

## 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)

### 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](http://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 MoTHER Pregnancy Registry by contacting 1-800-690-6720. (5.1, 8.1, 8.6, 17)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2012

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# FULL PRESCRIBING INFORMATION

## 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)

## 1 INDICATIONS AND USAGE

PERJETA is indicated for use 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.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Doses and Schedules

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

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

When administered with PERJETA, the recommended initial dose of docetaxel is 75 mg/m<sup>2</sup> administered as an intravenous infusion. The dose may be escalated to 100 mg/m<sup>2</sup> administered every 3 weeks if the initial dose is well tolerated.

### 2.2 Dose Modification

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

The infusion rate of PERJETA may be slowed or interrupted if the patient develops an infusion-associated reaction. The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction [*see Warnings and Precautions (5.2)*].

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

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

- a drop in LVEF to less than 40% or
- LVEF of 40% to 45% with a 10% or greater absolute decrease below pretreatment values [*see Warnings and Precautions (5.2)*]

PERJETA may be resumed if the LVEF has recovered to greater than 45% or to 40% to 45% associated with less than a 10% absolute decrease below pretreatment values.

If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinuation of PERJETA and trastuzumab should be strongly considered,

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38 unless the benefits for the individual patient are deemed to outweigh the risks [*see Warnings and*  
39 *Precautions (5.2)*].

40 PERJETA should be withheld or discontinued if trastuzumab treatment is withheld or  
41 discontinued.

42 If docetaxel is discontinued, treatment with PERJETA and trastuzumab may continue.

43 Dose reductions are not recommended for PERJETA.

44 For docetaxel dose modifications, see docetaxel prescribing information.

### 45 **2.3 Preparation for Administration**

46 Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus.

47 Do not mix PERJETA with other drugs.

#### 48 Preparation

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

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

### 59 **3 DOSAGE FORMS AND STRENGTHS**

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

### 61 **4 CONTRAINDICATIONS**

62 None.

### 63 **5 WARNINGS AND PRECAUTIONS**

#### 64 **5.1 Embryo-Fetal Toxicity**

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

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

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

## 82 **5.2 Left Ventricular Dysfunction**

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

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

98 Assess LVEF prior to initiation of PERJETA and at regular intervals (e.g., every three months)  
99 during treatment to ensure that LVEF is within the institution's normal limits. If LVEF is  
100  $< 40\%$ , or is  $40\%$  to  $45\%$  with a  $10\%$  or greater absolute decrease below the pretreatment value,  
101 withhold PERJETA and trastuzumab and repeat LVEF assessment within approximately  
102 3 weeks. Discontinue PERJETA and trastuzumab if the LVEF has not improved or has declined  
103 further, unless the benefits for the individual patient outweigh the risks [see *Dosage and*  
104 *Administration (2.2)*].

## 105 **5.3 Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis**

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

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

119 In the randomized trial, the overall frequency of hypersensitivity/anaphylaxis reactions was  
120  $10.8\%$  in the PERJETA-treated group and  $9.1\%$  in the placebo-treated group. The incidence of  
121 Grade 3 – 4 hypersensitivity/anaphylaxis reactions was  $2\%$  in the PERJETA-treated group and  
122  $2.5\%$  in the placebo-treated group according to National Cancer Institute – Common

123 Terminology Criteria for Adverse Events (NCI - CTCAE) (version 3). Overall, 4 patients in  
124 PERJETA-treated group and 2 patients in the placebo-treated group experienced anaphylaxis.

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

#### 130 **5.4 HER2 Testing**

131 Detection of HER2 protein overexpression is necessary for selection of patients appropriate for  
132 PERJETA therapy because these are the only patients studied and for whom benefit has been  
133 shown [*see Indications and Usage (1) and Clinical Studies (14)*]. In the randomized trial,  
134 patients with breast cancer were required to have evidence of HER2 overexpression defined as  
135 3+ IHC by Dako Herceptest™ or FISH amplification ratio  $\geq 2.0$  by Dako HER2 FISH  
136 PharmDx™ test kit. Only limited data were available for patients whose breast cancer was  
137 positive by FISH, but did not demonstrate protein overexpression by IHC.

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

### 143 **6 ADVERSE REACTIONS**

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

- 145 • Embryo-Fetal Toxicity [*see Warnings and Precautions (5.1)*]
- 146 • Left Ventricular Dysfunction [*see Warnings and Precautions (5.2)*]
- 147 • Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis [*see Warnings*  
148 *and Precautions (5.3)*]

#### 149 **6.1 Clinical Trials Experience**

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

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

156 The adverse reactions described in Table 1 were identified in 804 patients with HER2-positive  
157 metastatic breast cancer treated in the randomized trial. Patients were randomized to receive  
158 either PERJETA in combination with trastuzumab and docetaxel or placebo in combination with  
159 trastuzumab and docetaxel. The median duration of study treatment was 18.1 months for  
160 patients in the PERJETA-treated group and 11.8 months for patients in the placebo-treated  
161 group. No dose adjustment was permitted for PERJETA or trastuzumab. The rates of adverse  
162 events resulting in permanent discontinuation of all study therapy were 6.1% for patients in the  
163 PERJETA-treated group and 5.3% for patients in the placebo-treated group. Adverse events led  
164 to discontinuation of docetaxel alone in 23.6% of patients in the PERJETA-treated group and  
165 23.2% of patients in the placebo-treated group. Table 1 reports the adverse reactions that  
166 occurred in at least 10% of patients in the PERJETA-treated group.

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

175 **Table 1 Summary of Adverse Reactions Occurring in ≥ 10% of Patients on the**  
 176 **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 %
<b>General disorders and administration site conditions</b>				
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
<b>Skin and subcutaneous tissue disorders</b>				
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
<b>Gastrointestinal disorders</b>				
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
<b>Blood and lymphatic system disorders</b>				
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

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

177 \* In this table this denotes an adverse reaction that has been reported in association with a fatal  
178 outcome

179

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

182 **Skin and subcutaneous tissue disorders:** Paronychia (7.1% in the PERJETA-treated group vs.  
183 3.5% in the placebo-treated group)

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

186 **Cardiac disorders:** Left ventricular dysfunction (4.4% in the PERJETA-treated group vs. 8.3%  
187 in the placebo-treated group) including symptomatic left ventricular systolic dysfunction (CHF)  
188 (1.0% in the PERJETA-treated group vs. 1.8% in the placebo-treated group)

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

191 ***Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab after***  
192 ***Discontinuation of Docetaxel***

193 In the randomized trial, adverse reactions were reported less frequently after discontinuation of  
194 docetaxel treatment. All adverse reactions in the PERJETA and trastuzumab treatment group

195 occurred in < 10% of patients with the exception of diarrhea (19.1%), upper respiratory tract  
196 infection (12.8%), rash (11.7%), headache (11.4%), and fatigue (11.1%).

## 197 **6.2 Immunogenicity**

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

199 Patients in the randomized trial were tested at multiple time-points for antibodies to PERJETA.  
200 Approximately 2.8% (11/386) of patients in the PERJETA-treated group and 6.2% (23/372) of  
201 patients in the placebo-treated group tested positive for anti-PERJETA antibodies. Of these  
202 34 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to  
203 the anti-therapeutic antibodies (ATA). The presence of pertuzumab in patient serum at the levels  
204 expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-  
205 pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a  
206 result, data may not accurately reflect the true incidence of anti-pertuzumab antibody  
207 development.

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

## 214 **7 DRUG INTERACTIONS**

215 No drug-drug interactions were observed between pertuzumab and trastuzumab, or between  
216 pertuzumab and docetaxel.

## 217 **8 USE IN SPECIFIC POPULATIONS**

### 218 **8.1 Pregnancy**

#### 219 ***Pregnancy Category D***

##### 220 Risk Summary

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

229 If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving  
230 PERJETA, immediately report exposure to the Genentech Adverse Event Line at  
231 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the  
232 MotHER Pregnancy Registry by contacting 1-800-690-6720 [*see Patient Counseling*  
233 *Information (17)*].

##### 234 Animal Data

235 Reproductive toxicology studies have been conducted in cynomolgus monkeys. Pregnant  
236 monkeys were treated on Gestational Day (GD)19 with loading doses of 30 to 150 mg/kg  
237 pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in  
238 clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based

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239 on C<sub>max</sub>. Intravenous administration of pertuzumab from GD19 through GD50 (period of  
240 organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between  
241 GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with  
242 bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than  
243 the recommended human dose, based on C<sub>max</sub>). At Caesarean section on GD100,  
244 oligohydramnios, decreased relative lung and kidney weights and microscopic evidence of renal  
245 hypoplasia consistent with delayed renal development were identified in all pertuzumab dose  
246 groups. Pertuzumab exposure was reported in offspring from all treated groups, at levels of  
247 29% to 40% of maternal serum levels at GD100.

### 248 **8.3 Nursing Mothers**

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

### 255 **8.4 Pediatric Use**

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

### 257 **8.5 Geriatric Use**

258 Of 402 patients who received PERJETA in the randomized trial, 60 patients (15%) were  
259 ≥ 65 years of age and 5 patients (1%) were ≥ 75 years of age. No overall differences in efficacy  
260 and safety of PERJETA were observed between these patients and younger patients.

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

### 264 **8.6 Females of Reproductive Potential**

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

269 If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving  
270 PERJETA, immediately report exposure to the Genentech Adverse Event Line at  
271 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the  
272 MoTHER Pregnancy Registry by contacting 1-800-690-6720 [*see Patient Counseling*  
273 *Information (17)*].

### 274 **8.7 Renal Impairment**

275 Dose adjustments of PERJETA are not needed in patients with mild (creatinine clearance [CLcr]  
276 60 to 90 mL/min) or moderate (CLcr 30 to 60 mL/min) renal impairment. No dose adjustment  
277 can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min)  
278 because of the limited pharmacokinetic data available [*see Clinical Pharmacology (12.3)*].

### 279 **8.8 Hepatic Impairment**

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

282 **10 OVERDOSAGE**

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

284 **11 DESCRIPTION**

285 Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular  
286 dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein  
287 (HER2). Pertuzumab is produced by recombinant DNA technology in a mammalian cell  
288 (Chinese Hamster Ovary) culture containing the antibiotic, gentamicin. Gentamicin is not  
289 detectable in the final product. Pertuzumab has an approximate molecular weight of 148 kDa.

290 PERJETA is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous  
291 infusion. Each single use vial contains 420 mg of pertuzumab at a concentration of 30 mg/mL in  
292 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20.

293 **12 CLINICAL PHARMACOLOGY**

294 **12.1 Mechanism of Action**

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

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

306 **12.3 Pharmacokinetics**

307 Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2 – 25 mg/kg. Based on a  
308 population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was  
309 0.24 L/day and the median half-life was 18 days. With an initial dose of 840 mg followed by a  
310 maintenance dose of 420 mg every three weeks thereafter, the steady-state concentration of  
311 pertuzumab was reached after the first maintenance dose.

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

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

318 No dedicated renal impairment trial for PERJETA has been conducted. Based on the results of  
319 the population pharmacokinetic analysis, pertuzumab exposure in patients with mild (CLcr  
320 60 to 90 mL/min, n=200) and moderate renal impairment (CLcr 30 to 60 mL/min, n=71) were  
321 similar to those in patients with normal renal function (CLcr greater than 90 mL/min, n=200).  
322 No relationship between CLcr and pertuzumab exposure was observed over the range of  
323 observed CLcr (27 to 244 mL/min).

324 **12.6 Cardiac Electrophysiology**

325 The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of

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326 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with  
327 HER2-positive breast cancer in the randomized trial. No large changes in the mean QT interval  
328 (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in  
329 the trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded  
330 because of the limitations of the trial design.

### 331 **13 NONCLINICAL TOXICOLOGY**

#### 332 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

336 No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab.  
337 No adverse effects on male and female reproductive organs were observed in repeat-dose  
338 toxicity studies of up to six months duration in cynomolgus monkeys.

### 339 **14 CLINICAL STUDIES**

#### 340 **14.1 Metastatic Breast Cancer**

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

350 PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every  
351 3 weeks thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed  
352 by 6 mg/kg every 3 weeks thereafter. Patients were treated with PERJETA and trastuzumab  
353 until progression of disease, withdrawal of consent, or unacceptable toxicity. Docetaxel was  
354 given as an initial dose of 75 mg/m<sup>2</sup> by intravenous infusion every 3 weeks for at least 6 cycles.  
355 The docetaxel dose could be escalated to 100 mg/m<sup>2</sup> at the investigator's discretion if the initial  
356 dose was well tolerated. At the time of the primary analysis, the mean number of cycles of study  
357 treatment administered was 16.2 in the placebo-treated group and 19.9 in the PERJETA-treated  
358 group.

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

364 Patient demographic and baseline characteristics were balanced between the treatment arms.  
365 The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were  
366 Black. All were women with the exception of 2 patients. Seventeen percent of patients were  
367 enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor  
368 prognostic characteristics, including hormone receptor status (positive 48%, negative 50%),  
369 presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study  
370 arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2

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371 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone  
 372 receptor positive tumors, 45% received prior adjuvant hormonal therapy and 11% received  
 373 hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or  
 374 neoadjuvant trastuzumab.

375 The randomized trial demonstrated a statistically significant improvement in IRF-assessed PFS  
 376 in the PERJETA-treated group compared with the placebo-treated group [hazard ratio (HR) =  
 377 0.62 (95% CI: 0.51, 0.75),  $p < 0.0001$ ] and an increase in median PFS of 6.1 months (median  
 378 PFS of 18.5 months in the PERJETA-treated group vs. 12.4 months in the placebo-treated group)  
 379 (see Figure 1). The results for investigator-assessed PFS were comparable to those observed for  
 380 IRF-assessed PFS.

381 Consistent results were observed across several patient subgroups including age ( $< 65$  or  
 382  $\geq 65$  years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or  
 383 chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the  
 384 subgroup of patients with hormone receptor-negative disease ( $n=408$ ), the hazard ratio was 0.55  
 385 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease  
 386 ( $n=388$ ), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). In the subgroup of patients with disease  
 387 limited to non-visceral metastasis ( $n=178$ ), the hazard ratio was 0.96 (95% CI: 0.61, 1.52).

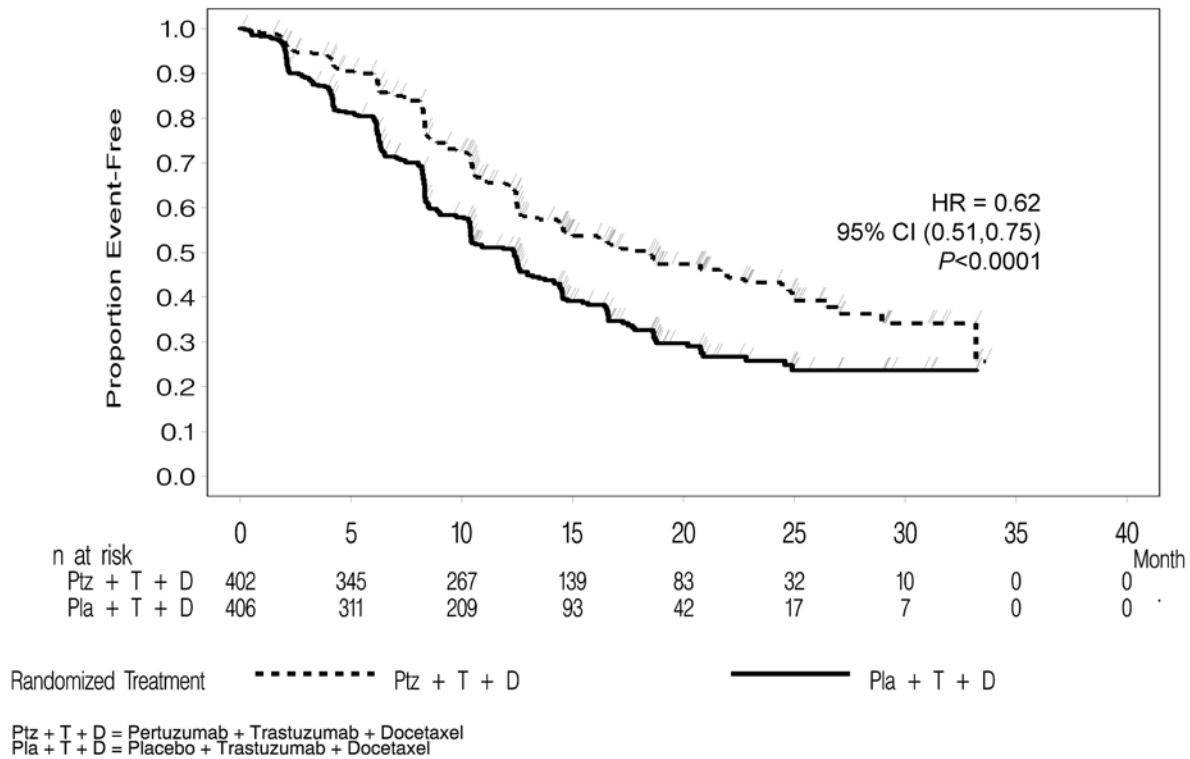
388 At the time of the PFS analysis, 165 patients had died. More deaths occurred in the placebo-  
 389 treated group (23.6%) compared with the PERJETA-treated group (17.2%). At the interim OS  
 390 analysis, the results were not mature and did not meet the pre-specified stopping boundary for  
 391 statistical significance. See Table 2 and Figure 2.

392 **Table 2 Summary of Efficacy from the Randomized Trial**

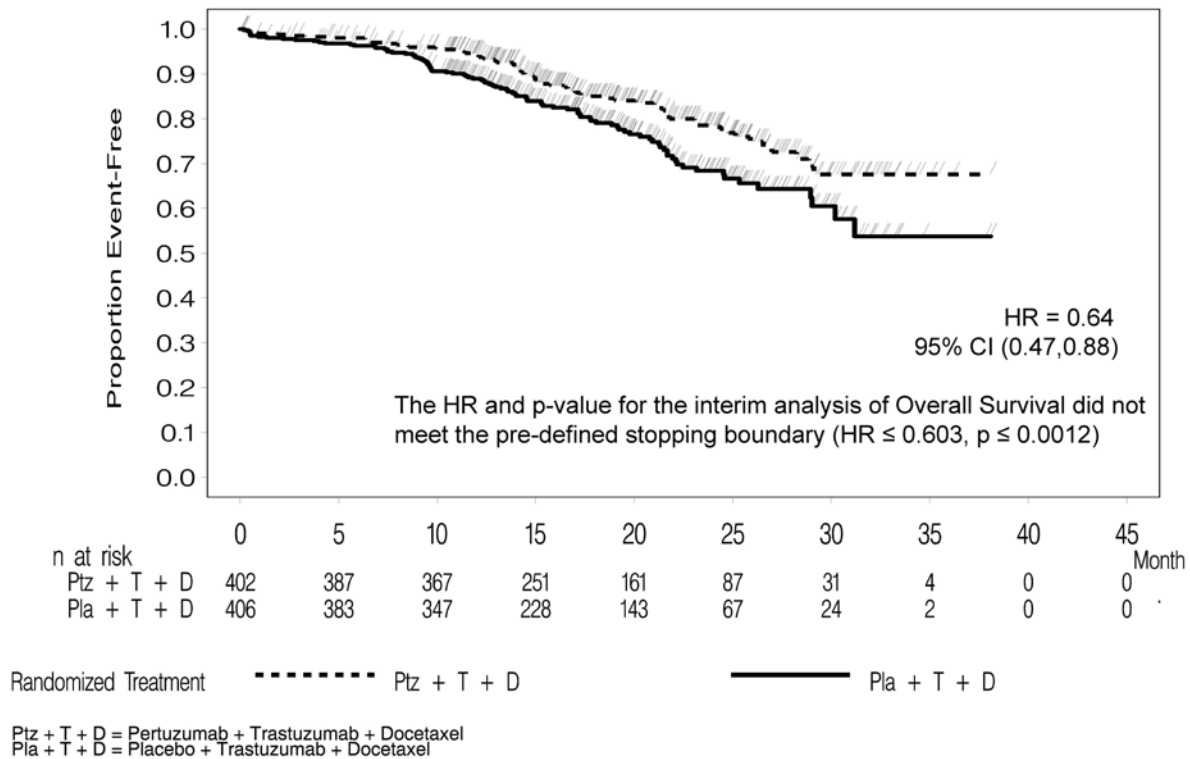
Parameter	PERJETA + trastuzumab + docetaxel n=402	Placebo + trastuzumab + docetaxel n=406	HR (95% CI)	p-value
<b>Progression-Free Survival (independent review)</b>			0.62 (0.51, 0.75)	$< 0.0001$
<b>No. of patients with an event</b>	191 (47.5%)	242 (59.6%)		
<b>Median months</b>	18.5	12.4		
<b>Overall Survival (interim analysis)</b>			0.64 (0.47, 0.88)	0.0053*
<b>No. of patients with an event</b>	69 (17.2%)	96 (23.6%)		
<b>Objective Response Rate (ORR)</b>				
<b>No. of patients analyzed</b>	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%)		
<b>Median Duration of Response (months)</b>	20.2	12.5		

393 \* The HR and p-value for the interim analysis of Overall Survival did not meet the pre-defined  
 394 stopping boundary ( $HR \leq 0.603$ ,  $p \leq 0.0012$ ).

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



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



402

403 **16 HOW SUPPLIED/STORAGE AND HANDLING**

404 **16.1 How Supplied**

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

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

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

409 **DO NOT FREEZE. DO NOT SHAKE.**

410 **17 PATIENT COUNSELING INFORMATION**

- 411 • Advise pregnant women and females of reproductive potential that PERJETA exposure can  
412 result in fetal harm, including embryo-fetal death or birth defects [*see Warnings and*  
413 *Precautions (5.1) and Use in Specific Populations (8.1)*]
- 414 • Advise females of reproductive potential to use effective contraception while receiving  
415 PERJETA and for 6 months following the last dose of PERJETA [*see Warnings and*  
416 *Precautions (5.1) and Use in Special Populations (8.6)*]
- 417 • Advise nursing mothers treated with PERJETA to discontinue nursing or discontinue  
418 PERJETA, taking into account the importance of the drug to the mother [*see Use in Specific*  
419 *Populations (8.3)*].
- 420 • Encourage women who are exposed to PERJETA during pregnancy to enroll in the MotHER  
421 Pregnancy Registry by contacting 1-800-690-6720 [*see Warnings and Precautions (5.1) and*  
422 *Use in Specific Populations (8.1)*]

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PERJETA™ (pertuzumab)

L01XC13

Manufactured by:

**Genentech, Inc.**

A Member of the Roche Group

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