 4.6 months as assessed by single-reader IRF and investigator review. The median duration of response by IRF assessment was not reached; the lower bound of the 95% CI was 6.2 months; the median duration of response by investigator assessment was 9.4 months.

Reviewer Comment: Supportive evidence that the T-DM1 has single agent activity in trastuzumab resistant patients.

7 Review of Safety

Safety Summary

In this BLA, the Applicant submitted safety data from 882 (original submission) and 884 (updated 90 day submission) Her2-positive metastatic breast cancer (MBC) patients exposed to ado-trastuzumab emtansine (T-DM1) at a dose of 3.6 mg/kg every 3 weeks. In addition, the Applicant submitted data from 519 (original submission) and 554 (updated 90-day submission) patients exposed to the control treatments.

Key safety findings from the pivotal EMILIA randomized controlled trial, and from the supportive safety database:

- **Deaths:** There were fewer deaths within 30 days on T-DM1 than lapatinib plus capecitabine (4 versus 18). Of these 4 deaths on T-DM1, one was considered drug related (metabolic encephalopathy).
- **Serious Adverse Events (SAE) and Dose Modifications:** There were less SAEs on the T-DM1 arm versus the lapatinib + capecitabine arm (15.5% versus 18%). In addition, there were fewer AEs leading to discontinuation (5.9% T-DM1, 7.6% lapatinib, 9.4% capecitabine) and AEs leading to dose reduction (15.1% T-DM1, 18.9% lapatinib, 38.5% capecitabine) with T-DM1.
- **Grade 3 and 4 Adverse Reactions:** There were fewer grade 3-4 adverse reactions on T-DM1 arm compared to the lapatinib plus capecitabine arm (41% vs. 57%). Grade 3-4 adverse events more common on T-DM1 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 EMILIA, the common adverse events with large differences between T-DM1 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 EMILIA, there was a higher incidence of liver enzyme elevation on T-DM1, and higher incidence of bilirubin elevations on lapatinib plus capecitabine. In the entire T-DM1 development program, there have been at least two cases of hepatic failure leading to death possibly related to T-DM1. Based on the available data, the potential of T-DM1 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 have been observed in the T-DM1 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 T-DM1 is less cardiotoxic than trastuzumab, and trastuzumab carries a boxed warning for cardiomyopathy, this reviewer recommends placing cardiac toxicity in a boxed warning on the label.
- **Neurologic Toxicity:** In the pivotal EMILIA trial, a higher incidence of grade 3-4 peripheral neuropathy was observed on the T-DM1 arm compared to the lapatinib plus capecitabine arm (3.1% versus 0.4%), with a lower incidence in the T-DM1 arm 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 T-DM1 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 T-DM1 patients who experienced pneumonitis, four resolved completely, one resolved to grade 1, and one was ongoing at data cut-off.
- **Thrombocytopenia:** In the pivotal study, there was a higher incidence of grade 3-4 thrombocytopenia on the T-DM1 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 T-DM1 patients 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 T-DM1 were reported as of November 9, 2012: one serious case and four non-serious. In the fatal case, the patient incorrectly received T-DM1 at 6 mg/kg and died approximately 3 weeks following the overdose. This reviewer could not exclude the possibility that the death was related to KADCYLA. We 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 ([xxx]-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.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical safety data supporting this BLA is primarily derived from the pivotal phase 3 study EMILIA (4370g). Additional supporting safety information is provided from 5 additional studies: the randomized phase 2 study versus trastuzumab and docetaxel (4450g); two single arm phase 2 studies (4374g and 4258g); one phase 1 study (3569g), and a QTc study (4688g). In addition, data from 43 patients from these studies who were also enrolled in study 4529g, the open-label extension study are included in this BLA. Table 22 outlines the safety studies submitted to the BLA, as well as the data cut-offs for initial submission and 90 day safety update.

Table 22: Summary of Safety Populations submitted to BLA

Study	Design	Population	1° EP	N ^a	Status	Cut-off (BLA)	Cut-off (90 day)
EMILIA 4370g	P3, randomized T-DM1 vs Lapatinib + Capecitabine	Her2+ MBC, previous taxane and trastuzumab	PFS/ OS	490	Ongoing	1/2012	5/2012
4450g	Ph2, randomized T-DM1 vs Docetaxel + Trastuzumab	Her2+ MBC, first line metastatic	PFS	104	Complete	8/2011	5/2012
4374g	Ph2 single arm	≥ 2 lines Her2+ MBC, previous lapatinib and trastuzumab	ORR	110	Complete	4/2011	4/2011
4258g	Ph2 single arm	≥ 1 line Her2+ MBC	ORR	112	Complete	6/2009	6/2009
3569g	Ph1 dose escalation single arm	≥ 1 line Her2+ MBC, previous trastuzumab	Safety/ PK	15	Complete	8/2009	8/2009
4688g	QTc single arm	≥ 1 line Her2+ MBC	QTc	51	Complete	5/2011	5/2011
4529g	Extension study	Previously enrolled in T-DM1 study	Safety	43	Ongoing	1/2012	5/2012

^a Exposed to T-DM1 3.6 mg/kg q 3 weeks

7.1.2 Categorization of Adverse Events

The Applicant defined adverse events (AEs) as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment (per ICH guidelines). In the initial BLA submission, adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. MedDRA 15.0 was used in the 90 day safety update. AEs were summarized by MedDRA primary system organ class (SOC), high level group term (HLGT), high level term (HLT) and Preferred term (PT). The NCI CTCAE version 3.0 was used to grade toxicities.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In total, with the August 24, 2012 BLA submission, the Applicant submitted safety data for 882 patients exposed to T-DM1 3.6 mg/kg q3w and 554 patients exposed to the control regimens.

In October 2012, the Applicant submitted the 90 day safety update report of the 882 patients exposed to T-DM1 3.6 mg/kg q3w and 554 patients exposed to the control regimens, including 57 patients on the expansion study (4529g) and 37 patients who crossed over from the docetaxel/ trastuzumab arm on study 4450g to receive second-line T-DM1. The clinical cut off for the safety update was May 24, 2012.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall Exposures

The pooled safety analysis population provided by the Applicant in the BLA 90 day safety update includes a total of 884 patients who received at least one dose of T-DM1 intravenous at 3.6 mg/kg (Table 23). The median number of doses received across studies was 10, with a range of 1 to 75 doses. The median treatment duration was 6.3 months, with a range of 0 to 51 months. In total, 66 (7.5%) patients were on treatment for 2 years or more, and 16 (1.8%) were on for 3 or more years.

A comparison of overall exposure between T-DM1 treated patients and lapatinib and capecitabine treated patients is presented in Table 24.

Table 23: Exposure Summary entire safety population- 90 day safety update

	EMILIA T-DM1 arm (n=490)	4450g T-DM1 arm (n=69*)	Single-arm pooled (N=288)	Total (N=884)
Median # doses received (range)	11.5 (1 – 48)	16 (1 – 47)	7 (1 – 75)	10 (1 – 75)
Average dose received (mg/kg)	3.48 (2.6 – 4)	3.5 (2 – 6)	3.51 (2.5 – 4.19)	3.5 (2.44 – 6)
Mean Dose Intensity (range)	97.4% (54.7 - 200.7)	94.8 % (61 – 158)	95.7 (55.1 – 107.5)	96.6 (54.7 – 200.7)
Median Treatment Duration, months	7.6 (0 – 32.7)	10.4 (0 – 32)	4.2 (0 – 51.3)	6.3 (0 – 51.3)
> 2 years on treatment	25 (5.1%)	NA	25 (8.7%)	66 (7.5%)
> 3 years on treatment	NA	NA	15 (5.2%)	16 (1.8%)
Infusion Interruption	5.9%	20.3%	12.8%	9.7%
Infusion premature discontinuation	1%	1.4%	0.3%	0.9%
Dose Reduction	18%	20.3%	14.9%	17.0%

Sources: EMILIA CSR, SCS, safety update

Table 24: Exposure Summary in EMILIA trial

	T-DM1 (N=490)	Lapatinib plus Capecitabine (N=488)	
	T-DM1	Lapatinib	Capecitabine
Mean Dose Intensity	97.4%	88.3%	74.8%
Median Dose Intensity	99.9%	92.7%	76.8%
Median Treatment Duration	7.6 months (0 – 32.7)	5.5 months (0 - 33.2)	5.3 months (0 – 32.5)
> 2 years	25 (5.1%)	10 (2.0%)	8 (1.6%)
Dose Reduction	18.0%	27.7%	54.8%
Dose Delay	21.2%	36.9%	43.9%

Sources: EMILIA CSR, SCS, safety update

Demographics:

See Section 6.1.2 TDM4450g /BO21976 (EMILIA) Demographics

7.2.2 Explorations for Dose Response

Please see Clinical Pharmacology/ Pharmacometrics Reviews by Drs Sarah Schreiber, Pengfei Song and Jian Wang for more information.

Briefly, the Clinical Pharmacology/ Pharmacometrics team conducted an extensive review of exposure-safety and exposure-efficacy relationships. They used the T-DM1 cycle 1 day 21 C_{min} value as a surrogate for exposure and divided patients in the T-DM1 arm of the EMILIA trial into four exposure quartiles. They found an exposure-efficacy relationship in that patients in the higher quartile T-DM1 exposure had improved response rate, PFS, and OS compared to the lower exposure quartiles. They did not observe exposure-safety relationships for Grade 3-5 thrombocytopenia, hepatotoxicity, or peripheral neuropathy. They observed slightly higher grade 3-4 adverse events in the lower exposure quartiles, but no significant differences in dose interruption, premature stopping, and dose reduction between exposure quartiles.

As a result of the possibility of enhanced efficacy in patients with higher exposure, a Post Marketing Commitment to take a step-wise evaluation of possible dose optimization is recommended.

7.2.3 Special Animal and/or In Vitro Testing

See Pharmacology/Toxicology review for more information.

7.2.4 Routine Clinical Testing

In the EMILIA trial, routine laboratory analyses (including CBC with differential, serum chemistry and liver tests), vital signs, urine pregnancy test, and physical exams were obtained at screening (-30 to -1), during each cycle, and at the study drug completion visit (30 days +/- 7 after last dose of study drug). To assess cardiac function, a Multi-Gated Acquisition Scan (MUGA) or an echocardiogram were performed at screening, weeks 6, 12 and every 12 weeks thereafter and at the study drug completion visit. Scheduled 12-lead ECGs were assessed at baseline and at study drug completion visit and in the QTc substudy. Urinalysis and INR and aPTT were collected at screening and study drug completion visit. See Table 6 for more information.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology review for more information.

Based on population pharmacokinetic analysis (PK), the clearance of T-DM1 was 0.68 L/day and the elimination half-life is approximately 4 days. No accumulation of T-Dm1 was observed after repeat dose IV infusion every 3 weeks.

Covariates affecting T-DM1 clearance based on the population PK model (n=671) include: body weight, tumor burden (by RECIST), shed Her2 extracellular domain

antigen, and baseline trastuzumab concentrations. However the magnitude of effect on T-DM1 exposure suggests that these covariates (with the exception of body weight) are unlikely to have a clinically meaningful impact on T-DM1 exposure. Therefore, body weight dosing (3.6 mg/kg) without correction for other covariates is appropriate.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Ado-trastuzumab emtansine is an antibody drug conjugate containing the Her2-neu targeting monoclonal antibody trastuzumab and the microtubule inhibitor emtansine (DM1). Adverse events associated with pharmacologic agents that block Her2 include cardiomyopathy, embryofetal toxicity, and pneumonitis. Adverse events associated with microtubule inhibitors include myelosuppression, thrombocytopenia, anemia, neurotoxicity, and hepatic toxicity.

7.3 Major Safety Results

7.3.1 Deaths

Deaths in the pivotal study EMILIA:

As of the January 15, 2012 data cut-off date from the original submission, a total of 223 deaths were reported: 94 patients (19.2%) on the T-DM1 arm and 129 patients (26.4%) on the lapatinib + capecitabine arm (one death on this arm occurred prior to the patient receiving treatment and thus is included in the ITT but not safety evaluable population).

With the 90 day Safety update (August 2012 cut-off), a total of 293 deaths were reported, 128 (26% on T-DM1) and 165 (34%) on lapatinib plus capecitabine. Table 25 shows the breakdown in deaths by clinical cut-off date. Note that two cause of deaths on the T-DM1 treatment arm were changed from "Adverse Event" to progressive disease by the later clinical cut-off.

Table 25: Deaths on the EMILIA study

	T-DM1 (N=490)		Lapatinib + Capecitabine (N=488)	
	14 January 2012 cut-off	24 August 2012 cut-off	14 January 2012 cut-off	24 August 2012 cut-off
All deaths	94 (26.2%)	128 (26.1%)	128 (26.2%)	165 (34%)
≤ 30 days last treatment	4 (0.8%)	4 (0.8%)	17 (3.5%)	18 (4%)
> 30 days last treatment	90 (18.4%)	124 (25.3%)	111 (22.7%)	147 (30%)
Cause of death				
Progressive disease	123 (25.2%)	125 (25.5%)	123 (25.2%)	160 (32.8%)
Adverse event	5 (1.0%)	3 (0.6%)	5 (1.0%)	5 (1.0%)

Sources: EMILIA CSR, SCS, safety update

Deaths within 30 days of last study treatment on EMILIA:

At the January 2012 cut off, 4 patients receiving T-DM1 (0.8%) and 17 patients receiving lapatinib and capecitabine (3.5%) died within 30 days of last study drug treatment. Of these, 3 patients receiving T-DM1 (0.6%) and 13 patients receiving lapatinib and capecitabine (2.7%) died due to disease progression, respectively. One patient receiving T-DM1 (0.2%) and four (0.8%) receiving lapatinib and capecitabine died due to a drug-related grade 5 adverse event. The one on-study death on T-DM1 was due to metabolic encephalopathy. The four deaths on lapatinib-capecitabine were: coronary artery disease, multi-organ failure, coma, and hydrocephalus.

T-DM1 Deaths <30 days on Emilia:

Patient 22251: 37 year old Black female initially diagnosed in October 2006 with stage 3, Hormone Receptor positive, HER2-positive breast cancer. Diagnosed with MBC March 2009. Previous systemic treatments included: tamoxifen, docetaxel, doxorubicin, cyclophosphamide, letrozole, fulvestrant, trastuzumab, and paclitaxel. At screening, the involved site of disease was bone and ECOG PS was 1. She received her first dose of T-DM1 3.6 mg/kg on (b) (6). On (b) (6) (study day 50) she developed grade 4 thrombocytopenia (platelet 17 K/cmm) that improved to grade 1 by study day 55. On study day 70 she developed grade 3 thrombocytopenia leading to dose delay and resolution by day 84. She was subsequently dose reduced to 3.0 mg/kg starting Day 85. On study day 226, she developed grade 2 gastroenteritis. On study day 253, T-DM1 was further reduced to 2.4 mg/kg due to the gastroenteritis. Her last dose of T-DM1 2.4 mg/kg (after 14 cycles) was (b) (6) (study day 316). On (b) (6) (study day

323) she complained of left lung numbness and was found to have a right posterior frontal lobe brain metastasis by MRI. She was started on intravenous dexamethasone for vasogenic edema. On (b) (6) (Study day 327) she experienced altered mental status and was hospitalized the next day. On (b) (6) (Study day 330) she was noted to be lethargic, unable to communicate. Her ALT was 224 U/L, AST 140 U/L, total bilirubin 2.2 mg/dL and Alkaline phosphatase 228 U/L. The following day (Study day 331) she was started on lactulose and diagnosed with **grade 4 metabolic encephalopathy**. Her ammonia level was 125 umol/L, creatinine 0.8 mg/dl, bun 15 mg/dL, potassium 4.0 mmol/L. On (b) (6) (Study day 336) her ALT was 155, AST 76, and total bilirubin 1.9 mg/dL. She died the following day (Study day 337) due to metabolic encephalopathy. The investigator considered the metabolic encephalopathy related to T-DM1.

Reviewer Comment: Although the investigator considered the metabolic encephalopathy as related to T-DM1, there were other more likely contributing factors, including brain metastases with vasogenic edema, corticosteroids, and other electrolyte imbalances.

7.3.2 Nonfatal Serious Adverse Events

In the EMILIA trial, as of the January 15, 2012 data cut-off date, 76 patients (15.5%) who received T-DM1, and 88 patients (18.0%) who received lapatinib plus capecitabine experienced Serious Adverse Events (SAEs). Table 26 highlights the most common (>1%) SAEs by preferred term.

Table 26: SAE preferred terms > 1% in either Treatment Arm

	T-DM1 (N=490)	Lapatinib + Capecitabine (N=488)
Diarrhea	2 (0.4%)	17 (3.5%)
Vomiting	6 (1.2%)	9 (1.8%)
Pyrexia	7 (1.4%)	3 (0.6%)
Pulmonary Embolism	0 (0.0%)	7 (1.4%)
Total SAE	76 (15.5%)	88 (18.0%)

Sources: EMILIA CSR

7.3.3 Dropouts and/or Discontinuations

As of the January 15, 2012 data cut-off date, 29 patients (5.9%) discontinued T-DM1 due to an AE, and 37 patients (7.6%) discontinued lapatinib due to an AE, and 46 patients (9.4%) discontinued capecitabine due to an AE (Table 27). Of the patients on

the lapatinib and capecitabine arm, 6 patients (1.2%) discontinued only lapatinib, 15 patients (3.1%) discontinued only capecitabine, and 31 patients (6.4%) discontinued both.

Table 27: Adverse Events leading to Discontinuations in EMILIA by Preferred Terms

	T-DM1 (N=490)	Lapatinib + Capecitabine (N=488)	
	T-DM1	Lapatinib	Capecitabine
Any Adverse Event	29 (5.9%)	37 (7.6%)	46 (9.4%)
Thrombocytopenia	10 (2.0%)	0 (0.0%)	0 (0.0%)
Leukopenia	1 (0.2%)	0 (0.0%)	2 (0.4%)
Anemia	1 (0.2%)	0 (0.0%)	1 (0.2%)
Neutropenia	0 (0.0%)	0 (0.0%)	1 (0.2%)
Angina Pectoris	0 (0.0%)	1 (0.2%)	1 (0.2%)
Left Ventricular Dysfunction	1 (0.2%)	0 (0.0%)	0 (0.0%)
Diarrhea	0 (0.0%)	12 (2.5%)	14 (2.9%)
Vomiting	0 (0.0%)	11 (2.3%)	9 (1.8%)
Abdominal Pain	0 (0.0%)	2 (0.4%)	2 (0.4%)
Stomatitis	0 (0.0%)	0 (0.0%)	2 (0.4%)
Gastritis	0 (0.0%)	1 (0.2%)	0 (0.0%)
Fatigue	0 (0.0%)	2 (0.4%)	2 (0.4%)
Mucosal Inflammation	0 (0.0%)	1 (0.2%)	1 (0.2%)
Hyperbilirubinemia	2 (0.4%)	0 (0.0%)	0 (0.0%)
Hepatitis Toxic	1 (0.2%)	0 (0.0%)	0 (0.0%)
Hepatotoxicity	1 (0.2%)	0 (0.0%)	0 (0.0%)
Paronychia	0 (0.0%)	1 (0.2%)	1 (0.2%)
Bronchitis	1 (0.2%)	0 (0.0%)	0 (0.0%)
Infusion Related Reaction	1 (0.2%)	0 (0.0%)	0 (0.0%)
AST Increase	4 (0.8%)	0 (0.0%)	0 (0.0%)
Blood bilirubin increased	2 (0.4%)	0 (0.0%)	0 (0.0%)
ALT Increased	1 (0.2%)	0 (0.0%)	0 (0.0%)
Ejection Fraction Decreased	0 (0.0%)	1 (0.2%)	0 (0.0%)
Dehydration	0 (0.0%)	1 (0.2%)	1 (0.2%)
Pain in Extremity	0 (0.0%)	1 (0.2%)	1 (0.2%)
Dizziness	0 (0.0%)	1 (0.2%)	1 (0.2%)
Hydrocephalus	0 (0.0%)	1 (0.2%)	1 (0.2%)
Lethargy Neuropathy Peripheral	1 (0.2%)	0 (0.0%)	0 (0.0%)
Sensory Disturbance	0 (0.0%)	0 (0.0%)	1 (0.2%)

Sources: EMILIA CSR

7.3.4 Significant Adverse Events

The most common grade 3-4 Adverse Events (>4%) on the T-DM1 arm were thrombocytopenia (13.5%), and AST elevation (4.5%) as highlighted in Table 28.

The most common grade 3-4 adverse events (>4%) on lapatinib plus capecitabine were: diarrhea (20.7%), hand-foot (17.2%), vomiting (4.5%), neutropenia (4.3%), and hypokalemia (4.3%).

Table 28: Grade 3-4 Adverse Events occurring > 2% in either treatment arm

AE by MedDRA PT	T-DM1 (N=490)	Lapatinib + Capecitabine (N=488)
Thrombocytopenia (%)	12.9%	0.2%
AST (%)	4.3%	0.8%
ALT (%)	2.9%	1.4%
Anemia (%)	2.7%	1.6%
Diarrhea (%)	1.6%	20.7%
Palmar-Plantar Erythrodysesthesia (%)	0.0%	16.4%
Vomiting (%)	0.8%	4.5%
Neutropenia (%)	2.0%	4.3%
Hypokalemia (%)	2.2%	4.1%
Fatigue (%)	2.4%	3.5%
Nausea (%)	0.8%	2.5%
Mucosal Inflammation (%)	0.2%	2.3%

Source: AE xpt, Demog.xpt

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Hepatotoxicity:

Hepatotoxicity conclusions: In EMILIA, there was a higher incidence of liver enzyme elevation on T-DM1, and higher incidence of bilirubin elevations on lapatinib plus capecitabine. In the entire T-DM1 development program, there have been at least two cases of hepatic failure leading to death possibly related to T-DM1. Based on the available data, the potential of T-DM1 causing rare but serious drug induced liver injury events is high. Therefore, a boxed warning is recommended.

Hepatotoxicity was identified by FDA as a safety concern early in the T-DM1 investigational drug development program. DOP-1 has collaborated intensively with OSE and Dr John Senior, FDA hepatology expert, on the T-DM1 liver toxicity safety signal.

In July 2012, at FDA request, the applicant submitted a drug safety report on hepatotoxicity including a summary of recommendations from their external panel of hepatology experts. Dr Senior of OSE/FDA submitted a review of this drug safety report

in September 2012. In November 2012, the applicant submitted to the BLA an update to this drug safety report.

Trastuzumab: there does not appear to be a significant risk of serious hepatotoxicity with clinical dysfunction associated with trastuzumab.

Maytansine (DM1) hepatotoxicity: Early clinical trials of the parent plant toxin maytansine in 1978-1980 showed frequent elevation of aminotransferases. ¹⁰⁻¹²

Nonclinical T-DM1 studies: please see the FDA review by toxicologist Dr. Dave Mcguinn for full details. Briefly, T-DM1 appeared to induce rises in transaminases and bilirubin in rats and increases in transaminases and alkaline phosphatase in monkeys. Notable histopathology changes in these species include Kupffer cell and hepatocyte hypertrophy/ vacuolation, hepatocellular and biliary epithelial degeneration/necrosis (non-inflammatory), sinusoidal endothelial cell hypertrophy, increased sinusoidal leukocytes, and multinucleated hepatocytes.

Clinical studies: Hepatotoxicity and drug induced liver injury has been observed with KADCYLA. 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 KADCYLA. Table 29 summarizes hepatotoxicity in the EMILIA study by MAED SMQ search. Cases of nodular regenerative hyperplasia, a benign, slowly evolving and cholestatic process were identified on liver biopsy in 3 cases in the T-DM1 development program to date. However, this review is focused on the life threatening cases of DILI.

Table 29: Hepatotoxicity summary in the EMILIA by MAED SMQ search

SMQ (Narrow Search)	ado-trastuzumab emtansine (N = 490)			Lapatinib+Capecitabine (N = 488)			ado-trastuzumab emtansine vs. Lapatinib+Cape		
	Events	N	Proportion (%)	Events	N	Proportion (%)	RD (per 100)	RR	Nominal P-value*
(1) Hepatic disorders	707	150	30.61	343	121	24.8	5.82	1.2	0.046
(2) Drug related hepatic disorders - comprehensive search	707	150	30.61	342	120	24.59	6.02	1.2	0.038
(3) Drug related hepatic disorders - severe events only	8	6	1.22	4	3	0.61	0.61	2.0	0.506
(4) Hepatitis, non-infectious	5	4	0.82	4	3	0.61	0.2	1.3	1
(4) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	3	2	0.41	0	0	0	0.41	3.0	0.499
(3) Liver related investigations, signs and symptoms	698	146	29.8	318	115	23.57	6.23	1.3	0.03
(3) Cholestasis and jaundice of hepatic origin	15	6	1.22	84	41	8.4	-7.18	0.1	5E-08
(3) Liver-related coagulation and bleeding disturbances	1	1	0.2	16	3	0.61	-0.41	0.3	0.373
(2) Liver infections	0	0	0	1	1	0.2	-0.2	0.5	0.499

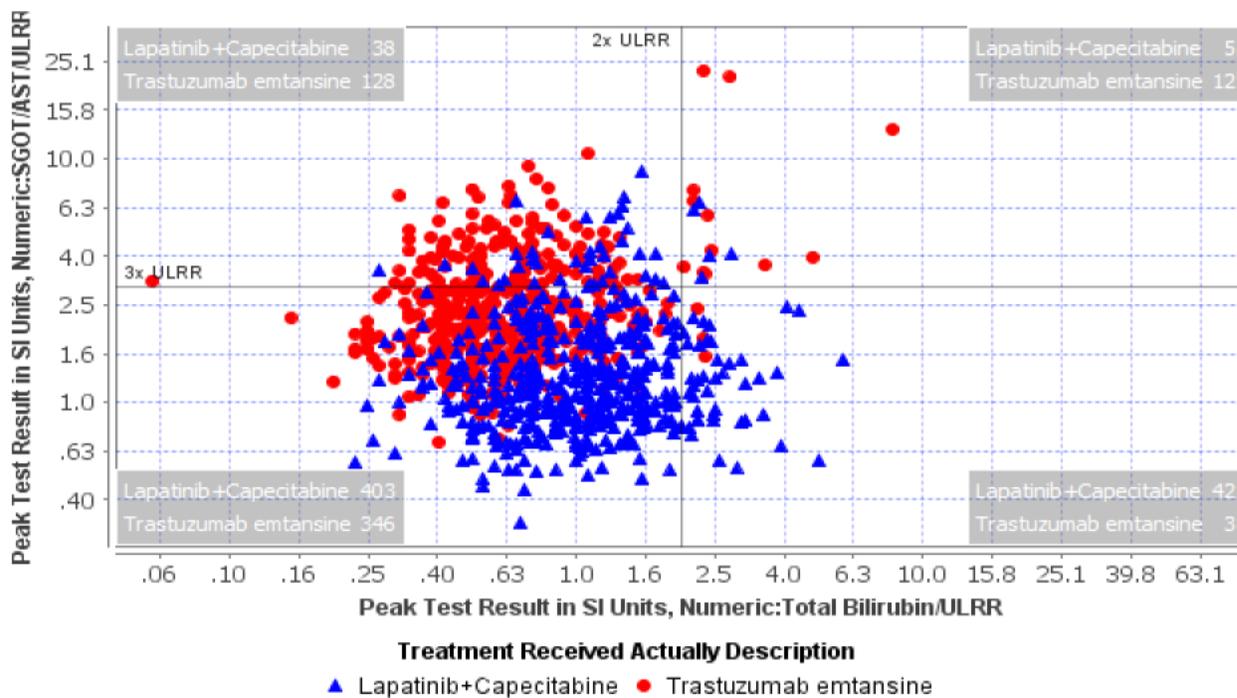
* this nominal p value is for exploratory purposes only.

Source: AE xpt, Demog.xpt, MAED

Liver test elevations in the EMILIA trial:

Liver test elevations were common on both treatment arms in EMILIA. On the T-DM1 treatment arm, the most common manifested as transaminase elevations, with AST more frequently elevated than ALT. On the lapatinib plus capecitabine arm, hyperbilirubinemia was more common. There were more cases of peak AST > 3 X ULN with total bilirubin > 2 X ULN on the T-DM1 treatment arm (Figure 13).

Figure 13: Scatter plot of peak bilirubin versus peak ALT by Treatment Arm in EMILIA trial



AST >3x ULN vs TBILI > 2x ULN with no AlkPhos filter

Source: AE xpt, Demog.xpt, JREVIEW

Selected Narratives of Hepatotoxicity in the EMILIA trial:

The following two T-DM1 subjects matched the SMQ narrow search “Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions”:

Subject 22001: 51 year old White female initially diagnosed with HER2+, HR negative EBC in 2000. In 2008, she was diagnosed with MBC. Previous systemic treatments for breast cancer included: Doxorubicin, tamoxifen, trastuzumab, docetaxel, carboplatin, and cytoxan. Her metastatic sites at baseline were left anterior cardiophrenic lymph nodes. Her medical problems included irritable bowel syndrome and hypertension. Concomitant meds included: omeprazole, fexofenadine, and flexiril. Her first dose of T-DM1 3.6 mg/kg was (b) (6). On (b) (6) (study day 477) she developed grade 3 peripheral neuropathy. On (b) (6) (Study day 490) T-DM1 was permanently discontinued due to peripheral neuropathy. On (b) (6) (Study day 512) abdominal varices were detected by CT scan (the 1st evidence of esophageal varices identified on CT was (b) (6)). There was no sign of progressive disease. A vascular ultrasound showed no evidence of thrombus. There was no evidence of cirrhosis per CT scan or biopsy. Un upper GI endoscopy revealed small esophageal varices and moderately large gastric varices in the fundus. There was no evidence of cirrhosis,

hepatitis or malignancy. The liver biopsy was not diagnostic of hepatoportal sclerosis. Per the applicant, there was no history of chronic liver disease, alcohol abuse, or viral hepatitis. In the investigator's opinion, the **non-cirrhotic portal hypertension** was related to T-DM1. Throughout the course of the study, the patient did not have elevation in total bilirubin, had minor transient elevations (up to 5x ULN) in transaminases.

Reviewer Comment: It is unclear if the portal hypertension is related to T-DM1. Per the records, the patient may have had pre-existing varices on scan prior to study entry and did not have a baseline EGD.

Subject 22403: 67 year old White female initially diagnosed with HER2+, HR+ stage 2 EBC in 2004. Diagnosed with MBC in 2008. Previous systemic treatments for breast cancer included: cyclophosphamide, 5-fu, doxorubicin, docetaxel, trastuzumab, and letrozole. Involved sites at screening included liver and lymph nodes. ECOG performance status at screening was 1. At screening Hepatitis C was negative for antigen and antibodies. Comorbidities included hypertension. Concomitant medications included: omeprazole, trimetazidine, perindopril, and furosemide. On (b) (6), she received her first dose of T-DM1 3.6 mg/kg. On (b) (6) (Study Day 168), she received her 9th cycle of T-DM1. On (b) (6) (Study Day 175), she was hospitalized with grade 3 thrombocytopenia without bleeding with a platelet count of 29 K/cmm. On (b) (6) (Study Day 180), her platelet count was 23 K/cmm (**grade 4 thrombocytopenia**). She was discharged on (b) (6) (Study Day 181), with a platelet count of 32 k/cmm. On (b) (6) (Study Day 187) she presented with **grade 3 epistaxis**, platelet count of 32 k/cmm and was again hospitalized. On (b) (6) (Study Day 188), she was noted to have AST 757 U/L (21.6 x ULN), ALT 856 U/L (19x ULN), total bilirubin 2.78 (2.8 x ULN), PTT 23.4 seconds, and **grade 3 hepatotoxicity**. On (b) (6) (Study Day 197), AST was 53 U/L (1.5 x ULN), ALT 107 (2.4 x ULN), PT 22.7 seconds, and platelets 123 K/cmm. The thrombocytopenia and hepatotoxicity were considered resolved. In response to events of thrombocytopenia and hepatotoxicity, T-DM1 was permanently discontinued. The investigator considered the thrombocytopenia and hepatotoxicity related to T-DM1.

Reviewer Comment: This is a likely Hy's law case as T-DM1, rather than concomitant medications or liver metastasis, is likely the key driver of this event. Reassuring that the liver parameters recovered when T-DM1 was held.

Deaths due to liver failure in the T-DM1 development program:

MCN 279997: 66 year old female with no liver or bone metastasis, no alcohol history but with lung metastases, fatty liver, borderline renal insufficiency, steroid-induced diabetes, hypothyroidism, hypertension, hypoalbuminemia and asthma. She was treated (b) (6) on protocol 4374g (phase 2 single arm). At screening January 2009, noted to have ALT of 82, Alkaline Phosphatase of 192 IU/L, with normal AST and TBL. After 3 doses of T-DM1 3.6 mg/kg she developed grade 2 confusion and rising creatinine (0.9 to 2.5 mg/dL) attributed to contrast nephropathy. Ten days later, fluid overload required hospitalization again for successful diuresis, but

she became anxious and required trazadone. Her last dose of T-DM1 was (b) (6) and a day later noted to have scleral icterus, cutaneous jaundice, TBILI 7.9, AST 505, ALP 970. The family reported perhaps giving her excessive trazadone. On (b) (6) CT showed fatty infiltration of liver without liver metastasis. A liver biopsy on (b) (6) showed fatty liver with steatohepatitis, and mild cholestasis. Despite falling ALT and AST she died on (b) (6), diagnosed as liver failure. No autopsy performed, but drug-induced liver injury was suspected. It was unclear whether T-DM1 or trazadone was more likely cause.

Reviewer Comment: *It is possible if not probable that T-DM1 contributed to the liver failure and death.*

MCN 1078747: 54 year old female treated in Calcutta India on study 4997g (TH3RESA phase 3 study). The patient was post-menopausal, and had IDC of left breast diagnosed as metastatic in November 2009. Previous treatments included docetaxel, epirubicin, trastuzumab, and paclitaxel. She had a history of hypertension and hypothyroidism. At screening she had liver metastasis of 1.4, 3.3, 6.0 cm in diameter. On 1 June 2012, screening lab tests showed ALT 39, AST 42, TBIL 1.2. On (b) (6), her baseline labs prior to receiving T-DM1 showed ALT 68, AST 70, TBIL 1.4 and subsequently received T-DM1 3.6 mg/kg. On (b) (6) she presented with jaundice, grade 4 bilirubin and altered mental status. On (b) (6) she was noted to have ALT 159, AST 820, TBL 12.8, creatinine 2.3, ammonia 78. On (b) (6) she died. No autopsy or testing for acute hepatitis was performed. Per the investigator, the fatal fulminant liver failure was related to T-DM1.

Reviewer Comment: *With rising liver tests between screening and baseline, this patient could have had an acute hepatitis developing. However, hepatitis testing was not performed. It is also not known whether T-DM1 contributed to this patient's rapid death.*

7.3.5.2 Cardiotoxicity

Summary: *LVEF declines and LV dysfunction has been observed in the T-DM1 development program. The incidence of cardiac toxicity appears to be no greater than that observed comparator arms in EMILIA (lapatinib plus capecitabine) and 4450g (trastuzumab plus docetaxel). Since there is no evidence that T-DM1 is less cardiotoxic than trastuzumab, and trastuzumab carries a boxed warning for cardiomyopathy, this reviewer recommends placing cardiac toxicity in a boxed warning on the label.*

Agents that target HER2 are known to cause cardiotoxicity, and trastuzumab has a boxed warning for cardiomyopathy. In the EMILIA trial, left ventricular ejection fraction (LVEF) was monitored at screening, weeks 6 and 12, and every 12 weeks thereafter.

An independent Cardiac Review Committee (CRC) monitored potential cases of left ventricular systolic function (LVSD) prior to each DMC review and reported their findings to the DMC. As part of this BLA review, I reviewed the CRC minutes. The CRC conducted adjudication for all patients with potential left ventricular dysfunction. The CRC did not find any patients on EMILIA on either treatment arm which they determined as an event. There were 5 cases (2 on T-DM1, 3 on lapatinib plus capecitabine) where the CRC was not able to reach a final adjudication decision and reported them to the DMC as “Not Evaluable”. On May 24, 2012, the decision was documented to disband the CRC. Table 30 summarizes the cardiac toxicity data on EMILIA and on the randomized phase 2 4450g of T-DM1 versus Herceptin and Docetaxel.

Table 30: Summary of Cardiac Toxicity in EMILIA and 4450g studies

	EMILIA		4450g	
	T-DM1 (N=490)	Lap + Cape (N=488)	T-DM1 (N=69)	Tras + Docetax (N=66)
Cardiac Failure (SMQ narrow)	4 (0.8%)	11 (2.3%)	3 (4.3%)	4 (6.0%)
LV Dysfunction (PT)				
Grade 1-2	4 (0.8%)	6 (1.2%)		
Grade 3	1 (0.2%)	0 (0.0%)		
LVEF Decline < 40%	3 (0.6%)	3 (0.6%)	1 (1.5%)	1 (1.5%)
LVEF Decline > 15% and drop to < LLN	8 (1.6%)	7 (1.4%)	3 (4.5%)	4 (6.1%)
New Segmental Wall Motion Abnormality	18 (3.7%)	27 (5.5%)	9 (14.8%)	7 (10.9%)

Sources: EMILIA CSR, 4450g CSR, SCS, safety update

Case of grade 3 LV dysfunction on T-DM1 treatment arm in EMILIA

Subject 19502: 46 year old Black female diagnosed with HER2+, HR+ MBC in 12/2009. Previous systemic treatments included docetaxel, trastuzumab and pertuzumab with no prior anthracyclines. Involved sites of MBC included liver, breast, skin/soft tissue, and lymph nodes. ECOG PS at screening was 1. Local screening LVEF was 55% with no wall motion abnormalities. Central screening LVEF was 31% with wall motion abnormalities. Comorbidities included hypertension. Concomitant meds included amlodipine, reglan, losartan, oxycodone, ativan, amitriptyline. She received her first treatment of T-DM1 3.6 mg/kg on (b) (6). On (b) (6) (Study Day 42), local echocardiogram showed LVEF 35% (central not available) and dilated cardiomyopathy. She was diagnosed with grade 3 left ventricular dysfunction. On (b) (6) (Study Day 57) an echocardiogram revealed an LVEF of 35% (central was 47.5%). The patient was treated with carvedilol. T-DM1 was discontinued, and on (b) (6) the patient performed study drug completion visit. She withdrew consent so no further follow-up was obtained. The investigator felt that left ventricular dysfunction

was related to T-DM1. Other possible etiologic factors were the patients use of cocaine laced marijuana.

Reviewer Comment: Unusual case in that there were such wide discrepancies between the screening local and central LVEF assessments by echocardiogram (55% vs. 31%) and the day 57 local and central LVEF read (35% vs. 47.5%). This calls into question the accuracy of these readings, which are subjective but typically not this variable between readers.

7.3.5.3 Neurotoxicity

Summary: In the pivotal trial, a higher incidence of grade 3-4 peripheral neuropathy was observed in the T-DM1 arm compared to the lapatinib plus capecitabine arm (3.1% versus 0.4%), with a lower incidence in the T-DM1 arm 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.

DM-1 or Maytansine, a microtubule inhibitor, is neurotoxic. In the pivotal EMILIA study, 23% of T-DM1 patients versus 18% of lapatinib + capecitabine patients experienced peripheral neuropathy. 3.1% of patients randomized to T-DM1 versus 0.4% of patients randomized to lapatinib + capecitabine experienced neurotoxicity (Table 31). In the randomized phase 2 TDM4450g versus trastuzumab and docetaxel, rates of peripheral neuropathy were higher on the trastuzumab docetaxel arm.

In EMILIA, of the 16 cases of > Grade 3 peripheral neuropathy on EMILIA, all patients were previously exposed to a taxane. The median time to onset was 287 days (64 – 1017). In one case, no resolution was reported. The median time to resolution was 15 days (1 – 185). Four (25%) patients had recurrence of grade 3 neuropathy with re-challenge.

Table 31: Peripheral Neuropathy in EMILIA and 4450g by MedDra 14.1 SMQ

	EMILIA		4450g	
	T-DM1 (N=490)	Lap + Cape (N=488)	T-DM1 (N=69)	Tras + Docet (N=66)
Grade 1	15.7%	12.7%	21.7%	21.2%
Grade 2	4.5%	5.1%	7.2%	24.2%
Grade 3	2.9%	0.4%	1.4%	6.1%
Grade 4	0.2%	0.0%	0.0%	0.0%
Total	23.3%	18.2%	30.4%	51.5%

Source: AE xpt, Demog.xpt, EMILIA CSR, 4450g CSR, SCS, 90 day update

7.3.5.4 Pneumonitis

In the EMILIA trial, 6 patients (1.2%) in the T-DM1 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 6 T-DM1 patients who experienced pneumonitis, four resolved completely, one resolved to grade 1, and one was ongoing at data cut-off.

7.3.5.5 Thrombocytopenia

In the pivotal study, there was a higher incidence of grade 3-4 thrombocytopenia on the T-DM1 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 T-DM1 patients 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.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the EMILIA trial, the most common adverse events ($\geq 25\%$) on T-DM1 included nausea, fatigue, thrombocytopenia, headache, and constipation. The most common adverse events ($\geq 25\%$) on lapatinib + capecitabine included diarrhea, nausea, fatigue, rash and hand-foot syndrome (Table 32).

Adverse events significantly more common [risk differences > 12 (per hundred)] on the T-DM1 arm include: thrombocytopenia, constipation, headache, AST increase, and epistaxis (Table 33). Adverse events significantly more common [risk differences > 12 (per hundred)] on the lapatinib plus capecitabine arm include: palmar-plantar erythrodysesthesia (hand foot), mucosal inflammation, diarrhea, and rash (Table 34).

Table 32: Adverse Events (all grades) > 10% in frequency on T-DM1 in EMILIA

<i>PT</i>	<i>ado-trastuzumab emtansine (N = 490)</i>			<i>Lapatinib+Capecitabine (N = 488)</i>		
	<i>Events</i>	<i>N</i>	<i>Proportion (%)</i>	<i>Events</i>	<i>N</i>	<i>Proportion (%)</i>
Nausea	418	192	39.18	400	218	44.67
Fatigue	313	172	35.1	237	136	27.87
Thrombocytopenia	506	137	27.96	22	12	2.46
Headache	213	133	27.14	81	68	13.93
Constipation	173	124	25.31	62	47	9.63
Diarrhoea	165	114	23.27	1150	389	79.71
AST increased	331	110	22.45	79	46	9.43
Decreased appetite	140	101	20.61	161	113	23.16
Epistaxis	172	99	20.2	46	39	7.99
Vomiting	142	93	18.98	236	143	29.3
Asthenia	182	87	17.76	150	81	16.6
Pyrexia	136	86	17.55	43	37	7.58
Arthralgia	122	85	17.35	43	38	7.79
ALT increased	252	83	16.94	69	43	8.81
Cough	110	83	16.94	65	60	12.3
Dry mouth	90	77	15.71	28	24	4.92
Myalgia	114	69	14.08	25	18	3.69
Back pain	81	64	13.06	62	50	10.25
Abdominal pain upper	64	57	11.63	56	41	8.4
Dyspnoea	65	56	11.43	45	36	7.38
Insomnia	65	54	11.02	46	41	8.4
Pain in extremity	65	52	10.61	69	52	10.66
Rash	71	52	10.61	206	130	26.64
Anaemia	137	51	10.41	77	39	7.99
Neuropathy peripheral	78	49	10	37	28	5.74

Source: AE xpt, Demog.xpt, MAED

Table 33: Treatment Emergent AEs more common on T-DM1

PT	ado-trastuzumab emtansine (N = 490)		Lapatinib+ Capecitabine (N = 488)		ado-trastuzumab emtansine vs Lapatinib+Capecitabine		
	N	Proportion (%)	N	Proportion (%)	RD (per hundred)	RR	Nominal P-value
Thrombocytopenia	137	27.96	12	2.46	25.5	11.37	4E-32
Constipation	124	25.31	47	9.63	15.67	2.628	9E-11
Headache	133	27.14	68	13.93	13.21	1.948	0.00000035
AST increased	110	22.45	46	9.43	13.02	2.382	0.00000026
Epistaxis	99	20.2	39	7.99	12.21	2.528	0.00000004
Dry mouth	77	15.71	24	4.92	10.8	3.195	0.00000024
Myalgia	69	14.08	18	3.69	10.39	3.818	0.00000008
Pyrexia	86	17.55	37	7.58	9.97	2.315	0.0000029
Arthralgia	85	17.35	38	7.79	9.56	2.228	0.0000075
ALT increased	83	16.94	43	8.81	8.13	1.922	0.00018
Fatigue	172	35.1	136	27.87	7.23	1.26	0.016
Urinary tract infection	44	8.98	17	3.48	5.5	2.578	0.00049
Chills	39	7.96	14	2.87	5.09	2.774	0.00057
Cough	83	16.94	60	12.3	4.64	1.378	0.046
Musculoskeletal pain	40	8.16	18	3.69	4.47	2.213	0.004
Neuropathy peripheral	49	10	28	5.74	4.26	1.743	0.017
Muscle spasms	32	6.53	12	2.46	4.07	2.656	0.003
Pain	33	6.73	13	2.66	4.07	2.528	0.004
Dyspnea	56	11.43	36	7.38	4.05	1.549	0.037

Source: AE xpt, Demog.xpt, MAED

Table 34: Treatment Emergent AEs More Common on Lapatinib + Capecitabine

PT	ado-trastuzumab emtansine (N = 490)		Lapatinib + Capecitabine (N = 488)		ado-trastuzumab emtansine vs Lapatinib + Capecitabine		
	N	Proportion (%)	N	Proportion (%)	RD (per hundred)	RR	Nominal P-value
Palmar-plantar erythrodysesthesia syndrome	6	1.22	283	57.99	-56.77	0.021	*****
Diarrhea	114	23.27	389	79.71	-56.45	0.292	1E-73
Rash	52	10.61	130	26.64	-16.03	0.398	9E-11
Mucosal inflammation	33	6.73	93	19.06	-12.32	0.353	0.000000006
Paronychia	1	0.2	52	10.66	-10.45	0.019	1E-15
Vomiting	93	18.98	143	29.3	-10.32	0.648	0.00018
Stomatitis	16	3.27	61	12.5	-9.23	0.261	0.000000046
Hyperbilirubinaemia	6	1.22	40	8.2	-6.97	0.149	0.000000091
Dry skin	17	3.47	49	10.04	-6.57	0.346	0.000037
Nail disorder	11	2.24	39	7.99	-5.75	0.281	0.000036
Nausea	192	39.18	218	44.67	-5.49	0.877	0.092
Skin fissures	1	0.2	27	5.53	-5.33	0.037	0.000000075
Dermatitis acneiform	2	0.41	26	5.33	-4.92	0.077	0.0000012
Skin hyperpigmentation	2	0.41	25	5.12	-4.71	0.08	0.0000022

Source: AE xpt, Demog.xpt, MAED

7.4.2 Laboratory Findings

FDA sent the Applicant an Information request on December 3, 2012 for further clarification regarding their method of generating laboratory values. The Applicant responded that laboratory results after the first dose of study treatment were considered post-baseline. This condition subsets records with a laboratory collection date after the first treatment date, or if the dates coincide, with a laboratory collection time after the first treatment administration. In this analysis, the denominator is the number of patients with non-missing baseline laboratory values and at least one non-missing post baseline values. For decreased neutrophils, the absolute neutrophils and neutrophil differentials were used. Table 35 summarizes the laboratory findings.

Table 35: Selected Laboratory Abnormalities in the EMILIA trial

	T-DM1			Lapatinib + Capecitabine		
	All Grade (%)	Grade 3 (%)	Grade 4 (%)	All Grade (%)	Grade 3 (%)	Grade 4 (%)
Increased Bilirubin	84/472 (17.8%)	2/472 (0.4%)	0/472 (0.0%)	265/462 (57.4%)	11/462 (2.4%)	0/462 (0.0%)
Increased AST	460/471 (97.7%)	35/471 (7.4%)	2/471 (0.4%)	302/459 (65.8%)	11/459 (2.4%)	0/459 (0.0%)
Increased ALT	387/472 (82.0%)	21/472 (4.5%)	1/472 (0.2%)	258/463 (55.7%)	14/463 (3.0%)	0/463 (0.0%)
Decreased platelet count	382/458 (83.4%)	65/458 (14.2%)	12/458 (2.6%)	97/452 (21.5%)	2/452 (0.4%)	2/452 (0.4%)
Decreased Hemoglobin	275/458 (60.0%)	18/458 (3.9%)	4/458 (0.9%)	293/452 (64.8%)	13/452 (2.9%)	1/452 (0.2%)
Decreased Neutrophils	177/451 (39.3%)	15/451 (3.3%)	2/451 (0.4%)	168/452 (37.2%)	29/452 (6.4%)	8/452 (1.8%)
Decreased Potassium	137/418 (32.8%)	13/418 (3.1%)	0/418 (0.0%)	129/415 (31.1%)	26/415 (6.3%)	4/415 (1.0%)

Sources: Labheme, Labchem, Jreview

7.4.3 Vital Signs

Vital signs were obtained at screening and during each follow up visit. No clinically meaningful vital sign changes were observed in the treatment arm as compared to the control arm.

7.4.4 Electrocardiograms (ECGs)

For full details, see Clinical Pharmacology review and QT-IRC review.

Study 4688g was a Phase 2, open-label, single-arm, multicenter study designed to evaluate the effect of T-DM1 (3.6 mg/kg every 3 weeks) on the duration of the QTc interval in 51 patients with HER2+ MBC. No large changes in the mean QT interval (i.e. > 20 ms) were detected.

7.4.5 Special Safety Studies/Clinical Trials

For full details, see Clinical Pharmacology review.

Renal Impairment:

No dedicated renal impairment study was conducted.

Based on a population pharmacokinetic analysis in 688 patients including moderate (creatinine clearance 30 to 60 mL/min, n=53) and mild (creatinine clearance 60 to 90 mL/min, n=254) renal impairment indicate the pharmacokinetics of T-DM1 are not impaired as compared to normal renal function (creatinine clearance \geq 90 mL/min, n=361). Data from only one patient with severe renal impairment (creatinine clearance \leq 30 mL/min) was available. Therefore, no dose adjustments of T-DM1 are recommended for mild or moderate renal impairment. We cannot make firm dose adjustment recommendations regarding severe renal impairment due to the limited data.

Hepatic Impairment:

At the time of this BLA review, a study is ongoing (BO25499) to evaluate the impact of hepatic impairment on T-DM1 pharmacokinetics. Submission of the report from this study is a recommended post-marketing requirement.

7.4.6 Immunogenicity

836 patients from six trials were tested for anti-therapeutic antibody (ATA) responses to T-DM1. Of these, 44/836 (5.3%) of patients tested positive for anti-TDM1 antibodies at one or more time points. However, this may be an under-estimate of the true incidence of anti-TDM1 antibody development as the presence of T-DM1 in the serum at the time of ATA sampling may interfere with the assay. In addition the neutralizing activity of anti-TDM1 antibodies had not been assessed by the applicant at the time of BLA submission.

7.5 Other Safety Explorations

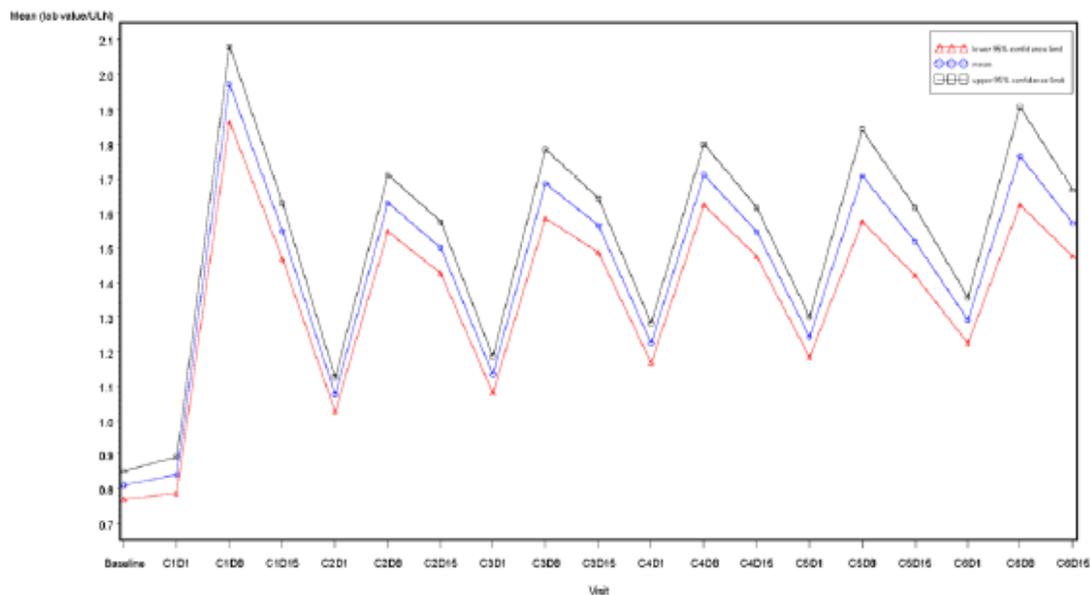
7.5.1 Dose Dependency for Adverse Events

In the Phase I study, TDM3569g, the maximum tolerated dose (MTD) of T-DM1 administered by IV infusion every 3 weeks was 3.6 mg/kg. Dose limiting toxicity (DLT) consisted of grade 4 thrombocytopenia in 2 of 3 patients treated at the 4.8 mg/kg dose level.

7.5.2 Time Dependency for Adverse Events

In the EMILIA trial, the mean ALT/AST would peak on day 8 after T-DM1 infusion (Figure 14). The nadir mean platelet count was lowest on day 8 after T-DM1 infusion (Figure 15).

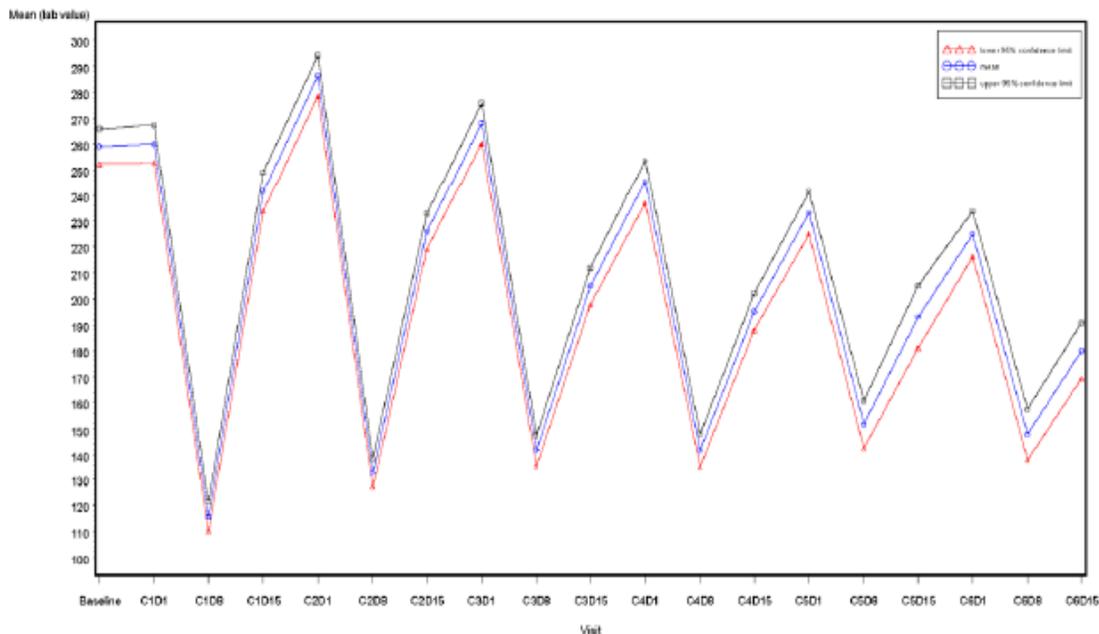
Figure 14: EMILIA mean AST by study visit on T-DM1 arm



Best Available
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Sources: CSR Figure 16

Figure 15: EMILIA mean platelet count by study visit on T-DM1 arm



Sources: CSR Figure 19

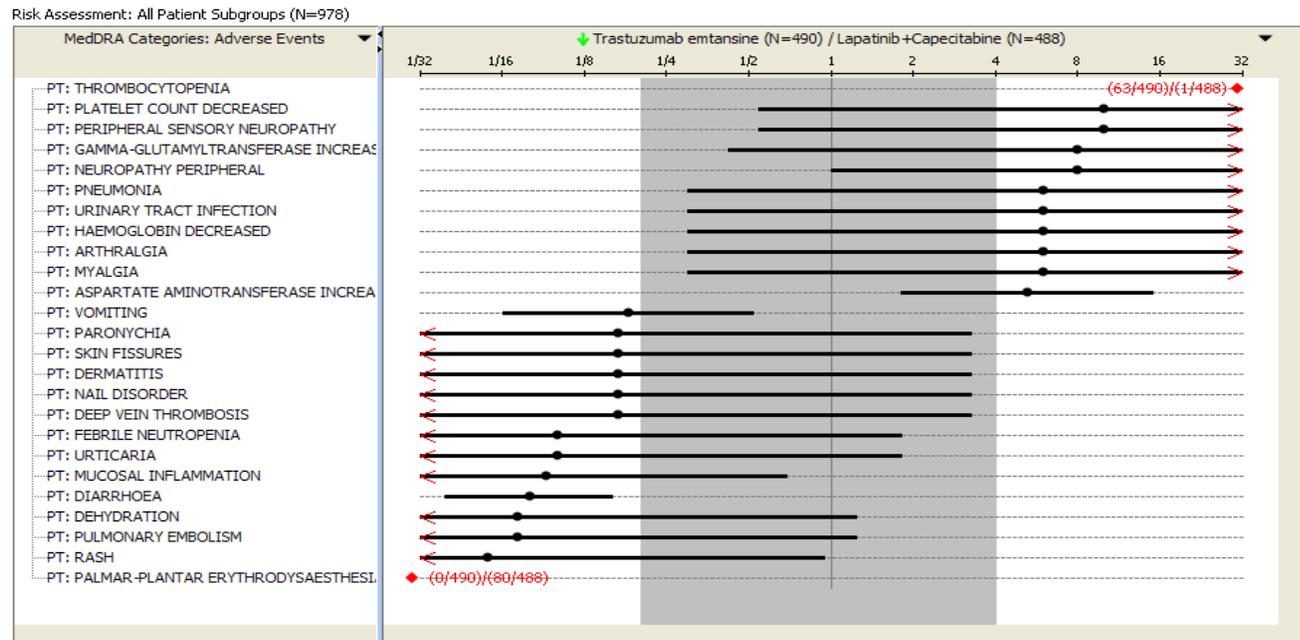
7.5.3 Drug-Demographic Interactions

Age:

Based on population pharmacokinetic analysis, there were no pharmacokinetic effects of T-DM1 base on the following age cutoffs: < 65 (n=577), 65 – 75 (n=78), > 75 (n=16).

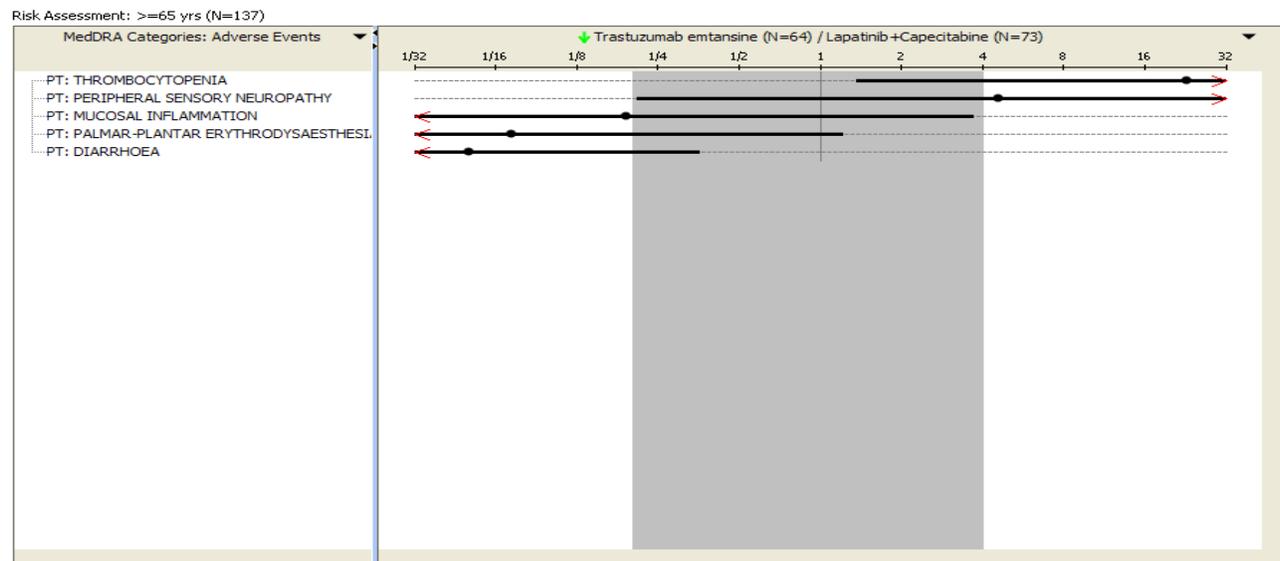
For the EMILIA trial, I performed a JReview assessment of relative risk assessment of grade 3-5 toxicities in the entire population (Figure 16), as well as for patients > 65 (Figure 17). In both populations, thrombocytopenia and peripheral neuropathy had the highest relative risk scores without appreciable differences between the entire population and the > 65 population.

Figure 16: Relative risk ratio of grade 3-5 AEs in EMILIA entire population



Source: J review

Figure 17: Relative risk ratio of grade 3-5 AEs in EMILIA Age > 65 population



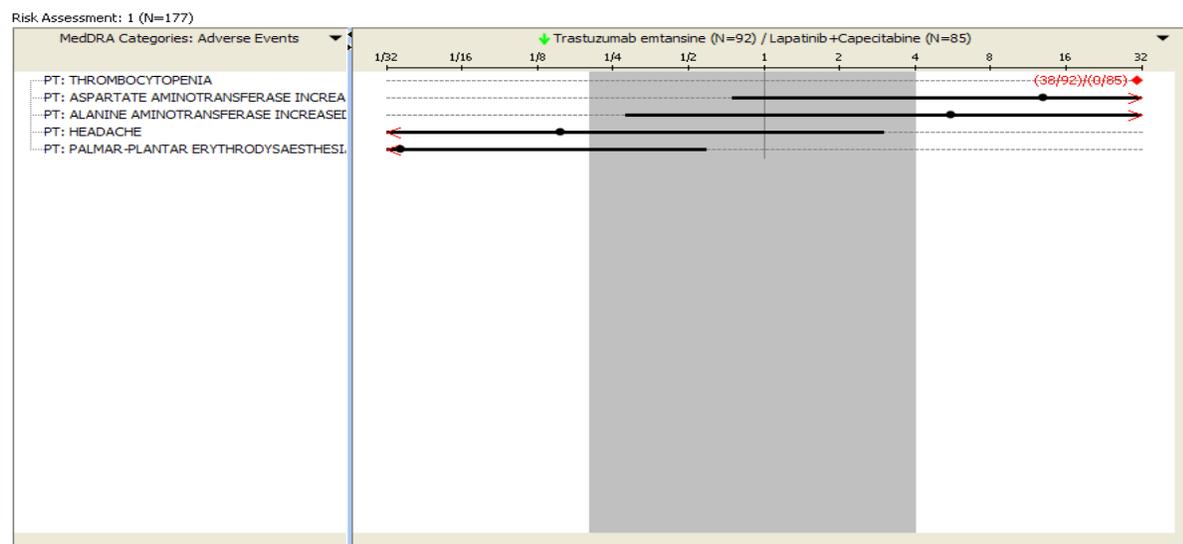
Source: J review

Asian population:

Based on population pharmacokinetic analysis, race (Asian n=73) and non-Asian (n=599) did not have a clinically meaningful effect on the pharmacokinetics of T-DM1.

In the Asian population in EMILIA, there is a higher incidence of grade 3-5 thrombocytopenia with T-DM1 (41% T-DM1 arm vs. 0% lapatinib + capecitabine arm) than in the general population (13% T-DM1 arm vs. 0.2% lapatinib + capecitabine arm). The review for relative risk ratio in Asian patients is provided in Figure 18.

Figure 18: Relative risk ratio of grade 3-5 AEs in EMILIA- Asian population



Source: J review

7.5.4 Drug-Disease Interactions

ado-trastuzumab emtansine specifically targets Her2/neu-positive cells and thus selectively targets tumor cells that over-express the Her2/neu antigen. Disease factors that may affect T-DM1 pharmacokinetics include tumor burden and shed Her2 antigen.

7.5.5 Drug-Drug Interactions

For full details, see *Clinical Pharmacology Review*.

No formal drug-drug interaction studies with T-DM1 have been conducted. In vitro studies indicate that DM1 is metabolized predominantly by CYP3A4 and to a lesser extent by CYP3A5. Therefore, strong CYP3A4 inhibitors should be avoided in patients receiving T-DM1 when possible.

DM1 did not appear to induce or inhibit P450 mediated metabolism at clinically relevant doses.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See *Pharmacology/Toxicology Review*

Based on a safety report of a patient with Myelodysplastic Syndrome (MDS), on 20 September 2012, I submitted an information request to report all patients who developed Acute Myeloid Leukemia (AML) or MDS on KADCYLA. The applicant submitted the following narratives.

Patient 6507: 40 year old female on 4258g (single arm ph2 in previously treated Her2+ MBC). Diagnosed with IDC right breast May 2000. Diagnosed with MBC in October 2001. Heavily pretreated with hormonal agents and chemotherapy including capecitabine, vinorelbine, carboplatin, gemcitabine. Enrolled on study 4258g with 1st dose T-DM1 3.6 mg/kg administered [REDACTED] (b) (6). On Day 22 she had Grade 3 neutropenia which resolved on Day 29. Cycle 2 was administered [REDACTED] (b) (6) (Day 29). On Day 43, the patient was diagnosed with Acute myeloid leukemia as well as Grade 4 leukocytosis, Grade 4 thrombocytopenia, and Grade 3 anemia. A bone marrow biopsy Day 44 showed AML with 28% blasts. Karyotype testing showed: 46, XX, der (7) t (1;7) (q21;q22) [19]/46, idem, dup (11) (q13q25). She was discontinued from the study Day 43. No BRCA data was provided. The investigator thought the AML was not related to T-DM1.

Reviewer Comment: *T-DM1 unlikely to be causative given the patients heavy pre-treatment with DNA damaging agents and the abrupt onset of AML (43 days) with limited exposure (2 doses of T-DM1).*

Patient 21354: 54 year old female on 4370g (EMILIA). Initially diagnosed with EBC in December 2006, diagnosed with MBC January 2009. Previous treatments included: doxorubicin, cyclophosphamide, paclitaxel, and vinorelbine. At baseline her hemoglobin was 10 g/dl (12-16 g/dl). She was randomized to and received her first dose of 3.6 mg/kg T-DM1 [REDACTED] (b) (6). On study day 134 she experienced grade 2 decreased hemoglobin. On study day 174, she received her 9th cycle of T-DM1 3.6 mg/kg. On Study Day 182, she experienced grade 1 neutropenia; Study Day 197 she was noted to have hemoglobin 7.6 g/dL, and platelets 90k and was diagnosed with grade 3 anemia and grade 1 thrombocytopenia. The same day, a bone marrow biopsy revealed hypercellularity (90%), 3% blasts with monoblast phenotype, normal karyotype (46, XX) and she was diagnosed with grade 2 MDS. No BRCA data has been provided. On Study Day 204, she received her 10th and last cycle of T-DM1. She was noted to have disease progression on Study Day 244. On Study Day 297, the patient died due to disease progression. The investigator felt that MDS was unrelated to T-DM1. Other factors could have included cyclophosphamide given in 2007 for adjuvant breast cancer.

Reviewer Comment: *T-DM1 unlikely to be causative given the patients heavy pre-treatment with topoisomerase inhibitors and alkylating agents.*

7.6.2 Human Reproduction and Pregnancy Data

See Pharmacology/Toxicology Review.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

A total of five cases of overdose with T-DM1 were reported as of November 9, 2012, one serious case and four non-serious (Table 36). A summary of the serious case is reviewed in detail.

Table 36: Summary of Overdoses in T-DM1 development program

Patient ID	Study	Treatment arm assigned	Medication Error	Adverse events
9248	4450g (Randomized Phase 2 T-DM1 vs. Trastuzumab + Docetaxel)	Trastuzumab + Docetaxel	Cycle 12 received 6 mg/kg of T-DM1 instead of Trastuzumab	Death 19 days later of unknown cause.
9249	4450g (Randomized Phase 2 T-DM1 vs. Trastuzumab + Docetaxel)	Trastuzumab + Docetaxel	Cycle 10 received 6 mg/kg of T-DM1 instead of Trastuzumab	Grade 2 thrombocytopenia (resolved)
47001	4788g (MARIANNE Ph3 T-DM1 +/- pertuzumab vs Tras + Taxane)	Trastuzumab + Docetaxel	Cycle 3 received 1 vial (1.8 mg/kg) T-DM1 instead of Trastuzumab; 2 vials of Trastuzumab	None
90502	4997g (TH3ESA Ph3 third line study against BSC)	Trastuzumab + Gemcitabine	Cycles 3 and 4 received T-DM1 6 mg/kg instead of Trastuzumab along with Gemcitabine	Grade 3 ALT/ AST (recovered)
N/A	Compassionate use program	Trastuzumab + Docetaxel + Pertuzumab	Cycle 3 received 4.6 mg/kg T-DM1 instead of Pertuzumab	Grade 2 nausea, fatigue; Grade 1 abdominal pain and dizziness all resolved.

Serious case of overdose:

Patient 9248: 57 year old Caucasian female initially diagnosed with stage I, HR+ IDC of the right breast in 1996. She was first diagnosed with Her2+ MBC in June 2006. Previous systemic treatments included tamoxifen, letrozole, exemestane, and fulvestrant.

In August 2009 she was enrolled on study 4450g, the randomized phase 2 of T-DM1 versus trastuzumab plus docetaxel. She was reported to have metastatic disease to the lung and possibly the skull. Her ECOG performance status at baseline was 0. An echocardiogram in August 2009 showed LVEF of 58% and mild to moderate aortic and mitral insufficiency. Her past medical history included hypertension and concomitant medications included enalapril and furosemide.

She was randomized to the trastuzumab plus docetaxel arm and her first dose (Cycle 1 Day 1) of trastuzumab 8 mg/kg and docetaxel 75 mg/m² (b) (6). The patient received Cycle 4 Day 1 of trastuzumab 6 mg/kg and docetaxel 75 mg/m² (b) (6) (Study Day 64). On an unspecified day in November she experienced “**compromised consciousness**” with deviation of conjugate gaze (this was not documented in the eCRF but was reported during neurologic consultation).

On Study Day 74, (b) (6) an echocardiogram showed probable aortic and mitral rheumatic heart disease, mild aortic and moderate mitral insufficiency. Her LVEF was noted to be normal. Severe dilatation of the left atrium was noted.

The patient reported that on (b) (6) (Study Day 165) she experienced a loss of consciousness. Per neurology, the event was self-limited, with deviation of conjugate gaze, salivation, no tongue-biting, incontinence or post-ictal status. The event was graded as grade 1 and unrelated to the anti-cancer agents. An EEG and CT of the head (b) (6) were unremarkable. On (b) (6) (Study Day 223) the patient received her last dose of docetaxel, which was permanently discontinued thereafter due to increased lacrimation. On (b) (6) (Study Day 263), her LVEF was noted on echocardiogram to be 60% with moderate enlargement of the left atrium. In mid May 2010 (date unspecified), she developed a short episode of expressive aphasia.

On (b) (6) (study Day 266), she was inadvertently administered T-DM1 6 mg/kg on Cycle 12 instead of trastuzumab. On (b) (6) she was noted to have a platelet count of 50k (140-400) and diagnosed with grade 2 thrombocytopenia. This resolved on (b) (6).

On (b) (6) (Study Day 284) a Holter monitor showed very frequent asymptomatic monomorphic single ventricular extra systoles. On (b) (6) (Study Day 285), the patient’s family informed the investigator of sudden death. The cardiologist did not believe that the extra systoles contributed to death. No autopsy was performed. The investigator considered the sudden death unrelated to T-DM1 overdose. The

investigator postulated a potential pulmonary embolism. The patient had a Partial Response which was sustained through tumor assessment [REDACTED] (b) (6).

Reviewer Comments: Given the lack of an autopsy, the cause of death is uncertain. One cannot rule out, however, that the T-DM1 overdose in some way contributed to her death.

8 Postmarket Experience

Ado-trastuzumab emtansine is not marketed in the US or other jurisdiction.

9 Appendices

9.1 Labeling Recommendations

The labeling negotiations were ongoing at the time of finalization of this review. Key recommendations included:

- Recommend a prefix prior to trastuzumab-emtansine to mitigate against medication error (see Overdose section 7.6.4)
- Specifying in 'Indications' section that patients either previously received trastuzumab and taxanes in the metastatic setting or progressed during or within six months of completing adjuvant therapy.
- A boxed warning for hepatotoxicity, cardiac toxicity, and embryofetal toxicity.

9.2 Advisory Committee Meeting

This BLA was not presented to an advisory committee because FDA review determined that KADCYLA clearly demonstrated a favorable benefit-risk profile in this serious and life threatening disease in a refractory patient population previously treated with taxanes and trastuzumab in an adequate and well controlled trial with sufficient supportive evidence.

9.3 Literature Review/References

- 1 Remillard, S., Rebhun, L. I., Howie, G. A. & Kupchan, S. M. ANTIMITOTIC ACTIVITY OF POTENT TUMOR INHIBITOR MAYTANSINE. *Science* **189**, 1002-1005, doi:10.1126/science.1241159 (1975).
- 2 Cassady, J. M., Chan, K. K., Floss, H. G. & Leistner, E. Recent developments in the maytansinoid antitumor agents. *Chem Pharm Bull (Tokyo)* **52**, 1-26 (2004).
- 3 Lewis Phillips, G. D. *et al.* Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Res* **68**, 9280-9290, doi:10.1158/0008-5472.CAN-08-1776 (2008).
- 4 Burris, H. A. Trastuzumab emtansine: a novel antibody-drug conjugate for HER2-positive breast cancer. *Expert Opin Biol Ther* **11**, 807-819, doi:10.1517/14712598.2011.580273 (2011).
- 5 Krop, I. E. *et al.* Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. *J Clin Oncol* **28**, 2698-2704, doi:10.1200/JCO.2009.26.2071 (2010).
- 6 Krop, I. E. *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* **30**, 3234-3241, doi:10.1200/JCO.2011.40.5902 (2012).
- 7 Slamon, D. J. *et al.* Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* **235**, 177-182 (1987).
- 8 Slamon, D. J. *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* **344**, 783-792, doi:10.1056/NEJM200103153441101 (2001).
- 9 Cameron, D. *et al.* A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat* **112**, 533-543, doi:10.1007/s10549-007-9885-0 (2008).
- 10 Eagan, R. T., Ingle, J. N., Rubin, J., Frytak, S. & Moertel, C. G. Early clinical study of an intermittent schedule for maytansine (NSC-153858): brief communication. *J Natl Cancer Inst* **60**, 93-96 (1978).
- 11 Blum, R. H. & Kahlert, T. Maytansine: a phase I study of an ansa macrolide with antitumor activity. *Cancer Treat Rep* **62**, 435-438 (1978).
- 12 Cabanillas, F. *et al.* Phase I study of maytansine using a 3-day schedule. *Cancer Treat Rep* **62**, 425-428 (1978).

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/s/

GIDEON M BLUMENTHAL
01/30/2013

LALEH AMIRI KORDESTANI
01/30/2013

PATRICIA CORTAZAR
01/30/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	have received prior treatment with trastuzumab and a taxane.				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	√			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			√	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	√			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	√			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	√			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	√			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	√			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	√			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	√			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	√			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			√	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			√	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	√			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	√			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	√			
34.	Are all datasets to support the critical safety analyses available and complete?	√			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	√			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	√			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	√			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	√			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	√			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Laleh Amiri-Kordestani

Reviewing Medical Officer

Date

Patricia Cortazar

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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LISA M SKARUPA
10/18/2012

LALEH AMIRI KORDESTANI
10/18/2012

PATRICIA CORTAZAR
10/21/2012