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INF-KAD-2022 02-0

Kadcyla®

Trastuzumab Emtansine

WARNING: Do not substitute Kadcyla for or with trastuzumab (Herceptin).
In order to prevent medication errors, check the vial labels to ensure the medicine being prepared and administered is Kadcyla (trastuzumab emtansine) and not trastuzumab (Herceptin).

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antibody drug conjugate antineoplastic agent.
ATC code – L01FD03

1.2 Type of Dosage Form

Sterile powder for concentrate for infusion solution.

1.3 Route of Administration

Intravenous (IV) infusion.

1.4 Sterile / Radioactive Statement

Sterile product.

1.5 Qualitative and Quantitative Composition

Active ingredient: Trastuzumab emtansine
Dosage Preparations:
100 mg single-use vial containing powder for concentrate for infusion solution designed to deliver 5 ml of 20 mg/ml of trastuzumab emtansine.
160 mg single-use vial containing powder for concentrate for infusion solution designed to deliver 8 ml of 20 mg/ml of trastuzumab emtansine.
Excipients: Polysorbate 20, Sodium hydroxide, Succinic acid, Sucrose

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Breast Cancer
Metastatic Breast Cancer (MBC)
Kadcyla, as a single agent, is indicated for the treatment of patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have received prior treatment with trastuzumab and a taxane, separately or in combination. Patients should have either:
- Received prior therapy for advanced or metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy.

Early Breast Cancer (EBC)
Kadcyla, as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease, after neoadjuvant trastuzumab and taxane-based treatment.

2.2 Dosage and Administration

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) AND NOT TRASTUZUMAB (HERCEPTIN).

Kadcyla therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients.
Patients treated with Kadcyla should have 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.

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

The safety and efficacy of alternating or switching between Kadcyla and products that are biosimilar but not deemed interchangeable to Kadcyla has not been established. Therefore, the benefit/risk of alternating or switching needs to be carefully considered.

Kadcyla must be reconstituted and diluted by a healthcare professional and administrated as an intravenous infusion *(see section 4.2 Special Instructions for Use, Handling and Disposal).* Do not administer as an intravenous push or bolus.

Schedule
The recommended dose of Kadcyla is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle).

Administer the initial dose 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 section 2.4.1 General, 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 section 2.4.1 General, Warnings and Precautions*). Discontinue Kadcyla for life-threatening infusion reactions.

Duration of treatment
Patients with EBC should receive treatment for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity.

Patients with MBC should receive treatment until disease progression or unmanageable toxicity.

Delayed or missed dose
If a planned dose of Kadcyla is missed, it should be administered as soon as possible; do not wait until the next planned cycle. 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.

Dose modifications
Management of symptomatic adverse events may require temporary interruption, dose reduction, or treatment discontinuation of Kadcyla as per guidelines provided in Tables 1 and 2.

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 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Table 2 Dose Modification Guidelines for Kadcyla

Dose Modification Guidelines for 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)	Discontinue Kadcyla
Increased Aspartate Transaminase (AST)	Grade 2 (> 3.0 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)	Discontinue Kadcyla
Hyperbilirubinemia	TBILI > 1.0 to ≤ 2.0× 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	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 LVEF < 45% is confirmed, 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, 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%	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	Discontinue Kadcyla if not resolving with standard treatment
	Grade 3-4	Discontinue Kadcyla
Dose Modifications for 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)	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)	Discontinue Kadcyla
Drug Induced Liver Injury (DILI)	Serum transaminases > 3 x 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	Discontinue Kadcyla
	LVEF <40%	Do not administer Kadcyla Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, 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, discontinue Kadcyla
	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	Continue treatment with Kadcyla. Repeat LVEF assessment within 3 weeks.
	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 to Grade ≤ 2

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.

2.2.1 Special Dosage Instructions

Geriatric use
There are insufficient data to establish the safety and efficacy of Kadcyla in patients 75 years of age or older. No dose adjustment of Kadcyla is required in patients aged ≥ 65 years *(see section 2.5.5 Geriatric Use).*

Pediatric use
The safety and efficacy of Kadcyla in children and adolescents (< 18 years) have not been established.

Renal impairment
No adjustment to the starting dose of Kadcyla is needed in patients with mild or moderate renal impairment *(see section 3.2.5 Pharmacokinetics in Special Populations).* 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 is required for patients with mild or moderate hepatic impairment *(see section 3.2.5 Pharmacokinetics in Special Populations).* 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 section 2.4 Warnings and Precautions, General, Hepatotoxicity*).

2.3 Contraindications

Kadcyla is contraindicated in patients with a known hypersensitivity to Kadcyla or any of the excipients.

2.4 Warnings and Precautions

2.4.1 General

Patients treated with Kadcyla must have confirmed HER2-positive tumour status as assessed by either HER2 protein over-expression or gene amplification.

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

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 *(see section 2.6 Undesirable Effects)*. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates.

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 setting, where Kadcyla should be permanently discontinued for ≥ Grade 3 or for Grade 2 not responding to standard treatment *(see section 2.2 Dosage and Administration, Dose Modifications)*.

Patients with dyspnea at rest due to complications of advanced malignancy, co-morbidities, and receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary events. Clinicians should consider the potential benefits vs risks of the use of trastuzumab emtansine in patients with pre-existing pulmonary conditions.

Hepatotoxicity
Serious hepatotoxicity has been reported, including liver failure and death, in patients treated with Kadcyla. Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1-4 transaminitis), has been observed while on treatment with Kadcyla in clinical trials *[see section 2.6 Undesirable Effects]*. 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 also been observed. 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 nodular regenerative hyperplasia (NRH) of the liver and some with a fatal outcome due to drug-induced liver injury have been observed in patients treated with Kadcyla in clinical trials. Observed cases may have been confounded by comorbidities and/or concomitant medications with known hepatotoxic potential.

Liver function should be monitored prior to initiation of treatment and each Kadcyla dose. Dose reductions or discontinuation for increased serum transaminases and total bilirubin are specified in *section 2.2 Dosage and Administration, Dose Modifications*.

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

Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies in patients treated with Kadcyla. 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.

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. 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.

Events of LVEF drop of >10% from baseline and/or CHF were observed in approximately 22% of patients with MBC in an observational study (BO39807) with baseline LVEF of 40-49% in a real world setting. Most of these patients had other cardiovascular risk factors. The decision to administer Kadcyla in patients with MBC with low LVEF must be made only after careful benefit risk assessment and cardiac function should be closely monitored in these patients.

Specific guidelines regarding dose modifications and discontinuation are provided in *Section 2.2 Dosage and Administration, Dose modifications*.

Infusion-Related Reactions
Treatment with Kadcyla has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR); treatment with Kadcyla is not recommended for these patients. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should be treated with caution. (see section regarding Pulmonary Toxicity) for further information.

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 general, these symptoms were not severe *(see Section 2.6 Undesirable Effects).* In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Kadcyla treatment should be interrupted in patients with severe IRR. Kadcyla treatment should be permanently discontinued in the event of a life threatening infusion-related reaction *(see section 2.2 Dosage and Administration, Dose modifications).*

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.

Hemorrhage
Cases of hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported with Kadcyla. Some of these bleeding events resulted in fatal outcomes. In some of the observed cases the patients were also receiving anti-coagulation therapy, antiplatelet therapy, or had thrombocytopenia, in others there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary.

Thrombocytopenia
Thrombocytopenia, or decreased platelet counts, was reported in patients in clinical trials of Kadcyla. The majority of these patients had Grade 1 or 2 events (≥50,000/mm^3), with the nadir occurring by day 8 and generally improving to grade 0 or 1 (≥75,000/mm^3) by the next scheduled dose. In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients.

Patients with thrombocytopenia (≤100,000/mm^3) and patients on anti-coagulant treatment should be monitored closely while on Kadcyla treatment. It is recommended that platelet counts are monitored prior to each Kadcyla dose. Rare cases of severe and prolonged thrombocytopenia (≥ Grade 3 thrombocytopenia lasting for more than 90 days) have been reported with Kadcyla. In most of these cases, patients received concomitant recombinant human thrombopoietin (rhTPO). Kadcyla has not been studied in patients with platelet counts ≤100,000/mm^3 prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater (<50,000/mm^3), do not administer Kadcyla until platelet counts recover to Grade 1 (≥75,000/mm^3). Please see *section 2.2 Dosage and Administration, Dose modifications*.

Neurotoxicity
Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of Kadcyla. Treatment with Kadcyla should be temporarily discontinued 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.

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. In the post marketing setting, very rare cases of epidermal injury or necrosis following extravasation have been observed. Specific treatment for Kadcyla extravasation is unknown at this time. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

2.4.2 Drug Abuse and Dependence

No data to report.

2.4.3 Ability to Drive and Use Machines

Kadcyla has no or negligible influence on the ability to drive and use machines. The significance of reported adverse reactions such as fatigue, headache, dizziness and blurred vision on the ability to drive or use machines is unknown. Patients experiencing symptoms of infusion related reactions (flushing, shivering fits, fever, trouble breathing, low blood pressure or a rapid heartbeat) should be advised not to drive and use machines until symptoms abate.

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Contraception

Women of child bearing potential and female partners of male patients of child bearing potential should use effective contraception while receiving Kadcyla and for at least 7 months following the last dose of Kadcyla.

2.5.2 Pregnancy

No clinical studies of Kadcyla in pregnant women have been performed. No reproductive and developmental toxicology studies have been conducted with Kadcyla. Trastuzumab, a component of Kadcyla, can cause fetal harm or death when administered to a pregnant woman. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia, have been reported in pregnant women receiving trastuzumab. Animal studies of maytansine, a closely related chemical entity of the same maytansinoid class as DM1, suggest that DM1, the microtubule inhibiting cytotoxic drug component of Kadcyla, is expected to be teratogenic and potentially embryotoxic.

Administration of Kadcyla to pregnant women is not recommended. 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.

Labor and Delivery

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

2.5.3 Lactation

It is not known whether Kadcyla is excreted in human breast milk. Since many drugs are 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 months following the last dose of Kadcyla.

2.5.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

2.5.5 Geriatric Use

There are insufficient data to establish the safety and efficacy of Kadcyla in patients 75 years of age or older.

2.5.6 Renal Impairment

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

2.5.7 Hepatic Impairment

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

2.6 Undesirable Effects

2.6.1 Clinical Trials

Early Breast Cancer

The safety of Kadcyla has been evaluated in 740 patients with EBC in Study BO27938 KATHERINE. Adverse drug reactions from KATHERINE (Table 3) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Table 3 Adverse drug reactions occurring in patients treated with Kadcyla in Study BO27938 (KATHERINE)

ADR (MedDRA)	Kadcyla		
System Organ Class	**All grades (%) n = 740**	**Grade 3 - 5 (%) n = 740**	**Frequency Category**
Blood and Lymphatic System Disorders			
Thrombocytopenia	28.5	5.7	very common
Anemia	10.1	1.1	very common
Neutropenia	8.2	1.2	common
Cardiac Disorders			
Left ventricular dysfunction	3.0	0.5	common
Eye Disorders			
Lacrimation increased	5.5	0	common
Dry eye	4.5	0	common
Vision blurred	3.9	0	common
Conjunctivitis	3.5	0	common
Gastrointestinal Disorders			
Nausea	41.6	0.5	very common
Constipation	17.0	0.1	very common
Stomatitis	15.1	0.1	very common
Vomiting	14.6	0.5	very common
Dry Mouth	13.5	0.1	very common
Diarrhea	12.3	0.8	very common
Abdominal pain	10.7	0.4	very common
Dyspepsia	4.3	0	common
General Disorders and Administration site conditions			
Fatigue	49.5	1.1	very common
Pyrexia	10.4	0	very common
Chills	5.3	0	common
Edema peripheral	3.9	0	common
Asthenia	0.4	0	uncommon
Hepatobiliary Disorders			
Nodular regenerative hyperplasia	0.3	0.3	uncommon
Immune System Disorders			
Drug hypersensitivity	2.7	0.4	common
Injury, Poisoning, and Procedural Complications			
Infusion related reaction	1.6	0	common
Radiation pneumonitis	1.5	0.3	common
Renal and Urinary Disorders			
Urinary tract infection	10.4	0.3	Very common
Investigations			
Transaminases increased	32.4	1.5	very common
Blood alkaline phosphatase increased	8.2	0.1	common
Blood bilirubin increased	6.6	0	common
Metabolism and Nutrition Disorders			
Hypokalemia	6.8	1.2	common
Musculoskeletal and Connective Tissue Disorders			
Musculoskeletal pain	30.4	0.7	very common
Arthralgia	25.9	0.1	very common
Myalgia	15.4	0.4	very common
Nervous System Disorders			
Headache	28.4	0	very common
Neuropathy peripheral	28.0	1.6	very common
Dizziness	9.5	0.1	common
Dysgeusia	8.1	0	common
Psychiatric Disorders			
Insomnia	13.6	0	very common
Respiratory, Thoracic, and Mediastinal Disorders			
Epistaxis	21.5	0	very common
Cough	13.5	0.1	very common
Dyspnea	8.4	0.1	common
Pneumonitis	1.1	0.1	common
Skin and Subcutaneous Tissue Disorders			
Pruritus	6.9	0	common
Rash	1.1	0	common
Vascular Disorders			
Hemorrhage	29.2	0.4*	very common
Hypertension	5.7	2.0	common

*Including one case of Grade 5 Hemorrhage.

Laboratory Abnormalities

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

Table 4 Laboratory abnormalities from patients in Study BO27938 (KATHERINE)

Parameter	Trastuzumab Emtansine		
	All Grade %	**Grade 3 %**	**Grade 4 %**
Hepatic			
Increased Bilirubin	12	0	0
Increased AST	79	<1	0
Increased ALT	55	<1	0
Hematologic			
Decreased Platelets	51	4	2
Decreased Hemoglobin	31	1	0
Decreased Neutrophils	24	1	0
Potassium			
Decreased Potassium	26	2	<1

Metastatic Breast Cancer

The safety of Kadcyla has been evaluated in 1871 patients in clinical trials. Adverse drug reactions from clinical trials (Table 5) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Table 5 Adverse drug reactions occurring in patients treated with Kadcyla in clinical trials

ADR (MedDRA)	Kadcyla		
System Organ Class	**All grades (%) n = 1871**	**Grade 3 - 5 (%) n = 1871**	**Frequency Category**
Blood and Lymphatic System Disorders			
Thrombocytopenia	24.9	8.7	very common
Anemia	14.6	3.8	very common
Neutropenia	8.1	2.6	common
Cardiac Disorders			
Left ventricular dysfunction	2.2	0.4	common
Eye Disorders			
Dry eye	5.7	0.0	common
Lacrimation increased	4.1	0.0	common
Vision blurred	4.0	0.0	common
Conjunctivitis	3.8	0.0	common
Gastrointestinal Disorders			
Nausea	40.0	0.8	very common
Constipation	23.7	0.4	very common
Vomiting	19.9	1.0	very common
Diarrhea	19.2	0.7	very common
Dry Mouth	16.0	<0.1	very common
Abdominal pain	15.9	0.9	very common
Stomatitis	15.4	0.1	very common
Dyspepsia	8.0	0.1	common
General Disorders and Administration site conditions			
Fatigue	36.8	2.5	very common
Pyrexia	23.0	0.2	very common
Asthenia	16.3	1.1	very common
Chills	10.3	≤0.1	very common
Edema peripheral	8.1	0.1	common
Hepatobiliary Disorders			
Hepatic failure	0.1	0.1	uncommon
Nodular regenerative hyperplasia	0.1	0.0	uncommon
Portal hypertension	0.3	0.1	uncommon
Immune System Disorders			
Drug hypersensitivity	2.6	0.1	common
Infections and Infestations			
Urinary tract infection	11.9	0.4	very common
Injury, Poisoning, and Procedural Complications			
Infusion related reaction	4.0	0.3	common
Investigations			
Transaminases increased	24.2	7.2	very common
Blood alkaline phosphatase increased	5.3	0.5	common
Metabolism and Nutrition Disorders			
Hypokalemia	11.0	2.4	very common
Musculoskeletal and Connective Tissue Disorders			
Musculoskeletal pain	35.5	2.4	very common
Arthralgia	18.9	0.6	very common
Myalgia	12.9	0.3	very common
Nervous System Disorders			
Headache	28.1	0.6	very common
Neuropathy peripheral	22.8	1.3	very common
Dizziness	9.5	0.2	common
Dysgeusia	6.4	0.0	common
Psychiatric Disorders			
Insomnia	11.7	0.2	very common
Respiratory, Thoracic, and Mediastinal Disorders			
Epistaxis	24.3	0.4	very common
Cough	19.5	0.1	very common
Dyspnea	13.4	1.5	very common
Pneumonitis	0.7	0.1	uncommon
Skin and Subcutaneous Tissue Disorders			
Rash	12.4	0.3	very common
Pruritus	6.0	≤0.1	common
Vascular Disorders			
Hemorrhage	34.8	2.2	very common
Hypertension	6.5	1.7	common

Laboratory Abnormalities

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

Table 6 Laboratory abnormalities from patients in study TDM4370g/BO21977

	Trastuzumab emtansine		
Parameter	**All Grade %**	**Grade 3 %**	**Grade 4 %**
Hepatic			
Increased Bilirubin	21	<1	0
Increased AST	98	8	<1
Increased ALT	82	5	<1
Hematologic			
Decreased Platelets	85	14	3
Decreased Hemoglobin	63	5	1
Decreased Neutrophils	41	4	<1
Potassium			
Decreased Potassium	35	3	<1

2.6.2 Postmarketing Experience

Not applicable.

2.7 Overdose

There is no known antidote for trastuzumab emtansine overdose. In case of overdose, the patient should be closely monitored. Cases of overdose have been reported with trastuzumab emtansine treatment, most associated with thrombocytopenia, and there was one death. In the fatal case, the patient incorrectly received trastuzumab emtansine 6 mg/kg and died approximately 3 weeks following the overdose; a cause of death and a causal relationship to Kadcyla were not established.

2.8 Interactions with other Medicinal Products and other Forms of Interaction

No formal drug-drug interaction studies with Kadcyla in humans have been conducted. *In vitro* metabolism studies in human liver microsomes suggest that DM1, a component of trastuzumab emtansine, is metabolised mainly by CYP3A4 and, to a lesser extent, by CYP3A5. Concomitant use of strong CYP3A4 inhibitors (e.g. ketonazole, 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 coadministered and Kadcyla treatment cannot be delayed, patients should be closely monitored for adverse reactions.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Kadcyla, trastuzumab emtansine, is a HER2-targeted antibody-drug conjugate which contains the humanised 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 internalisation and subsequent lysosomal degradation, resulting in intracellular 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 signalling 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 polymerisation, both DM1 and Kadcyla cause cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death.
- 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.

3.1.2 Clinical / Efficacy Studies

Efficacy

Early Breast Cancer

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

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 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 tumor 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).

Patient demographics and baseline tumor characteristics were balanced between treatment arms. The median age was approximately 49 years (range 23-80 years), 72.8% were White, 8.7% were Asian and 2.7% were Black or African American. All but 5 patients were women. 22.5 percent of patients were enrolled in North America, 54.2% in Europe and 23.3% throughout the rest of the world. Tumor prognostic characteristics including hormone receptor status (positive: 72.3%, negative: 27.7%), clinical stage at presentation (inoperable: 25.3%, operable: 74.8%) and pathological nodal status after preoperative therapy (node positive: 46.4%, node negative not evaluated: 53.6%) were similar in the study arms.

The majority of the patients (76.9%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. 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 trastuzumab emtansine 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 years IDFS rates were 88.3% vs. 77.0% in trastuzumab emtansine vs. trastuzumab arms, respectively. See Table 7 and Figure 1.

Table 7 Summary of Efficacy from BO27938 (KATHERINE) study

	Trastuzumab N= 743	**Trastuzumab Emtansine N= 743**
Primary Endpoint		
Invasive Disease Free Survival (IDFS)[3]		
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[2], % [95% CI]	77.0 [73.78, 80.26]	88.3 [85.81, 90.72]
Secondary Endpoints[1]		
IDFS including second primary non-breast cancer		
Number (%) of patients with event	167 (22.5%)	95 (12.8%)
HR [95% CI]	0.51 [0.40, 0.66]	
p-value (Log-Rank test, unstratified)	<0.0001	
3 year event-free rate[2], % [95% CI]	76.9 [73.65, 80.14]	87.7 [85.18, 90.18]
Disease Free Survival (DFS)		
Number (%) of patients with event	167 (22.5%)	98 (13.2%)
HR [95% CI]	0.53 [0.41, 0.68]	
p-value (Log-Rank test, unstratified)	<0.0001	
3 year event-free rate[2], % [95% CI]	76.9 [73.65, 80.14]	87.4 [84.88, 89.93]
Overall Survival (OS)[3]		
Number (%) of patients with event	56 (7.5%)	42 (5.7%)
HR [95% CI]	0.70 [0.47, 1.05]	
p-value (Log-Rank test, unstratified)	0.0848	
5 year survival rate[2], % [95% CI]	86.8 [80.95, 92.63]	92.1 [89.44, 94.74]
Distant recurrence-free interval (DRFI)		
Number (%) of patients with event	121 (16.3%)	78 (10.5%)
HR [95% CI]	0.60 [0.45, 0.79]	
p-value (Log-Rank test, unstratified)	0.0003	
3 year event-free rate[2], % [95% CI]	83.0 [80.10, 85.92]	89.7 [87.37, 92.01]

Key to abbreviations (Table 7): HR: Hazard Ratio; CI: Confidence Intervals,
1. Hierarchical testing applied for IDFS and OS
2. 3-year event-free rate and 5-year survival rate derived from Kaplan-Meier estimates
3. Data from first interim analysis

Figure 1 Kaplan-Meier Curve of Invasive Disease Free Survival in Katherine

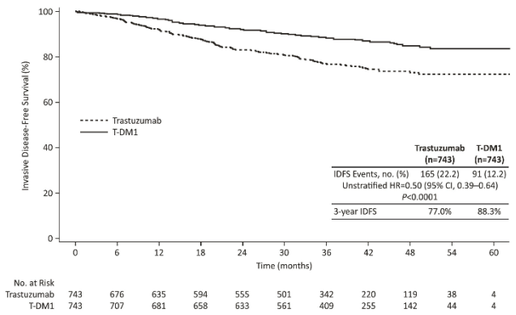
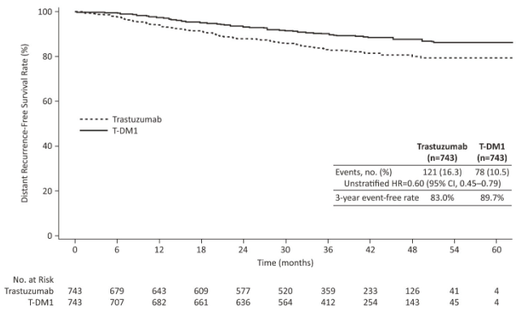
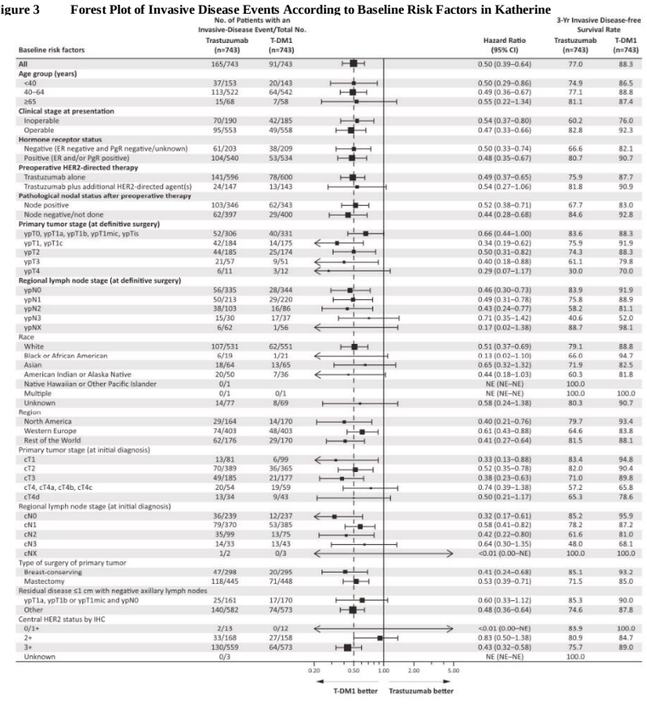


Figure 2 Kaplan-Meier Curve of Distant Recurrence-Free Interval in Katherine



In KATHERINE, consistent treatment benefit of Kadcyla for IDFS was seen in all the pre specified subgroups evaluated, supporting the robustness of the overall result (see figure 3). In the subgroup of patients with hormone receptor-negative disease (n=412, 27.7%), the hazard ratio for IDFS was 0.50 (95% CI: 0.33, 0.74). In the subgroup of patients with homone receptor-positive disease (n=1074, 72.3%), the hazard ratio for IDFS was 0.48 (95% CI: 0.35, 0.67). In the subgroup of patients who received neoadjuvant trastuzumab with chemotherapy (n=1196, 80.5%), the hazard ratio for IDFS was 0.49 (95% CI: 0.37, 0.65). In the subgroup of patients who received neoadjuvant trastuzumab plus a second HER2- directed therapy with chemotherapy (n=290, 19.5%), the hazard ratio for IDFS was 0.54 (95% CI: 0.27, 1.06). Patients who received Perjeta as a second neoadjuvant HER2-directed agent (n=272, 93.8%), had an IDFS hazard ratio of 0.50 (95% CI: 0.25, 1.00). The IDFS hazard ratio in patients who were node-positive after preoperative therapy (n=689, 46.4%) was 0.52 (95% CI: 0.38, 0.71). In patients who were node-negative or not evaluated after preoperative therapy (n=797, 53.6%), the hazard ratio for IDFS was 0.44 (95% CI: 0.28, 0.68).

Figure 3 Forest Plot of Invasive Disease Events According to Baseline Risk Factors in Katherine



Patient reported outcomes included the assessment of patient-reported global health status, role and physical function, and treatment symptoms using the EORTC QLQ-C30 and EORTC QLQ-BR23. In the analyses of patient-reported outcomes, a 10-point difference was considered clinically meaningful.

Patients' function, global health status, and symptom scores showed no clinically meaningful change from baseline over the course of treatment or during follow-up. Mean change from baseline at Cycle 11 for physical function was -0.6 (95% CI -1.9-0.7) in the trastuzumab emtansine arm and 1.8 (95% CI 0.6-3.1) in the trastuzumab arm; global health status was 0.4 (95% CI -2.2-1.3) in the trastuzumab emtansine arm and 1.4 (95% CI -0.2-3.0) in the trastuzumab arm. No clear differences were observed in function, global health status, or symptoms between the two treatment arms and at no timepoint during the study were the average scores on those scales of patients in the trastuzumab emtansine arm clinically worse than those of patients in the trastuzumab arm.

Metastatic Breast Cancer

A Phase III, randomised, multicentre, international, open-label clinical trial (*TDM4370g/BO21977*) was conducted in patients with HER2-positive unresectable locally advanced breast cancer 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. Baseline patient and tumour characteristics were well balanced between treatment groups. For patients randomised to Kadcyla, the median age was 53 years, most patients were female (99.8%), the majority were Caucasian (72%), 18% were Asian and 57% had estrogen-receptor and/or progesterone-receptor positive disease. The study compared the safety and efficacy of Kadcyla with that of lapatinib plus capecitabine. A total of 991 patients were randomised with Kadcyla or lapatinib plus capecitabine as follows:

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

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) and landmark (1-year and 2-year) survival rates.

Time to symptom progression, as defined by a 5-point decrease in the score derived from the trials outcome index-breast (TOI-B) subscale of the Functional Assessment of Cancer Therapy-Breast Quality of Life (FACT-B QoL) questionnaire was also assessed during the clinical trial. A change of 5 points in the TOI-B is considered clinically significant.

Of 495 patients who received Kadcyla, 65 patients (13%) were ≥65 years of age and 11 patients (2%) were ≥75 years of age. A trend for treatment benefit with Kadcyla compared to the control arm in terms of PFS and OS for the subgroup of patients who were 65 to 74 years old was observed, total n=113; HR 0.88, (95% CI: 0.53, 1.45) and 0.74 (95% CI 0.37, 1.47) respectively. For patients ≥75 years of age, based on IRC assessments, the hazard ratios for PFS and OS were 3.51 (95% CI: 1.22, 10.13) and 3.45 (95% CI: 0.94, 12.65), respectively. The subgroup of patients 75 years or above did not demonstrate a benefit for PFS or OS, but was too small (n=25) to draw any definitive conclusions.

Table 8 Summary of efficacy from TDM4370g/BO21977 (EMILIA) study

	Lapatinib+Capecitabine N=496	Trastuzumab Emtansine 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	
Landmark 1 year survival rate (95% CI)	78.4% (74.62, 82.26)	85.2% (81.99, 88.49)
Landmark 2 year survival rate (95% CI)	51.8% (45.92, 57.73)	64.7% (59.31, 70.19)
Key Secondary Endpoints		
Investigator-assessed PFS		
Number (%) of patients with event	335 (67.5%)	287 (58.0%)
Median duration of PFS (months)	5.8	9.4
HR (95% CI)	0.658 (0.560, 0.774)	
p-value (Log-Rank test*)	<0.0001	
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	
Duration of Objective Response (months)		
Number of patients with OR	120	173
Median 95% CI	6.5 (5.45, 7.16)	12.6(8.38, 20.76)
Time to Symptom Progression		
Number of evaluable patients	445	450
Number (%) of patients with event	257 (57.8%)	246 (54.7%)
Median time to event (months)	4.6	7.1
HR, 95% CI	0.796 (0.667, 0.951)	
p-value (Log-Rank test*)	0.0121	

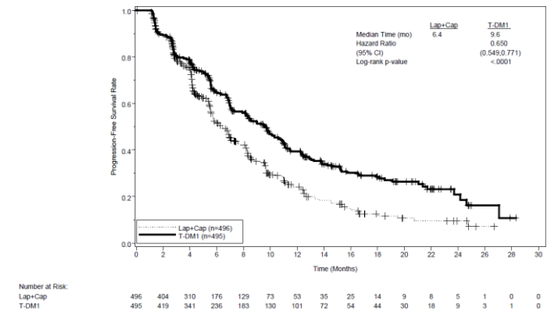
PFS: progression-free survival; OR: objective response

* 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.

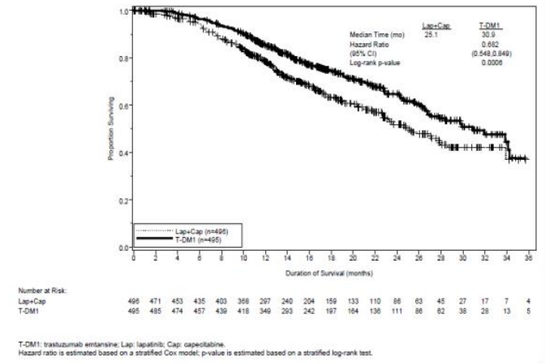
A treatment benefit was seen in the subgroup of patients who had not received any prior systemic anti-cancer therapy in the metastatic setting (n=118); hazard ratios for PFS and OS were 0.51 (95% CI: 0.30, 0.85) and 0.61 (95% CI: 0.32, 1.16), respectively. The median PFS and OS for the KADCYLA group were 10.8 months and not reached, respectively, compared with 5.7 months and 27.9 months, respectively, for the lapatinib plus capecitabine group.

Figure 4 Kaplan-Meier curve of IRC-assessed progression-free survival



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 5 Kaplan-Meier curve of overall survival



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.

A Phase II, single-arm, open-label study (TDM4374g) evaluated the effects of Kadcyla in patients with HER2-positive metastatic breast cancer. 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% (95% CI: 24.1, 42.1), n=36 responders, by both IRC and investigator review. The median duration of response by IRC was not reached (95% CI, 4.6 months to not estimable).

3.1.3 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 were also positive for neutralizing antibodies. In the KATHERINE (BO27938) study, 3.7% (15/401) of patients tested positive for anti-Kadcyla antibodies, of which 5 of were also 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.

3.2 Pharmacokinetic Properties

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

3.2.1 Absorption

Kadcyla is administered IV. There have been no studies performed with other routes of administration.

3.2.2 Distribution

Kadcyla when administered intravenously every 3 weeks exhibited linear pharmacokinetics 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. In *in vitro* studies, DM1 was 93% bound to human plasma proteins and was shown to be a substrate of P-glycoprotein (P-gp).

Patients in Study TDM4370g/BO21977 and Study BO29738 who received 3.6 mg/kg of Kadcyla intravenously every 3 weeks had a mean maximum serum concentration (C_{max}) of trastuzumab emtansine in Cycle 1 of 83.4 (± 16.5) µg/ml and 72.6 (± 24.3) µg/ml, respectively. Based on population pharmacokinetic analysis, following intravenous administration, the central volume of distribution of trastuzumab emtansine was (3.13 l) and approximated that of plasma volume.

3.2.3 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 BO29738, mean maximum DM1 levels in Cycle 1 following Kadcyla administration were consistently low and averaged 4.61 (± 1.61) ng/ml 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 metabolised mainly by CYP3A4 and to a lesser extent by CYP3A5.

3.2.4 Elimination

Based on population pharmacokinetic (PK) analysis, following IV administration of Kadcyla in patients with HER2-positive metastatic breast cancer, the clearance of trastuzumab emtansine was 0.68 l/day and the elimination half-life ($t_{1/2}$) was approximately 4 days. No accumulation of trastuzumab emtansine was observed after repeated dosing of IV infusion every 3 weeks.

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

3.2.5 Pharmacokinetics in Special Populations

The population pharmacokinetic analysis of trastuzumab emtansine showed that race did not appear to influence the pharmacokinetics of Kadcyla. Because most of the patients in Kadcyla clinical studies were females, effect of gender on the pharmacokinetics of Kadcyla was not formally evaluated.

Geriatric population

The population pharmacokinetic analysis of trastuzumab emtansine showed that age did not affect the pharmacokinetics of Kadcyla. No significant difference was observed in the pharmacokinetics of trastuzumab emtansine among patients <65 years (n=577), patients between 65 and 75 years (n=78) and patients >75 years (n=16).

Renal impairment

The population pharmacokinetic analysis of trastuzumab emtansine showed that creatinine clearance does not affect pharmacokinetics of Kadcyla. Pharmacokinetics of trastuzumab emtansine in patients with mild (creatinine clearance CLcr 60–89 ml/min, n=254) or moderate (CLcr 30–59 ml/min, n=53) renal impairment were similar to those in patients with normal renal function (CLcr ≥90 ml/min, n=361). Pharmacokinetic data in patients with severe renal impairment (CLcr 15–29 ml/min) is limited (n=1), therefore no dosage recommendations can be made.

Hepatic impairment

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 comparable between patients with and without hepatic impairment.
- 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 or moderate hepatic dysfunction was within the range observed in patients with normal hepatic function.

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

3.3 Nonclinical Safety

3.3.1 Carcinogenicity

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

3.3.2 Genotoxicity

No evidence of mutagenic activity was observed in an *in vitro* bacterial reverse mutation assay of DM1. In an *in vivo* micronucleus assay of trastuzumab emtansine in cynomolgus monkeys, no evidence of chromosomal damage to bone marrow cells was observed. However, 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 trastuzumab emtansine is an aneugen and/or clastogen.

3.3.3 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.

3.3.4 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 programme. 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.

3.3.5 Other

Not applicable.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Vials

Store in a refrigerator at 2–8°C. Do not freeze.

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. Particulates may be observed on storage if diluted in 0.9% Sodium Chloride Injection, therefore, a 0.2 or 0.22 micron in-line polyethersulfone (PES) filter is required for administration *(see section 4.2 Special Instructions for Use, Handling and Disposal).*

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

4.2 Special Instructions for Use, Handling and Disposal

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.

- 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 2–8°C; discard unused Kadcyla after 24 hours.

Reconstituted solution should be inspected visually for particulate matter and discolouration prior to administration. The reconstituted solution should be free of visible particulates, clear to slightly opalescent. The colour of the reconstituted solution should be colourless to pale brown. Do not use if reconstituted solution contains visible particulates, or is cloudy, or is discoloured.

Instructions for dilution:

Determine the volume of the solution required based on a dose of 3.6 mg Kadcyla per kg body weight *(see section 2.2 for dose reduction schedule)*:

$$\textbf{Volume}\ (\text{ml}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\text{mg/kg})}{\textbf{20}\ \text{mg/ml (concentration of reconstituted solution)}}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 ml of 0.45% sodium chloride or 0.9% sodium chloride. Dextrose (5%) solution should not be used. 0.45% sodium chloride may be used without a 0.2 or 0.22 micron in-line polyethersulfone (PES) filter. If 0.9% sodium chloride is used for infusion, a 0.2 or 0.22 micron in-line 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°C - 8°C. Do not freeze or shake the infusion 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.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimised. 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.

4.3 Packs

Vials 100 mg 1

Vials 160 mg 1

Medicine: keep out of reach of children

Current at February 2022

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