PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrKADCYLA®

trastuzumab emtansine for injection

100 mg and 160 mg, sterile powder, intravenous infusion only

Antineoplastic Agent

Hoffmann-La Roche Limited
7070 Mississauga Road
Mississauga, Ontario, Canada
L5N 5M8

Date of Initial Approval:
September 11, 2013
Date of Revision:
November 25, 2019

Submission Control No: 227372

RECENT MAJOR LABEL CHANGES

INDICATIONS, Early Breast Cancer (1) 11/2019

TABLE OF CONTENTS

RECENT MAJOR LABEL CHANGES 2
TABLE OF CONTENTS 2
PART I: HEALTH PROFESSIONAL INFORMATION 4
1 INDICATIONS 4
1.1 Pediatrics 4
1.2 Geriatrics 4
2 CONTRAINDICATIONS 4
3 SERIOUS WARNINGS AND PRECAUTIONS BOX 5
4 DOSAGE AND ADMINISTRATION 5
4.1 Dosing Considerations 5
4.2 Recommended Dose and Dosage Adjustment 6
4.3 Administration 10
4.4 Reconstitution 10
4.5 Missed Dose 11
5 OVERDOSAGE 11
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 11
7 DESCRIPTION 11
8 WARNINGS AND PRECAUTIONS 12
8.1 Special Populations 16
8.1.1 Females and Males of Reproductive Potential 16
8.1.2 Pregnant Women 16
8.1.3 Breast-feeding 16
8.1.4 Pediatrics 16
8.1.5 Geriatrics 16
8.1.6 Hepatic Impairment 17
8.1.7 Ethnic origin 17
9 ADVERSE REACTIONS 17
9.1 Adverse Reaction Overview 17
9.2 Clinical Trial Adverse Reactions 18
9.3 Less Common Clinical Trial Adverse Reactions 27
9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data 28
9.5 Post-Market Adverse Reactions 29

10 DRUG INTERACTIONS 29
10.1 Drug-Drug Interactions 29
10.2 Drug-Food Interactions 30
10.3 Drug-Herb Interactions 30
10.4 Drug-Laboratory Test Interactions 30
11 ACTION AND CLINICAL PHARMACOLOGY 30
11.1 Mechanism of Action 30
11.2 Pharmacodynamics 31
11.3 Pharmacokinetics 31
12 STORAGE, STABILITY AND DISPOSAL 33
13 SPECIAL HANDLING INSTRUCTIONS 33
PART II: SCIENTIFIC INFORMATION 34
14 PHARMACEUTICAL INFORMATION 34
15 CLINICAL TRIALS 34
15.1 Trial Design and Study Demographics 34
15.2 Study Results 36
16 MICROBIOLOGY 45
17 NON-CLINICAL TOXICOLOGY 45
PATIENT MEDICATION INFORMATION 51

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Metastatic Breast Cancer (MBC)
Kadcyla (trastuzumab emtansine for injection) monotherapy is indicated for the treatment of HER2-positive metastatic breast cancer patients who received both prior treatment with trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy.

Early Breast Cancer (EBC)
Kadcyla monotherapy is indicated for the adjuvant treatment of HER2-positive early breast cancer patients who have residual invasive disease following neoadjuvant taxane and trastuzumab-based treatment.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 age): No dose adjustment of the Kadcyla starting dose is required in patients aged > 65 to < 75 years of age. There are insufficient data to establish the safety and efficacy of Kadcyla in patients 75 years of age or older (see WARNINGS AND PRECAUTIONS: Special Populations, Geriatrics).

2 CONTRAINDICATIONS

Kadcyla is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **There is a risk of medication errors between Kadcyla (trastuzumab emtansine for injection) and trastuzumab. In order to minimize this risk, check the vial labels to ensure that the drug being prepared and administered is Kadcyla (trastuzumab emtansine for injection) and not trastuzumab. Kadcyla should be prescribed using both the trade name and non-proprietary name (see DOSAGE AND ADMINISTRATION: Dosing Considerations).**
- Liver Toxicity: Hepatotoxicity, liver failure and death have occurred in Kadcyla-treated patients. Monitor hepatic function prior to initiation and prior to each dose. Institute dose modifications or permanently discontinue as appropriate (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic).
- Cardiotoxicity: Kadcyla may lead to reductions in left ventricular ejection fraction (LVEF). Assess LVEF prior to initiation. Monitor during treatment and withhold dosing or discontinue as appropriate (see WARNINGS AND PRECAUTIONS: Cardiovascular).
- Hemorrhage: Fatal cases of hemorrhage occurred in clinical trials among patients with no known identified risk factors, as well as among patients with thrombocytopenia and those receiving anti-coagulation and antiplatelet therapy. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary (see WARNINGS AND PRECAUTIONS: Hematologic).
- Interstitial lung disease (ILD): Cases of ILD, including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical trials with Kadcyla. It is recommended that treatment with Kadcyla be permanently discontinued in patients who are diagnosed with ILD or pneumonitis (see WARNINGS AND PRECAUTIONS: Respiratory).
- Embryo-fetal Toxicity: Kadcyla can cause fetal harm or death of the fetus. Advise women of potential risk to the fetus (see WARNINGS AND PRECAUTIONS: Special Populations, Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Kadcyla should only be used in patients with HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH) or by fluorescence in situ hybridization (FISH) assessed by a validated test in an accredited laboratory.

There is a risk of medication errors between Kadcyla (trastuzumab emtansine) and trastuzumab. In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is Kadcyla (trastuzumab emtansine for injection) and not trastuzumab. Ensure that the recommended Kadcyla dose is administered (see DOSAGE AND ADMINISTRATION section). These will avoid overdose and toxicity (see OVERDOSAGE section).

Kadcyla should only be administered under the supervision of a health professional experienced in the treatment of cancer patients.

Kadcyla must be reconstituted and diluted by an appropriately trained health professional. Kadcyla should be administrated as an intravenous infusion (see DOSAGE AND ADMINISTRATION: Administration). Do not administer as an intravenous push or bolus.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose:
The recommended starting dose of Kadcyla is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle). Do not administer Kadcyla at doses > 3.6 mg/kg.

Patients with early breast cancer (EBC) should receive Kadcyla for 14 cycles or until there is disease progression or unmanageable toxicity.

Patients with metastatic breast cancer (MBC) should receive Kadcyla until disease progression or unmanageable toxicity.

Administer the initial Kadcyla dose of 3.6 mg/kg as a 90-minute intravenous infusion. Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion-related reactions. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration (see WARNINGS AND PRECAUTIONS: Extravasation).

If prior infusions were well tolerated, subsequent doses of Kadcyla may be administered as 30-minute infusions and patients should be observed during the infusions and for at least 30 minutes after infusion.

The infusion rate of Kadcyla should be slowed or interrupted if the patient develops infusion-related symptoms (see WARNINGS AND PRECAUTIONS: Infusion-Related Reactions, Hypersensitivity Reactions). Permanently discontinue Kadcyla for life-threatening infusion reactions.

Dose Adjustment:
Management of symptomatic adverse events may require temporary interruption, dose reduction, or treatment discontinuation of Kadcyla as per guidelines provided in Table 1, Table 2 and **Table 3**.

Kadcyla dose should not be re-escalated after a dose reduction is made.

Table 1 Dose Reduction Schedule

Dose reduction Schedule	Dose Level
Starting Dose	3.6 mg/kg
First dose reduction	3.0 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Permanently discontinue treatment

Table 2 Dose Modification Guidelines for Kadcyla Patients with MBC

Adverse reaction	Severity	Treatment modification
Increased Transaminase (AST/ALT)	Grade 2 (> 2.5 to ≤ 5× the ULN)	Treat at the same dose level
	Grade 3 (> 5 to ≤ 20× the ULN)	Do not administer Kadcyla until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level
	Grade 4 (> 20× the ULN)	Permanently discontinue Kadcyla
Hyperbilirubinemia	Grade 2 (> 1.5 to ≤ 3× the ULN)	Do not administer Kadcyla until total bilirubin recovers to Grade ≤ 1, and then treat at the same dose level.
	Grade 3 (> 3 to ≤ 10× the ULN)	Do not administer Kadcyla until total bilirubin recovers to Grade ≤ 1 and then reduce one dose level.
	Grade 4 (> 10× the ULN)	Permanently discontinue Kadcyla
Drug Induced Liver Injury (DILI)	Serum transaminases > 3× ULN and concomitant total bilirubin > 2× ULN	Permanently discontinue Kadcyla in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue Kadcyla
Thrombocytopenia	Grade 3 (25,000 to < 50,000/mm^3)	Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then treat at the same dose level
	Grade 4 (< 25,000/mm^3)	Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then reduce one dose level
Left Ventricular Dysfunction	Symptomatic CHF	Permanently discontinue Kadcyla
	LVEF <40%	Do not administer Kadcyla Repeat LVEF assessment within 3 weeks. If LVEF <40% is confirmed, permanently discontinue Kadcyla
	LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	Do not administer Kadcyla Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, permanently discontinue Kadcyla
	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	Continue treatment with Kadcyla. Repeat LVEF assessment within 3 weeks.

Adverse reaction	Severity	Treatment modification
	LVEF > 45%	Continue treatment with Kadcyla.
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue Kadcyla
Peripheral Neuropathy	Grade 3-4	Do not administer Kadcyla until resolution ≤ Grade 2

Table 3 Dose Modification Guidelines for Kadcyla Patients with EBC

Adverse reaction	Severity	Treatment modification
Increased Alanine Transaminase (ALT)	Grade 2-3 (> 3.0 to ≤ 20× ULN on day of scheduled treatment)	Do not administer Kadcyla until ALT recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20× ULN at any time)	Permanently discontinue Kadcyla
Increased Aspartate Transaminase (AST)	Grade 2 (> 3 to ≤ 5× ULN on day of scheduled treatment)	Do not administer Kadcyla until AST recovers to Grade ≤ 1, and then treat at the same dose level
	Grade 3 (> 5 to ≤ 20× ULN on day of scheduled treatment)	Do not administer Kadcyla until AST recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20× ULN at any time)	Permanently discontinue Kadcyla
Hyperbilirubinemia	TBILI > 1 to ≤ 2× the ULN on day of scheduled treatment	Do not administer Kadcyla until total bilirubin recovers to ≤ 1.0× ULN, and then reduce one dose level
	TBILI > 2× ULN at any time	Permanently discontinue Kadcyla
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue Kadcyla
Thrombocytopenia	Grade 2-3 on day of scheduled treatment (25,000 to < 75,000/mm^3)	Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then treat at the same dose level. If a patient requires 2 delays due to thrombocytopenia, consider reducing dose by one level.
	Grade 4 at any time < 25,000/mm^3	Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then reduce one dose level.
Left Ventricular Dysfunction	LVEF < 45%	Do not administer Kadcyla Repeat LVEF assessment within 3 weeks. If

Adverse reaction	Severity	Treatment modification
		LVEF < 45% is confirmed, permanently discontinue Kadcyla.
	LVEF 45% to < 50% and decrease is ≥ 10% points from baseline*	Do not administer Kadcyla Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to < 10% points from baseline, permanently discontinue Kadcyla.
	LVEF 45% to < 50% and decrease is < 10% points from baseline*	Continue treatment with Kadcyla. Repeat LVEF assessment within 3 weeks.
	LVEF ≥ 50%	Continue treatment with Kadcyla.
Heart Failure	Symptomatic CHF, Grade 3-4 LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45%	Permanently discontinue Kadcyla
Peripheral Neuropathy	Grade 3-4	Do not administer Kadcyla until resolution ≤ Grade 2
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue Kadcyla
Radiotherapy-Related Pneumonitis	Grade 2	Permanently discontinue Kadcyla if not resolving with standard treatment
	Grade 3-4	Permanently discontinue Kadcyla

ALT = alanine transaminase; AST = aspartate transaminase, CHF = congestive heart failure, DILI= Drug Induced Liver Injury; LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction, TBILI = Total Bilirubin, ULN = upper limit of normal

*Prior to starting Kadcyla treatment.

Geriatric Use (> 65 years of age): No adjustment to the starting dose of Kadcyla is required in patients aged > 65 to < 75 years of age. There are limited number of patients ≥ 75 years of age enrolled into clinical trials with Kadcyla (see WARNINGS AND PRECAUTIONS: Special Populations, Geriatrics).

Renal Impairment: No adjustment to the starting dose of Kadcyla is recommended in patients with mild or moderate renal impairment (see ACTIONS AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Renal Insufficiency). The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data.

Hepatic Impairment: No adjustment to the starting dose of Kadcyla is recommended in patients with mild or moderate hepatic impairment despite lower overall exposure of

trastuzumab emtansine in these patients (see ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Hepatic Insufficiency). Kadcyla has not been studied in patients with severe hepatic impairment. Treatment of patients with hepatic impairment should be undertaken with caution due to known hepatotoxicity observed with Kadcyla (see WARNINGS AND PRECAUTIONS: Hepatotoxicity).

4.3 Administration

Appropriate aseptic technique should be used. Appropriate procedures for the preparation of chemotherapeutic drugs should be used.

The reconstituted product contains no preservative and is intended for single use only. Discard any unused portion.

Reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted solution should be free of visible particulates, clear to slightly opalescent. The color of the reconstituted solution should be colorless to pale brown. Do not administer if reconstituted solution contains visible particulates, or is cloudy or discolored.

4.4 Reconstitution

Vial Size	Volume of Diluent to be Added to the Vial	Nominal Concentration per mL
100 mg	**5 mL Sterile Water**	**20 mg per mL**
160 mg	**8 mL Sterile Water**	**20 mg per mL**

- Using a sterile syringe, slowly inject 5 mL of Sterile Water for Injection into the 100 mg vial, or 8 mL of Sterile Water for Injection into the 160 mg Kadcyla vial.
- Swirl the vial gently until completely dissolved. DO NOT SHAKE!
- Store reconstituted Kadcyla at 2-8ºC; discard unused Kadcyla after 24 hours.

Instructions for dilution:
Determine the volume of the solution required based on the dose to be administered. The standard dose is 3.6 mg Kadcyla/kg body weight; however, reduced doses may be required to manage certain toxicities (see Tables 2 and 3):

Volume (mL) = [Body weight (kg) x dose (mg/kg)] /

20 mg/mL (concentration of reconstituted solution)

The appropriate amount of solution should be withdrawn from one or more vials and added to an infusion bag containing 250 mL of 0.45% sodium chloride or 0.9% sodium chloride. Choose the appropriate vial sizes to minimize the amount of Kadcyla that is discarded.

Dextrose (5%) solution should not be used. 0.45% sodium chloride may be used without a 0.2-micron in-line (non-protein adsorptive)/0.22 micron polyethersulfone (PES) filter. If 0.9% sodium chloride is used for infusion, a 0.2-micron in-line (non-protein adsorptive)/ 0.22 micron polyethersulfone (PES) filter is required. Once the infusion is prepared, it should be administered immediately. If not used immediately, the infusion can be stored for up to 24 hours in a refrigerator at 2-8°C. The infusion cannot be frozen or shaken during storage.

Incompatibilities:
Dextrose (5%) solution should not be used since it causes aggregation of the protein.

Kadcyla should not be mixed or diluted with other drugs.

4.5 Missed Dose

If a planned dose of Kadcyla is missed, it should be administered as soon as possible as per clinical judgment. Do not wait until the next planned cycle if clinically appropriate. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion may be administered at the rate the patient tolerated the most recent infusion.

5 OVERDOSAGE

There is a risk of Kadcyla overdose due to medication errors. Ensure that the authorized Kadcyla (trastuzumab emtansine for injection) dose and NOT trastuzumab dose is administered. For management of a suspected drug overdose, contact your regional poison control centre.

There is no known antidote for Kadcyla overdose. In case of overdose, the patient should be closely monitored. Cases of overdose have been reported with Kadcyla treatment, most associated with thrombocytopenia, and there was one death. In the fatal case, the patient incorrectly received Kadcyla 6 mg/kg and died approximately 3 weeks following the overdose; a cause of death and a causal relationship to Kadcyla were unknown.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous (IV) infusion	100 mg single-use vial	polysorbate 20, sodium hydroxide, succinic acid, and sucrose.
	160 mg single-use vial	

100 mg single-use vial containing sterile powder for concentrate for infusion solution designed to deliver 5 mL of 20 mg/mL of trastuzumab emtansine.

160 mg single-use vial containing sterile powder for concentrate for infusion solution designed to deliver 8 mL of 20 mg/mL of trastuzumab emtansine.

7 DESCRIPTION

Kadcyla (trastuzumab emtansine) is a HER2-targeted antibody-drug conjugate which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule-inhibitory drug DM1 (a derivative of maytansine) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex. An average of 3.5 DM1 molecules are conjugated to each molecule of trastuzumab.

8 WARNINGS AND PRECAUTIONS

General

Kadcyla should only be prescribed and initiated by health professionals experienced with cancer therapeutic drugs.

Kadcyla should be prescribed using both the trade name and non-proprietary name. In order to improve traceability of biological medicinal products, the trade name and the lot number of the administered product should be clearly recorded (or stated) in the patient file.

Cardiovascular

Left Ventricular Dysfunction
Patients treated with Kadcyla are at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) < 40% has been observed in patients treated with Kadcyla, and therefore symptomatic congestive heart failure (CHF) is a potential risk. Across metastatic breast cancer (MBC) and early breast cancer (EBC) clinical trials, left ventricular dysfunction occurred in the Kadcyla-treated patients. Long-term effects of Kadcyla on cardiotoxicity is unknown (see ADVERSE REACTIONS).

Standard cardiac function testing (echocardiogram or multigated acquisition (MUGA) scanning) should be performed prior to initiation and at regular intervals (e.g. every three months) during treatment with Kadcyla. Dosing reductions or permanent discontinuation of Kadcyla therapy may be required (see DOSAGE AND ADMINISTRATION: Dose Adjustments). Evaluation of cardiac function following treatment discontinuation, in particular for patients with pre-existing cardiac dysfunction or with LVEF decline, should be considered and ordered based upon clinician judgment.

Treatment with Kadcyla has not been studied in patients with LVEF <50% prior to initiation of treatment.

Driving and Operating Machinery

Kadcyla may impair the ability to drive and use machines as adverse reactions including fatigue, headache, dizziness and blurred vision have been reported. Patients experiencing infusion-related reactions (flushing, shivering fits, trouble breathing, low blood pressure or rapid heartbeat) should be advised not to drive and use machines until symptoms abate.

Hematologic

Hemorrhage
Bleeding events with fatal outcomes have occurred. Severe cases of hemorrhagic events, including central nervous system, respiratory and gastrointestinal hemorrhage, have been reported with Kadcyla. In some of the cases, there were no known additional risk factors, while in others the patients were also receiving anti-coagulation therapy, antiplatelet therapy, or had thrombocytopenia. Caution is advised and additional monitoring is recommended when Kadcyla is administered to patients who have decreased platelet counts or who require anti-coagulation or antiplatelet therapies.

Thrombocytopenia

Thrombocytopenia, or decreased platelet counts, was commonly reported in patients in clinical trials of Kadcyla. An increase in the incidence and severity of thrombocytopenia has been observed in Asian patients treated with Kadcyla vs. non-Asian patients. In the pivotal EBC study, ≥ Grade 3 thrombocytopenia occurred in 12 of 64 Asian patients (18.8%) and in to 30 of 676 (4.4%) non-Asian patients treated with Kadcyla and serious adverse events of thrombocytopenia occurred in 5 of 64 (7.8%) Asian patients and in 5 of 676 (0.7%) non-Asian patients.

Patients with thrombocytopenia (<100,000/mm^3) and patients on anti-coagulation treatment should be monitored closely while on Kadcyla treatment. Platelet counts should be monitored prior to each Kadcyla dose. Kadcyla has not been studied in patients with platelet counts <100,000/mm^3 prior to initiation of treatment.

For patients with EBC, in the event of decreased platelet counts to ≥ Grade 2 (<75,000/mm^3), do not administer Kadcyla until platelet counts recover to Grade 1 (≥75,000/mm^3). For patients with MBC, in the event of decreased platelet count to ≥ Grade 3 (<50,000/mm^3), do not administer Kadcyla until platelet counts recover to Grade 1 (≥75,000/mm^3) (see DOSAGE AND ADMINISTRATION: Dose Adjustment).

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1-4 transaminitis), have occurred with Kadcyla treatment in clinical trials (see ADVERSE REACTIONS: Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data). In patients with MBC, transaminase elevations were generally transient with peak elevation at day 8 after therapy and subsequent recovery to Grade 1 or less prior to the next cycle. A cumulative effect of Kadcyla on transaminases has been observed. MBC patients with elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of Kadcyla in the majority of the cases.

Serious hepatobiliary disorders, including fatalities, have been reported including severe drug induced liver injury (with hepatic encephalopathy) and liver failure associated with nodular regenerative hyperplasia (NRH) of the liver. Cases of NRH have been observed in Kadcyla treated patients enrolled in clinical trials of both MBC and EBC. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension. Diagnosis of NRH can be confirmed only by histopathology. NRH should be considered in all patients with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on the computed tomography (CT) scan of the liver but with normal transaminases and no other manifestations of cirrhosis. Upon diagnosis of NRH, Kadcyla treatment must be permanently discontinued.

Liver function should be monitored prior to initiation of treatment and prior to each Kadcyla dose. Dose reductions or discontinuations for increased serum transaminases and total bilirubin are specified in DOSAGE AND ADMINISTRATION: Dose Adjustment.

Kadcyla has not been studied in patients with serum transaminases > 2.5x ULN or total bilirubin > 1.5x ULN prior to initiation of treatment in MBC or in patients with serum transaminases > 1.5x ULN or total bilirubin > 1.0x ULN prior to initiation of treatment in EBC. Kadcyla treatment should be permanently discontinued in patients with serum transaminases > 3x ULN and concomitant total bilirubin > 2x ULN.

Immune

Infusion-Related Reactions
Treatment with Kadcyla has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRRs); treatment with Kadcyla is not recommended for these patients.

Infusion-related reactions, characterized by one or more of the following symptoms - flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia have been reported in clinical trials of Kadcyla. In most patients, these reactions were ≤ Grade 2 and resolved over the course of several hours to a day after the infusion was terminated. Patients should be observed closely for IRRs, especially during the first infusion. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Kadcyla treatment should be interrupted in patients with severe IRR (≥Grade 3). Kadcyla treatment should be permanently discontinued in the event of a life-threatening IRR (see DOSAGE AND ADMINISTRATION: Dose Adjustment).

Hypersensitivity Reactions
Patients should be observed closely for hypersensitivity reactions, especially during the first infusion. Hypersensitivity, including serious, anaphylactic-like reactions, has been observed in clinical trials with treatment of Kadcyla. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

Monitoring and Laboratory Tests

Selection of Patients/Diagnostic Tests
Kadcyla should only be used in patients with HER2 positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH) or by fluorescence in situ hybridization (FISH) assessed by a validated test.

Monitoring
Patients should be assessed prior to starting Kadcyla and monitored throughout treatment with the following assessments. Test results should be within guidelines presented in Tables 1, 2 and 3 found in Section 4.2 of this Product Monograph prior to dosing with appropriate changes to the dosing regimen if required.

Prior to each dose (or if clinically indicated):

- Pregnancy test (if applicable)
- Liver function tests: ALT, AST, total bilirubin
- Hematology: CBC (platelet count)

Every 3 months (or as clinically indicated):

- Left ventricular ejection fraction: either echocardiogram or MUGA

Neurologic

Neurotoxicity
Peripheral neuropathy, predominantly sensory (e.g. numbness, tingling, pain, crawling sensation, pins and needles in hands and feet), has been reported in clinical trials of Kadcyla. Treatment with Kadcyla should be withheld in patients experiencing Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to ≤ Grade 2. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity.

Respiratory

Pulmonary Toxicity
Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical trials with Kadcyla. In MBC, ILD reported as pneumonitis had an incidence of 0.8% (7 out of 884), with one Grade 3 case reported as pneumonitis and one case of Grade 2 pneumonitis which later resulted in Grade 4 Acute Respiratory Distress Syndrome (ARDS) upon rechallenge with Kadcyla. In EBC, pneumonitis was reported at an incidence of 1.1% (8 out of 740 patients treated with KADCYLA), with one case (0.1%) of Grade 3 pneumonitis (see ADVERSE REACTIONS). Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as part of an infusion-related reaction.

Kadcyla may also increase the risk of radiation pneumonitis in EBC patients receiving radiation therapy as part of adjuvant therapy. In the pivotal EBC trial, radiation pneumoinitis was reported at an incidence of 1.8% in Kadcyla treated patients who received radiation therapy (11 out of 623), with two cases of Grade 3 radiation pneumonitis (see ADVERSE REACTIONS).

It is recommended that treatment with Kadcyla be permanently discontinued in patients who are diagnosed with ILD or pneumonitis, except for radiation pneumonitis in the adjuvant EBC setting, where Kadcyla should only be permanently discontinued for ≥ Grade 3 events or when Grade 2 events do not respond to standard treatment (see DOSAGE AND ADMINISTRATION, Dose Adjustments).

Patients with dyspnea at rest due to complications of advanced malignancy or co-morbidities may be at increased risk of pulmonary events when treated with Kadcyla.

Skin (Local) Reactions at Vaccination Sites

Extravasation
In Kadcyla clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. These reactions have been observed more frequently within 24 hours of infusion. Specific treatment for Kadcyla extravasation is unknown at this time. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

8.1 Special Populations

8.1.1 Females and Males of Reproductive Potential

Women of child bearing potential and male partners of female patients of childbearing potential should use at least two effective contraception methods while receiving Kadcyla and for at least 7 months following the last dose of Kadcyla. If pregnancy occurs, the physician should be immediately informed.

8.1.2 Pregnant Women

Kadcyla can cause fetal harm or death when administered to a pregnant woman. No clinical studies of Kadcyla in pregnant women have been performed. No reproductive and developmental toxicology studies have been conducted with Kadcyla.

However, in the post-marketing setting, some pregnant women receiving trastuzumab, the antibody component of Kadcyla, developed oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death. In addition, the mechanism of action of DM1, the microtubule inhibiting cytotoxic drug component of Kadcyla, suggest that DM1 can cause teratogenicity and embryotoxicity.

Kadcyla should not be administered to pregnant women. Women who become pregnant must contact their doctor and should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Kadcyla, close monitoring by a multidisciplinary team is recommended.

The safe use of Kadcyla during labor and delivery has not been established.

8.1.3 Breast-feeding

It is not known whether Kadcyla is excreted in human breast milk. A study conducted in lactating cynomolgus monkeys demonstrated that trastuzumab was secreted in the milk. As human IgG is excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Kadcyla, women should discontinue nursing prior to initiating treatment with Kadcyla. Women may begin nursing 7 weeks following last dose of Kadcyla after concluding treatment.

8.1.4 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

8.1.5 Geriatrics

Geriatrics (≥ 65 to < 75 years of age): Of 495 patients who were randomized to Kadcyla in the pivotal metastatic breast cancer (MBC) study, 65 patients (13%) were ≥ 65 to < 75 years of age. Of the 743 patients who were randomized to Kadcyla in the pivotal EBC study, 58 patients (8%) were ≥ 65 to < 75 years of age. No overall differences in the safety or effectiveness of Kadcyla were observed in patients aged ≥ 65 to < 75 years of age compared to patients < 65 years of age in the MBC or EBC studies.

Geriatrics (≥75 years of age): Only eleven patients (2%) in the pivotal MBC study were ≥ 75 years of age and only two patients (0.3%) in the pivotal EBC study were ≥ 75 years of age. There are insufficient data to establish the safety and efficacy of Kadcyla in patients 75 years of age or older.

8.1.6 Hepatic Impairment

Treatment of patients with hepatic impairment should be undertaken with caution and with increased monitoring of liver function due to known hepatotoxicity observed with Kadcyla (see WARNINGS AND PRECAUTIONS: Hepatotoxicity).

8.1.7 Ethnic origin

In the pivotal EBC study, Grade ≥ 3 thrombocytopenia occurred in 12 of 64 Asian patients (18.8%) and in 30 of 676 (4.4%) non-Asian patients treated with Kadcyla and serious adverse events of thrombocytopenia occurred in 5 of 64 (7.8%) Asian patients and in 5 of 676 (0.7%) non-Asian patients.

In EBC, the incidence of hemorrhage events with trastuzumab emtansine was moderately higher in Asian patients (37.5% vs 28.4%), while the incidence of severe (Grade ≥ 3) hemorrhage events and serious hemorrhage events with trastuzumab emtansine was very low irrespective of the race, with occurrence limited to a single Asian patient. In the MBC population, the incidence of hemorrhages was similar in Asian and in non-Asian patients. This includes severe (Grade ≥ 3), serious and fatal hemorrhages, where no difference between Asian and non-Asian patients was noted.

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

The most common adverse reactions (≥ 10%) with Kadcyla in MBC were nausea, musculoskeletal pain, fatigue, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, diarrhea, epistaxis, anemia, peripheral neuropathy, arthralgia, vomiting, pyrexia, abdominal pain, cough, asthenia, dry mouth, myalgia, stomatitis, insomnia, rash, dyspnea, urinary tract infection, dizziness, and hypokalemia.

The most common adverse reactions (≥ 10%) with Kadcyla in EBC were fatigue, nausea, increased transaminases, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, peripheral neuropathy, arthralgia, epistaxis, constipation, myalgia, stomatitis, vomiting, insomnia, dry mouth, cough, diarrhea, abdominal pain, pyrexia, urinary tract infection, and anemia.

The most common serious adverse reactions (≥ 1%) with Kadcyla in MBC were vomiting and pyrexia. The most common serious adverse reactions (≥ 1%) with Kadcyla in EBC were mastitis and thrombocytopenia.

Deaths have occurred in clinical studies with Kadcyla (see later in this section, Additional Information on Selected Adverse Reactions). Dose modification guidelines for Kadcyla patients with increased transaminases, hyperbilirubinemia, drug induced liver injury, nodular regenerative hyperplasia, thrombocytopenia, left ventricular dysfunction, heart failure,

peripheral neuropathy, pulmonary toxicity, and radiotherapy related pneumonitis are described (see DOSAGE AND ADMINISTRATION, Dosage Adjustment).

9.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Metastatic Breast Cancer

The safety of Kadcyla (trastuzumab emtansine) has been evaluated in more than 880 patients in clinical trials. Table 5 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Kadcyla in the pivotal study TDM4370g/BO21977 (EMILIA). Table 7 summarizes the adverse reactions that have been reported in association with the use of Kadcyla across MBC clinical trials.

Table 5 Summary of ADRs Occurring in ≥ 1% of Patients on the Kadcyla Treatment Arm in the Randomized Study TDM4370g/BO21977 (EMILIA)

Adverse Drug Reactions (MedDRA) System Organ Class	Kadcyla (3.6 mg/kg) n=490 Frequency %		Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488 Frequency %	
	All grades n (%)	Grade 3 – 4 n (%)	All grades n (%)	Grade 3 – 4 n (%)
Blood and Lymphatic System Disorders				
Thrombocytopenia	154 (31.4)	73 (14.9)	16 (3.3)	2 (0.4)
Anemia	72 (14.7)	22 (4.5)	51 (10.5)	12 (2.5)
Neutropenia	37 (7.6)	11 (2.2)	53 (10.9)	22 (4.5)
Leukopenia	21 (4.3)	5 (1.0)	23 (4.7)	6 (1.2)
Cardiac Disorders				
Left ventricular dysfunction	10 (2.0)	1 (0.2)	16 (3.3)	2 (0.4)
Eye Disorders				
Vision blurred	22 (4.5)	0	4 (0.8)	0
Conjunctivitis	20 (4.1)	0	11 (2.3)	0
Dry eye	20 (4.1)	0	15 (3.1)	0
Lacrimation increased	16 (3.3)	0	12 (2.5)	0
Gastrointestinal Disorders				
Nausea	196 (40.0)	4 (0.8)	221 (45.3)	12 (2.5)
Constipation	131 (26.7)	2 (0.4)	55 (11.3)	0.0
Diarrhea	122 (24.9)	9 (1.8)	390 (79.9)	102 (20.9)
Vomiting	94 (19.2)	4 (0.8)	146 (29.9)	22 (4.5)
Abdominal pain	91 (18.6)	4 (0.8)	86 (17.6)	8 (1.6)
Dry Mouth	82 (16.7)	0	24 (4.9)	1 (0.2)
Stomatitis	69 (14.1)	1 (0.2)	160 (32.8)	12 (2.4)
Dyspepsia	45 (9.2)	0	56 (11.5)	2 (0.4)
Gingival bleeding	21 (4.3)	0	7 (1.4)	0

Adverse Drug Reactions (MedDRA) System Organ Class	Kadcyla (3.6 mg/kg) n=490 Frequency %		Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488 Frequency %	
	All grades n (%)	Grade 3 – 4 n (%)	All grades n (%)	Grade 3 – 4 n (%)
General Disorders and Administration Site Conditions				
Fatigue	179 (36.5)	12 (2.4)	138(28.3)	17 (3.5)
Pyrexia	91 (18.6)	1 (0.2)	41 (8.4)	2 (0.4)
Asthenia	88 (18.0)	2 (0.4)	87 (17.8)	8 (1.6)
Chills	38 (7.8)	0	15 (3.1)	0
Peripheral edema	35 (7.1)	0	40 (8.2)	1 (0.2)
Immune System Disorders				
Drug hypersensitivity	11 (2.2)	0	4 (0.8)	0
Infections and Infestations				
Urinary tract infection	58 (11.8)	3 (0.6)	24 (4.9)	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	7 (1.4)	0	1 (0.2)	0
Investigations				
Increased transaminases	141 (28.8)	39 (8.0)	70 (14.3)	12 (2.5)
Blood alkaline phosphatase increased	23 (4.7)	2 (0.4)	18 (3.7)	2 (0.4)
Metabolism and Nutrition Disorders				
Hypokalemia	50 (10.2)	13 (2.7)	48 (9.8)	23 (4.7)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain	182 (37.1)	9 (1.8)	150 (30.7)	7 (1.4)
Arthralgia	96 (19.6)	3 (0.6)	43 (8.8)	0
Myalgia	69 (14.1)	3 (0.6)	18 (3.7)	0
Nervous System Disorders				
Headache	140 (28.6)	4 (0.8)	72 (14.8)	4 (0.8)
Peripheral neuropathy	106 (21.6)	12 (2.4)	66 (13.5)	1 (0.2)
Dizziness	52 (10.6)	2 (0.4)	53 (10.9)	1 (0.2)
Dysgeusia	40 (8.2)	0	20 (4.1)	1 (0.2)
Psychiatric Disorders				
Insomnia	60 (12.2)	2 (0.4)	43 (8.8)	1 (0.2)
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	113 (23.1)	1 (0.2)	41 (8.4)	0
Cough	90 (18.4)	1 (0.2)	64 (13.1)	1 (0.2)
Dyspnea	58 (11.8)	4 (0.8)	39 (8.0)	2 (0.4)
Pneumonitis	6 (1.2)	0	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	58 (11.8)	0	134 (27.5)	10 (2.0)
Pruritus	27 (5.5)	1 (0.2)	46 (9.4)	0
Alopecia	17 (3.5)	0	22 (4.5)	0
Nail disorder	14 (2.9)	0	45 (9.2)	3 (0.6)
Palmar−plantar erythrodysaesthesia syndrome	7 (1.4)	0	288 (59.0)	86 (17.6)

Adverse Drug Reactions (MedDRA) System Organ Class	Kadcyla (3.6 mg/kg) n=490 Frequency %		Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488 Frequency %	
	All grades n (%)	Grade 3 – 4 n (%)	All grades n (%)	Grade 3 – 4 n (%)
Urticaria	5 (1.0)	0	7 (1.4)	5 (1.0)
Vascular Disorders				
Hemorrhage	163 (33.3)	10 (2.0)	81 (16.6)	4 (0.8)
Hypertension	26 (5.3)	6 (1.2)	11 (2.3)	2 (0.4)

Table 6 Summary of Selected Adverse Events* (AEs) Occurring with an Overall ≥2% Higher Incidence in Patients within the Kadcyla Treatment Arm Compared to the Lapatinib + Capecitabine Treatment Arm in the Randomized Study TDM4370g/BO21977 (EMILIA)

Selected Adverse Event Category MedDRA Preferred Term	Kadcyla (3.6 mg/kg) n=490 Frequency %	Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488 Frequency %
	All grades n (%)	All grades n (%)
Eye Disorders		
-Overall-	36 (7.3)	11 (2.3)
Vision Blurred	22 (4.5)	4 (0.8)
Visual Impairment	7 (1.4)	2 (0.4)
Visual Acuity Reduced	4 (0.8)	3 (0.6)
Photopsia	2 (0.4)	0
Amblyopia	1 (0.2)	0
Blindness Transient	1 (0.2)	0
Diplopia	0	1 (0.2)
Optic Neuropathy	1 (0.2)	0
Scintillating Scotoma	0	1 (0.2)
Hemorrhage		
-Overall-	163 (33.3)	81 (16.6)
Epistaxis	113 (23.1)	41 (8.4)
Gingival Bleeding	21 (4.3)	7 (1.4)
Vaginal Hemorrhage	13 (2.7)	9 (1.8)
Contusion	8 (1.6)	5 (1.0)
Rectal Hemorrhage	8 (1.6)	5 (1.0)
Petechiae	12 (2.4)	0
Hematochezia	6 (1.2)	4 (0.8)
Menorrhagia	3 (0.6)	4 (0.8)
Metrorrhagia	5 (1.0)	2 (0.4)
Hematoma	6 (1.2)	0
Hemoptysis	4 (0.8)	2 (0.4)
Ecchymosis	5 (1.0)	0
Hemorrhoidal Hemorrhage	1 (0.2)	3 (0.6)
Skin Hemorrhage	2 (0.4)	2 (0.4)

Selected Adverse Event Category MedDRA Preferred Term	Kadcyla (3.6 mg/kg) n=490 Frequency %	Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488 Frequency %
	All grades n (%)	**All grades n (%)**
Gastrointestinal Hemorrhage	2 (0.4)	0
Hemorrhage	1 (0.2)	1 (0.2)
Lip Hemorrhage	1 (0.2)	1 (0.2)
Mouth Hemorrhage	2 (0.4)	0
Tongue Hemorrhage	2 (0.4)	0
Anal Hemorrhage	0	1 (0.2)
Conjunctival Hemorrhage	1 (0.2)	0
Cystitis Hemorrhage	0	1 (0.2)
Extradural Hematoma	0	1 (0.2)
Genital Hemorrhage	0	1 (0.2)
Hematemesis	0	1 (0.2)
Hematuria	0	1 (0.2)
Hemorrhagic Diathesis	1 (0.2)	0
Intestinal Hemorrhage	1 (0.2)	0
Nail Bed Bleeding	0	1 (0.2)
Nipple Exudate Bloody	0	1 (0.2)
Pelvic Hematoma	1 (0.2)	0
Peptic Ulcer Hemorrhage	0	1 (0.2)
Post Procedural Hematoma	1 (0.2)	0
Post Procedural Hemorrhage	1 (0.2)	0
Purpura	0	1 (0.2)
Subdural Hemorrhage	0	1 (0.2)
Tumour Hemorrhage	0	1 (0.2)
Ulcer Hemorrhage	1 (0.2)	0
Upper Gastrointestinal Hemorrhage	1 (0.2)	0
Uternine Hemorrhage	1 (0.2)	0
Wound Hemorrhage	0	1 (0.2
Hepatotoxicity		
-Overall-	159 (32.4)	128 (26.2)
Aspartate Aminotransferase Increased	113 (23.1)	49 (10.0)
Alanine Aminotransferase Increased	87 (17.8)	45 (9.2)
Hyperbilirubinemia	8 (1.6)	44 (9.0)
Blood Bilirubin Increased	15 (3.1)	31 (6.4)
Blood Alkaline Phosphatase Increased	23 (4.7)	18 (3.7)
Transaminases Increased	16 (3.3)	5 (1.0)
Gamma−Glutamyltransferase Increased	10 (2.0)	0
Hypoalbuminemia	4 (0.8)	4 (0.8)
Liver Function Test Abnormal	4 (0.8)	3 (0.6)
Cytolytic Hepatitis	3 (0.6)	3 (0.6)
Jaundice	0	4 (0.8)

Selected Adverse Event Category MedDRA Preferred Term	Kadcyla (3.6 mg/kg) n=490 Frequency %	Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488 Frequency %
	All grades n (%)	**All grades n (%)**
Hepatic Enzyme Increased	2 (0.4)	1 (0.2)
Hepatic Pain	3 (0.6)	0
Portal Hypertension	2 (0.4)	0
Spider Naevus	2 (0.4)	0
Aspartate Aminotransferase Abnormal	1 (0.2)	0
Hepatic Function Abnormal	0	1 (0.2)
Hepatitis Toxic	1 (0.2)	0
Hepatotoxicity	1 (0.2	0
Hypertransaminasemia	0	1 (0.2)
IRR Hypersensitivity		
-Overall-	21 (4.3)	0
Hypersensitivity	7 (1.4)	0
Infusion Related Reaction	7 (1.4)	0
Face Edema	3 (0.6)	0
Urticaria	2 (0.4)	0
Eye Edema	1 (0.2)	0
Pharyngeal Edema	1 (0.2)	0
Peripheral Neuropathy		
-Overall-	127 (25.9)	92 (18.9)
Neuropathy Peripheral	53 (10.8)	28 (5.7)
Peripheral Sensory Neuropathy	32 (6.5)	26 (5.3)
Paraesthesia	31 (6.3)	18 (3.7)
Hypoaesthesia	14 (2.9)	9 (1.8)
Muscular Weakness	6 (1.2)	11 (2.3)
Neurotoxicity	6 (1.2)	2 (0.4)
Peripheral Motor Neuropathy	5 (1.0)	2 (0.4)
Burning Sensation	3 (0.6)	2 (0.4)
Polyneuropathy	4 (0.8)	1 (0.2)
Gait Disturbance	1 (0.2)	3 (0.6)
Neuralgia	3 (0.6)	1 (0.2)
Sensory Disturbance	1 (0.2)	3 (0.6)
Dyaesthesia	1 (0.2)	1 (0.2)
Formication	2 (0.4)	0
Motor Dysfunction	1 (0.2)	1 (0.2)
Areflexia	1 (0.2)	0
Hypotonia	0	1 (0.2)
Skin Burning sensation	0	1 (0.2)
Thrombocytopenia		
-Overall-	155 (31.6)	16 (3.3)
Thrombocytopenia	143 (29.2)	14 (2.9)
Platelet Count Decreased	14 (2.9)	3 (0.6)
Platelet Disorder	1 (0.2)	0

*Adverse Event – defined as an event reported regardless of causality

Table 7 Summary of ADRs occurring in ≥1% of MBC patients treated with Kadcyla

ADR (MedDRA)	Kadcyla	
System Organ Class	**All grades n (%) n = 884**	**Grade 3 – 5 n (%) n = 884**
Blood and Lymphatic System Disorders		
Thrombocytopenia	284 (32.1)	105 (11.9)
Anemia	153 (17.3)	31 (3.5)
Neutropenia	68 (7.7)	19 (2.1)
Leukopenia	46 (5.2)	5 (0.6)
Cardiac Disorders		
Left ventricular dysfunction	19 (2.1)	3 (0.3)
Eye Disorders		
Dry eye	51 (5.8)	0
Lacrimation increased	42 (4.8)	0
Vision blurred	45 (5.1)	0
Conjunctivitis	37 (4.2)	0
Gastrointestinal Disorders		
Nausea	380 (43.0)	10 (1.1)
Constipation	234 (26.5)	5 (0.6)
Vomiting	185 (20.9)	8 (0.9)
Diarrhea	188 (21.3)	9 (1.0)
Dry Mouth	165 (18.7)	0
Abdominal pain	166 (18.8)	8 (0.9)
Stomatitis	133 (15.0)	1 (0.1)
Dyspepsia	82 (9.3)	1 (0.1)
Gingival bleeding	31 (3.5)	0
General Disorders and Administration Site Conditions		
Fatigue	410 (46.4)	28 (3.2)
Pyrexia	209 (23.6)	3 (0.3)
Asthenia	125 (14.1)	8 (0.9)
Chills	95 (10.7)	0
Edema peripheral	81 (9.2)	1 (0.1)
Immune System Disorders		
Drug hypersensitivity	25 (2.8)	0
Infections and Infestations		
Urinary tract infection	122 (13.8)	3 (0.3)
Injury, Poisoning, and Procedural Complications		
Infusion related reaction	40 (4.5)	1 (0.1)
Investigations		
Transaminases increased	253 (28.6)	64 (7.2)
Blood alkaline phosphatase increased	57 (6.4)	4 (0.5)
Metabolism and Nutrition Disorders		
Hypokalemia	142 (16.1)	29 (3.3)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	361 (40.8)	28 (3.2)
Arthralgia	178 (20.1)	8 (0.9)
Myalgia	110 (12.4)	3 (0.3)

ADR (MedDRA)	Kadcyla	
System Organ Class	**All grades n (%) n = 884**	**Grade 3 – 5 n (%) n = 884**
Nervous System Disorders		
Headache	260 (29.4)	5 (0.6)
Peripheral neuropathy	199 (22.5)	15 (1.7)
Dizziness	88 (10.0)	3 (0.3)
Dysgeusia	70 (7.9)	0
Memory impairment	12 (1.4)	1 (0.1)
Psychiatric Disorders		
Insomnia	105 (11.9)	2 (0.2)
Respiratory, Thoracic, and Mediastinal Disorders		
Epistaxis	223 (25.2)	4 (0.5)
Cough	181 (20.5)	1 (0.1)
Dyspnea	131 (14.8)	13 (1.5)
Skin and Subcutaneous Tissue Disorders		
Rash	115 (13.0)	0
Pruritus	49 (5.5)	1 (0.1)
Alopecia	33 (3.7)	0
Nail disorder	26 (2.9)	0
Palmar−plantar erythrodysaesthesia syndrome	11 (1.2)	0
Urticaria	10 (1.1)	0
Vascular Disorders		
Hemorrhage	323 (36.5)	18 (2.0)
Hypertension	58 (6.6)	9 (1.0)

Early Breast Cancer

The safety of Kadcyla has been evaluated in 740 patients with EBC in Study BO27938 (KATHERINE) treated in the adjuvant setting with up to 14 cycles of Kadcyla. The patients enrolled on study had residual invasive disease following neoadjuvant trastuzumab and taxane-based therapy.

Table 8 summarizes the ADRs that have been reported in association with the use of Kadcyla in the pivotal study BO27938 (KATHERINE).

Table 8 Summary of ADRs Occurring in ≥ 1% of Patients on the Kadcyla Treatment Arm in the Randomized Study BO27938 (KATHERINE)

Adverse Drug Reactions (MedDRA) System Organ Class	Kadcyla (3.6 mg/kg) n=740 Frequency %		Trastuzumab (6 mg/kg) n=720 Frequency%	
	All grades n (%)	Grade 3 – 4 n (%)	All grades n (%)	Grade 3 – 4 n (%)
Blood and Lymphatic System Disorders				
Thrombocytopenia	211 (28.5)	42 (5.7)	17 (2.4)	2 (0.3)
Anemia	75 (10.1)	8 (1.1)	62 (8.6)	1 (0.1)
Neutropenia	61 (8.2)	9 (1.2)	36 (5.0)	5 (0.7)
Leukopenia	61 (8.2)	0	42 (5.8)	1 (0.1)
Cardiac Disorders				
Left ventricular dysfunction	22 (3.0)	4 (0.5)	35 (4.9)	7 (1.0)
Eye Disorders				
Lacrimation increased	41 (5.5)	0	13 (1.8)	0
Dry eye	33 (4.5)	0	16 (2.2)	0
Vision Blurred	29 (3.9)	0	17 (2.4)	0
Conjunctivitis	26 (3.5)	0	14 (1.9)	0
Gastrointestinal Disorders				
Nausea	308 (41.6)	4 (0.5)	94 (13.1)	2 (0.3)
Diarrhea	91 (12.3)	6 (0.8)	90 (12.5)	2 (0.3)
Constipation	126 (17.0)	1 (0.1)	59 (8.2)	0
Stomatitis	112 (15.1)	1 (0.1)	57 (7.9)	1 (0.1)
Vomiting	108 (14.6)	4 (0.5)	37 (5.1)	2 (0.3)
Abdominal pain	79 (10.7)	3 (0.4)	49 (6.8)	2 (0.3)
Dry Mouth	100 (13.5)	1 (0.1)	9 (1.3)	0
Dyspepsia	32 (4.3)	0	26 (3.6)	0
Gingival bleeding	9 (1.2)	0	1 (0.1)	0
General Disorders and Administration Site Conditions				
Fatigue	366 (49.5)	8 (1.1)	243(33.8)	1 (0.1)
Pyrexia	77 (10.4)	0	29 (4.0)	0
Peripheral edema	29 (3.9)	0	52 (7.2)	0
Chills	39 (5.3)	0	14 (1.9)	0
Immune System Disorders				
Drug hypersensitivity	20 (2.7)	3 (0.4)	15 (2.1)	1 (0.1)
Infections and Infestations				
Urinary tract infection	77 (10.4)	2 (0.3)	44 (6.1)	1 (0.1)
Injury, Poisoning, and Procedural Complications				
Radiation Pneumonitis	11 (1.5)	2 (0.3)	5 (0.7)	0
Infusion-related reaction	12 (1.6)	0	4 (0.6)	0
Investigations				
Increased transaminases	240 (32.4)	11 (1.5)	57 (7.9)	3 (0.4)
Blood alkaline phosphatase increased	61 (8.2)	1 (0.1)	13 (1.8)	0

Adverse Drug Reactions (MedDRA) System Organ Class	Kadcyla (3.6 mg/kg) n=740 Frequency %		Trastuzumab (6 mg/kg) n=720 Frequency%	
	All grades n (%)	Grade 3 – 4 n (%)	All grades n (%)	Grade 3 – 4 n (%)
Blood Bilirubin Increased	49 (6.6)	0	2 (0.3)	0
Metabolism and Nutrition Disorders				
Hypokalemia	50 (6.8)	9 (1.2)	14 (1.9)	1 (0.1)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain	225 (30.4)	5 (0.7)	209 (29.0)	5 (0.7)
Arthralgia	192 (25.9)	1 (0.1)	148 (20.6)	0
Myalgia	114 (15.4)	0	80 (11.1)	0
Nervous System Disorders				
Headache	210 (28.4)	0	122 (16.9)	1 (0.1)
Peripheral neuropathy	207 (28.0)	12 (1.6)	102 (14.2)	1 (0.1)
Dizziness	70 (9.5)	1 (0.1)	57 (7.9)	2 (0.3)
Dysgeusia	60 (8.1)	0	11 (1.5)	0
Psychiatric Disorders				
Insomnia	101 (13.6)	0	86 (11.9)	1 (0.1)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	100 (13.5)	1 (0.1)	86 (11.9)	0
Epistaxis	159 (21.5)	0	25 (3.5)	0
Dyspnea	62 (8.4)	1 (0.1)	53 (7.4)	0
Pneumonitis	8 (1.1)	1 (0.1)	1 (0.1)	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	51 (6.9)	0	42 (5.8)	1 (0.1)
Alopecia	18 (2.4)	0	7 (1.0)	0
Urticaria	9 (1.2)	0	6 (0.8)	1 (0.1)
Rash	8 (1.1)	0	7 (1.0)	0
Palmar−plantar erythrodysaesthesia syndrome	8 (1.1)	0	6 (0.8)	0
Vascular Disorders				
Hemorrhage	216 (29.2)	2 (0.3)	69 (9.6)	2 (0.3)
Hypertension	42 (5.7)	15 (2.0)	35 (4.9)	9 (1.3)

9.3 Less Common Clinical Trial Adverse Reactions

The following significant adverse reactions were reported at an incidence of < 1%:

Metastatic Breast Cancer
Hepatobiliary Disorders: Hepatic Failure (0.1%), Hepatoxicity (0.3%), Nodular Regenerative Hyperplasia (0.1%), Portal Hypertension (0.1%)
Respiratory, Thoracic, and Mediastinal Disorders: Pneumonitis (0.9%)

Early Breast Cancer
Nervous System Disorders: Memory Impairment (0.9%)
General Disorders and Administration: Asthenia (0.4%)
Skin and Subcutaneous Tissue Disorder: Nail Disorder (0.3%)
Hepatobiliary Disorders: Nodular Regenerative Hyperplasia (0.3%)

9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Metastatic Breast Cancer

The following table displays laboratory abnormalities observed in patients treated with Kadcyla in clinical trial TDM4370g/BO21977 (EMILIA).

Table 9 Laboratory abnormalities observed in patients in study TDM4370g/BO21977 (EMILIA)

Parameter	Kadcyla (3.6 mg/kg)			Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2)		
	All grade n (%)	Grade 3 n (%)	Grade 4 n (%)	All grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematologic						
Decreased platelet count	407 (84)	69 (14)	15 (3)	101 (21)	2 (<1)	3 (<1)
Decreased hemoglobin	300 (62)	20 (4)	5 (1)	312 (64)	14 (3)	1 (<1)
Decreased neutrophils	186 (39)	17 (4)	3 (<1)	184 (38)	30 (6)	10 (2)
Hepatic						
Increased bilirubin	95 (20)	3 (<1)	0 (0)	276 (57)	11 (2)	0 (0)
Increased AST	475 (98)	35 (7)	2 (<1)	311 (65)	12 (3)	0 (0)
Increased ALT	397 (82)	23 (5)	1 (<1)	259 (54)	14 (3)	0 (0)
Potassium						
Decreased potassium	148 (34)	14 (3)	1 (<1)	132 (31)	26 (6)	4 (<1)

Early Breast Cancer

The following table displays laboratory abnormalities observed in patients treated with Kadcyla in clinical trial BO27938 (KATHERINE).

Table 10 Laboratory abnormalities observed in patients in Study BO27938 (KATHERINE)

Parameter	Kadcyla			Trastuzumab		
	All grade n (%)	Grade 3 n (%)	Grade 4 n (%)	All grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Hepatic						
Increased Bilirubin	85 (12)	0	0	26 (4)	2 (<1)	3 (<1)
Increased AST	583 (79)	6 (<1)	0	153 (21)	14 (3)	1 (<1)
Increased ALT	409 (55)	409 (<1)	0	150 (21)	30 (6)	10 (2)
Hematologic						
Decreased Platelets	347 (51)	29 (4)	16 (2)	92 (13)	11 (2)	0 (0)
Decreased Hemoglobin	229 (31)	8 (1)	0	206 (29)	12 (3)	0 (0)
Decreased Neutrophils	174 (24)	10 (1)	0	133 (19)	14 (3)	0 (0)
Potassium						
Decreased Potassium	191 (26)	15 (2)	4 (<1)	68 (9)	26 (6)	4 (<1)

Additional Information on Selected Adverse Reactions

Death
In the metastatic setting, five deaths (1%) due to reasons other than progressive disease occurred in each arm of the pivotal trial. In the Kadcyla arm, four of the five patients had neutropenic sepsis/infection, pneumonia or metabolic encephalopathy, and died between 21-35 days after the last dose of Kadcyla. In the lapatinib and capecitabine arm, the five deaths were due to coronary artery disease, multi-organ failure, coma, hydrocephalus or acute respiratory distress syndrome. In the other Kadcyla MBC clinical trials, two patients treated with Kadcyla died of an unknown cause while nine additional patients had AEs leading to death. These patients had hepatic failure, abnormal hepatic function, bacterial sepsis, respiratory failure, interstitial lung disease or sudden death. Fatal cases of hepatic failure, abnormal hepatic function and metabolic encephalopathy are also described in the WARNINGS and PRECAUTIONS: Hepatotoxicity

In the EBC setting, one fatal AE (intracranial hemorrhage) occurred with Kadcyla. There were 5 deaths which occurred more than 30 days after the last study treatment and were not related to study treatment or study procedures due to reasons other than progressive disease. In the Kadcyla arm, one death was due to cerebrovascular event with renal insufficiency and another reported as death after osteosynthesis. In the trastuzumab arm, two deaths were due to pneumonia and one due to a cerebrovascular event.

Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response to Kadcyla. A total of 1243 patients from seven clinical studies were tested at multiple time points for anti-drug antibody (ADA) responses to Kadcyla. Following Kadcyla dosing, 5.1% (63/1243) of patients tested positive for anti-Kadcyla antibodies at one or more post-dose time points. In the Phase I and Phase II studies, 6.4% (24/376) of patients tested positive for anti-Kadcyla antibodies. In the EMILIA study (TDM4370g/BO21977), 5.2% (24/466) of patients tested positive for anti-Kadcyla antibodies, of which 13 patients also tested positive for neutralizing antibodies. In the KATHERINE (BO27938) study, 3.7% (15/401) of patients tested positive for anti-Kadcyla antibodies, of which 5 patients also tested positive for neutralizing antibodies. Due to the low incidence of ADA, conclusions cannot be made on the impact of anti-Kadcyla antibodies on the pharmacokinetics, safety, and efficacy of Kadcyla.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to Kadcyla with the incidence of antibodies to other products may be misleading.

9.5 Post-Market Adverse Reactions

No new ADRs have been identified in the post-market setting.

10 DRUG INTERACTIONS

10.1 Drug-Drug Interactions

No formal drug-drug interaction studies with Kadcyla (trastuzumab emtansine) in humans have been conducted. *In vitro* metabolism studies in human liver microsomes suggest that DM1, the cytotoxic component of Kadcyla (trastuzumab emtansine), is metabolized mainly by CYP3A4 and, to a lesser extent, by CYP3A5. DM1 does not induce or inhibit P450-mediated

metabolism *in vitro*. Caution should be taken when Kadcyla is co-administered with potent CYP3A inhibitors.

Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with Kadcyla should be avoided due to the potential for an increase in DM1 exposure and toxicity. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying Kadcyla treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is co-administered and Kadcyla treatment cannot be delayed, patients should be closely monitored for adverse reactions.

10.2 Drug-Food Interactions

Interactions with food have not been established.

10.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.4 Drug-Laboratory Test Interactions

No drug-laboratory interactions have been established.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Kadcyla, trastuzumab emtansine, is a HER2-targeted antibody-drug conjugate which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex. An average of 3.5 DM1 molecules are conjugated to each molecule of trastuzumab. Conjugation of DM1 to trastuzumab confers selectivity of the cytotoxic agent for HER2-overexpressing tumour cells, thereby increasing intracellular delivery of DM1 directly to malignant cells. Upon binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).

Kadcyla has the mechanisms of action of both trastuzumab and DM1

- Trastuzumab emtansine, like trastuzumab, binds to domain IV of the HER2 extracellular domain (ECD), as well as to Fcγ receptors and complement C1q. In addition, Kadcyla, like trastuzumab, inhibits shedding of the HER2 ECD, inhibits signaling through the phosphatidylinositol 3-kinase (PI3-K) pathway, and mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in human breast cancer cells that overexpress HER2.
- DM1, the cytotoxic drug component of Kadcyla, binds to tubulin. By inhibiting tubulin polymerization, DM1 causes cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death. Results from *in vitro* cytotoxicity assays show that DM1 is 20-200 times more potent than taxanes and vinca alkaloids.

- The MCC linker is designed to limit systemic release and increase targeted delivery of DM1, as demonstrated by detection of very low levels of free DM1 in plasma.

11.2 Pharmacodynamics

The anti-tumor activity of trastuzumab emtansine was evaluated in HER2-overexpressing human breast cancer cells *in vitro* and in mouse tumor xenograft models. In trastuzumab-sensitive cancer cells, trastuzumab emtansine is more potent than trastuzumab both *in vitro* and *in vivo*. Moreover, both trastuzumab-insensitive and lapatinib-resistant breast cancer cells are highly sensitive to trastuzumab emtansine. In preclinical studies, trastuzumab emtansine was demonstrated to retain therapeutic properties of trastuzumab such as inhibition of HER2 extracellular domain shedding, suppression of HER2-activated signaling pathways, and mediation of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, the direct effect of trastuzumab is cytostasis due to arrest of cells in the G1 cell cycle phase, with no induction of cell death. As expected of an anti-mitotic agent, treatment with trastuzumab emtansine results in mitotic (G2/M phase) arrest, apoptosis (programmed cell death) and cellular lysis in HER2-overexpressing breast cancer cells.

11.3 Pharmacokinetics

The population pharmacokinetic analysis of trastuzumab emtansine suggested no difference in Kadcyla exposure based on disease status (adjuvant vs. metastatic setting).

Absorption: Kadcyla is administered intravenously. There have been no studies performed with other routes of administration.

Distribution: In the phase I study TDM3569g and the phase III study BO27938, Kadcyla when administered intravenously every 3 weeks exhibited linear pharmacokinetics (i.e., linear increase of C_{max} and AUC_{inf}) across doses ranging from 2.4 to 4.8 mg/kg; patients who received doses less than or equal to 1.2 mg/kg had faster clearance. Patients in Study TDM4370g/BO21977 and Study BO27938 who received 3.6 mg/kg of Kadcyla intravenously every 3 weeks had a mean (±SD) maximum serum concentration (C_{max}) of trastuzumab emtansine in Cycle 1 of 83.4 (±16.5) μg/mL (n=292) and 72.6 (± 24.3) μg/mL, respectively. The mean steady-state volume of distribution (Vss) in patients who received 3.6 mg/kg of Kadcyla every 3 weeks ranged from 28.4 to 58.4 mL/kg across six Phase I/II/III clinical studies.

Metabolism: Kadcyla is expected to undergo catabolism by means of proteolysis in cellular lysosomes, with no significant involvement of cytochrome P450 isoenzymes. Catabolites including Lys-MCC-DM1, MCC-DM1 and DM1 are detected at low levels in human plasma. In Study TDM4370g/BO21977 and Study BO27938, mean (±SD) maximum DM1 levels in Cycle 1 following Kadcyla administration were consistently low and averaged 4.61 (± 1.61) ng/mL (n=287) and 4.71 (± 2.25) ng/mL, respectively.

In vitro metabolism studies in human liver microsomes suggest that DM1, a component of trastuzumab emtansine, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5.

Excretion: The pharmacokinetics of Kadcyla when administered intravenously at 3.6 mg/kg every three weeks were similar in HER2-positive metastatic breast cancer patients across the six clinical studies. The mean clearance ranged from 7 to 13 mL/day/kg and the estimated mean terminal half-life ranged from 3.1 to 4.5 days across the six studies. No accumulation of trastuzumab emtansine was observed after repeated dosing of IV infusion every 3 weeks.

The body weight based dose of 3.6 mg/kg every 3 weeks is considered appropriate based on efficacy and safety data observed in the clinical studies.

In nonclinical studies, catabolites of trastuzumab emtansine including DM1, Lys-MCC-DM1, and MCC-DM1 are mainly excreted in the bile with minimal elimination in urine.

Special Populations and Conditions

Geriatrics* (≥65 years of age)*: Analysis of the key PK parameters of trastuzumab emtansine (i.e., CL, Vss, AUC_{inf}, and C_{max}) for patients who received 3.6 mg/kg every 3 weeks across the six studies showed that age (<65 (n=532); 65-75 (n= 72); >75 (n=17)) did not have a clinical meaningful effect on the pharmacokinetics of Kadcyla.

Sex: Because most of the patients in Kadcyla clinical studies were females, effect of gender on the pharmacokinetics of Kadcyla was not formally evaluated.

Ethnic origin: Ethnic origin did not appear to influence the pharmacokinetics of Kadcyla. The key PK parameters of Kadcyla (i.e., CL, Vss, AUC_{inf}, and C_{max}) when administered at 3.6 mg/kg every 3 weeks in White patients (n=489) were comparable to those in Asian patients (n=70).

Hepatic Insufficiency: The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of Kadcyla to metastatic HER2-positive breast cancer patients with normal hepatic function (n=10), mild (Child-Pugh A; n=10) and moderate (Child-Pugh B; n=8) hepatic impairment.

- Plasma concentrations of DM1 and DM1-containing catabolites (Lys-MCC-DM1 and MCC-DM1) were low and variable between patients with and without hepatic impairment. AUC for DM1 and DM1-containing catabolites has not been determined as most of the measured concentrations are below assay quantitation limits.
- Systemic exposures (AUC) of trastuzumab emtansine at Cycle 1 in patients with mild and moderate hepatic impairment were approximately 38% and 67% lower than that of patients with normal hepatic function, respectively. Trastuzumab emtansine exposure (AUC) at Cycle 3 after repeated dosing in patients with mild hepatic dysfunction was 14% lower compared to patients with normal hepatic function. There are insufficient data to characterize trastuzumab emtansine exposure beyond Cycle 1 in patients with moderate hepatic impairment.

No formal pharmacokinetic study has been conducted and no population PK data was collected in patients with severe hepatic impairment (Child-Pugh class C).

Renal Insufficiency: The key PK parameters of trastuzumab emtansine (i.e., CL, Vss, AUC_{inf}, and C_{max}) when administered at 3.6 mg/kg every 3 weeks in patients with mild (creatinine clearance CLcr 60-89 mL/min, n=237) and moderate (CLcr 30 to 59 mL/min, n=45) renal

impairment were similar to those in patients with normal renal function (CLcr ≥90 mL/min, n=337). Pharmacokinetic data in patients with severe renal impairment (CLcr 15-29 mL/min) is limited (n=1), therefore no dosage recommendations can be made.

12 STORAGE, STABILITY AND DISPOSAL

Storage of Vials:
Store unreconstituted vials at 2–8°C.

This medicine should not be used after the expiry date (EXP) shown on the pack.

Shelf-life of the reconstituted solution:
Product vials reconstituted with sterile water for injection should be used immediately following reconstitution. If not used immediately, the reconstituted vials can be stored for up to 24 hours at 2-8°C, and must be discarded thereafter.

Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product:
The reconstituted Kadcyla solution diluted in polyvinyl chloride (PVC) or latex-free PVC-free polyolefin bags containing 0.9% Sodium Chloride Injection, or 0.45% Sodium Chloride Injection, may be stored at 2–8°C for up to 24 hours prior to use. This storage time is in addition to the time allowed for the reconstituted vials. Particulates may be observed on storage if diluted in 0.9% Sodium Chloride Injection, therefore, a 0.2-micron in-line (non-protein adsorptive) /0.22 micron polyethersulfone (PES) filter is required for administration (see DOSAGE AND ADMINISTRATION).

Do not freeze the solution for infusion containing the reconstituted product.

13 SPECIAL HANDLING INSTRUCTIONS

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Local requirements should be followed for the disposal process of unused/expired medicines or waste material.

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

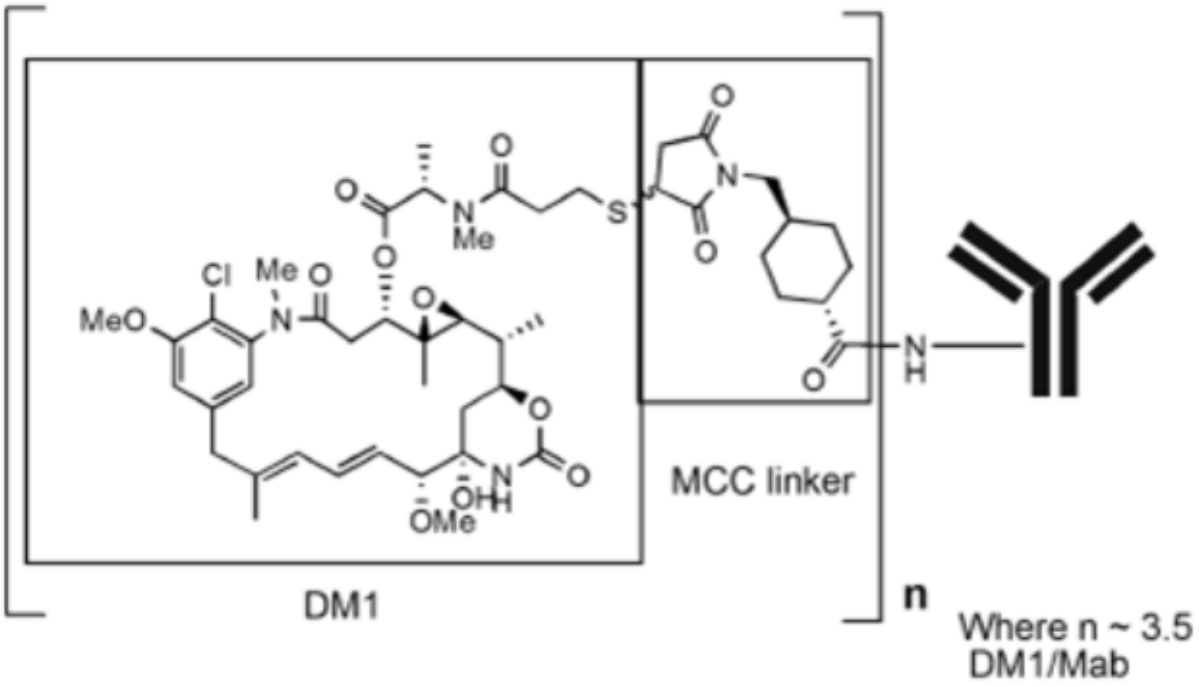
Drug Substance

Proper name: trastuzumab emtansine

Chemical name: Immunoglobulin G1, anti-(human p185neu receptor) (human-mouse monoclonal rhuMab HER2 γ1-chain), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer, tetraamide with $N^{2'}$– [3-[[1-[(4-carboxycyclohexyl) methyl]-2,5-dioxo-3-pyrrolidinyl]thio]-1-oxopropyl]-$N^{2'}$-deacetylmaytansine

Molecular mass: 148,781 Da

Structural formula:



15 CLINICAL TRIALS

15.1 Trial Design and Study Demographics

An overview of the study designs and demographic characteristics of patients enrolled in each clinical study are presented in Table 11.

Table 11 Summary of trial design and patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Metastatic Breast Cancer					
TDM4370g / BO21977 (EMILIA)	A Phase III randomized, multicenter, open-label study	Kadcyla: 3.6 mg/kg q3w, IV or Lapatinib 1250 mg/day, po + Capecitabine 1000 mg/m^2 twice daily on Days 1-14	Kadcyla: 495 patients treated Lapatinib + Capecitabine: 496 patients treated	Kadcyla: 52.2 (25 - 84) Lapatinib + Capecitabine: 53.2 (24 - 83)	Kadcyla: Female: 494 (99.8%) Male: 1 (0.2%) Lapatinib + Capecitabine: Female: 492 (99.2%) Male: 4 (0.8%)
TDM4450g/ BO21976	A Phase II randomized, multicenter, open-label, study	Kadcyla: 3.6 mg/kg q3w, IV or Trastuzumab: 8 mg/kg loading dose; 6mg/kg q3w, IV + Docetaxel: 75 or 100 mg/m^2 q3w, IV	Kadcyla: 67 patients treated Trastuzumab + Docetaxel: 70 patients enrolled, (2 not treated)	Kadcyla: 54.3 (27 - 82) Trastuzumab + Docetaxel: 52.1 (33-75)	Kadcyla: Female: 67 (100.0%) Trastuzumab + Docetaxel: Female: 70 (100.0%)
TDM4374g	A Phase II, single-arm, open-label study	Kadcyla: 3.6 mg/kg q3w , IV	110 patients treated	53.0 (34 - 77)	Female: 108 (98.2%) Male: 2 (1.8%)
TDM4258g	A Phase II single-arm, open-label study	Kadcyla: 3.6 mg/kg q3w, IV	112 treated patients	55.0 (33 - 82)	Female: 111 (99.1%) Male: 1 (0.9%)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Early Breast Cancer					
BO27938 (KATHERINE)	Phase III, randomized, multicenter, multinational, two-arm, open label study	Trastuzumab: 6 mg/kg IV q3w for 14 cycles (8 mg/kg loading dose given if longer than 6 weeks since last dose of trastuzumab) OR Kadcyla: 3.6 mg/kg q3w IV for 14 cycles	Trastuzumab: 743 patients enrolled, 720 patients treated Kadcyla: 743 patients enrolled, 740 patients treated	Trastuzumab: 49.2 (23 – 80) Kadcyla: 49.0 (24 – 79)	Trastuzumab: Female: 740 (99.6%) Male: 3 (0.4%) Kadcyla: Female: 741 (99.7%) Male: 2 (0.3%)

15.2 Study Results

Metastatic Breast Cancer (MBC):
A Phase III, randomized, multicentre, international, open-label clinical trial (*TDM4370g/BO21977*) was conducted in patients with HER2-positive unresectable locally advanced breast cancer (LABC) or MBC who had received prior taxane and trastuzumab-based therapy, including patients who received prior therapy with trastuzumab and a taxane in the adjuvant setting and who relapsed within six months of completing adjuvant therapy. Prior to enrollment, breast tumour samples were required to be centrally confirmed for HER2-positive disease defined as a score of 3+ by IHC or gene amplification by ISH. The study compared the safety and efficacy of Kadcyla with that of lapatinib plus capecitabine. A total of 991 patients were randomized (1:1) to Kadcyla or lapatinib plus capecitabine as follows:

- Kadcyla Arm (n=495): Kadcyla 3.6 mg/kg intravenously (IV) over 30−90 minutes on Day 1 of a 21-day cycle
- Control Arm (lapatinib plus capecitabine) (n=496): lapatinib 1250 mg/day orally once per day of a 21-day cycle plus capecitabine 1000 mg/m^2 orally twice daily on Days 1−14 of a 21-day cycle

Patients received Kadcyla or lapatinib plus capecitabine until progression of disease (as assessed by the investigator), withdrawal of consent or unmanageable toxicity. At the time of the primary analysis, median time on study drug was 5.7 months (range: 0-28.4) for Kadcyla, 4.9 months (range: 0-30.8) for lapatinib, and 4.8 months (range: 0-30.4) for capecitabine. At the time of the second interim analysis, the median time on study drug was 7.6 months (range 0-34.8) for Kadcyla, 5.5 months (range 0-33.3) for lapatinib, and 5.3 months (range 0-33.3) for capecitabine. Randomization was stratified by world region (United States, Western Europe, other), number of prior chemotherapy regimens for unresectable locally advanced or

metastatic disease (0-1, >1) and visceral versus non-visceral disease as determined by the investigators.

Baseline patient and tumour characteristics were well balanced between treatment groups. All patients had metastatic disease at study entry. Patient demographics are summarized in Table 12.

Table 12 Patient Demographics TDM4370g/BO21977 (EMILIA) study

	Lapatinib+Capecitabine N = 496	**Kadcyla N = 495**
Age (years)		
Median	53	53
Range	24-83	25-84
Sex, n (%)		
Female	492 (99.2)	494 (99.8)
Male	4 (0.8)	1 (0.2)
Race, n (%)		
Caucasian	374 (75.4)	358 (72.3)
Asian	86 (17.3)	94 (19.0)
Black	21 (4.2)	29 (5.9)
Other	10 (2)	7 (1.4)
Not available	5 (1.0)	7 (1.4)
ECOG Performance status, n (%)		
0	312 (62.9)	299 (60.4)
1	176 (35.5)	194 (39.2)
Not available	8 (1.6)	2 (<1)
Site of disease involvement, n (%)		
Visceral	335 (67.5)	334 (67.5)
Nonvisceral	161 (32.5)	161 (32.5)
Hormone-receptor status, n (%)		
ER-positive, PR-positive, or both	263 (53)	282 (57.0)
ER-negative and PR-negative	224 (45.2)	202 (40.8)
Unknown, ER-negative PR unknown	9 (1.8)	11 (2.3)
Number of metastatic sites (IRC)		
1	151 (30.4)	143 (28.9)
2	156 (31.5)	155 (31.3)
3+	175 (35.3)	189 (38.2)
Missing	14 (2.8)	8 (1.6)
Measurable disease (IRC)		
No	107 (21.6)	98 (19.8)
Yes	389 (78.4)	397 (80.2)
Prior chemotherapy regimens for locally advanced or metastatic disease		
0-1	305 (61.5)	304 (61.4)
>1	191 (38.5)	191 (38.6)

The majority of patients (88%) had received prior systemic treatment in the metastatic setting. Twelve percent of patients had prior treatment only in the neoadjuvant or adjuvant setting and had disease relapse within 6 months of treatment. All but one patient received trastuzumab prior to study entry; approximately 85% of patients received prior trastuzumab in the metastatic setting. Over 99% percent of patients had received a taxane, and 61% of patients had received an anthracycline prior to study entry. Overall, patients received a median of 3 systemic agents in the metastatic setting. Among patients with hormone receptor-positive tumours, 44.4% received prior adjuvant hormonal therapy and 44.8% received hormonal therapy for locally advanced/metastatic disease.

The co-primary efficacy endpoints of the study were progression-free survival (PFS) as assessed by an independent review committee (IRC), and overall survival (OS). PFS was defined as the time from randomization to documented IRC-assessed PD or death from any cause (whichever occurred earlier). OS was defined as the time from the date of randomization to the date of death from any cause.

Key secondary endpoints included PFS (investigator-assessed), the objective response rate (ORR), the duration of response, and the time to symptom progression.

Table 13 Summary of efficacy from TDM4370g/BO21977 (EMILIA) study

	Lapatinib+Capecitabine N = 496	**Kadcyla N = 495**
Primary Endpoints		
IRC-assessed PFS		
Number (%) of patients with event	304 (61.3%)	265 (53.5%)
Median duration of PFS (months)	6.4	9.6
Hazard Ratio (stratified*)	0.650	
95% CI for Hazard Ratio	(0.549 , 0.771)	
p-value (Log-Rank test, stratified*)	<0.0001	
Overall Survival*		
Number (%) of patients who died	182 (36.7%)	149 (30.1%)
Median duration of survival (months)	25.1	30.9
Hazard Ratio (stratified*)	0.682	
95% CI for Hazard Ratio	(0.548, 0.849)	
p-value (Log-Rank test*)	0.0006	
Key Secondary Endpoints		
Objective Response Rate		
Patients with measurable disease	389	397
Number of patients with OR (%)	120 (30.8%)	173 (43.6%)
Diff, (95% CI);	12.7% (6.0%, 19.4%)	
p-value (Mantel-Haenszel chi-squared test*)	0.0002	

	Lapatinib+Capecitabine N = 496	Kadcyla N = 495
Duration of Objective Response (months)		
Number of patients with OR	120	173
Median	6.5	12.6

PFS: progression-free survival; OR: objective response

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

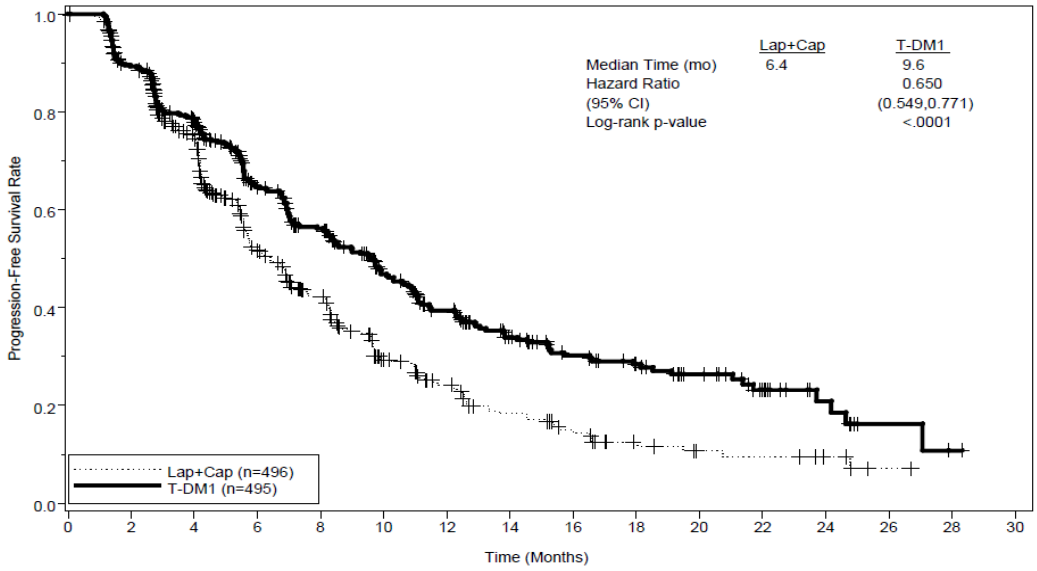
** The first interim analysis of overall survival (OS) was performed at the time of primary PFS analysis. Strong treatment effect was observed, but pre-specified efficacy boundary was not crossed. A second interim analysis for OS was conducted when 331 OS events were observed and the results are presented in this table. The p-value met the O'Brien Fleming stopping boundary of the Lan Demets alpha spending function for the 2nd OS interim analysis (p = 0.0037).

A treatment benefit with Kadcyla in terms of PFS and OS was observed in most patient subgroups based on stratification factors, key baseline demographic and disease characteristics, and prior treatments. In the subgroup of patients with non-measurable disease (n=205), based on IRC assessments, the hazard ratios for PFS and OS were 0.91 (95% CI: 0.59, 1.42) and 0.96 (95% CI: 0.54, 1.68), respectively; in patients with measurable disease the hazard ratios were 0.62 (95% CI: 0.52, 0.75) and 0.65 (95% CI: 0.51, 0.82), respectively. The PFS and OS hazard ratios in patients who were younger than 65 years old (n=853) were 0.62 (95% CI: 0.52, 0.74) and 0.66 (95% CI: 0.52, 0.83), respectively. In patients ≥ 65 years old (n=138), the hazard ratios for PFS and OS were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively.

Pre-specified subgroup analyses utilizing non-visceral and visceral evaluations based solely on investigator judgment at the time of randomization revealed IRC-assessed PFS hazard ratios of 0.96 (95% CI: 0.71, 1.30) and 0.55 (95% CI: 0.45, 0.67) for the non-visceral and visceral disease subgroups, respectively. For OS, the hazard ratios were 1.05 (95% CI: 0.69, 1.61) and 0.59 (95% CI: 0.46, 0.76), respectively.

To examine the possibility that heterogeneity of assessment or other factors may have affected the subgroup analysis, post-hoc analyses were performed using consistent definition of visceral disease = lung, liver, pleural effusion and ascites and applied to the IRC assessments of disease. These analyses revealed IRC-assessed PFS hazard ratios of 0.69 (95% CI: 0.51, 0.95) and 0.64 (95% CI: 0.53, 0.78) for the non-visceral and visceral subgroups, respectively. The hazard ratios for OS were 0.59 (95% CI: 0.37, 0.94) and 0.73 (95% CI: 0.57, 0.94), respectively.

Figure 1 **Kaplan-Meier curve of IRC-assessed progression-free survival**

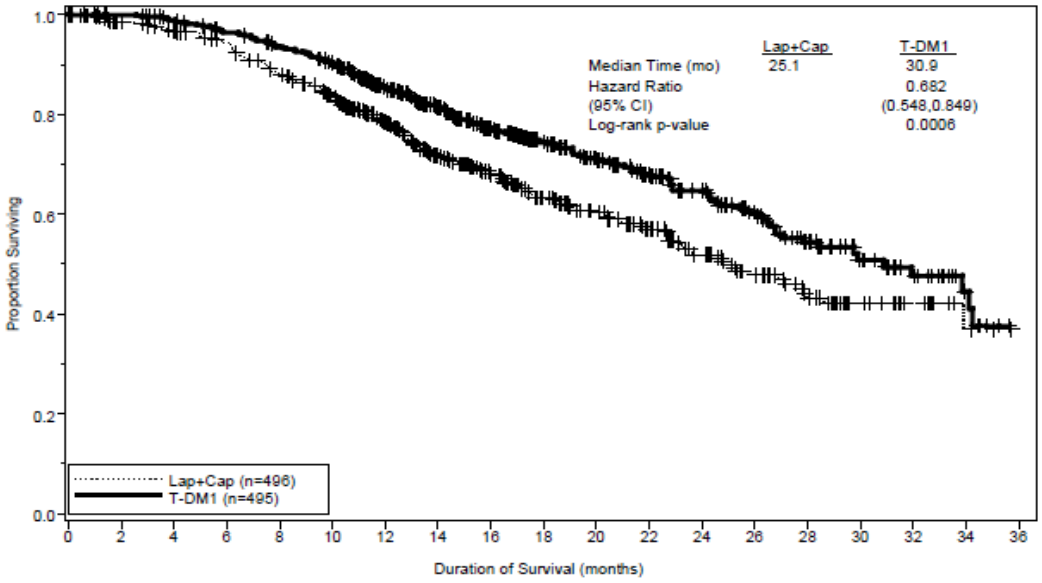


Number at Risk:

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

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

Figure 2 **Kaplan-Meier curve of overall survival**



Number at Risk:

Lap+Cap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

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

Other MBC Clinical Studies

A randomized, multicentre, open-label phase II, study (TDM4450g/BO21976) evaluated the effects of Kadcyla versus trastuzumab plus docetaxel in patients with HER2-positive MBC who had not received prior chemotherapy for metastatic disease. Patients were randomized to receive Kadcyla 3.6 mg/kg IV every 3 weeks (n=67) or trastuzumab 8 mg/kg IV loading dose followed by 6 mg/kg IV every 3 weeks plus docetaxel 75-100 mg/m^2 IV every 3 weeks (n=70).

The primary endpoint was PFS assessed by investigator. The median PFS was 9.2 months in the trastuzumab plus docetaxel arm and 14.2 months in the Kadcyla arm with a median follow-up of approximately 14 months in both arms. The ORR was 58.0% with trastuzumab plus docetaxel and 64.2% with Kadcyla. The median duration of response was not reached with Kadcyla vs. median duration 9.5 months in the control arm. The median OS was not reached in both arms.

A Phase II, single-arm, open-label study (TDM4374g) evaluated the effects of Kadcyla in patients with HER2-positive incurable locally advanced, or MBC. All patients were previously treated with HER2-directed therapies (trastuzumab and lapatinib), and chemotherapy (anthracycline, taxane, and capecitabine) in the neoadjuvant, adjuvant, locally advanced, or metastatic setting. The median number of anti-cancer agents that patients received in any setting was 8.5 (range, 5–19) and in the metastatic setting was 7.0 (range, 3–17), including all agents intended for the treatment of breast cancer.

Patients (n=110) received 3.6 mg/kg of Kadcyla intravenously every 3 weeks until disease progression or unacceptable toxicity.

The key efficacy analyses were ORR based on independent radiologic review and duration of objective response. The ORR was 32.7%, n=36 responders, by both IRC and investigator review. The median duration of response by IRC was not reached (4.6 months to not estimable).

A Phase II single-arm, open label study evaluated the effects of Kadcyla (TDM4258g) in patients with HER2-positive incurable LABC or MBC with a history of progression on HER2-directed therapy and at least one chemotherapy agent for MBC. Patients (n= 112) received Kadcyla administered at a dose of 3.6 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity for a maximum of 1 year.

The primary endpoint was ORR based on independent radiologic review. The administration of Kadcyla in patients with HER2-positive MBC previously treated with HER2-targeted therapy demonstrated single-agent activity with a confirmed ORR of 26.9%, as determined by the independent radiologic review, and a confirmed ORR of 38.9%, as assessed by the investigator. Kadcyla demonstrated anti-tumour activity in patients previously treated with both lapatinib and trastuzumab, with a confirmed ORR of 24.2% by independent radiologic review. The median duration of response by independent radiologic review assessment was not reached because of insufficient events and was 9.4 months per investigator assessment.

Early Breast Cancer (EBC):

KATHERINE (BO27938) was a randomized, multicenter, open-label trial of 1486 patients with HER2-positive, early breast cancer with residual invasive tumour in the breast and/or axillary lymph nodes following taxane and trastuzumab-based therapy as part of a neoadjuvant regimen before trial enrollment. Patients may have also received an anthracycline as part of neoadjuvant treatment. Patients received radiotherapy and/or hormonal therapy concurrent

with study treatment as per local guidelines. Breast tumour samples were required to show HER2 overexpression defined as 3+ IHC or ISH amplification ratio ≥ 2.0 determined at a central laboratory. Patients were randomized (1:1) to receive trastuzumab or Kadcyla. Randomization was stratified by clinical stage at presentation, hormone receptor status, preoperative HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent[s]), and pathological nodal status evaluated after preoperative therapy.

Patients were excluded from the study if any of the following criteria were met: gross residual disease remaining after mastectomy or positive margins after breast-conserving surgery; progressive disease during neoadjuvant therapy; and cardiopulmonary dysfunction, including heart failure of New York Heart Association (NYHA) class II (mild symptoms and function limitation) or higher or a history of a reduction in the left ventricular ejection fraction to < 40% with previous therapy.

Kadcyla was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with Kadcyla or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity, whichever occurred first. At the time of the primary analysis, median treatment duration was 10 months (range: 1–12) for Kadcyla, and median treatment duration was 10 months (range: 1–13) for trastuzumab. Patients who discontinued Kadcyla could complete the duration of their intended study treatment up to 14 cycles of HER2-directed therapy with trastuzumab, if appropriate, based on toxicity considerations and investigator discretion.

The primary efficacy endpoint of the study was Invasive Disease Free Survival (IDFS). IDFS was defined as the time from the date of randomization to first occurrence of ipsilateral invasive breast tumour recurrence, ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Additional endpoints included IDFS including second primary non-breast cancer, disease free survival (DFS), overall survival (OS), and distant recurrence-free interval (DRFI).

Table 14 Patient Demographics BO27938 (KATHERINE) study

	trastuzumab N = 743	**Kadcyla N = 743**
Age (years)		
Median	49	49
Range	23-80	24-79
Sex, n (%)		
Female	740 (99.6)	741 (99.7)
Male	3 (0.4)	2 (0.3)
Race, n (%)		
Caucasian	531 (71.5)	551 (74.2)
Asian	64 (8.6)	65 (8.7)
American Indian or Alaska Native	50 (6.7)	36 (4.8)
Black or African American	19 (2.6)	22 (2.8)
Other	79 (10.6)	70 (9.4)
Region, n (%)		
North America	164 (22.1)	170 (22.9)
Western Europe	403 (54.2)	403 (54.2)

	trastuzumab N = 743	Kadcyla N = 743
Rest of World	176 (23.7)	170 (22.9)
ECOG Performance status, n (%)		
0	613 (82.5)	597 (80.3)
1	130 (17.5)	146 (19.7)
Hormone-receptor status (eCRF), n (%)		
Positive (ER and/or PgR positive)	540 (72.7)	534 (71.9)
Negative (ER negative and PgR negative/unknown)	203 (27.3)	209 (28.1)
Preoperative HER2-directed therapy (eCRF), n (%)		
Trastuzumab only	596 (80.2)	600 (80.8)
Trastuzumab plus additional HER2-directed therapy	147 (19.8)	143 (19.2)
Preoperative Pertuzumab (eCRF), n (%)		
Received pertuzumab	139 (18.7)	133 (17.9)
Did not receive pertuzumab	604 (81.3)	610 (82.1)
Prior Anthracycline received, n (%)		
Received prior anthracycline	564 (75.9)	579 (77.9)
Did not receive prior anthracycline	179 (24.1)	164 (22.1)

The majority of the patients (76.9%) had received an anthracycline-containing neoadjuvant chemotherapy regimen and 19.5% of patients received another HER2-targeted agent in addition to trastuzumab as a component of neoadjuvant therapy. Pertuzumab was the second therapy in 93.8% of patients who received a second neoadjuvant HER2-directed agent.

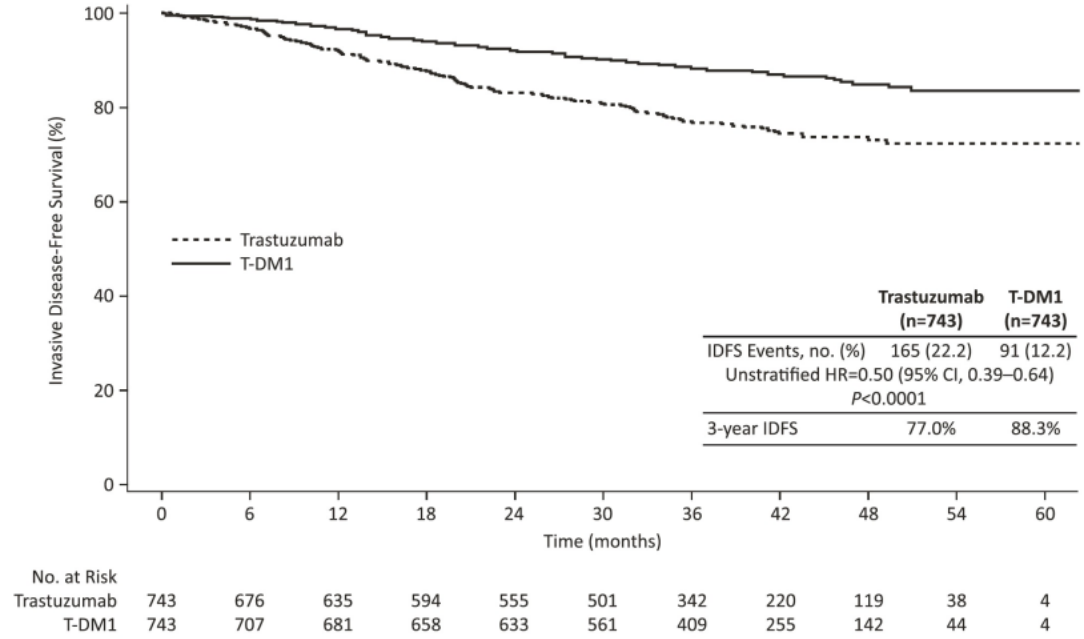
A clinically meaningful and statistically significant improvement in IDFS was observed in patients who received Kadcyla compared with trastuzumab (HR = 0.50, 95% CI [0.39, 0.64], p <0.0001), corresponding to a 50% reduction in risk of an IDFS event. Estimates of 3-year event-free rates were 88.3% vs. 77.0% in Kadcyla vs. trastuzumab arms, respectively. See Table 15 and Figure 3.

Table 15 Summary of Efficacy from BO27938 (KATHERINE) study

	Trastuzumab N = 743	Kadcyla N = 743
Primary Endpoint		
Invasive Disease Free Survival (IDFS)		
Number (%) of patients with event	165 (22.2%)	91 (12.2%)
HR [95% CI]	0.50 [0.39, 0.64]	
p-value (Log-Rank test, unstratified)	<0.0001	
3 year event-free rate[1], % [95% CI]	77.0 [73.78, 80.26]	88.3 [85.81, 90.72]

Key to abbreviations (Table 15): HR: Hazard Ratio; CI: Confidence Intervals,
1. 3-year event-free rate derived from Kaplan-Meier estimates

Figure 3 Kaplan-Meier Curve of Invasive Disease Free Survival in BO27938 (KATHERINE)



In BO27938 (KATHERINE), consistent treatment benefit of Kadcyla for IDFS was seen in all the pre-specified subgroups evaluated, supporting the robustness of the overall results. The primary IDFS analysis is also supported by secondary outcome measures. More patients treated with trastuzumab vs. Kadcyla experienced a disease-free survival (DFS) event (23% vs. 13%; HR = 0.53). More patients treated with trastuzumab vs. Kadcyla experienced an IDFS including second primary non-breast cancer event (22.5% vs. 12.4%, HR = 0.51). Distant recurrence as the first invasive event occurred in 16% of trastuzumab vs.10.5% of Kadcyla treated patients (HR = 0.60).

16 MICROBIOLOGY

Not Applicable.

17 NON-CLINICAL TOXICOLOGY

General
Trastuzumab emtansine was generally well tolerated in rats (a nonbinding species) and cynomolgus monkeys (a relevant binding species) in single- and repeat-dose toxicity studies. The identified toxicities in both species were generally limited to findings consistent with the pharmacology of DM1 including hepatotoxicity, hematologic/bone marrow toxicity (including decreased platelet levels), lymphoid depletion in the spleen and thymus, neurotoxicity (monkeys only), reproductive toxicity (rats only) and increased numbers of mitotic figures in cells of epithelial and phagocytic origin.

Single-Dose Toxicity Studies:
In rats, a single IV dose of trastuzumab emtansine resulted in mortality and morbidity at a dose of 60 mg/kg. Animals had body weight loss, evidence of hepatotoxicity, peripheral granulocytosis, and decreased platelet levels. Males had adverse effects in the testicle and epididymis, including degeneration of seminiferous tubules with hemorrhage in the testes associated with increased weights of testes and epididymides at a severely toxic dose level (60 mg/kg; about 4 times the clinical exposure based on AUC), and females had hemorrhage and necrosis of the corpus luteum in ovaries. Trastuzumab emtansine doses of 6 and 20 mg/kg were tolerated with no adverse clinical signs; the target organs affected were comparable to those affected at 60 mg/kg with the exception of changes to the male and female reproductive organs, and with less severity. In cynomolgus monkeys, a single IV dose of trastuzumab emtansine was well tolerated following administration of 3, 10, or 30 mg/kg with evidence of hepatotoxicity and decreased platelet levels observed at 30 mg/kg. The toxicity of DM1 was also investigated in rats. A single IV dose was tolerated up to 0.2 mg/kg. With the exception of axonal degeneration which was observed only in monkeys, the toxicities observed after administration of DM1 were comparable to those observed in rats and monkeys administered trastuzumab emtansine.

The findings from the single-dose toxicity studies with trastuzumab emtansine and DM1 are summarized in Table 16.

Repeat-Dose Toxicity Studies:
In cynomolgus monkeys, IV administration of trastuzumab emtansine every three weeks for 4 or 8 doses at 3, 10, and 30 mg/kg, and 1, 3, and 10 mg/kg, respectively, followed by a 3- or 6-week recovery period, was well tolerated at all dose levels evaluated, with no signs of overt toxicity. The main toxicologic findings attributed to treatment with trastuzumab emtansine were comparable across both studies, and included hepatotoxicity, lymphoid depletion in the spleen and thymus, microscopic changes in the lacrimal glands, and irreversible axonal degeneration in the sciatic nerve and spinal cord. Based on the mechanism of action of the cytotoxic component DM1, there is clinical potential for neurotoxicity. Decreases in weights of the epididymides, prostate, testes, seminal vesicles, and uterus were also observed, but the interpretation of these results is unclear due to the varied sexual maturity of enrolled animals. The findings from the repeat-dose toxicity studies with trastuzumab emtansine are summarized in Table 17 Table 17.

Carcinogenicity:
No carcinogenicity studies have been performed to establish the carcinogenic potential of Kadcyla.

Genotoxicity:
In a rat bone marrow micronucleus assay, DM1 was positive for micronuclei formation after a single low dose in the DM1 concentration range measured in humans given trastuzumab emtansine, confirming that Kadcyla is an aneugen and/or clastogen. No evidence of mutagenic activity was observed in an *in vitro* bacterial reverse mutation assay of DM1. In an *in vitro micronucleus* assay of trastuzumab emtansine in cynomolgus monkeys, no evidence of chromosomal damage to bone marrow cells was observed. The findings from the mutagenicity studies are summarized in Table 18Table 18.

Impairment of Fertility:
No fertility studies in animals have been performed to evaluate the effect of Kadcyla. However, based on results from general animal toxicity studies, adverse effects on fertility can be expected (see Single-Dose Toxicity Studies and Repeat-Dose Toxicity Studies).

Reproductive toxicity:
Dedicated embryo-fetal development studies have not been conducted in animals with trastuzumab emtansine. Developmental toxicity of trastuzumab has been identified in the clinical setting although it was not predicted in the non-clinical program. In addition, developmental toxicity of maytansine has been identified in non-clinical studies which suggests that DM1, the microtubule-inhibiting cytotoxic maytansinoid drug component of trastuzumab emtansine, will be similarly teratogenic and potentially embryotoxic.

Special Toxicity Studies:
Specific toxicity studies conducted with trastuzumab emtansine and DM1 include: *in vitro* hERG assay in human embryonic kidney (HEK293) cell, a cardiovascular safety pharmacology study in cynomolgus monkeys, an *in vitro* hemolytic potential and blood compatibility, a tissue cross-reactivity and a bridging study in cynomolgus monkeys. Details from these studies are provided in Table 19.

Table 16 Single-Dose Toxicity Studies

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Doses (mg/kg)[a]	Duration of Dosing
04-1214-1459	Single-Dose Toxicity	Rat/Sprague-Dawley	10/M, 10/F	IV	trastuzumab emtansine: 6, <u>20</u>, 60	NA
Comments: Trastuzumab emtansine was not tolerated in rats administered a single IV dose of 60 mg/kg based on clinical signs, body weight loss, and high rate of morbidity/mortality.						
04-0976-1459	Single-Dose Toxicity	Cynomolgus Monkey[b]	6/M, 6/F	IV	trastuzumab emtansine: 3, 10, <u>30</u>	NA
Comments: Trastuzumab emtansine was well tolerated up to 30 mg/kg. Adverse effects on the liver and decreased platelet levels that were observed at 30 mg/kg were reversible after a 3-week recovery period. The HNSTD was 30 mg/kg.						
05-1191	Single-Dose Toxicity	Rat/Sprague-Dawley	10/M, 10/F	IV	DM1: 0.05, 0.1, <u>0.2</u>	NA
Comments: DM1 was well tolerated in rats up to 0.2 mg/kg. Effects on the liver, platelets, and lymphoid organs were comparable to those observed in rats and monkeys administered trastuzumab emtansine, and were reversible after a 3-week recovery period. The HNSTD was 0.2 mg/kg.						

IV= intravenous; NA- not applicable

[a] Unless otherwise specified.

[b] *Macaca fascicularis.*

The highest non−severely toxic dose (HNSTD) for each study is denoted by underline

Table 17 Repeat-Dose Toxicity Studies:

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Doses (mg/kg)[a]	Duration of Dosing
04-0977-1459	Repeat-Dose Toxicity	Cynomolgus monkey[b]	7/M, 7/F	IV	Trastuzumab emtansine: 3, <u>10</u>, 30	Four doses (one dose every three weeks)
Comments: Trastuzumab emtansine was well tolerated up to 30 mg/kg with no overt signs of toxicity. Notable trastuzumab emtansine−related changes at 10 and 30 mg/kg consisted primarily of increases in serum liver enzymes and decreases in red-cell mass and platelets.						
07-0653	Repeat-Dose Toxicity	Cynomolgus monkey[b]	6/M, 6/ F	IV	Trastuzumab emtansine: 1, 3, <u>10</u>	Eight doses (one dose every three weeks)
Comments: Trastuzumab emtansine was well tolerated up to 10 mg/kg. Notable trastuzumab emtansine−related changes at 10 mg/kg consisted primarily of increases in serum liver enzymes and decreases in red-cell mass and platelets. Overall, the findings observed between the first and last dose cycle in this study were comparable, indicating that chronic dosing of trastuzumab emtansine did not result in cumulative toxicities.						

IV=intravenous

[a] Unless otherwise specified.

[b] *Macaca fascicularis.*

The highest non−severely toxic dose (HNSTD) for each study is denoted by underline

Table 18 Mutagenicity Studies

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Doses (mg/kg)[a]	Duration of Dosing
09-2654	*In vitro*	*Salmonella – Escherichia coli*	NA[b]	*In vitro*	DM1: 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, and 5000 µg/plate	NA
Comments: Results indicated DM1 was negative in the *Salmonella−Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay under the conditions of this study						
09-2726	*In vivo*	Rat/Sprague-Dawley	5M, 5F	*In vivo*	DM1: 0.01, 0.05, 0.1, and 0.2	Single dose
Comments: DM1 induced a dose-dependent increase in micronucleus frequency at 0.05, 0.1, and 0.2 mg/kg, demonstrating evidence of aneugenicity and/or clastogenicity						
07-0653	*In vivo*	Cynomolgus Monkey[b]	6/M, 6/ F	IV	Trastuzumab emtansine: 1, 3, 10	21 Weeks
Comments: there was no evidence of micronuclei induction in bone marrow collected 7 days after the last dose.						

IV= intravenous; NA= not applicable

[a] Unless otherwise specified.

[b] *Macaca fascicularis.*

Table 19 Special Toxicity Studies

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Doses (mg/kg)[a]	Duration of Dosing
09-0234	hERG Assay	Human embryonic kidney (HEK293) cell	NA	*In vitro*	DM1: 2.6, 8.8, and 29.5 µM	NA
Comments: DM1 inhibited hERG potassium current by (Mean ± SEM; n = 3) 0.3 ± 0.6% at 2.6 µM, 1.0 ± 0.5% at 8.8 µM and 2.5 ± 0.4% at 29.5 µM versus 0.6 ± 0.3% in control. IC20 and IC50 were estimated to be greater than 29.5 µM.						
04-1031-1605	Cardiovascular Safety Pharmacology	Cynomolgus Monkey[b]	4/F	IV	Trastuzumab emtansine: 3, 10, 30	Single dose
Comments: Trastuzumab emtansine did not affect ECG parameters, including QT/QTc. At 30 mg/kg trastuzumab emtansine, modest increases in systolic, diastolic, and mean arterial pressures were observed. Changes were most consistently observed on Day 5 post-dose, but were variable in onset and duration in individual monkeys.						
04-1257-1459	Hemolytic Potential and Blood Compatibility	Cynomolgus monkey and human blood, serum, and plasma	NA	*In vitro*	Trastuzumab emtansine: 0, 1.25, 2.5, or 5 mg/mL	NA
Comments: Hemolytic potential: no trastuzumab emtansine–related hemolysis in human and monkey serum and plasma. Blood and plasma compatibility: Trastuzumab emtansine compatible in human and monkey blood and plasma.						
04-1215-1605	Tissue Cross-Reactivity	Cynomolgus monkey and human tissue	NA	*In vitro*	Trastuzumab emtansine: 1.0 or 10.0 µg/mL	NA
Comments: Trastuzumab emtansine-specific binding observed at 1.0 and 10.0 µg/mL in both human and cynomolgus monkey tissues, and consisted primarily of epithelial, spindle, glial, and mononuclear cell staining in several tissues. Binding in monkey tissues was similar to that of human tissues yet less prevalent.						
05-0848	Bridging Study	Cynomolgus monkey[b]	3/M, 3/F	IV	Trastuzumab emtansine: 3, 5%−7% UM 10, 5%−7% UM 30, 5%−7% UM	Single dose
Comments: Trastuzumab emtansine was well tolerated up to 30 mg/kg. Body weight loss (females), adverse effects on the liver and decreased platelet levels observed at 30 mg/kg were reversible after a 3-week recovery period. Minimal non-reversible axonal degeneration in the sciatic nerve was observed at 30 mg/kg.						

IV= intravenous; NA= not applicable; UM= Unconjugated Maytansinoid

[a] Unless otherwise specified.

[b] *Macaca fascicularis.*

The highest non−severely toxic dose (HNSTD) for each study is denoted by underline

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrKADCYLA®
trastuzumab emtansine

Read this carefully before you start taking Kadcyla and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Kadcyla.

Serious Warnings and Precautions

- **Medication Errors:** There is a risk of Kadcyla overdose due to medication errors. Verify with the healthcare professional that the authorized Kadcyla (trastuzumab emtansine) dose and NOT trastuzumab is used.

- **Liver Problems:** Kadcyla can cause inflammation and damage to liver cells. Severe liver damage may result in liver failure and death. To monitor liver problems, your blood will be checked regularly for increases in levels of liver enzymes.

- **Heart Problems:** Kadcyla can weaken the heart muscle leading to problems pumping the blood around your body and causing shortness of breath at rest, chest pain, swollen ankles or arms, and a sensation of rapid or irregular heartbeats. Your heart function will be checked before and regularly during treatment.

- **Bleeding Problems:** Platelets in the blood help blood clot. Kadcyla can lower the number of platelets in your blood and cause life-threatening bleeding. In some cases, bleeding has been fatal. The risk of bleeding is increased when taking Kadcyla with other medications used to thin your blood or prevent blood clots. Your doctor should provide additional monitoring if you are taking one of these other drugs.

- **Lung problems:** Kadcyla can cause lung problems, including inflammation (swelling) of the lung tissue, leading to lung failure and death.

- **Embryo-fetal toxicity (Harm to Unborn Baby):** Kadcyla can cause harm to the fetus (unborn baby), or death of the fetus, when taken by a pregnant woman. Women who could become pregnant need to use two effective birth control methods during Kadcyla treatment and for at least 7 months after treatment with Kadcyla**.**

What is Kadcyla used for?
Kadcyla pronounced “Kad-s(eye)-la” is used to treat people with breast cancer when:

- the cancer cells produce a large amount of HER2 proteins - your healthcare provider will test your cancer for this
- you have already received the medicine trastuzumab separately or in combination with a chemotherapy medicine from the class called taxane e.g. paclitaxel or docetaxel

- the cancer has spread to areas near the breast or to other parts of your body (metastasized)
- the cancer has not spread to other parts of the body and treatment is going to be given after surgery (treatment after surgery is called adjuvant therapy)

How does Kadcyla work?
Kadcyla is made up of two types of medicine that are linked together. One part belongs to a group of medicines called monoclonal antibodies (trastuzumab) and the other belongs to a group of medicines called anti-mitotics (DM1).

Kadcyla recognizes the cancer cells in the body by attaching to HER2 proteins. When Kadcyla attaches to the HER2 cancer cells, it may slow or stop the growth of the cancer or may also kill the cancer cells. After Kadcyla attaches to HER2 proteins, it enters the cancer cells where it releases the anti-mitotic drug DM1. DM1 may also kill the cancer cells.

What are the ingredients in Kadcyla?
Medicinal ingredients: trastuzumab and DM1
Non-medicinal ingredients: polysorbate 20, sodium hydroxide, succinic acid, and sucrose.

Kadcyla comes in the following dosage forms:
Single-use vial containing either 100 mg or 160 mg of trastuzumab emtansine.

Do not use Kadcyla if:
You should not be given Kadcyla if you are allergic to this drug or to any ingredients in the formulation (see 'What are the ingredients in Kadcyla'). If you are not sure, talk to your healthcare professional before you are given Kadcyla.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Kadcyla. Talk about any health conditions or problems you may have, including if you:
- you have ever had a serious infusion-related (allergic) reaction when treated with trastuzumab
- you are receiving treatment with blood thinner medications
- you have any history of liver problems. Your doctor will check your blood to test your liver function before and regularly during treatment.
- you are pregnant, think you may be pregnant or are planning to have a baby.

Other warnings you should know about:
Kadcyla can make some existing conditions worse, or cause side effects. See 'What are the possible side effects of using Kadcyla?' below.

Patients aged below 18 years: Kadcyla should not be used in these patients as there is no information on how well it works and if it is safe to use in these younger patients.

Pregnancy, breast-feeding and fertility: Kadcyla is not recommended if you are pregnant. There is no information about the safety of Kadcyla in pregnant women. Kadcyla may affect fertility based on animal studies.

- Tell your doctor before using Kadcyla if you are pregnant, think you may be pregnant or are planning to have a baby.

- Use effective contraception to avoid becoming pregnant while you are being treated with Kadcyla. Also, use this contraception for 7 months after your last dose. Female partners of male patients should also use effective contraception. Talk to your healthcare provider about the best contraception for you.
- If you do become pregnant during treatment with Kadcyla, tell your healthcare provider straight away.

Do not breast-feed during treatment with Kadcyla and for 7 months after stopping treatment. It is not known whether the ingredients in Kadcyla pass into breast-milk. Talk to your doctor about this.

Driving and using machines: Kadcyla may impair your ability to drive or use machines. If you experience infusion-related reactions (e.g. flushing, shivering fits, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of your face, tongue, or trouble swallowing) do not drive and use machines until symptoms abate completely.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Kadcyla:
Tell your healthcare professional if you are taking, have recently taken or might take any other medicines.

This includes medicines obtained without a prescription and herbal medicines. In particular, tell your healthcare professional if you are taking blood thinners.

How to take Kadcyla:
Kadcyla will be given to you by a healthcare professional in a hospital or clinic:

Usual dose:
- It is given by a drip into a vein (intravenous infusion) once every 3 weeks at a starting dose of 3.6 mg of Kadcyla for every kilogram of your body weight.
- The first infusion will be given to you over 90 minutes. You will be watched by a healthcare provider while it is being given and for at least 90 minutes following the initial dose, in case you have any side effects.
- If the first infusion is well tolerated, the infusion on your next visit may be given over 30 minutes. You will be watched by a healthcare provider while it is being given and for at least 30 minutes following the dose, in case you have any side effects.
- The total number of infusions that you will be given depends on how you respond to the treatment and which indication is treated.
- If you experience side effects, your doctor may decide to carry on your treatment but lower your dose, delay the next dose or stop the treatment.

Overdose:

If you think you have been given too much Kadcyla, tell your healthcare professional, hospital emergency department or regional poison control centre immediately even if there are no symptoms.

There is a risk of Kadcyla overdose due to medication errors. Verify with the healthcare professional that the authorized Kadcyla (trastuzumab emtansine) dose and NOT trastuzumab dose is used.

Missed Dose:
If you forget or miss your Kadcyla appointment, discuss this as soon as possible with your healthcare professional to make another appointment.

Do not stop having this medicine without talking to your healthcare professional first. If you have any further questions on the use of this medicine, ask your healthcare professional.

What are possible side effects from using Kadcyla?

Like all medicines, this medicine can cause unwanted effects. Tell your health care professional if you notice any of the side effects given below.

Very common (may affect more than 1 in 10 people):
- Jaundice
- Unexpected bleeding
- Tiredness
- Feeling sick (nausea, vomiting)
- Headache
- Muscle or joint pain
- Abdominal pain
- Constipation
- Nerve damage
- Diarrhea
- Dry mouth
- Swelling of the mouth
- Chills or flu like symptoms
- Difficulty sleeping
- Decrease in your potassium levels (shown in a blood test)
- Decreased red blood cells (shown in a blood test)

Common (may affect up to 1 in 10 people):
- Heart problems
- Allergic Reactions during or following infusions
- Decreased white blood cells (shown in a blood test)
- Swollen mouth or eyelids
- Dry eyes, watery eyes or blurred vision
- Increase in blood pressure
- Dizziness
- Loss of taste
- Itching

- Breathing problems, including shortness of breath
- Memory loss

Uncommon (may affect up to 1 in 100 people):

- KADCYLA can cause a condition known as nodular regenerative hyperplasia of the liver. Over time, this may lead to symptoms such as a bloated sensation or swelling of the abdomen due to fluid accumulation or bleeding from abnormal blood vessels in the gullet or rectum.

These are not all the possible side effects you may feel when taking Kadcyla. If you experience any side effects not listed here, contact your healthcare professional.

If you get any of the side effects after your treatment with Kadcyla has been stopped, talk to your doctor and tell them that you have been treated with Kadcyla.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and call get immediate medical help
	Only if severe	In all cases	
VERY COMMON Unexpected bleeding from the nose, gums	✓		
Your skin and whites of your eyes get yellow		✓	
COMMON Shortness of breath at rest, chest pain, swollen ankles or arms, sensation of rapid or irregular heartbeats		✓	
Tenderness or redness of your skin, or swelling at the injection site.		✓	
Flushing, shivering fits, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of your face, tongue, trouble swallowing		✓	
Tingling, pain, numbness, itching, crawling sensation, pins and needles in your hands and feet	✓		
Shortness of breath, cough with fever		✓	
UNCOMMON Blood in stools, swelling of the abdomen	✓		
If you become pregnant		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Kadcyla will be stored by the healthcare professionals at the hospital or clinic.
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton after EXP. The expiry date refers to the last day of that month.
- Store vials in a refrigerator at (2-8°C).

When prepared, as a solution for infusion Kadcyla is stable for up to 24 hours at 2-8°C, and must be discarded thereafter. Do not use Kadcyla if you notice any particles or it is the wrong colour see 'What dosage forms it comes in'.

- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

If you want more information about Kadcyla:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for health professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.rochecanada.com, or by calling 1-888-762-4388

This leaflet was prepared by Hoffmann-La Roche Limited.

Last Revised:

Hoffmann-La Roche Limited
Mississauga, ON L5N 5M8