

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: LEFT VENTRICULAR DYSFUNCTION and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Left Ventricular Dysfunction:** PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function. (2.2, 5.1, 6.1)
- **Embryo-fetal Toxicity:** Exposure to PERJETA can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception. (5.2, 8.1, 8.3)

RECENT MAJOR CHANGES

Warnings and Precautions (5.2)

03/2016

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

- **Left Ventricular Dysfunction:** Monitor LVEF and withhold dosing as appropriate. (5.1, 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

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of PERJETA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2016

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1 **FULL PRESCRIBING INFORMATION**

2

WARNING: LEFT VENTRICULAR DYSFUNCTION AND EMBRYO-FETAL TOXICITY

- **Left Ventricular Dysfunction:** PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function. (2.2, 5.1, 6.1)
- **Embryo-fetal Toxicity:** Exposure to PERJETA can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception. (5.2, 8.1, 8.3)

3 **1 INDICATIONS AND USAGE**

4 **1.1 Metastatic Breast Cancer (MBC)**

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

8 **1.2 Neoadjuvant Treatment of Breast Cancer**

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

16 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.

22 **2 DOSAGE AND ADMINISTRATION**

23 **2.1 Recommended Doses and Schedules**

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

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

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

35 **Metastatic Breast Cancer (MBC)**

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

39 **Neoadjuvant Treatment of Breast Cancer**

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

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

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

55 **2.2 Dose Modification**

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

62 PERJETA should be discontinued if trastuzumab treatment is discontinued.

63 Dose reductions are not recommended for PERJETA.

64 For docetaxel dose modifications, see relevant prescribing information.

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

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

- 67 • a drop in LVEF to less than 45% or
- 68 • LVEF of 45% to 49% with a 10% or greater absolute decrease below pretreatment values
69 [see *Warnings and Precautions (5.1)*]

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

72 If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has
73 declined further, PERJETA and trastuzumab should be discontinued, unless the benefits for the
74 individual patient are deemed to outweigh the risks [see *Warnings and Precautions (5.1)*].

75 **Infusion-Related Reactions**

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

78 **Hypersensitivity Reactions/Anaphylaxis**

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

81 **2.3 Preparation for Administration**

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

84 Preparation

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

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

95 **3 DOSAGE FORMS AND STRENGTHS**

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

97 **4 CONTRAINDICATIONS**

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

100 **5 WARNINGS AND PRECAUTIONS**

101 **5.1 Left Ventricular Dysfunction**

102 Decreases in LVEF have been reported with drugs that block HER2 activity, including
103 PERJETA. In Study 1, for patients with MBC, PERJETA in combination with trastuzumab and
104 docetaxel was not associated with increases in the incidence of symptomatic left ventricular
105 systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with
106 trastuzumab and docetaxel [see Clinical Studies (14.1)]. Left ventricular dysfunction occurred in
107 4.4% of patients in the PERJETA-treated group and 8.3% of patients in the placebo-treated
108 group. Symptomatic left ventricular systolic dysfunction (congestive heart failure) occurred in
109 1.0% of patients in the PERJETA-treated group and 1.8% of patients in the placebo-treated
110 group [see Adverse Reactions (6.1)]. Patients who have received prior anthracyclines or prior
111 radiotherapy to the chest area may be at higher risk of decreased LVEF.

112 In patients receiving neoadjuvant treatment in Study 2, the incidence of LVSD was higher in the
113 PERJETA-treated groups compared to the trastuzumab- and docetaxel-treated group. An
114 increased incidence of LVEF declines was observed in patients treated with PERJETA in

115 combination with trastuzumab and docetaxel. In the overall treatment period, LVEF decline
116 > 10% and a drop to less than 50% occurred in 1.9% of patients treated with neoadjuvant
117 trastuzumab and docetaxel as compared to 8.4% of patients treated with neoadjuvant PERJETA
118 in combination with trastuzumab and docetaxel. Symptomatic LVSD occurred in 0.9% of
119 patients treated with neoadjuvant PERJETA in combination with trastuzumab and no patients in
120 the other 3 arms. LVEF recovered to $\geq 50\%$ in all patients.

121 In patients receiving neoadjuvant PERJETA in Study 3, in the overall treatment period, LVEF
122 decline > 10% and a drop to less than 50% occurred in 6.9% of patients treated with PERJETA
123 plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 16.0% of
124 patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 10.5% of
125 patients treated with PERJETA in combination with TCH. Symptomatic LVSD occurred in
126 4.0% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, 1.3% of
127 patients treated with PERJETA in combination with TCH, and none of the patients treated with
128 PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel.
129 LVEF recovered to $\geq 50\%$ in all but one patient.

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

135 Assess LVEF prior to initiation of PERJETA and at regular intervals (e.g., every three months in
136 the metastatic setting and every six weeks in the neoadjuvant setting) during treatment to ensure
137 that LVEF is within the institution's normal limits. If LVEF is $< 45\%$, or is 45% to 49% with a
138 10% or greater absolute decrease below the pretreatment value, withhold PERJETA and
139 trastuzumab and repeat LVEF assessment within approximately 3 weeks. Discontinue
140 PERJETA and trastuzumab if the LVEF has not improved or has declined further, unless the
141 benefits for the individual patient outweigh the risks [*see Dosage and Administration (2.2)*].

142 **5.2 Embryo-Fetal Toxicity**

143 Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal harm
144 when administered to a pregnant woman. PERJETA is a HER2/neu receptor antagonist. Cases
145 of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia,
146 skeletal abnormalities, and neonatal death have been reported with use of another HER2/neu
147 receptor antagonist (trastuzumab) during pregnancy. In an animal reproduction study,
148 administration of pertuzumab to pregnant cynomolgus monkeys during the period of
149 organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal
150 death at exposures 2.5 to 20 times the exposure in humans at the recommended dose, based on
151 C_{max} .

152 Verify the pregnancy status of females of reproductive potential prior to the initiation of
153 PERJETA. Advise pregnant women and females of reproductive potential that exposure to
154 PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to
155 conception can result in fetal harm, including embryo-fetal death or birth defects. Advise
156 females of reproductive potential to use effective contraception during treatment and for 7
157 months following the last dose of PERJETA in combination with trastuzumab [*see Use in*
158 *Specific Populations (8.1, 8.3)*].

159 **5.3 Infusion-Related Reactions**

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

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

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

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

181 **5.4 Hypersensitivity Reactions/Anaphylaxis**

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

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

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

197 **5.5 HER2 Testing**

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

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

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

210 **6 ADVERSE REACTIONS**

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

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

216 **6.1 Clinical Trials Experience**

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

220 ***Metastatic Breast Cancer (MBC)***

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

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

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

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

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

248 **Skin and subcutaneous tissue disorders:** Paronychia (7.1% in the PERJETA-treated group vs.
249 3.5% in the placebo-treated group)

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

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

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

257 ***Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab after***
258 ***Discontinuation of Docetaxel***

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

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

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

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

272

273

274

**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

275

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

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

282 **Immune system disorders:** Hypersensitivity (1.9% in the T+D arm, 5.6% in the Ptz+T+D arm,
283 5.6% in the Ptz+T arm and 5.3% in the Ptz+D arm)

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

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

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

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

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

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

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

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

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

313

314 **Table 3 Summary of Adverse Reactions Occurring in ≥ 10% of Patients Receiving**
 315 **Neoadjuvant Treatment with PERJETA in Study 3**

Body System/Adverse Reactions	PERJETA + trastuzumab + FEC followed by PERJETA + trastuzumab + docetaxel n=72		PERJETA + trastuzumab + docetaxel following FEC n=75		PERJETA + TCH n=76	
	Frequency rate %		Frequency rate %		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

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

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

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

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

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

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

335 **6.2 Immunogenicity**

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

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

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

352 **7 DRUG INTERACTIONS**

353 No drug-drug interactions were observed between pertuzumab and trastuzumab, or between
354 pertuzumab and docetaxel.

355 **8 USE IN SPECIFIC POPULATIONS**

356 **8.1 Pregnancy**

357 Pregnancy Exposure Registry and Pharmacovigilance Program

358 There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to
359 PERJETA during pregnancy. Encourage women who receive PERJETA in combination with
360 trastuzumab during pregnancy or within 7 months prior to conception, to enroll in the MoTHER

361 Pregnancy Registry by contacting 1-800-690-6720 or visiting
362 <http://www.motherpregnancyregistry.com/>.

363
364 In addition, there is a pregnancy pharmacovigilance program for PERJETA. If PERJETA is
365 administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA or
366 within 7 months following the last dose of PERJETA in combination with trastuzumab, health
367 care providers and patients should immediately report PERJETA exposure to Genentech at 1-
368 888-835-2555.

369 Risk Summary

371 Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal
372 harm when administered to a pregnant woman. There are no available data on the use of
373 PERJETA in pregnant women. However, in post-marketing reports, use of another HER2/neu
374 receptor antagonist (trastuzumab) during pregnancy resulted in cases of oligohydramnios and
375 oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and
376 neonatal death. In an animal reproduction study, administration of pertuzumab to pregnant
377 cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed
378 fetal kidney development, and embryo-fetal deaths at clinically relevant exposures that were
379 2.5 to 20-fold greater than exposures in humans receiving the recommended dose, based on C_{max}
380 [see Data]. Apprise the patient of the potential risks to a fetus. There are clinical
381 considerations if PERJETA in combination with trastuzumab is used during pregnancy or within
382 7 months prior to conception [see Clinical Considerations].

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

387 Clinical Considerations

389 *Fetal/Neonatal Adverse Reactions*

390 Monitor women who received PERJETA in combination with trastuzumab during pregnancy or
391 within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform
392 fetal testing that is appropriate for gestational age and consistent with community standards of
393 care.

394 Data

396 *Animal Data*

397 Pregnant cynomolgus monkeys were treated on Gestational Day (GD)19 with loading doses of
398 30 to 150 mg/kg pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose
399 levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than exposures in humans
400 receiving the recommended dose, based on C_{max} . Intravenous administration of pertuzumab
401 from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent
402 increases in embryo-fetal death between GD25 to GD70. The incidences of embryo-fetal loss
403 were 33, 50, and 85% for dams treated with bi-weekly pertuzumab doses of 10, 30, and
404 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on
405 C_{max}). At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney
406 weights, and microscopic evidence of renal hypoplasia consistent with delayed renal

407 development were identified in all pertuzumab dose groups. Pertuzumab exposure was reported
408 in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

409 **8.2 Lactation**

410 Risk Summary

411 There is no information regarding the presence of pertuzumab in human milk, the effects on the
412 breastfed infant or the effects on milk production. Published data suggest that human IgG is
413 present in human milk but does not enter the neonatal and infant circulation in substantial
414 amounts. Consider the developmental and health benefits of breast feeding along with the
415 mother's clinical need for PERJETA treatment and any potential adverse effects on the breastfed
416 child from PERJETA or from the underlying maternal condition. This consideration should also
417 take into account the elimination half-life of pertuzumab and the trastuzumab wash out period of
418 7 months.

419 **8.3 Females and Males of Reproductive Potential**

420 Pregnancy Testing

421 Verify the pregnancy status of females of reproductive potential prior to the initiation of
422 PERJETA.

423

424 Contraception

425 *Females*

426 Based on the mechanism of action and animal data, PERJETA can cause embryo-fetal harm
427 when administered during pregnancy. Advise females of reproductive potential to use effective
428 contraception during treatment and for 7 months following the last dose of PERJETA in
429 combination with trastuzumab [*see Use in Specific Populations (8.1)*].

430 **8.4 Pediatric Use**

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

432 **8.5 Geriatric Use**

433 Of 402 patients who received PERJETA in Study 1, 60 patients (15%) were ≥ 65 years of age
434 and 5 patients (1%) were ≥ 75 years of age. No overall differences in efficacy and safety of
435 PERJETA were observed between these patients and younger patients.

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

439 **8.6 Renal Impairment**

440 Dose adjustments of PERJETA are not needed in patients with mild (creatinine clearance [CLcr]
441 60 to 90 mL/min) or moderate (CLcr 30 to 60 mL/min) renal impairment. No dose adjustment
442 can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min)
443 because of the limited pharmacokinetic data available [*see Clinical Pharmacology (12.3)*].

444 **8.7 Hepatic Impairment**

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

447 **10 OVERDOSAGE**

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

449 **11 DESCRIPTION**

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

455 PERJETA is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous
456 infusion. Each single use vial contains 420 mg of pertuzumab at a concentration of 30 mg/mL in
457 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20.

458 **12 CLINICAL PHARMACOLOGY**

459 **12.1 Mechanism of Action**

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

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

471 **12.3 Pharmacokinetics**

472 Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2 – 25 mg/kg. Based on a
473 population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was
474 0.24 L/day and the median half-life was 18 days. With an initial dose of 840 mg followed by a
475 maintenance dose of 420 mg every three weeks thereafter, the steady-state concentration of
476 pertuzumab was reached after the first maintenance dose.

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

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

484 No dedicated renal impairment trial for PERJETA has been conducted. Based on the results of
485 the population pharmacokinetic analysis, pertuzumab exposure in patients with mild (CLcr
486 60 to 90 mL/min, n=200) and moderate renal impairment (CLcr 30 to 60 mL/min, n=71) were
487 similar to those in patients with normal renal function (CLcr greater than 90 mL/min, n=200).
488 No relationship between CLcr and pertuzumab exposure was observed over the range of
489 observed CLcr (27 to 244 mL/min).

490 **12.6 Cardiac Electrophysiology**

491 The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of
492 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with

493 HER2-positive breast cancer in Study 1. No large changes in the mean QT interval (i.e., greater
494 than 20 ms) from placebo based on Fridericia correction method were detected in the trial. A
495 small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the
496 limitations of the trial design.

497 **13 NONCLINICAL TOXICOLOGY**

498 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

505 **14 CLINICAL STUDIES**

506 **14.1 Metastatic Breast Cancer**

507 Study 1 was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-
508 positive metastatic breast cancer. HER2 overexpression was defined as a score of 3+ IHC or
509 FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were
510 randomly allocated 1:1 to receive placebo plus trastuzumab and docetaxel or PERJETA plus
511 trastuzumab and docetaxel. Randomization was stratified by prior treatment (prior or no prior
512 adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) and geographic region (Europe,
513 North America, South America, and Asia). Patients with prior adjuvant or neoadjuvant therapy
514 were required to have a disease-free interval of greater than 12 months before trial enrollment.

515 PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every
516 3 weeks thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed
517 by 6 mg/kg every 3 weeks thereafter. Patients were treated with PERJETA and trastuzumab
518 until progression of disease, withdrawal of consent, or unacceptable toxicity. Docetaxel was
519 given as an initial dose of 75 mg/m² by intravenous infusion every 3 weeks for at least 6 cycles.
520 The docetaxel dose could be escalated to 100 mg/m² at the investigator's discretion if the initial
521 dose was well tolerated. At the time of the primary analysis, the mean number of cycles of study
522 treatment administered was 16.2 in the placebo-treated group and 19.9 in the PERJETA-treated
523 group.

524 The primary endpoint of Study 1 was progression-free survival (PFS) as assessed by an
525 independent review facility (IRF). PFS was defined as the time from the date of randomization
526 to the date of disease progression or death (from any cause) if the death occurred within
527 18 weeks of the last tumor assessment. Additional endpoints included overall survival (OS),
528 PFS (investigator-assessed), objective response rate (ORR), and duration of response.

529 Patient demographic and baseline characteristics were balanced between the treatment arms.
530 The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were
531 Black. All were women with the exception of 2 patients. Seventeen percent of patients were
532 enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor
533 prognostic characteristics, including hormone receptor status (positive 48%, negative 50%),
534 presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study
535 arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2
536 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone
537 receptor positive tumors, 45% received prior adjuvant hormonal therapy and 11% received

538 hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or
539 neoadjuvant trastuzumab.

540 Study 1 demonstrated a statistically significant improvement in IRF-assessed PFS in the
541 PERJETA-treated group compared with the placebo-treated group [hazard ratio (HR)=0.62 (95%
542 CI: 0.51, 0.75), $p < 0.0001$] and an increase in median PFS of 6.1 months (median PFS of
543 18.5 months in the PERJETA-treated group vs. 12.4 months in the placebo-treated group) (see
544 Figure 1). The results for investigator-assessed PFS were comparable to those observed for IRF-
545 assessed PFS.

546 Consistent results were observed across several patient subgroups including age (< 65 or
547 ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or
548 chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the
549 subgroup of patients with hormone receptor-negative disease ($n=408$), the hazard ratio was 0.55
550 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease
551 ($n=388$), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). In the subgroup of patients with disease
552 limited to non-visceral metastasis ($n=178$), the hazard ratio was 0.96 (95% CI: 0.61, 1.52).

553 At the time of the final PFS analysis, 165 patients had died, and more deaths had occurred in the
554 placebo-treated group (23.6%) compared with the PERJETA-treated group (17.2%); OS was not
555 mature and interim OS analysis results did not meet the pre-specified stopping boundary for
556 statistical significance. The final analysis of OS (Table 4, Figure 2) was performed when 389
557 patients had died (221 in the placebo-treated group and 168 in the PERJETA-treated group). A
558 statistically significant OS improvement in favor of the PERJETA-treated group was
559 demonstrated [HR=0.68 (95% CI: 0.56, 0.84), $p=0.0002$] with an increase in median OS of 15.7
560 months (median OS of 56.5 months in the PERJETA-treated group vs. 40.8 months in the
561 placebo-treated group). OS results in patient subgroups were consistent with those observed for
562 IRF-assessed PFS with the exception of the subgroup of patients with disease limited to non-
563 visceral metastasis [HR=1.11 (95% CI: 0.66, 1.85)].

564
565

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	343	336		

(ORR, independent review)	275 (80.2%)	233 (69.3%)		
No. of patients analyzed	19 (5.5%)	14 (4.2%)		
Objective response (CR + PR)	256 (74.6%)	219 (65.2%)		
Complete response (CR)	20.2	12.5		
Partial Response (PR)				
Median Duration of Response (months)				
Difference in ORR	10.8%			
95% CI	(4.2%, 17.5%)			0.0011

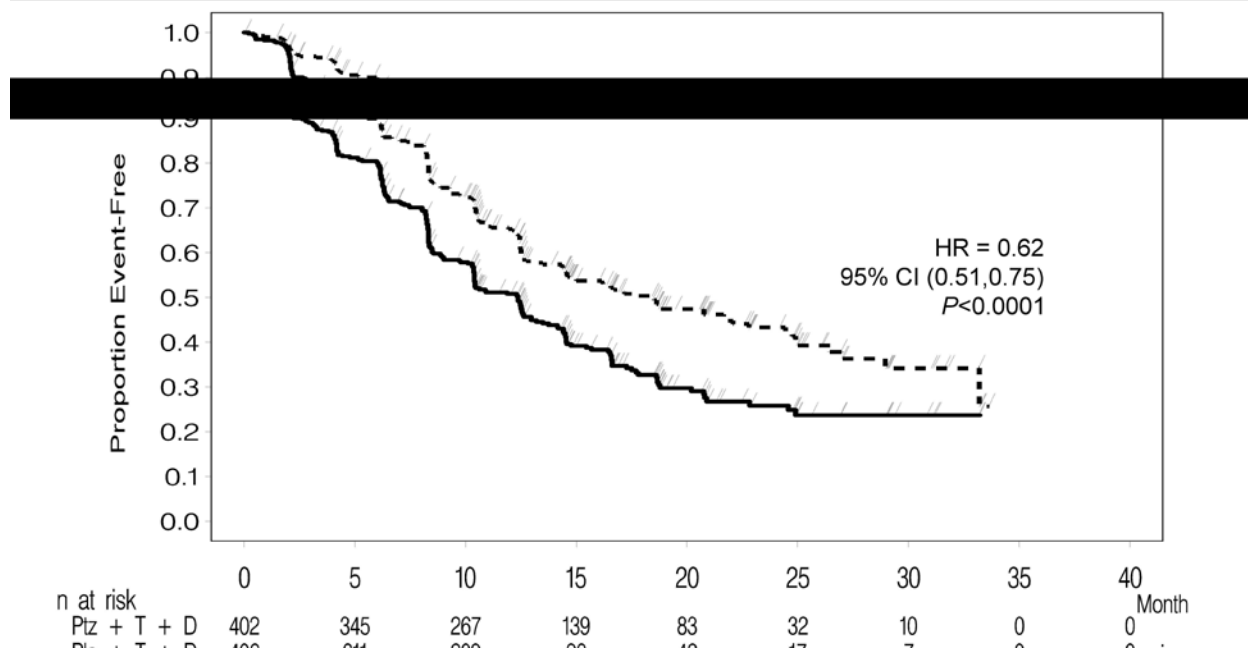
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568 * Final analysis of overall survival, cutoff date Feb 2014

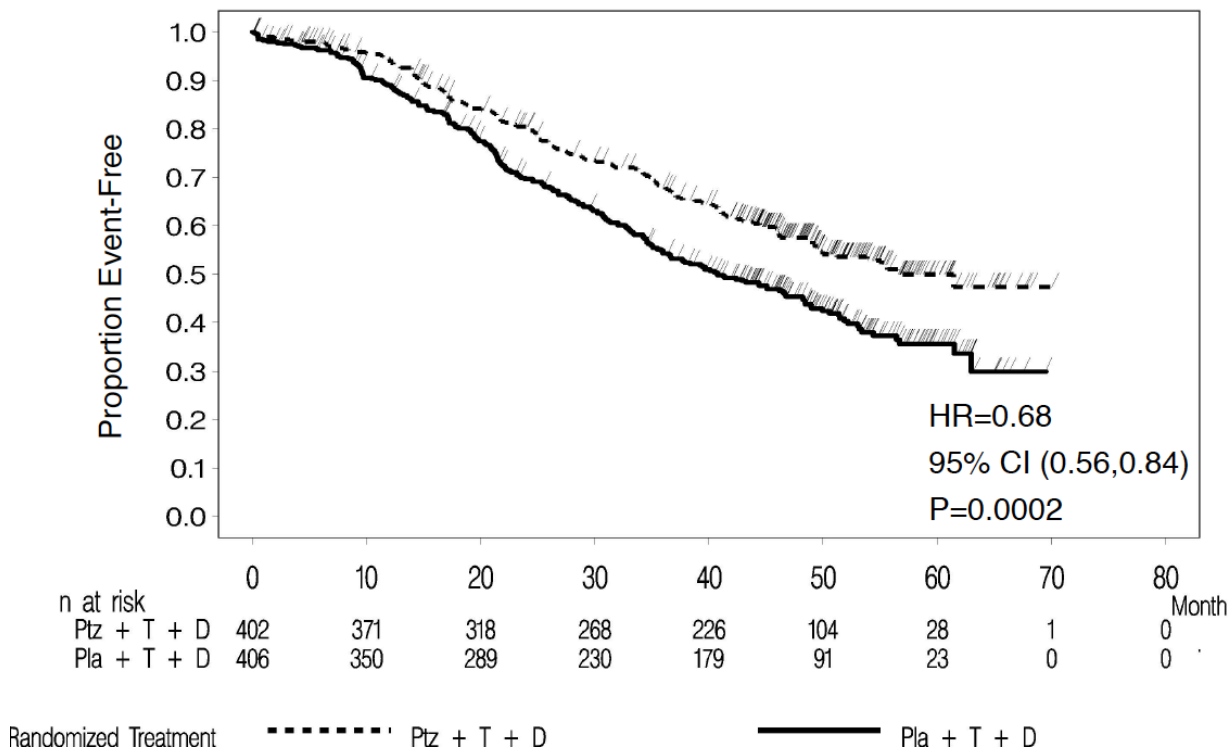
569 CI=Confidence Interval

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



571

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



573

574 14.2 Neoadjuvant Treatment of Breast Cancer

575 Study 2

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

585 PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every
 586 3 weeks for 4 cycles. Trastuzumab was given intravenously at an initial dose of 8 mg/kg,
 587 followed by 6 mg/kg every 3 weeks for 4 cycles. Docetaxel was given as an initial dose of
 588 75 mg/m² by intravenous infusion every 3 weeks for 4 cycles. The docetaxel dose could be
 589 escalated to 100 mg/m² at the investigator's discretion if the initial dose was well tolerated.
 590 Following surgery all patients received 3 cycles of 5-fluorouracil (600 mg/m²), epirubicin
 591 (90 mg/m²), and cyclophosphamide (600 mg/m²) (FEC) given intravenously every 3 weeks and
 592 trastuzumab administered intravenously every 3 weeks to complete 1 year of therapy. After
 593 surgery, patients in the PERJETA plus trastuzumab arm received docetaxel every 3 weeks for
 594 4 cycles prior to FEC.

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

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

603 The efficacy results are summarized in Table 5. Statistically significant improvements in pCR
 604 rates by both the study and FDA-preferred definitions were observed in patients receiving
 605 PERJETA plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus
 606 docetaxel. The pCR rates and magnitude of improvement with PERJETA were lower in the
 607 subgroup of patients with hormone receptor-positive tumors compared to patients with hormone
 608 receptor-negative tumors.

609 **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]

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

611 CI=Confidence Interval

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

613 ² 95% CI for one sample binomial using Pearson-Clopper method.

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

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

616

617 *Study 3*

618 An additional phase 2 neoadjuvant study was conducted in 225 patients with HER2-positive
 619 locally advanced, operable, or inflammatory (T2-4d) breast cancer designed primarily to assess
 620 cardiac safety in which all arms included PERJETA. HER2 overexpression was defined as a

621 score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central
622 laboratory.

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

629 PERJETA was given by intravenous infusion at an initial dose of 840 mg, followed by 420 mg
630 every 3 weeks. Trastuzumab was given by intravenous infusion at an initial dose of 8 mg/kg,
631 followed by 6 mg/kg every 3 weeks. 5-Fluorouracil (500 mg/m²), epirubicin (100 mg/m²), and
632 cyclophosphamide (600 mg/m²) were given intravenously every 3 weeks for 3 cycles. In the
633 PERJETA plus trastuzumab, docetaxel, and FEC arms, docetaxel was given as an initial dose of
634 75 mg/m² by intravenous infusion every 3 weeks for 3 cycles with the option to escalate to 100
635 mg/m² at the investigator's discretion if the initial dose was well tolerated. However, in the
636 PERJETA plus TCH arm, docetaxel was given intravenously at 75 mg/m² (no escalation was
637 permitted) and carboplatin (AUC 6) was given intravenously every 3 weeks for 6 cycles.
638 Following surgery all patients received trastuzumab to complete 1 year of therapy, which was
639 administered intravenously every 3 weeks.

640 Demographics were well balanced (median age was 49-50 years old, the majority were
641 Caucasian (76%)) and all were female. Overall 6% of patients had inflammatory cancer, 25%
642 had locally advanced cancer and 69% had operable cancer, with approximately half the patients
643 in each treatment group having ER-positive and/or PgR-positive disease.

644 The pCR (ypT0/is ypN0) rates were 56.2% (95% CI: 44.1%, 67.8%), 54.7% (95% CI: 42.7%,
645 66.2%), and 63.6% (95% CI: 51.9%, 74.3%) for patients treated with PERJETA plus
646 trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, PERJETA plus
647 trastuzumab and docetaxel following FEC, or PERJETA plus TCH, respectively. The pCR rates
648 were lower in the subgroups of patients with hormone receptor-positive tumors: 41.0% (95% CI:
649 25.6%, 57.9%), 45.7% (95% CI: 28.8%, 63.4%), and 47.5% (95% CI: 31.5%, 63.9%) than with
650 hormone receptor-negative tumors: 73.5% (95% CI: 55.6%, 87.1%), 62.5% (95% CI: 45.8%,
651 77.3%), and 81.1% (95% CI: 64.8%, 92.0%), respectively.

652 **16 HOW SUPPLIED/STORAGE AND HANDLING**

653 **16.1 How Supplied**

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

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

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

658 **DO NOT FREEZE. DO NOT SHAKE.**

659 **17 PATIENT COUNSELING INFORMATION**

660 **Left Ventricular Dysfunction**

- 661 • Advise patients to contact a health care professional immediately for any of the following:
662 new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of
663 the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of
664 consciousness [*see Warnings and Precautions (5.1)*].

665 Embryo-Fetal Toxicity

- 666 • Advise pregnant women and females of reproductive potential that exposure to PERJETA in
667 combination with trastuzumab during pregnancy or within 7 months prior to conception can
668 result in fetal harm. Advise female patients to contact their healthcare provider with a known
669 or suspected pregnancy [*see Use in Specific Populations (8.1)*].
- 670 • Advise women who are exposed to PERJETA in combination with trastuzumab during
671 pregnancy or within 7 months prior to conception that there is a pregnancy exposure registry
672 and a pregnancy pharmacovigilance program that monitors pregnancy outcomes. Encourage
673 these patients to enroll in the MoTHER Pregnancy Registry and report their pregnancy to
674 Genentech [*see Use in Specific Populations (8.1)*].
- 675 • Advise females of reproductive potential to use effective contraception during treatment and
676 for 7 months following the last dose of PERJETA in combination with trastuzumab [*see Use*
677 *in Specific Populations (8.3)*].

678

PERJETA[®] (pertuzumab)

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

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South San Francisco, CA 94080-4990

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