

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) for injection, for intravenous use
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 subclinical 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. (2.3, 5.1)

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. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.3)

-----RECENT MAJOR CHANGES-----

Dosage and Administration (2.1)	04/2017
Warnings and Precautions (5.3)	03/2016

-----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)

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin (1, 2.1).

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

For intravenous (IV) infusion only. Do not administer as an IV push or bolus. (2.2)

Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine. (2.2)

Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1, 2.1)

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.2)

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 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Herceptin, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy, 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 (2.2)

- 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 (2.2)

- 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-----

- For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution
- For Injection: 420 mg lyophilized powder in a multiple-dose vial for reconstitution

-----CONTRAINDICATIONS-----

- None. (4)

-----WARNINGS AND PRECAUTIONS-----

- Exacerbation of Chemotherapy-Induced Neutropenia. (5.5, 6.1)

-----ADVERSE REACTIONS-----

Adjuvant Breast Cancer

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

Metastatic Breast Cancer

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

Metastatic Gastric Cancer

- Most common adverse reactions (≥ 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-----

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2017

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FULL PRESCRIBING INFORMATION

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

Cardiomyopathy

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

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and withhold Herceptin in patients with metastatic disease for clinically significant decrease in left ventricular function [see *Dosage and Administration (2.3) and Warnings and Precautions (5.1)*].

Infusion Reactions; Pulmonary Toxicity

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

Embryo-Fetal Toxicity

Exposure to Herceptin during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception [see *Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)*].

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

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

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

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin [see *Dosage and Administration (2.1)*].

1.2 Metastatic Breast Cancer

Herceptin is indicated:

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

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin [see *Dosage and Administration (2.1)*].

1.3 Metastatic Gastric Cancer

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

47 Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin [*see*
48 *Dosage and Administration (2.1)*].

50 2 DOSAGE AND ADMINISTRATION

51 2.1 Patient Selection

52 Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor
53 specimens [*see Indications and Usage (1) and Clinical Studies (14)*]. Assessment of HER2 protein
54 overexpression and HER2 gene amplification should be performed using FDA-approved tests
55 specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on
56 the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene
57 amplification is available at: <http://www.fda.gov/CompanionDiagnostics>.

58 Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric
59 cancer should be performed using FDA-approved tests specifically for gastric cancers due to
60 differences in gastric vs. breast histopathology, including incomplete membrane staining and more
61 frequent heterogeneous expression of HER2 seen in gastric cancers.

62 Improper assay performance, including use of suboptimally fixed tissue, failure to utilize
63 specified reagents, deviation from specific assay instructions, and failure to include appropriate
64 controls for assay validation, can lead to unreliable results.

65 2.2 Recommended Doses and Schedules

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

69 *Adjuvant Treatment, Breast Cancer*

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

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

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

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

- 80 • Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
- 81 • Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every
82 three weeks [*see Dosage and Administration (2.3)*].
- 83 • Extending adjuvant treatment beyond one year is not recommended [*see Adverse Reactions*
84 *(6.1)*].

85 *Metastatic Treatment, Breast Cancer*

- 86 • Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as
87 a 90-minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as
88 30-minute intravenous infusions until disease progression.

89 *Metastatic Gastric Cancer*

- 90 • Administer Herceptin at an initial dose of 8 mg/kg as a 90-minute intravenous infusion
91 followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30–90 minutes every
92 three weeks until disease progression [*see Dosage and Administration (2.3)*].

2.3 Important Dosing Considerations

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

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

Infusion Reactions

[See Boxed Warning, Warnings and Precautions (5.2)]

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

Cardiomyopathy

[See Boxed Warning, Warnings and Precautions (5.1)]

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

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

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

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

2.4 Preparation for Administration

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

420 mg Multiple-dose vial

Reconstitution

Reconstitute each 420 mg vial of Herceptin with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multiple-dose solution containing 21 mg/mL trastuzumab that delivers 20 mL (420 mg trastuzumab). In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Herceptin. The stream of diluent should be directed into the lyophilized cake. The reconstituted vial yields a solution for multiple-dose use, containing 21 mg/mL trastuzumab.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE.**
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.

- 139 • Parenteral drug products should be inspected visually for particulate matter and discoloration
140 prior to administration, whenever solution and container permit. Inspect visually for
141 particulates and discoloration. The solution should be free of visible particulates, clear to
142 slightly opalescent and colorless to pale yellow.
- 143 • Store reconstituted Herceptin in the refrigerator at 2°C to 8°C (36°F to 46°F); discard unused
144 Herceptin after 28 days. If Herceptin is reconstituted with SWFI without preservative, use
145 immediately and discard any unused portion. **Do not freeze.**

146 *Dilution*

- 147 • Determine the dose (mg) of Herceptin [*see Dosage and Administration (2.2)*]. Calculate the
148 volume of the 21 mg/mL reconstituted Herceptin solution needed, withdraw this amount from
149 the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection,
150 USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- 151 • Gently invert the bag to mix the solution.
- 152 • The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags
153 containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to
154 46°F) for no more than 24 hours prior to use. **Do not freeze.**

156 150 mg Single-dose vial

157 *Reconstitution*

158 Reconstitute each 150 mg vial of Herceptin with 7.4 mL of Sterile Water for Injection (SWFI)
159 (not supplied) to yield a single-dose solution containing 21 mg/mL trastuzumab that delivers 7.15
160 mL (150 mg trastuzumab).

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

- 162 • Using a sterile syringe, slowly inject 7.4 mL of SWFI (not supplied) into the vial containing
163 the lyophilized 150 mg Herceptin, directing the diluent stream into the lyophilized cake. The
164 reconstituted vial yields a solution for single-dose use, containing 21 mg/mL trastuzumab.
- 165 • Swirl the vial gently to aid reconstitution. **DO NOT SHAKE.**
- 166 • Slight foaming of the product may be present upon reconstitution. Allow the vial to stand
167 undisturbed for approximately 5 minutes.
- 168 • Parenteral drug products should be inspected visually for particulate matter and discoloration
169 prior to administration, whenever solution and container permit. Inspect visually for
170 particulates and discoloration. The solution should be free of visible particulates, clear to
171 slightly opalescent and colorless to pale yellow.
- 172 • Use the Herceptin solution immediately following reconstitution with SWFI, as it contains no
173 preservative and is intended for single-dose only. If not used immediately, store the
174 reconstituted Herceptin solution for up to 24 hours at 2°C to 8°C (36°F to 46°F); discard any
175 unused Herceptin after 24 hours. **Do not freeze.**

176 *Dilution*

- 177 • Determine the dose (mg) of Herceptin [*see Dosage and Administration (2.1)*].
- 178 • Calculate the volume of the 21 mg/mL reconstituted Herceptin solution needed.
- 179 • Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of
180 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- 181 • Gently invert the bag to mix the solution.
- 182 • The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags
183 containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to
184 46°F) for no more than 24 hours prior to use. Discard after 24 hours. This storage time is
185 additional to the time allowed for the reconstituted vials. **Do not freeze.**

186

187 **3 DOSAGE FORMS AND STRENGTHS**

- 188 • For injection: 150 mg lyophilized powder in a single-dose vial
189 • For injection: 420 mg lyophilized powder in a multiple-dose vial.

191 **4 CONTRAINDICATIONS**

192 None.

194 **5 WARNINGS AND PRECAUTIONS**

195 **5.1 Cardiomyopathy**

196 Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling
197 cardiac failure, cardiomyopathy, and cardiac death [see *Boxed Warning: Cardiomyopathy*].

198 Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

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

203 Withhold Herceptin for $\geq 16\%$ absolute decrease in LVEF from pre-treatment values or an LVEF
204 value below institutional limits of normal and $\geq 10\%$ absolute decrease in LVEF from pretreatment
205 values [see *Dosage and Administration (2.3)*]. The safety of continuation or resumption of
206 Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been
207 studied.

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

210 *Cardiac Monitoring*

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

- 213 • Baseline LVEF measurement immediately prior to initiation of Herceptin
214 • LVEF measurements every 3 months during and upon completion of Herceptin
215 • Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left
216 ventricular cardiac dysfunction [see *Dosage and Administration (2.3)*]
217 • LVEF measurements every 6 months for at least 2 years following completion of Herceptin as
218 a component of adjuvant therapy.

219 In Study 1, 15% (158/1031) of patients discontinued Herceptin due to clinical evidence of
220 myocardial dysfunction or significant decline in LVEF after a median follow-up duration of
221 8.7 years in the AC-TH arm. In Study 3 (one-year Herceptin treatment), the number of patients who
222 discontinued Herceptin due to cardiac toxicity at 12.6 months median duration of follow-up was
223 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) of patients in the TCH arm (1.5% during the
224 chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) of patients in the
225 AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase)
226 discontinued Herceptin due to cardiac toxicity.

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

234

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.

240

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

244 5.2 Infusion Reactions

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

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

254 Interrupt Herceptin infusion in all patients experiencing dyspnea, clinically significant
255 hypotension, and intervention of medical therapy administered (which may include epinephrine,
256 corticosteroids, diphenhydramine, bronchodilators, and oxygen). Patients should be evaluated and
257 carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation
258 should be strongly considered in all patients with severe infusion reactions.

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

264 **5.3 Embryo-Fetal Toxicity**

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

269 Verify the pregnancy status of females of reproductive potential prior to the initiation of
270 Herceptin. Advise pregnant women and females of reproductive potential that exposure to
271 Herceptin during pregnancy or within 7 months prior to conception can result in fetal harm. Advise
272 females of reproductive potential to use effective contraception during treatment and for 7 months
273 following the last dose of Herceptin [*see Use in Specific Populations (8.1, 8.3) and Clinical*
274 *Pharmacology (12.3)*].

275 **5.4 Pulmonary Toxicity**

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

282 **5.5 Exacerbation of Chemotherapy-Induced Neutropenia**

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

288

289 **6 ADVERSE REACTIONS**

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

- 291 • Cardiomyopathy [*see Warnings and Precautions (5.1)*]
- 292 • Infusion Reactions [*see Warnings and Precautions (5.2)*]
- 293 • Embryo-Fetal Toxicity [*see Warnings and Precautions (5.3)*]
- 294 • Pulmonary Toxicity [*see Warnings and Precautions (5.4)*]
- 295 • Exacerbation of Chemotherapy-Induced Neutropenia [*see Warnings and Precautions (5.5)*]

296

297 The most common adverse reactions in patients receiving Herceptin in the adjuvant and metastatic
298 breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased
299 cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions
300 requiring interruption or discontinuation of Herceptin treatment include CHF, significant decline in

301 left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity [*see Dosage and*
302 *Administration (2.3)*].

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

310 **6.1 Clinical Trials Experience**

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

314 *Adjuvant Breast Cancer Studies*

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

318 The data summarized in Table 3 below, from Study 3, reflect exposure to Herceptin in
319 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18.
320 Among the 3386 patients enrolled in the observation and one-year Herceptin arms of Study 3 at a
321 median duration of follow-up of 12.6 months in the Herceptin arm, the median age was 49 years
322 (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.
323

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%)
Asthenia	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.

325

326 In Study 3, a comparison of 3-weekly Herceptin treatment for two years versus one year was also
327 performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year Herceptin
328 treatment arm (8.1% versus 4.6% in the one-year Herceptin treatment arm). More patients
329 experienced at least one adverse reaction of Grade 3 or higher in the 2-year Herceptin treatment arm
330 (20.4%) compared with the one-year Herceptin treatment arm (16.3%).

331 The safety data from Studies 1 and 2 were obtained from 3655 patients, of whom 2000 received
332 Herceptin; the median treatment duration was 51 weeks. The median age was 49 years (range:
333 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian.

334 In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5
335 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The
336 following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater
337 among patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone: fatigue
338 (29.5% vs. 22.4%), infection (24.0% vs. 12.8%), hot flashes (17.1% vs. 15.0%), anemia (12.3% vs.
339 6.7%), dyspnea (11.8% vs. 4.6%), rash/desquamation (10.9% vs. 7.6%), leukopenia (10.5% vs.
340 8.4%), neutropenia (6.4% vs. 4.3%), headache (6.2% vs. 3.8%), pain (5.5% vs. 3.0%), edema (4.7%
341 vs. 2.7%), and insomnia (4.3% vs. 1.5%). The majority of these events were Grade 2 in severity.

342 In Study 2, data collection was limited to the following investigator-attributed treatment-related
343 adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic
344 toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes,
345 motor neuropathy, and sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during
346 chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of
347 Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving Herceptin plus
348 chemotherapy as compared to chemotherapy alone: arthralgia (12.2% vs. 9.1%), nail changes
349 (11.5% vs. 6.8%), dyspnea (2.4% vs. 0.2%), and diarrhea (2.2% vs. 0%). The majority of these
350 events were Grade 2 in severity.

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

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

359 *Metastatic Breast Cancer Studies*

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

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

369 Among the 352 patients treated in single agent studies (213 patients from Study 6), the median
 370 age was 50 years (range 28–86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in
 371 other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed
 372 by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months
 373 and ≥ 12 months were 31% and 16%, respectively.
 374

Table 4
 Per-Patient Incidence of Adverse Reactions Occurring in ≥ 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%

375

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.

376

377 *Metastatic Gastric Cancer*

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

381 chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was
 382 administered at 80 mg/m² on Day 1 and the fluoropyrimidine was administered as either
 383 capecitabine 1000 mg/m² orally twice a day on Days 1–14 or 5-fluorouracil 800 mg/m²/day as a
 384 continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day
 385 cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin
 386 infusions administered was eight.
 387

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)

388

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

392 *Cardiomyopathy*

393 Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant
394 treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months
395 (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and
396 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
397 patients with post-AC LVEF evaluation were not permitted to initiate Herceptin following
398 completion of AC chemotherapy due to cardiac dysfunction (LVEF < LLN or ≥ 16 point decline in
399 LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of
400 new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and
401 paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients
402 receiving one-year Herceptin monotherapy compared to observation in Study 3 (see Table 6,
403 Figures 1 and 2). The per-patient incidence of new-onset cardiac dysfunction, as measured by
404 LVEF, remained similar when compared to the analysis performed at a median follow-up of 2.0
405 years in the AC-TH arm. This analysis also showed evidence of reversibility of left ventricular
406 dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC-TH group being
407 asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.

408

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).

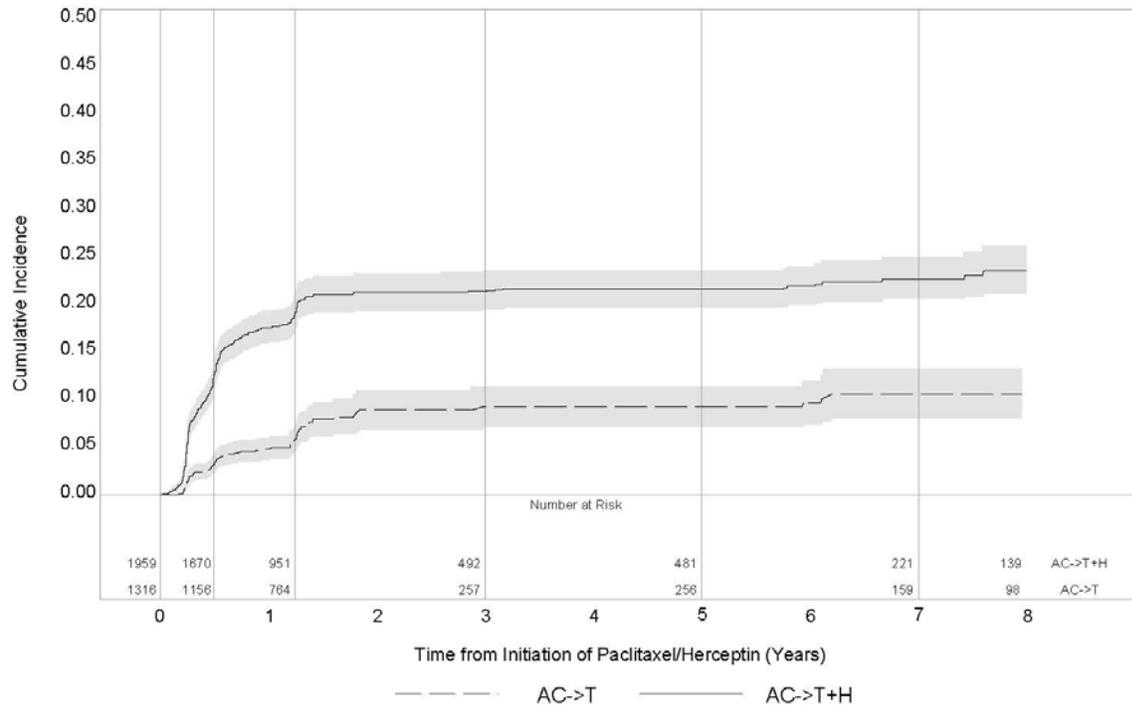
^c Median duration of follow-up for Studies 1 and 2 combined was 8.3 years in the AC→TH arm.

^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

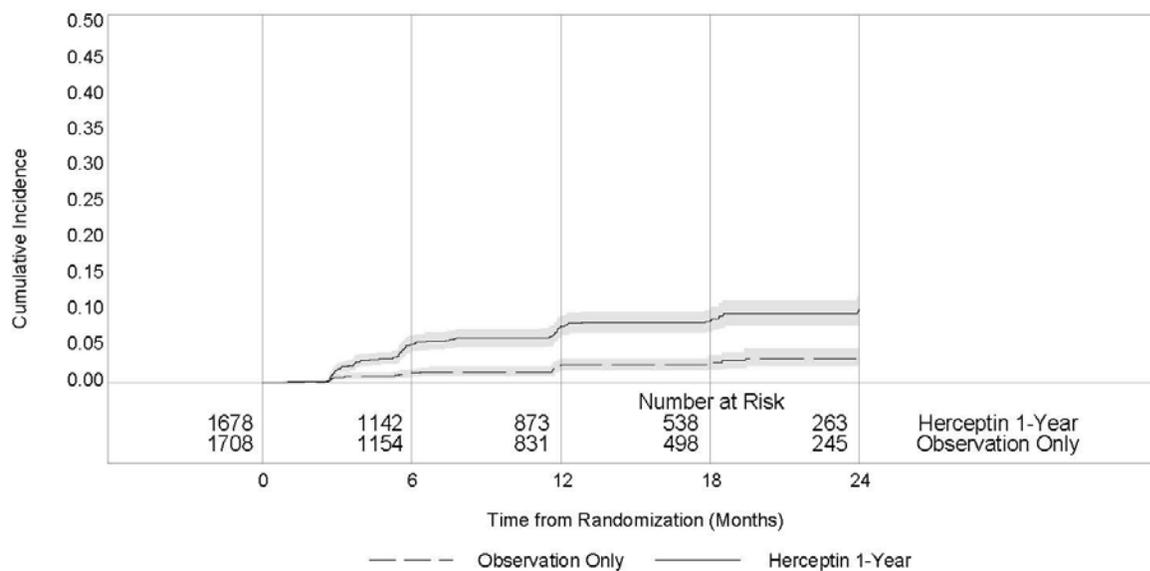


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Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

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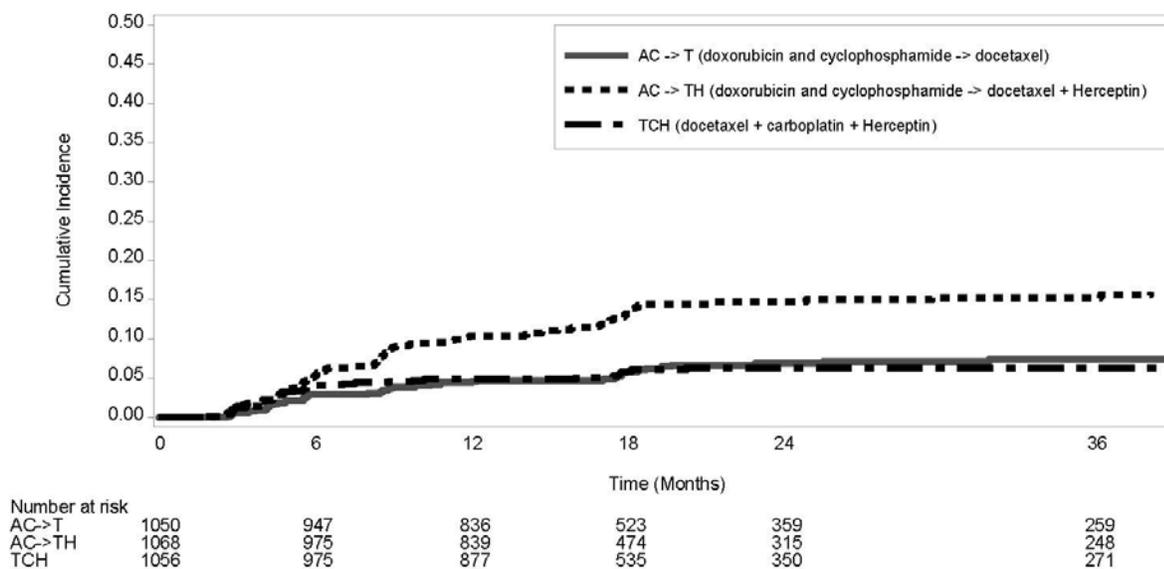
Figure 2
Study 3: Cumulative Incidence of Time to First LVEF
Decline of ≥ 10 Percentage Points from Baseline and to
Below 50% with Death as a Competing Risk Event



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428

Time 0 is the date of randomization.

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



429
430
431

Time 0 is the date of randomization.

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

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

440 *Infusion Reactions*

441 During the first infusion with Herceptin, the symptoms most commonly reported were chills and
442 fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with
443 acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of
444 Herceptin infusion); permanent discontinuation of Herceptin for infusion reactions was required in
445 $< 1\%$ of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases
446 at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and
447 asthenia. Infusion reactions occurred in 21% and 35% of patients, and were severe in 1.4% and 9%
448 of patients, on second or subsequent Herceptin infusions administered as monotherapy or in
449 combination with chemotherapy, respectively. In the post-marketing setting, severe infusion
450 reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

451 *Anemia*

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

460 *Neutropenia*

461 In randomized controlled clinical trials in the adjuvant setting, the incidence of selected
462 NCI-CTC Grade 4–5 neutropenia (1.7% vs. 0.8% [Study 2]) and of selected Grade 2–5 neutropenia
463 (6.4% vs. 4.3% [Study 1]) were increased in patients receiving Herceptin and chemotherapy
464 compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients
465 with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and
466 of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in
467 combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7
468 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone
469 arm, the incidence of NCI-CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile
470 neutropenia 5.1% compared to 2.8%.

471 *Infection*

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

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

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

483 *Pulmonary Toxicity*

484 *Adjuvant Breast Cancer*

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

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

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

497 *Metastatic Breast Cancer*

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

504 *Thrombosis/Embolism*

505 In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher
506 in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies
507 (2.6% vs. 1.5% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]).

508 *Diarrhea*

509 Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC
510 Grade 2–5 diarrhea (6.7% vs. 5.4% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (2.2% vs. 0%
511 [Study 2]), and of Grade 1–4 diarrhea (7% vs. 1% [Study 3; one-year Herceptin treatment at
512 12.6 months median duration of follow-up]) were higher in patients receiving Herceptin as compared
513 to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher [5.7% AC-TH, 5.5% TCH
514 vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among
515 women receiving Herceptin. Of patients receiving Herceptin as a single agent for the treatment of
516 metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was
517 observed in patients receiving Herceptin in combination with chemotherapy for treatment of
518 metastatic breast cancer.

519 *Renal Toxicity*

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

525 In the post-marketing setting, rare cases of nephrotic syndrome with pathologic evidence of
526 glomerulopathy have been reported. The time to onset ranged from 4 months to approximately
527 18 months from initiation of Herceptin therapy. Pathologic findings included membranous

528 glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications
529 included volume overload and congestive heart failure.

530 **6.2 Immunogenicity**

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

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

542 **6.3 Post-Marketing Experience**

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

- 546 • Infusion reaction [*see Warnings and Precautions (5.2)*]
- 547 • Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal
548 abnormalities, and neonatal death [*see Warnings and Precautions (5.3)*]
- 549 • Glomerulopathy [*see Adverse Reactions (6.1)*]
- 550 • Immune thrombocytopenia

551

552 **7 DRUG INTERACTIONS**

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

558

559 **8 USE IN SPECIFIC POPULATIONS**

560 **8.1 Pregnancy**

561 Pregnancy Exposure Registry and Pharmacovigilance Program

562 There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to
563 Herceptin during pregnancy. Encourage women who receive Herceptin during pregnancy or within
564 7 months prior to conception to enroll in the MoTHER Pregnancy Registry by contacting 1-800-690-
565 6720 or visiting <http://www.motherpregnancyregistry.com/>.

566 In addition, there is a pregnancy pharmacovigilance program for Herceptin. If Herceptin is
567 administered during pregnancy, or if a patient becomes pregnant while receiving Herceptin or within
568 7 months following the last dose of Herceptin, health care providers and patients should immediately
569 report Herceptin exposure to Genentech at 1-888-835-2555.

570 Risk Summary

571 Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing
572 reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and of
573 oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and
574 neonatal death [*see Data*]. Apprise the patient of the potential risks to a fetus. There are clinical

575 considerations if Herceptin is used in a pregnant woman or if a patient becomes pregnant within 7
576 months following the last dose of Herceptin [see *Clinical Considerations*].

577 The estimated background risk of major birth defects and miscarriage for the indicated population
578 is unknown. In the U.S. general population, the estimated background risk of major birth defects
579 and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

580 Clinical Considerations

581 *Fetal/Neonatal Adverse Reactions*

582 Monitor women who received Herceptin during pregnancy or within 7 months prior to conception
583 for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for
584 gestational age and consistent with community standards of care.

585 Data

586 *Human Data*

587 In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios
588 and of oligohydramnios sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal
589 abnormalities, and neonatal death. These case reports described oligohydramnios in pregnant
590 women who received Herceptin either alone or in combination with chemotherapy. In some case
591 reports, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin therapy
592 resumed after amniotic index improved and oligohydramnios recurred.

593 *Animal Data*

594 In studies where trastuzumab was administered to pregnant Cynomolgus monkeys during the
595 period of organogenesis at doses up to 25 mg/kg given twice weekly (up to 25 times the
596 recommended weekly human dose of 2 mg/kg), trastuzumab crossed the placental barrier during the
597 early (Gestation Days 20 to 50) and late (Gestation Days 120 to 150) phases of gestation. The
598 resulting concentrations of trastuzumab in fetal serum and amniotic fluid were approximately 33%
599 and 25%, respectively, of those present in the maternal serum but were not associated with adverse
600 developmental effects.

601 **8.2 Lactation**

602 Risk Summary

603 There is no information regarding the presence of trastuzumab in human milk, the effects on the
604 breastfed infant, or the effects on milk production. Published data suggest human IgG is present in
605 human milk but does not enter the neonatal and infant circulation in substantial amounts.
606 Trastuzumab was present in the milk of lactating Cynomolgus monkeys but not associated with
607 neonatal toxicity [see *Data*]. Consider the developmental and health benefits of breastfeeding along
608 with the mother's clinical need for Herceptin treatment and any potential adverse effects on the
609 breastfed child from Herceptin or from the underlying maternal condition. This consideration should
610 also take into account the trastuzumab wash out period of 7 months [see *Clinical Pharmacology*
611 (12.3)].

612 Data

613 In lactating Cynomolgus monkeys, trastuzumab was present in breast milk at about 0.3% of
614 maternal serum concentrations after pre- (beginning Gestation Day 120) and post-partum (through
615 Post-partum Day 28) doses of 25 mg/kg administered twice weekly (25 times the recommended
616 weekly human dose of 2 mg/kg of Herceptin). Infant monkeys with detectable serum levels of
617 trastuzumab did not exhibit any adverse effects on growth or development from birth to 1 month of
618 age.

619

620 **8.3 Females and Males of Reproductive Potential**

621 Pregnancy Testing

622 Verify the pregnancy status of females of reproductive potential prior to the initiation of
623 Herceptin.

624 Contraception

625 *Females*

626 Herceptin can cause embryo-fetal harm when administered during pregnancy. Advise females of
627 reproductive potential to use effective contraception during treatment with Herceptin and for 7
628 months following the last dose of Herceptin [*see Use in Specific Populations (8.1) and Clinical*
629 *Pharmacology (12.3)*].

630 **8.4 Pediatric Use**

631 The safety and effectiveness of Herceptin in pediatric patients have not been established.

632 **8.5 Geriatric Use**

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

643 In Study 7 (metastatic gastric cancer), of the 294 patients treated with Herceptin, 108 (37%) were
644 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or
645 effectiveness were observed.

646

647 **10 OVERDOSAGE**

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

650

651 **11 DESCRIPTION**

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

657 Herceptin (trastuzumab) is a sterile, white to pale yellow, preservative-free lyophilized powder for
658 Injection, for intravenous administration.

659 Each multiple-dose vial of Herceptin delivers 420 mg trastuzumab, 381.8 mg α,α -trehalose
660 dihydrate, 9.5 mg L-histidine HCl monohydrate, 6.1 mg L-histidine, and 1.7 mg polysorbate 20.
661 Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution containing
662 21 mg/mL trastuzumab at a pH of approximately 6. If Herceptin is reconstituted with SWFI without
663 preservative, the reconstituted solution is considered single-dose.

664 Each single-dose vial of Herceptin delivers 150 mg trastuzumab, 136.2 mg α,α -trehalose
665 dihydrate, 3.4 mg L-histidine HCl monohydrate, 2.2 mg L-histidine, and 0.6 mg polysorbate 20.
666 Reconstitution with 7.4 mL of sterile water for injection (SWFI) yields a solution containing 21
667 mg/mL trastuzumab that delivers 7.15 mL (150 mg trastuzumab), at a pH of approximately 6.

669 **12 CLINICAL PHARMACOLOGY**670 **12.1 Mechanism of Action**

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

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

678 **12.2 Pharmacodynamics**679 *Cardiac Electrophysiology*

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

685 **12.3 Pharmacokinetics**

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

690 Although the average trastuzumab exposure was higher following the first cycle in breast cancer
 691 patients receiving the three-weekly schedule compared to the weekly schedule of Herceptin, the
 692 average steady-state exposure was essentially the same at both dosages. The average trastuzumab
 693 exposure following the first cycle and at steady state as well as the time to steady state was higher in
 694 breast cancer patients compared to MGC patients at the same dosage; however, the reason for this
 695 exposure difference is unknown. Additional predicted trastuzumab exposure and PK parameters
 696 following the first Herceptin cycle and at steady state exposure are described in Tables 7 and 8,
 697 respectively.

698 Population PK based simulations indicate that following discontinuation of Herceptin,
 699 concentrations in at least 95% of breast cancer and MGC patients will decrease to approximately 3%
 700 of the population predicted steady-state trough serum concentration (approximately 97% washout)
 701 by 7 months [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)*].

702

703

704 **Table 7**
 705 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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709

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

^a Steady-state trough serum concentration of trastuzumab

^b Maximum steady-state serum concentration of trastuzumab

710
711
712

Specific Populations

713
714 Based on a population pharmacokinetic analysis, no clinically significant differences were observed
715 in the pharmacokinetics of trastuzumab based on age (< 65 (n = 1294); ≥ 65 (n = 288)), race (Asian
716 (n = 264); non-Asian (n = 1324)) and renal impairment (mild (creatinine clearance [CLcr] 60 to
717 90 mL/min) (n = 636) or moderate (CLcr 30 to 60 mL/min) (n = 133)). The pharmacokinetics of
718 trastuzumab in patients with severe renal impairment, end-stage renal disease with or without
719 hemodialysis, or hepatic impairment is unknown.

Drug Interaction Studies

720
721 There have been no formal drug interaction studies performed with Herceptin in humans. Clinically
722 significant interactions between Herceptin and concomitant medications used in clinical trials have
723 not been observed.

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

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

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

734

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

736
737 Herceptin has not been tested for carcinogenic potential.

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

743 A fertility study was conducted in female Cynomolgus monkeys at doses up to 25 times the
744 weekly recommended human dose of 2 mg/kg of trastuzumab and has revealed no evidence of
745 impaired fertility, as measured by menstrual cycle duration and female sex hormone levels.
746

747 **14 CLINICAL STUDIES**

748 **14.1 Adjuvant Breast Cancer**

749 The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2
750 overexpressing breast cancer were evaluated in an integrated analysis of two randomized,
751 open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final
752 overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of
753 3386 women at definitive Disease-Free Survival analysis for one-year Herceptin treatment versus
754 observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4).

755 *Studies 1 and 2*

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

762 Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by
763 paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin).
764 In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m² and cyclophosphamide
765 600 mg/m². Paclitaxel was administered either weekly (80 mg/m²) or every 3 weeks (175 mg/m²)
766 for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in
767 Study 2. Herceptin was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a
768 dose of 2 mg/kg weekly for a total of 52 weeks. Herceptin treatment was permanently discontinued
769 in patients who developed congestive heart failure, or persistent/recurrent LVEF decline [*see*
770 *Dosage and Administration (2.3)*]. Radiation therapy, if administered, was initiated after the
771 completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy.
772 The primary endpoint of the combined efficacy analysis was Disease-Free Survival (DFS), defined
773 as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second
774 primary cancer, or death. The secondary endpoint was overall survival (OS).

775 A total of 3752 patients were included in the joint efficacy analysis of the primary endpoint of
776 DFS following a median follow-up of 2.0 years in the AC→paclitaxel + Herceptin arm. The
777 pre-planned final OS analysis from the joint analysis included 4063 patients and was performed
778 when 707 deaths had occurred after a median follow-up of 8.3 years in the AC→paclitaxel +
779 Herceptin arm. The data from both arms in Study 1 and two of the three study arms in Study 2 were
780 pooled for efficacy analyses. The patients included in the primary DFS analysis had a median age of
781 49 years (range, 22–80 years; 6% > 65 years), 84% were white, 7% black, 4% Hispanic, and 4%
782 Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1,
783 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or
784 PR+ tumors. Similar demographic and baseline characteristics were reported for the efficacy
785 evaluable population, after 8.3 years of median follow-up in the AC→paclitaxel + Herceptin arm.

786 *Study 3*

787 In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or
788 gene amplification (by FISH) as determined at a central laboratory. Patients with node-negative
789 disease were required to have ≥ T1c primary tumor. Patients with a history of congestive heart
790 failure or LVEF < 55%, uncontrolled arrhythmias, angina requiring medication, clinically significant

791 valvular heart disease, evidence of transmural infarction on ECG, poorly controlled hypertension
792 (systolic > 180 mm Hg or diastolic > 100 mm Hg) were not eligible.

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

802 A protocol specified interim efficacy analysis comparing one-year Herceptin treatment to
803 observation was performed at a median follow-up duration of 12.6 months in the Herceptin arm and
804 formed the basis for the definitive DFS results from this study. Among the 3386 patients
805 randomized to the observation (n = 1693) and Herceptin one-year (n = 1693) treatment arms, the
806 median age was 49 years (range 21–80), 83% were Caucasian, and 13% were Asian. Disease
807 characteristics: 94% infiltrating ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32%
808 node negative, and in 11% of patients, nodal status was not assessable due to prior neo-adjuvant
809 chemotherapy. Ninety-six percent (1055/1098) of patients with node-negative disease had high-risk
810 features: among the 1098 patients with node-negative disease, 49% (543) were ER– and PgR–, and
811 47% (512) were ER and/or PgR+ and had at least one of the following high-risk features:
812 pathological tumor size greater than 2 cm, Grade 2–3, or age < 35 years. Prior to randomization,
813 94% of patients had received anthracycline-based chemotherapy regimens.

814 After the definitive DFS results comparing observation to one-year Herceptin treatment were
815 disclosed, a prospectively planned analysis that included comparison of one year versus two years of
816 Herceptin treatment at a median follow-up duration of 8 years was performed. Based on this
817 analysis, extending Herceptin treatment for a duration of two years did not show additional benefit
818 over treatment for one year [Hazard Ratios of two-years Herceptin versus one-year Herceptin
819 treatment in the intent to treat (ITT) population for Disease-Free Survival (DFS) = 0.99 (95% CI:
820 0.87, 1.13), p-value = 0.90 and Overall Survival (OS) = 0.98 (0.83, 1.15); p-value = 0.78].

821 *Study 4*

822 In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only)
823 as determined at a central laboratory. Patients were required to have either node-positive disease, or
824 node-negative disease with at least one of the following high-risk features: ER/PR-negative, tumor
825 size > 2 cm, age < 35 years, or histologic and/or nuclear Grade 2 or 3. Patients with a history of
826 CHF, myocardial infarction, Grade 3 or 4 cardiac arrhythmia, angina requiring medication, clinically
827 significant valvular heart disease, poorly controlled hypertension (diastolic > 100 mm Hg), any T4 or
828 N2, or known N3 or M1 breast cancer were not eligible.

829 Patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by
830 docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus Herceptin
831 (AC-TH), or docetaxel and carboplatin plus Herceptin (TCH). In both the AC-T and AC-TH arms,
832 doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² were administered every 3 weeks for
833 four cycles; docetaxel 100 mg/m² was administered every 3 weeks for four cycles. In the TCH arm,
834 docetaxel 75 mg/m² and carboplatin (at a target AUC of 6 mg/mL/min as a 30- to 60-minute
835 infusion) were administered every 3 weeks for six cycles. Herceptin was administered weekly
836 (initial dose of 4 mg/kg followed by weekly dose of 2 mg/kg) concurrently with either T or TC, and
837 then every 3 weeks (6 mg/kg) as monotherapy for a total of 52 weeks. Radiation therapy, if
838 administered, was initiated after completion of chemotherapy. Patients with ER+ and/or PR+ tumors
839 received hormonal therapy. Disease-Free Survival (DFS) was the main outcome measure.

840 Among the 3222 patients randomized, the median age was 49 (range 22 to 74 years; 6%
841 ≥ 65 years). Disease characteristics included 54% ER+ and/or PR+ and 71% node positive. Prior to
842 randomization, all patients underwent primary surgery for breast cancer.

843 The results for DFS for the integrated analysis of Studies 1 and 2, Study 3, and Study 4 and OS
844 results for the integrated analysis of Studies 1 and 2, and Study 3 are presented in Table 9. For
845 Studies 1 and 2, the duration of DFS following a median follow-up of 2.0 years in the AC \rightarrow TH arm
846 is presented in Figure 4, and the duration of OS after a median follow-up of 8.3 years in the
847 AC \rightarrow TH arm is presented in Figure 5. The duration of DFS for Study 4 is presented in Figure 6.
848 Across all four studies, at the time of definitive DFS analysis, there were insufficient numbers of
849 patients within each of the following subgroups to determine if the treatment effect was different
850 from that of the overall patient population: patients with low tumor grade, patients within specific
851 ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients >65 years of
852 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
853 follow-up [AC \rightarrow TH], the survival rate was estimated to be 86.9% in the AC \rightarrow TH arm and 79.4% in
854 the AC \rightarrow T arm. The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age,
855 hormone receptor status, number of positive lymph nodes, tumor size and grade, and
856 surgery/radiation therapy was consistent with the treatment effect in the overall population. In
857 patients ≤ 50 years of age ($n = 2197$), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in
858 patients > 50 years of age ($n = 1866$), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the
859 subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive)
860 ($n = 2223$), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with
861 hormone receptor-negative disease (ER-negative and PR-negative) ($n = 1830$), the hazard ratio for
862 OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm ($n = 1604$), the
863 hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2
864 cm ($n = 2448$), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80).

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.

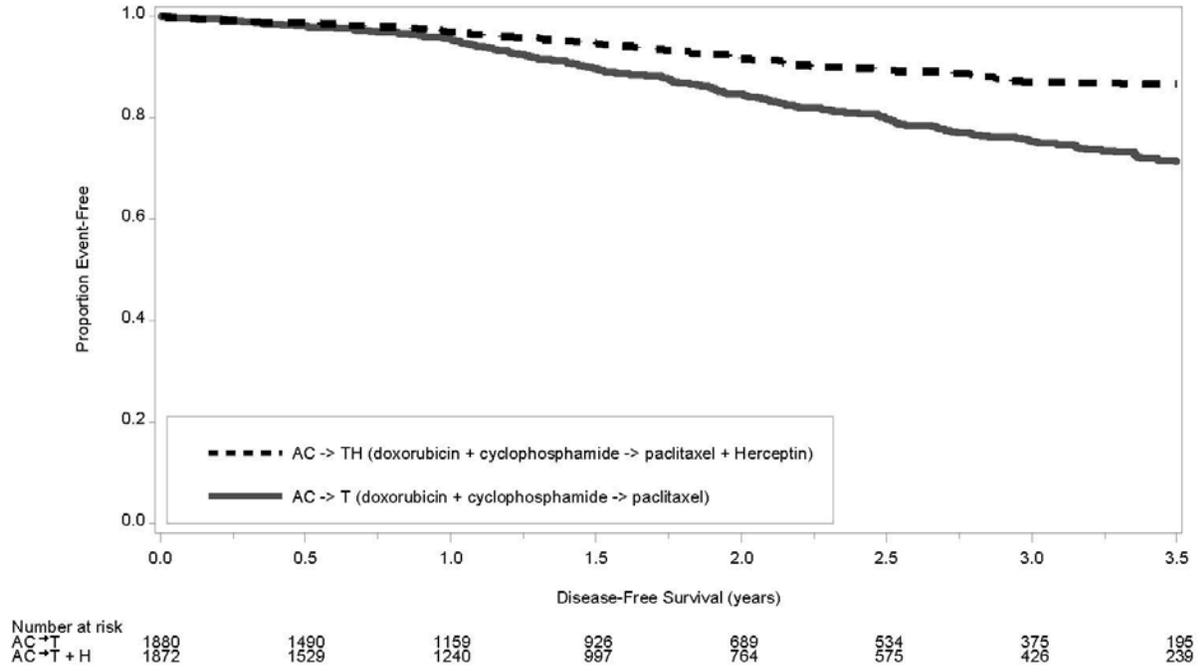
^h NS = non-significant.

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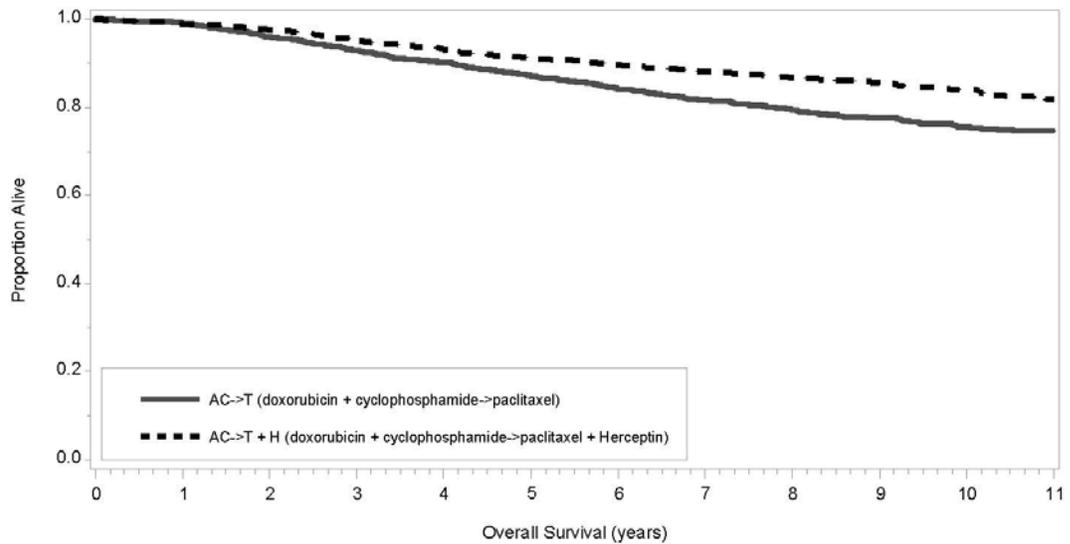
Figure 4
Duration of Disease-Free Survival in
Patients with Adjuvant Treatment of Breast Cancer (Studies 1 and 2)



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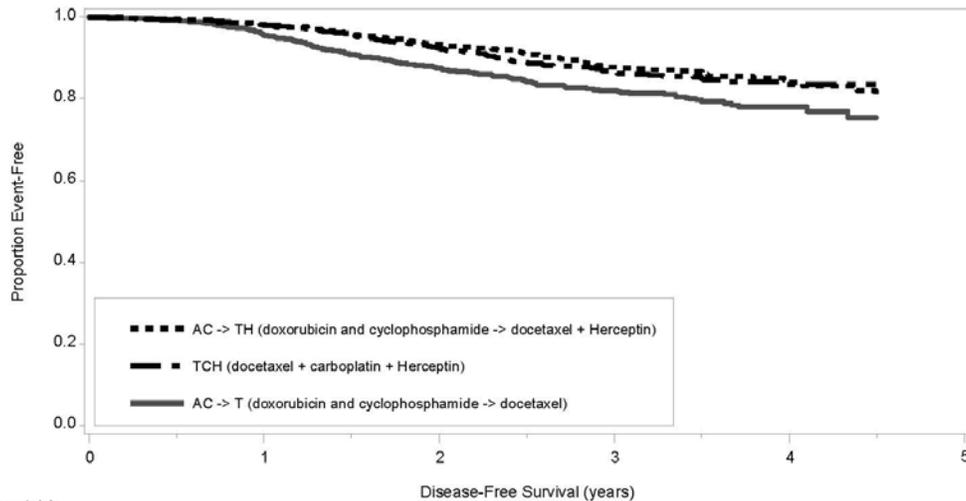
Figure 5
Duration of Overall Survival in Patients with
Adjuvant Treatment of Breast Cancer (Studies 1 and 2)



Number at risk	0	1	2	3	4	5	6	7	8	9	10	11
AC->T	2032	1961	1883	1806	1732	1643	1538	1377	979	630	399	151
AC->T + H	2031	1992	1957	1897	1843	1787	1714	1533	1127	787	485	159

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



Number at risk	0	1	2	3	4	5
AC->T	1073	971	802	417	103	
AC->TH	1074	1023	885	457	128	
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.

878

879 Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were
880 conducted for patients in Studies 2 and 3, where central laboratory testing data were available.
881 The results are shown in Table 10. The number of events in Study 2 was small with the exception of

882 the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions
 883 cannot be drawn regarding efficacy within other subgroups due to the small number of events.
 884 The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the
 885 IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups.
 886

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.

887

14.2 Metastatic Breast Cancer

888 The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were
 889 studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5,
 890 n = 469 patients) and an open-label single agent clinical trial (Study 6, n = 222 patients). Both trials
 891 studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients
 892 were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by
 893 immunohistochemical assessment of tumor tissue performed by a central testing lab.
 894

Previously Untreated Metastatic Breast Cancer (Study 5)

895 Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with
 896 metastatic breast cancer who had not been previously treated with chemotherapy for metastatic
 897 disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+,
 898 or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were
 899 eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or
 900 in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly
 901 doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the
 902 adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m² over 3 hours every 21 days for at
 903 least six cycles); for all other patients, chemotherapy consisted of anthracycline plus
 904 cyclophosphamide (AC: doxorubicin 60 mg/m² or epirubicin 75 mg/m² plus 600 mg/m²
 905 cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to
 906

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

909 Based on the determination by an independent response evaluation committee, the patients
 910 randomized to Herceptin and chemotherapy experienced a significantly longer median time to
 911 disease progression, a higher overall response rate (ORR), and a longer median duration of response
 912 as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin
 913 and chemotherapy also had a longer median survival (see Table 11). These treatment effects were
 914 observed both in patients who received Herceptin plus paclitaxel and in those who received
 915 Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.
 916

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.

917

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

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.

920

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

922 Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial
923 (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following
924 one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had
925 received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for
926 metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue.
927 Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin at
928 2 mg/kg IV.

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

934 **14.3 Metastatic Gastric Cancer**

935 The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine
936 (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or
937 gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial,
938 594 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine
939 (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic
940 vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes
941 vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil).
942 All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients
943 were also required to have adequate cardiac function (e.g., LVEF > 50%).

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

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

951 The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were
 952 Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1;
 953 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these
 954 patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant
 955 therapy, and 2% had received prior radiotherapy.

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

961

Table 13
 Study 7: Overall Survival in ITT Population

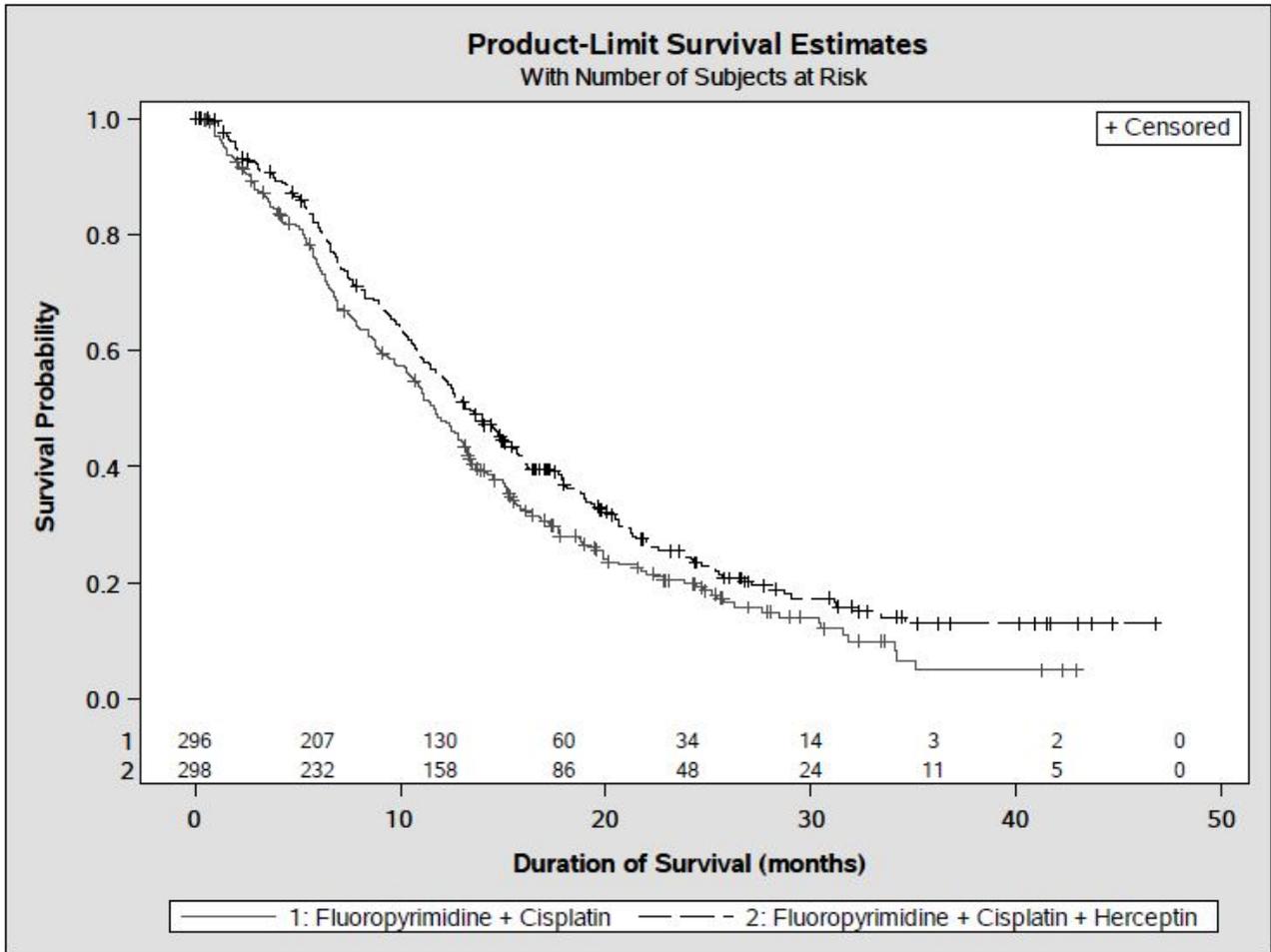
	FC Arm N = 296	FC + H Arm N = 298
<u>Definitive (Second Interim) Overall Survival</u>		
No. Deaths (%)	184 (62.2%)	167 (56.0%)
Median	11.0	13.5
95% CI (mos.)	(9.4, 12.5)	(11.7, 15.7)
Hazard Ratio	0.73	
95% CI	(0.60, 0.91)	
p-value*, two-sided	0.0038	
<u>Updated Overall Survival</u>		
No. Deaths (%)	227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

970

971 **16 HOW SUPPLIED/STORAGE AND HANDLING**

972 **16.1 How Supplied**

973 **420 mg Multiple-dose vial**

974 Herceptin (trastuzumab) for Injection 420 mg/vial is supplied in a multiple-dose vial as a
975 lyophilized sterile powder, under vacuum. Each carton contains one multiple-dose vial of Herceptin
976 and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl
977 alcohol as a preservative.

978 NDC 50242-333-01.

979 **150 mg Single-dose vial**

980 Herceptin (trastuzumab) for Injection 150 mg/vial is supplied in a single-dose vial as a lyophilized
981 sterile powder, under vacuum. Each carton contains one single-dose vial of Herceptin.

982 NDC 50242-132-01.

983 **16.2 Storage**

984 Store Herceptin vials in the refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution.

985

986 **17 PATIENT COUNSELING INFORMATION**

987 **Cardiomyopathy**

- 988 • Advise patients to contact a health care professional immediately for any of the following: new
989 onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face,

990 palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness
991 [see Boxed Warning: Cardiomyopathy].

992

993 Embryo-Fetal Toxicity

- 994 • Advise pregnant women and females of reproductive potential that Herceptin exposure during
995 pregnancy or within 7 months prior to conception can result in fetal harm. Advise female
996 patients to contact their healthcare provider with a known or suspected pregnancy [see Use in
997 *Specific Populations (8.1)*].
- 998 • Advise women who are exposed to Herceptin during pregnancy or who become pregnant within
999 7 months following the last dose of Herceptin that there is a pregnancy exposure registry and a
1000 pregnancy pharmacovigilance program that monitor pregnancy outcomes. Encourage these
1001 patients to enroll in the MotHER Pregnancy Registry and report their pregnancy to Genentech
1002 [see Use in *Specific Populations (8.1)*].
- 1003 • Advise females of reproductive potential to use effective contraception during treatment and for
1004 7 months following the last dose of Herceptin [see Use in *Specific Populations (8.3)*].

1005

HERCEPTIN[®] [trastuzumab]

Manufactured by:

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A Member of the Roche Group

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