

1.14.1.3 Draft Labeling Text

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KADCYLA safely and effectively. See full prescribing information for KADCYLA.

KADCYLA™ (ado-trastuzumab emtansine) for injection, for intravenous use

Initial U.S. Approval: {YYYY}

WARNING: HEPATOTOXICITY, CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- Do not substitute KADCYLA for or with trastuzumab. (2.1)
- 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. (2.2, 5.1)
- KADCYLA may lead to reductions in left ventricular ejection fraction (LVEF). Assess LVEF prior to initiation. Monitor and withhold dosing or discontinue as appropriate. (2.2, 5.2)
- Can cause fetal harm. Advise women of potential risk to the fetus. (5.3, 8.1, 8.6)

INDICATIONS AND USAGE

KADCYLA is a HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

- Received prior therapy for metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy. (1)

DOSAGE AND ADMINISTRATION

- For intravenous infusion only. Do not administer as an intravenous push or bolus. Do not use Dextrose (5%) solution. (2.3)
- The recommended dose of KADCYLA is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Do not administer KADCYLA at doses greater than 3.6 mg/kg. Do not substitute KADCYLA for or with trastuzumab. (2.1)
- Management of adverse events (infusion-related reactions, hepatotoxicity, left ventricular cardiac dysfunction, thrombocytopenia, pulmonary toxicity or peripheral neuropathy) may require temporary

interruption, dose reduction, or treatment discontinuation of KADCYLA. (2.2)

DOSAGE FORMS AND STRENGTHS

Lyophilized powder in single-use vials containing 100 mg per vial or 160 mg per vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Pulmonary Toxicity: Permanently discontinue KADCYLA in patients diagnosed with interstitial lung disease or pneumonitis. (2.2, 5.4)
- Infusion-Related Reactions, Hypersensitivity Reactions: Monitor for signs and symptoms during and after infusion. If significant infusion-related reactions or hypersensitivity reactions occur, slow or interrupt the infusion and administer appropriate medical therapies. Permanently discontinue KADCYLA for life threatening infusion-related reaction. (2.1, 2.2, 5.5)
- Thrombocytopenia: Monitor platelet counts prior to each KADCYLA dose. Institute dose modifications as appropriate. (2.2, 5.6)
- Neurotoxicity: Monitor for signs or symptoms. Withhold dosing temporarily for patients experiencing Grade 3 or 4 peripheral neuropathy. (2.2, 5.7, 13.2)
- HER2 Testing: Perform using FDA-approved tests by laboratories with demonstrated proficiency. (5.8)

ADVERSE REACTIONS

The most common adverse drug reactions (frequency > 25%) with KADCYLA (n=884 treated patients) were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue nursing or discontinue KADCYLA taking into consideration the importance of the drug to the mother. (8.3)
- Females of Reproductive Potential: Counsel females on pregnancy prevention and planning. Encourage patient participation in the MoHER Pregnancy Registry by contacting 1-800-690-6720). (5.3, 8.1, 8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: {insert date MM/YYYY}

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1 **FULL PRESCRIBING INFORMATION**

2 **Do Not Substitute KADCYLA for or with Trastuzumab**

3
4 **WARNING: HEPATOTOXICITY, CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY**

- 5
- 6 • Hepatotoxicity: Serious hepatotoxicity has been reported, including liver failure and
7 death in patients treated with KADCYLA. Monitor serum transaminases and bilirubin
8 prior to initiation of KADCYLA treatment and prior to each KADCYLA dose.
9 Reduce dose or discontinue KADCYLA as appropriate in cases of increased serum
10 transaminases or total bilirubin. (2.2, 5.1)
 - 11 • Cardiac Toxicity: KADCYLA administration may lead to reductions in left
12 ventricular ejection fraction (LVEF). Evaluate left ventricular function in all patients
13 prior to and during treatment with KADCYLA. Withhold treatment for clinically
14 significant decrease in left ventricular function. (2.2, 5.2)
 - 15 • Embryo-Fetal Toxicity: Exposure to KADCYLA can result in embryo-fetal death or
16 birth defects. Advise patients of these risks and the need for effective contraception.
17 (5.3, 8.1, 8.6)

18 **1 INDICATIONS AND USAGE**

19 KADCYLA™, as a single agent, is indicated for the treatment of patients with HER2-positive,
20 metastatic breast cancer who previously received trastuzumab and a taxane, separately or in
21 combination. Patients should have either:

- 22 • Received prior therapy for metastatic disease, or
- 23 • Developed disease recurrence during or within six months of completing adjuvant
24 therapy.

25 **2 DOSAGE AND ADMINISTRATION**

26 **2.1 Recommended Doses and Schedules**

27 The recommended dose of KADCYLA is 3.6 mg/kg given as an intravenous infusion
28 every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Do not
29 administer KADCYLA at doses greater than 3.6 mg/kg. Do not substitute KADCYLA for or with
30 trastuzumab.

31 Closely monitor the infusion site for possible subcutaneous infiltration during drug
32 administration [see Warnings and Precautions (5.9)].

33 First infusion: Administer infusion over 90 minutes. Patients should be observed during the
34 infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion-
35 related reactions [see Warnings and Precautions (5.5)].

36 Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated.
37 Patients should be observed during the infusion and for at least 30 minutes after infusion.

38 **2.2 Dose Modifications**

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

If a planned dose is delayed or 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-

40 week interval between doses. The infusion may be administered at the dose and rate the patient
41 tolerated in the most recent infusion.

42 The infusion rate of KADCYLA should be slowed or interrupted if the patient develops an
43 infusion-related reaction. Permanently discontinue KADCYLA for life-threatening infusion-
44 related reactions [see Warnings and Precautions (5.5)].

45 Management of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction,
46 thrombocytopenia, pulmonary toxicity or peripheral neuropathy may require temporary
47 interruption, dose reduction or treatment discontinuation of KADCYLA as per guidelines
48 provided in Tables 1 to 5.

49 **Table 1 Recommended Dose Reduction Schedule for Adverse Events**

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

50

51 **Hepatotoxicity [see Warnings and Precautions (5.1)]**

52 A reduction in the dose of KADCYLA is recommended in the case of hepatotoxicity exhibited as
53 increases in serum transaminases and/or hyperbilirubinemia (see Tables 2 and 3).

54 **Table 2 Dose Modification Guidelines for Increased Serum Transaminases (AST/ALT)**

Grade 2 (> 2.5 to $\leq 5 \times$ ULN)	Grade 3 (> 5 to $\leq 20 \times$ ULN)	Grade 4 ($> 20 \times$ ULN)
Treat at same dose level.	Do not administer KADCYLA until AST/ALT recovers to Grade ≤ 2 , and then reduce one dose level.	Permanently discontinue KADCYLA.

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.

55

56 **Table 3 Dose Modification Guidelines for Hyperbilirubinemia**

Grade 2 (> 1.5 to $\leq 3 \times$ ULN)	Grade 3 (> 3 to $\leq 10 \times$ ULN)	Grade 4 ($> 10 \times$ ULN)
Do not administer KADCYLA until total bilirubin recovers to Grade ≤ 1 , and then treat at same dose level.	Do not administer KADCYLA until total bilirubin recovers to Grade ≤ 1 , and then reduce one dose level.	Permanently discontinue KADCYLA.

57

58 Permanently discontinue KADCYLA treatment in patients with serum transaminases $> 3 \times$ ULN
59 and concomitant total bilirubin $> 2 \times$ ULN.

60 Permanently discontinue KADCYLA in patients diagnosed with nodular regenerative
61 hyperplasia (NRH).

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67 **Left Ventricular Dysfunction [see Warnings and Precautions (5.2)]**

68 **Table 4 Dose Modifications for Left Ventricular Dysfunction**

Symptomatic CHF	LVEF < 40%	LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	LVEF > 45%
Discontinue KADCYLA	Do not administer KADCYLA. Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue KADCYLA.	Do not administer KADCYLA. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue KADCYLA.	Continue treatment with KADCYLA. Repeat LVEF assessment within 3 weeks.	Continue treatment with KADCYLA.

69 CHF = Congestive Heart Failure; LVEF = Left Ventricular Ejection Fraction

70

71 **Thrombocytopenia [see Warnings and Precautions (5.6)]**

72 A reduction in dose is recommended in the case of Grade 4 thrombocytopenia
73 (platelets < 25,000/mm³) (see Table 5).

74 **Table 5 Dose Modification Guidelines for Thrombocytopenia**

Grade 3	Grade 4
PLT 25,000/mm ³ to < 50,000/mm ³	PLT < 25,000/mm ³
Do not administer KADCYLA until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm ³), and then treat at same dose level.	Do not administer KADCYLA until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm ³), and then reduce one dose level.

PLT = Platelets

75

76 **Pulmonary Toxicity [see Warnings and Precautions (5.4)]**

77 KADCYLA should be permanently discontinued in patients diagnosed with interstitial lung
78 disease (ILD) or pneumonitis.

79 **Peripheral Neuropathy [see Warnings and Precautions (5.7)]**

80 KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral
81 neuropathy until resolution to ≤ Grade 2.

82 **2.3 Preparation for Administration**

83 In order to prevent medication errors it is important to check the vial labels to ensure that the
84 drug being prepared and administered is KADCYLA (ado-trastuzumab emtansine) and not
85 trastuzumab.

86

87 **Administration:**

- 88 • Administer KADCYLA as an intravenous infusion only with a 0.22 micron in-line
89 non-protein adsorptive polyethersulfone (PES) filter. Do not administer as an intravenous
90 push or bolus.
- 91 • Do not mix KADCYLA, or administer as an infusion, with other medicinal products.
- 92 • In order to improve traceability of biological medicinal products, the tradename of the
93 administered product should be clearly recorded (or stated) in the patient file.

94 **Reconstitution:**

- 95 • Use aseptic technique for reconstitution and preparation of dosing solution. Appropriate
96 procedures for the preparation of chemotherapeutic drugs should be used.
- 97 • Using a sterile syringe, slowly inject 5 mL of Sterile Water for Injection into the 100 mg
98 KADCYLA vial, or 8 mL of Sterile Water for Injection into the 160 mg KADCYLA vial to
99 yield a solution containing 20 mg/mL. Swirl the vial gently until completely dissolved. Do
100 not shake. Inspect the reconstituted solution for particulates and discoloration.
- 101 • The reconstituted solution should be clear to slightly opalescent and free of visible
102 particulates. The color of the reconstituted solution should be colorless to pale brown. Do
103 not use if the reconstituted solution contains visible particulates or is cloudy or discolored.
- 104 • The reconstituted lyophilized vials should be used immediately following reconstitution with
105 Sterile Water for Injection. If not used immediately, the reconstituted KADCYLA vials can
106 be stored for up to 4 hours in a refrigerator at 2°C to 8°C (36°F to 46°F); discard unused
107 KADCYLA after 4 hours. Do not freeze.
- 108 • The reconstituted product contains no preservative and is intended for single-use only.

109 **Dilution:**

- 110 Determine the correct dose (mg) of KADCYLA [see *Dosage and Administration (2.1)*].
- 111 • Calculate the volume of the 20 mg/mL reconstituted KADCYLA solution needed.
- 112 • Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9%
113 Sodium Chloride Injection. Do not use Dextrose (5%) solution.
- 114 • Gently invert the bag to mix the solution in order to avoid foaming.
- 115 • The diluted KADCYLA infusion solution should be used immediately. If not used
116 immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up
117 to 4 hours prior to use. Do not freeze or shake.

118 **3 DOSAGE FORMS AND STRENGTHS**

119 Lyophilized powder in single-use vials: 100 mg per vial or 160 mg per vial of ado-trastuzumab
120 emtansine.

121 **4 CONTRAINDICATIONS**

122 None.

123 **5 WARNINGS AND PRECAUTIONS**

124 **5.1 Hepatotoxicity**

125 Hepatotoxicity, predominantly in the form of asymptomatic, transient increases in the
126 concentrations of serum transaminases, has been observed in clinical trials with KADCYLA [see
127 *Adverse Reactions (6.1)*]. Serious hepatobiliary disorders, including at least two fatal cases of
128 severe drug-induced liver injury and associated hepatic encephalopathy, have been reported in

129 clinical trials with KADCYLA. Some of the observed cases may have been confounded by
130 comorbidities and/or concomitant medications with known hepatotoxic potential.

131 Monitor serum transaminases and bilirubin prior to initiation of KADCYLA treatment and prior
132 to each KADCYLA dose. Patients with known active hepatitis B virus or hepatitis C virus were
133 excluded from Study 1 [see *Clinical Studies (14.1)*]. Reduce the dose or discontinue
134 KADCYLA as appropriate in cases of increased serum transaminases and/or total bilirubin [see
135 *Dosage and Administration (2.2)*]. Permanently discontinue KADCYLA treatment in patients
136 with serum transaminases > 3 x ULN and concomitant total bilirubin > 2 x ULN. KADCYLA
137 has not been studied in patients with serum transaminases > 2.5 x ULN or bilirubin > 1.5 x ULN
138 prior to the initiation of treatment.

139 In clinical trials of KADCYLA, cases of nodular regenerative hyperplasia (NRH) of the liver
140 have been identified from liver biopsies (3 cases out of 884 treated patients). Two of these three
141 cases of NRH were observed in the randomized trial (Study 1) [see *Adverse Reactions (6.1)*].
142 NRH is a rare liver condition characterized by widespread benign transformation of hepatic
143 parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension.
144 The diagnosis of NRH can be confirmed only by histopathology. NRH should be considered in
145 all patients with clinical symptoms of portal hypertension but with normal transaminases and no
146 manifestations of cirrhosis. Upon diagnosis of NRH, KADCYLA treatment must be
147 permanently discontinued.

148 **5.2 Left Ventricular Dysfunction**

149 Patients treated with KADCYLA are at increased risk of developing left ventricular dysfunction.
150 A decrease of LVEF to < 40% has been observed in patients treated with KADCYLA. In the
151 randomized trial (Study 1), left ventricular dysfunction occurred in 1.8% of patients in the
152 KADCYLA-treated group and 3.3% of patients in the lapatinib plus capecitabine-treated group
153 [see *Adverse Reactions (6.1)*].

154 Assess LVEF prior to initiation of KADCYLA and at regular intervals (e.g. every three months)
155 during treatment to ensure the LVEF is within the institution's normal limits. Treatment with
156 KADCYLA has not been studied in patients with LVEF < 50% prior to initiation of treatment.
157 If, at routine monitoring, LVEF is < 40%, or is 40% to 45% with a 10% or greater absolute
158 decrease below the pretreatment value, withhold KADCYLA and repeat LVEF assessment
159 within approximately 3 weeks. Permanently discontinue KADCYLA if the LVEF has not
160 improved or has declined further [see *Dosage and Administration (2.2)*]. Patients with a history
161 of symptomatic congestive heart failure (CHF), serious cardiac arrhythmia, or history of
162 myocardial infarction or unstable angina within 6 months were excluded from Study 1 [see
163 *Clinical Studies (14.1)*].

164 **5.3 Embryo-Fetal Toxicity**

165 KADCYLA can cause fetal harm when administered to a pregnant woman. There are no
166 adequate and well-controlled studies of KADCYLA in pregnant women and no reproductive and
167 developmental toxicology studies have been conducted with ado-trastuzumab emtansine.
168 Nevertheless, treatment with trastuzumab, the antibody component of KADCYLA, during
169 pregnancy in the postmarketing setting has resulted in oligohydramnios, some associated with
170 fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death. DM1, the cytotoxic
171 component of KADCYLA, can be expected to cause embryo-fetal toxicity based on its
172 mechanism of action.

173 If KADCYLA is used during pregnancy, or if the patient becomes pregnant while receiving
174 KADCYLA, apprise the patient of the potential hazard to the fetus [see *Use in Specific*
175 *Populations (8.1)*].

176 Verify pregnancy status prior to the initiation of KADCYLA. Advise patients of the risks of
177 embryo-fetal death and birth defects and the need for contraception during and after treatment.
178 Advise patients to contact their healthcare provider immediately if they suspect they may be
179 pregnant. If KADCYLA is administered during pregnancy or if a patient becomes pregnant
180 while receiving KADCYLA, immediately report exposure to the Genentech Adverse Event Line
181 at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the
182 MoTHER Pregnancy Registry by contacting 1-800-690-6720 [*see Patient Counseling*
183 *Information (17)*].

184 **5.4 Pulmonary Toxicity**

185 Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory
186 distress syndrome or fatal outcome have been reported in clinical trials with KADCYLA.
187 Pneumonitis at an incidence of 0.8% (7 out of 884 treated patients) has been reported, with one
188 case of grade 3 pneumonitis. Signs and symptoms include dyspnea, cough, fatigue, and
189 pulmonary infiltrates. These events may or may not occur as sequelae of infusion reactions. In
190 the randomized trial (Study 1), the overall frequency of pneumonitis was 1.2% [*see Adverse*
191 *Reactions (6.1)*].

192 Permanently discontinue treatment with KADCYLA in patients diagnosed with ILD or
193 pneumonitis.

194 Patients with dyspnea at rest due to complications of advanced malignancy and co-morbidities
195 may be at increased risk of pulmonary toxicity.

196 **5.5 Infusion-Related Reactions, Hypersensitivity Reactions**

197 Treatment with KADCYLA has not been studied in patients who had trastuzumab permanently
198 discontinued due to infusion-related reactions (IRR) and/or hypersensitivity; treatment with
199 KADCYLA is not recommended for these patients.

200 Infusion-related reactions, characterized by one or more of the following symptoms – flushing,
201 chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia have been
202 reported in clinical trials of KADCYLA. In the randomized trial (Study 1), the overall frequency
203 of IRRs in patients treated with KADCYLA was 1.4% [*see Adverse Reactions (6.1)*]. In most
204 patients, these reactions resolved over the course of several hours to a day after the infusion was
205 terminated. KADCYLA treatment should be interrupted in patients with severe IRR.
206 KADCYLA treatment should be permanently discontinued in the event of a life-threatening IRR
207 [*see Dosage and Administration (2.2)*]. Patients should be observed closely for IRR reactions,
208 especially during the first infusion.

209 One case of a serious, allergic/anaphylactic-like reaction has been observed in clinical trials of
210 single-agent KADCYLA. Medications to treat such reactions, as well as emergency equipment,
211 should be available for immediate use.

212 **5.6 Thrombocytopenia**

213 Thrombocytopenia, or decreased platelet count, was reported in clinical trials of KADCYLA
214 (103 of 884 treated patients with \geq Grade 3; 283 of 884 treated patients with any Grade). The
215 majority of these patients had Grade 1 or 2 events ($<$ LLN to \geq 50,000/mm³) with the nadir
216 occurring by day 8 and generally improving to Grade 0 or 1 (\geq 75,000 /mm³) by the next
217 scheduled dose. In clinical trials of KADCYLA, the incidence and severity of thrombocytopenia
218 were higher in Asian patients. Independent of race, the incidence of severe hemorrhagic events
219 in patients treated with KADCYLA was low.

220 In the randomized trial (Study 1), the overall frequency of thrombocytopenia was 31.2% in the
221 KADCYLA-treated group and 3.3% in the lapatinib plus capecitabine-treated group [*see Adverse*

222 *Reactions (6.1)*. The incidence of \geq Grade 3 thrombocytopenia was 14.5% in the KADCYLA-
223 treated group and 0.4% in the lapatinib plus capecitabine-treated group. In Asian patients, the
224 incidence of \geq Grade 3 thrombocytopenia was 45.1% in the KADCYLA-treated group and 1.3%
225 in the lapatinib plus capecitabine-treated group.

226 Monitor platelet counts prior to initiation of KADCYLA and prior to each KADCYLA dose [*see*
227 *Dosage and Administration (2.2)*]. KADCYLA has not been studied in patients with platelet
228 counts $<100,000/\text{mm}^3$ prior to initiation of treatment. In the event of decreased platelet count to
229 Grade 3 or greater ($< 50,000/\text{mm}^3$) do not administer KADCYLA until platelet counts recover to
230 Grade 1 ($\geq 75,000/\text{mm}^3$) [*see Dosage and Administration (2.2)*]. Patients with
231 thrombocytopenia ($< 100,000/\text{mm}^3$) and patients on anti-coagulant treatment should be closely
232 monitored during treatment with KADCYLA.

233 **5.7 Neurotoxicity**

234 Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical
235 trials of KADCYLA (14 of 884 treated patients with \geq Grade 3; 196 of 884 treated patients with
236 any Grade). In the randomized trial (Study 1), the overall frequency of peripheral neuropathy
237 was 21.2% in the KADCYLA-treated group and 13.5% in the lapatinib plus capecitabine-treated
238 group [*see Adverse Reactions (6.1)*]. The incidence of \geq Grade 3 peripheral neuropathy was
239 2.2% in the KADCYLA-treated group and 0.2% in the lapatinib plus capecitabine-treated group.

240 KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral
241 neuropathy until resolution to \leq Grade 2. Patients should be clinically monitored on an ongoing
242 basis for signs or symptoms of neurotoxicity [*see Nonclinical Toxicology (13.2)*].

243 **5.8 HER2 Testing**

244 Detection of HER2 protein overexpression or gene amplification is necessary for selection of
245 patients appropriate for KADCYLA therapy because these are the only patients studied for
246 whom benefit has been shown [*see Indications and Usage (1), Clinical Studies (14.1)*]. In the
247 randomized study (Study 1), patients with breast cancer were required to have evidence of HER2
248 overexpression defined as 3+ IHC by Dako Herceptest™ or evidence of overexpression defined
249 as FISH amplification ratio ≥ 2.0 by Dako HER2 FISH PharmDx™ test kit. Only limited data
250 were available for patients whose breast cancer was positive by FISH and 0 or 1+ by IHC.

251 Assessment of HER2 status should be performed by laboratories with demonstrated proficiency
252 in the specific technology being utilized. Improper assay performance, including use of sub-
253 optimally fixed tissue, failure to utilize specified reagents, deviation from specific assay
254 instructions, and failure to include appropriate controls for assay validation, can lead to
255 unreliable results.

256 **5.9 Extravasation**

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

262 **6 ADVERSE REACTIONS**

263 The following adverse reactions are discussed in greater detail in other sections of the label:

- 264 • Hepatotoxicity [*See Warnings and Precautions (5.1)*]
- 265 • Left Ventricular Dysfunction [*See Warnings and Precautions (5.2)*]
- 266 • Embryo-Fetal Toxicity [*See Warnings and Precautions (5.3)*]

- 267 • Pulmonary Toxicity [*See Warnings and Precautions (5.4)*]
- 268 • Infusion-Related Reactions, Hypersensitivity Reactions [*See Warnings and Precautions*
- 269 *(5.5)*]
- 270 • Thrombocytopenia [*See Warnings and Precautions (5.6)*]
- 271 • Neurotoxicity [*See Warnings and Precautions (5.7)*]

272 **6.1 Clinical Trials Experience**

273 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
274 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials
275 of another drug and may not reflect the rates observed in practice.

276 In clinical trials, KADCYLA has been evaluated as single-agent in 884 patients with HER2-
277 positive metastatic breast cancer. The most common (frequency $\geq 25\%$) adverse drug reactions
278 (ADRs) seen in 884 patients treated with KADCYLA were fatigue, nausea, musculoskeletal
279 pain, thrombocytopenia, headache, increased transaminases, and constipation.

280 The ADRs described in Table 6 were identified in patients with HER2-positive metastatic breast
281 cancer treated in a randomized trial (Study 1) [*see Clinical Studies (14.1)*]. Patients were
282 randomized to receive KADCYLA or lapatinib plus capecitabine. The median duration of study
283 treatment was 7.6 months for patients in the KADCYLA-treated group and 5.5 months and 5.3
284 months for patients treated with lapatinib and capecitabine, respectively. Two hundred and
285 eleven (43.1%) patients experienced \geq Grade 3 adverse events in the KADCYLA-treated group
286 compared with 289 (59.2%) patients in the lapatinib plus capecitabine-treated group. Dose
287 adjustments for KADCYLA were permitted [*see Dosage and Administration (2.2)*]. Thirty-two
288 patients (6.5%) discontinued KADCYLA due to an adverse event, compared with 41 patients
289 (8.4%) who discontinued lapatinib, and 51 patients (10.5%) who discontinued capecitabine due
290 to an adverse event. The most common adverse events leading to KADCYLA withdrawal were
291 thrombocytopenia and increased transaminases. Eighty patients (16.3%) treated with
292 KADCYLA had adverse events leading to dose reductions. The most frequent adverse events
293 leading to dose reduction of KADCYLA (in $\geq 1\%$ of patients) included thrombocytopenia,
294 increased transaminases, and peripheral neuropathy. Adverse events that led to dose delays
295 occurred in 116 (23.7%) of KADCYLA treated patients. The most frequent adverse events
296 leading to a dose delay of KADCYLA (in $\geq 1\%$ of patients) were neutropenia,
297 thrombocytopenia, leukopenia, fatigue, increased transaminases and pyrexia.

298 Table 6 reports the ADRs that occurred in patients in the KADCYLA-treated group (n=490) of
299 the randomized trial (Study 1). Selected laboratory abnormalities are shown in Table 7. The
300 most common ADRs seen with KADCYLA in the randomized trial (frequency $> 25\%$) were
301 nausea, fatigue, musculoskeletal pain, thrombocytopenia, increased transaminases, headache, and
302 constipation. The most common NCI-CTCAE (version 3) \geq Grade 3 ADRs (frequency $>2\%$)
303 were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy
304 and fatigue.

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312 **Table 6 Summary of Adverse Drug Reactions Occurring in Patients on the KADCYLA**
313 **Treatment Arm in the Randomized Trial (Study 1)**

Adverse Drug Reactions (MedDRA) System Organ Class	KADCYLA (3.6 mg/kg) n=490 Frequency rate %		Lapatinib (1250 mg) + Capecitabine (2000 mg/m ²) n=488 Frequency rate %	
	All grades (%)	Grade 3 – 4 (%)	All grades (%)	Grade 3 – 4 (%)
Blood and Lymphatic System Disorders				
Neutropenia	6.7	2.0	9.0	4.3
Anemia	14.3	4.1	10.5	2.5
Thrombocytopenia	31.2	14.5	3.3	0.4
Cardiac Disorders				
Left ventricular dysfunction	1.8	0.2	3.3	0.4
Eye Disorders				
Lacrimation increased	3.3	0	2.5	0
Dry eye	3.9	0	3.1	0
Vision blurred	4.5	0	0.8	0
Conjunctivitis	3.9	0	2.3	0
Gastrointestinal Disorders				
Dyspepsia	9.2	0	11.5	0.4
Stomatitis	14.1	0.2	32.6	2.5
Dry Mouth	16.7	0	4.9	0.2
Abdominal pain	18.6	0.8	17.6	1.6
Vomiting	19.2	0.8	29.9	4.5
Diarrhea	24.1	1.6	79.7	20.7
Constipation	26.5	0.4	11.1	0
Nausea	39.8	0.8	45.1	2.5
General Disorders and Administration				
Peripheral edema	7.1	0	8.2	0.2
Chills	7.6	0	3.1	0
Pyrexia	18.6	0.2	8.4	0.4
Asthenia	17.8	0.4	17.6	1.6
Fatigue	36.3	2.5	28.3	3.5
Hepatobiliary Disorders				
Nodular regenerative hyperplasia*	0.4	ND	0	0
Portal hypertension*	0.4	0.2	0	0
Immune System Disorders				
Drug hypersensitivity	2.2	0	0.8	0
Injury, Poisoning, and Procedural				
Infusion-related reaction	1.4	0	0.2	0
Infections and Infestations				
Urinary tract infection	9.4	0.6	3.9	0
Investigations				
Blood alkaline phosphatase	4.7	0.4	3.7	0.4

Adverse Drug Reactions (MedDRA) System Organ Class	KADCYLA (3.6 mg/kg) n=490 Frequency rate %		Lapatinib (1250 mg) + Capecitabine (2000 mg/m ²) n=488 Frequency rate %	
	All grades (%)	Grade 3 – 4 (%)	All grades (%)	Grade 3 – 4 (%)
increased				
Increased transaminases	28.8	8.0	14.3	2.5
Metabolism and Nutrition Disorders				
Hypokalemia	10.2	2.7	9.4	4.7
Musculoskeletal and Connective Tissue Disorders				
Myalgia	14.1	0.6	3.7	0
Arthralgia	19.2	0.6	8.4	0
Musculoskeletal pain	36.1	1.8	30.5	1.4
Nervous System Disorders				
Dysgeusia	8.0	0	4.1	0.2
Dizziness	10.2	0.4	10.7	0.2
Peripheral neuropathy	21.2	2.2	13.5	0.2
Headache	28.2	0.8	14.5	0.8
Psychiatric Disorders				
Insomnia	12.0	0.4	8.6	0.2
Respiratory, Thoracic, and Mediastinal Disorders				
Pneumonitis	1.2	0	0	0
Dyspnea	12.0	0.8	8.0	0.4
Cough	18.2	0.2	13.1	0.2
Epistaxis	22.5	0.2	8.4	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	5.5	0.2	9.2	0
Rash	11.6	0	27.5	1.8
Vascular Disorders				
Hypertension	5.1	1.2	2.3	0.4

314 * Nodular Regenerative Hyperplasia and Portal Hypertension occurred in the same patient.

315 ND = Not determined

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327 **Table 7 Selected Laboratory Abnormalities**

Parameter	KADCYLA (3.6 mg/kg)			Lapatinib (1250 mg) + Capecitabine (2000 mg/m ²)		
	All Grade %	Grade 3 %	Grade 4 %	All Grade %	Grade 3 %	Grade 4 %
Increased bilirubin	17	<1	0	57	2	0
Increased AST	98	7	<1	65	3	0
Increased ALT	82	5	<1	54	3	0
Decreased platelet count	83	14	3	21	<1	<1
Decreased hemoglobin	60	4	1	64	3	<1
Decreased neutrophils	39	3	<1	38	6	2
Decreased potassium	33	3	0	31	6	<1

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329 **6.2 Immunogenicity**

330 As with all therapeutic proteins, there is the potential for an immune response to KADCYLA.
331 A total of 836 patients from six clinical studies were tested at multiple time points for anti-
332 therapeutic antibody (ATA) responses to KADCYLA. Following KADCYLA dosing, 5.3%
333 (44/836) of patients tested positive for anti-KADCYLA antibodies at one or more post-dose time
334 points. The presence of KADCYLA in patient serum at the time of ATA sampling may interfere
335 with the ability of this assay to detect anti-KADCYLA antibodies. As a result, data may not
336 accurately reflect the true incidence of anti-KADCYLA antibody development. In addition,
337 neutralizing activity of anti-KADCYLA antibodies has not been assessed.

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

344 **7 DRUG INTERACTIONS**

345 No formal drug-drug interaction studies with KADCYLA have been conducted. *In vitro* studies
346 indicate that DM1, the cytotoxic component of KADCYLA, is metabolized mainly by CYP3A4
347 and to a lesser extent by CYP3A5. Concomitant use of strong CYP3A4 inhibitors (e.g.,
348 ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir,
349 ritonavir, saquinavir, telithromycin, and voriconazole) with KADCYLA should be avoided due
350 to the potential for an increase in DM1 exposure and toxicity. Consider an alternate medication
351 with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4
352 inhibitors is unavoidable, consider delaying KADCYLA treatment until the strong CYP3A4
353 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the
354 inhibitors) when possible. If a strong CYP3A4 inhibitor is coadministered and KADCYLA
355 treatment cannot be delayed, patients should be closely monitored for adverse reactions.

356 **8 USE IN SPECIFIC POPULATIONS**

357 **8.1 Pregnancy**

358 Pregnancy Category D [see Warnings and Precautions (5.3)]

359 Risk Summary

360 KADCYLA can cause fetal harm when administered to a pregnant woman. There are no
361 adequate and well-controlled studies of KADCYLA in pregnant women. No reproductive and

362 developmental toxicology studies have been conducted with ado-trastuzumab emtansine.
363 Nevertheless, two components of KADCYLA (trastuzumab and DM1) are known or suspected
364 to cause fetal harm or death when administered to a pregnant woman. If KADCYLA is
365 administered during pregnancy, or if a patient becomes pregnant while receiving KADCYLA,
366 apprise the patient of the potential hazard to the fetus. Patients should be advised to use effective
367 contraception during treatment with KADCYLA and for 6 months following the last dose of
368 KADCYLA.

369 If KADCYLA is administered during pregnancy or if a patient becomes pregnant while receiving
370 KADCYLA, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-
371 2555. Encourage women who may be exposed during pregnancy to enroll in the MoTHER
372 Pregnancy Registry by contacting 1-800-690-6720 [*see Patient Counseling Information (17)*].

373 Human Data

374 In the post-marketing setting, treatment with trastuzumab during pregnancy has resulted in cases
375 of oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and
376 neonatal death. These case reports described oligohydramnios in pregnant women who received
377 trastuzumab either alone or in combination with chemotherapy. In some case reports, amniotic fluid
378 index increased after trastuzumab was stopped. In one case, trastuzumab therapy resumed after the
379 amniotic fluid index improved, and oligohydramnios recurred.

380 Animal Data

381 There were no reproductive and developmental toxicology studies conducted with ado-
382 trastuzumab emtansine. DM1, the cytotoxic component of KADCYLA, disrupts microtubule
383 function. DM1 is toxic to rapidly dividing cells in animals and is genotoxic, suggesting it has the
384 potential to cause embryotoxicity and teratogenicity. In studies where trastuzumab was
385 administered to pregnant monkeys at doses up to 25 mg/kg (about 7 times the clinical dose),
386 trastuzumab crossed the placental barrier during the early and late phases of gestation. The
387 resulting concentrations of trastuzumab in fetal blood and amniotic fluid were approximately
388 33% and 25%, respectively, of those present in the maternal serum but were not associated with
389 adverse findings.

390 **8.3 Nursing Mothers**

391 It is not known whether KADCYLA, specifically, is excreted in human milk, but IgG is known
392 to be excreted in human milk. In lactating monkeys, trastuzumab was excreted in small amounts
393 (about 0.3% of maternal serum concentrations) in breast milk after post-partum doses of 25
394 mg/kg (about 7 times the clinical dose of KADCYLA). Because many drugs are excreted in
395 human milk and because of the potential for serious adverse reactions in nursing infants from
396 KADCYLA, a decision should be made whether to discontinue nursing or discontinue
397 KADCYLA, taking into account the importance of the drug to the mother [*see Warnings and*
398 *Precautions (5.3)*].

399 **8.4 Pediatric Use**

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

401 **8.5 Geriatric Use**

402 Of 495 patients who were randomized to KADCYLA in the randomized trial (Study 1) [*see*
403 *Clinical Studies (14.1)*], 65 patients (13%) were \geq 65 years of age and 11 patients (2%) were \geq
404 75 years of age. In patients \geq 65 years old (n=138 across both treatment arms) the hazard ratios
405 for progression-free survival (PFS) and Overall Survival (OS) were 1.06 (95% CI: 0.68, 1.66)
406 and 1.05 (95% CI: 0.58, 1.91), respectively.

407 Population pharmacokinetic analysis indicates that age does not have a clinically meaningful
408 effect on the pharmacokinetics of ado-trastuzumab emtansine [see *Clinical Pharmacology*
409 (12.3)].

410 **8.6 Females of Reproductive Potential**

411 KADCYLA can cause embryo-fetal harm when administered during pregnancy. Counsel
412 patients regarding pregnancy prevention and planning. Advise females of reproductive potential
413 to use effective contraception while receiving KADCYLA and for 6 months following the last
414 dose of KADCYLA.

415 If KADCYLA is administered during pregnancy or if the patient becomes pregnant while
416 receiving KADCYLA, immediately report exposure to the Genentech Adverse Event Line at 1-
417 888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the
418 MoHER Pregnancy Registry by contacting 1-800-690-6720 [see *Patient Counseling*
419 *Information* (17)].

420 **8.7 Renal Impairment**

421 No dedicated renal impairment trial for KADCYLA has been conducted. Based on the
422 population pharmacokinetics, as well as analysis of Grade 3 or greater adverse drug reactions
423 and dose modifications, dose adjustments of KADCYLA are not needed in patients with mild
424 (creatinine clearance [CLcr] 60 to 89 mL/min) or moderate (CLcr 30 to 59 mL/min) renal
425 impairment. No dose adjustment can be recommended for patients with severe renal impairment
426 (CLcr less than 30 mL/min) because of the limited data available [see *Clinical Pharmacology*
427 (12.3)].

428 **8.8 Hepatic Impairment**

429 *In vitro* studies in human liver microsomes indicates that DM1 is metabolized by CYP3A4/5.
430 The influence of hepatic impairment on the pharmacokinetics of ado-trastuzumab emtansine
431 conjugate has not been determined.

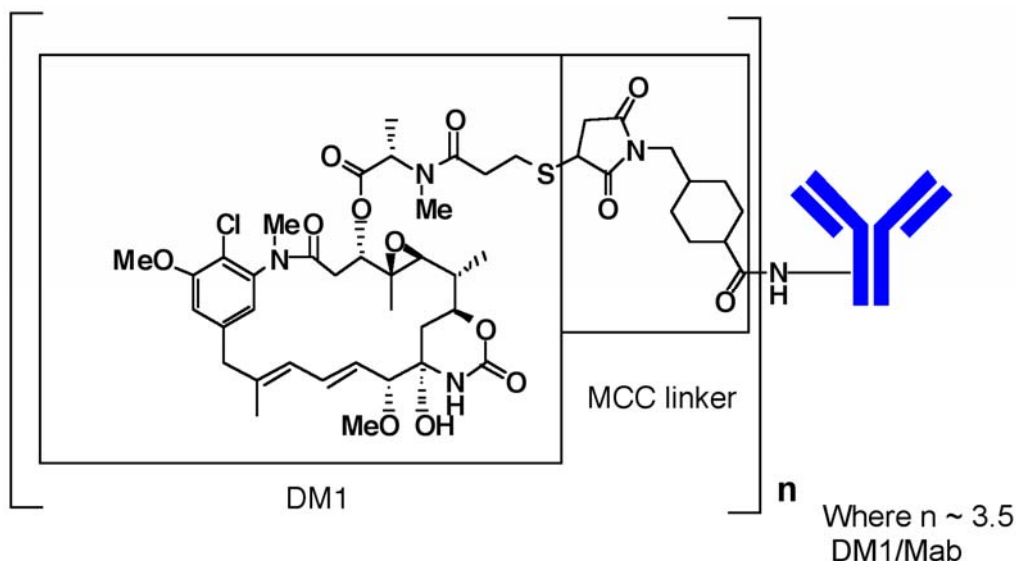
432 **10 OVERDOSAGE**

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

438 **11 DESCRIPTION**

439 KADCYLA (ado-trastuzumab emtansine) is a HER2-targeted antibody-drug conjugate (ADC)
440 which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the
441 microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker MCC
442 (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1
443 complex.

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



449

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

452 KADCYLA (ado-trastuzumab emtansine) is a sterile, white to off-white preservative free
453 lyophilized powder in single-use vials. Each vial contains 100 mg or 160 mg ado-trastuzumab
454 emtansine. Following reconstitution, each single-use vial contains ado-trastuzumab emtansine
455 (20 mg/mL), polysorbate 20 [0.02% (w/v)], sodium succinate (10 mM), and sucrose [6% (w/v)]
456 with a pH of 5.0 and density of 1.026 g/mL. The resulting solution containing 20 mg/mL ado-
457 trastuzumab emtansine is administered by intravenous infusion following dilution.

458 12 CLINICAL PHARMACOLOGY

459 12.1 Mechanism of Action

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

470 12.3 Pharmacokinetics

471 The pharmacokinetics of KADCYLA was evaluated in a phase 1 study and in a population
472 pharmacokinetic analysis for the ado-trastuzumab emtansine conjugate (ADC) using pooled data
473 from 5 trials in patients with breast cancer. A linear two-compartment model with first-order
474 elimination from the central compartment adequately describes the ADC concentration-time
475 profile. In addition to ADC, the pharmacokinetics of total antibody (conjugated and
476 unconjugated trastuzumab), DM1 were also determined. The pharmacokinetics of KADCYLA
477 are summarized below.

478 *Distribution*

479 Maximum concentrations (C_{max}) of ADC and DM1 were observed close to the end of infusion.
480 In Study 1, mean (SD) ADC and DM1 Cycle 1 C_{max} following KADCYLA administration was
481 83.4 (16.5) $\mu\text{g/mL}$ and 4.61 (1.61) ng/mL , respectively.

482 *In vitro*, the mean binding of DM1 to human plasma proteins was 93%. *In vitro*, DM1 was a
483 substrate of P-glycoprotein (P-gp).

484 Based on population pharmacokinetic analysis, the central volume of distribution of ADC was
485 3.13 L.

486 **Metabolism**

487 *In vitro* studies indicate that DM1, the small molecule component of KADCYLA, undergoes
488 metabolism by CYP3A4/5. DM1 did not inhibit or induce major CYP450 enzymes *in vitro*. In
489 human plasma, ado-trastuzumab emtansine catabolites MCC-DM1, Lys-MCC-DM1, and DM1
490 were detected at low levels.

491 **Elimination**

492 Based on population pharmacokinetic analysis, following intravenous infusion of KADCYLA,
493 the clearance of the ADC was 0.68 L/day and the elimination half-life ($t_{1/2}$) was approximately 4
494 days. No accumulation of KADCYLA was observed after repeated dosing of intravenous
495 infusion every 3 weeks.

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

504 **Effect of Renal Impairment**

505 Based on population pharmacokinetic analysis in 668 patients, including moderate (CL_{cr} 30 - 59
506 mL/min, n=53) and mild (CL_{cr} 60 - 89 mL/min, n=254) renal impairment, indicate that
507 pharmacokinetics of the ADC is not affected by mild to moderate renal impairment as compared
508 to normal renal function ($CL_{cr} \geq 90$ mL/min, n=361). Data from only one patient with severe
509 renal impairment ($CL_{cr} < 30$ mL/min) is available [see *Use in Specific Populations* (8.7)].

510 **Effects of Age and Race**

511 Based on population pharmacokinetic analysis, age (< 65 (n=577); 65 - 75 (n=78); > 75 (n=16))
512 and race (Asian (n=73); non-Asian (n=598)) do not have a clinically meaningful effect on the
513 pharmacokinetics of ado-trastuzumab emtansine.

514 **12.6 Cardiac Electrophysiology**

515 The effect of multiple doses of KADCYLA (3.6 mg/kg every 3 weeks) on the QTc interval was
516 evaluated in an open label, single arm study in 51 patients with HER2-positive metastatic breast
517 cancer. No large changes in the mean QT interval (i.e., > 20 ms) were detected in the study.

518 **13 NONCLINICAL TOXICOLOGY**

519 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

520 Carcinogenicity studies have not been conducted with ado-trastuzumab emtansine.

521 DM1 was aneugenic or clastogenic in an *in vivo* single-dose rat bone marrow micronucleus assay
522 at exposures that were comparable to mean maximum concentrations of DM1 measured in
523 humans administered KADCYLA. DM1 was not mutagenic in an *in vitro* bacterial reverse
524 mutation (Ames) assay.

525 Based on results from animal toxicity studies, KADCYLA may impair fertility in humans. In a
526 single-dose toxicity study of ado-trastuzumab emtansine in rats, degeneration of seminiferous
527 tubules with hemorrhage in the testes associated with increased weights of testes and
528 epididymides at a severely toxic dose level (60 mg/kg; about 4 times the clinical exposure based
529 on AUC) were observed. The same dose in female rats resulted in signs of hemorrhage and
530 necrosis of the corpus luteum in ovaries. In monkeys dosed with ado-trastuzumab emtansine
531 once every three weeks for 12 weeks (four doses), at up to 30 mg/kg (about 7 times the clinical
532 exposure based on AUC), there were decreases in the weights of epididymides, prostate, testes,
533 seminal vesicles and uterus, although the interpretation of these effects is unclear due to the
534 varied sexual maturity of enrolled animals.

535 **13.2 Animal Toxicology and/or Pharmacology**

536 In monkeys, treatment with doses of ado-trastuzumab emtansine up to 30 mg/kg (about 7 times
537 the clinical exposure based on AUC) caused dose dependent axonal degeneration in the sciatic
538 nerve with hypertrophy or hyperplasia of the Schwann cells, and axonal degeneration of the
539 dorsal funiculus in the spinal cord. Based on the mechanism of action of the cytotoxic
540 component DM1, there is clinical potential for neurotoxicity [*see Warnings and Precautions*
541 (5.7)].

542 **14 CLINICAL STUDIES**

543 **14.1 Metastatic Breast Cancer**

544 The efficacy of KADCYLA was evaluated in a randomized, multicenter, open-label trial of 991
545 patients with HER2-positive, unresectable locally advanced or metastatic breast cancer. Prior
546 taxane and trastuzumab-based therapy was required before trial enrollment. Patients with only
547 prior adjuvant therapy were required to have disease recurrence during or within six months of
548 completing adjuvant therapy. Breast tumor samples were required to show HER2
549 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a central
550 laboratory. Patients were randomly allocated (1:1) to receive lapatinib plus capecitabine or
551 KADCYLA. Randomization was stratified by world region (United States, Western Europe,
552 other), number of prior chemotherapy regimens for unresectable locally advanced or metastatic
553 disease (0–1, >1) and visceral versus non-visceral disease as determined by the investigators.

554 KADCYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Lapatinib was
555 administered at 1250 mg/day orally once per day of a 21-day cycle and capecitabine was
556 administered at 1000 mg/m² orally twice daily on Days 1–14 of a 21-day cycle. Patients were
557 treated with KADCYLA or lapatinib plus capecitabine until progression of disease, withdrawal
558 of consent, or unacceptable toxicity. At the time of the primary analysis, median time on study
559 drug was 5.7 months (range: 0–28.4) for KADCYLA, 4.9 months (range: 0–30.8) for lapatinib,
560 and 4.8 months (range: 0–30.4) for capecitabine.

561 The co-primary efficacy endpoints of the study were progression-free survival (PFS) based on
562 tumor response assessments by an independent review committee (IRC), and overall survival
563 (OS). PFS was defined as the time from the date of randomization to the date of disease
564 progression or death from any cause (whichever occurred earlier). Overall survival was defined
565 as the time from the date of randomization to the date of death from any cause. Additional
566 endpoints included PFS (based on investigator tumor response assessments), objective response
567 rate (ORR), duration of response and time to symptom progression.

568 Patient demographics and baseline tumor characteristics were balanced between treatment arms.
569 All patients had metastatic disease at study entry. The median age was approximately 53 years
570 (range 24–84 years), 74% were White, 18% were Asian and 5% were Black. All but 5 patients
571 were women. Twenty-seven percent of patients were enrolled in United States, 32% in Europe
572 and 16% in Asia. Tumor prognostic characteristics including hormone receptor status (positive:

573 55%, negative: 43%), presence of visceral disease (68%) and non-visceral disease only (33%)
574 and the number of metastatic sites (< 3: 61%, ≥ 3: 37%) were similar in the study arms.

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

584 The randomized trial demonstrated a statistically significant improvement in IRC-assessed PFS
585 in the KADCYLA-treated group compared with the lapatinib plus capecitabine-treated group
586 [hazard ratio (HR) = 0.65, 95% CI: 0.55, 0.77, $p < 0.0001$], and an increase in median PFS of 3.2
587 months (median PFS of 9.6 months in the KADCYLA-treated group vs. 6.4 months in the
588 lapatinib plus capecitabine group). See Table 8 and Figure 1. The results for investigator-
589 assessed PFS were similar to those observed for IRC-assessed PFS.

590 At the time of PFS analysis, 223 patients had died. More deaths occurred in the lapatinib plus
591 capecitabine arm (26%) compared with the KADCYLA arm (19%), however the results of this
592 interim OS analysis did not meet the pre-specified stopping boundary for statistical significance.
593 At the time of the second interim OS analysis, 331 events had occurred. The co-primary
594 endpoint of OS was met; OS was significantly improved in patients receiving KADCYLA (HR =
595 0.68, 95% CI: 0.55, 0.85, $p = 0.0006$). This result crossed the pre-specified efficacy stopping
596 boundary (HR = 0.73 or $p = 0.0037$). The median duration of survival was 30.9 months in the
597 KADCYLA arm vs. 25.1 months in the lapatinib plus capecitabine arm. See Table 8 and Figure
598 2.

599 A treatment benefit with KADCYLA in terms of PFS and OS was observed in patient subgroups
600 based on stratification factors, key baseline demographic and disease characteristics, and prior
601 treatments. In the subgroup of patients with hormone receptor-negative disease (n=426), the
602 hazard ratios for PFS and OS were 0.56 (95% CI: 0.44, 0.72) and 0.75 (95% CI: 0.54, 1.03),
603 respectively. In the subgroup of patients with hormone receptor-positive disease (n=545), the
604 hazard ratios for PFS and OS were 0.72 (95% CI: 0.58, 0.91) and 0.62 (95% CI: 0.46, 0.85),
605 respectively. In the subgroup of patients with non-measurable disease (n=205), based on IRC
606 assessments, the hazard ratios for PFS and OS were 0.91 (95% CI: 0.59, 1.42) and 0.96 (95% CI:
607 0.54, 1.68), respectively; in patients with measurable disease the hazard ratios were 0.62 (95%
608 CI: 0.52, 0.75) and 0.65 (95% CI: 0.51, 0.82), respectively. The PFS and OS hazard ratios in
609 patients who were younger than 65 years old (n=853) were 0.62 (95% CI: 0.52, 0.74) and 0.66
610 (95% CI: 0.52, 0.83), respectively. In patients ≥ 65 years old (n=138), the hazard ratios for PFS
611 and OS were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively.

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619 **Table 8 Summary of Efficacy from Study 1**

	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)

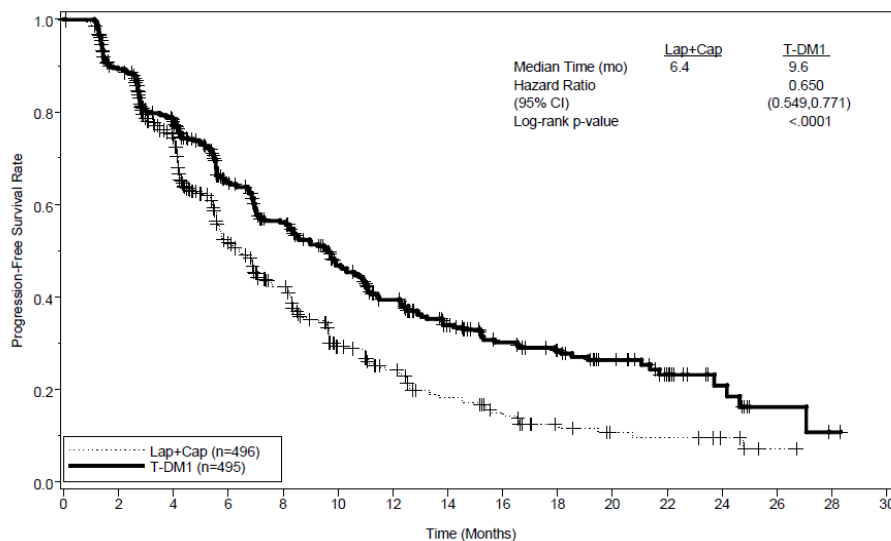
PFS: progression-free survival; OR: objective response

* 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.

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640 **Figure 1 Kaplan-Meier Curve of IRC-Assessed Progression-Free Survival for Study 1**



Number at Risk:
 Lap+Cap
 T-DM1

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

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

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642 **Figure 2 Kaplan-Meier Curve of Overall Survival for Study 1**

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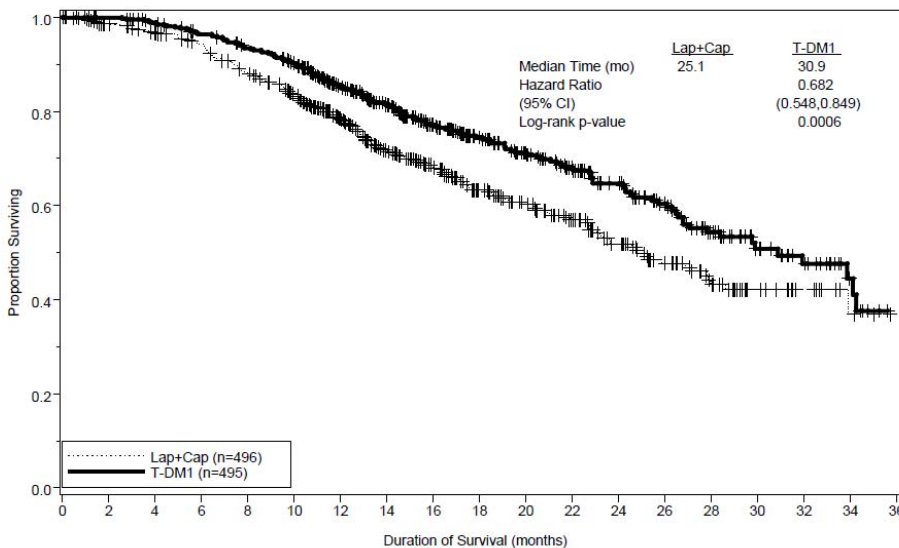
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Number at Risk:
 Lap+Cap
 T-DM1

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

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

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656 **15 REFERENCES**

659 1. OSHA Hazardous Drugs. OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

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661 **16 HOW SUPPLIED/STORAGE AND HANDLING**

662 **16.1 How Supplied/Storage**

663 KADCYLA (ado-trastuzumab emtansine) is supplied as:

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

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

667 **16.2 Special Handling**

668 Follow procedures for proper handling and disposal of anticancer drugs¹.

669 **17 PATIENT COUNSELING INFORMATION**

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

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

678 • Advise pregnant women and females of reproductive potential that KADCYLA exposure can
679 result in fetal harm, including embryo-fetal death or birth defects [*see Warnings and*
680 *Precautions (5.3), Use in Specific Populations (8.1, 8.6)*].

681 • Advise females of reproductive potential to use effective contraception while receiving
682 KADCYLA and for 6 months following the last dose of KADCYLA [*See Warnings and*
683 *Precautions (5.3) and Use in Specific Populations (8.1, 8.6)*].

684 • Advise nursing mothers treated with KADCYLA to discontinue nursing or discontinue
685 KADCYLA, taking into account the importance of the drug to the mother [*see Use in*
686 *Specific Populations (8.3)*].

687 • Encourage women who are exposed to KADCYLA during pregnancy to enroll in the
688 MoTHER Pregnancy Registry by contacting 1-800-690-6720 [*see Warnings and Precautions*
689 *(5.3) and Use in Specific Populations (8.1, 8.6)*].

690

KADCYLA™ [ado-trastuzumab emtansine]

4862200

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

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South San Francisco, CA 94080-4990

U.S. License No: 1048

Initial U.S. Approval: {Month Year}

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