

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PERJETA® (pertuzumab)
Injection, for intravenous use
Initial U.S. Approval: 2012

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception. (5.1, 8.1, 8.6)

RECENT MAJOR CHANGES

Dosage and Administration (2.1) 04/2013

INDICATIONS AND USAGE

PERJETA is a HER2/neu receptor antagonist indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. (1)

DOSAGE AND ADMINISTRATION

- For intravenous infusion only. Do not administer as an intravenous push or bolus. (2.3)
- The initial dose is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion. (2.1)

DOSAGE FORMS AND STRENGTHS

- 420 mg/14 mL single-use vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Embryo-fetal toxicity: Fetal harm can occur when administered to a pregnant woman. (5.1, 8.1)
- Left Ventricular Dysfunction: Monitor LVEF and withhold dosing as appropriate. (5.2, 6.1)
- Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis: Monitor for signs and symptoms. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies. (5.3)
- HER2 testing: Perform using FDA-approved tests by laboratories with demonstrated proficiency. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (> 30%) with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. (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 PERJETA, 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. (5.1, 8.1, 8.6, 17)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: EMBRYO-FETAL TOXICITY

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Doses and Schedules
- 2.2 Dose Modification
- 2.3 Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Embryo-Fetal Toxicity
- 5.2 Left Ventricular Dysfunction
- 5.3 Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis
- 5.4 HER2 Testing

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use

8.5 Geriatric Use

8.6 Females of Reproductive Potential

8.7 Renal Impairment

8.8 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

12.6 Cardiac Electrophysiology

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the Full Prescribing Information are not listed.

1 FULL PRESCRIBING INFORMATION

2 **WARNING: EMBRYO-FETAL TOXICITY**

Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception. (5.1, 8.1, 8.6)

3 **1 INDICATIONS AND USAGE**

4 PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment
5 of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2
6 therapy or chemotherapy for metastatic disease.
7

8 **2 DOSAGE AND ADMINISTRATION**

9 **2.1 Recommended Doses and Schedules**

10 The initial dose of PERJETA is 840 mg administered as a 60-minute intravenous infusion,
11 followed every 3 weeks thereafter by a dose of 420 mg administered as an intravenous infusion
12 over 30 to 60 minutes.

13 When administered with PERJETA, the recommended initial dose of trastuzumab is 8 mg/kg
14 administered as a 90-minute intravenous infusion, followed every 3 weeks thereafter by a dose of
15 6 mg/kg administered as an intravenous infusion over 30 to 90 minutes.

16 When administered with PERJETA, the recommended initial dose of docetaxel is 75 mg/m²
17 administered as an intravenous infusion. The dose may be escalated to 100 mg/m² administered
18 every 3 weeks if the initial dose is well tolerated.

19 PERJETA, trastuzumab, and docetaxel should be administered sequentially. PERJETA and
20 trastuzumab can be given in any order. Docetaxel should be administered after PERJETA and
21 trastuzumab. An observation period of 30 to 60 minutes is recommended after each PERJETA
22 infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel [*see*
23 *Warnings and Precautions (5.3)*].

24 **2.2 Dose Modification**

25 For delayed or missed doses, if the time between two sequential infusions is less than 6 weeks,
26 the 420 mg dose of PERJETA should be administered. Do not wait until the next planned dose.
27 If the time between two sequential infusions is 6 weeks or more, the initial dose of 840 mg
28 PERJETA should be re-administered as a 60-minute intravenous infusion followed every
29 3 weeks thereafter by a dose of 420 mg administered as an intravenous infusion over
30 30 to 60 minutes.

31 The infusion rate of PERJETA may be slowed or interrupted if the patient develops an
32 infusion-associated reaction. The infusion should be discontinued immediately if the patient
33 experiences a serious hypersensitivity reaction [*see Warnings and Precautions (5.3)*].

34 **Left Ventricular Ejection Fraction (LVEF):**

35 Withhold PERJETA and trastuzumab dosing for at least 3 weeks for either:

- 36 • a drop in LVEF to less than 40% or

- 37 • LVEF of 40% to 45% with a 10% or greater absolute decrease below pretreatment values
38 [see *Warnings and Precautions (5.2)*]
- 39 PERJETA may be resumed if the LVEF has recovered to greater than 45% or to 40% to 45%
40 associated with less than a 10% absolute decrease below pretreatment values.
- 41 If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has
42 declined further, discontinuation of PERJETA and trastuzumab should be strongly considered,
43 unless the benefits for the individual patient are deemed to outweigh the risks [see *Warnings and*
44 *Precautions (5.2)*].
- 45 PERJETA should be withheld or discontinued if trastuzumab treatment is withheld or
46 discontinued.
- 47 If docetaxel is discontinued, treatment with PERJETA and trastuzumab may continue.
- 48 Dose reductions are not recommended for PERJETA.
- 49 For docetaxel dose modifications, see docetaxel prescribing information.

50 **2.3 Preparation for Administration**

51 Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus.
52 Do not mix PERJETA with other drugs.

53 Preparation

54 Prepare the solution for infusion, using aseptic technique, as follows:

- 55 • Parenteral drug products should be inspected visually for particulates and discoloration
56 prior to administration.
- 57 • Withdraw the appropriate volume of PERJETA solution from the vial(s).
- 58 • Dilute into a 250 mL 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag.
- 59 • Mix diluted solution by gentle inversion. Do not shake.
- 60 • Administer immediately once prepared.
- 61 • If the diluted infusion solution is not used immediately, it can be stored at 2°C to 8°C for
62 up to 24 hours.
- 63 • Dilute with 0.9% Sodium Chloride injection only. Do not use dextrose (5%) solution.

64 **3 DOSAGE FORMS AND STRENGTHS**

65 PERJETA (pertuzumab) 420 mg/14 mL (30 mg/mL) in a single-use vial

66 **4 CONTRAINDICATIONS**

67 None.

68 **5 WARNINGS AND PRECAUTIONS**

69 **5.1 Embryo-Fetal Toxicity**

70 PERJETA can cause fetal harm when administered to a pregnant woman. Treatment of pregnant
71 cynomolgus monkeys with pertuzumab resulted in oligohydramnios, delayed fetal kidney
72 development, and embryo-fetal death. If PERJETA is administered during pregnancy, or if the
73 patient becomes pregnant while receiving this drug, the patient should be apprised of the
74 potential hazard to a fetus [see *Use in Specific Populations (8.1)*].

75 Verify pregnancy status prior to the initiation of PERJETA. Advise patients of the risks of
76 embryo-fetal death and birth defects and the need for contraception during and after treatment.
77 Advise patients to contact their healthcare provider immediately if they suspect they may be
78 pregnant. If PERJETA is administered during pregnancy or if a patient becomes pregnant while
79 receiving PERJETA, immediately report exposure to the Genentech Adverse Event Line at
80 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the
81 MotHER Pregnancy Registry by contacting 1-800-690-6720 [see *Patient Counseling*
82 *Information (17)*].

83 Monitor patients who become pregnant during PERJETA therapy for oligohydramnios. If
84 oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and
85 consistent with community standards of care. The efficacy of intravenous hydration in the
86 management of oligohydramnios due to PERJETA exposure is not known.

87 **5.2 Left Ventricular Dysfunction**

88 Decreases in LVEF have been reported with drugs that block HER2 activity, including
89 PERJETA. In the randomized trial, PERJETA in combination with trastuzumab and docetaxel
90 was not associated with increases in the incidence of symptomatic left ventricular systolic
91 dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with
92 trastuzumab and docetaxel [see *Clinical Studies (14.1)*]. Left ventricular dysfunction occurred in
93 4.4% of patients in the PERJETA-treated group and 8.3% of patients in the placebo-treated
94 group. Symptomatic left ventricular systolic dysfunction (congestive heart failure) occurred in
95 1.0% of patients in the PERJETA-treated group and 1.8% of patients in the placebo-treated
96 group [see *Adverse Reactions (6.1)*]. Patients who have received prior anthracyclines or prior
97 radiotherapy to the chest area may be at higher risk of decreased LVEF.

98 PERJETA has not been studied in patients with a pretreatment LVEF value of $\leq 50\%$, a prior
99 history of CHF, decreases in LVEF to $< 50\%$ during prior trastuzumab therapy, or conditions
100 that could impair left ventricular function such as uncontrolled hypertension, recent myocardial
101 infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline
102 exposure to $> 360 \text{ mg/m}^2$ of doxorubicin or its equivalent.

103 Assess LVEF prior to initiation of PERJETA and at regular intervals (e.g., every three months)
104 during treatment to ensure that LVEF is within the institution's normal limits. If LVEF is
105 $< 40\%$, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value,
106 withhold PERJETA and trastuzumab and repeat LVEF assessment within approximately
107 3 weeks. Discontinue PERJETA and trastuzumab if the LVEF has not improved or has declined
108 further, unless the benefits for the individual patient outweigh the risks [see *Dosage and*
109 *Administration (2.2)*].

110 **5.3 Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis**

111 PERJETA has been associated with infusion and hypersensitivity reactions [see *Adverse*
112 *Reactions (6.1)*]. An infusion reaction was defined in the randomized trial as any event
113 described as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release
114 syndrome occurring during an infusion or on the same day as the infusion. The initial dose of
115 PERJETA was given the day before trastuzumab and docetaxel to allow for the examination of
116 PERJETA-associated reactions. On the first day, when only PERJETA was administered, the
117 overall frequency of infusion reactions was 13.0% in the PERJETA-treated group and 9.8% in
118 the placebo-treated group. Less than 1% were grade 3 or 4. The most common infusion
119 reactions ($\geq 1.0\%$) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and
120 vomiting.

121 During the second cycle when all drugs were administered on the same day, the most common
122 infusion reactions in the PERJETA-treated group ($\geq 1.0\%$) were fatigue, dysgeusia,
123 hypersensitivity, myalgia, and vomiting.

124 In the randomized trial, the overall frequency of hypersensitivity/anaphylaxis reactions was
125 10.8% in the PERJETA-treated group and 9.1% in the placebo-treated group. The incidence of
126 Grade 3 – 4 hypersensitivity/anaphylaxis reactions was 2% in the PERJETA-treated group and
127 2.5% in the placebo-treated group according to National Cancer Institute – Common
128 Terminology Criteria for Adverse Events (NCI - CTCAE) (version 3). Overall, 4 patients in
129 PERJETA-treated group and 2 patients in the placebo-treated group experienced anaphylaxis.

130 Observe patients closely for 60 minutes after the first infusion and for 30 minutes after
131 subsequent infusions of PERJETA. If a significant infusion-associated reaction occurs, slow or
132 interrupt the infusion and administer appropriate medical therapies. Monitor patients carefully
133 until complete resolution of signs and symptoms. Consider permanent discontinuation in
134 patients with severe infusion reactions [*see Dosage and Administration (2.2)*].

135 **5.4 HER2 Testing**

136 Detection of HER2 protein overexpression is necessary for selection of patients appropriate for
137 PERJETA therapy because these are the only patients studied and for whom benefit has been
138 shown [*see Indications and Usage (1) and Clinical Studies (14)*]. In the randomized trial,
139 patients with breast cancer were required to have evidence of HER2 overexpression defined as
140 3+ IHC by Dako Herceptest™ or FISH amplification ratio ≥ 2.0 by Dako HER2 FISH
141 PharmDx™ test kit. Only limited data were available for patients whose breast cancer was
142 positive by FISH, but did not demonstrate protein overexpression by IHC.

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

148 **6 ADVERSE REACTIONS**

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

- 150 • Embryo-Fetal Toxicity [*see Warnings and Precautions (5.1)*]
- 151 • Left Ventricular Dysfunction [*see Warnings and Precautions (5.2)*]
- 152 • Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis [*see Warnings*
153 *and Precautions (5.3)*]

154 **6.1 Clinical Trials Experience**

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

158 In clinical trials, PERJETA has been evaluated in more than 1400 patients with various
159 malignancies and treatment with PERJETA was predominantly in combination with other
160 anti-neoplastic agents.

161 The adverse reactions described in Table 1 were identified in 804 patients with HER2-positive
162 metastatic breast cancer treated in the randomized trial. Patients were randomized to receive
163 either PERJETA in combination with trastuzumab and docetaxel or placebo in combination with

164 trastuzumab and docetaxel. The median duration of study treatment was 18.1 months for
165 patients in the PERJETA-treated group and 11.8 months for patients in the placebo-treated
166 group. No dose adjustment was permitted for PERJETA or trastuzumab. The rates of adverse
167 events resulting in permanent discontinuation of all study therapy were 6.1% for patients in the
168 PERJETA-treated group and 5.3% for patients in the placebo-treated group. Adverse events led
169 to discontinuation of docetaxel alone in 23.6% of patients in the PERJETA-treated group and
170 23.2% of patients in the placebo-treated group. Table 1 reports the adverse reactions that
171 occurred in at least 10% of patients in the PERJETA-treated group.

172 The most common adverse reactions (> 30%) seen with PERJETA in combination with
173 trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and
174 peripheral neuropathy. The most common NCI - CTCAE (version 3) Grade 3 – 4 adverse
175 reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral
176 neuropathy, anemia, asthenia, and fatigue. An increased incidence of febrile neutropenia was
177 observed for Asian patients in both treatment arms compared with patients of other races and
178 from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was
179 higher in the pertuzumab-treated group (26%) compared with the placebo-treated group (12%).

Table 1 Summary of Adverse Reactions Occurring in $\geq 10\%$ of Patients on the PERJETA Treatment Arm in the Randomized Trial

Body System/Adverse Reactions	PERJETA + trastuzumab + docetaxel n=407		Placebo + trastuzumab + docetaxel n=397	
	Frequency rate %		Frequency rate %	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
General disorders and administration site conditions				
Fatigue	37.6	2.2	36.8	3.3
Asthenia	26.0	2.5	30.2	1.5
Edema peripheral	23.1	0.5	30.0	0.8
Mucosal inflammation	27.8	1.5	19.9	1.0
Pyrexia	18.7	1.2	17.9	0.5
Skin and subcutaneous tissue disorders				
Alopecia	60.9	0.0	60.5	0.3
Rash	33.7	0.7	24.2	0.8
Nail disorder	22.9	1.2	22.9	0.3
Pruritus	14.0	0.0	10.1	0.0
Dry skin	10.6	0.0	4.3	0.0
Gastrointestinal disorders				
Diarrhea	66.8	7.9	46.3	5.0
Nausea	42.3	1.2	41.6	0.5
Vomiting	24.1	1.5	23.9	1.5
Constipation	15.0	0.0	24.9	1.0
Stomatitis	18.9	0.5	15.4	0.3
Blood and lymphatic system disorders				
Neutropenia	52.8	48.9	49.6	45.8
Anemia	23.1	2.5	18.9	3.5
Leukopenia	18.2	12.3	20.4	14.6
Febrile neutropenia*	13.8	13.0	7.6	7.3
Nervous system disorders				
Neuropathy peripheral	32.4	3.2	33.8	2.0
Headache	20.9	1.2	16.9	0.5
Dysgeusia	18.4	0.0	15.6	0.0
Dizziness	12.5	0.5	12.1	0.0
Musculoskeletal and connective tissue				

disorders				
Myalgia	22.9	1.0	23.9	0.8
Arthralgia	15.5	0.2	16.1	0.8
Infections and infestations				
Upper respiratory tract infection	16.7	0.7	13.4	0.0
Nasopharyngitis	11.8	0.0	12.8	0.3
Respiratory, thoracic and mediastinal disorders				
Dyspnea	14.0	1.0	15.6	2.0
Metabolism and nutrition disorders				
Decreased appetite	29.2	1.7	26.4	1.5
Eye disorders				
Lacrimation increased	14.0	0.0	13.9	0.0
Psychiatric disorders				
Insomnia	13.3	0.0	13.4	0.0

182 * In this table this denotes an adverse reaction that has been reported in association with a fatal
183 outcome

184

185 **The following clinically relevant adverse reactions were reported in < 10% of patients in**
186 **the PERJETA-treated group:**

187 **Skin and subcutaneous tissue disorders:** Paronychia (7.1% in the PERJETA-treated group vs.
188 3.5% in the placebo-treated group)

189 **Respiratory, thoracic and mediastinal disorders:** Pleural effusion (5.2% in the PERJETA-
190 treated group vs. 5.8% in the placebo-treated group)

191 **Cardiac disorders:** Left ventricular dysfunction (4.4% in the PERJETA-treated group vs. 8.3%
192 in the placebo-treated group) including symptomatic left ventricular systolic dysfunction (CHF)
193 (1.0% in the PERJETA-treated group vs. 1.8% in the placebo-treated group)

194 **Immune system disorders:** Hypersensitivity (10.1% in the PERJETA-treated group vs. 8.6% in
195 placebo-treated group)

196 ***Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab after***
197 ***Discontinuation of Docetaxel***

198 In the randomized trial, adverse reactions were reported less frequently after discontinuation of
199 docetaxel treatment. All adverse reactions in the PERJETA and trastuzumab treatment group
200 occurred in < 10% of patients with the exception of diarrhea (19.1%), upper respiratory tract
201 infection (12.8%), rash (11.7%), headache (11.4%), and fatigue (11.1%).

202 **6.2 Immunogenicity**

203 As with all therapeutic proteins, there is the potential for an immune response to PERJETA.

204 Patients in the randomized trial were tested at multiple time-points for antibodies to PERJETA.
205 Approximately 2.8% (11/386) of patients in the PERJETA-treated group and 6.2% (23/372) of
206 patients in the placebo-treated group tested positive for anti-PERJETA antibodies. Of these

207 34 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to
208 the anti-therapeutic antibodies (ATA). The presence of pertuzumab in patient serum at the levels
209 expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-
210 pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a
211 result, data may not accurately reflect the true incidence of anti-pertuzumab antibody
212 development.

213 Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods
214 used. Additionally, the observed incidence of a positive result in a test method may be
215 influenced by several factors, including sample handling, timing of sample collection, drug
216 interference, concomitant medication, and the underlying disease. For these reasons, comparison
217 of the incidence of antibodies to PERJETA with the incidence of antibodies to other products
218 may be misleading.

219 **7 DRUG INTERACTIONS**

220 No drug-drug interactions were observed between pertuzumab and trastuzumab, or between
221 pertuzumab and docetaxel.

222 **8 USE IN SPECIFIC POPULATIONS**

223 **8.1 Pregnancy**

224 *Pregnancy Category D*

225 Risk Summary

226 There are no adequate and well-controlled studies of PERJETA in pregnant women. Based on
227 findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant
228 woman. The effects of PERJETA are likely to be present during all trimesters of pregnancy.
229 Pertuzumab administered to pregnant cynomolgus monkeys resulted in oligohydramnios,
230 delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures of
231 2.5 to 20-fold greater than the recommended human dose, based on C_{max} . If PERJETA is
232 administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA, the
233 patient should be apprised of the potential hazard to the fetus.

234 If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving
235 PERJETA, immediately report exposure to the Genentech Adverse Event Line at
236 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the
237 MotHER Pregnancy Registry by contacting 1-800-690-6720 [*see Patient Counseling*
238 *Information (17)*].

239 Animal Data

240 Reproductive toxicology studies have been conducted in cynomolgus monkeys. Pregnant
241 monkeys were treated on Gestational Day (GD)19 with loading doses of 30 to 150 mg/kg
242 pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in
243 clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based
244 on C_{max} . Intravenous administration of pertuzumab from GD19 through GD50 (period of
245 organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between
246 GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with
247 bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than
248 the recommended human dose, based on C_{max}). At Caesarean section on GD100,
249 oligohydramnios, decreased relative lung and kidney weights and microscopic evidence of renal
250 hypoplasia consistent with delayed renal development were identified in all pertuzumab dose

251 groups. Pertuzumab exposure was reported in offspring from all treated groups, at levels of
252 29% to 40% of maternal serum levels at GD100.

253 **8.3 Nursing Mothers**

254 It is not known whether PERJETA is excreted in human milk, but human IgG is excreted in
255 human milk. Because many drugs are secreted in human milk and because of the potential for
256 serious adverse reactions in nursing infants from PERJETA, a decision should be made whether
257 to discontinue nursing, or discontinue drug, taking into account the elimination half-life of
258 PERJETA and the importance of the drug to the mother [*See Warnings and Precautions (5.1),*
259 *Clinical Pharmacology (12.3)*].

260 **8.4 Pediatric Use**

261 The safety and effectiveness of PERJETA have not been established in pediatric patients.

262 **8.5 Geriatric Use**

263 Of 402 patients who received PERJETA in the randomized trial, 60 patients (15%) were
264 ≥ 65 years of age and 5 patients (1%) were ≥ 75 years of age. No overall differences in efficacy
265 and safety of PERJETA were observed between these patients and younger patients.

266 Based on a population pharmacokinetic analysis, no significant difference was observed in the
267 pharmacokinetics of pertuzumab between patients < 65 years ($n=306$) and patients ≥ 65 years
268 ($n=175$).

269 **8.6 Females of Reproductive Potential**

270 PERJETA can cause embryo-fetal harm when administered during pregnancy. Counsel patients
271 regarding pregnancy prevention and planning. Advise females of reproductive potential to use
272 effective contraception while receiving PERJETA and for 6 months following the last dose of
273 PERJETA.

274 If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving
275 PERJETA, immediately report exposure to the Genentech Adverse Event Line at
276 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the
277 MotHER Pregnancy Registry by contacting 1-800-690-6720 [*see Patient Counseling*
278 *Information (17)*].

279 **8.7 Renal Impairment**

280 Dose adjustments of PERJETA are not needed in patients with mild (creatinine clearance [CLCr]
281 60 to 90 mL/min) or moderate (CLCr 30 to 60 mL/min) renal impairment. No dose adjustment
282 can be recommended for patients with severe renal impairment (CLCr less than 30 mL/min)
283 because of the limited pharmacokinetic data available [*see Clinical Pharmacology (12.3)*].

284 **8.8 Hepatic Impairment**

285 No clinical studies have been conducted to evaluate the effect of hepatic impairment on the
286 pharmacokinetics of pertuzumab.

287 **10 OVERDOSAGE**

288 No drug overdoses have been reported with PERJETA to date.

289 **11 DESCRIPTION**

290 Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular
291 dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein
292 (HER2). Pertuzumab is produced by recombinant DNA technology in a mammalian cell

293 (Chinese Hamster Ovary) culture containing the antibiotic, gentamicin. Gentamicin is not
294 detectable in the final product. Pertuzumab has an approximate molecular weight of 148 kDa.
295 PERJETA is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous
296 infusion. Each single use vial contains 420 mg of pertuzumab at a concentration of 30 mg/mL in
297 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20.

298 **12 CLINICAL PHARMACOLOGY**

299 **12.1 Mechanism of Action**

300 Pertuzumab targets the extracellular dimerization domain (Subdomain II) of the human
301 epidermal growth factor receptor 2 protein (HER2) and, thereby, blocks ligand-dependent
302 heterodimerization of HER2 with other HER family members, including EGFR, HER3 and
303 HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two
304 major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase
305 (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis,
306 respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity
307 (ADCC).

308 While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of
309 pertuzumab and trastuzumab significantly augmented anti-tumor activity in
310 HER2-overexpressing xenograft models.

311 **12.3 Pharmacokinetics**

312 Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2 – 25 mg/kg. Based on a
313 population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was
314 0.24 L/day and the median half-life was 18 days. With an initial dose of 840 mg followed by a
315 maintenance dose of 420 mg every three weeks thereafter, the steady-state concentration of
316 pertuzumab was reached after the first maintenance dose.

317 The population PK analysis suggested no PK differences based on age, gender, and ethnicity
318 (Japanese vs. non-Japanese). Baseline serum albumin level and lean body weight as covariates
319 only exerted a minor influence on PK parameters. Therefore, no dose adjustments based on
320 body weight or baseline albumin level are needed.

321 No drug-drug interactions were observed between pertuzumab and trastuzumab, or between
322 pertuzumab and docetaxel in a sub-study of 37 patients in the randomized trial.

323 No dedicated renal impairment trial for PERJETA has been conducted. Based on the results of
324 the population pharmacokinetic analysis, pertuzumab exposure in patients with mild (CLcr
325 60 to 90 mL/min, n=200) and moderate renal impairment (CLcr 30 to 60 mL/min, n=71) were
326 similar to those in patients with normal renal function (CLcr greater than 90 mL/min, n=200).
327 No relationship between CLcr and pertuzumab exposure was observed over the range of
328 observed CLcr (27 to 244 mL/min).

329 **12.6 Cardiac Electrophysiology**

330 The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of
331 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with
332 HER2-positive breast cancer in the randomized trial. No large changes in the mean QT interval
333 (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in
334 the trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded
335 because of the limitations of the trial design.

336 **13 NONCLINICAL TOXICOLOGY**

337 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

338 Long-term studies in animals have not been performed to evaluate the carcinogenic potential of
339 pertuzumab.

340 Studies have not been performed to evaluate the mutagenic potential of pertuzumab.

341 No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab.

342 No adverse effects on male and female reproductive organs were observed in repeat-dose
343 toxicity studies of up to six months duration in cynomolgus monkeys.

344 **14 CLINICAL STUDIES**

345 **14.1 Metastatic Breast Cancer**

346 The randomized trial was a multicenter, double-blind, placebo-controlled trial of 808 patients
347 with HER2-positive metastatic breast cancer. Breast tumor specimens were required to show
348 HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a
349 central laboratory. Patients were randomized 1:1 to receive placebo plus trastuzumab and
350 docetaxel or PERJETA plus trastuzumab and docetaxel. Randomization was stratified by prior
351 treatment (prior or no prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) and
352 geographic region (Europe, North America, South America, and Asia). Patients with prior
353 adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than
354 12 months before trial enrollment.

355 PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every
356 3 weeks thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed
357 by 6 mg/kg every 3 weeks thereafter. Patients were treated with PERJETA and trastuzumab
358 until progression of disease, withdrawal of consent, or unacceptable toxicity. Docetaxel was
359 given as an initial dose of 75 mg/m² by intravenous infusion every 3 weeks for at least 6 cycles.
360 The docetaxel dose could be escalated to 100 mg/m² at the investigator's discretion if the initial
361 dose was well tolerated. At the time of the primary analysis, the mean number of cycles of study
362 treatment administered was 16.2 in the placebo-treated group and 19.9 in the PERJETA-treated
363 group.

364 The primary endpoint of the randomized trial was progression-free survival (PFS) as assessed by
365 an independent review facility (IRF). PFS was defined as the time from the date of
366 randomization to the date of disease progression or death (from any cause) if the death occurred
367 within 18 weeks of the last tumor assessment. Additional endpoints included overall survival
368 (OS), PFS (investigator-assessed), objective response rate (ORR) and duration of response.

369 Patient demographic and baseline characteristics were balanced between the treatment arms.
370 The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were
371 Black. All were women with the exception of 2 patients. Seventeen percent of patients were
372 enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor
373 prognostic characteristics, including hormone receptor status (positive 48%, negative 50%),
374 presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study
375 arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2
376 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone
377 receptor positive tumors, 45% received prior adjuvant hormonal therapy and 11% received
378 hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or
379 neoadjuvant trastuzumab.

380 The randomized trial demonstrated a statistically significant improvement in IRF-assessed PFS

381 in the PERJETA-treated group compared with the placebo-treated group [hazard ratio (HR) =
382 0.62 (95% CI: 0.51, 0.75), $p < 0.0001$] and an increase in median PFS of 6.1 months (median
383 PFS of 18.5 months in the PERJETA-treated group vs. 12.4 months in the placebo-treated group)
384 (see Figure 1). The results for investigator-assessed PFS were comparable to those observed for
385 IRF-assessed PFS.

386 Consistent results were observed across several patient subgroups including age (< 65 or
387 ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or
388 chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the
389 subgroup of patients with hormone receptor-negative disease ($n=408$), the hazard ratio was 0.55
390 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease
391 ($n=388$), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). In the subgroup of patients with disease
392 limited to non-visceral metastasis ($n=178$), the hazard ratio was 0.96 (95% CI: 0.61, 1.52).

393 At the time of the final PFS analysis, 165 patients had died, and more deaths had occurred in the
394 placebo-treated group (23.6%) compared with the PERJETA-treated group (17.2%); OS was not
395 mature and interim OS analysis results did not meet the pre-specified stopping boundary for
396 statistical significance. A second interim analysis of OS, conducted after an additional year of
397 follow-up, demonstrated a statistically significant improvement in OS [HR=0.66 (95% CI: 0.52,
398 0.84), $p=0.0008$]. See Table 2 and Figure 2. OS results in patient subgroups were consistent
399 with those observed for IRF-assessed PFS with the exception of the subgroup of patients with
400 disease limited to non-visceral metastasis [HR = 1.42 (95% CI: 0.71, 2.84)].

Table 2 Summary of Efficacy from the Randomized Trial

Parameter	PERJETA + trastuzumab + docetaxel n=402	Placebo + trastuzumab + docetaxel n=406	HR (95% CI)	p-value
Progression-Free Survival (independent review)				
No. of patients with an event	191 (47.5%)	242 (59.6%)	0.62	< 0.0001
Median months	18.5	12.4	(0.51, 0.75)	
Overall Survival (second interim analysis)				
No. of patients who died	113 (28.1%)	154 (37.9%)	0.66	0.0008*
Median months	NR	37.6	(0.52, 0.84)	
Objective Response Rate (ORR, independent review)				
No. of patients analyzed	343	336		
Objective response (CR + PR)	275 (80.2%)	233 (69.3%)		
Complete response (CR)	19 (5.5%)	14 (4.2%)		
Partial Response (PR)	256 (74.6%)	219 (65.2%)		
Median Duration of Response (months)	20.2	12.5		
Difference in ORR 95% CI	10.8% (4.2%, 17.5%)			0.0011

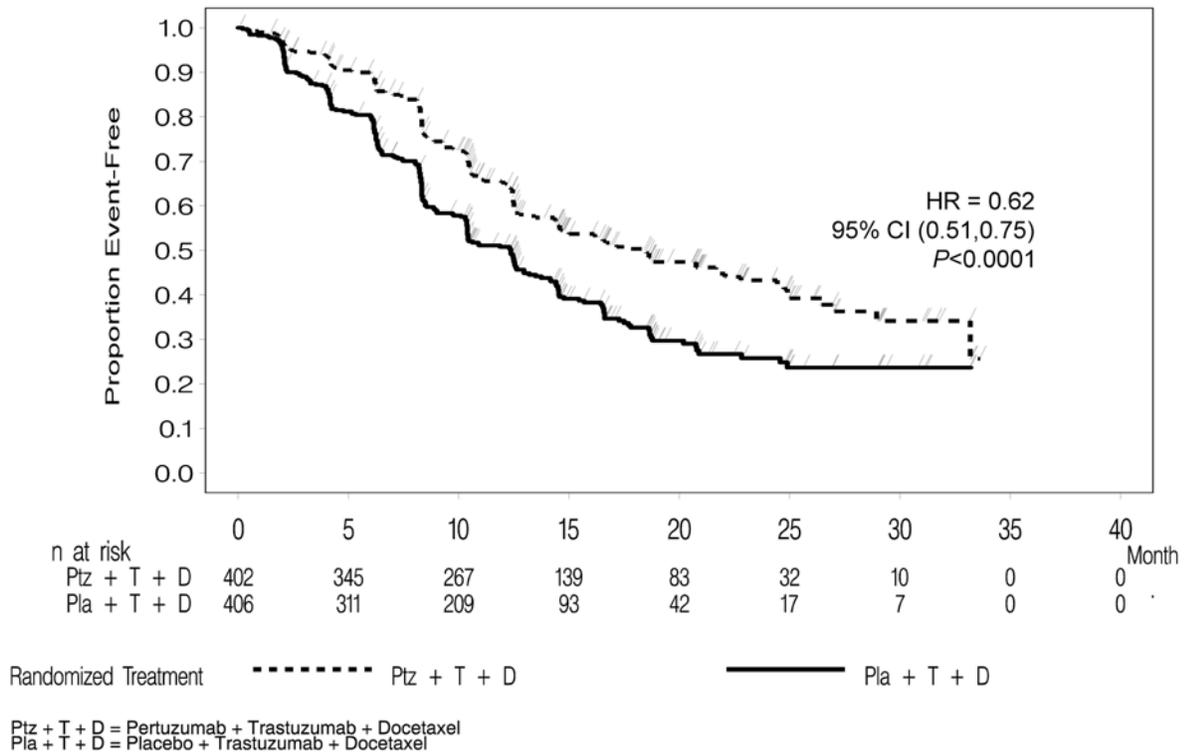
402 * The HR and p-value for the second interim analysis of Overall Survival crossed the pre-defined
403 efficacy stopping boundary ($HR \leq 0.739$, $p \leq 0.0138$).

404 NR=Not reached

405 CI=Confidence Interval

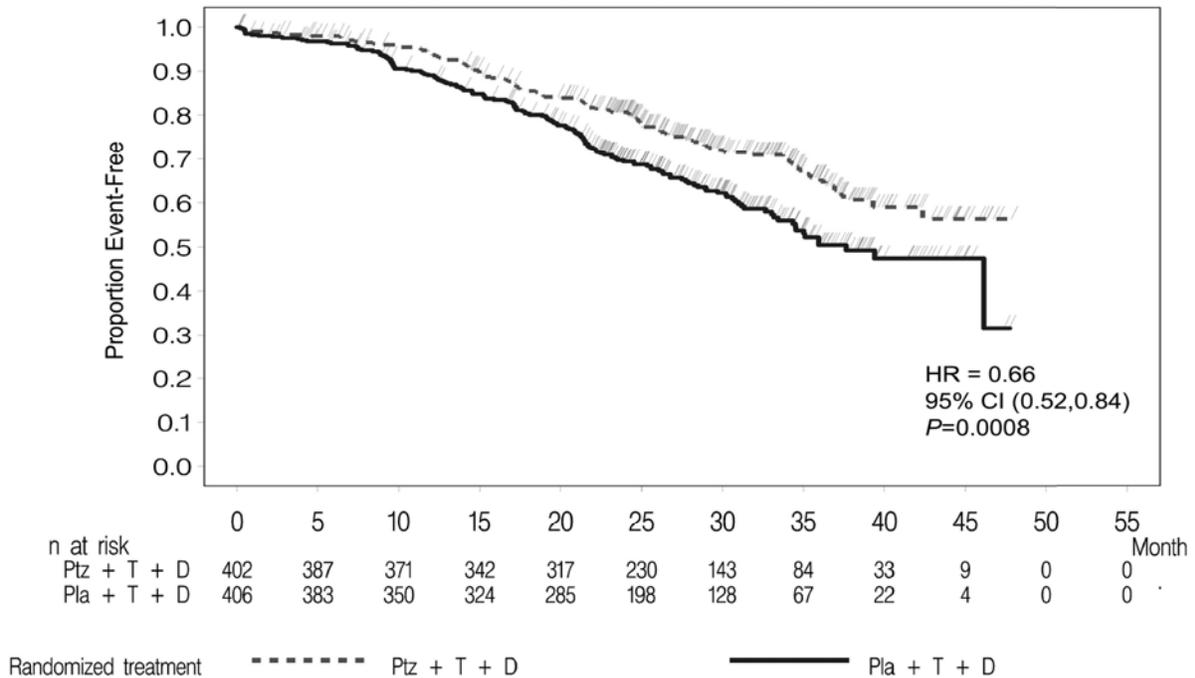
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Figure 1 Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival for the Randomized Trial



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Figure 2 Kaplan-Meier Curve of Overall Survival for the Randomized Trial



411
412

413 **16 HOW SUPPLIED/STORAGE AND HANDLING**

414 **16.1 How Supplied**

415 PERJETA is supplied as a 420 mg/14 mL (30 mg/mL) single-use vial containing preservative-
416 free solution. NDC 50242-145-01.

417 Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use.

418 Keep vial in the outer carton in order to protect from light.

419 **DO NOT FREEZE. DO NOT SHAKE.**

420 **17 PATIENT COUNSELING INFORMATION**

- 421 • Advise pregnant women and females of reproductive potential that PERJETA exposure can
422 result in fetal harm, including embryo-fetal death or birth defects [*see Warnings and*
423 *Precautions (5.1) and Use in Specific Populations (8.1)*]
- 424 • Advise females of reproductive potential to use effective contraception while receiving
425 PERJETA and for 6 months following the last dose of PERJETA [*see Warnings and*
426 *Precautions (5.1) and Use in Special Populations (8.6)*]
- 427 • Advise nursing mothers treated with PERJETA to discontinue nursing or discontinue
428 PERJETA, taking into account the importance of the drug to the mother [*see Use in Specific*
429 *Populations (8.3)*].
- 430 • Encourage women who are exposed to PERJETA during pregnancy to enroll in the MoTHER
431 Pregnancy Registry by contacting 1-800-690-6720 [*see Warnings and Precautions (5.1) and*
432 *Use in Specific Populations (8.1)*]

PERJETA[®] (pertuzumab)

L01XC13

Manufactured by:

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A Member of the Roche Group

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