

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: CARDIOMYOPATHY and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.
Cardiomyopathy: PERJETA can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF. Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function. (2.2, 5.2, 6.1)

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)

-----**RECENT MAJOR CHANGES**-----
None

-----**INDICATIONS AND USAGE**-----
PERJETA is a HER2/neu receptor antagonist indicated for:

- Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. (1.1)
- Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival. (1.2, 2.1, 14.2)

Limitations of Use:

- The safety of PERJETA as part of a doxorubicin-containing regimen has not been established.
- The safety of PERJETA administered for greater than 6 cycles for early breast cancer has not been established.

-----**DOSAGE AND ADMINISTRATION**-----

- **For intravenous infusion only.** Do not administer as an intravenous push or bolus. (2.3)
- The initial PERJETA 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)

- **MBC:** Administer PERJETA, trastuzumab, and docetaxel by intravenous infusion every 3 weeks. (2.1)
 - **Neoadjuvant:** Administer PERJETA, trastuzumab, and docetaxel by intravenous infusion preoperatively every 3 weeks for 3 to 6 cycles. (2.1)
- DOSAGE FORMS AND STRENGTHS**-----
- 420 mg/14 mL single-use vial. (3)

-----**CONTRAINDICATIONS**-----

PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients. (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-Related Reactions:** Monitor for signs and symptoms. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies. (5.3)
- **Hypersensitivity Reactions/Anaphylaxis:** Monitor for signs and symptoms. If a severe hypersensitivity reaction/anaphylaxis occurs, discontinue the infusion immediately and administer appropriate medical therapies. (5.4)
- **HER2 testing:** Perform using FDA-approved tests by laboratories with demonstrated proficiency. (5.5)

-----**ADVERSE REACTIONS**-----

Metastatic Breast Cancer

- 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)

Neoadjuvant Treatment of Breast Cancer

- The most common adverse reactions (> 30%) with PERJETA in combination with trastuzumab and docetaxel were alopecia, diarrhea, nausea, and neutropenia. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and docetaxel when given for 3 cycles following 3 cycles of FEC were fatigue, alopecia, diarrhea, nausea, vomiting, and neutropenia. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with docetaxel, carboplatin, and trastuzumab (TCH) were fatigue, alopecia, diarrhea, nausea, vomiting, neutropenia, thrombocytopenia, and anemia. (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: 03/2015

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: CARDIOMYOPATHY AND EMBRYO-FETAL TOXICITY**

Cardiomyopathy

PERJETA administration can result in subclinical and clinical cardiac failure. Evaluate left ventricular function in all patients prior to and during treatment with PERJETA. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function. (2.2, 5.2, 6.1)

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
4 **1 INDICATIONS AND USAGE**

5 **1.1 Metastatic Breast Cancer (MBC)**

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

9 **1.2 Neoadjuvant Treatment of Breast Cancer**

10 PERJETA is indicated for use in combination with trastuzumab and docetaxel for the
11 neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early
12 stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete
13 treatment regimen for early breast cancer. This indication is based on demonstration of an
14 improvement in pathological complete response rate. No data are available demonstrating
15 improvement in event-free survival or overall survival [*see Clinical Studies (14.2) and Dosage*
16 *and Administration (2.1)*].

17 **Limitations of Use:**

- 18 • The safety of PERJETA as part of a doxorubicin-containing regimen has not been
19 established.
- 20 • The safety of PERJETA administered for greater than 6 cycles for early breast cancer has
21 not been established.
22

23 **2 DOSAGE AND ADMINISTRATION**

24 **2.1 Recommended Doses and Schedules**

25 The initial dose of PERJETA is 840 mg administered as a 60-minute intravenous infusion,
26 followed every 3 weeks by a dose of 420 mg administered as an intravenous infusion over
27 30 to 60 minutes.

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

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

36 ***Metastatic Breast Cancer (MBC)***

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

40 ***Neoadjuvant Treatment of Breast Cancer***

41 PERJETA should be administered every 3 weeks for 3 to 6 cycles as part of one of the following
42 treatment regimens for early breast cancer [see *Clinical Studies (14.2)*]:

- 43 • Four preoperative cycles of PERJETA in combination with trastuzumab and docetaxel
44 followed by 3 postoperative cycles of fluorouracil, epirubicin, and cyclophosphamide
45 (FEC) as given in Study 2
- 46 • Three preoperative cycles of FEC alone followed by 3 preoperative cycles of PERJETA
47 in combination with docetaxel and trastuzumab as given in Study 3
- 48 • Six preoperative cycles of PERJETA in combination with docetaxel, carboplatin, and
49 trastuzumab (TCH) (escalation of docetaxel above 75 mg/m² is not recommended) as
50 given in Study 3

51 Following surgery, patients should continue to receive trastuzumab to complete 1 year of
52 treatment. There is insufficient evidence to recommend continued use of PERJETA for greater
53 than 6 cycles for early breast cancer. There is insufficient evidence to recommend concomitant
54 administration of an anthracycline with PERJETA, and there are no safety data to support
55 sequential use of doxorubicin with PERJETA.

56 **2.2 Dose Modification**

57 For delayed or missed doses, if the time between two sequential infusions is less than 6 weeks,
58 the 420 mg dose of PERJETA should be administered. Do not wait until the next planned dose.
59 If the time between two sequential infusions is 6 weeks or more, the initial dose of 840 mg
60 PERJETA should be re-administered as a 60-minute intravenous infusion followed every
61 3 weeks thereafter by a dose of 420 mg administered as an intravenous infusion over
62 30 to 60 minutes.

63 PERJETA should be discontinued if trastuzumab treatment is discontinued.

64 Dose reductions are not recommended for PERJETA.

65 For docetaxel dose modifications, see relevant prescribing information.

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

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

- 68 • a drop in LVEF to less than 45% or
- 69 • LVEF of 45% to 49% with a 10% or greater absolute decrease below pretreatment values
70 [see *Warnings and Precautions (5.2)*]

71 PERJETA may be resumed if the LVEF has recovered to greater than 49% or to 45% to 49%
72 associated with less than a 10% absolute decrease below pretreatment values.

73 If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has
74 declined further, PERJETA and trastuzumab should be discontinued, unless the benefits for the
75 individual patient are deemed to outweigh the risks [see *Warnings and Precautions (5.2)*].

76 ***Infusion-Related Reactions***

77 The infusion rate of PERJETA may be slowed or interrupted if the patient develops an
78 infusion-related reaction [*see Warnings and Precautions (5.3)*].

79 ***Hypersensitivity Reactions/Anaphylaxis***

80 The infusion should be discontinued immediately if the patient experiences a serious
81 hypersensitivity reaction [*see Warnings and Precautions (5.4)*].

82 **2.3 Preparation for Administration**

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

85 Preparation

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

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

96 **3 DOSAGE FORMS AND STRENGTHS**

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

98 **4 CONTRAINDICATIONS**

99 PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of
100 its excipients.

101 **5 WARNINGS AND PRECAUTIONS**

102 **5.1 Embryo-Fetal Toxicity**

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

108 Verify pregnancy status prior to the initiation of PERJETA. Advise patients of the risks of
109 embryo-fetal death and birth defects and the need for contraception during and after treatment.
110 Advise patients to contact their healthcare provider immediately if they suspect they may be
111 pregnant. If PERJETA is administered during pregnancy or if a patient becomes pregnant while
112 receiving PERJETA, immediately report exposure to the Genentech Adverse Event Line at
113 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the
114 MoTHER Pregnancy Registry by contacting 1-800-690-6720 [*see Patient Counseling*
115 *Information (17)*].

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

120 **5.2 Left Ventricular Dysfunction**

121 Decreases in LVEF have been reported with drugs that block HER2 activity, including
122 PERJETA. In Study 1, for patients with MBC, PERJETA in combination with trastuzumab and
123 docetaxel was not associated with increases in the incidence of symptomatic left ventricular
124 systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with
125 trastuzumab and docetaxel [see *Clinical Studies (14.1)*]. Left ventricular dysfunction occurred in
126 4.4% of patients in the PERJETA-treated group and 8.3% of patients in the placebo-treated
127 group. Symptomatic left ventricular systolic dysfunction (congestive heart failure) occurred in
128 1.0% of patients in the PERJETA-treated group and 1.8% of patients in the placebo-treated
129 group [see *Adverse Reactions (6.1)*]. Patients who have received prior anthracyclines or prior
130 radiotherapy to the chest area may be at higher risk of decreased LVEF.

131 In patients receiving neoadjuvant treatment in Study 2, the incidence of LVSD was higher in the
132 PERJETA-treated groups compared to the trastuzumab- and docetaxel-treated group. An
133 increased incidence of LVEF declines was observed in patients treated with PERJETA in
134 combination with trastuzumab and docetaxel. In the overall treatment period, LVEF decline
135 > 10% and a drop to less than 50% occurred in 1.9% of patients treated with neoadjuvant
136 trastuzumab and docetaxel as compared to 8.4% of patients treated with neoadjuvant PERJETA
137 in combination with trastuzumab and docetaxel. Symptomatic LVSD occurred in 0.9% of
138 patients treated with neoadjuvant PERJETA in combination with trastuzumab and no patients in
139 the other 3 arms. LVEF recovered to $\geq 50\%$ in all patients.

140 In patients receiving neoadjuvant PERJETA in Study 3, in the overall treatment period, LVEF
141 decline > 10% and a drop to less than 50% occurred in 6.9% of patients treated with PERJETA
142 plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 16.0% of
143 patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 10.5% of
144 patients treated with PERJETA in combination with TCH. Symptomatic LVSD occurred in
145 4.0% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, 1.3% of
146 patients treated with PERJETA in combination with TCH, and none of the patients treated with
147 PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel.
148 LVEF recovered to $\geq 50\%$ in all but one patient.

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

154 Assess LVEF prior to initiation of PERJETA and at regular intervals (e.g., every three months in
155 the metastatic setting and every six weeks in the neoadjuvant setting) during treatment to ensure
156 that LVEF is within the institution's normal limits. If LVEF is $< 45\%$, or is 45% to 49% with a
157 10% or greater absolute decrease below the pretreatment value, withhold PERJETA and
158 trastuzumab and repeat LVEF assessment within approximately 3 weeks. Discontinue
159 PERJETA and trastuzumab if the LVEF has not improved or has declined further, unless the
160 benefits for the individual patient outweigh the risks [see *Dosage and Administration (2.2)*].

161 **5.3 Infusion-Related Reactions**

162 PERJETA has been associated with infusion reactions [see *Adverse Reactions (6.1)*]. An
163 infusion reaction was defined in Study 1 as any event described as hypersensitivity, anaphylactic
164 reaction, acute infusion reaction, or cytokine release syndrome occurring during an infusion or
165 on the same day as the infusion. The initial dose of PERJETA was given the day before
166 trastuzumab and docetaxel to allow for the examination of PERJETA-associated reactions. On
167 the first day, when only PERJETA was administered, the overall frequency of infusion reactions
168 was 13.0% in the PERJETA-treated group and 9.8% in the placebo-treated group. Less than 1%
169 were Grade 3 or 4. The most common infusion reactions ($\geq 1.0\%$) were pyrexia, chills, fatigue,
170 headache, asthenia, hypersensitivity, and vomiting.

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

174 In Study 2 and Study 3, PERJETA was administered on the same day as the other study
175 treatment drugs. Infusion reactions were consistent with those observed in Study 1, with a
176 majority of reactions being National Cancer Institute - Common Terminology Criteria for
177 Adverse Events (NCI - CTCAE v3.0) Grade 1 – 2.

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

183 **5.4 Hypersensitivity Reactions/Anaphylaxis**

184 In Study 1, the overall frequency of hypersensitivity/anaphylaxis reactions was 10.8% in the
185 PERJETA-treated group and 9.1% in the placebo-treated group. The incidence of Grade 3 – 4
186 hypersensitivity/anaphylaxis reactions was 2.0% in the PERJETA-treated group and 2.5% in the
187 placebo-treated group according to NCI - CTCAE v3.0. Overall, 4 patients in PERJETA-treated
188 group and 2 patients in the placebo-treated group experienced anaphylaxis.

189 In Study 2 and Study 3, hypersensitivity/anaphylaxis events were consistent with those observed
190 in Study 1. In Study 2, two patients in the PERJETA- and docetaxel-treated group experienced
191 anaphylaxis. In Study 3, the overall frequency of hypersensitivity/anaphylaxis was highest in the
192 PERJETA plus TCH treated group (13.2%), of which 2.6% were NCI-CTCAE (version 3) Grade
193 3 – 4.

194 Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity,
195 including anaphylaxis, has been observed in clinical trials with treatment of PERJETA [see
196 *Clinical Trials Experience (6.1)*]. Medications to treat such reactions, as well as emergency
197 equipment, should be available for immediate use. PERJETA is contraindicated in patients with
198 known hypersensitivity to pertuzumab or to any of its excipients [see *Contraindications (4)*].

199 **5.5 HER2 Testing**

200 Detection of HER2 protein overexpression is necessary for selection of patients appropriate for
201 PERJETA therapy because these are the only patients studied and for whom benefit has been
202 shown [see *Indications and Usage (1) and Clinical Studies (14)*]. Patients with breast cancer
203 were required to have evidence of HER2 overexpression defined as 3+ IHC or FISH
204 amplification ratio ≥ 2.0 in the clinical studies. Only limited data were available for patients

205 whose breast cancer was positive by FISH, but did not demonstrate protein overexpression by
206 IHC.

207 Assessment of HER2 status should be performed by laboratories using FDA-approved tests with
208 demonstrated proficiency in the specific technology being utilized. Improper assay performance,
209 including use of sub-optimally fixed tissue, failure to utilize specified reagents, deviation from
210 specific assay instructions, and failure to include appropriate controls for assay validation, can
211 lead to unreliable results.

212 **6 ADVERSE REACTIONS**

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

- 214 • Embryo-Fetal Toxicity [*see Warnings and Precautions (5.1)*]
- 215 • Left Ventricular Dysfunction [*see Warnings and Precautions (5.2)*]
- 216 • Infusion-Related Reactions [*see Warnings and Precautions (5.3)*]
- 217 • Hypersensitivity Reactions/Anaphylaxis [*see Warnings and Precautions (5.4)*]

218 **6.1 Clinical Trials Experience**

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

222 ***Metastatic Breast Cancer (MBC)***

223 The adverse reactions described in Table 1 were identified in 804 patients with HER2-positive
224 metastatic breast cancer treated in Study 1. Patients were randomized to receive either
225 PERJETA in combination with trastuzumab and docetaxel or placebo in combination with
226 trastuzumab and docetaxel. The median duration of study treatment was 18.1 months for
227 patients in the PERJETA-treated group and 11.8 months for patients in the placebo-treated
228 group. No dose adjustment was permitted for PERJETA or trastuzumab. The rates of adverse
229 events resulting in permanent discontinuation of all study therapy were 6.1% for patients in the
230 PERJETA-treated group and 5.3% for patients in the placebo-treated group. Adverse events led
231 to discontinuation of docetaxel alone in 23.6% of patients in the PERJETA-treated group and
232 23.2% of patients in the placebo-treated group. Table 1 reports the adverse reactions that
233 occurred in at least 10% of patients in the PERJETA-treated group. The safety profile of
234 PERJETA remained unchanged with an additional 2.75 years of follow-up (median total follow-
235 up of 50 months) in Study 1.

236 The most common adverse reactions (> 30%) seen with PERJETA in combination with
237 trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and
238 peripheral neuropathy. The most common NCI - CTCAE v3.0 Grade 3 – 4 adverse reactions
239 (> 2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy,
240 anemia, asthenia, and fatigue. An increased incidence of febrile neutropenia was observed for
241 Asian patients in both treatment arms compared with patients of other races and from other
242 geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in
243 the pertuzumab-treated group (26%) compared with the placebo-treated group (12%).

244
245

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

Body System/ Adverse Reactions	PERJETA + trastuzumab + docetaxel n=407 Frequency rate %		Placebo + trastuzumab + docetaxel n=397 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

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

248 **The following clinically relevant adverse reactions were reported in < 10% of patients in**
249 **the PERJETA-treated group in Study 1:**

250 **Skin and subcutaneous tissue disorders:** Paronychia (7.1% in the PERJETA-treated group vs.
251 3.5% in the placebo-treated group)

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

254 **Cardiac disorders:** Left ventricular dysfunction (4.4% in the PERJETA-treated group vs. 8.3%
255 in the placebo-treated group) including symptomatic left ventricular systolic dysfunction (CHF)
256 (1.0% in the PERJETA-treated group vs. 1.8% in the placebo-treated group)

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

259 ***Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab after***
260 ***Discontinuation of Docetaxel***

261 In Study 1, adverse reactions were reported less frequently after discontinuation of docetaxel
262 treatment. All adverse reactions in the PERJETA and trastuzumab treatment group occurred in
263 < 10% of patients with the exception of diarrhea (19.1%), upper respiratory tract infection
264 (12.8%), rash (11.7%), headache (11.4%), and fatigue (11.1%).

265 ***Neoadjuvant Treatment of Breast Cancer (Study 2)***

266 In Study 2, the most common adverse reactions seen with PERJETA in combination with
267 trastuzumab and docetaxel administered for 4 cycles were similar to those seen in the PERJETA-
268 treated group in Study 1. The most common adverse reactions (> 30%) were alopecia,

269 neutropenia, diarrhea, and nausea. The most common NCI – CTCAE v3.0 Grade 3 – 4 adverse
270 reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, and diarrhea. In this group,
271 one patient permanently discontinued neoadjuvant treatment due to an adverse event. Table 2
272 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with
273 PERJETA for breast cancer in Study 2.

274

275

276

**Table 2 Summary of Adverse Reactions Occurring in ≥ 10%
in the Neoadjuvant Setting for Patients Receiving PERJETA in Study 2**

Body System/ Adverse Reactions	Trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab n=108 Frequency rate %		PERJETA + docetaxel n=108 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions								
Fatigue	27.1	0.0	26.2	0.9	12.0	0.0	25.5	1.1
Asthenia	17.8	0.0	20.6	1.9	2.8	0.0	16.0	2.1
Edema peripheral	10.3	0.0	2.8	0.0	0.9	0.0	5.3	0.0
Mucosal inflammation	21.5	0.0	26.2	1.9	2.8	0.0	25.5	0.0
Pyrexia	10.3	0.0	16.8	0.0	8.3	0.0	8.5	0.0
Skin and subcutaneous tissue disorders								
Alopecia	66.4	0.0	65.4	0.0	2.8	0.0	67.0	0.0
Rash	21.5	1.9	26.2	0.9	11.1	0.0	28.7	1.1
Gastrointestinal disorders								
Diarrhea	33.6	3.7	45.8	5.6	27.8	0.0	54.3	4.3
Nausea	36.4	0.0	39.3	0.0	13.9	0.0	36.2	1.1
Vomiting	12.1	0.0	13.1	0.0	4.6	0.0	16.0	2.1
Stomatitis	7.5	0.0	17.8	0.0	4.6	0.0	9.6	0.0
Blood and lymphatic system disorders								
Neutropenia	63.6	58.9	50.5	44.9	0.9	0.9	64.9	57.4
Leukopenia	21.5	11.2	9.3	4.7	0.0	0.0	13.8	8.5
Nervous system disorders								
Headache	11.2	0.0	11.2	0.0	13.9	0.0	12.8	0.0
Dysgeusia	10.3	0.0	15.0	0.0	4.6	0.0	7.4	0.0
Peripheral Sensory Neuropathy	12.1	0.9	8.4	0.9	1.9	0.0	10.6	0.0

Musculoskeletal and connective tissue disorders								
Myalgia	22.4	0.0	22.4	0.0	9.3	0.0	21.3	0.0
Arthralgia	8.4	0.0	10.3	0.0	4.6	0.0	9.6	0.0
Metabolism and nutrition disorders								
Decreased appetite	6.5	0.0	14.0	0.0	1.9	0.0	14.9	0.0
Psychiatric disorders								
Insomnia	11.2	0.0	8.4	0.0	3.7	0.0	8.5	0.0

277

278 **The following adverse reactions were reported in < 10% of patients receiving neoadjuvant**
279 **treatment and occurred more frequently in PERJETA-treated groups in Study 2:**
280 **(Ptz=pertuzumab; T=trastuzumab; D=docetaxel)**

281 **Blood and lymphatic system disorders:** Anemia (6.5% in the T+D arm, 2.8% in the Ptz+T+D
282 arm, 4.6% in the Ptz+T arm and 8.5% in the Ptz+D arm), Febrile neutropenia (6.5% in the T+D
283 arm, 8.4% in the Ptz+T+D arm, 0.0% in the Ptz+T arm and 7.4% in the Ptz+D arm)

284 **Immune system disorders:** Hypersensitivity (1.9% in the T+D arm, 5.6% in the Ptz+T+D arm,
285 5.6% in the Ptz+T arm and 5.3% in the Ptz+D arm)

286 **Nervous system disorders:** Dizziness (3.7% in the T+D arm, 2.8% in the Ptz+T+D arm, 5.6%
287 in the Ptz+T arm and 3.2% in the Ptz+D arm)

288 **Infections and infestations:** Upper respiratory tract infection (2.8% in the T+D arm, 4.7% in
289 the Ptz+T+D arm, 1.9% in the Ptz+T arm and 7.4% in the Ptz+D arm)

290 **Respiratory, thoracic and mediastinal disorders:** Dyspnea (3.7% in the T+D arm, 4.7% in the
291 Ptz+T+D arm, 2.8% in the Ptz+T arm and 2.1% in the Ptz+D arm)

292 **Cardiac disorders:** Left ventricular dysfunction (0.9% in the T+D arm, 2.8% in the Ptz+T+D
293 arm, 0.0% in the Ptz+T arm, and 1.1% in the Ptz+D arm) including symptomatic left ventricular
294 dysfunction (CHF) (0.9% in the Ptz+T arm and 0.0% in the T+D arm, Ptz+T+D arm, and Ptz+D
295 arm)

296 **Eye disorders:** Lacrimation increased (1.9% in the T+D arm, 3.7% in the Ptz+T+D arm, 0.9%
297 in the Ptz+T arm, and 4.3% in the Ptz+D arm)

298 ***Neoadjuvant Treatment of Breast Cancer (Study 3)***

299 In Study 3, when PERJETA was administered in combination with trastuzumab and docetaxel
300 for 3 cycles following 3 cycles of FEC, the most common adverse reactions (> 30%) were
301 diarrhea, nausea, alopecia, neutropenia, vomiting, and fatigue. The most common NCI-CTCAE
302 (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, leukopenia, febrile
303 neutropenia, diarrhea, left ventricular dysfunction, anemia, dyspnea, nausea, and vomiting.

304 Similarly, when PERJETA was administered in combination with docetaxel, carboplatin, and
305 trastuzumab (TCH) for 6 cycles, the most common adverse reactions (> 30%) were diarrhea,
306 alopecia, neutropenia, nausea, fatigue, vomiting, anemia, and thrombocytopenia. The most
307 common NCI-CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia,
308 febrile neutropenia, anemia, leukopenia, diarrhea, thrombocytopenia, vomiting, fatigue, ALT
309 increased, hypokalemia, and hypersensitivity.

310 The rates of adverse events resulting in permanent discontinuation of any component of
311 neoadjuvant treatment were 6.7% for patients receiving PERJETA in combination with
312 trastuzumab and docetaxel following FEC and 7.9% for patients receiving PERJETA in
313 combination with TCH. Table 3 reports the adverse reactions that occurred in patients who
314 received neoadjuvant treatment with PERJETA for breast cancer in Study 3.

315

316 **Table 3 Summary of Adverse Reactions Occurring in $\geq 10\%$ of Patients Receiving**
317 **Neoadjuvant Treatment with PERJETA in Study 3**

Body System/Adverse Reactions	PERJETA + trastuzumab + FEC followed by PERJETA + trastuzumab + docetaxel n=72 Frequency rate %		PERJETA + trastuzumab + docetaxel following FEC n=75 Frequency rate %		PERJETA + TCH n=76 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions						
Fatigue	36.1	0.0	36.0	0.0	42.1	3.9
Asthenia	9.7	0.0	14.7	1.3	13.2	1.3
Edema peripheral	11.1	0.0	4.0	0.0	9.2	0.0
Mucosal inflammation	23.6	0.0	20.0	0.0	17.1	1.3
Pyrexia	16.7	0.0	9.3	0.0	15.8	0.0
Skin and subcutaneous tissue disorders						
Alopecia	48.6	0.0	52.0	0.0	55.3	0.0
Rash	19.4	0.0	10.7	0.0	21.1	1.3
Dry skin	5.6	0.0	9.3	0.0	10.5	0.0
Palmar-Plantar Erythrodysesthesia Syndrome	6.9	0.0	10.7	0.0	7.9	0.0
Gastrointestinal disorders						
Diarrhea	61.1	4.2	61.3	5.3	72.4	11.8
Dyspepsia	25.0	1.4	8	0.0	22.4	0.0
Nausea	52.8	0.0	53.3	2.7	44.7	0.0
Vomiting	40.3	0.0	36.0	2.7	39.5	5.3

Constipation	18.1	0.0	22.7	0.0	15.8	0.0
Stomatitis	13.9	0.0	17.3	0.0	11.8	0.0
Blood and lymphatic system disorders						
Neutropenia	51.4	47.2	46.7	42.7	48.7	46.1
Anemia	19.4	1.4	9.3	4.0	38.2	17.1
Leukopenia	22.2	19.4	16.0	12.0	17.1	11.8
Febrile neutropenia	18.1	18.1	9.3	9.3	17.1	17.1
Thrombocytopenia	6.9	0.0	1.3	0.0	30.3	11.8
Immune system disorders						
Hypersensitivity	9.7	2.8	1.3	0.0	11.8	2.6
Nervous system disorders						
Neuropathy peripheral	5.6	0.0	1.3	0.0	10.5	0.0
Headache	22.2	0.0	14.7	0.0	17.1	0.0
Dysgeusia	11.1	0.0	13.3	0.0	21.1	0.0
Dizziness	8.3	0.0	8.0	1.3	15.8	0.0
Musculoskeletal and connective tissue disorders						
Myalgia	16.7	0.0	10.7	1.3	10.5	0.0
Arthralgia	11.1	0.0	12.0	0.0	6.6	0.0
Respiratory, thoracic, and mediastinal disorders						
Cough	9.7	0.0	5.3	0.0	11.8	0.0
Dyspnea	12.5	0.0	8.0	2.7	10.5	1.3
Epistaxis	11.1	0.0	10.7	0.0	15.8	1.3
Oropharyngeal pain	8.3	0.0	6.7	0.0	11.8	0.0
Metabolism and nutrition disorders						
Decreased appetite	20.8	0.0	10.7	0.0	21.1	0.0
Eye disorders						
Lacrimation increased	12.5	0.0	5.3	0.0	7.9	0.0
Psychiatric disorders						
Insomnia	11.1	0.0	13.3	0.0	21.1	0.0
Investigations						
ALT increased	6.9	0.0	2.7	0.0	10.5	3.9

318 FEC=5-fluorouracil, epirubicin, cyclophosphamide, TCH=docetaxel, carboplatin, trastuzumab

319 **The following selected adverse reactions were reported in < 10% of patients receiving**
320 **neoadjuvant treatment in Study 3: (Ptz=pertuzumab; T=trastuzumab; D=docetaxel;**
321 **FEC= fluorouracil, epirubicin, and cyclophosphamide; TCH=docetaxel, carboplatin, and**
322 **trastuzumab)**

323 **Skin and subcutaneous tissue disorders:** Nail disorder (9.7% in the Ptz+T+FEC/Ptz+T+D
324 arm, 6.7% in the FEC/Ptz+T+D arm, and 9.2% in the Ptz+TCH arm), Paronychia (0% in the
325 Ptz+T+FEC/Ptz+T+D and 1.3% in both the FEC/Ptz+T+D and Ptz+TCH arms), Pruritis (2.8% in
326 the Ptz+T+FEC/Ptz+T+D arm, 4.0% in the FEC/Ptz+T+D arm, and 3.9% in the Ptz+TCH arm)

327 **Infections and infestations:** Upper respiratory tract infection (8.3% in the
328 Ptz+T+FEC/Ptz+T+D arm, 4.0% in the FEC/Ptz+T+D arm, and 2.6% in the Ptz+TCH arm),
329 Nasopharyngitis (6.9% in the Ptz+T+FEC/Ptz+T+D arm, 6.7% in the FEC/Ptz+T+D arm, and
330 7.9% in the Ptz+TCH arm)

331 **Respiratory, thoracic, and mediastinal disorders:** Pleural effusion (1.4% in the
332 Ptz+T+FEC/Ptz+T+D arm and 0% in the FEC/Ptz+T+D and Ptz+TCH arm)

333 **Cardiac disorders:** Left ventricular dysfunction (5.6% in the Ptz+T+FEC/Ptz+T+D arm, 4.0%
334 in the FEC/Ptz+T+D arm, and 2.6% in the Ptz+TCH arm) including symptomatic left ventricular
335 systolic dysfunction (CHF) (2.7% in the FEC/Ptz+T+D arm and 0% in the Ptz+T+FEC/Ptz+T+D
336 and Ptz+TCH arms)

337 **6.2 Immunogenicity**

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

339 Patients in Study 1 were tested at multiple time-points for antibodies to PERJETA.
340 Approximately 2.8% (11/386) of patients in the PERJETA-treated group and 6.2% (23/372) of
341 patients in the placebo-treated group tested positive for anti-PERJETA antibodies. Of these
342 34 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to
343 the anti-therapeutic antibodies (ATA). The presence of pertuzumab in patient serum at the levels
344 expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-
345 pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a
346 result, data may not accurately reflect the true incidence of anti-pertuzumab antibody
347 development.

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

354 **7 DRUG INTERACTIONS**

355 No drug-drug interactions were observed between pertuzumab and trastuzumab, or between
356 pertuzumab and docetaxel.

357 **8 USE IN SPECIFIC POPULATIONS**

358 **8.1 Pregnancy**

359 *Pregnancy Category D*

360 Risk Summary

361 There are no adequate and well-controlled studies of PERJETA in pregnant women. Based on
362 findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant
363 woman. The effects of PERJETA are likely to be present during all trimesters of pregnancy.
364 Pertuzumab administered to pregnant cynomolgus monkeys resulted in oligohydramnios,
365 delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures of
366 2.5 to 20-fold greater than the recommended human dose, based on C_{max} . If PERJETA is
367 administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA, the
368 patient should be apprised of the potential hazard to the fetus.

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

374 Animal Data

375 Reproductive toxicology studies have been conducted in cynomolgus monkeys. Pregnant
376 monkeys were treated on Gestational Day (GD)19 with loading doses of 30 to 150 mg/kg
377 pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in
378 clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based
379 on C_{max} . Intravenous administration of pertuzumab from GD19 through GD50 (period of
380 organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between
381 GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with
382 bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than
383 the recommended human dose, based on C_{max}). At Caesarean section on GD100,
384 oligohydramnios, decreased relative lung and kidney weights, and microscopic evidence of renal
385 hypoplasia consistent with delayed renal development were identified in all pertuzumab dose
386 groups. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29%
387 to 40% of maternal serum levels at GD100.

388 **8.3 Nursing Mothers**

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

395 **8.4 Pediatric Use**

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

397 **8.5 Geriatric Use**

398 Of 402 patients who received PERJETA in Study 1, 60 patients (15%) were \geq 65 years of age
399 and 5 patients (1%) were \geq 75 years of age. No overall differences in efficacy and safety of

400 PERJETA were observed between these patients and younger patients.

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

404 **8.6 Females of Reproductive Potential**

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

409 If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving
410 PERJETA, immediately report exposure to the Genentech Adverse Event Line at
411 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the
412 MotHER Pregnancy Registry by contacting 1-800-690-6720 [*see Patient Counseling*
413 *Information (17)*].

414 **8.7 Renal Impairment**

415 Dose adjustments of PERJETA are not needed in patients with mild (creatinine clearance [CLcr]
416 60 to 90 mL/min) or moderate (CLcr 30 to 60 mL/min) renal impairment. No dose adjustment
417 can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min)
418 because of the limited pharmacokinetic data available [*see Clinical Pharmacology (12.3)*].

419 **8.8 Hepatic Impairment**

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

422 **10 OVERDOSAGE**

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

424 **11 DESCRIPTION**

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

430 PERJETA is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous
431 infusion. Each single use vial contains 420 mg of pertuzumab at a concentration of 30 mg/mL in
432 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20.

433 **12 CLINICAL PHARMACOLOGY**

434 **12.1 Mechanism of Action**

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

443 While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of
444 pertuzumab and trastuzumab augmented anti-tumor activity in HER2-overexpressing xenograft
445 models.

446 **12.3 Pharmacokinetics**

447 Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2 – 25 mg/kg. Based on a
448 population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was
449 0.24 L/day and the median half-life was 18 days. With an initial dose of 840 mg followed by a
450 maintenance dose of 420 mg every three weeks thereafter, the steady-state concentration of
451 pertuzumab was reached after the first maintenance dose.

452 The population PK analysis suggested no PK differences based on age, gender, ethnicity
453 (Japanese vs. non-Japanese), or disease status (neoadjuvant versus metastatic setting). Baseline
454 serum albumin level and lean body weight as covariates only exerted a minor influence on PK
455 parameters. Therefore, no dose adjustments based on body weight or baseline albumin level are
456 needed.

457 No drug-drug interactions were observed between pertuzumab and trastuzumab, or between
458 pertuzumab and docetaxel in a sub-study of 37 patients in Study 1.

459 No dedicated renal impairment trial for PERJETA has been conducted. Based on the results of
460 the population pharmacokinetic analysis, pertuzumab exposure in patients with mild (CLcr
461 60 to 90 mL/min, n=200) and moderate renal impairment (CLcr 30 to 60 mL/min, n=71) were
462 similar to those in patients with normal renal function (CLcr greater than 90 mL/min, n=200).
463 No relationship between CLcr and pertuzumab exposure was observed over the range of
464 observed CLcr (27 to 244 mL/min).

465 **12.6 Cardiac Electrophysiology**

466 The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of
467 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with
468 HER2-positive breast cancer in Study 1. No large changes in the mean QT interval (i.e., greater
469 than 20 ms) from placebo based on Fridericia correction method were detected in the trial. A
470 small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the
471 limitations of the trial design.

472 **13 NONCLINICAL TOXICOLOGY**

473 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

480 **14 CLINICAL STUDIES**

481 **14.1 Metastatic Breast Cancer**

482 Study 1 was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-
483 positive metastatic breast cancer. HER2 overexpression was defined as a score of 3+ IHC or
484 FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were
485 randomly allocated 1:1 to receive placebo plus trastuzumab and docetaxel or PERJETA plus

486 trastuzumab and docetaxel. Randomization was stratified by prior treatment (prior or no prior
487 adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) and geographic region (Europe,
488 North America, South America, and Asia). Patients with prior adjuvant or neoadjuvant therapy
489 were required to have a disease-free interval of greater than 12 months before trial enrollment.

490 PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every
491 3 weeks thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed
492 by 6 mg/kg every 3 weeks thereafter. Patients were treated with PERJETA and trastuzumab
493 until progression of disease, withdrawal of consent, or unacceptable toxicity. Docetaxel was
494 given as an initial dose of 75 mg/m² by intravenous infusion every 3 weeks for at least 6 cycles.
495 The docetaxel dose could be escalated to 100 mg/m² at the investigator's discretion if the initial
496 dose was well tolerated. At the time of the primary analysis, the mean number of cycles of study
497 treatment administered was 16.2 in the placebo-treated group and 19.9 in the PERJETA-treated
498 group.

499 The primary endpoint of Study 1 was progression-free survival (PFS) as assessed by an
500 independent review facility (IRF). PFS was defined as the time from the date of randomization
501 to the date of disease progression or death (from any cause) if the death occurred within
502 18 weeks of the last tumor assessment. Additional endpoints included overall survival (OS),
503 PFS (investigator-assessed), objective response rate (ORR), and duration of response.

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

515 Study 1 demonstrated a statistically significant improvement in IRF-assessed PFS in the
516 PERJETA-treated group compared with the placebo-treated group [hazard ratio (HR)=0.62 (95%
517 CI: 0.51, 0.75), p < 0.0001] and an increase in median PFS of 6.1 months (median PFS of
518 18.5 months in the PERJETA-treated group vs. 12.4 months in the placebo-treated group) (see
519 Figure 1). The results for investigator-assessed PFS were comparable to those observed for IRF-
520 assessed PFS.

521 Consistent results were observed across several patient subgroups including age (< 65 or
522 ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or
523 chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the
524 subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55
525 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease
526 (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). In the subgroup of patients with disease
527 limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52).

528 At the time of the final PFS analysis, 165 patients had died, and more deaths had occurred in the
529 placebo-treated group (23.6%) compared with the PERJETA-treated group (17.2%); OS was not
530 mature and interim OS analysis results did not meet the pre-specified stopping boundary for
531 statistical significance. The final analysis of OS (Table 4, Figure 2) was performed when 389

532 patients had died (221 in the placebo-treated group and 168 in the PERJETA-treated group). A
533 statistically significant OS improvement in favor of the PERJETA-treated group was
534 demonstrated [HR=0.68 (95% CI; 0.56, 0.84), p=0.0002] with an increase in median OS of 15.7
535 months (median OS of 56.5 months in the PERJETA-treated group vs. 40.8 months in the
536 placebo-treated group). OS results in patient subgroups were consistent with those observed for
537 IRF-assessed PFS with the exception of the subgroup of patients with disease limited to non-
538 visceral metastasis [HR=1.11 (95% CI: 0.66, 1.85)].

539

540

Table 4 Summary of Efficacy from Study 1

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* (final analysis)				
No. of patients who died	168 (41.8%)	221 (54.4%)	0.68	0.0002
Median months	56.5	40.8	(0.56, 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

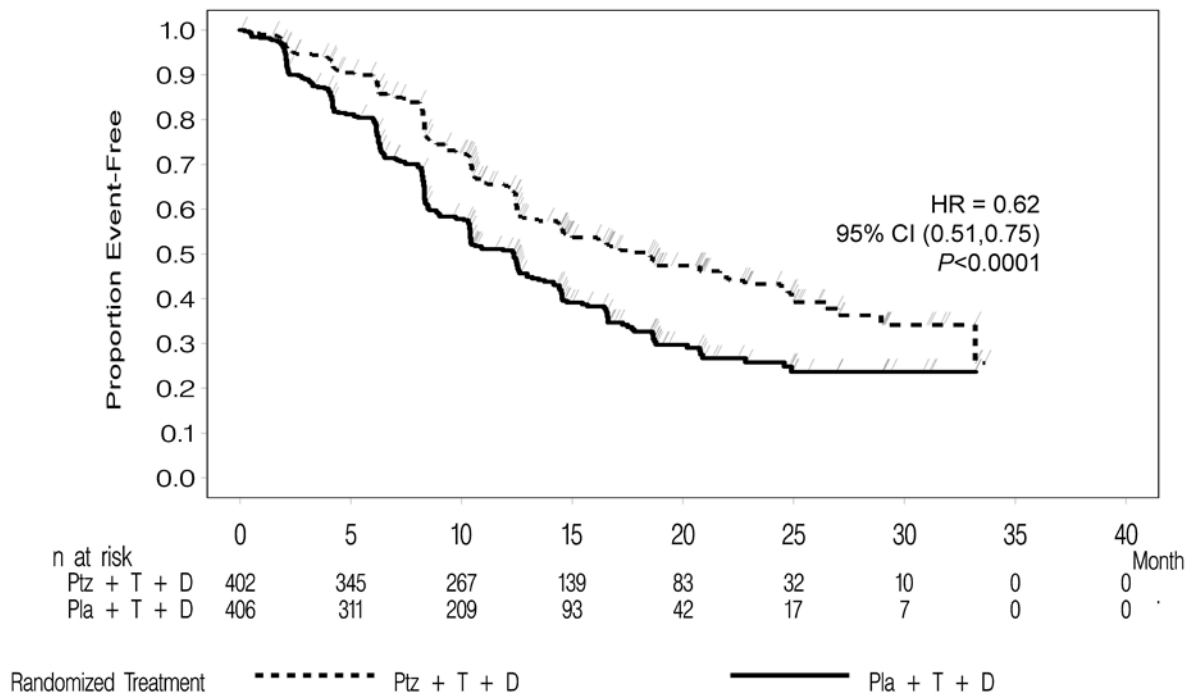
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543 * Final analysis of overall survival, cutoff date Feb 2014

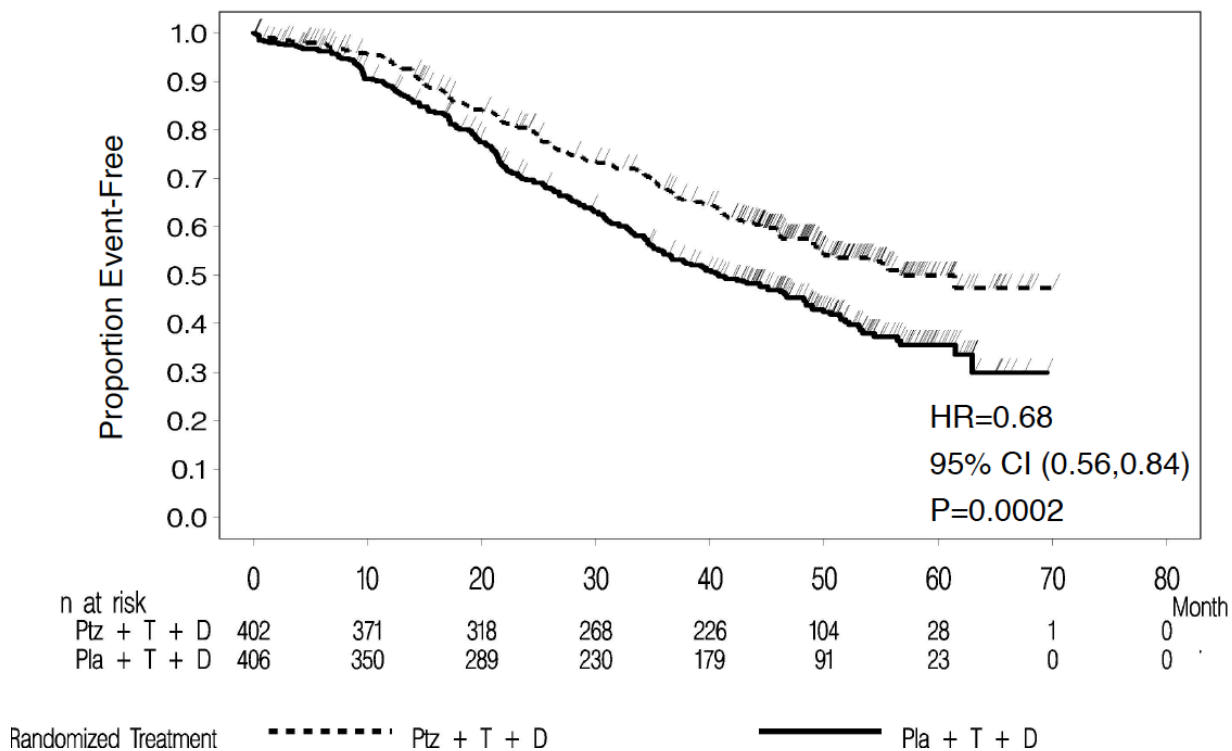
544 CI=Confidence Interval

545 **Figure 1 Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival for Study 1**



546
547

Figure 2 Kaplan-Meier Curve of Overall Survival for Study 1 (Final Analysis)



548

549 **14.2 Neoadjuvant Treatment of Breast Cancer**

550 *Study 2*

551 Study 2 was a multicenter, randomized trial conducted in 417 patients with operable, locally
552 advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for
553 neoadjuvant therapy. HER2 overexpression was defined as a score of 3+ IHC or FISH
554 amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were
555 randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery as follows:
556 trastuzumab plus docetaxel, PERJETA plus trastuzumab and docetaxel, PERJETA plus
557 trastuzumab, or PERJETA plus docetaxel. Randomization was stratified by breast cancer type
558 (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone
559 receptor (PgR) positivity.

560 PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every
561 3 weeks for 4 cycles. Trastuzumab was given intravenously at an initial dose of 8 mg/kg,
562 followed by 6 mg/kg every 3 weeks for 4 cycles. Docetaxel was given as an initial dose of
563 75 mg/m² by intravenous infusion every 3 weeks for 4 cycles. The docetaxel dose could be
564 escalated to 100 mg/m² at the investigator’s discretion if the initial dose was well tolerated.
565 Following surgery all patients received 3 cycles of 5-fluorouracil (600 mg/m²), epirubicin
566 (90 mg/m²), and cyclophosphamide (600 mg/m²) (FEC) given intravenously every 3 weeks and
567 trastuzumab administered intravenously every 3 weeks to complete 1 year of therapy. After
568 surgery, patients in the PERJETA plus trastuzumab arm received docetaxel every 3 weeks for
569 4 cycles prior to FEC.

570 The primary endpoint of the study was pathological complete response (pCR) rate in the breast
571 (ypT0/is). The FDA-preferred definition of pCR is the absence of invasive cancer in the breast
572 and lymph nodes (ypT0/is ypN0).

573 Demographics were well balanced (median age was 49 – 50 years old, the majority were
574 Caucasian (71%) and all were female. Overall, 7% of patients had inflammatory cancer, 32%
575 had locally advanced cancer, and 61% had operable cancer. Approximately half the patients in
576 each treatment group had hormone receptor-positive disease (defined as ER-positive and/or PgR-
577 positive).

578 The efficacy results are summarized in Table 5. Statistically significant improvements in pCR
579 rates by both the study and FDA-preferred definitions were observed in patients receiving
580 PERJETA plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus
581 docetaxel. The pCR rates and magnitude of improvement with PERJETA were lower in the
582 subgroup of patients with hormone receptor-positive tumors compared to patients with hormone
583 receptor-negative tumors.

584 **Table 5 Summary of Efficacy from Study 2**

Endpoint/Study Population	H+T	Ptz+H+T	Ptz+H	Ptz+T
Overall ITT	N=107	N=107	N=107	N=96
pCR¹, n (%) [95% CI]²	23 (21.5%) [14.1, 30.5]	42 (39.3%) [30.0, 49.2]	12 (11.2%) [5.9, 18.8]	17 (17.7%) [10.7, 26.8]
p-value (with Simes correction for CMH test)³		0.0063 (vs. H+T)	0.0223 (vs. H+T)	0.0018 (vs. Ptz+H+T)

Hormone receptor-positive subgroup	N=50	N=50	N=51 ⁴	N=46
pCR¹, n (%) [95% CI]²	6 (12.0%) [4.5, 24.3]	11 (22.0%) [11.5, 36.0]	1 (2.0%) [0.1, 10.5]	4 (8.7%) [2.4, 20.8]
Hormone receptor-negative subgroup	N=57	N=57	N=55 ⁴	N=50
pCR¹, n (%) [95% CI]²	17 (29.8%) [18.4, 43.4]	31 (54.4%) [40.7, 67.6]	11 (20.0%) [10.4, 33.0]	13 (26.0%) [14.6, 40.3]

585 T=docetaxel, Ptz=PERJETA, H=trastuzumab

586 CI=Confidence Interval

587 ¹ ypT0/is ypN0 (absence of invasive cancer in the breast and lymph nodes)

588 ² 95% CI for one sample binomial using Pearson-Clopper method.

589 ³ p-value from Cochran-Mantel-Haenszel (CMH) test, with Simes multiplicity adjustment

590 ⁴ One patient had unknown hormone receptor status. The patient did not achieve a pCR.

591

592 *Study 3*

593 An additional phase 2 neoadjuvant study was conducted in 225 patients with HER2-positive
594 locally advanced, operable, or inflammatory (T2-4d) breast cancer designed primarily to assess
595 cardiac safety in which all arms included PERJETA. HER2 overexpression was defined as a
596 score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central
597 laboratory.

598 Patients were randomly allocated to receive 1 of 3 neoadjuvant regimens prior to surgery as
599 follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with PERJETA
600 and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in
601 combination with PERJETA, or 6 cycles of docetaxel, carboplatin, and trastuzumab (TCH) in
602 combination with PERJETA. Randomization was stratified by breast cancer type (operable,
603 locally advanced, or inflammatory) and ER and/or PgR positivity.

604 PERJETA was given by intravenous infusion at an initial dose of 840 mg, followed by 420 mg
605 every 3 weeks. Trastuzumab was given by intravenous infusion at an initial dose of 8 mg/kg,
606 followed by 6 mg/kg every 3 weeks. 5-Fluorouracil (500 mg/m²), epirubicin (100 mg/m²), and
607 cyclophosphamide (600 mg/m²) were given intravenously every 3 weeks for 3 cycles. In the
608 PERJETA plus trastuzumab, docetaxel, and FEC arms, docetaxel was given as an initial dose of
609 75 mg/m² by intravenous infusion every 3 weeks for 3 cycles with the option to escalate to 100
610 mg/m² at the investigator's discretion if the initial dose was well tolerated. However, in the
611 PERJETA plus TCH arm, docetaxel was given intravenously at 75 mg/m² (no escalation was
612 permitted) and carboplatin (AUC 6) was given intravenously every 3 weeks for 6 cycles.
613 Following surgery all patients received trastuzumab to complete 1 year of therapy, which was
614 administered intravenously every 3 weeks.

615 Demographics were well balanced (median age was 49-50 years old, the majority were

616 Caucasian (76%)) and all were female. Overall 6% of patients had inflammatory cancer, 25%

617 had locally advanced cancer and 69% had operable cancer, with approximately half the patients
618 in each treatment group having ER-positive and/or PgR-positive disease.

619 The pCR (ypT0/is ypN0) rates were 56.2% (95% CI: 44.1%, 67.8%), 54.7% (95% CI: 42.7%,
620 66.2%), and 63.6% (95% CI: 51.9%, 74.3%) for patients treated with PERJETA plus
621 trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, PERJETA plus
622 trastuzumab and docetaxel following FEC, or PERJETA plus TCH, respectively. The pCR rates
623 were lower in the subgroups of patients with hormone receptor-positive tumors: 41.0% (95% CI:
624 25.6%, 57.9%), 45.7% (95% CI: 28.8%, 63.4%), and 47.5% (95% CI: 31.5%, 63.9%) than with
625 hormone receptor-negative tumors: 73.5% (95% CI: 55.6%, 87.1%), 62.5% (95% CI: 45.8%,
626 77.3%), and 81.1% (95% CI: 64.8%, 92.0%), respectively.

627 **16 HOW SUPPLIED/STORAGE AND HANDLING**

628 **16.1 How Supplied**

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

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

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

633 **DO NOT FREEZE. DO NOT SHAKE.**

634 **17 PATIENT COUNSELING INFORMATION**

- 635 • Advise pregnant women and females of reproductive potential that PERJETA exposure can
636 result in fetal harm, including embryo-fetal death or birth defects [*see Warnings and*
637 *Precautions (5.1) and Use in Specific Populations (8.1)*]
- 638 • Advise females of reproductive potential to use effective contraception while receiving
639 PERJETA and for 6 months following the last dose of PERJETA [*see Warnings and*
640 *Precautions (5.1) and Use in Special Populations (8.6)*]
- 641 • Advise nursing mothers treated with PERJETA to discontinue nursing or discontinue
642 PERJETA, taking into account the importance of the drug to the mother [*see Use in Specific*
643 *Populations (8.3)*].
- 644 • Encourage women who are exposed to PERJETA during pregnancy to enroll in the MotHER
645 Pregnancy Registry by contacting 1-800-690-6720 [*see Warnings and Precautions (5.1) and*
646 *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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