

### 1.14.1.3 Final Labeling Text

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

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

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

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

#### RECENT MAJOR CHANGES

Indications and Usage, Metastatic Gastric Cancer (1.3)	10/2010
Dosage and Administration (2.1)	10/2010
Warnings and Precautions, Embryo-Fetal Toxicity (5.3)	10/2010
Warnings and Precautions, HER2 Testing (5.6)	10/2010

#### 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).

#### 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

- Cardiomyopathy (5.1, 6.1)
- Infusion Reactions (5.2, 6.1)
- Embryo-fetal Toxicity. Pregnancy registry available (1-800-690-6720) (5.3, 8.1)
- Pulmonary Toxicity (5.4, 6.1)
- 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)

#### USE IN SPECIFIC POPULATIONS

Nursing Mothers: Discontinue nursing or discontinue Herceptin. (8.3)

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).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2010

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\* Sections or subsections omitted from the Full Prescribing Information are not listed.

## **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 Warnings and Precautions (5.1) and Dosage and Administration (2.2)]

#### **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. [see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]

## **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.

43 **2 DOSAGE AND ADMINISTRATION**

44 **2.1 Recommended Doses and Schedules**

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

46 *Adjuvant Treatment, Breast Cancer:*

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

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

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

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

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

60 [see *Dose Modifications (2.2)*]

61 *Metastatic Treatment, Breast Cancer:*

- 62 • Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as  
63 a 90 minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as  
64 30 minute intravenous infusions until disease progression.

65 *Metastatic Gastric Cancer*

- 66 • Administer Herceptin at an initial dose of 8 mg/kg as a 90 minute intravenous infusion  
67 followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30-90 minutes every  
68 three weeks until disease progression [see *Dose Modifications (2.2)*].

69 **2.2 Dose Modifications**

70 *Infusion Reactions*

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

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

75 *Cardiomyopathy*

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

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

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

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

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

87 **2.3 Preparation for Administration**

88 *Reconstitution*

89 Reconstitute each 440 mg vial of Herceptin with 20 mL of Bacteriostatic Water for Injection  
90 (BWFBI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution  
91 containing 21 mg/mL trastuzumab. In patients with known hypersensitivity to benzyl alcohol,  
92 reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single  
93 use solution.

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

- 95 • Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the  
96 lyophilized cake of Herceptin. The stream of diluent should be directed into the lyophilized  
97 cake.
- 98 • Swirl the vial gently to aid reconstitution. **DO NOT SHAKE.**
- 99 • Slight foaming of the product may be present upon reconstitution. Allow the vial to stand  
100 undisturbed for approximately 5 minutes.
- 101 • Parenteral drug products should be inspected visually for particulate matter and discoloration  
102 prior to administration, whenever solution and container permit. Inspect visually for  
103 particulates and discoloration. The solution should be free of visible particulates, clear to  
104 slightly opalescent and colorless to pale yellow.
- 105 • Store reconstituted Herceptin at 2–8°C; discard unused Herceptin after 28 days. If Herceptin  
106 is reconstituted with SWFI without preservative, use immediately and discard any unused  
107 portion.

#### 108 *Dilution*

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

### 115 **3 DOSAGE FORMS AND STRENGTHS**

116 440 mg lyophilized powder per multi-use vial.

### 118 **4 CONTRAINDICATIONS**

119 None.

### 121 **5 WARNINGS AND PRECAUTIONS**

#### 122 **5.1 Cardiomyopathy**

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

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

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

#### 135 *Cardiac Monitoring*

136 Conduct thorough cardiac assessment, including history, physical examination, and determination  
 137 of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:  
 138 • Baseline LVEF measurement immediately prior to initiation of Herceptin  
 139 • LVEF measurements every 3 months during and upon completion of Herceptin  
 140 • Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left  
 141 ventricular cardiac dysfunction [*see Dosage and Administration (2.2)*]  
 142 • LVEF measurements every 6 months for at least 2 years following completion of Herceptin as  
 143 a component of adjuvant therapy.

144 In Study 1, 16% (136/844) of patients discontinued Herceptin due to clinical evidence of myocardial  
 145 dysfunction or significant decline in LVEF. In Study 3, the number of patients who discontinued  
 146 Herceptin due to cardiac toxicity was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) patients  
 147 in the TCH arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and  
 148 5.7% (61/1068) patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during  
 149 the monotherapy phase) discontinued Herceptin due to cardiac toxicity.

150 Among 32 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive  
 151 heart failure, one patient died of cardiomyopathy and all other patients were receiving cardiac  
 152 medication at last follow-up. Approximately half of the surviving patients had recovery to a normal  
 153 LVEF (defined as  $\geq 50\%$ ) on continuing medical management at the time of last follow-up.  
 154 Incidence of congestive heart failure is presented in Table 1. The safety of continuation or  
 155 resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has  
 156 not been studied.  
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**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	2% (32/1677)	0.4% (7/1600)
3	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> Includes 1 patient with fatal cardiomyopathy.

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

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**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 (AC) <sup>b</sup>	Cardiac Dysfunction	28%	7%	19%	3%
5 (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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In Study 4, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the Herceptin containing regimens: (AC-TH: 0.3% (3/1068) and TCH 0.2% (2/1056)) as compared to none in AC-T.

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## 5.2 Infusion Reactions

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

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

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

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

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## 5.3 Embryo-Fetal Toxicity

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Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise women of the potential hazard to the fetus resulting from Herceptin exposure during pregnancy and provide contraception counseling to women of childbearing potential. [see *Use in Specific Populations (8.1)*, *Patient Counseling Information (17)* ].

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## 5.4 Pulmonary Toxicity

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

## 5.5 Exacerbation of Chemotherapy-Induced Neutropenia

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

## 5.6 HER2 Testing

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

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

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

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

Treatment outcomes for metastatic gastric cancer (Study 7), based on HER2 gene amplification (FISH) and HER2 protein overexpression (IHC) test results are provided in [Table 12](#).

## 6 ADVERSE REACTIONS

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

- Cardiomyopathy [see *Warnings and Precautions (5.1)*]
- Infusion reactions [see *Warnings and Precautions (5.2)*]
- Embryo-fetal Toxicity [see *Warnings and Precautions (5.3)*]
- Pulmonary toxicity [see *Warnings and Precautions (5.4)*]
- Exacerbation of chemotherapy-induced neutropenia [see *Warnings and Precautions (5.5)*]

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

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

## 250 **6.1 Clinical Trials Experience**

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

### 254 *Adjuvant Breast Cancer Studies*

255 The data below reflect exposure to Herceptin across three randomized, open-label studies,  
256 Studies 1, 2, and 3, with (n= 3355) or without (n= 3308) trastuzumab in the adjuvant treatment of  
257 breast cancer.

258 The data summarized in [Table 3](#) below, from Study 3, reflect exposure to Herceptin in  
259 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18.  
260 Among the 3386 patients enrolled in Study 3, the median age was 49 years (range: 21 to 80 years),  
261 83% of patients were Caucasian, and 13% were Asian.  
262

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

Adverse Reaction	1 Year Herceptin (n= 1678)	Observation (n=1708)
<u>Cardiac</u>		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias <sup>b</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%)
Pruritis	40 (2%)	10 (0.6%)

**Table 3 (cont'd)**  
Adverse Reactions for Study 3, All Grades<sup>a</sup>:

Adverse Reaction	1 Year Herceptin (n= 1678)	Observation (n=1708)
<u>General Disorders</u>		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Aesthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (.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> The incidence of Grade 3/4 adverse reactions was <1% in both arms for each listed term.

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

264

265 The data from Studies 1 and 2 were obtained from 3206 patients, of whom 1635 received  
266 Herceptin; the median treatment duration was 50 weeks. The median age was 49 years (range:  
267 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 4% Asian.

268 In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5  
269 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The  
270 following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater  
271 among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone:  
272 arthralgia (31% vs. 28%), fatigue (28% vs. 22%), infection (22% vs. 14%), hot flashes (17% vs.  
273 15%), anemia (13% vs. 7%), dyspnea (12% vs. 4%), rash/desquamation (11% vs. 7%), neutropenia  
274 (7% vs. 5%), headache (6% vs. 4%), and insomnia (3.7% vs. 1.5%). The majority of these events  
275 were Grade 2 in severity.

276 In Study 2, data collection was limited to the following investigator-attributed treatment-related  
277 adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic  
278 toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes,  
279 motor neuropathy, sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during  
280 chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of  
281 Grade 2–5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin  
282 plus chemotherapy as compared to chemotherapy alone: arthralgia (11% vs. 8.4%), myalgia (10%  
283 vs. 8%), nail changes (9% vs. 7%), and dyspnea (2.5% vs. 0.1%). The majority of these events were  
284 Grade 2 in severity.

285 Safety data from Study 4 reflect exposure to Herceptin as part of an adjuvant treatment regimen  
286 from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TCH: n=1056].  
287 The overall median treatment duration was 54 weeks in both the AC-TH and TCH arms.  
288 The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including  
289 weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy  
290 period. Among these patients, the median age was 49 years (range 22 to 74 years). In Study 4, the

291 toxicity profile was similar to that reported in Studies 1, 2, and 3 with the exception of a low  
 292 incidence of CHF in the TCH arm.

293 *Metastatic Breast Cancer Studies*

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

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

303 Among the 352 patients treated in single agent studies (213 patients from Study 6), the median  
 304 age was 50 years (range 28–86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in  
 305 other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed  
 306 by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for  $\geq 6$  months  
 307 and  $\geq 12$  months were 31% and 16%, respectively.  
 308

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

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

309

**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> n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC <sup>b</sup> n = 143	AC <sup>b</sup> Alone n = 135
<u>Digestive</u>					
Nausea	33%	51%	9%	76%	77%
Diarrhea	25%	45%	29%	45%	26%
Vomiting	23%	37%	28%	53%	49%
Nausea and vomiting	8%	14%	11%	18%	9%
Anorexia	14%	24%	16%	31%	26%
<u>Heme &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.

310

311 *Metastatic Gastric Cancer*

312 The data below are based on the exposure of 294 patients to Herceptin in combination with a  
313 fluoropyrimidine (capecitabine or 5-FU) and cisplatin (Study 7). In the Herceptin plus

314 chemotherapy arm, the initial dose of Herceptin 8 mg/kg was administered on Day 1 (prior to  
 315 chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was  
 316 administered at 80 mg/m<sup>2</sup> on Day 1 and the fluoropyrimidine was administered as either  
 317 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  
 318 continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day  
 319 cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin  
 320 infusions administered was eight.  
 321

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

Body System/Adverse Event	Herceptin +FC (N = 294) N (%)		FC (N = 290) N (%)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
<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)

322

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

326 *Cardiomyopathy*

327 Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant  
 328 treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months  
 329 (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and  
 330 2, 23 months in the AC-T arm, 24 months in the AC-TH arm. In Studies 1 and 2, 6% of patients  
 331 were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac  
 332 dysfunction (LVEF < 50% or ≥ 15 point decline in LVEF from baseline to end of AC). Following  
 333 initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was  
 334 higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel  
 335 alone in Studies 1 and 2, and in patients receiving Herceptin monotherapy compared to observation  
 336 in Study 3 (see Table 6, [Figures 1](#) and [2](#)).

337

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

	LVEF <50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF <50%	≥10% decrease	≥16% decrease	<20% and ≥10%	≥20%
<b>Studies 1 &amp; 2<sup>b</sup></b>					
AC→TH (n=1606)	22.8% (366)	18.3% (294)	11.7% (188)	33.4% (536)	9.2% (148)
AC→T (n=1488)	9.1% (136)	5.4% (81)	2.2% (33)	18.3% (272)	2.4% (36)
<b>Study 3</b>					
Herceptin (n=1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n=1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
<b>Study 4<sup>c</sup></b>					
TCH (n=1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n=1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n=1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

<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.

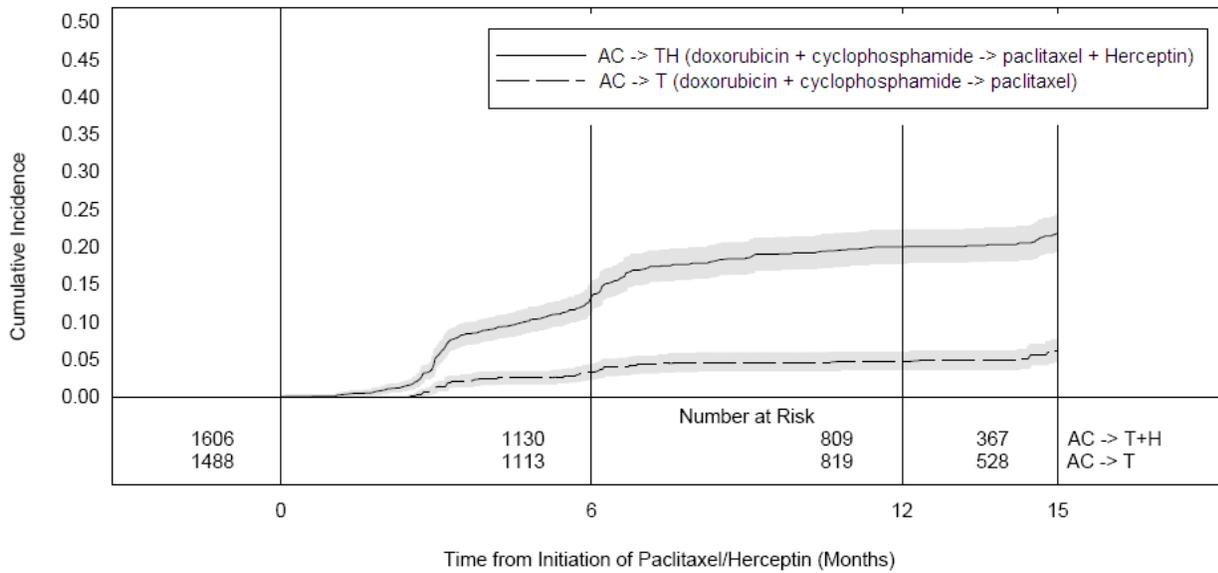
<sup>b</sup> Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

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

338

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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

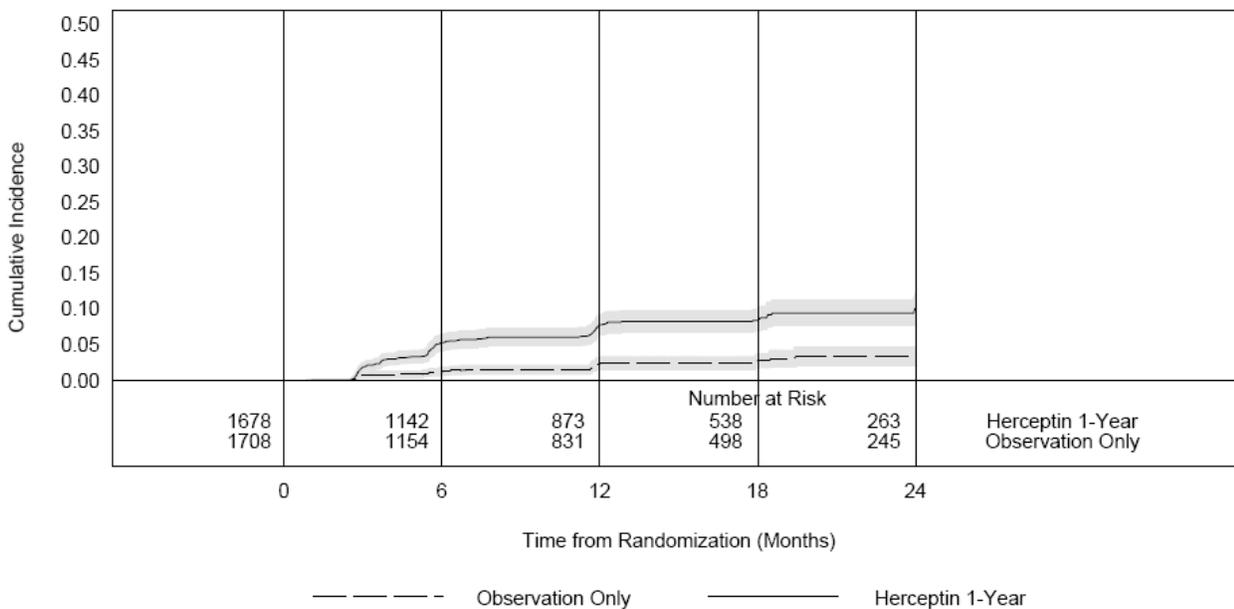


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Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

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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

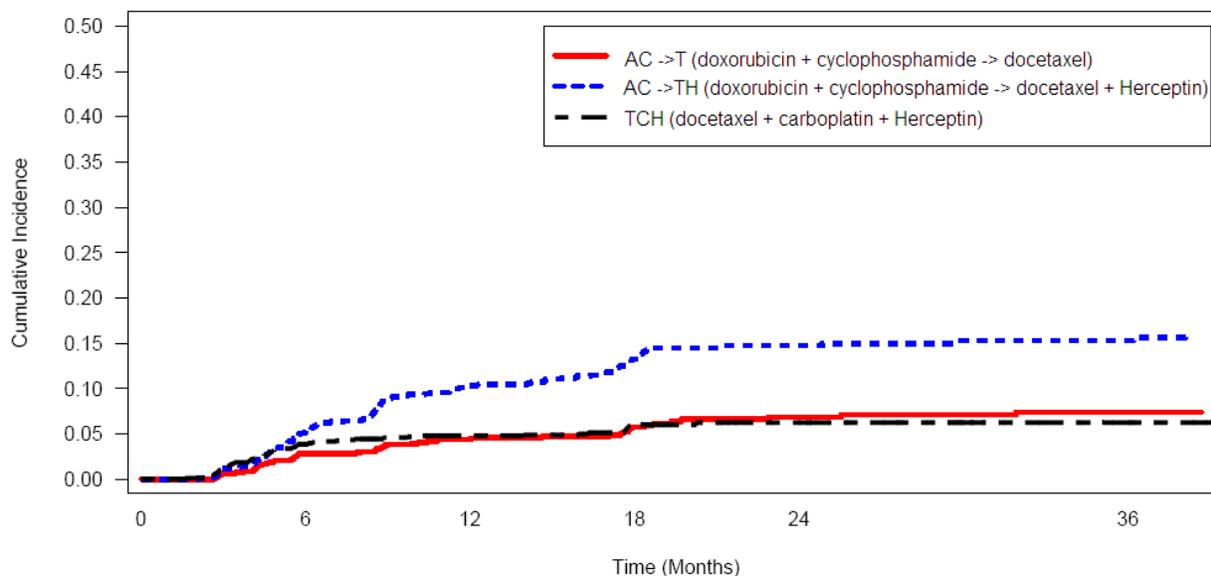


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Time 0 is the date of randomization.

353  
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356

**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



	Time (Months)					
Number at risk	0	6	12	18	24	36
AC->T	1050	947	836	523	359	259
AC->TH	1068	975	839	474	315	248
TCH	1056	975	877	535	350	271

357  
358  
359

Time 0 is the date of randomization.

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

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

### 368 *Infusion Reactions*

369 During the first infusion with Herceptin, the symptoms most commonly reported were chills and  
370 fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with  
371 acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of  
372 Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity was required in  
373  $<1\%$  of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at  
374 tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and  
375 asthenia. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9%  
376 of patients, on second or subsequent Herceptin infusions administered as monotherapy or in  
377 combination with chemotherapy, respectively. In the post-marketing setting, severe infusion  
378 reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

### 379 *Anemia*

380 In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]),  
381 of selected NCI-CTC Grade 2–5 anemia (12.5% vs. 6.6% [Study 1]), and of anemia requiring  
382 transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and  
383 chemotherapy compared with those receiving chemotherapy alone. Following the administration of

384 Herceptin as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was < 1%. In  
385 Study 7 (metastatic gastric cancer) on the Herceptin containing arm as compared to the  
386 chemotherapy alone arm the overall incidence of anemia was 28% compared 21% and of NCI CTC  
387 Grade 3/4 anemia was 12.2% compared to 10.3%.

### 388 *Neutropenia*

389 In randomized controlled clinical trials in the adjuvant setting, the incidence of selected  
390 NCI-CTC Grade 4–5 neutropenia (2% vs. 0.7% [Study 2]) and of selected Grade 2–5 neutropenia  
391 (7.1% vs. 4.5% [Study 1]) were increased in patients receiving Herceptin and chemotherapy  
392 compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients  
393 with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and  
394 of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in  
395 combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7  
396 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone  
397 arm, the incidence of NCI CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile  
398 neutropenia 5.1% compared to 2.8%.

### 399 *Infection*

400 The overall incidences of infection (46% vs. 30% [Study 5]), of selected NCI-CTC Grade 2–5  
401 infection/febrile neutropenia (22% vs. 14% [Study 1]) and of selected Grade 3–5 infection/febrile  
402 neutropenia (3.3% vs. 1.4%) [Study 2]), were higher in patients receiving Herceptin and  
403 chemotherapy compared with those receiving chemotherapy alone. The most common site of  
404 infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract.

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

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

### 411 *Pulmonary Toxicity*

#### 412 *Adjuvant Breast Cancer*

413 Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC  
414 Grade 2–5 pulmonary toxicity (14% vs. 5% [Study 1]) and of selected NCI-CTC Grade 3–5  
415 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4 % vs. 1% [Study 2]) was higher  
416 in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The most  
417 common pulmonary toxicity was dyspnea (NCI-CTC Grade 2–5: 12% vs. 4% [Study 1]; NCI-CTC  
418 Grade 2–5: 2.5% vs. 0.1% [Study 2]).

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

423 In Study 3, there were 4 cases of interstitial pneumonitis in Herceptin-treated patients compared to  
424 none in the control arm.

#### 425 *Metastatic Breast Cancer*

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

432 *Thrombosis/Embolism*

433 In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher  
434 in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies  
435 (3.0% vs. 1.3% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]).

436 *Diarrhea*

437 Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC  
438 Grade 2–5 diarrhea (6.2% vs. 4.8% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (1.6% vs. 0%  
439 [Study 2]), and of Grade 1–4 diarrhea (7% vs. 1% [Study 3]) were higher in patients receiving  
440 Herceptin as compared to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher  
441 [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH  
442 vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single  
443 agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased  
444 incidence of diarrhea was observed in patients receiving Herceptin in combination with  
445 chemotherapy for treatment of metastatic breast cancer.

446 *Renal Toxicity*

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

452 In the postmarketing setting, rare cases of nephrotic syndrome with pathologic evidence of  
453 glomerulopathy have been reported. The time to onset ranged from 4 months to approximately  
454 18 months from initiation of Herceptin therapy. Pathologic findings included membranous  
455 glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications  
456 included volume overload and congestive heart failure.

457 **6.2 Immunogenicity**

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

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

469 **6.3 Post-Marketing Experience**

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

- 473 • Infusion reaction [*see Warnings and Precautions (5.2)*]
  - 474 • Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal  
475 abnormalities, and neonatal death [*see Warnings and Precautions (5.3)*]
  - 476 • Glomerulopathy [*see Adverse Reactions (6.1)*]
- 477

478 **7 DRUG INTERACTIONS**

479 In Study 5, the mean serum trough concentration of trastuzumab was consistently elevated  
480 approximately 1.5-fold, when administered in combination with paclitaxel as compared to trough  
481 concentrations of trastuzumab when administered in combination with an anthracycline and  
482 cyclophosphamide.

483 In other pharmacokinetic studies, where Herceptin was administered in combination with  
484 paclitaxel, docetaxel or doxorubicin, Herceptin did not alter the plasma concentrations of these  
485 chemotherapeutic agents, or the metabolites that were analyzed. In a drug interaction substudy  
486 conducted in patients in Study 7, the pharmacokinetics of cisplatin, capecitabine and their  
487 metabolites were not altered when administered in combination with Herceptin.  
488

489 **8 USE IN SPECIFIC POPULATIONS**

490 **8.1 Pregnancy: Category D [see Warnings and Precautions (5.3), Nonclinical Toxicology (13.2)]**

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

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

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

503 Advise women of the potential hazard to the fetus resulting from Herceptin exposure during  
504 pregnancy. Encourage pregnant women with breast cancer who are using Herceptin to enroll in  
505 MotHER-the Herceptin Pregnancy Registry: phone 1-800-690-6720. [see *Patient Counseling*  
506 *Information (17)*].

507 No teratogenic effects were observed in offspring from reproduction studies in cynomolgus  
508 monkeys at doses up to 25 times the recommended weekly human dose of 2 mg/kg trastuzumab. In  
509 mutant mice lacking HER2, embryos died in early gestation. Trastuzumab exposure was reported at  
510 delivery in offspring of cynomolgus monkeys treated during the early (Days 20-50 of gestation) or  
511 late (Days 120-150 of gestation) fetal development periods, at levels of 15 to 28% of the maternal  
512 blood levels.

513 **8.3 Nursing Mothers**

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

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

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

526 **8.4 Pediatric Use**

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

528 **8.5 Geriatric Use**

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

539 In Study 7 (metastatic gastric cancer), of the 294 patients treated with Herceptin 108 (37%) were  
540 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or  
541 effectiveness were observed.

542

543 **10 OVERDOSAGE**

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

546

547 **11 DESCRIPTION**

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

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

558

559 **12 CLINICAL PHARMACOLOGY**

560 **12.1 Mechanism of Action**

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

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

568 **12.2 Pharmacokinetics**

569 The pharmacokinetics of trastuzumab were studied in women with metastatic breast cancer. Short  
570 duration intravenous infusions of 10 to 500 mg Herceptin once weekly demonstrated dose-dependent  
571 pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level.

572 The half-life averaged 2 and 12 days at the 10 and 500 mg dose levels, respectively. The volume of  
573 distribution of trastuzumab was approximately that of serum volume (44 mL/kg). At the highest  
574 weekly dose studied (500 mg), mean peak serum concentrations were 377 mcg/mL.

575 In studies using an initial dose of 4 mg/kg followed by a weekly dose of 2 mg/kg, a mean half-life  
576 of 6 days (range 1–32 days) was observed. Between weeks 16 and 32, trastuzumab serum  
577 concentrations reached a steady state with mean trough and peak concentrations of approximately  
578 79 mcg/mL and 123 mcg/mL, respectively.

579 In a study of women receiving adjuvant therapy for breast cancer, a mean half-life of trastuzumab  
580 of 16 days (range: 11–23 days) was observed after an initial dose of 8 mg/kg followed by a dose of  
581 6 mg/kg every three weeks. Between weeks 6 and 37, trastuzumab serum concentrations reached a  
582 steady-state with mean trough and peak concentrations of 63 mcg/mL and 216 mcg/mL,  
583 respectively.

584 In patients with metastatic gastric cancer (Study 7), mean serum trastuzumab trough  
585 concentrations at steady state were 24 to 63% lower as compared to the concentrations observed in  
586 patients with breast cancer receiving treatment for metastatic disease in combination with paclitaxel,  
587 as monotherapy for metastatic disease, or as adjuvant monotherapy.

588 Sixty-four percent (286/447) of women with metastatic breast cancer had detectable circulating  
589 extracellular domain of the HER2 receptor (shed antigen), which ranged as high as 1880 ng/mL  
590 (median 11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have  
591 lower serum trough concentrations.

592 Data suggest that the disposition of trastuzumab is not altered based on age or serum creatinine  
593 ( $\leq 2.0$  mg creatinine/dL).

594

## 595 **13 NONCLINICAL TOXICOLOGY**

### 596 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

597 Herceptin has not been tested for carcinogenic potential.

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

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

### 606 **13.2 Animal Toxicology and/or Pharmacology**

#### 607 *Reproductive Toxicology Studies*

608 Reproductive toxicology studies have been conducted in cynomolgus monkeys at doses up to 25  
609 times the weekly recommended human dose of 2 mg/kg Herceptin and have revealed no evidence of  
610 impaired fertility or harm to the fetus. However, HER2 protein expression is high in many  
611 embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died  
612 in early gestation. Placental transfer of trastuzumab was detected at Caesarean section in offspring  
613 from pregnant cynomolgus monkeys dosed during the early (Days 20–50 of gestation) or late (Days  
614 120–150 of gestation) fetal development periods.

615

616 **14 CLINICAL STUDIES**

617 **14.1 Adjuvant Breast Cancer**

618 The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2  
619 overexpressing breast cancer were evaluated in an integrated analysis of two randomized,  
620 open-label, clinical trials (Studies 1 and 2) with a total of 3752 women, a third randomized,  
621 open-label, clinical trial (Study 3) with a total of 3386 women, and a fourth randomized, open-label  
622 clinical trial with a total of 3222 patients (Study 4).

623 *Studies 1 and 2*

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

630 Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by  
631 paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin).  
632 In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide  
633 600 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>)  
634 for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in  
635 Study 2. Herceptin was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a  
636 dose of 2 mg/kg weekly for a total of 52 weeks. Herceptin treatment was permanently discontinued  
637 in patients who developed congestive heart failure, or persistent/recurrent LVEF decline [*see Dosage*  
638 *and Administration (2.2)*]. Radiation therapy, if administered, was initiated after the completion of  
639 chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-free  
640 survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral  
641 breast cancer, other second primary cancer, or death, was the main outcome measure of the  
642 combined efficacy analysis.

643 A total of 3752 patients were included in the efficacy analyses. The data from both arms in  
644 Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. Of these  
645 patients, the median age was 49 years (range, 22–80 years; 6% > 65 years), 84% were white,  
646 7% black, 4% Hispanic, and 4% Asian/Pacific Islander. Disease characteristics included 90%  
647 infiltrating ductal histology, 38% T1, 91% nodal involvement, 27% intermediate and 66% high  
648 grade pathology, and 53% ER+ and/or PR+ tumors. At the time of randomization 53% of the  
649 population were to receive paclitaxel on a weekly regimen, and the remainder were to receive a  
650 q3 week schedule of paclitaxel.

651 *Study 3*

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

658 Patients were randomized (1:1) upon completion of definitive surgery, and at least four cycles of  
659 chemotherapy to receive no additional treatment (n = 1693) or 1 year of Herceptin treatment  
660 (n = 1693). Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients  
661 with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator  
662 discretion. Herceptin was administered with an initial dose of 8 mg/kg followed by subsequent

663 doses of 6 mg/kg once every three weeks for a total of 52 weeks. The main outcome measure was  
664 disease-free survival (DFS), defined as in Studies 1 and 2.

665 Among the 3386 patients randomized to the two treatment arms, the median age was 49 years  
666 (range 21–80), 83% were Caucasian, and 13% were Asian. Disease characteristics: 94% infiltrating  
667 ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32% node negative, and in 11% of  
668 patients, nodal status was not assessable due to prior neo-adjuvant chemotherapy.

669 Ninety-six percent (1055/1098) of patients with node-negative disease had high-risk features:  
670 among the 1098 patients with node-negative disease, 49% (543) were ER– and PgR–, and 47%  
671 (512) were ER and/or PgR + and had at least one of the following high-risk features: pathological  
672 tumor size greater than 2 cm, Grade 2–3, or age < 35 years. Prior to randomization, 94% of patients  
673 had received anthracycline-based chemotherapy regimens.

#### 674 *Study 4*

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

682 Patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by  
683 docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus Herceptin  
684 (AC-TH), or docetaxel and carboplatin plus Herceptin (TCH). In both the AC-T and AC-TH arms,  
685 doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup> were administered every 3 weeks for  
686 four cycles; docetaxel 100 mg/m<sup>2</sup> was administered every 3 weeks for four cycles. In the TCH arm,  
687 docetaxel 75 mg/m<sup>2</sup> and carboplatin (at a target AUC of 6 mg/mL/min as a 30- to 60-minute  
688 infusion) were administered every 3 weeks for six cycles. Herceptin was administered weekly  
689 (initial dose of 4 mg/kg followed by weekly dose of 2 mg/kg) concurrently with either T or TC, and  
690 then every 3 weeks (6 mg/kg) as monotherapy for a total of 52 weeks. Radiation therapy, if  
691 administered, was initiated after completion of chemotherapy. Patients with ER+ and/or PR+ tumors  
692 received hormonal therapy. Disease-free survival (DFS) was the main outcome measure.

693 Among the 3222 patients randomized, the median age was 49 (range 22 to 74 years; 6%  
694 ≥65 years). Disease characteristics included 54% ER+ and/or PR+ and 71% node positive. Prior to  
695 randomization, all patients underwent primary surgery for breast cancer.

696

**Table 7**  
Efficacy Results from Adjuvant Treatment of  
Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	Hazard ratio (95% CI) p value	Deaths	Hazard ratio p value
<u>Studies 1 + 2<sup>c</sup></u>				
AC→TH (n=1872)	133	0.48 <sup>a</sup> (0.39, 0.59) p=< 0.0001 <sup>b</sup>	62	0.67 p=NS <sup>d</sup>
AC→T (n = 1880)	261		92	
<u>Study 3</u>				
Chemo→ Herceptin (n=1693 )	127	0.54 (0.44, 0.67) p=< 0.0001 <sup>c</sup>	31	0.75 p=NS <sup>d</sup>
Chemo→ Observation (n = 1693)	219		40	
<u>Study 4<sup>f</sup></u>				
TCH (n=1075)	134	0.67 (0.54 – 0.84) p=0.0006 <sup>b,g</sup>	56	
AC→TH (n=1074)	121	0.60 (0.48 – 0.76) p=< 0.0001 <sup>b,g</sup>	49	
AC→T (n=1073)	180		80	

CI = confidence interval.

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

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

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

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

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

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

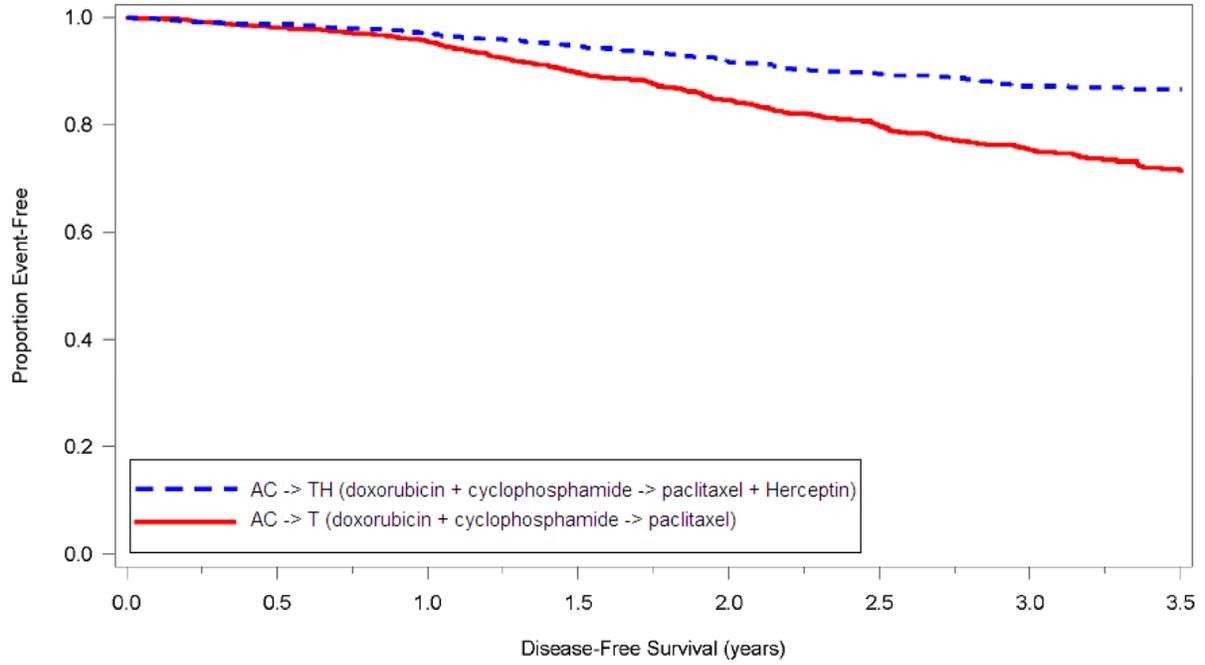
<sup>g</sup> A two-sided alpha level of 0.025 for each comparison.

697

698 The results for DFS for the integrated analysis of Studies 1 and 2, Study 3, and Study 4 are  
699 presented in [Table 7](#). The duration of DFS for Studies 1 and 2 is presented in [Figure 4](#), and the  
700 duration of DFS for Study 4 is presented in [Figure 5](#). Across all four studies, there were insufficient  
701 numbers of patients within each of the following subgroups to determine if the treatment effect was  
702 different from that of the overall patient population: patients with low tumor grade, patients within  
703 specific ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients  
704 >65 years of age.  
705

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

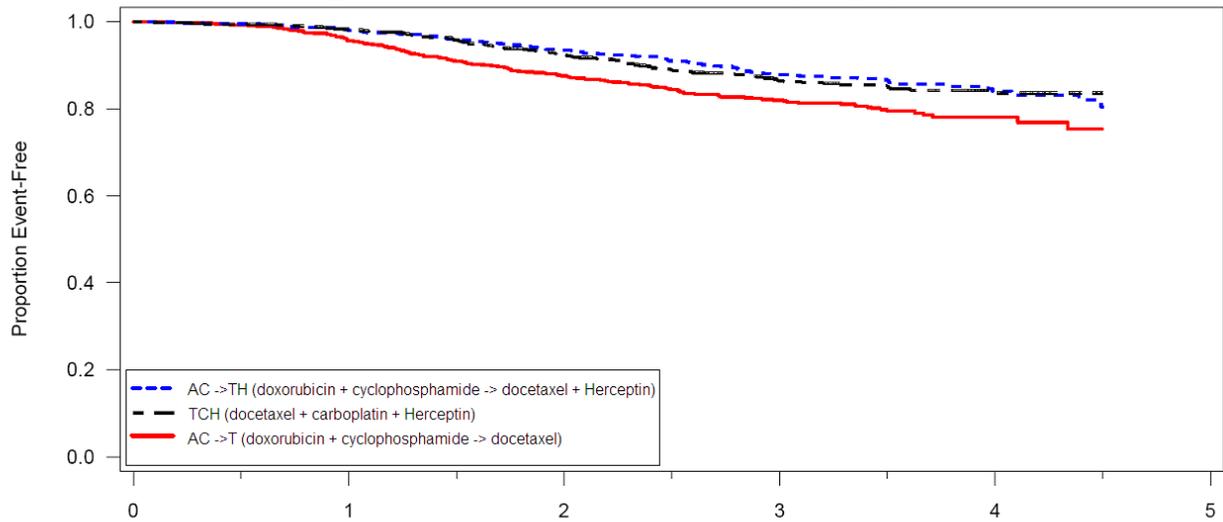


Number at risk								
AC→ T	1880	1490	1159	926	689	534	375	195
AC→ T + H	1872	1529	1240	997	764	575	426	239

709  
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**Figure 5**  
Duration of Disease-Free Survival in Patients with  
Adjuvant Treatment of Breast Cancer (Study 4)



	Disease-Free Survival (years)			
Number at risk				
AC->T	1073	971	802	417
AC->TH	1074	1023	885	457
TCH	1075	1018	877	447

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

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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 8](#). The number of events in Study 2 was small with the exception of the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups.

**Table 8**  
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	
	Number of Patients	Hazard Ratio DFS (95% CI)	Number of Patients	Hazard Ratio DFS (95% CI)
<b>IHC 3+</b>				
FISH (+)	1170	0.42 (0.27, 0.64)	91	0.56 (0.13, 2.50)
FISH (-)	51	0.71 (0.04, 11.79)	8	—
FISH Unknown	51	0.69 (0.09, 5.14)	2258	0.53 (0.41, 0.69)
IHC < 3+ / FISH (+)	174	1.01 (0.18, 5.65)	299 <sup>b</sup>	0.53 (0.20, 1.42)
IHC unknown / FISH (+)	—	—	724	0.59 (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+.

724

## 725 14.2 Metastatic Breast Cancer

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

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

733 Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with  
734 metastatic breast cancer who had not been previously treated with chemotherapy for metastatic  
735 disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+,  
736 or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were  
737 eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or  
738 in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly  
739 doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the  
740 adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m<sup>2</sup> over 3 hours every 21 days for at  
741 least six cycles); for all other patients, chemotherapy consisted of anthracycline plus  
742 cyclophosphamide (AC: doxorubicin 60 mg/m<sup>2</sup> or epirubicin 75 mg/m<sup>2</sup> plus 600 mg/m<sup>2</sup>  
743 cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to  
744 receive chemotherapy alone in this study received Herceptin at the time of disease progression as  
745 part of a separate extension study.

746 Based upon the determination by an independent response evaluation committee the patients  
747 randomized to Herceptin and chemotherapy experienced a significantly longer median time to  
748 disease progression, a higher overall response rate (ORR), and a longer median duration of response,  
749 as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin  
750 and chemotherapy also had a longer median survival (see [Table 9](#)). These treatment effects were

751 observed both in patients who received Herceptin plus paclitaxel and in those who received  
 752 Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.  
 753

**Table 9**  
 Study 5: Efficacy Results in  
 First-Line Treatment for Metastatic Breast Cancer

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

754  
 755 Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients  
 756 with the highest level of HER2 protein overexpression (3+) (see [Table 10](#)).  
 757

**Table 10**  
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.

758

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

760 Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial  
761 (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following  
762 one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had  
763 received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for  
764 metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue.  
765 Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin at  
766 2 mg/kg IV.

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

772 **14.3 Metastatic Gastric Cancer**

773 The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine  
774 (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or  
775 gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial,  
776 594 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine  
777 (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic  
778 vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes  
779 vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil).  
780 All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients  
781 were also required to have adequate cardiac function (e.g., LVEF > 50%).

782 On the Herceptin-containing arm, Herceptin was administered as an IV infusion at an initial dose  
783 of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms

784 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  
 785 infusion. On both study arms capecitabine was administered at 1000 mg/m<sup>2</sup> dose orally twice daily  
 786 (total daily dose 2000 mg/m<sup>2</sup>) for 14 days of each 21 day cycle for 6 cycles. Alternatively continuous  
 787 intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m<sup>2</sup>/day from Day 1  
 788 through Day 5 every three weeks for 6 cycles.

789 The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were  
 790 Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1;  
 791 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these  
 792 patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant  
 793 therapy, and 2% had received prior radiotherapy.

794 The main outcome measure of Study 7 was overall survival (OS), analyzed by the unstratified log-  
 795 rank test. The final OS analysis based on 351 deaths was statistically significant (nominal  
 796 significance level of 0.0193). An updated OS analysis was conducted at one year after the final  
 797 analysis. The efficacy results of both the final and the updated analyses are summarized in Table 11  
 798 Figure 6.  
 799

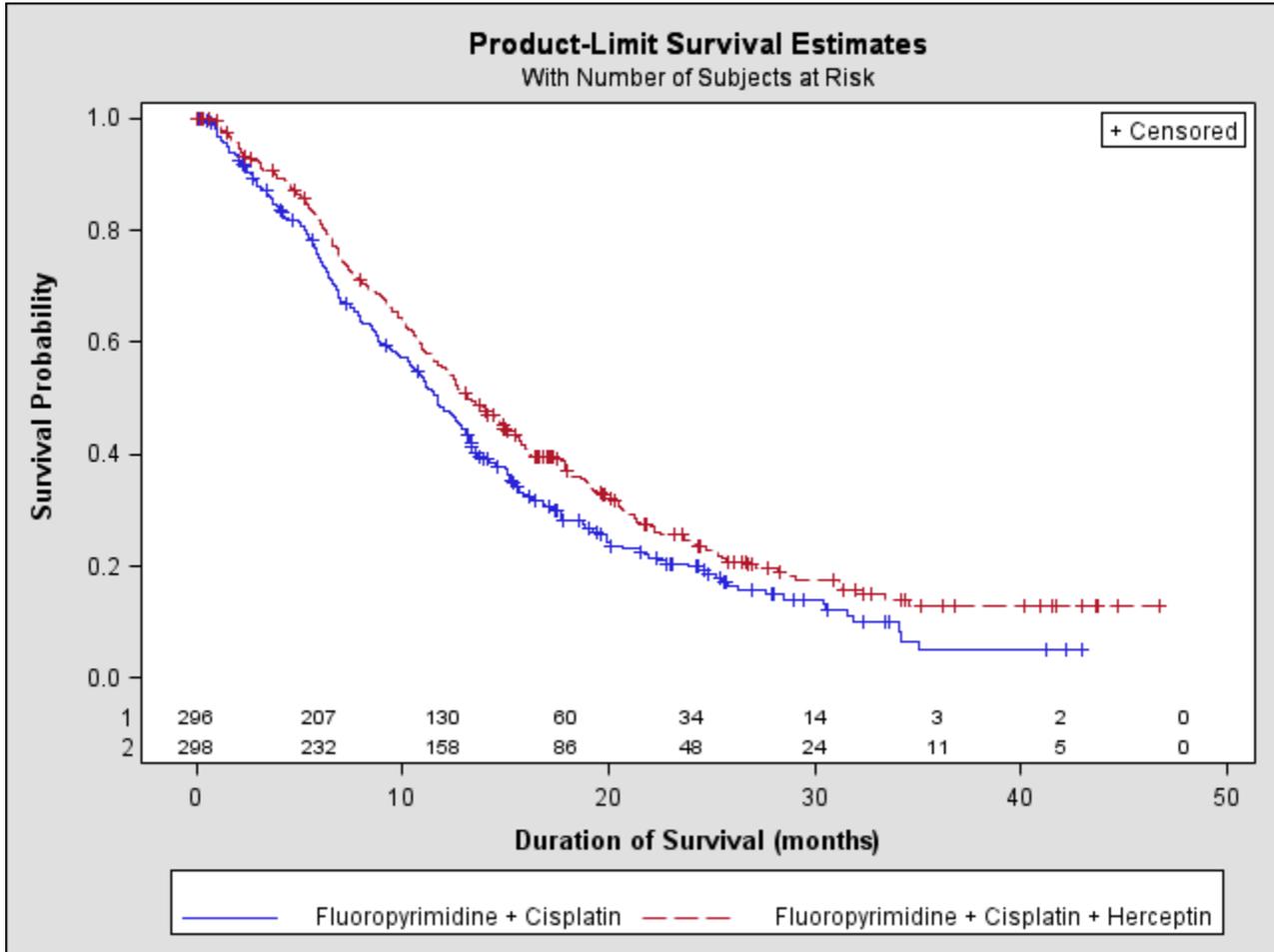
**Table 11**  
 Study 7: Overall Survival in ITT Population

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

\* Comparing with the nominal significance level of 0.0193.

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**Figure 6**  
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 12.

**Table 12**  
Exploratory Analyses by HER2 Status using Updated Overall Survival Results

	FC (N= 296) <sup>a</sup>	FC+H (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+.

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809 **16 HOW SUPPLIED/STORAGE AND HANDLING**

810 **16.1 How Supplied**

811 Herceptin is supplied in a multi-use vial containing 440 mg trastuzumab as a lyophilized sterile  
812 powder, under vacuum. Each carton contains one vial Herceptin<sup>®</sup> and one vial (20 mL) of  
813 Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.  
814 NDC 50242-134-68.

815 **16.2 Stability and Storage**

816 Vials of Herceptin are stable at 2–8°C (36–46°F) prior to reconstitution. Do not use beyond the  
817 expiration date stamped on the vial. A vial of Herceptin reconstituted with BWFI, as supplied, is  
818 stable for 28 days after reconstitution when stored refrigerated at 2–8°C (36–46°F). Discard any  
819 remaining multi-dose reconstituted solution after 28 days. A vial of Herceptin reconstituted with  
820 unpreserved SWFI (not supplied) should be used immediately and any unused portion discarded.

821 **Do Not Freeze** Herceptin following reconstitution or dilution.

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

825 **17 PATIENT COUNSELING INFORMATION**

- 826 • Advise patients to contact a health care professional immediately for any of the following: new  
827 onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face,  
828 palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness  
829 [*see Boxed Warning [Cardiomyopathy](#)*].
- 830 • Advise pregnant women and women of childbearing potential that Herceptin exposure can  
831 result in fetal harm [*see Warnings and Precautions (5.3) and Use in Specific Populations*  
832 *(8.1)*].
- 833 • Advise women of childbearing potential to use effective contraceptive methods during  
834 treatment and for a minimum of six months following Herceptin [*see Warnings and*  
835 *Precautions (5.3)*].
- 836 • Advise nursing mothers treated with Herceptin to discontinue nursing or discontinue Herceptin,  
837 taking into account the importance of the drug to the mother [*see Use in Specific Populations*  
838 *(8.3)*].
- 839 • Encourage women who are exposed to Herceptin during pregnancy to enroll in MotHER- the  
840 Herceptin Pregnancy Registry (1-800-690-6720) [*see Warnings and Precautions (5.3) and Use*  
841 *in Specific Populations (8.1)*].
- 842

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**HERCEPTIN<sup>®</sup> [trastuzumab]**

Manufactured by:

Genentech, Inc.

**A Member of the Roche Group**

1 DNA Way

South San Francisco, CA 94080-4990

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Initial US Approval: September 1998

Revision Date: October 2010

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