(8%), dyspnea (8%), neutropenia (8%), blood bilirubin increased (7%), hypokalemia (7%), pruritus (7%), hypertension (6%), lacrimation increased (6%), chills (5%), dry eye (4.5%), dyspepsia (4.3%), peripheral edema (3.9%),vision blurred (3.9%), conjunctivitis (3.5%), left ventricular dysfunction (3.0%), drug hypersensitivity (2.7%), infusion-related reaction (1.6%), radiation pneumonitis (1.5%), pneumonitis (1.1%), rash (1.1%), asthenia (0.4%), nodular regenerative hyperplasia (0.3%).

Table 6 Selected Laboratory Abnormalities (KATHERINE)

Parameter	KADCYLA n=740			Trastuzumab n=720		
	All Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**	**All Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Chemistry						
Increased AST	79	0.8	0	21	0.1	0
Increased ALT	55	0.7	0	21	0.1	0
Decreased potassium	26	2	0.5	9	0.7	0.1
Increased bilirubin	12	0	0	4	0.7	0
Hematology						
Decreased platelet count	51	4	2	13	0.1	0.1
Decreased hemoglobin	31	1	0	29	0.3	0
Decreased neutrophils	24	1	0	19	0.6	0.6

6.2 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 clinical studies, 6.4% (24/376) of patients tested positive for anti-KADCYLA antibodies. In EMILIA, 5.2% (24/466) of patients tested positive for anti-KADCYLA antibodies, of which 13 were also positive for neutralizing antibodies. In KATHERINE, 3.7% (15/401) of patients tested positive for anti-KADCYLA antibodies, of which 5 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. The presence of KADCYLA in patient serum at the time of ADA sampling may interfere with the ability of this assay to detect anti-KADCYLA antibodies. As a result, data may not accurately reflect the true incidence of anti-KADCYLA antibody development.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to KADCYLA with the incidence of antibodies to other products may be misleading. Clinical significance of anti-KADCYLA antibodies is not yet known.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of KADCYLA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse Reactions from Observational Studies

- CHF and > 10% reduction in LVEF in patients with HER2-positive metastatic breast cancer with a baseline LVEF of 40-49% treated with KADCYLA *[see Warnings and Precautions (5.2)]*.

Adverse Reactions from Postmarketing Spontaneous Reports

- Tumor lysis syndrome (TLS)
- Skin/tissue necrosis after extravasation

7 DRUG INTERACTIONS

No formal drug-drug interaction studies with KADCYLA have been conducted. *In vitro* studies indicate that DM1, the cytotoxic component of KADCYLA, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5. 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 coadministered and KADCYLA treatment cannot be delayed, patients should be closely monitored for adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Pharmacovigilance Program

There is a pregnancy pharmacovigilance program for KADCYLA. If KADCYLA is administered during pregnancy, or if a patient becomes pregnant while receiving KADCYLA or within 7 months following the last dose of KADCYLA, health care providers and patients should immediately report KADCYLA exposure to Genentech at 1-888-835-2555.

Risk Summary

KADCYLA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of KADCYLA in pregnant women. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death were observed in the postmarketing setting in patients treated with trastuzumab, the antibody component of KADCYLA *[see Data]*. Based on its mechanism of action, the DM1 component of KADCYLA can also cause embryo-fetal harm when administered to a pregnant woman [*see Data*]. Apprise the patient of the potential risks to a fetus. There are clinical considerations if KADCYLA is used in a pregnant woman, or if a patient becomes pregnant within 7 months following the last dose of KADCYLA *[see Clinical Considerations]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received KADCYLA during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

There are no available data on the use of KADCYLA in pregnant women. In the post-marketing setting, cases of oligohydramnios, and of oligohydramnios sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal abnormalities and neonatal death were observed after treatment with trastuzumab during pregnancy. These case reports described oligohydramnios in pregnant women who received trastuzumab either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after trastuzumab was stopped. In one case, trastuzumab therapy resumed after amniotic index improved, and oligohydramnios recurred.

Animal Data

There were no reproductive and developmental toxicology studies conducted with ado-trastuzumab emtansine. DM1, the cytotoxic component of KADCYLA, disrupts microtubule function. DM1 is toxic to rapidly dividing cells in animals and is genotoxic, suggesting it has the potential to cause embryotoxicity and teratogenicity. In studies where trastuzumab was administered to pregnant cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (about 7 times the clinical dose), trastuzumab crossed the placental barrier during the early (Gestation Days 20 to 50) and late (Gestation Days 120 to 150) phases of gestation. The resulting concentrations of trastuzumab in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ado-trastuzumab emtansine in human milk, the effects on the breastfed infant, or the effects on milk production. DM1, the cytotoxic component of KADCYLA, may cause serious adverse reactions in breastfed infants based on its mechanism of action *[see Data]*. Advise women not to breastfeed during treatment and for 7 months following the last dose of KADCYLA.

Data

There were no animal lactation studies conducted with ado-trastuzumab emtansine or the cytotoxic component of KADCYLA (DM1). In lactating cynomolgus monkeys, trastuzumab was present in breast milk at about 0.3% of maternal serum concentrations after pre- (beginning Gestation Day 120) and post-partum (through Post-partum Day 28) doses of 25 mg/kg administered twice weekly (about 7 times the clinical dose of KADCYLA). Infant monkeys with detectable serum levels of trastuzumab did not exhibit any adverse effects on growth or development from birth to 1 month of age.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of KADCYLA.

Contraception

Females

KADCYLA can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of KADCYLA [*see Use in Specific Populations (8.1)*].

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with KADCYLA and for 4 months following the last dose.

Infertility

Based on results from animal toxicity studies, KADCYLA may impair fertility in females and males of reproductive potential. It is not known if the effects are reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of KADCYLA have not been established in pediatric patients.

8.5 Geriatric Use

Of the 495 patients who were randomized to KADCYLA in EMILIA *[see Clinical Studies (14.1)]*, 65 patients (13%) were ≥ 65 years of age and 11 patients (2%) were ≥ 75 years of age. In patients ≥ 65 years old (n=138 across both treatment arms) the hazard ratios for progression-free survival (PFS) and overall survival (OS) were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively. No overall differences in the safety of KADCYLA were observed in patients aged ≥ 65 compared to patients < 65 years of age. EMILIA did not include sufficient numbers of patients aged ≥ 75 years to draw conclusions on the safety or effectiveness of KADCYLA in this age group.

Of the 743 patients who were randomized to KADCYLA in KATHERINE *[see Clinical Studies (14.2)]*, 58 patients (8%) were ≥ 65 years of age and 2 patients (0.3%) were ≥ 75 years of age. No overall differences in the safety or effectiveness of KADCYLA were observed in patients aged ≥ 65 compared to patients < 65 years of age. KATHERINE did not include sufficient numbers of patients aged ≥ 75 years to draw conclusions on the safety or effectiveness of KADCYLA in this age group.

Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of ado-trastuzumab emtansine *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No dedicated renal impairment trial for KADCYLA has been conducted. Based on the population pharmacokinetics, as well as analysis of Grade 3 or greater adverse reactions and dose modifications, dose adjustments of KADCYLA are not needed in patients with mild (creatinine clearance [CLcr] 60 to 89 mL/min) or moderate (CLcr 30 to 59 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited data available *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No adjustment to the starting dose is required for patients with mild or moderate hepatic impairment *[see Clinical Pharmacology (12.3)]*. KADCYLA was not studied in patients with severe hepatic impairment. Closely monitor patients with hepatic impairment due to known hepatotoxicity observed with KADCYLA [*see Warnings and Precautions, Hepatotoxicity (5.1)*].

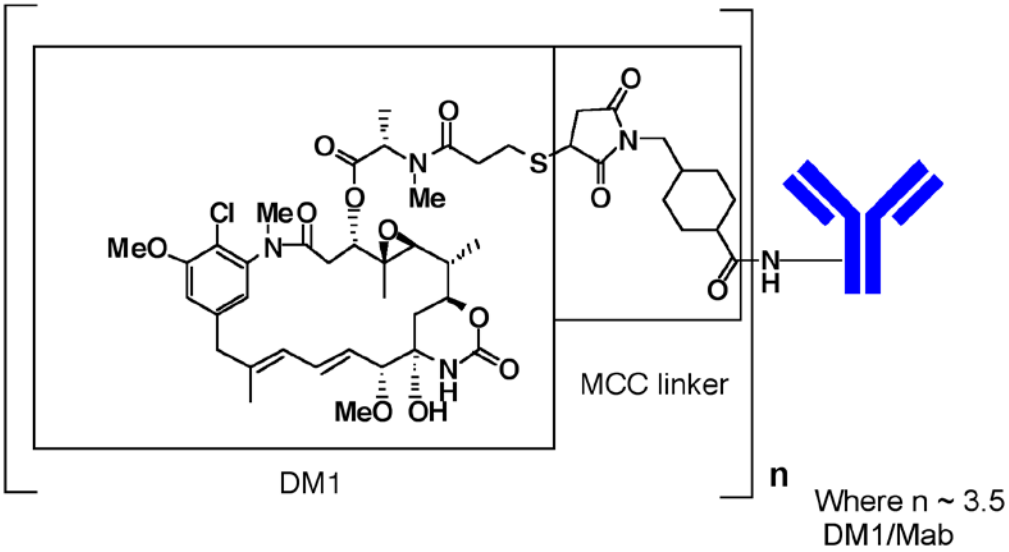
10 OVERDOSAGE

There is no known antidote for overdose of KADCYLA. In clinical trials, overdose of KADCYLA has been reported at approximately two times the recommended dose which resulted in Grade 2 thrombocytopenia (resolved 4 days later) and one death. In the fatal case, the patient incorrectly received KADCYLA at 6 mg/kg and died approximately 3 weeks following the overdose; a cause of death and a causal relationship to KADCYLA were not established.

11 DESCRIPTION

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

The antibody trastuzumab, is a well characterized recombinant monoclonal antibody product produced by mammalian (Chinese hamster ovary) cells, and the small molecule components (DM1 and MCC) are produced by chemical synthesis. Ado-trastuzumab emtansine contains an average of 3.5 DM1 molecules per antibody. Ado-trastuzumab emtansine has the following chemical structure:



Note: The bracketed structure is DM1 plus MCC which represents the emtansine component. The n is, on average, 3.5 DM1 molecules per trastuzumab (Mab) molecule.

KADCYLA (ado-trastuzumab emtansine) is a sterile, white to off-white preservative free lyophilized powder in single-dose vials. Each vial contains 100 mg or 160 mg ado-trastuzumab emtansine. Following reconstitution, each single-dose vial contains ado-trastuzumab emtansine (20 mg/mL), polysorbate 20 [0.02% (w/v)], sodium succinate (10 mM), and sucrose [6% (w/v)] with a pH of 5.0. The resulting solution containing 20 mg/mL ado-trastuzumab emtansine is administered by intravenous infusion following dilution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Cardiac Electrophysiology

Table 7Summary of Efficacy from EMILIA

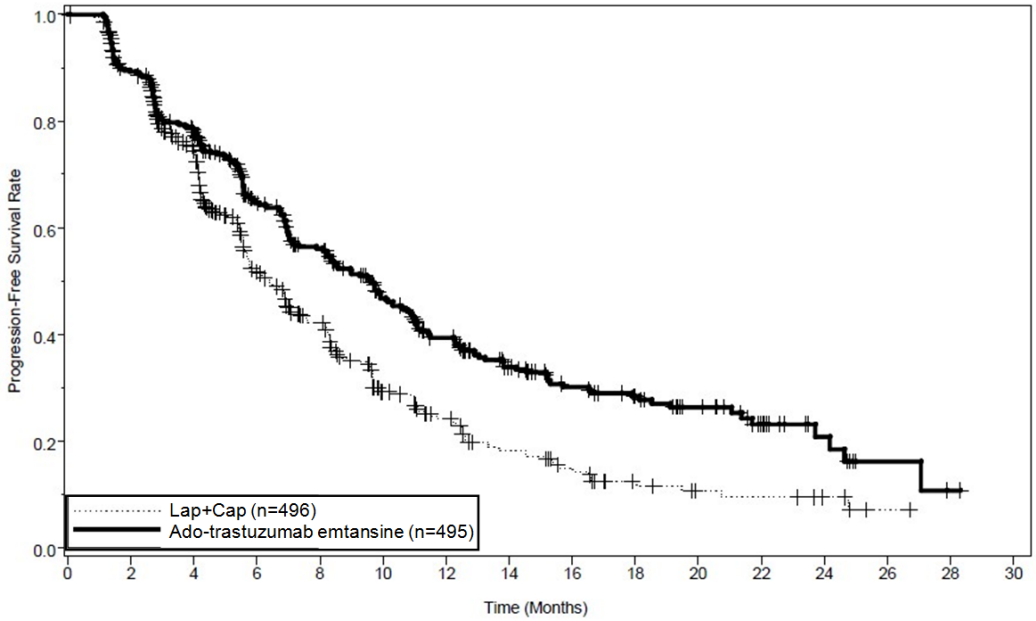
	KADCYLA N=495	Lapatinib+Capecitabine N=496
Progression-Free Survival (independent review)		
Number (%) of patients with event	265 (53.5%)	304 (61.3%)
Median duration of PFS (months)	9.6	6.4
Hazard Ratio (stratified*)	0.650	
95% CI for Hazard Ratio	(0.549, 0.771)	
p-value (Log-Rank test, stratified*)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

PFS: progression-free survival; OR: objective response

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

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

Figure 1 Kaplan-Meier Curve of IRC-Assessed Progression-Free Survival for EMILIA

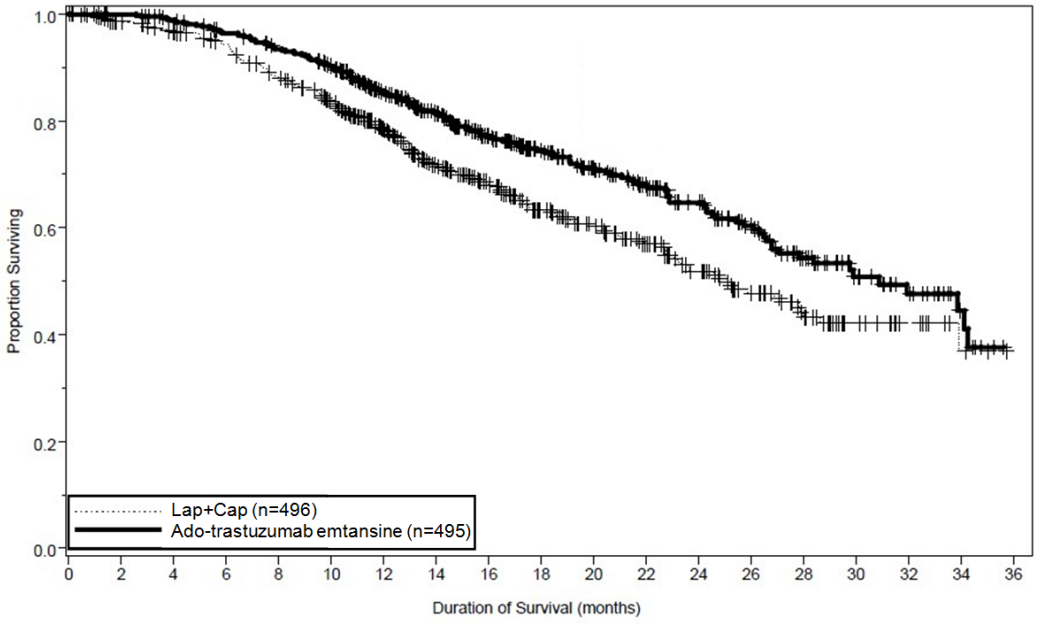


Number at Risk:

Lap+Cap (n=496)	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
Ado-trastuzumab emtansine (n=495)	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

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

Figure 2 Kaplan-Meier Curve of Overall Survival for EMILIA



Number at Risk:

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

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.

14.2 Early Breast Cancer

KATHERINE (NCT01772472) was a randomized, multicenter, open-label trial of 1486 patients with HER2-positive, early breast cancer. Patients were required to have had neoadjuvant taxane and trastuzumab-based therapy with residual invasive tumor in the breast and/or axillary lymph nodes. 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 using Ventana's PATHWAY anti-HER2-/neu (4B5) Rabbit Monoclonal Primary Antibody or INFORM HER2 Dual ISH DNA Probe Cocktail assays. Patients were randomized (1:1) to receive KADCYLA or trastuzumab. 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 evaluation 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. At the time of the major efficacy outcome analysis, median treatment duration was 10 months for both KADCYLA- and trastuzumab-treated patients. Patients who discontinued KADCYLA for reasons other than disease recurrence could complete the remainder of the planned HER2-directed therapy with trastuzumab if appropriate based on toxicity considerations and investigator discretion.

The major efficacy outcome 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 efficacy outcomes included IDFS including second primary non-breast cancer, disease free survival (DFS), and overall survival (OS).

Patient demographics and baseline tumor characteristics were generally balanced between treatment arms. The median age was approximately 49 years (range 23-80 years), 73% were White, 9% were Asian, 6% were American Indian or Alaska Native and 3% were Black or African American. Most patients (99.7%) were women. Enrollment by region was as follows: 23% in North America, 54% in Europe and 23% throughout the rest of the world. Tumor prognostic characteristics including hormone receptor status (positive: 72%, negative: 28%), clinical stage at presentation (inoperable: 25%, operable: 75%) and pathological nodal status after preoperative therapy (node positive: 46%, node negative or not evaluated: 54%) were similar across study arms.

The majority of patients (77%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. Twenty percent of patients received another HER2-targeted agent in addition to trastuzumab as a component of neoadjuvant therapy; 94% of these patients received pertuzumab.

After a median follow-up of 40 months, a statistically significant improvement in IDFS was observed in patients who received KADCYLA compared with trastuzumab. The OS data were not mature at the time of the IDFS analysis (98 deaths [6.6%] occurred in 1486 patients). The efficacy results from KATHERINE are summarized in Table 8 and Figure 3.

Consistent results were observed with KADCYLA in terms of IDFS across subgroups based on stratification factors, key baseline demographic and disease characteristics, and prior treatments.

Table 8 Efficacy Results from KATHERINE

	KADCYLA N=743	Trastuzumab N=743
Invasive Disease-Free Survival (IDFS)[1,4]		
Number (%) of patients with event	91 (12.2%)	165 (22.2%)
HR [95% CI][2]	0.50 [0.39, 0.64]	
p-value (Log-Rank test, unstratified)	< 0.0001	
3-year event-free rate[3], % [95% CI]	88.3 [85.8, 90.7]	77.0 [73.8, 80.7]
IDFS including second primary non-breast cancer		
Number (%) of patients with event	95 (12.8%)	167 (22.5%)
HR [95% CI][2]	0.51 [0.40, 0.66]	
3-year event-free rate[3], % [95% CI]	87.7 [85.2, 90.2]	76.9 [73.7, 80.1]
Disease-Free Survival (DFS)		
Number (%) of patients with event	98 (13.2%)	167 (22.5%)
HR [95% CI][2]	0.53 [0.41, 0.68]	
3-year event-free rate[3], % [95% CI]	87.4 [84.9, 89.9]	76.9 [73.7, 80.1]

HR: Hazard Ratio; CI: Confidence Intervals,

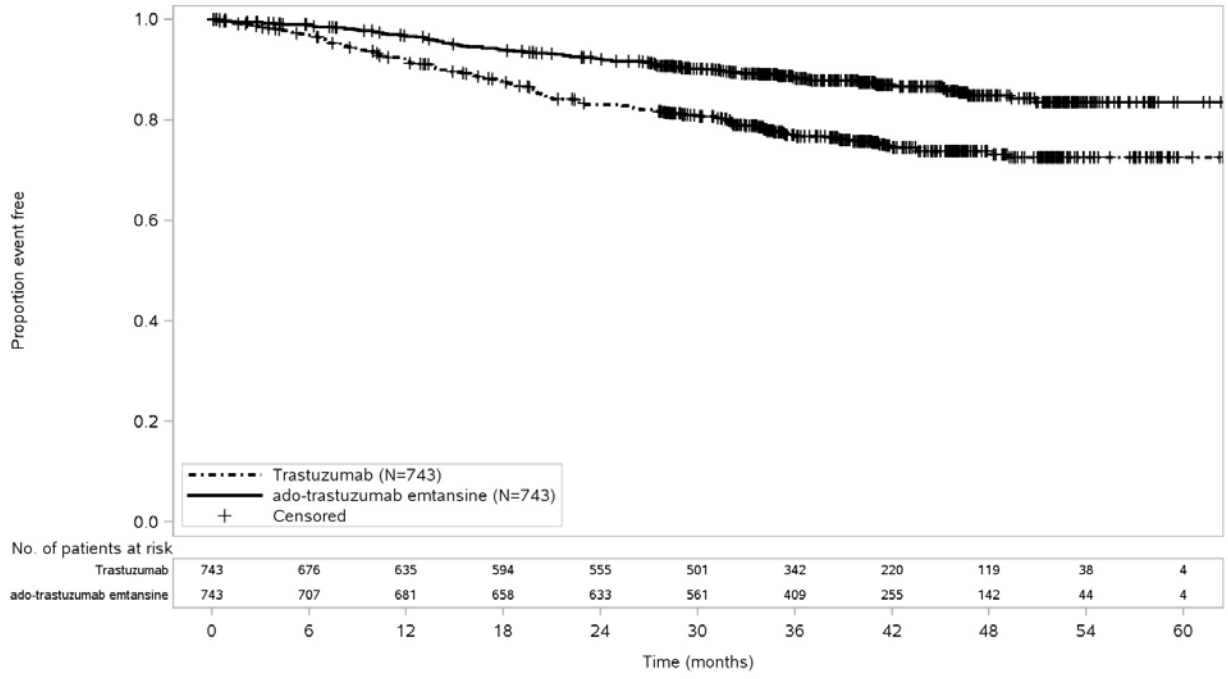
[1] Hierarchical testing applied for IDFS and OS

[2] Unstratified analysis

[3] 3-year event-free rate derived from Kaplan-Meier estimates

[4] Data from the pre-specified interim analysis (67% of the number of events for the planned final analysis) with the p-value compared with the allocated alpha of 0.012

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



15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA.* http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied/Storage

KADCYLA (ado-trastuzumab emtansine) is supplied as:

Carton Contents	NDC
One 100 mg vial, single-dose vial	NDC 50242-088-01
One 160 mg vial, single-dose vial	NDC 50242-087-01

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution. *Do not freeze or shake.*

16.2 Special Handling

Follow procedures for proper handling and disposal of anticancer drugs.

17 PATIENT COUNSELING INFORMATION

Hepatotoxicity

- Inform patients of the possibility of severe liver injury and advise patients to immediately seek medical attention if they experience symptoms of acute hepatitis such as nausea, vomiting, abdominal pain (especially RUQ abdominal pain), jaundice, dark urine, generalized pruritus, anorexia, etc. *[see Warnings and Precautions (5.1)]*.

Left Ventricular Dysfunction

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential that KADCYLA exposure during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1, 8.3)]*.
- Advise women who are exposed to KADCYLA during pregnancy or who become pregnant within 7 months following the last dose of KADCYLA that there is a pregnancy pharmacovigilance program that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to Genentech *[see Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of KADCYLA *[see Use in Specific Populations (8.1, 8.3)]*.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months following the last dose of KADCYLA *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise women not to breastfeed during treatment and for 7 months after the last dose of KADCYLA *[see Use in Specific Populations (8.2)]*.

KADCYLA® [ado-trastuzumab emtansine]

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A Member of the Roche Group
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U.S. License No: 1048