

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

HERCEPTIN® (trastuzumab)
Intravenous Infusion
Initial U.S. Approval: 1998

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

See full prescribing information for complete boxed warning
Cardiomyopathy: Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy. (5.1, 2.2)

Infusion reactions, Pulmonary toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

Embryo-Fetal Toxicity: Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. (5.3, 8.1, 8.6)

RECENT MAJOR CHANGES

Dosage and Administration (2)	04/2015
Warnings and Precautions (5)	04/2015

INDICATIONS AND USAGE

Herceptin is a HER2/neu receptor antagonist indicated for:

- the treatment of HER2 overexpressing breast cancer (1.1, 1.2).
- the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma (1.3)

DOSAGE AND ADMINISTRATION

For intravenous (IV) infusion only. Do not administer as an IV push or bolus (5.2).

Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine. (2.1)

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.1)
Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 52 weeks, or
- Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks.

Metastatic HER2-Overexpressing Breast Cancer (2.1)

- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.
- ### Metastatic HER2-overexpressing Gastric Cancer (2.1)
- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

DOSAGE FORMS AND STRENGTHS

- Multidose vial nominally containing 440 mg Herceptin as a lyophilized, sterile powder. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- Exacerbation of Chemotherapy-Induced Neutropenia (5.5, 6.1)
- HER2 testing should be performed using FDA-approved tests by laboratories with demonstrated proficiency. (5.6)

ADVERSE REACTIONS

Adjuvant Breast Cancer

- Most common adverse reactions ($\geq 5\%$) are headache, diarrhea, nausea, and chills. (6.1)

Metastatic Breast Cancer

- Most common adverse reactions ($\geq 10\%$) are fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash. (6.1)

Metastatic Gastric Cancer

- Most common adverse reactions ($\geq 10\%$) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. (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 Herceptin. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2015

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL**
3 **TOXICITY, and PULMONARY TOXICITY**

4 **Cardiomyopathy**

5 **Herceptin administration can result in sub-clinical and clinical cardiac failure. The**
6 **incidence and severity was highest in patients receiving Herceptin with**
7 **anthracycline-containing chemotherapy regimens.**

8 **Evaluate left ventricular function in all patients prior to and during treatment with**
9 **Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and**
10 **withhold Herceptin in patients with metastatic disease for clinically significant decrease in left**
11 **ventricular function. [see Warnings and Precautions (5.1) and Dosage and Administration (2.2)]**

12 **Infusion Reactions; Pulmonary Toxicity**

13 **Herceptin administration can result in serious and fatal infusion reactions and pulmonary**
14 **toxicity. Symptoms usually occur during or within 24 hours of Herceptin administration.**
15 **Interrupt Herceptin infusion for dyspnea or clinically significant hypotension. Monitor**
16 **patients until symptoms completely resolve. Discontinue Herceptin for anaphylaxis,**
17 **angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. [see Warnings**
18 **and Precautions (5.2, 5.4)]**

19 **Embryo-Fetal Toxicity**

20 **Exposure to Herceptin during pregnancy can result in oligohydramnios and**
21 **oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and**
22 **neonatal death. [see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]**
23

24 **1 INDICATIONS AND USAGE**

25 **1.1 Adjuvant Breast Cancer**

26 Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node
27 negative (ER/PR negative or with one high risk feature [see Clinical Studies (14.1)]) breast cancer

- 28 • as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either
- 29 paclitaxel or docetaxel
- 30 • with docetaxel and carboplatin
- 31 • as a single agent following multi-modality anthracycline based therapy.

32 **1.2 Metastatic Breast Cancer**

33 Herceptin is indicated:

- 34 • In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic
- 35 breast cancer
- 36 • As a single agent for treatment of HER2-overexpressing breast cancer in patients who have
- 37 received one or more chemotherapy regimens for metastatic disease.

38 **1.3 Metastatic Gastric Cancer**

39 Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the
40 treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction
41 adenocarcinoma, who have not received prior treatment for metastatic disease.
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43 2 DOSAGE AND ADMINISTRATION

44 2.1 Recommended Doses and Schedules

- 45 • **Do not administer as an intravenous push or bolus. Do not mix Herceptin with other**
- 46 **drugs.**
- 47 • **Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine.**

48 *Adjuvant Treatment, Breast Cancer:*

49 Administer according to one of the following doses and schedules for a total of 52 weeks of
50 Herceptin therapy:

51 During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

- 52 • Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an
53 intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks
54 (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- 55 • One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an
56 intravenous infusion over 30–90 minutes every three weeks.

57 As a single agent within three weeks following completion of multi-modality, anthracycline-
58 based chemotherapy regimens:

- 59 • Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
- 60 • Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every
61 three weeks.

62 [*see Dosage and Administration (2.2)*]

- 63 • Extending adjuvant treatment beyond one year is not recommended [*see Adverse Reactions*
64 (6.1)].

65 *Metastatic Treatment, Breast Cancer:*

- 66 • Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as
67 a 90 minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as
68 30 minute intravenous infusions until disease progression.

69 *Metastatic Gastric Cancer:*

- 70 • Administer Herceptin at an initial dose of 8 mg/kg as a 90 minute intravenous infusion
71 followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30-90 minutes every
72 three weeks until disease progression [*see Dosage and Administration (2.2)*].

73 2.2 Important Dosing Considerations

74 If the patient has missed a dose of Herceptin by one week or less, then the usual maintenance dose
75 (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg) should be administered as soon as
76 possible. Do not wait until the next planned cycle. Subsequent Herceptin maintenance doses should
77 be administered 7 days or 21 days later according to the weekly or three-weekly schedules,
78 respectively.

79 If the patient has missed a dose of Herceptin by more than one week, a re-loading dose of
80 Herceptin should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; three-
81 weekly schedule: 8 mg/kg), as soon as possible. Subsequent Herceptin maintenance doses (weekly
82 schedule: 2 mg/kg; three-weekly schedule 6 mg/kg) should be administered 7 days or 21 days later
83 according to the weekly or three-weekly schedules, respectively.

84 *Infusion Reactions*

85 [*see Boxed Warning, Warnings and Precautions (5.2)*]

- 86 • Decrease the rate of infusion for mild or moderate infusion reactions
- 87 • Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- 88 • Discontinue Herceptin for severe or life-threatening infusion reactions.

89 *Cardiomyopathy*

90 *[see Boxed Warning, Warnings and Precautions (5.1)]*

91 Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin and at regular
92 intervals during treatment. Withhold Herceptin dosing for at least 4 weeks for either of the
93 following:

- 94 • $\geq 16\%$ absolute decrease in LVEF from pre-treatment values
- 95 • LVEF below institutional limits of normal and $\geq 10\%$ absolute decrease in LVEF from
96 pretreatment values.

97 Herceptin may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the
98 absolute decrease from baseline is $\leq 15\%$.

99 Permanently discontinue Herceptin for a persistent (> 8 weeks) LVEF decline or for suspension of
100 Herceptin dosing on more than 3 occasions for cardiomyopathy.

101 **2.3 Preparation for Administration**

102 To prevent medication errors, it is important to check the vial labels to ensure that the drug being
103 prepared and administered is Herceptin (trastuzumab) and not ado-trastuzumab emtansine.

104 *Reconstitution*

105 Reconstitute each 440 mg vial of Herceptin with 20 mL of Bacteriostatic Water for Injection
106 (BWFJ), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution
107 containing 21 mg/mL trastuzumab. In patients with known hypersensitivity to benzyl alcohol,
108 reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single
109 use solution.

110 Use appropriate aseptic technique when performing the following reconstitution steps:

- 111 • Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the
112 lyophilized cake of Herceptin. The stream of diluent should be directed into the lyophilized
113 cake.
- 114 • Swirl the vial gently to aid reconstitution. **DO NOT SHAKE.**
- 115 • Slight foaming of the product may be present upon reconstitution. Allow the vial to stand
116 undisturbed for approximately 5 minutes.
- 117 • Parenteral drug products should be inspected visually for particulate matter and discoloration
118 prior to administration, whenever solution and container permit. Inspect visually for
119 particulates and discoloration. The solution should be free of visible particulates, clear to
120 slightly opalescent and colorless to pale yellow.
- 121 • Store reconstituted Herceptin at 2–8°C; discard unused Herceptin after 28 days. If Herceptin
122 is reconstituted with SWFI without preservative, use immediately and discard any unused
123 portion.

124 *Dilution*

- 125 • Determine the dose (mg) of Herceptin *[see Dosage and Administration (2.1)]*. Calculate the
126 volume of the 21 mg/mL reconstituted Herceptin solution needed, withdraw this amount from
127 the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection,
128 USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- 129 • Gently invert the bag to mix the solution.

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131 **3 DOSAGE FORMS AND STRENGTHS**

132 440 mg lyophilized powder per multi-use vial.

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134 **4 CONTRAINDICATIONS**

135 None.

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137 5 WARNINGS AND PRECAUTIONS

138 5.1 Cardiomyopathy

139 Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling
140 cardiac failure, cardiomyopathy, and cardiac death [see *Boxed Warning: Cardiomyopathy*].
141 Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

142 There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among
143 patients receiving Herceptin as a single agent or in combination therapy compared with those not
144 receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an
145 anthracycline.

146 Withhold Herceptin for $\geq 16\%$ absolute decrease in LVEF from pre-treatment values or an LVEF
147 value below institutional limits of normal and $\geq 10\%$ absolute decrease in LVEF from pretreatment
148 values [see *Dosage and Administration (2.2)*]. The safety of continuation or resumption of
149 Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been
150 studied.

151 Patients who receive anthracycline after stopping Herceptin may also be at increased risk of
152 cardiac dysfunction [see *Drug Interactions (7)* and *Clinical Pharmacology (12.3)*].

153 *Cardiac Monitoring*

154 Conduct thorough cardiac assessment, including history, physical examination, and determination
155 of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:

- 156 • Baseline LVEF measurement immediately prior to initiation of Herceptin
- 157 • LVEF measurements every 3 months during and upon completion of Herceptin
- 158 • Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left
159 ventricular cardiac dysfunction [see *Dosage and Administration (2.2)*]
- 160 • LVEF measurements every 6 months for at least 2 years following completion of Herceptin as
161 a component of adjuvant therapy.

162 In Study 1, 15% (158/1031) of patients discontinued Herceptin due to clinical evidence of
163 myocardial dysfunction or significant decline in LVEF after a median follow-up duration of
164 8.7 years in the AC-TH arm. In Study 3 (one-year Herceptin treatment), the number of patients who
165 discontinued Herceptin due to cardiac toxicity at 12.6 months median duration of follow-up was
166 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) patients in the TCH arm (1.5% during the
167 chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) patients in the
168 AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase)
169 discontinued Herceptin due to cardiac toxicity.

170 Among 64 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive
171 heart failure, one patient died of cardiomyopathy, one patient died suddenly without documented
172 etiology and 33 patients were receiving cardiac medication at last follow-up. Approximately 24% of
173 the surviving patients had recovery to a normal LVEF (defined as $\geq 50\%$) and no symptoms on
174 continuing medical management at the time of last follow-up. Incidence of congestive heart failure
175 is presented in Table 1. The safety of continuation or resumption of Herceptin in patients with
176 Herceptin-induced left ventricular cardiac dysfunction has not been studied.

177

Table 1
Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

Study	Regimen	Incidence of CHF	
		Herceptin	Control
1 & 2 ^a	AC ^b →Paclitaxel+Herceptin	3.2% (64/2000) ^c	1.3% (21/1655)
3 ^d	Chemo → Herceptin	2% (30/1678)	0.3% (5/1708)
4	AC ^b →Docetaxel+Herceptin	2% (20/1068)	0.3% (3/1050)
4	Docetaxel+Carbo+Herceptin	0.4% (4/1056)	0.3% (3/1050)

^a Median follow-up duration for studies 1 and 2 combined was 8.3 years in the AC→TH arm.

^b Anthracycline (doxorubicin) and cyclophosphamide.

^c Includes 1 patient with fatal cardiomyopathy and 1 patient with sudden death without documented etiology.

^d Includes NYHA II-IV and cardiac death at 12.6 months median duration of follow-up in the one-year Herceptin arm.

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In Study 3 (one-year Herceptin treatment), at a median follow-up duration of 8 years, the incidence of severe CHF (NYHA III & IV) was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Table 2
Incidence of Cardiac Dysfunction^a in Metastatic Breast Cancer Studies

Study	Event	Incidence			
		NYHA I-IV		NYHA III-IV	
		Herceptin	Control	Herceptin	Control
5 (AC) ^b	Cardiac Dysfunction	28%	7%	19%	3%
5 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
6	Cardiac Dysfunction ^c	7%	N/A	5%	N/A

^a Congestive heart failure or significant asymptomatic decrease in LVEF.

^b Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

^c Includes 1 patient with fatal cardiomyopathy.

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In Study 4, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the Herceptin containing regimens: (AC-TH: 0.3% (3/1068) and TCH 0.2% (2/1056)) as compared to none in AC-T.

5.2 Infusion Reactions

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Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. [see Adverse Reactions (6.1)]

In postmarketing reports, serious and fatal infusion reactions have been reported. Severe reactions which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

197 Interrupt Herceptin infusion in all patients experiencing dyspnea, clinically significant
198 hypotension, and intervention of medical therapy administered, which may include: epinephrine,
199 corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and
200 carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation
201 should be strongly considered in all patients with severe infusion reactions.

202 There are no data regarding the most appropriate method of identification of patients who may
203 safely be retreated with Herceptin after experiencing a severe infusion reaction. Prior to resumption
204 of Herceptin infusion, the majority of patients who experienced a severe infusion reaction were
205 pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated Herceptin
206 infusions, others had recurrent severe infusion reactions despite pre-medications.

207 **5.3 Embryo-Fetal Toxicity**

208 Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing
209 reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and
210 oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and
211 neonatal death. If the patient becomes pregnant while taking Herceptin or within 7 months
212 following the last dose of Herceptin, apprise the patient of the potential hazard to a fetus [*see Use in*
213 *Specific Populations (8.1)*].

214 Advise females of reproductive potential to avoid becoming pregnant while taking Herceptin. If
215 contraceptive methods are being considered, use effective contraception during treatment and for at
216 least 7 months after receiving the last dose of Herceptin [*see Use in Specific Populations (8.6)*].

217 **5.4 Pulmonary Toxicity**

218 Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes
219 dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic
220 pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and
221 pulmonary fibrosis. Such events can occur as sequelae of infusion reactions [*see Warnings and*
222 *Precautions (5.2)*]. Patients with symptomatic intrinsic lung disease or with extensive tumor
223 involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

224 **5.5 Exacerbation of Chemotherapy-Induced Neutropenia**

225 In randomized, controlled clinical trials the per-patient incidences of NCI CTC Grade 3–4
226 neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination
227 with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The
228 incidence of septic death was similar among patients who received Herceptin and those who did not.
229 [*see Adverse Reactions (6.1)*]

230 **5.6 HER2 Testing**

231 Detection of HER2 protein overexpression is necessary for selection of patients appropriate for
232 Herceptin therapy because these are the only patients studied and for whom benefit has been shown.
233 Due to differences in tumor histopathology, use FDA-approved tests for the specific tumor type
234 (breast or gastric/gastroesophageal adenocarcinoma) to assess HER2 protein overexpression and
235 HER2 gene amplification. Tests should be performed by laboratories with demonstrated proficiency
236 in the specific technology being utilized. Improper assay performance, including use of
237 suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay
238 instructions, and failure to include appropriate controls for assay validation, can lead to unreliable
239 results.

240 Several FDA-approved commercial assays are available to aid in the selection of breast cancer and
241 metastatic gastric cancer patients for Herceptin therapy. Users should refer to the package inserts of
242 specific assay kits for information on the Intended Use, and the validation and performance of each
243 assay. Limitations in assay precision make it inadvisable to rely on a single method to rule out
244 potential Herceptin benefit.

245 Treatment outcomes for adjuvant breast cancer (Studies 2 and 3) and for metastatic breast cancer
246 (Study 5) as a function of IHC and FISH testing are provided in Tables 8 and 10.

247 Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric
248 cancer should be performed using FDA-approved tests specifically for gastric cancers due to
249 differences in gastric vs. breast histopathology, including incomplete membrane staining and more
250 frequent heterogeneous expression of HER2 seen in gastric cancers. Study 7 demonstrated that gene
251 amplification and protein overexpression were not as well correlated as with breast cancer.
252 Treatment outcomes for metastatic gastric cancer (Study 7), based on HER2 gene amplification
253 (FISH) and HER2 protein overexpression (IHC) test results are provided in Table 14.
254

255 **6 ADVERSE REACTIONS**

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

- 257 • Cardiomyopathy [see Warnings and Precautions (5.1)]
- 258 • Infusion reactions [see Warnings and Precautions (5.2)]
- 259 • Embryo-fetal Toxicity [see Warnings and Precautions (5.3)]
- 260 • Pulmonary toxicity [see Warnings and Precautions (5.4)]
- 261 • Exacerbation of chemotherapy-induced neutropenia [see Warnings and Precautions (5.5)]
262

263 The most common adverse reactions in patients receiving Herceptin in the adjuvant and metastatic
264 breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased
265 cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions
266 requiring interruption or discontinuation of Herceptin treatment include CHF, significant decline in
267 left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity [see Dosage and
268 Administration (2.2)].

269 In the metastatic gastric cancer setting, the most common adverse reactions ($\geq 10\%$) that were
270 increased ($\geq 5\%$ difference) in the Herceptin arm as compared to the chemotherapy alone arm were
271 neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections,
272 fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most
273 common adverse reactions which resulted in discontinuation of treatment on the Herceptin-
274 containing arm in the absence of disease progression were infection, diarrhea, and febrile
275 neutropenia.

276 **6.1 Clinical Trials Experience**

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

280 *Adjuvant Breast Cancer Studies*

281 The data below reflect exposure to one-year Herceptin therapy across three randomized,
282 open-label studies, Studies 1, 2, and 3, with (n=3678) or without (n= 3363) trastuzumab in the
283 adjuvant treatment of breast cancer.

284 The data summarized in Table 3 below, from Study 3, reflect exposure to Herceptin in
285 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18.
286 Among the 3386 patients enrolled in the observation and one-year Herceptin arms of Study 3 at a
287 median duration of follow-up of 12.6 months in the Herceptin arm, the median age was 49 years
288 (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.
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Table 3
Adverse Reactions for Study 3^a, All Grades^b

Adverse Reaction	One Year Herceptin (n= 1678)	Observation (n=1708)
<u>Cardiac</u>		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias ^c	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
<u>Respiratory Thoracic Mediastinal Disorders</u>		
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
<u>Gastrointestinal Disorders</u>		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
<u>Musculoskeletal & Connective Tissue Disorders</u>		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
<u>Nervous System Disorders</u>		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
<u>Skin & Subcutaneous Tissue Disorders</u>		
Rash	70 (4%)	10 (0.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritus	40 (2%)	10 (0.6%)

Table 3 (cont'd)
Adverse Reactions for Study 3^a, All Grades^b

Adverse Reaction	One Year Herceptin (n= 1678)	Observation (n=1708)
<u>General Disorders</u>		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Aesthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (0.06%)	0 (0%)
<u>Infections</u>		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	39 (3%)	13 (0.8%)
<u>Immune System Disorders</u>		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

^a Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

^b The incidence of Grade 3 or higher adverse reactions was <1% in both arms for each listed term.

^c Higher level grouping term.

291

292 In Study 3, a comparison of 3-weekly Herceptin treatment for two years versus one year was also
293 performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year Herceptin
294 treatment arm (8.1% versus 4.6% in the one-year Herceptin treatment arm). More patients
295 experienced at least one adverse reaction of grade 3 or higher in the 2-year Herceptin treatment arm
296 (20.4%) compared with the one-year Herceptin treatment arm (16.3%).

297 The safety data from Studies 1 and 2 were obtained from 3655 patients, of whom 2000 received
298 Herceptin; the median treatment duration was 51 weeks. The median age was 49 years (range:
299 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian.

300 In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5
301 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The
302 following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater
303 among patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone: fatigue
304 (29.5% vs. 22.4%), infection (24.0% vs. 12.8%), hot flashes (17.1% vs. 15.0%), anemia (12.3% vs.
305 6.7%), dyspnea (11.8% vs. 4.6%), rash/desquamation (10.9% vs. 7.6%), leukopenia (10.5% vs.
306 8.4%), neutropenia (6.4% vs. 4.3%), headache (6.2% vs. 3.8%), pain (5.5% vs. 3.0%), edema (4.7%
307 vs. 2.7%) and insomnia (4.3% vs. 1.5%). The majority of these events were Grade 2 in severity.

308 In Study 2, data collection was limited to the following investigator-attributed treatment-related
309 adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic
310 toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes,
311 motor neuropathy, sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during
312 chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of
313 Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving Herceptin plus
314 chemotherapy as compared to chemotherapy alone: arthralgia (12.2% vs. 9.1%), nail changes
315 (11.5% vs. 6.8%), dyspnea (2.4% vs. 0.2%), and diarrhea (2.2% vs. 0%). The majority of these
316 events were Grade 2 in severity.

317 Safety data from Study 4 reflect exposure to Herceptin as part of an adjuvant treatment regimen
318 from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TCH: n=1056].

319 The overall median treatment duration was 54 weeks in both the AC-TH and TCH arms.
 320 The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including
 321 weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy
 322 period. Among these patients, the median age was 49 years (range 22 to 74 years). In Study 4, the
 323 toxicity profile was similar to that reported in Studies 1, 2, and 3 with the exception of a low
 324 incidence of CHF in the TCH arm.

325 *Metastatic Breast Cancer Studies*

326 The data below reflect exposure to Herceptin in one randomized, open-label study, Study 5, of
 327 chemotherapy with (n=235) or without (n=234) trastuzumab in patients with metastatic breast
 328 cancer, and one single-arm study (Study 6; n=222) in patients with metastatic breast cancer. Data in
 329 Table 4 are based on Studies 5 and 6.

330 Among the 464 patients treated in Study 5, the median age was 52 years (range: 25–77 years).
 331 Eighty-nine percent were White, 5% Black, 1% Asian and 5% other racial/ethnic groups.
 332 All patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The
 333 percentages of patients who received Herceptin treatment for ≥ 6 months and ≥ 12 months were 58%
 334 and 9%, respectively.

335 Among the 352 patients treated in single agent studies (213 patients from Study 6), the median
 336 age was 50 years (range 28–86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in
 337 other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed
 338 by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months
 339 and ≥ 12 months were 31% and 16%, respectively.
 340

Table 4
 Per-Patient Incidence of Adverse Reactions Occurring in $\geq 5\%$ of Patients in
 Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent ^a n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC ^b n = 143	AC ^b Alone n = 135
<u>Body as a Whole</u>					
Pain	47%	61%	62%	57%	42%
Asthenia	42%	62%	57%	54%	55%
Fever	36%	49%	23%	56%	34%
Chills	32%	41%	4%	35%	11%
Headache	26%	36%	28%	44%	31%
Abdominal pain	22%	34%	22%	23%	18%
Back pain	22%	34%	30%	27%	15%
Infection	20%	47%	27%	47%	31%
Flu syndrome	10%	12%	5%	12%	6%
Accidental injury	6%	13%	3%	9%	4%
Allergic reaction	3%	8%	2%	4%	2%
<u>Cardiovascular</u>					
Tachycardia	5%	12%	4%	10%	5%
Congestive heart failure	7%	11%	1%	28%	7%

341

Table 4 (cont'd)

Per-Patient Incidence of Adverse Reactions Occurring in $\geq 5\%$ of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent ^a n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC ^b n = 143	AC ^b Alone n = 135
<u>Digestive</u>					
Nausea	33%	51%	9%	76%	77%
Diarrhea	25%	45%	29%	45%	26%
Vomiting	23%	37%	28%	53%	49%
Nausea and vomiting	8%	14%	11%	18%	9%
Anorexia	14%	24%	16%	31%	26%
<u>Heme & Lymphatic</u>					
Anemia	4%	14%	9%	36%	26%
Leukopenia	3%	24%	17%	52%	34%
<u>Metabolic</u>					
Peripheral edema	10%	22%	20%	20%	17%
Edema	8%	10%	8%	11%	5%
<u>Musculoskeletal</u>					
Bone pain	7%	24%	18%	7%	7%
Arthralgia	6%	37%	21%	8%	9%
<u>Nervous</u>					
Insomnia	14%	25%	13%	29%	15%
Dizziness	13%	22%	24%	24%	18%
Paresthesia	9%	48%	39%	17%	11%
Depression	6%	12%	13%	20%	12%
Peripheral neuritis	2%	23%	16%	2%	2%
Neuropathy	1%	13%	5%	4%	4%
<u>Respiratory</u>					
Cough increased	26%	41%	22%	43%	29%
Dyspnea	22%	27%	26%	42%	25%
Rhinitis	14%	22%	5%	22%	16%
Pharyngitis	12%	22%	14%	30%	18%
Sinusitis	9%	21%	7%	13%	6%
<u>Skin</u>					
Rash	18%	38%	18%	27%	17%
Herpes simplex	2%	12%	3%	7%	9%
Acne	2%	11%	3%	3%	< 1%
<u>Urogenital</u>					
Urinary tract infection	5%	18%	14%	13%	7%

^a Data for Herceptin single agent were from 4 studies, including 213 patients from Study 6.

^b Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

342

343 *Metastatic Gastric Cancer*

344 The data below are based on the exposure of 294 patients to Herceptin in combination with a
 345 fluoropyrimidine (capecitabine or 5-FU) and cisplatin (Study 7). In the Herceptin plus
 346 chemotherapy arm, the initial dose of Herceptin 8 mg/kg was administered on Day 1 (prior to

347 chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was
 348 administered at 80 mg/m² on Day 1 and the fluoropyrimidine was administered as either
 349 capecitabine 1000 mg/m² orally twice a day on Days 1–14 or 5-fluorouracil 800 mg/m²/day as a
 350 continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day
 351 cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin
 352 infusions administered was eight.
 353

Table 5
 Study 7: Per Patient Incidence of Adverse Reactions of All Grades
 (Incidence ≥5% between Arms) or Grade 3/4 (Incidence >1% between Arms)
 and Higher Incidence in Herceptin Arm

Body System/Adverse Event	Herceptin +FC (N = 294) N (%)		FC (N = 290) N (%)	
	<u>All Grades</u>	<u>Grades 3/4</u>	<u>All Grades</u>	<u>Grades 3/4</u>
<u>Investigations</u>				
Neutropenia	230 (78)	101 (34)	212 (73)	83 (29)
Hypokalemia	83 (28)	28 (10)	69 (24)	16 (6)
Anemia	81 (28)	36 (12)	61 (21)	30 (10)
Thrombocytopenia	47 (16)	14 (5)	33 (11)	8 (3)
<u>Blood And Lymphatic System Disorders</u>				
Febrile Neutropenia	—	15 (5)	—	8 (3)
<u>Gastrointestinal Disorders</u>				
Diarrhea	109 (37)	27 (9)	80 (28)	11 (4)
Stomatitis	72 (24)	2 (1)	43 (15)	6 (2)
Dysphagia	19 (6)	7 (2)	10 (3)	1 (≤1)
<u>Body as a Whole</u>				
Fatigue	102 (35)	12 (4)	82 (28)	7 (2)
Fever	54 (18)	3 (1)	36 (12)	0 (0)
Mucosal Inflammation	37 (13)	6 (2)	18 (6)	2 (1)
Chills	23 (8)	1 (≤1)	0 (0)	0 (0)
<u>Metabolism And Nutrition Disorders</u>				
Weight Decrease	69 (23)	6 (2)	40 (14)	7 (2)
<u>Infections And Infestations</u>				
Upper Respiratory Tract Infections	56 (19)	0 (0)	29 (10)	0 (0)
Nasopharyngitis	37 (13)	0 (0)	17 (6)	0 (0)
<u>Renal And Urinary Disorders</u>				
Renal Failure and Impairment	53 (18)	8 (3)	42 (15)	5 (2)
<u>Nervous System Disorders</u>				
Dysgeusia	28 (10)	0 (0)	14 (5)	0 (0)

354

355 The following subsections provide additional detail regarding adverse reactions observed in clinical
356 trials of adjuvant breast, metastatic breast cancer, metastatic gastric cancer, or post-marketing
357 experience.

358 *Cardiomyopathy*

359 Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant
360 treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months
361 (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and
362 2, 7.9 years in the AC-T arm, 8.3 years in the AC-TH arm. In Studies 1 and 2, 6% of all randomized
363 patients with post-AC LVEF evaluation were not permitted to initiate Herceptin following
364 completion of AC chemotherapy due to cardiac dysfunction (LVEF < LLN or ≥ 16 point decline in
365 LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of
366 new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and
367 paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients
368 receiving one-year Herceptin monotherapy compared to observation in Study 3 (see Table 6,
369 Figures 1 and 2). The per-patient incidence of new-onset cardiac dysfunction, as measured by
370 LVEF, remained similar when compared to the analysis performed at a median follow-up of 2.0
371 years in the AC-TH arm. This analysis also showed evidence of reversibility of left ventricular
372 dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC-TH group being
373 asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.

374

Table 6^a
Per-patient Incidence of New Onset
Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

	LVEF <50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF <50%	≥10% decrease	≥16% decrease	<20% and ≥10%	≥20%
Studies 1 & 2^{b,c}					
AC→TH (n=1856)	23.1% (428)	18.5% (344)	11.2% (208)	37.9% (703)	8.9% (166)
AC→T (n=1170)	11.7% (137)	7.0% (82)	3.0% (35)	22.1% (259)	3.4% (40)
Study 3^d					
Herceptin (n=1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n=1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
Study 4^e					
TCH (n=1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n=1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n=1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

^a For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization.

^b Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

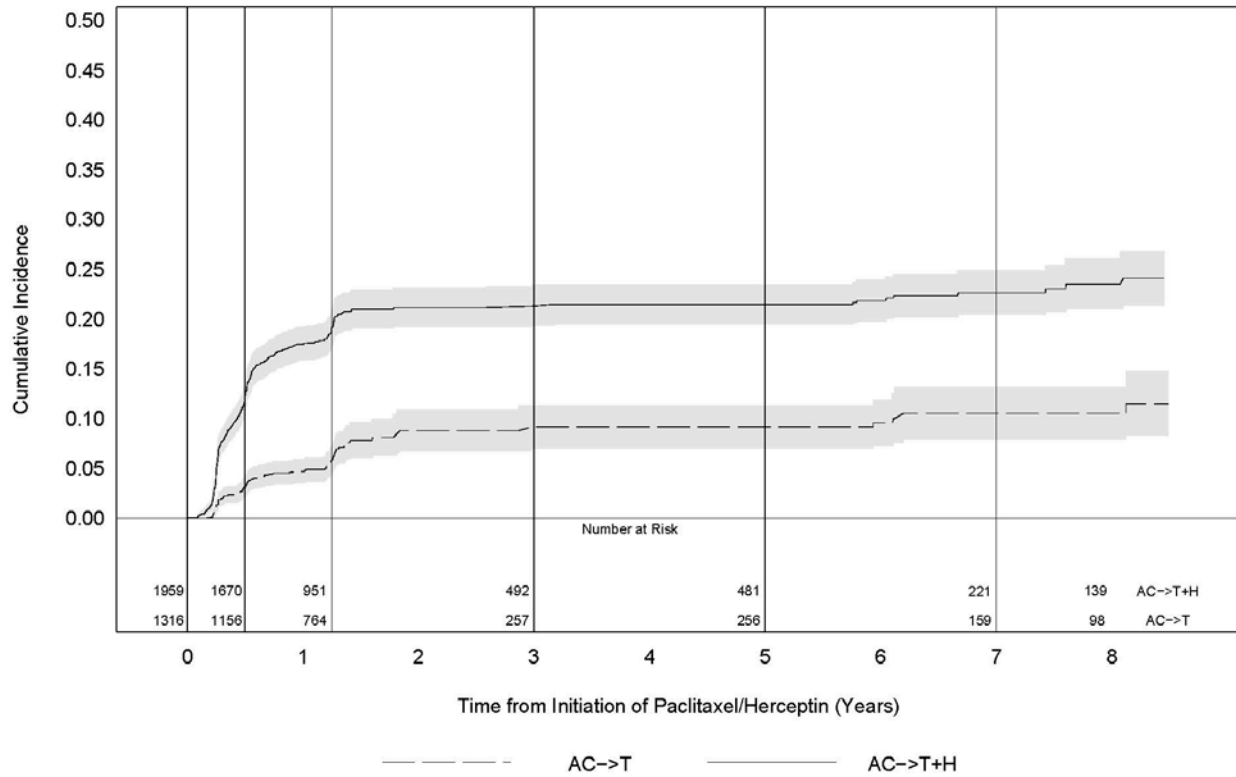
^c Median duration of follow-up for studies 1 and 2 combined was 8.3 years in the AC→TH arm.

^d Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

^e Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

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Figure 1
Studies 1 and 2: Cumulative Incidence of Time to First LVEF
Decline of ≥ 10 Percentage Points from Baseline and to
Below 50% with Death as a Competing Risk Event

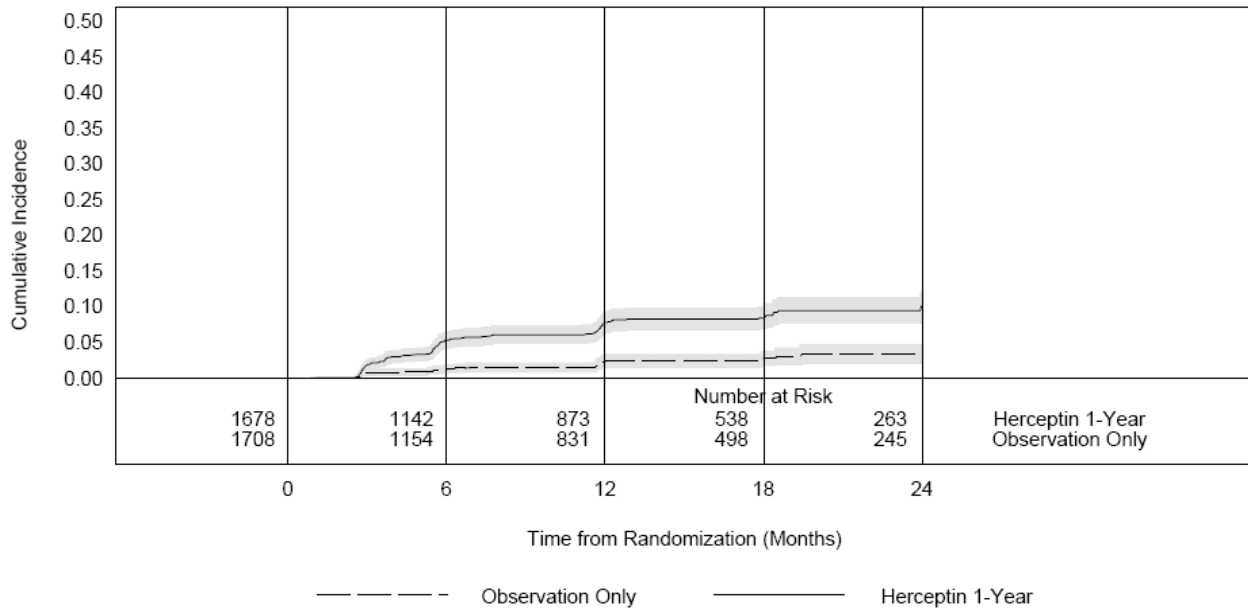


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Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

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386
387

Figure 2
Study 3: Cumulative Incidence of Time to First LVEF
Decline of ≥ 10 Percentage Points from Baseline and to
Below 50% with Death as a Competing Risk Event

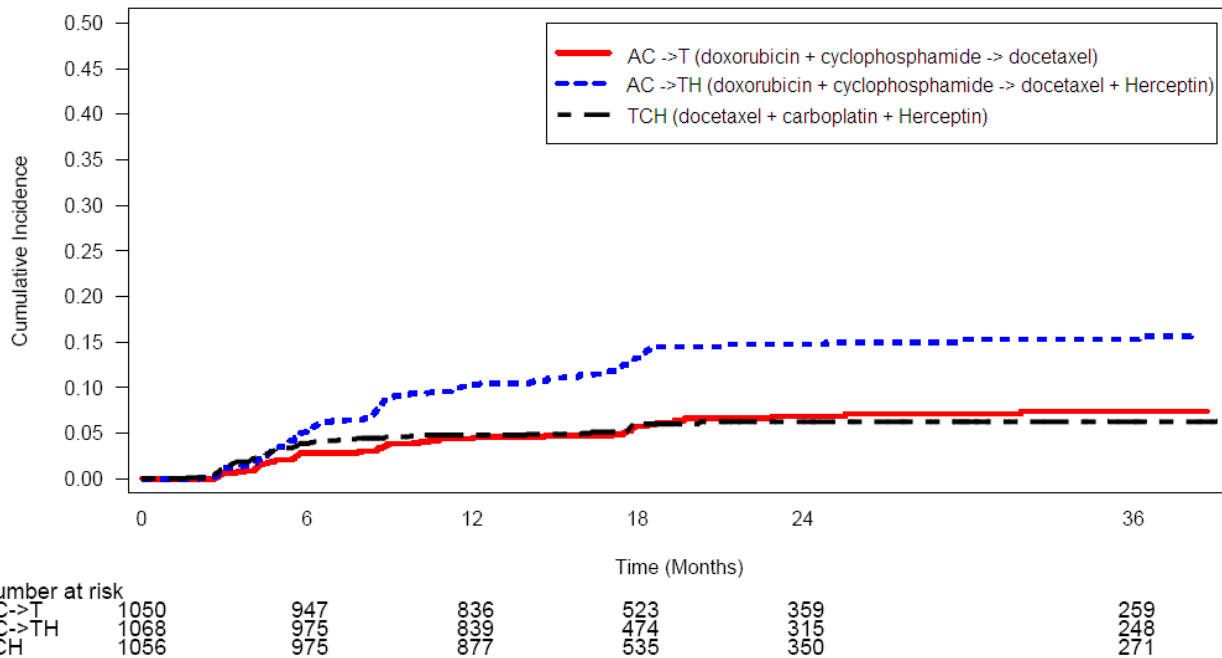


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Time 0 is the date of randomization.

391
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Figure 3
Study 4: Cumulative Incidence of Time to First LVEF
Decline of ≥ 10 Percentage Points from Baseline and to
Below 50% with Death as a Competing Risk Event



395
396
397

Time 0 is the date of randomization.

398 The incidence of treatment emergent congestive heart failure among patients in the metastatic
399 breast cancer trials was classified for severity using the New York Heart Association classification
400 system (I–IV, where IV is the most severe level of cardiac failure) (see Table 2). In the metastatic
401 breast cancer trials the probability of cardiac dysfunction was highest in patients who received
402 Herceptin concurrently with anthracyclines.

403 In Study 7, 5.0% of patients in the Herceptin plus chemotherapy arm compared to 1.1% of
404 patients in the chemotherapy alone arm had LVEF value below 50% with a $\geq 10\%$ absolute decrease
405 in LVEF from pretreatment values.

406 *Infusion Reactions*

407 During the first infusion with Herceptin, the symptoms most commonly reported were chills and
408 fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with
409 acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of
410 Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity was required in
411 $< 1\%$ of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at
412 tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and
413 asthenia. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9%
414 of patients, on second or subsequent Herceptin infusions administered as monotherapy or in
415 combination with chemotherapy, respectively. In the post-marketing setting, severe infusion
416 reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

417 *Anemia*

418 In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]),
419 of selected NCI-CTC Grade 2–5 anemia (12.3% vs. 6.7% [Study 1]), and of anemia requiring
420 transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and
421 chemotherapy compared with those receiving chemotherapy alone. Following the administration of
422 Herceptin as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was $< 1\%$. In
423 Study 7 (metastatic gastric cancer) on the Herceptin containing arm as compared to the
424 chemotherapy alone arm the overall incidence of anemia was 28% compared 21% and of NCI CTC
425 Grade 3/4 anemia was 12.2% compared to 10.3%.

426 *Neutropenia*

427 In randomized controlled clinical trials in the adjuvant setting, the incidence of selected
428 NCI-CTC Grade 4–5 neutropenia (1.7% vs. 0.8% [Study 2]) and of selected Grade 2–5 neutropenia
429 (6.4% vs. 4.3% [Study 1]) were increased in patients receiving Herceptin and chemotherapy
430 compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients
431 with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and
432 of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in
433 combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7
434 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone
435 arm, the incidence of NCI CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile
436 neutropenia 5.1% compared to 2.8%.

437 *Infection*

438 The overall incidences of infection (46% vs. 30% [Study 5]), of selected NCI-CTC Grade 2–5
439 infection/febrile neutropenia (24.3% vs. 13.4% [Study 1]) and of selected Grade 3–5
440 infection/febrile neutropenia (2.9% vs. 1.4%) [Study 2]), were higher in patients receiving Herceptin
441 and chemotherapy compared with those receiving chemotherapy alone. The most common site of
442 infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract.

443 In Study 4, the overall incidence of infection was higher with the addition of Herceptin to AC-T
444 but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC Grade 3–4
445 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms.

446 In a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of
447 febrile neutropenia was higher (23% vs. 17%) in patients receiving Herceptin in combination with
448 myelosuppressive chemotherapy as compared to chemotherapy alone.

449 *Pulmonary Toxicity*

450 *Adjuvant Breast Cancer*

451 Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC
452 Grade 2–5 pulmonary toxicity (14.3% vs. 5.4% [Study 1]) and of selected NCI-CTC Grade 3–5
453 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4 % vs. 0.9% [Study 2]) was
454 higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The
455 most common pulmonary toxicity was dyspnea (NCI-CTC Grade 2–5: 11.8% vs. 4.6% [Study 1];
456 NCI-CTC Grade 2–5: 2.4% vs. 0.2% [Study 2]).

457 Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving Herceptin compared
458 with 0.3% of those receiving chemotherapy alone. Fatal respiratory failure occurred in 3 patients
459 receiving Herceptin, one as a component of multi-organ system failure, as compared to 1 patient
460 receiving chemotherapy alone.

461 In Study 3, there were 4 cases of interstitial pneumonitis in the one-year Herceptin treatment arm
462 compared to none in the observation arm at a median follow-up duration of 12.6 months.

463 *Metastatic Breast Cancer*

464 Among women receiving Herceptin for treatment of metastatic breast cancer, the incidence of
465 pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the
466 post-marketing experience as part of the symptom complex of infusion reactions. Pulmonary events
467 include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic
468 pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see *Warnings*
469 *and Precautions (5.4)*.

470 *Thrombosis/Embolism*

471 In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher
472 in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies
473 (2.6% vs. 1.5% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]).

474 *Diarrhea*

475 Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC
476 Grade 2–5 diarrhea (6.7% vs. 5.4% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (2.2% vs. 0%
477 [Study 2]), and of Grade 1–4 diarrhea (7% vs. 1% [Study 3; one-year Herceptin treatment at
478 12.6 months median duration of follow-up]) were higher in patients receiving Herceptin as compared
479 to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher [5.7% AC-TH, 5.5% TCH
480 vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among
481 women receiving Herceptin. Of patients receiving Herceptin as a single agent for the treatment of
482 metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was
483 observed in patients receiving Herceptin in combination with chemotherapy for treatment of
484 metastatic breast cancer.

485 *Renal Toxicity*

486 In Study 7 (metastatic gastric cancer) on the Herceptin-containing arm as compared to the
487 chemotherapy alone arm the incidence of renal impairment was 18% compared to 14.5%. Severe
488 (Grade 3/4) renal failure was 2.7% on the Herceptin-containing arm compared to 1.7% on the
489 chemotherapy only arm. Treatment discontinuation for renal insufficiency/failure was 2% on the
490 Herceptin-containing arm and 0.3% on the chemotherapy only arm.

491 In the postmarketing setting, rare cases of nephrotic syndrome with pathologic evidence of
492 glomerulopathy have been reported. The time to onset ranged from 4 months to approximately
493 18 months from initiation of Herceptin therapy. Pathologic findings included membranous

494 glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications
495 included volume overload and congestive heart failure.

496 **6.2 Immunogenicity**

497 As with all therapeutic proteins, there is a potential for immunogenicity. Among 903 women with
498 metastatic breast cancer, human anti-human antibody (HAHA) to Herceptin was detected in one
499 patient using an enzyme-linked immunosorbent assay (ELISA). This patient did not experience an
500 allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast
501 cancer.

502 The incidence of antibody formation is highly dependent on the sensitivity and the specificity of
503 the assay. Additionally, the observed incidence of antibody (including neutralizing antibody)
504 positivity in an assay may be influenced by several factors including assay methodology, sample
505 handling, timing of sample collection, concomitant medications, and underlying disease. For these
506 reasons, comparison of the incidence of antibodies to Herceptin with the incidence of antibodies to
507 other products may be misleading.

508 **6.3 Post-Marketing Experience**

509 The following adverse reactions have been identified during post approval use of Herceptin.
510 Because these reactions are reported voluntarily from a population of uncertain size, it is not always
511 possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- 512 • Infusion reaction [*see Warnings and Precautions (5.2)*]
 - 513 • Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal
514 abnormalities, and neonatal death [*see Warnings and Precautions (5.3)*]
 - 515 • Glomerulopathy [*see Adverse Reactions (6.1)*]
- 516

517 **7 DRUG INTERACTIONS**

518 Patients who receive anthracycline after stopping Herceptin may be at increased risk of cardiac
519 dysfunction because of trastuzumab's long wash out period based on population PK analysis [*see*
520 *Clinical Pharmacology (12.3)*]. If possible, physicians should avoid anthracycline-based therapy for
521 up to 7 months after stopping Herceptin. If anthracyclines are used, the patient's cardiac function
522 should be monitored carefully.

523

524 **8 USE IN SPECIFIC POPULATIONS**

525 **8.1 Pregnancy: Category D [*see Warnings and Precautions (5.3)*]**

526 Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing
527 reports use of Herceptin during pregnancy resulted in cases of oligohydramnios and of
528 oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and
529 neonatal death.

530 These case reports described oligohydramnios in pregnant women who received Herceptin either
531 alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased
532 after Herceptin was stopped. In one case, Herceptin therapy resumed after the amniotic fluid index
533 improved, and oligohydramnios recurred.

534 Monitor women exposed to Herceptin during pregnancy for oligohydramnios. If oligohydramnios
535 occurs, perform fetal testing that is appropriate for gestational age and consistent with community
536 standards of care. The efficacy of IV hydration in management of oligohydramnios due to Herceptin
537 exposure is not known.

538 Advise women of the potential hazard to the fetus resulting from Herceptin exposure during
539 pregnancy. If Herceptin is administered during pregnancy, or if a patient becomes pregnant while
540 receiving Herceptin or within 7 months following the last dose of Herceptin, immediately report
541 Herceptin exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women

542 who may be exposed to Herceptin during pregnancy or within 7 months of conception, to enroll in
543 the MotHER Pregnancy Registry by contacting 1-800-690-6720.

544 No teratogenic effects were observed in offspring from pregnant cynomolgus monkeys
545 administered trastuzumab during the period of organogenesis at doses up to 25 times the
546 recommended weekly human dose of 2 mg/kg. Trastuzumab administration to cynomolgus
547 monkeys during early gestation (Days 20 to 50) or late gestation (Days 120 to 150) resulted in
548 offspring with trastuzumab plasma levels of 15 to 28% of maternal plasma levels.

549 In mutant mice lacking HER2, embryos died in early gestation.

550 **8.3 Nursing Mothers**

551 It is not known whether Herceptin is excreted in human milk, but human IgG is excreted in human
552 milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant
553 circulation in substantial amounts.

554 Trastuzumab was present in the breast milk of lactating cynomolgus monkeys given 12.5 times
555 the recommended weekly human dose of 2 mg/kg of Herceptin. Infant monkeys with detectable
556 serum levels of trastuzumab did not have any adverse effects on growth or development from birth
557 to 3 months of age; however, trastuzumab levels in animal breast milk may not accurately reflect
558 human breast milk levels.

559 Because many drugs are secreted in human milk and because of the potential for serious adverse
560 reactions in nursing infants from Herceptin, a decision should be made whether to discontinue
561 nursing, or discontinue drug, taking into account the elimination half-life of trastuzumab and the
562 importance of the drug to the mother.

563 **8.4 Pediatric Use**

564 The safety and effectiveness of Herceptin in pediatric patients has not been established.

565 **8.5 Geriatric Use**

566 Herceptin has been administered to 386 patients who were 65 years of age or over (253 in the
567 adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac
568 dysfunction was increased in geriatric patients as compared to younger patients in both those
569 receiving treatment for metastatic disease in Studies 5 and 6, or adjuvant therapy in Studies 1 and 2.
570 Limitations in data collection and differences in study design of the 4 studies of Herceptin in
571 adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of
572 Herceptin in older patients is different from younger patients. The reported clinical experience is not
573 adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of Herceptin
574 treatment in older patients is different from that observed in patients <65 years of age for metastatic
575 disease and adjuvant treatment.

576 In Study 7 (metastatic gastric cancer), of the 294 patients treated with Herceptin 108 (37%) were
577 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or
578 effectiveness were observed.

579 **8.6 Females of Reproductive Potential**

580 Herceptin can cause embryo-fetal harm when administered during pregnancy. Advise females of
581 reproductive potential to avoid becoming pregnant while taking Herceptin. If contraceptive methods
582 are being considered, use effective contraception while receiving Herceptin and for at least 7 months
583 following the last dose of Herceptin [*see Use in Specific Populations (8.1)*].
584

585 **10 OVERDOSAGE**

586 There is no experience with overdosage in human clinical trials. Single doses higher than 8 mg/kg
587 have not been tested.
588

589 **11 DESCRIPTION**

590 Herceptin (trastuzumab) is a humanized IgG1 kappa monoclonal antibody that selectively binds
591 with high affinity to the extracellular domain of the human epidermal growth factor receptor 2
592 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell
593 (Chinese Hamster Ovary) culture containing the antibiotic gentamicin. Gentamicin is not detectable
594 in the final product.

595 Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous
596 administration. Each multi-use vial of Herceptin contains 440 mg trastuzumab, 400 mg
597 α,α -trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20,
598 USP. Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution
599 containing 21 mg/mL trastuzumab at a pH of approximately 6.

601 **12 CLINICAL PHARMACOLOGY**

602 **12.1 Mechanism of Action**

603 The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa,
604 which is structurally related to the epidermal growth factor receptor. Herceptin has been shown, in
605 both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress
606 HER2.

607 Herceptin is a mediator of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*,
608 Herceptin-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing
609 cancer cells compared with cancer cells that do not overexpress HER2.

610 **12.2 Pharmacodynamics**

611 *Cardiac Electrophysiology*

612 The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval
613 duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically
614 relevant effect on the QTc interval duration and there was no apparent relationship between serum
615 trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive
616 solid tumors.

617 **12.3 Pharmacokinetics**

618 The pharmacokinetics of trastuzumab was evaluated in a pooled population pharmacokinetic (PK)
619 model analysis of 1,582 subjects with primarily breast cancer and metastatic gastric cancer (MGC)
620 receiving intravenous Herceptin. Total trastuzumab clearance increases with decreasing
621 concentrations due to parallel linear and non-linear elimination pathways.

622 Although the average trastuzumab exposure was higher following the first cycle in breast cancer
623 patients receiving the three-weekly schedule compared to the weekly schedule of Herceptin, the
624 average steady-state exposure was essentially the same at both dosages. The average trastuzumab
625 exposure following the first cycle and at steady state as well as the time to steady state was higher in
626 breast cancer patients compared to MGC patients at the same dosage; however, the reason for this
627 exposure difference is unknown. Additional predicted trastuzumab exposure and PK parameters
628 following the first Herceptin cycle and at steady state exposure are described in Tables 7 and 8,
629 respectively.

630 Population PK based simulations indicate that following discontinuation of Herceptin,
631 concentrations in at least 95% of breast cancer and MGC patients will decrease to approximately 3%
632 of the population predicted steady-state trough serum concentration (approximately 97% washout)
633 by 7 months [see *Warnings and Precautions* (5.1) and *Use in Specific Populations* (8.1, 8.6)].

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Table 7
Population Predicted Cycle 1 PK Exposures (median with 5th - 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	C _{min} (µg/mL)	C _{max} (µg/mL)	AUC _{0-21days} (µg.day/mL)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	29.4 (5.8 - 59.5)	178 (117 - 291)	1373 (736 - 2245)
	MGC	274	23.1 (6.1 - 50.3)	132 (84.2 - 225)	1109 (588 - 1938)
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	37.7 (12.3 - 70.9)	88.3 (58 - 144)	1066 (586 - 1754)

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Table 8
Population Predicted Steady State PK Exposures (median with 5th - 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	C _{min,ss} ^a (µg/mL)	C _{max,ss} ^b (µg/mL)	AUC _{ss, 0-21 days} (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	47.4 (5 - 115)	179 (107 - 309)	1794 (673 - 3618)	12	0.173 - 0.283
	MGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 - 2875)	9	0.189 - 0.337
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	66.1 (14.9 - 142)	109 (51.0 - 209)	1765 (647 - 3578)	12	0.201 - 0.244

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^a Steady-state trough serum concentration of trastuzumab

^b Maximum steady-state serum concentration of trastuzumab

Specific Populations: Based on a population pharmacokinetic analysis, no clinically significant differences were observed in the pharmacokinetics of trastuzumab based on age (<65 (n=1294); ≥65 (n=288)), race (Asian (n=264); non-Asian (n=1324)) and renal impairment (mild (creatinine clearance [CL_{cr}] 60 to 90 mL/min) (n=636) or moderate (CL_{cr} 30 to 60 mL/min) (n=133)). The pharmacokinetics of trastuzumab in patients with severe renal impairment, end-stage-renal disease with or without hemodialysis, or hepatic impairment is unknown.

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Drug Interaction Studies:

There have been no formal drug interaction studies performed with Herceptin in humans. Clinically significant interactions between Herceptin and concomitant medications used in clinical trials have not been observed.

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Paclitaxel and doxorubicin: Concentrations of paclitaxel and doxorubicin and their major metabolites (i.e., 6- α hydroxyl-paclitaxel [POH], and doxorubicinol [DOL], respectively) were not altered in the presence of trastuzumab when used as combination therapy in clinical trials. Trastuzumab concentrations were not altered as part of this combination therapy.

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Docetaxel and carboplatin: When Herceptin was administered in combination with docetaxel or carboplatin, neither the plasma concentrations of docetaxel or carboplatin nor the plasma concentrations of trastuzumab was altered.

663 *Cisplatin and capecitabine*: In a drug interaction substudy conducted in patients in Study 7, the
664 pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered
665 in combination with Herceptin.
666

667 **13 NONCLINICAL TOXICOLOGY**

668 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

669 Herceptin has not been tested for carcinogenic potential.

670 No evidence of mutagenic activity was observed when trastuzumab was tested in the standard
671 Ames bacterial and human peripheral blood lymphocyte mutagenicity assays, at concentrations of up
672 to 5000 mcg/mL. In an *in vivo* micronucleus assay, no evidence of chromosomal damage to mouse
673 bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg Herceptin.

674 A fertility study conducted in female cynomolgus monkeys at doses up to 25 times the weekly
675 recommended human dose of 2 mg/kg trastuzumab and has revealed no evidence of impaired
676 fertility, as measured by menstrual cycle duration and female sex hormone levels. Studies to
677 evaluate the effects of trastuzumab on male fertility have not been conducted.
678

679 **14 CLINICAL STUDIES**

680 **14.1 Adjuvant Breast Cancer**

681 The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2
682 overexpressing breast cancer, were evaluated in an integrated analysis of two randomized,
683 open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final
684 overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of
685 3386 women at definitive Disease Free Survival analysis for one-year Herceptin treatment versus
686 observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4).
687 *Studies 1 and 2*

688 In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by
689 IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to
690 randomization (Study 2) or was required to be performed at a reference laboratory (Study 1).
691 Patients with a history of active cardiac disease based on symptoms, abnormal electrocardiographic,
692 radiologic, or left ventricular ejection fraction findings or uncontrolled hypertension
693 (diastolic > 100 mmHg or systolic > 200 mmHg) were not eligible.

694 Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by
695 paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin).
696 In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m² and cyclophosphamide
697 600 mg/m². Paclitaxel was administered either weekly (80 mg/m²) or every 3 weeks (175 mg/m²)
698 for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in
699 Study 2. Herceptin was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a
700 dose of 2 mg/kg weekly for a total of 52 weeks. Herceptin treatment was permanently discontinued
701 in patients who developed congestive heart failure, or persistent/recurrent LVEF decline [*see*
702 *Dosage and Administration (2.2)*]. Radiation therapy, if administered, was initiated after the
703 completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy.
704 The primary endpoint of the combined efficacy analysis was Disease-free survival (DFS), defined as
705 the time from randomization to recurrence, occurrence of contralateral breast cancer, other second
706 primary cancer, or death. The secondary endpoint was overall survival (OS).

707 A total of 3752 patients were included in the joint efficacy analysis of the primary endpoint of
708 DFS following a median follow-up of 2.0 years in the AC→paclitaxel + Herceptin arm. The
709 pre-planned final OS analysis from the joint analysis included 4063 patients and was performed

710 when 707 deaths had occurred after a median follow-up of 8.3 years in the AC→paclitaxel +
711 Herceptin arm. The data from both arms in Study 1 and two of the three study arms in Study 2 were
712 pooled for efficacy analyses. The patients included in the primary DFS analysis had a median age of
713 49 years (range, 22–80 years; 6% > 65 years), 84% were white, 7% black, 4% Hispanic, and 4%
714 Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1,
715 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or
716 PR+ tumors. Similar demographic and baseline characteristics were reported for the efficacy
717 evaluable population, after 8.3 years of median follow-up in the AC→paclitaxel + Herceptin arm.

718 *Study 3*

719 In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or
720 gene amplification (by FISH) as determined at a central laboratory. Patients with node-negative
721 disease were required to have ≥ T1c primary tumor. Patients with a history of congestive heart
722 failure or LVEF <55%, uncontrolled arrhythmias, angina requiring medication, clinically significant
723 valvular heart disease, evidence of transmural infarction on ECG, poorly controlled hypertension
724 (systolic > 180 mm Hg or diastolic > 100 mm Hg) were not eligible.

725 Study 3 was designed to compare one and two years of three-weekly Herceptin treatment versus
726 observation in patients with HER2 positive EBC following surgery, established chemotherapy and
727 radiotherapy (if applicable). Patients were randomized (1:1:1) upon completion of definitive
728 surgery, and at least four cycles of chemotherapy to receive no additional treatment, or one year of
729 Herceptin treatment or two years of Herceptin treatment. Patients undergoing a lumpectomy had
730 also completed standard radiotherapy. Patients with ER+ and/or PgR+ disease received systemic
731 adjuvant hormonal therapy at investigator discretion. Herceptin was administered with an initial
732 dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every three weeks. The main
733 outcome measure was disease-free survival (DFS), defined as in Studies 1 and 2.

734 A protocol specified interim efficacy analysis comparing one-year Herceptin treatment to
735 observation was performed at a median follow-up duration of 12.6 months in the Herceptin arm and
736 formed the basis for the definitive DFS results from this study. Among the 3386 patients
737 randomized to the observation (n = 1693) and Herceptin one-year (n = 1693) treatment arms, the
738 median age was 49 years (range 21–80), 83% were Caucasian, and 13% were Asian. Disease
739 characteristics: 94% infiltrating ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32%
740 node negative, and in 11% of patients, nodal status was not assessable due to prior neo-adjuvant
741 chemotherapy. Ninety-six percent (1055/1098) of patients with node-negative disease had high-risk
742 features: among the 1098 patients with node-negative disease, 49% (543) were ER– and PgR–, and
743 47% (512) were ER and/or PgR + and had at least one of the following high-risk features:
744 pathological tumor size greater than 2 cm, Grade 2–3, or age < 35 years. Prior to randomization,
745 94% of patients had received anthracycline-based chemotherapy regimens.

746 After the definitive DFS results comparing observation to one-year Herceptin treatment were
747 disclosed, a prospectively planned analysis that included comparison of one year versus two years of
748 Herceptin treatment at a median follow-up duration of 8 years was performed. Based on this
749 analysis, extending Herceptin treatment for a duration of two years did not show additional benefit
750 over treatment for one year [Hazard Ratios of two-years Herceptin versus one-year Herceptin
751 treatment in the intent to treat (ITT) population for Disease Free Survival (DFS) = 0.99 (95% CI:
752 0.87, 1.13), p-value = 0.90 and Overall Survival (OS) = 0.98 (0.83, 1.15); p-value = 0.78].

753 *Study 4*

754 In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only)
755 as determined at a central laboratory. Patients were required to have either node-positive disease, or
756 node-negative disease with at least one of the following high-risk features: ER/PR-negative, tumor
757 size > 2 cm, age < 35 years, or histologic and/or nuclear Grade 2 or 3. Patients with a history of

758 CHF, myocardial infarction, Grade 3 or 4 cardiac arrhythmia, angina requiring medication, clinically
759 significant valvular heart disease, poorly controlled hypertension (diastolic > 100 mmHg), any T4 or
760 N2 or known N3 or M1 breast cancer were not eligible.

761 Patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by
762 docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus Herceptin
763 (AC-TH), or docetaxel and carboplatin plus Herceptin (TCH). In both the AC-T and AC-TH arms,
764 doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² were administered every 3 weeks for
765 four cycles; docetaxel 100 mg/m² was administered every 3 weeks for four cycles. In the TCH arm,
766 docetaxel 75 mg/m² and carboplatin (at a target AUC of 6 mg/mL/min as a 30- to 60-minute
767 infusion) were administered every 3 weeks for six cycles. Herceptin was administered weekly
768 (initial dose of 4 mg/kg followed by weekly dose of 2 mg/kg) concurrently with either T or TC, and
769 then every 3 weeks (6 mg/kg) as monotherapy for a total of 52 weeks. Radiation therapy, if
770 administered, was initiated after completion of chemotherapy. Patients with ER+ and/or PR+ tumors
771 received hormonal therapy. Disease-free survival (DFS) was the main outcome measure.

772 Among the 3222 patients randomized, the median age was 49 (range 22 to 74 years; 6%
773 ≥65 years). Disease characteristics included 54% ER+ and/or PR+ and 71% node positive. Prior to
774 randomization, all patients underwent primary surgery for breast cancer.

775 The results for DFS for the integrated analysis of Studies 1 and 2, Study 3, and Study 4 and OS
776 results for the integrated analysis of Studies 1 and 2, and Study 3 are presented in Table 9. For
777 Studies 1 and 2, the duration of DFS following a median follow-up of 2.0 years in the AC→TH arm,
778 is presented in Figure 4, and the duration of OS after a median follow-up of 8.3 years in the
779 AC→TH arm is presented in Figure 5. The duration of DFS for Study 4 is presented in Figure 6.
780 Across all four studies, at the time of definitive DFS analysis, there were insufficient numbers of
781 patients within each of the following subgroups to determine if the treatment effect was different
782 from that of the overall patient population: patients with low tumor grade, patients within specific
783 ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients >65 years of
784 age. For Studies 1 and 2, the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74). At 8.3 years of median
785 follow-up [AC→TH], the survival rate was estimated to be 86.9% in the AC→TH arm and 79.4% in
786 the AC→T arm. The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age,
787 hormone receptor status, number of positive lymph nodes, tumor size and grade, and
788 surgery/radiation therapy, was consistent with the treatment effect in the overall population. In
789 patients ≤ 50 years of age (n=2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in
790 patients > 50 years of age (n=1866), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the
791 subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive)
792 (n=2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with
793 hormone receptor-negative disease (ER-negative and PR-negative) (n=1830), the hazard ratio for OS
794 was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤2 cm (n=1604), the
795 hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size >2
796 cm (n=2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80).

797

Table 9
Efficacy Results from Adjuvant Treatment of
Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	DFS Hazard ratio (95% CI) p value	Deaths (OS events)	OS Hazard ratio p value
Studies 1 + 2^a				
AC→TH (n = 1872) ^b (n = 2031) ^c	133 ^b	0.48 ^{b,d} (0.39, 0.59) p < 0.0001 ^e	289 ^c	0.64 ^{c,d} (0.55, 0.74) p < 0.0001 ^e
AC→T (n = 1880) ^b (n = 2032) ^c	261 ^b		418 ^c	
Study 3^f				
Chemo→ Herceptin (n = 1693)	127	0.54 (0.44, 0.67) p < 0.0001 ^g	31	0.75 p = NS ^h
Chemo→ Observation (n = 1693)	219		40	
Study 4ⁱ				
TCH (n = 1075)	134	0.67 (0.54 – 0.84) p = 0.0006 ^{e,j}	56	
AC→TH (n = 1074)	121	0.60 (0.48 – 0.76) p < 0.0001 ^{e,i}	49	
AC→T (n = 1073)	180		80	

CI = confidence interval.

^a Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

^b Efficacy evaluable population, for the primary DFS analysis, following a median follow-up of 2.0 years in the AC→TH arm.

^c Efficacy evaluable population, for the final OS analysis, following 707 deaths (8.3 years of median follow-up in the AC→TH arm).

^d Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

^e stratified log-rank test.

^f At definitive DFS analysis with median duration of follow-up of 12.6 months in the one-year Herceptin treatment arm.

^g log-rank test.

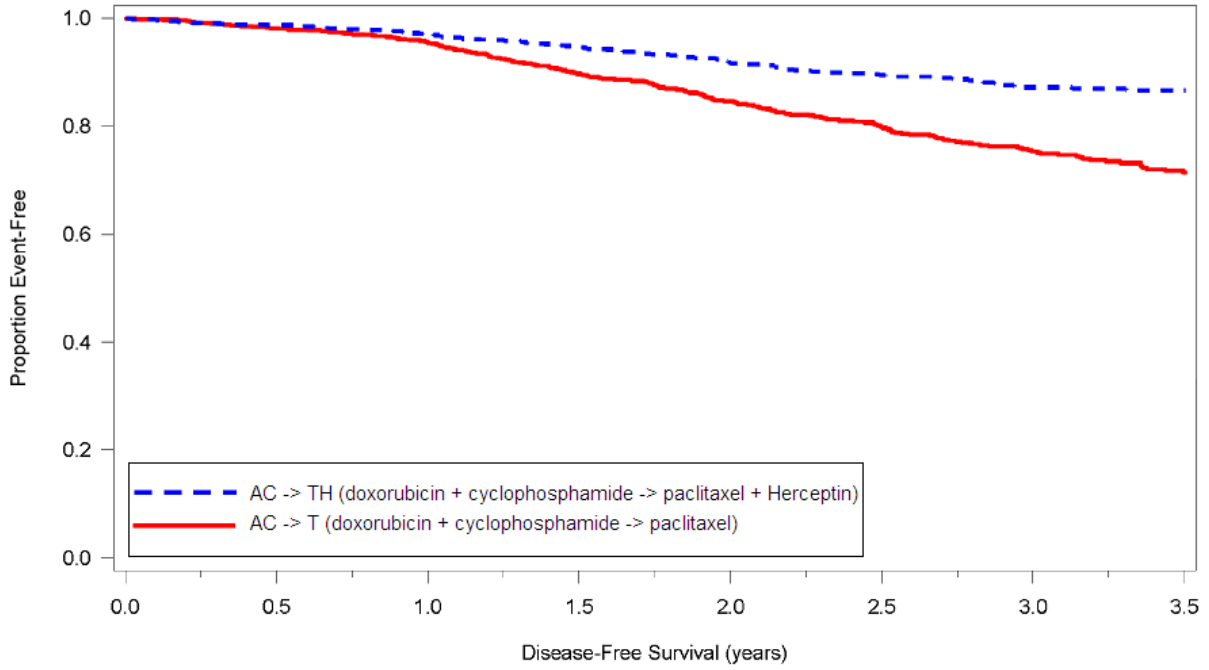
^h NS= non-significant.

ⁱ Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

^j A two-sided alpha level of 0.025 for each comparison.

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Figure 4
Duration of Disease-Free Survival in
Patients with Adjuvant Treatment of Breast Cancer (Studies 1 and 2)

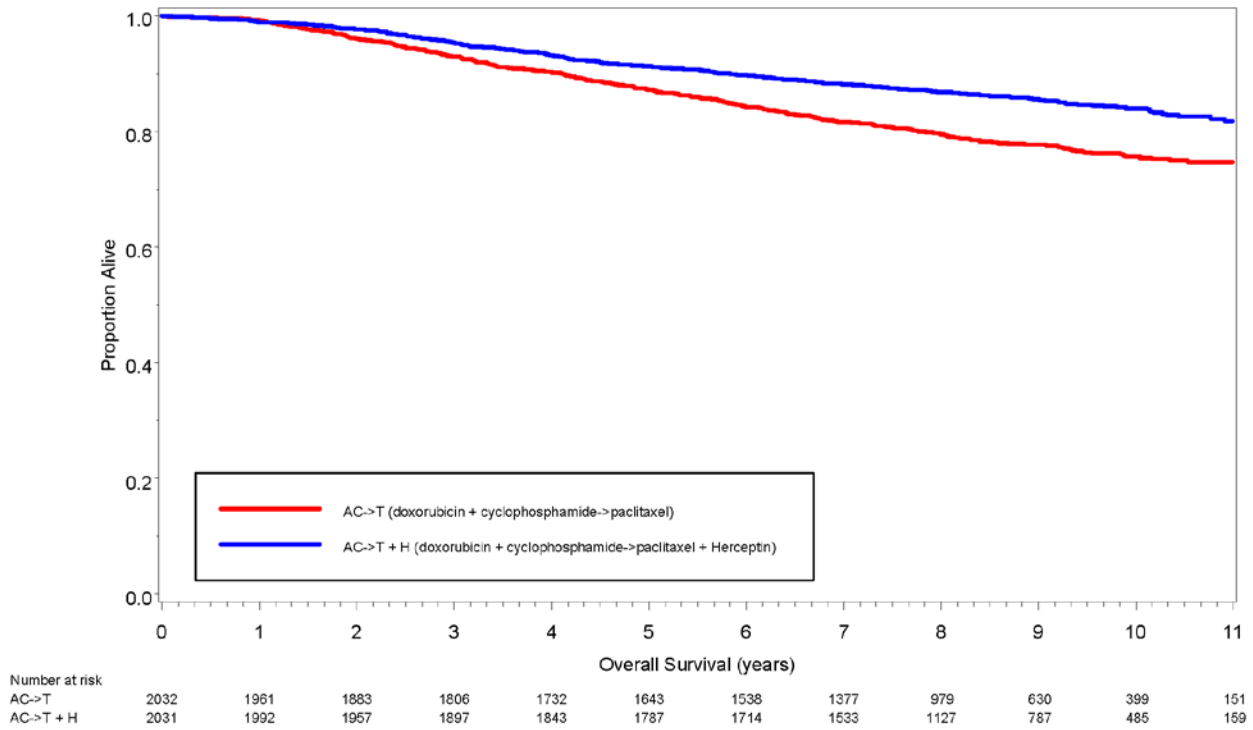


Number at risk								
AC→ T	1880	1490	1159	926	689	534	375	195
AC→ T + H	1872	1529	1240	997	764	575	426	239

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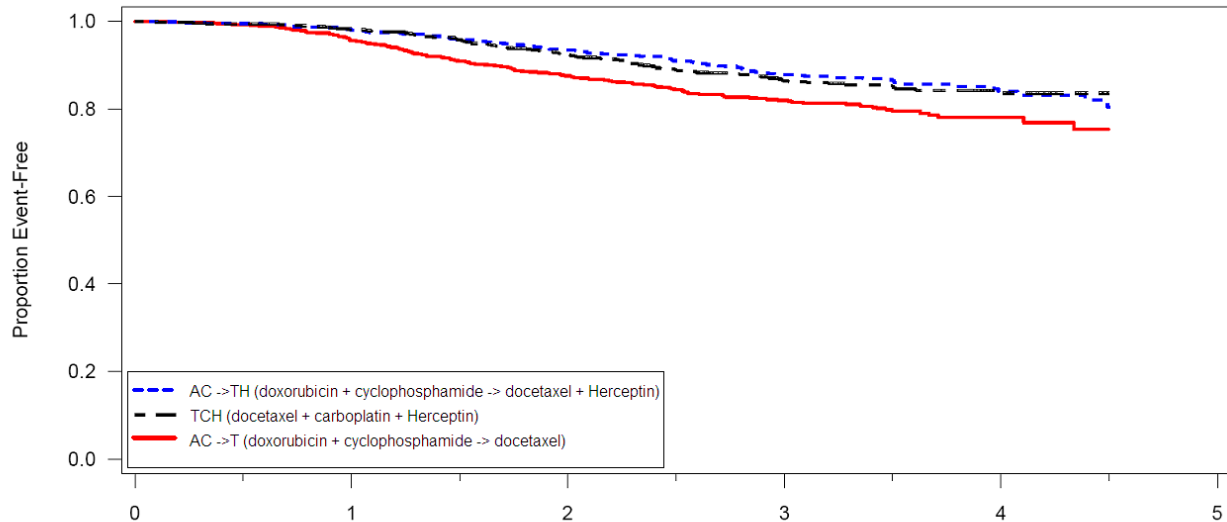
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Figure 5
Duration of Overall Survival in Patients with
Adjuvant Treatment of Breast Cancer (Studies 1 and 2)



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Figure 6
Duration of Disease-Free Survival in Patients with
Adjuvant Treatment of Breast Cancer (Study 4)



Number at risk	Disease-Free Survival (years)					
	0	1	2	3	4	5
AC->T	1073	971	802	417	103	
AC->TH	1074	1023	885	457	126	
TCH	1075	1018	877	447	126	

AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and Herceptin; TH=docetaxel and Herceptin.
Kaplan-Meier estimates are shown.

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814 Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were
815 conducted for patients in Studies 2 and 3, where central laboratory testing data were available.

816 The results are shown in Table 10. The number of events in Study 2 was small with the exception of
 817 the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions
 818 cannot be drawn regarding efficacy within other subgroups due to the small number of events.
 819 The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the
 820 IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups.
 821

Table 10
 Treatment Outcomes in Studies 2 and 3 as a Function of
 HER2 Overexpression or Amplification

HER2 Assay Result ^a	Study 2		Study 3 ^c	
	Number of Patients	Hazard Ratio DFS (95% CI)	Number of Patients	Hazard Ratio DFS (95% CI)
IHC 3+				
FISH (+)	1170	0.42 (0.27, 0.64)	91	0.56 (0.13, 2.50)
FISH (-)	51	0.71 (0.04, 11.79)	8	—
FISH Unknown	51	0.69 (0.09, 5.14)	2258	0.53 (0.41, 0.69)
IHC < 3+ / FISH (+)	174	1.01 (0.18, 5.65)	299 ^b	0.53 (0.20, 1.42)
IHC unknown / FISH (+)	—	—	724	0.59 (0.38, 0.93)

^a IHC by HercepTest, FISH by PathVysion (HER2/CEP17 ratio \geq 2.0) as performed at a central laboratory.

^b All cases in this category in Study 3 were IHC 2+.

^c Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

822

823 14.2 Metastatic Breast Cancer

824 The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were
 825 studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5,
 826 n=469 patients) and an open-label single agent clinical trial (Study 6, n=222 patients). Both trials
 827 studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients
 828 were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by
 829 immunohistochemical assessment of tumor tissue performed by a central testing lab.

830 *Previously Untreated Metastatic Breast Cancer (Study 5)*

831 Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with
 832 metastatic breast cancer who had not been previously treated with chemotherapy for metastatic
 833 disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+,
 834 or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were
 835 eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or
 836 in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly
 837 doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the
 838 adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m² over 3 hours every 21 days for at
 839 least six cycles); for all other patients, chemotherapy consisted of anthracycline plus
 840 cyclophosphamide (AC: doxorubicin 60 mg/m² or epirubicin 75 mg/m² plus 600 mg/m²
 841 cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to

842 receive chemotherapy alone in this study received Herceptin at the time of disease progression as
 843 part of a separate extension study.

844 Based upon the determination by an independent response evaluation committee the patients
 845 randomized to Herceptin and chemotherapy experienced a significantly longer median time to
 846 disease progression, a higher overall response rate (ORR), and a longer median duration of response,
 847 as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin
 848 and chemotherapy also had a longer median survival (see Table 11). These treatment effects were
 849 observed both in patients who received Herceptin plus paclitaxel and in those who received
 850 Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.
 851

Table 11
 Study 5: Efficacy Results in
 First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Herceptin + All Chemo- therapy (n = 235)	All Chemo- therapy (n = 234)	Herceptin + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Herceptin + AC ^a (n = 143)	AC (n = 138)
Primary Endpoint						
<u>Median</u> <u>TTP(mos)</u> ^{b,c}	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
p-value ^d	< 0.0001		< 0.0001		0.002	
Secondary Endpoints						
<u>Overall</u> <u>Response</u> <u>Rate</u> ^b	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value ^e	< 0.001		< 0.001		0.10	
<u>Median Resp</u> <u>Duration</u> <u>(mos)</u> ^{b,c}	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% Quartile	6, 15	4, 8	5, 11	4, 7	6, 15	4, 8
<u>Med Survival</u> <u>(mos)</u> ^c	25.1	20.3	22.1	18.4	26.8	21.4
95% CI	22, 30	17, 24	17, 29	13, 24	23, 33	18, 27
p-value ^d	0.05		0.17		0.16	

^a AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

^b Assessed by an independent Response Evaluation Committee.

^c Kaplan-Meier Estimate.

^d log-rank test.

^e χ^2 -test.

852

853 Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients
 854 with the highest level of HER2 protein overexpression (3+) (see Table 12).
 855

Table 12
Treatment Effects in Study 5 as a
Function of HER2 Overexpression or Amplification

HER2 Assay Result	Number of Patients (N)	Relative Risk ^b for Time to Disease Progression (95% CI)	Relative Risk ^b for Mortality (95% CI)
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)
FISH (+) ^a	325	0.44 (0.34, 0.57)	0.70 (0.53, 0.91)
FISH (-) ^a	126	0.62 (0.42, 0.94)	1.06 (0.70, 1.63)
CTA 2+	120	0.76 (0.50, 1.15)	1.26 (0.82, 1.94)
FISH (+)	32	0.54 (0.21, 1.35)	1.31 (0.53, 3.27)
FISH (-)	83	0.77 (0.48, 1.25)	1.11 (0.68, 1.82)
CTA 3+	349	0.42 (0.33, 0.54)	0.70 (0.51, 0.90)
FISH (+)	293	0.42 (0.32, 0.55)	0.67 (0.51, 0.89)
FISH (-)	43	0.43 (0.20, 0.94)	0.88 (0.39, 1.98)

^a FISH testing results were available for 451 of the 469 patients enrolled on study.

^b The relative risk represents the risk of progression or death in the Herceptin plus chemotherapy arm versus the chemotherapy arm.

856

857 *Previously Treated Metastatic Breast Cancer (Study 6)*

858 Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial
859 (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following
860 one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had
861 received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for
862 metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue.
863 Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin at
864 2 mg/kg IV.

865 The ORR (complete response+partial response), as determined by an independent Response
866 Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate.
867 Complete responses were observed only in patients with disease limited to skin and lymph nodes.
868 The overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that
869 tested as CTA 2+, it was 6%.

870 **14.3 Metastatic Gastric Cancer**

871 The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine
872 (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or
873 gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial,
874 594 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine
875 (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic
876 vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes
877 vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil).
878 All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients
879 were also required to have adequate cardiac function (e.g., LVEF > 50%).

880 On the Herceptin-containing arm, Herceptin was administered as an IV infusion at an initial dose
881 of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms
882 cisplatin was administered at a dose of 80 mg/m² Day 1 every 3 weeks for 6 cycles as a 2 hour IV

883 infusion. On both study arms capecitabine was administered at 1000 mg/m² dose orally twice daily
 884 (total daily dose 2000 mg/m²) for 14 days of each 21 day cycle for 6 cycles. Alternatively continuous
 885 intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m²/day from Day 1
 886 through Day 5 every three weeks for 6 cycles.

887 The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were
 888 Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1;
 889 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these
 890 patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant
 891 therapy, and 2% had received prior radiotherapy.

892 The main outcome measure of Study 7 was overall survival (OS), analyzed by the unstratified log-
 893 rank test. The final OS analysis based on 351 deaths was statistically significant (nominal
 894 significance level of 0.0193). An updated OS analysis was conducted at one year after the final
 895 analysis. The efficacy results of both the final and the updated analyses are summarized in Table 13
 896 and Figure 7.
 897

Table 13
 Study 7: Overall Survival in ITT Population

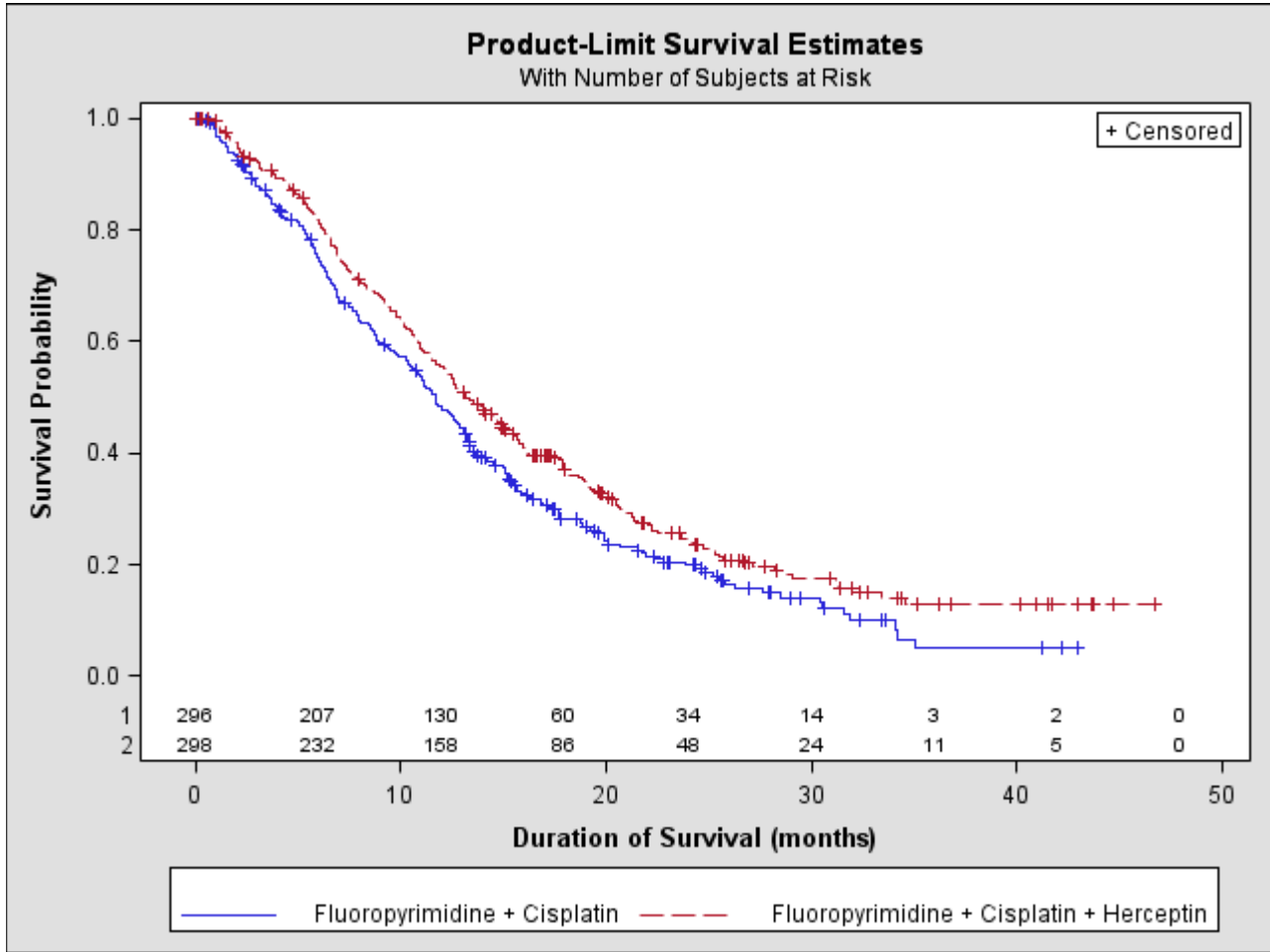
	FC Arm N=296	FC + H Arm N=298
<u>Definitive (Second Interim) Overall Survival</u>		
No. Deaths (%)	184 (62.2%)	167 (56.0%)
Median	11.0	13.5
95% CI (mos.)	(9.4, 12.5)	(11.7, 15.7)
Hazard Ratio	0.73	
95% CI	(0.60, 0.91)	
p-value*, two-sided	0.0038	
<u>Updated Overall Survival</u>		
No. Deaths (%)	227 (76.7%)	221 (74.2%)
Median	11.7	13.1
95% CI (mos.)	(10.3, 13.0)	(11.9, 15.1)
Hazard Ratio	0.80	
95% CI	(0.67, 0.97)	

* Comparing with the nominal significance level of 0.0193.

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Figure 7
Updated Overall Survival in Patients with Metastatic Gastric Cancer (Study 7)



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An exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein overexpression (IHC) testing is summarized in Table 14.

Table 14
Exploratory Analyses by HER2 Status using Updated Overall Survival Results

	FC (N= 296) ^a	FC+H (N=298) ^b
<u>FISH+ / IHC 0, 1+ subgroup (N=133)</u>		
No. Deaths / n (%)	57/71 (80%)	56/62 (90%)
Median OS Duration (mos.)	8.8	8.3
95% CI (mos.)	(6.4, 11.7)	(6.2, 10.7)
Hazard ratio (95% CI)	1.33 (0.92, 1.92)	
<u>FISH+ / IHC2+ subgroup (N=160)</u>		
No. Deaths / n (%)	65/80 (81%)	64/80 (80%)
Median OS Duration (mos.)	10.8	12.3
95% CI (mos.)	(6.8, 12.8)	(9.5, 15.7)
Hazard ratio (95% CI)	0.78 (0.55, 1.10)	
<u>FISH+ or FISH-/IHC3+^c subgroup (N=294)</u>		
No. Deaths / n (%)	104/143 (73%)	96/151 (64%)
Median OS Duration (mos.)	13.2	18.0
95% CI (mos.)	(11.5, 15.2)	(15.5, 21.2)
Hazard ratio (95% CI)	0.66 (0.50, 0.87)	

^a Two patients on the FC arm who were FISH+ but IHC status unknown were excluded from the exploratory subgroup analyses.

^b Five patients on the Herceptin-containing arm who were FISH+, but IHC status unknown were excluded from the exploratory subgroup analyses.

^c Includes 6 patients on chemotherapy arm, 10 patients on Herceptin arm with FISH-, IHC3+ and 8 patients on chemotherapy arm, 8 patients on Herceptin arm with FISH status unknown, IHC 3+.

906

907 **16 HOW SUPPLIED/STORAGE AND HANDLING**

908 **16.1 How Supplied**

909 Herceptin is supplied in a multi-use vial containing 440 mg trastuzumab as a lyophilized sterile
910 powder, under vacuum. Each carton contains one vial Herceptin[®] and one vial (20 mL) of
911 Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.
912 NDC 50242-134-68.

913 **16.2 Stability and Storage**

914 Vials of Herceptin are stable at 2–8°C (36–46°F) prior to reconstitution. Do not use beyond the
915 expiration date stamped on the vial. A vial of Herceptin reconstituted with BWFI, as supplied, is
916 stable for 28 days after reconstitution when stored refrigerated at 2–8°C (36–46°F). Discard any
917 remaining multi-dose reconstituted solution after 28 days. A vial of Herceptin reconstituted with
918 unpreserved SWFI (not supplied) should be used immediately and any unused portion discarded.
919 **Do Not Freeze** Herceptin following reconstitution or dilution.

920 The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags
921 containing 0.9% Sodium Chloride Injection, USP, should be stored at 2–8°C (36–46°F) for no more
922 than 24 hours prior to use.

923 **17 PATIENT COUNSELING INFORMATION**

- 924 • Advise patients to contact a health care professional immediately for any of the following: new
925 onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face,
926 palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness
927 [*see Boxed Warning: Cardiomyopathy*].
- 928 • Advise pregnant women and females of reproductive potential that Herceptin exposure can
929 result in fetal harm [*see Use in Specific Populations (8.1)*].
- 930 • Advise women who are exposed to Herceptin during pregnancy or become pregnant within 7
931 months following the last dose of Herceptin, to immediately report exposure to the Genentech
932 Adverse Event Line at 1-888-835-2555 [*see Use in Specific Populations (8.1, 8.6)*].
- 933 • Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes
934 in women exposed to Herceptin during pregnancy or within 7 months of conception. To enroll
935 the patient in the MoTHER Pregnancy Registry call 1-800-690-6720 [*see Use in Specific*
936 *Populations (8.1)*].
- 937 • Advise females of reproductive potential to avoid becoming pregnant while taking Herceptin. If
938 contraceptive methods are being considered, advise female patients to use effective
939 contraception during treatment and for at least 7 months following the last dose of Herceptin
940 [*see Use in Specific Populations (8.1, 8.6)*].
- 941 • Advise nursing mothers treated with Herceptin to discontinue nursing or discontinue Herceptin,
942 taking into account the importance of the drug to the mother [*see Use in Specific Populations*
943 *(8.3)*].
- 944

HERCEPTIN[®] [trastuzumab]

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

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South San Francisco, CA 94080-4990

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