

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

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

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

See full prescribing information for complete boxed warning  
**Cardiomyopathy:** Herceptin can result in 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. (2.2, 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 (2.2) | 04/2015 |
| Warnings and Precautions (5.1)  | 04/2015 |
| 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)

**DOSAGE AND ADMINISTRATION**

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

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

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

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 52 weeks, or
  - Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks.
- Metastatic HER2-Overexpressing Breast Cancer (2.1)**
- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.
- Metastatic HER2-Overexpressing Gastric Cancer (2.1)**
- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

**DOSAGE FORMS AND STRENGTHS**

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

**CONTRAINDICATIONS**

- None. (4)

**WARNINGS AND PRECAUTIONS**

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

**ADVERSE REACTIONS**

**Adjuvant Breast Cancer**

- Most common adverse reactions (≥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](http://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: 03/2016

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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 (2.2) 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
- with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

### **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.

### **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.

## 44 2 DOSAGE AND ADMINISTRATION

### 45 2.1 Recommended Doses and Schedules

46 • **Do not administer as an intravenous push or bolus. Do not mix Herceptin with other**  
47 **drugs.**

48 • **Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine.**

#### 49 *Adjuvant Treatment, Breast Cancer:*

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

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

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

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

- 60 • Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
- 61 • Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every  
62 three weeks [*see Dosage and Administration (2.2)*].
- 63 • Extending adjuvant treatment beyond one year is not recommended [*see Adverse Reactions*  
64 (6.1)].

#### 65 *Metastatic Treatment, Breast Cancer:*

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

#### 69 *Metastatic Gastric Cancer:*

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

### 73 2.2 Important Dosing Considerations

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

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

#### 84 *Infusion Reactions*

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

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

89

90 *Cardiomyopathy*

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

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

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

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

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

102 **2.3 Preparation for Administration**

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

105 *Reconstitution*

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

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

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

125 *Dilution*

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

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132 **3 DOSAGE FORMS AND STRENGTHS**

133 440 mg lyophilized powder per multi-use vial.

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135 **4 CONTRAINDICATIONS**

136 None.

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## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cardiomyopathy

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

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

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

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

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

#### *Cardiac Monitoring*

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

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

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

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

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

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

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

<sup>b</sup> Anthracycline (doxorubicin) and cyclophosphamide.

<sup>c</sup> Includes 1 patient with fatal cardiomyopathy and 1 patient with sudden death without documented etiology.

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

179  
180 In Study 3 (one-year Herceptin treatment), at a median follow-up duration of 8 years, the incidence  
181 of severe CHF (NYHA III & IV) was 0.8%, and the rate of mild symptomatic and asymptomatic left  
182 ventricular dysfunction was 4.6%.  
183

**Table 2**  
Incidence of Cardiac Dysfunction<sup>a</sup> in Metastatic Breast Cancer Studies

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

<sup>a</sup> Congestive heart failure or significant asymptomatic decrease in LVEF.

<sup>b</sup> Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

<sup>c</sup> Includes 1 patient with fatal cardiomyopathy.

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

## 188 5.2 Infusion Reactions

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

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

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

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

### 208 **5.3 Embryo-Fetal Toxicity**

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

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

### 219 **5.4 Pulmonary Toxicity**

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

### 226 **5.5 Exacerbation of Chemotherapy-Induced Neutropenia**

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

### 232 **5.6 HER2 Testing**

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

242 Several FDA-approved commercial assays are available to aid in the selection of breast cancer and  
243 metastatic gastric cancer patients for Herceptin therapy. Users should refer to the package inserts of  
244 specific assay kits for information on the Intended Use, and the validation and performance of each

245 assay. Limitations in assay precision make it inadvisable to rely on a single method to rule out  
246 potential Herceptin benefit.

247 Treatment outcomes for adjuvant breast cancer (Studies 2 and 3) and for metastatic breast cancer  
248 (Study 5) as a function of IHC and FISH testing are provided in Tables 10 and 12.

249 Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric  
250 cancer should be performed using FDA-approved tests specifically for gastric cancers due to  
251 differences in gastric vs. breast histopathology, including incomplete membrane staining and more  
252 frequent heterogeneous expression of HER2 seen in gastric cancers. Study 7 demonstrated that gene  
253 amplification and protein overexpression were not as well correlated as with breast cancer.

254 Treatment outcomes for metastatic gastric cancer (Study 7) based on HER2 gene amplification  
255 (FISH) and HER2 protein overexpression (IHC) test results are provided in Table 14.

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## 257 **6 ADVERSE REACTIONS**

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

- 259 • Cardiomyopathy [*see Warnings and Precautions (5.1)*]
- 260 • Infusion Reactions [*see Warnings and Precautions (5.2)*]
- 261 • Embryo-Fetal Toxicity [*see Warnings and Precautions (5.3)*]
- 262 • Pulmonary Toxicity [*see Warnings and Precautions (5.4)*]
- 263 • Exacerbation of Chemotherapy-induced Neutropenia [*see Warnings and Precautions (5.5)*]

264

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

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

### 278 **6.1 Clinical Trials Experience**

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

#### 282 *Adjuvant Breast Cancer Studies*

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

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

291

**Table 3**  
Adverse Reactions for Study 3<sup>a</sup>, All Grades<sup>b</sup>

| Adverse Reaction   | One Year Herceptin<br>(n = 1678) | Observation<br>(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 <sup>c</sup>                         | 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 &amp; 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 &amp; 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<sup>a</sup>, All Grades<sup>b</sup>

| Adverse Reaction               | One Year Herceptin<br>(n = 1678) | Observation<br>(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%)                    |

<sup>a</sup> Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

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

<sup>c</sup> Higher level grouping term.

293

294 In Study 3, a comparison of 3-weekly Herceptin treatment for two years versus one year was also  
295 performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year Herceptin  
296 treatment arm (8.1% versus 4.6% in the one-year Herceptin treatment arm). More patients  
297 experienced at least one adverse reaction of Grade 3 or higher in the 2-year Herceptin treatment arm  
298 (20.4%) compared with the one-year Herceptin treatment arm (16.3%).

299 The safety data from Studies 1 and 2 were obtained from 3655 patients, of whom 2000 received  
300 Herceptin; the median treatment duration was 51 weeks. The median age was 49 years (range:  
301 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian.

302 In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5  
303 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The  
304 following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater  
305 among patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone: fatigue  
306 (29.5% vs. 22.4%), infection (24.0% vs. 12.8%), hot flashes (17.1% vs. 15.0%), anemia (12.3% vs.  
307 6.7%), dyspnea (11.8% vs. 4.6%), rash/desquamation (10.9% vs. 7.6%), leukopenia (10.5% vs.  
308 8.4%), neutropenia (6.4% vs. 4.3%), headache (6.2% vs. 3.8%), pain (5.5% vs. 3.0%), edema (4.7%  
309 vs. 2.7%) and insomnia (4.3% vs. 1.5%). The majority of these events were Grade 2 in severity.

310 In Study 2, data collection was limited to the following investigator-attributed treatment-related  
311 adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic  
312 toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes,  
313 motor neuropathy, sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during  
314 chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of  
315 Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving Herceptin plus  
316 chemotherapy as compared to chemotherapy alone: arthralgia (12.2% vs. 9.1%), nail changes  
317 (11.5% vs. 6.8%), dyspnea (2.4% vs. 0.2%), and diarrhea (2.2% vs. 0%). The majority of these  
318 events were Grade 2 in severity.

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

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

327 *Metastatic Breast Cancer Studies*

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

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

337 Among the 352 patients treated in single agent studies (213 patients from Study 6), the median  
338 age was 50 years (range 28–86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in  
339 other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed  
340 by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months  
341 and ≥ 12 months were 31% and 16%, respectively.  
342

**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 <sup>a</sup><br>n = 352 | Herceptin +<br>Paclitaxel<br>n = 91 | Paclitaxel<br>Alone<br>n = 95 | Herceptin +<br>AC <sup>b</sup><br>n = 143 | AC <sup>b</sup> Alone<br>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%                               |

343

**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 <sup>a</sup><br>n = 352 | Herceptin +<br>Paclitaxel<br>n = 91 | Paclitaxel<br>Alone<br>n = 95 | Herceptin +<br>AC <sup>b</sup><br>n = 143 | AC <sup>b</sup> Alone<br>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 &amp; 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%                               |

<sup>a</sup> Data for Herceptin single agent were from 4 studies, including 213 patients from Study 6.

<sup>b</sup> Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

344

345 *Metastatic Gastric Cancer*

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

349 chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was  
350 administered at 80 mg/m<sup>2</sup> on Day 1 and the fluoropyrimidine was administered as either  
351 capecitabine 1000 mg/m<sup>2</sup> orally twice a day on Days 1–14 or 5-fluorouracil 800 mg/m<sup>2</sup>/day as a  
352 continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day  
353 cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin  
354 infusions administered was eight.  
355

**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<br>(N = 294)<br>N (%) |                   | FC<br>(N = 290)<br>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)             |

356

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

360 *Cardiomyopathy*

361 Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant  
362 treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months  
363 (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and  
364 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  
365 patients with post-AC LVEF evaluation were not permitted to initiate Herceptin following  
366 completion of AC chemotherapy due to cardiac dysfunction (LVEF < LLN or  $\geq 16$  point decline in  
367 LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of  
368 new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and  
369 paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients  
370 receiving one-year Herceptin monotherapy compared to observation in Study 3 (see Table 6,  
371 Figures 1 and 2). The per-patient incidence of new-onset cardiac dysfunction, as measured by  
372 LVEF, remained similar when compared to the analysis performed at a median follow-up of 2.0  
373 years in the AC-TH arm. This analysis also showed evidence of reversibility of left ventricular  
374 dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC-TH group being  
375 asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.  
376

**Table 6<sup>a</sup>**  
Per-patient Incidence of New Onset  
Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

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

<sup>a</sup> 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.

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

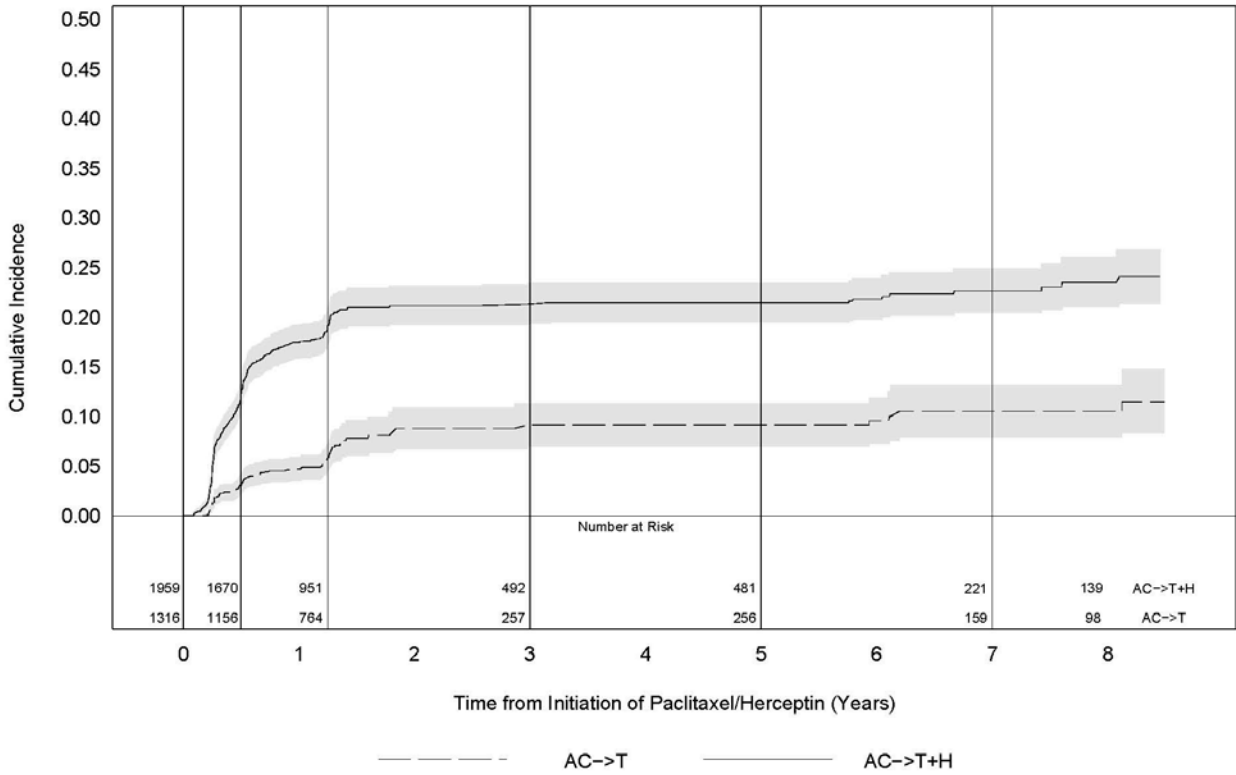
<sup>c</sup> Median duration of follow-up for Studies 1 and 2 combined was 8.3 years in the AC→TH arm.

<sup>d</sup> Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

<sup>e</sup> 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  $\geq 10$  Percentage Points from Baseline and to  
 Below 50% with Death as a Competing Risk Event

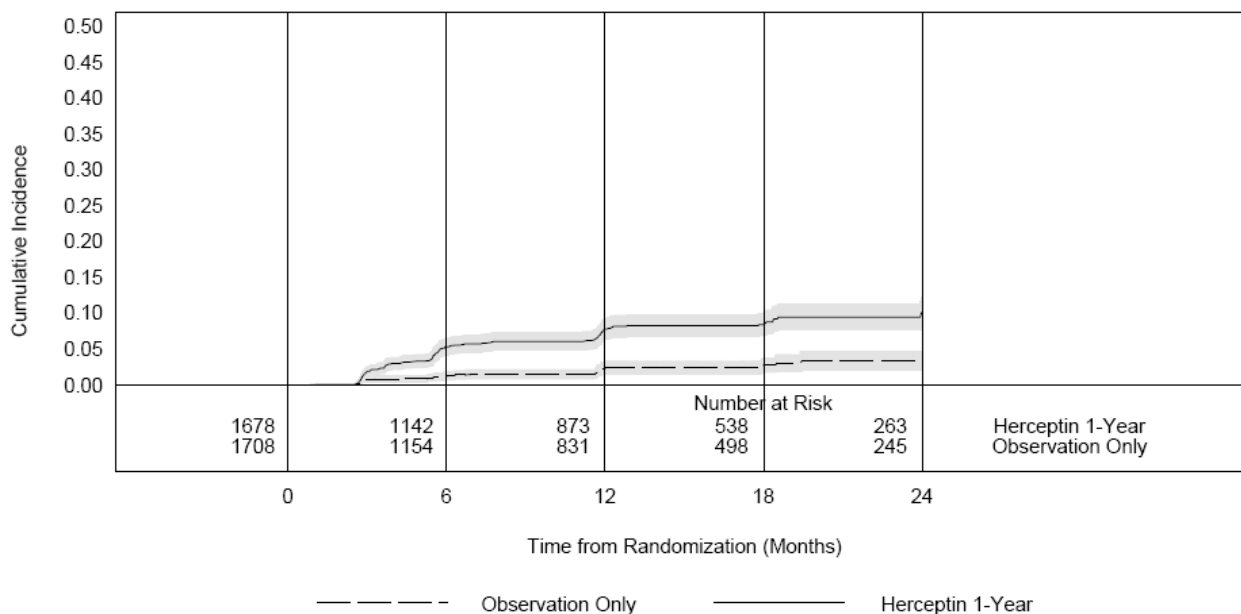


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Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

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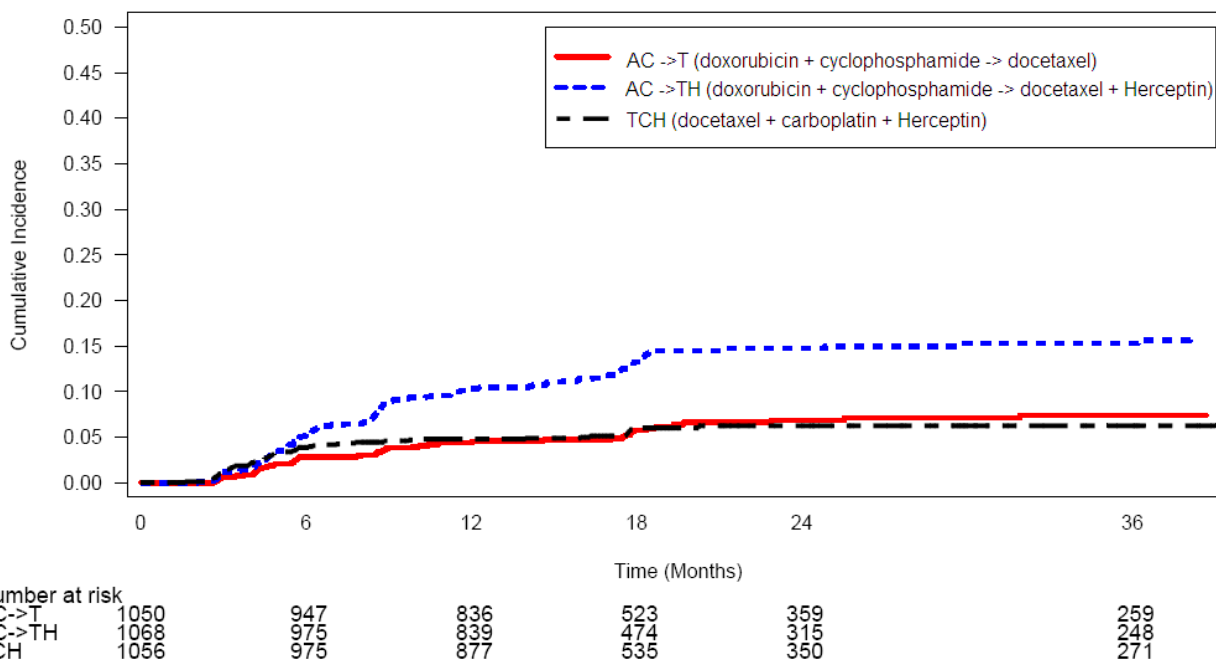
**Figure 2**  
 Study 3: Cumulative Incidence of Time to First LVEF  
 Decline of  $\geq 10$  Percentage Points from Baseline and to  
 Below 50% with Death as a Competing Risk Event



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Time 0 is the date of randomization.

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



397  
 398  
 399

Time 0 is the date of randomization.

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

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

#### 408 *Infusion Reactions*

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

#### 419 *Anemia*

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

#### 428 *Neutropenia*

429 In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTC  
430 Grade 4–5 neutropenia (1.7% vs. 0.8% [Study 2]) and of selected Grade 2–5 neutropenia (6.4% vs.  
431 4.3% [Study 1]) were increased in patients receiving Herceptin and chemotherapy compared with  
432 those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic  
433 breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile  
434 neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination  
435 with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7 (metastatic  
436 gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone arm, the  
437 incidence of NCI-CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile neutropenia  
438 5.1% compared to 2.8%.

#### 439 *Infection*

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

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

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

#### 451 *Pulmonary Toxicity*

##### 452 *Adjuvant Breast Cancer*

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

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

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

##### 465 *Metastatic Breast Cancer*

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

##### 472 *Thrombosis/Embolism*

473 In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher  
474 in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies  
475 (2.6% vs. 1.5% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]).

##### 476 *Diarrhea*

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

##### 487 *Renal Toxicity*

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

493 In the post-marketing setting, rare cases of nephrotic syndrome with pathologic evidence of  
494 glomerulopathy have been reported. The time to onset ranged from 4 months to approximately  
495 18 months from initiation of Herceptin therapy. Pathologic findings included membranous

496 glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications  
497 included volume overload and congestive heart failure.

## 498 **6.2 Immunogenicity**

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

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

## 510 **6.3 Post-Marketing Experience**

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

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

519

## 520 **7 DRUG INTERACTIONS**

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

526

## 527 **8 USE IN SPECIFIC POPULATIONS**

### 528 **8.1 Pregnancy**

#### 529 Pregnancy Exposure Registry and Pharmacovigilance Program

530 There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to  
531 Herceptin during pregnancy. Encourage women who receive Herceptin during pregnancy or within  
532 7 months prior to conception to enroll in the MoTHER Pregnancy Registry by contacting 1-800-690-  
533 6720 or visiting <http://www.motherpregnancyregistry.com/>.

534 In addition, there is a pregnancy pharmacovigilance program for Herceptin. If Herceptin is  
535 administered during pregnancy, or if a patient becomes pregnant while receiving Herceptin or within  
536 7 months following the last dose of Herceptin, health care providers and patients should immediately  
537 report Herceptin exposure to Genentech at 1-888-835-2555.

#### 538 Risk Summary

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

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

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

#### 548 Clinical Considerations

##### 549 *Fetal/Neonatal Adverse Reactions*

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

#### 553 Data

##### 554 *Human Data*

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

##### 561 *Animal Data*

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

## 569 **8.2 Lactation**

### 570 Risk Summary

571 There is no information regarding the presence of trastuzumab in human milk, the effects on the  
572 breastfed infant, or the effects on milk production. Published data suggest human IgG is present in  
573 human milk but does not enter the neonatal and infant circulation in substantial amounts.  
574 Trastuzumab was present in the milk of lactating Cynomolgus monkeys but not associated with  
575 neonatal toxicity [see *Data*]. Consider the developmental and health benefits of breastfeeding along  
576 with the mother's clinical need for Herceptin treatment and any potential adverse effects on the  
577 breastfed child from Herceptin or from the underlying maternal condition. This consideration should  
578 also take into account the trastuzumab wash out period of 7 months [see *Clinical Pharmacology*  
579 *(12.3)*].

### 580 Data

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

587

### 588 **8.3 Females and Males of Reproductive Potential**

#### 589 Pregnancy Testing

590 Verify the pregnancy status of females of reproductive potential prior to the initiation of  
591 Herceptin.

#### 592 Contraception

##### 593 *Females*

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

### 598 **8.4 Pediatric Use**

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

### 600 **8.5 Geriatric Use**

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

611 In Study 7 (metastatic gastric cancer), of the 294 patients treated with Herceptin, 108 (37%) were  
612 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or  
613 effectiveness were observed.

614

## 615 **10 OVERDOSAGE**

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

618

## 619 **11 DESCRIPTION**

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

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

630

## 631 **12 CLINICAL PHARMACOLOGY**

### 632 **12.1 Mechanism of Action**

633 The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa,  
634 which is structurally related to the epidermal growth factor receptor. Herceptin has been shown, in

635 both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress  
636 HER2.

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

## 640 12.2 Pharmacodynamics

### 641 *Cardiac Electrophysiology*

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

## 647 12.3 Pharmacokinetics

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

652 Although the average trastuzumab exposure was higher following the first cycle in breast cancer  
653 patients receiving the three-weekly schedule compared to the weekly schedule of Herceptin, the  
654 average steady-state exposure was essentially the same at both dosages. The average trastuzumab  
655 exposure following the first cycle and at steady state as well as the time to steady state was higher in  
656 breast cancer patients compared to MGC patients at the same dosage; however, the reason for this  
657 exposure difference is unknown. Additional predicted trastuzumab exposure and PK parameters  
658 following the first Herceptin cycle and at steady state exposure are described in Tables 7 and 8,  
659 respectively.

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

664

665

**Table 7**

666 Population Predicted Cycle 1 PK Exposures (Median with 5<sup>th</sup> – 95<sup>th</sup> Percentiles) in Breast Cancer  
667 and MGC Patients

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

668

669  
670  
671

**Table 8**  
Population Predicted Steady State PK Exposures (Median with 5<sup>th</sup> - 95<sup>th</sup> Percentiles) in Breast Cancer and MGC Patients

| Schedule              | Primary tumor type | N    | C <sub>min,ss</sub> <sup>a</sup> (µg/mL) | C <sub>max,ss</sub> <sup>b</sup> (µg/mL) | AUC <sub>ss, 0-21 days</sub> (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<br>(5 - 115)                        | 179<br>(107 - 309)                       | 1794<br>(673 - 3618)                     | 12                          | 0.173 - 0.283                          |
|                       | MGC                | 274  | 32.9<br>(6.1 - 88.9)                     | 131<br>(72.5 - 251)                      | 1338<br>(557 - 2875)                     | 9                           | 0.189 - 0.337                          |
| 4 mg/kg + 2 mg/kg qw  | Breast cancer      | 1195 | 66.1<br>(14.9 - 142)                     | 109<br>(51.0 - 209)                      | 1765<br>(647 - 3578)                     | 12                          | 0.201 - 0.244                          |

672 <sup>a</sup> Steady-state trough serum concentration of trastuzumab  
673 <sup>b</sup> Maximum steady-state serum concentration of trastuzumab  
674

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

681 *Drug Interaction Studies:*  
682 There have been no formal drug interaction studies performed with Herceptin in humans. Clinically  
683 significant interactions between Herceptin and concomitant medications used in clinical trials have  
684 not been observed.

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

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

692 *Cisplatin and capecitabine:* In a drug interaction substudy conducted in patients in Study 7, the  
693 pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered  
694 in combination with Herceptin.  
695

## 696 13 NONCLINICAL TOXICOLOGY

### 697 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

698 Herceptin has not been tested for carcinogenic potential.

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

704 A fertility study was conducted in female Cynomolgus monkeys at doses up to 25 times the  
705 weekly recommended human dose of 2 mg/kg of trastuzumab and has revealed no evidence of  
706 impaired fertility, as measured by menstrual cycle duration and female sex hormone levels.  
707

## 708 **14 CLINICAL STUDIES**

### 709 **14.1 Adjuvant Breast Cancer**

710 The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2  
711 overexpressing breast cancer were evaluated in an integrated analysis of two randomized,  
712 open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final  
713 overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of  
714 3386 women at definitive Disease-Free Survival analysis for one-year Herceptin treatment versus  
715 observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4).

#### 716 *Studies 1 and 2*

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

723 Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by  
724 paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin).  
725 In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide  
726 600 mg/m<sup>2</sup>. Paclitaxel was administered either weekly (80 mg/m<sup>2</sup>) or every 3 weeks (175 mg/m<sup>2</sup>)  
727 for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in  
728 Study 2. Herceptin was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a  
729 dose of 2 mg/kg weekly for a total of 52 weeks. Herceptin treatment was permanently discontinued  
730 in patients who developed congestive heart failure, or persistent/recurrent LVEF decline [*see*  
731 *Dosage and Administration* (2.2)]. Radiation therapy, if administered, was initiated after the  
732 completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy.  
733 The primary endpoint of the combined efficacy analysis was Disease-Free Survival (DFS), defined  
734 as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second  
735 primary cancer, or death. The secondary endpoint was overall survival (OS).

736 A total of 3752 patients were included in the joint efficacy analysis of the primary endpoint of  
737 DFS following a median follow-up of 2.0 years in the AC→paclitaxel + Herceptin arm. The  
738 pre-planned final OS analysis from the joint analysis included 4063 patients and was performed  
739 when 707 deaths had occurred after a median follow-up of 8.3 years in the AC→paclitaxel +  
740 Herceptin arm. The data from both arms in Study 1 and two of the three study arms in Study 2 were  
741 pooled for efficacy analyses. The patients included in the primary DFS analysis had a median age of  
742 49 years (range, 22–80 years; 6% > 65 years), 84% were white, 7% black, 4% Hispanic, and 4%  
743 Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1,  
744 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or  
745 PR+ tumors. Similar demographic and baseline characteristics were reported for the efficacy  
746 evaluable population, after 8.3 years of median follow-up in the AC→paclitaxel + Herceptin arm.

#### 747 *Study 3*

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

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

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

763 A protocol specified interim efficacy analysis comparing one-year Herceptin treatment to  
764 observation was performed at a median follow-up duration of 12.6 months in the Herceptin arm and  
765 formed the basis for the definitive DFS results from this study. Among the 3386 patients  
766 randomized to the observation (n = 1693) and Herceptin one-year (n = 1693) treatment arms, the  
767 median age was 49 years (range 21–80), 83% were Caucasian, and 13% were Asian. Disease  
768 characteristics: 94% infiltrating ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32%  
769 node negative, and in 11% of patients, nodal status was not assessable due to prior neo-adjuvant  
770 chemotherapy. Ninety-six percent (1055/1098) of patients with node-negative disease had high-risk  
771 features: among the 1098 patients with node-negative disease, 49% (543) were ER– and PgR–, and  
772 47% (512) were ER and/or PgR + and had at least one of the following high-risk features:  
773 pathological tumor size greater than 2 cm, Grade 2–3, or age < 35 years. Prior to randomization,  
774 94% of patients had received anthracycline-based chemotherapy regimens.

775 After the definitive DFS results comparing observation to one-year Herceptin treatment were  
776 disclosed, a prospectively planned analysis that included comparison of one year versus two years of  
777 Herceptin treatment at a median follow-up duration of 8 years was performed. Based on this  
778 analysis, extending Herceptin treatment for a duration of two years did not show additional benefit  
779 over treatment for one year [Hazard Ratios of two-years Herceptin versus one-year Herceptin  
780 treatment in the intent to treat (ITT) population for Disease-Free Survival (DFS) = 0.99 (95% CI:  
781 0.87, 1.13), p-value = 0.90 and Overall Survival (OS) = 0.98 (0.83, 1.15); p-value = 0.78].

#### 782 *Study 4*

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

790 Patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by  
791 docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus Herceptin  
792 (AC-TH), or docetaxel and carboplatin plus Herceptin (TCH). In both the AC-T and AC-TH arms,  
793 doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup> were administered every 3 weeks for  
794 four cycles; docetaxel 100 mg/m<sup>2</sup> was administered every 3 weeks for four cycles. In the TCH arm,  
795 docetaxel 75 mg/m<sup>2</sup> and carboplatin (at a target AUC of 6 mg/mL/min as a 30- to 60-minute  
796 infusion) were administered every 3 weeks for six cycles. Herceptin was administered weekly  
797 (initial dose of 4 mg/kg followed by weekly dose of 2 mg/kg) concurrently with either T or TC, and  
798 then every 3 weeks (6 mg/kg) as monotherapy for a total of 52 weeks. Radiation therapy, if  
799 administered, was initiated after completion of chemotherapy. Patients with ER+ and/or PR+ tumors  
800 received hormonal therapy. Disease-Free Survival (DFS) was the main outcome measure.

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

804 The results for DFS for the integrated analysis of Studies 1 and 2, Study 3, and Study 4 and OS  
805 results for the integrated analysis of Studies 1 and 2, and Study 3 are presented in Table 9. For  
806 Studies 1 and 2, the duration of DFS following a median follow-up of 2.0 years in the AC $\rightarrow$ TH arm  
807 is presented in Figure 4, and the duration of OS after a median follow-up of 8.3 years in the  
808 AC $\rightarrow$ TH arm is presented in Figure 5. The duration of DFS for Study 4 is presented in Figure 6.  
809 Across all four studies, at the time of definitive DFS analysis, there were insufficient numbers of  
810 patients within each of the following subgroups to determine if the treatment effect was different  
811 from that of the overall patient population: patients with low tumor grade, patients within specific  
812 ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients  $>65$  years of  
813 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  
814 follow-up [AC $\rightarrow$ TH], the survival rate was estimated to be 86.9% in the AC $\rightarrow$ TH arm and 79.4% in  
815 the AC $\rightarrow$ T arm. The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age,  
816 hormone receptor status, number of positive lymph nodes, tumor size and grade, and  
817 surgery/radiation therapy was consistent with the treatment effect in the overall population. In  
818 patients  $\leq 50$  years of age ( $n = 2197$ ), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in  
819 patients  $> 50$  years of age ( $n = 1866$ ), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the  
820 subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive)  
821 ( $n = 2223$ ), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with  
822 hormone receptor-negative disease (ER-negative and PR-negative) ( $n = 1830$ ), the hazard ratio for  
823 OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size  $\leq 2$  cm ( $n = 1604$ ), the  
824 hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size  $> 2$   
825 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<br>events    | DFS Hazard<br>ratio<br>(95% CI)<br>p-value                     | Deaths<br>(OS events) | OS Hazard ratio<br>p-value                                     |
|---|------------------|--|-----------------------|--|
| <b>Studies 1 + 2<sup>a</sup></b>                            |                  |  |                       |  |
| AC→TH<br>(n = 1872) <sup>b</sup><br>(n = 2031) <sup>c</sup> | 133 <sup>b</sup> | 0.48 <sup>b,d</sup><br>(0.39, 0.59)<br>p < 0.0001 <sup>e</sup> | 289 <sup>c</sup>      | 0.64 <sup>c,d</sup><br>(0.55, 0.74)<br>p < 0.0001 <sup>e</sup> |
| AC→T<br>(n = 1880) <sup>b</sup><br>(n = 2032) <sup>c</sup>  | 261 <sup>b</sup> |  | 418 <sup>c</sup>      |  |
| <b>Study 3<sup>f</sup></b>                                  |                  |  |                       |  |
| Chemo→<br>Herceptin<br>(n = 1693)                           | 127              | 0.54<br>(0.44, 0.67)<br>p < 0.0001 <sup>g</sup>                | 31                    | 0.75<br>p = NS <sup>h</sup>                                    |
| Chemo→<br>Observation<br>(n = 1693)                         | 219              |  | 40                    |  |
| <b>Study 4<sup>i</sup></b>                                  |                  |  |                       |  |
| TCH<br>(n = 1075)   | 134              | 0.67<br>(0.54 – 0.84)<br>p = 0.0006 <sup>e,j</sup>             | 56                    |  |
| AC→TH<br>(n = 1074)   | 121              | 0.60<br>(0.48 – 0.76)<br>p < 0.0001 <sup>e,i</sup>             | 49                    |  |
| AC→T<br>(n = 1073)  | 180              |  | 80                    |  |

CI = confidence interval.

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

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

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

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

<sup>e</sup> stratified log-rank test.

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

<sup>g</sup> log-rank test.

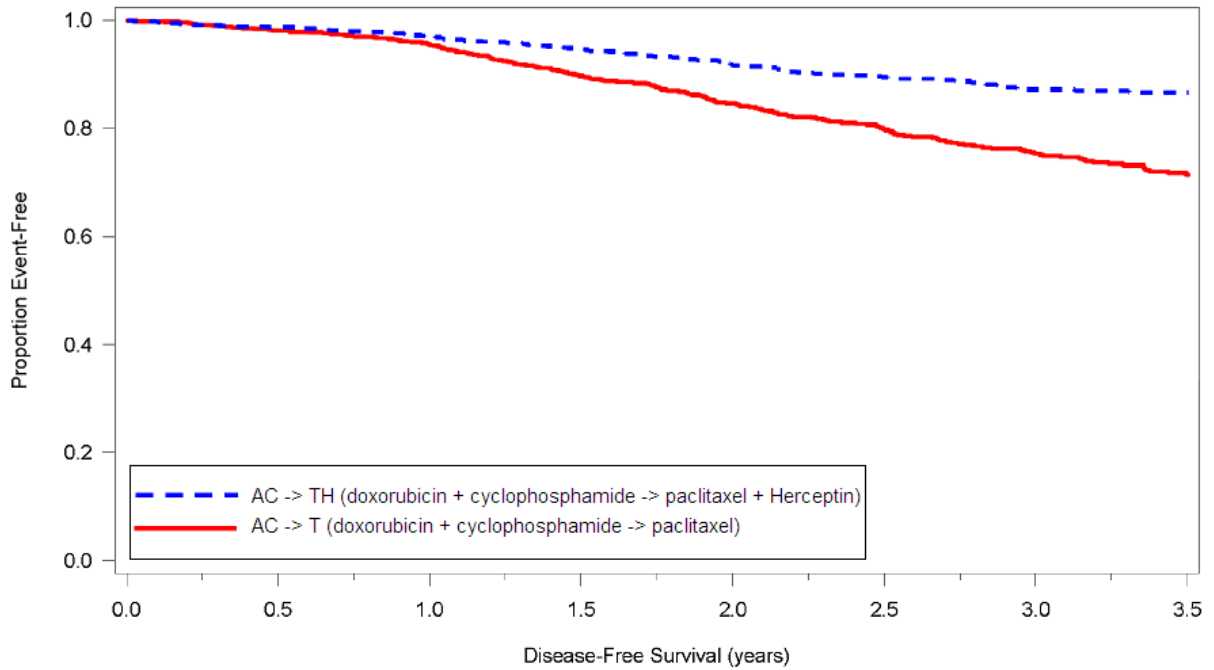
<sup>h</sup> NS = non-significant.

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

<sup>j</sup> A two-sided alpha level of 0.025 for each comparison.

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

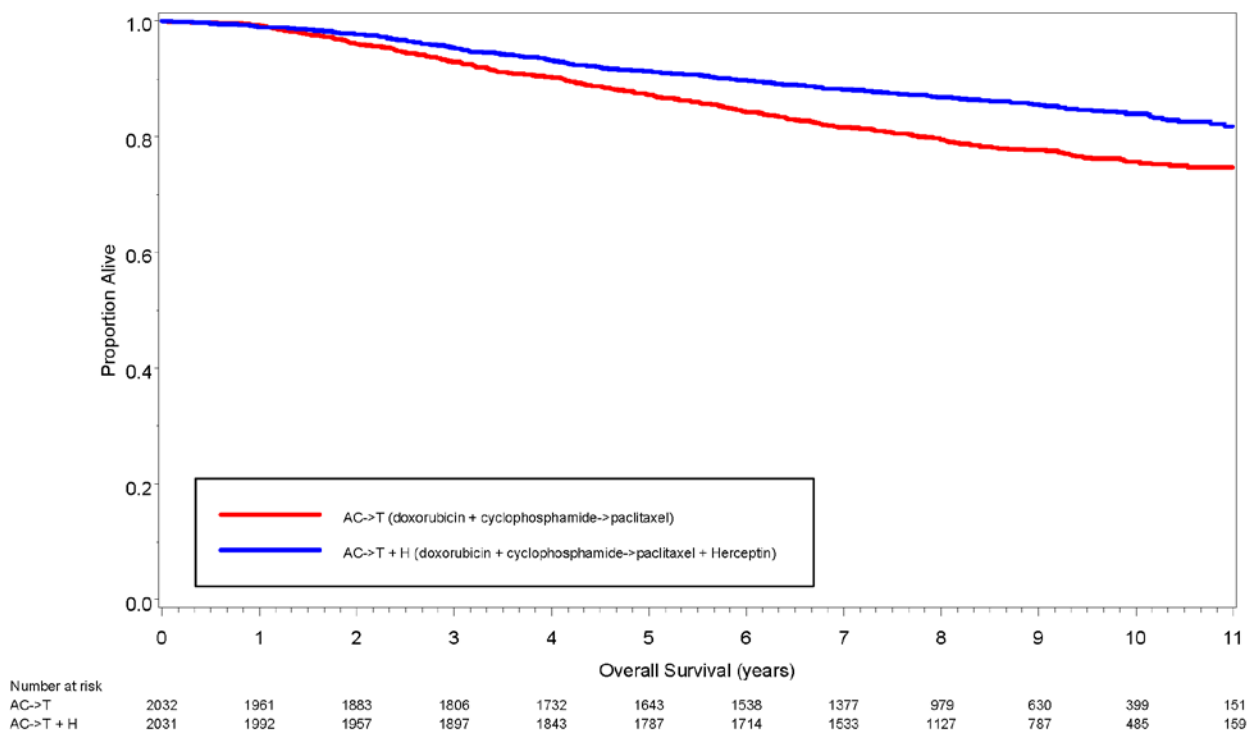


| Number at risk |      | 0.0  | 0.5  | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 3.5 |
|----------------|------|------|------|-----|-----|-----|-----|-----|-----|
| AC -> T        | 1880 | 1490 | 1159 | 926 | 689 | 534 | 375 | 195 |     |
| AC -> T + H    | 1872 | 1529 | 1240 | 997 | 764 | 575 | 426 | 239 |     |

830  
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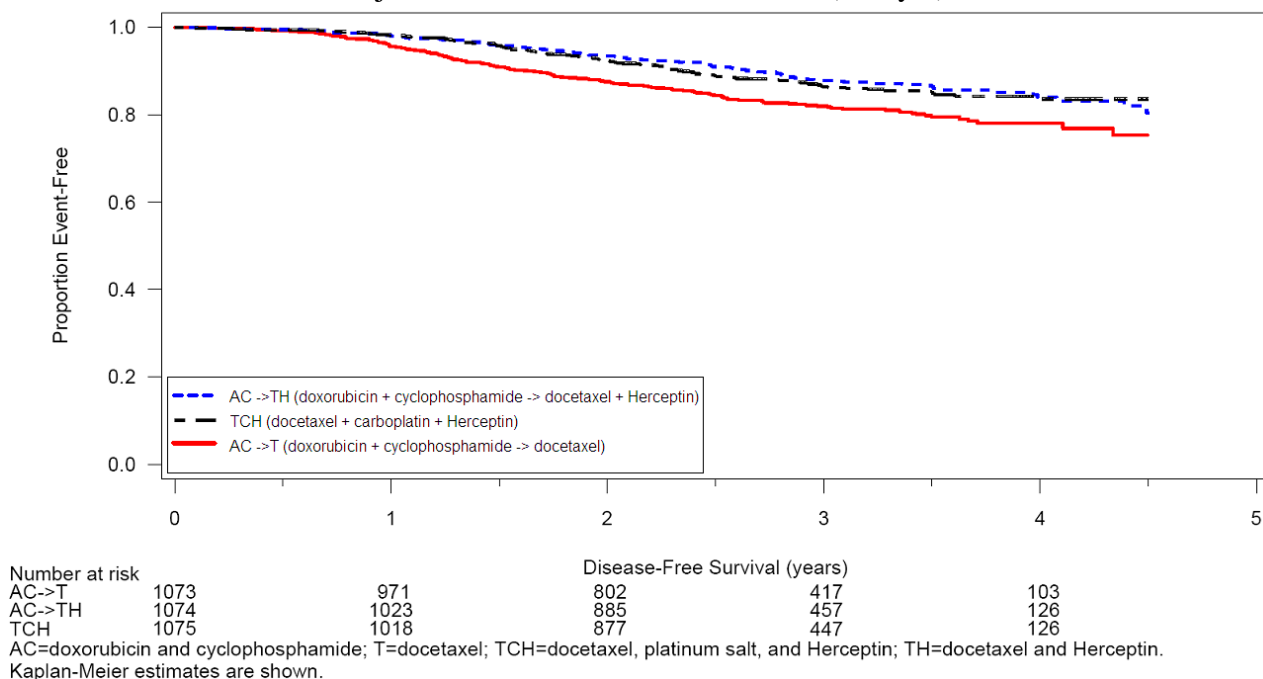
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**Figure 5**  
 Duration of Overall Survival in Patients with  
 Adjuvant Treatment of Breast Cancer (Studies 1 and 2)



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



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

843 the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions  
844 cannot be drawn regarding efficacy within other subgroups due to the small number of events.  
845 The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the  
846 IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups.  
847

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

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

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

<sup>b</sup> All cases in this category in Study 3 were IHC 2+.

<sup>c</sup> Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

848

## 849 **14.2 Metastatic Breast Cancer**

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

### 856 *Previously Untreated Metastatic Breast Cancer (Study 5)*

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

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

870 Based upon the determination by an independent response evaluation committee the patients  
871 randomized to Herceptin and chemotherapy experienced a significantly longer median time to  
872 disease progression, a higher overall response rate (ORR), and a longer median duration of response,  
873 as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin  
874 and chemotherapy also had a longer median survival (see Table 11). These treatment effects were  
875 observed both in patients who received Herceptin plus paclitaxel and in those who received  
876 Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.  
877

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

|   | Combined Results                                  |                                    | Paclitaxel Subgroup                   |                        | AC Subgroup                                 |                 |
|---|---|------------------------------------|---------------------------------------|------------------------|---|-----------------|
|   | Herceptin +<br>All Chemo-<br>therapy<br>(n = 235) | All Chemo-<br>therapy<br>(n = 234) | Herceptin +<br>Paclitaxel<br>(n = 92) | Paclitaxel<br>(n = 96) | Herceptin +<br>AC <sup>a</sup><br>(n = 143) | AC<br>(n = 138) |
| <b><u>Primary Endpoint</u></b>                                      |   |                                    |                                       |                        |   |                 |
| <u>Median</u><br><u>TTP(mos)<sup>b,c</sup></u>                      | 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 <sup>d</sup>  | < 0.0001  |                                    | < 0.0001                              |                        | 0.002                                       |                 |
| <b><u>Secondary Endpoints</u></b>                                   |   |                                    |                                       |                        |   |                 |
| <u>Overall</u><br><u>Response</u><br><u>Rate<sup>b</sup></u>        | 45  | 29                                 | 38                                    | 15                     | 50  | 38              |
| 95% CI  | 39, 51  | 23, 35                             | 28, 48                                | 8, 22                  | 42, 58                                      | 30, 46          |
| p-value <sup>e</sup>  | < 0.001   |                                    | < 0.001                               |                        | 0.10  |                 |
| <u>Median Resp</u><br><u>Duration</u><br><u>(mos)<sup>b,c</sup></u> | 8.3   | 5.8                                | 8.3                                   | 4.3                    | 8.4   | 6.4             |
| 25%, 75%<br>Quartile  | 6, 15   | 4, 8                               | 5, 11                                 | 4, 7                   | 6, 15                                       | 4, 8            |
| <u>Med Survival</u><br><u>(mos)<sup>c</sup></u>                     | 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 <sup>d</sup>  | 0.05  |                                    | 0.17                                  |                        | 0.16  |                 |

<sup>a</sup> AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

<sup>b</sup> Assessed by an independent Response Evaluation Committee.

<sup>c</sup> Kaplan-Meier Estimate.

<sup>d</sup> log-rank test.

<sup>e</sup>  $\chi^2$ -test.

878  
879 Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients  
880 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 <sup>b</sup> for Time to Disease Progression (95% CI) | Relative Risk <sup>b</sup> for Mortality (95% CI) |
|-----------------------|------------------------|---|---|
| CTA 2+ or 3+          | 469                    | 0.49 (0.40, 0.61)   | 0.80 (0.64, 1.00)                                 |
| FISH (+) <sup>a</sup> | 325                    | 0.44 (0.34, 0.57)   | 0.70 (0.53, 0.91)                                 |
| FISH (-) <sup>a</sup> | 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)                                 |

<sup>a</sup> FISH testing results were available for 451 of the 469 patients enrolled on study.

<sup>b</sup> The relative risk represents the risk of progression or death in the Herceptin plus chemotherapy arm versus the chemotherapy arm.

881

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

883 Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial  
884 (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following  
885 one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had  
886 received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for  
887 metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue.  
888 Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin at  
889 2 mg/kg IV.

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

895 **14.3 Metastatic Gastric Cancer**

896 The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine  
897 (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or  
898 gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial,  
899 594 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine  
900 (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic  
901 vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes  
902 vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil).  
903 All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients  
904 were also required to have adequate cardiac function (e.g., LVEF > 50%).

905 On the Herceptin-containing arm, Herceptin was administered as an IV infusion at an initial dose  
906 of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms  
907 cisplatin was administered at a dose of 80 mg/m<sup>2</sup> Day 1 every 3 weeks for 6 cycles as a 2 hour IV

908 infusion. On both study arms capecitabine was administered at 1000 mg/m<sup>2</sup> dose orally twice daily  
909 (total daily dose 2000 mg/m<sup>2</sup>) for 14 days of each 21 day cycle for 6 cycles. Alternatively,  
910 continuous intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m<sup>2</sup>/day  
911 from Day 1 through Day 5 every three weeks for 6 cycles.

912 The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were  
913 Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1;  
914 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these  
915 patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant  
916 therapy, and 2% had received prior radiotherapy.

917 The main outcome measure of Study 7 was overall survival (OS), analyzed by the unstratified log-  
918 rank test. The final OS analysis based on 351 deaths was statistically significant (nominal  
919 significance level of 0.0193). An updated OS analysis was conducted at one year after the final  
920 analysis. The efficacy results of both the final and the updated analyses are summarized in Table 13  
921 and Figure 7.  
922

**Table 13**  
Study 7: Overall Survival in ITT Population

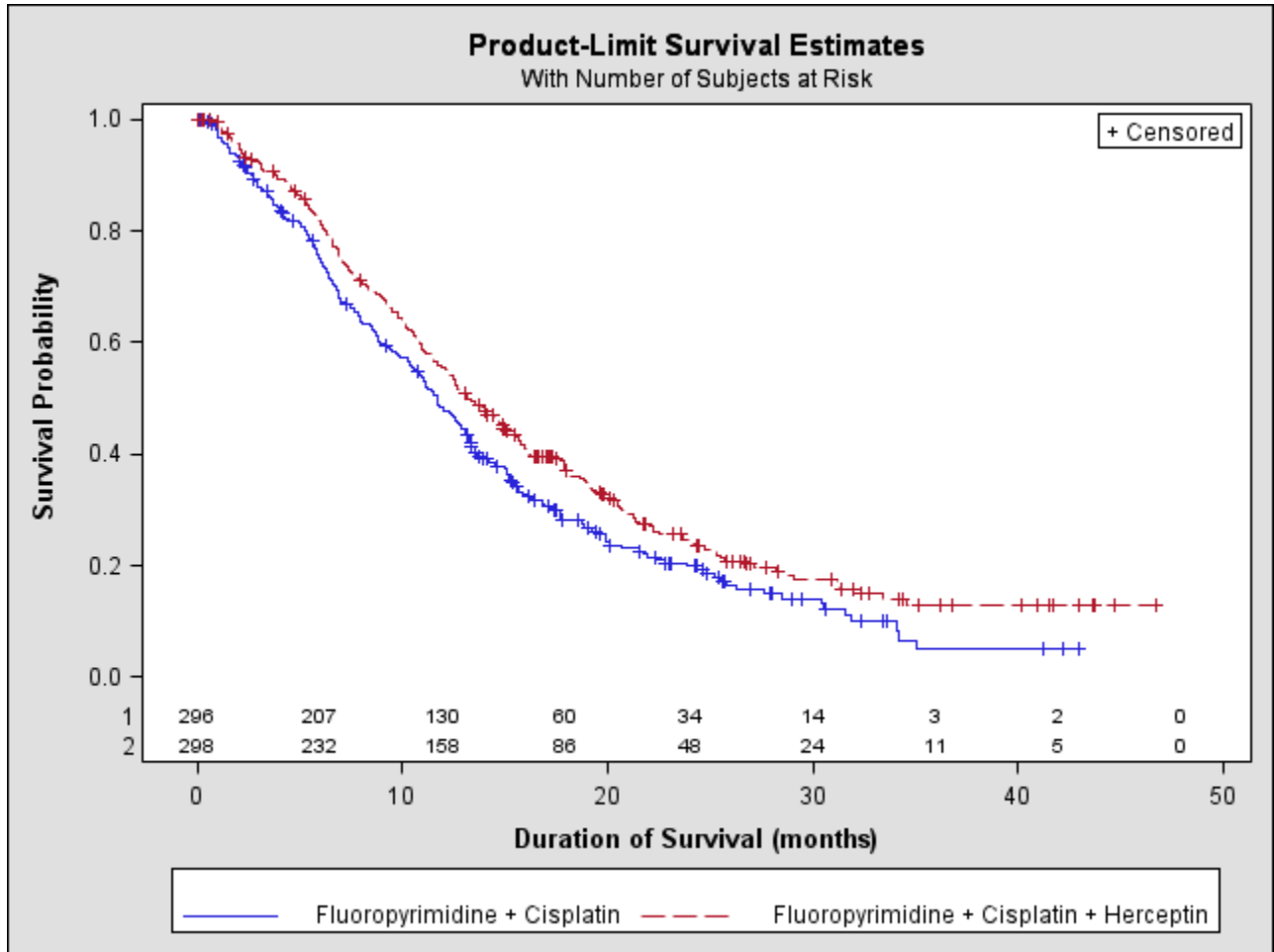
|   | FC Arm<br>N = 296 | FC + H Arm<br>N = 298 |
|---|-------------------|-----------------------|
| <u>Definitive (Second Interim) Overall Survival</u> |                   |                       |
| No. Deaths (%)                                      | 184 (62.2%)       | 167 (56.0%)           |
| 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<br>(N = 296) <sup>a</sup> | FC+H<br>(N = 298) <sup>b</sup> |
|--|------------------------------|--------------------------------|
| <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+<sup>c</sup> 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)            |                                |

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

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

<sup>c</sup> 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+.

931

## 932 16 HOW SUPPLIED/STORAGE AND HANDLING

### 933 16.1 How Supplied

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

### 938 16.2 Stability and Storage

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

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

- 948
- 949 **17 PATIENT COUNSELING INFORMATION**
- 950 **Cardiomyopathy**
- 951 • Advise patients to contact a health care professional immediately for any of the following: new
- 952 onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face,
- 953 palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness
- 954 [*see Boxed Warning: Cardiomyopathy*].
- 955
- 956 **Embryo-Fetal Toxicity**
- 957 • Advise pregnant women and females of reproductive potential that Herceptin exposure during
- 958 pregnancy or within 7 months prior to conception can result in fetal harm. Advise female
- 959 patients to contact their healthcare provider with a known or suspected pregnancy [*see Use in*
- 960 *Specific Populations (8.1)*].
- 961 • Advise women who are exposed to Herceptin during pregnancy or who become pregnant within
- 962 7 months following the last dose of Herceptin that there is a pregnancy exposure registry and a
- 963 pregnancy pharmacovigilance program that monitor pregnancy outcomes. Encourage these
- 964 patients to enroll in the MoHER Pregnancy Registry and report their pregnancy to Genentech
- 965 [*see Use in Specific Populations (8.1)*].
- 966 • Advise females of reproductive potential to use effective contraception during treatment and for
- 967 7 months following the last dose of Herceptin [*see Use in Specific Populations (8.3)*].
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**HERCEPTIN<sup>®</sup> [trastuzumab]**

Manufactured by:

**Genentech, Inc.**

A Member of the Roche Group

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