

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, 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)

RECENT MAJOR CHANGES

Indications and Usage, Metastatic Gastric Cancer (1.3) 10/2010
Dosage and Administration (2.1) 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)
- Exacerbation of Chemotherapy-Induced Neutropenia (5.3, 6.1)
- Pulmonary Toxicity (5.4, 6.1)
- HER2 testing should be performed using FDA-approved tests by laboratories with demonstrated proficiency. (5.5)
- Embryo-fetal Toxicity (5.6, 8.1)

ADVERSE REACTIONS

Adjuvant Breast Cancer

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

Metastatic Breast Cancer

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

Metastatic Gastric Cancer

- Most common adverse reactions (≥10%) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. (6.1)

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.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING – CARDIOMYOPATHY, INFUSION REACTIONS, PULMONARY TOXICITY

1 INDICATIONS AND USAGE

- Adjuvant Breast Cancer
- Metastatic Breast Cancer
- Metastatic Gastric Cancer

2 DOSAGE AND ADMINISTRATION

- Recommended Doses and Schedules
- Dose Modifications
- Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- Cardiomyopathy
- Infusion Reactions
- Exacerbation of Chemotherapy-Induced Neutropenia
- Pulmonary Toxicity
- HER2 Testing

6 ADVERSE REACTIONS

- Clinical Trials Experience
- Immunogenicity
- Post-Marketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Nursing Mothers
- Pediatric Use
- Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- Adjuvant Breast Cancer
- Metastatic Breast Cancer
- Metastatic Gastric Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING

- How Supplied
- Stability and Storage

17 PATIENT COUNSELING INFORMATION

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

1 FULL PRESCRIBING INFORMATION

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

4 **Cardiomyopathy**

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

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

12 **Infusion Reactions; Pulmonary Toxicity**

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

20 **1 INDICATIONS AND USAGE**

21 **1.1 Adjuvant Breast Cancer**

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

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

28 **1.2 Metastatic Breast Cancer**

29 Herceptin is indicated:

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

34 **1.3 Metastatic Gastric Cancer**

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

38 **2 DOSAGE AND ADMINISTRATION**

39 **2.1 Recommended Doses and Schedules**

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

41 *Adjuvant Treatment, Breast Cancer:*

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

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

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

50 As a single agent within three weeks following completion of multi-modality, anthracycline-based
51 chemotherapy regimens.

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

55 [*see Dose Modifications (2.2)*]

56 *Metastatic Treatment, Breast Cancer:*

- 57 • Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as
58 a 90 minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as
59 30 minute intravenous infusions until disease progression.

60 *Metastatic Gastric Cancer*

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

64 **2.2 Dose Modifications**

65 *Infusion Reactions*

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

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

70 *Cardiomyopathy*

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

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

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

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

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

82 **2.3 Preparation for Administration**

83 *Reconstitution*

84 Reconstitute each 440 mg vial of Herceptin with 20 mL of Bacteriostatic Water for Injection
85 (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution
86 containing 21 mg/mL trastuzumab. In patients with known hypersensitivity to benzyl alcohol,
87 reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single
88 use solution.

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

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

103 *Dilution*

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

109 **3 DOSAGE FORMS AND STRENGTHS**

110 440 mg lyophilized powder per multi-use vial.

111 **4 CONTRAINDICATIONS**

112 None.

113 **5 WARNINGS AND PRECAUTIONS**

114 **5.1 Cardiomyopathy**

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

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

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

127 *Cardiac Monitoring*

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

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

136 In Study 1, 16% (136/844) of patients discontinued Herceptin due to clinical evidence of myocardial
 137 dysfunction or significant decline in LVEF. In Study 3, the number of patients who discontinued
 138 Herceptin due to cardiac toxicity was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) patients
 139 in the TCH arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and
 140 5.7% (61/1068) patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during
 141 the monotherapy phase) discontinued Herceptin due to cardiac toxicity.

142 Among 32 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive
 143 heart failure, one patient died of cardiomyopathy and all other patients were receiving cardiac
 144 medication at last follow-up. Approximately half of the surviving patients had recovery to a normal
 145 LVEF (defined as $\geq 50\%$) on continuing medical management at the time of last follow-up.
 146 Incidence of congestive heart failure is presented in Table 1. The safety of continuation or
 147 resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has
 148 not been studied.
 149

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

Study	Regimen	Incidence of CHF	
		Herceptin	Control
1 & 2 ^a	AC ^b →Paclitaxel+Herceptin	2% (32/1677)	0.4% (7/1600)
3	Chemo → Herceptin	2% (30/1678)	0.3% (5/1708)
4	AC ^b →Docetaxel+Herceptin	2% (20/1068)	0.3% (3/1050)
4	Docetaxel+Carbo+Herceptin	0.4% (4/1056)	0.3% (3/1050)

^a Includes 1 patient with fatal cardiomyopathy.

^b Anthracycline (doxorubicin) and cyclophosphamide

150

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

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

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

^b Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

^c Includes 1 patient with fatal cardiomyopathy.

151

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

155 **5.2 Infusion Reactions**

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

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

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

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

175 **5.3 Exacerbation of Chemotherapy-Induced Neutropenia**

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

181 **5.4 Pulmonary Toxicity**

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

188 **5.5 HER2 Testing**

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

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

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

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

205 Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric
206 cancer should be performed using FDA-approved tests specifically for gastric cancers due to
207 differences in gastric vs. breast histopathology, including incomplete membrane staining and more
208 frequent heterogeneous expression of HER2 seen in gastric cancers. Study 7 demonstrated that gene
209 amplification and protein overexpression were not as well correlated as with breast cancer.
210 Treatment outcomes for metastatic gastric cancer (Study 7), based on HER2 gene amplification
211 (FISH) and HER2 protein overexpression (IHC) test results are provided in [Table 12](#).

212 **5.6 Embryo-Fetal Toxicity**

213 Herceptin can cause fetal harm when administered to a pregnant woman. Post-marketing case
214 reports suggest that Herceptin use during pregnancy increases the risk of oligohydramnios during the
215 second and third trimesters. If Herceptin is used during pregnancy or if a woman becomes pregnant
216 while taking Herceptin, she should be apprised of the potential hazard to a fetus. [*see Use in Specific*
217 *Populations (8.1)*].
218

219 **6 ADVERSE REACTIONS**

220
221 The following adverse reactions are discussed in greater detail in other sections of the label:

- 222 • Cardiomyopathy [*see Warnings and Precautions (5.1)*]
 - 223 • Infusion reactions [*see Warnings and Precautions (5.2)*]
 - 224 • Exacerbation of chemotherapy-induced neutropenia [*see Warnings and Precautions (5.3)*]
 - 225 • Pulmonary toxicity [*see Warnings and Precautions (5.4)*]
- 226

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

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

240 **6.1 Clinical Trials Experience**

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

244 *Adjuvant Breast Cancer Studies*

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

248 The data summarized in [Table 3](#) below, from Study 3, reflect exposure to Herceptin in
249 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18.
250 Among the 3386 patients enrolled in Study 3, the median age was 49 years (range: 21 to 80 years),
251 83% of patients were Caucasian, and 13% were Asian.
252

Table 3
Adverse Reactions for Study 3, All Grades^a:

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 ^b	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
<u>Respiratory Thoracic Mediastinal Disorders</u>		
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
<u>Gastrointestinal Disorders</u>		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
<u>Musculoskeletal & Connective Tissue Disorders</u>		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
<u>Nervous System Disorders</u>		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
<u>Skin & Subcutaneous Tissue Disorders</u>		
Rash	70 (4%)	10 (.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritis	40 (2%)	10 (0.6%)

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

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%)

^a The incidence of Grade 3/4 adverse reactions was <1% in both arms for each listed term.

^b Higher level grouping term.

254

255 The data from Studies 1 and 2 were obtained from 3206 patients, of whom 1635 received
256 Herceptin; the median treatment duration was 50 weeks. The median age was 49 years (range:
257 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 4% Asian.

258 In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5
259 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The
260 following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater
261 among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone:
262 arthralgia (31% vs. 28%), fatigue (28% vs. 22%), infection (22% vs. 14%), hot flashes (17% vs.
263 15%), anemia (13% vs. 7%), dyspnea (12% vs. 4%), rash/desquamation (11% vs. 7%), neutropenia
264 (7% vs. 5%), headache (6% vs. 4%), and insomnia (3.7% vs. 1.5%). The majority of these events
265 were Grade 2 in severity.

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

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

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

283 *Metastatic Breast Cancer Studies*

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

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

293 Among the 352 patients treated in single agent studies (213 patients from Study 6), the median
 294 age was 50 years (range 28–86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in
 295 other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed
 296 by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months
 297 and ≥ 12 months were 31% and 16%, respectively.
 298

Table 4

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

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

299

Table 4 (cont'd)

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

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

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

^b Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

300

301 *Metastatic Gastric Cancer*

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

304 chemotherapy arm, the initial dose of Herceptin 8 mg/kg was administered on Day 1 (prior to
 305 chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was
 306 administered at 80 mg/m² on Day 1 and the fluoropyrimidine was administered as either
 307 capecitabine 1000 mg/m² orally twice a day on Days 1-14 or 5-fluorouracil 800 mg/m²/day as a
 308 continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day
 309 cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin
 310 infusions administered was eight.
 311

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)

312

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

316 *Cardiomyopathy*

317 Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant
 318 treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months
 319 (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and
 320 2, 23 months in the AC-T arm, 24 months in the AC-TH arm. In Studies 1 and 2, 6% of patients
 321 were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac
 322 dysfunction (LVEF < 50% or ≥ 15 point decline in LVEF from baseline to end of AC). Following
 323 initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was
 324 higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel
 325 alone in Studies 1 and 2, and in patients receiving Herceptin monotherapy compared to observation
 326 in Study 3 (see Table 6, Figures 1 and 2).

327

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

	LVEF <50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF <50%	≥10% decrease	≥16% decrease	<20% and ≥10%	≥20%
Studies 1 & 2^b					
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)
Study 3					
Herceptin (n=1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n=1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
Study 4^c					
TCH (n=1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n=1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n=1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

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

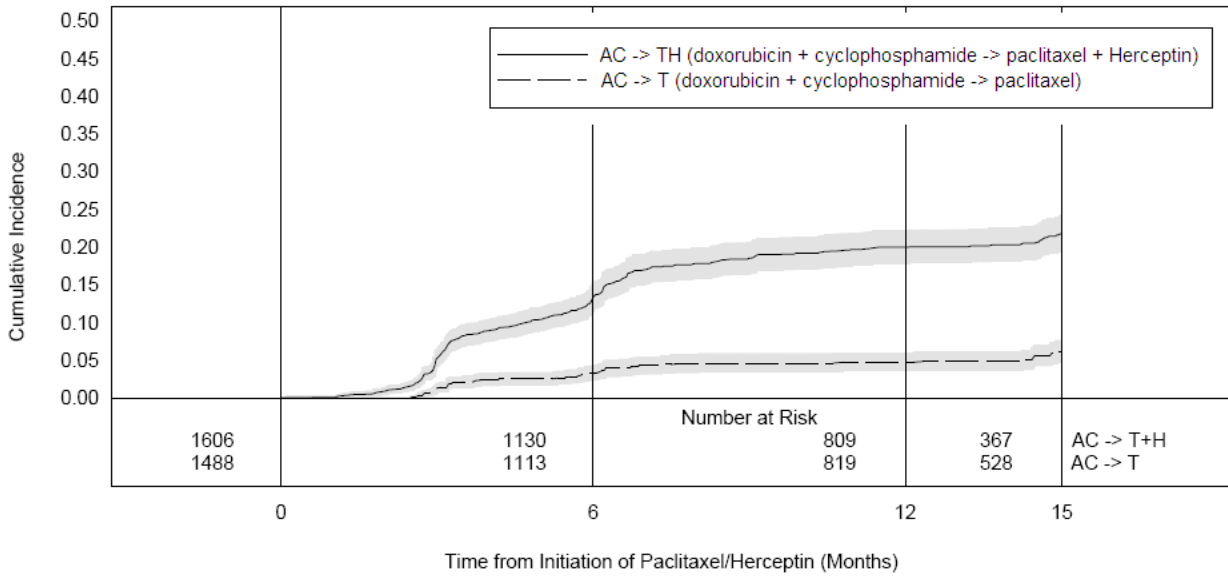
^b Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

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

328

329
330
331
332

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

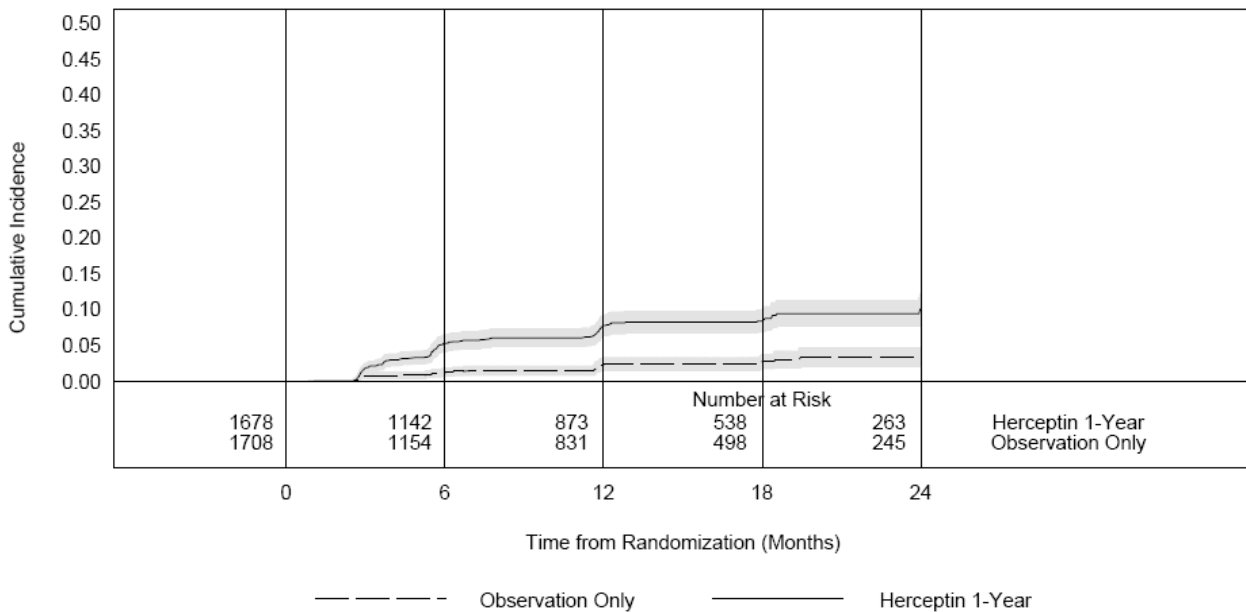


333
334
335

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

336
337
338
339

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

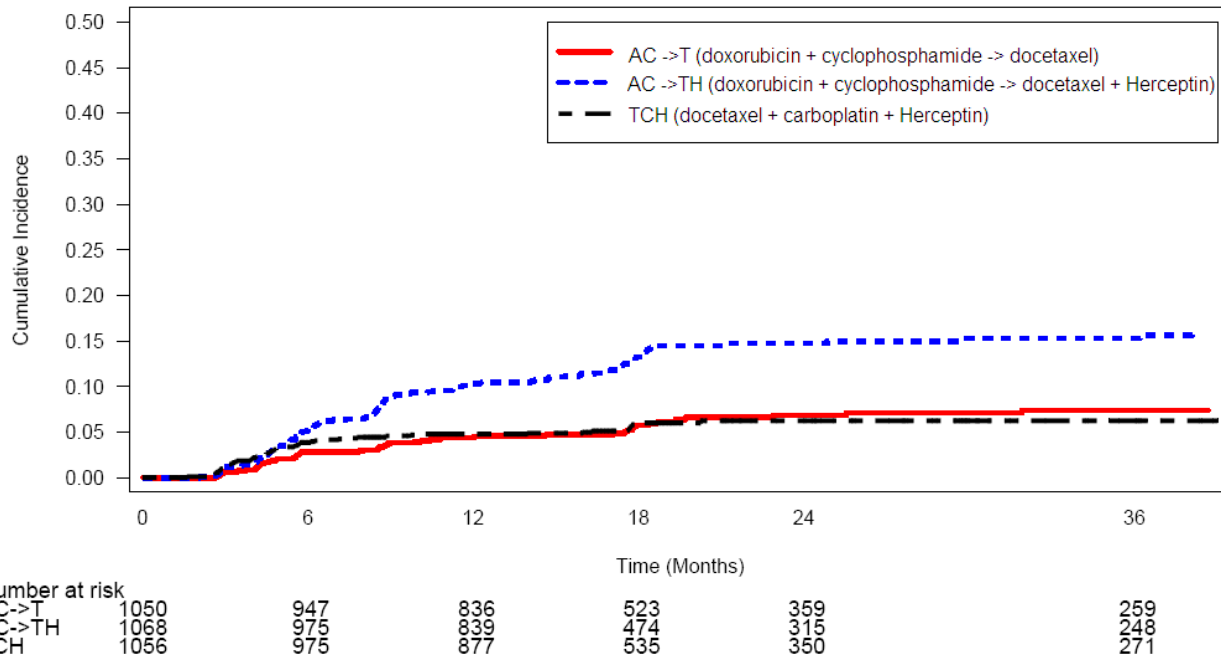


340
341
342

Time 0 is the date of randomization.

343
344
345
346

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



347
348
349

Time 0 is the date of randomization.

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

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

358

359 *Infusion Reactions*

360 During the first infusion with Herceptin, the symptoms most commonly reported were chills and
361 fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with
362 acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of
363 Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity was required in
364 $<1\%$ of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at
365 tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and
366 asthenia. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9%
367 of patients, on second or subsequent Herceptin infusions administered as monotherapy or in
368 combination with chemotherapy, respectively. In the post-marketing setting, severe infusion
369 reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

370

371 *Anemia*

372 In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]),
373 of selected NCI-CTC Grade $\bar{2}$ -5 anemia (12.5% vs. 6.6% [Study 1]), and of anemia requiring
374 transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and

375 chemotherapy compared with those receiving chemotherapy alone. Following the administration of
376 Herceptin as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was < 1%. In
377 Study 7 (metastatic gastric cancer) on the Herceptin containing arm as compared to the
378 chemotherapy alone arm the overall incidence of anemia was 28% compared 21% and of NCI CTC
379 Grade 3/4 anemia was 12.2% compared to 10.3%.

380 381 *Neutropenia*

382 In randomized controlled clinical trials in the adjuvant setting, the incidence of selected
383 NCI-CTC Grade 4–5 neutropenia (2% vs. 0.7% [Study 2]) and of selected Grade 2–5 neutropenia
384 (7.1% vs. 4.5% [Study 1]) were increased in patients receiving Herceptin and chemotherapy
385 compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients
386 with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and
387 of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in
388 combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7
389 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone
390 arm, the incidence of NCI CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile
391 neutropenia 5.1% compared to 2.8%.

392 393 *Infection*

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

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

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

405 406 *Pulmonary Toxicity*

407 *Adjuvant Breast Cancer*

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

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

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

420 *Metastatic Breast Cancer*

421 Among women receiving Herceptin for treatment of metastatic breast cancer, the incidence of
422 pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the

423 post-marketing experience as part of the symptom complex of infusion reactions. Pulmonary events
424 include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic
425 pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see *Warnings*
426 *and Precautions* (5.4).

427 *Thrombosis/Embolism*

428 In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher
429 in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies
430 (3.0% vs. 1.3% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]).

431 *Diarrhea*

432 Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC
433 Grade 2–5 diarrhea (6.2% vs. 4.8% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (1.6% vs. 0%
434 [Study 2]), and of Grade 1–4 diarrhea (7% vs. 1% [Study 3]) were higher in patients receiving
435 Herceptin as compared to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher
436 [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH
437 vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single
438 agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased
439 incidence of diarrhea was observed in patients receiving Herceptin in combination with
440 chemotherapy for treatment of metastatic breast cancer.

441 *Renal Toxicity*

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

447 In the postmarketing setting, rare cases of nephrotic syndrome with pathologic evidence of
448 glomerulopathy have been reported. The time to onset ranged from 4 months to approximately
449 18 months from initiation of Herceptin therapy. Pathologic findings included membranous
450 glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications
451 included volume overload and congestive heart failure.

452 **6.2 Immunogenicity**

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

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

464 **6.3 Post-Marketing Experience**

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

- 468 • Infusion reaction [*see Warnings and Precautions* (5.2)]
- 469 • Oligohydramnios [*see Warnings and Precautions* (5.6)]

- Glomerulopathy [*see Adverse Reactions (6.1)*]

7 DRUG INTERACTIONS

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Category D [*see Warnings and Precautions (5.6)*]

Herceptin can cause fetal harm when administered to a pregnant woman. Post-marketing case reports suggest that Herceptin use during pregnancy increases the risk for oligohydramnios during the second and third trimester. If Herceptin is used during pregnancy or if a woman becomes pregnant while taking Herceptin, she should be apprised of the potential hazard to a fetus.

In the postmarketing setting, oligohydramnios was reported in women who received Herceptin during pregnancy, either alone or in combination with chemotherapy. In half of these women, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin was resumed after the amniotic fluid index improved, and oligohydramnios recurred.

Women using Herceptin during pregnancy should be monitored for oligohydramnios. If oligohydramnios occurs, fetal testing should be done that is appropriate for gestational age and consistent with community standards of care. Additional intravenous (IV) hydration has been helpful when oligohydramnios has occurred following administration of other chemotherapy agents, however the effects of additional IV hydration with Herceptin treatment are not known.

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

Registry

Pregnant women with breast cancer who are using Herceptin are encouraged to enroll in MoTHER—the Herceptin Pregnancy Registry: phone 1-800-690-6720.

8.3 Nursing Mothers

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

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

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

521 **8.4 Pediatric Use**

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

523 **8.5 Geriatric Use**

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

534 In Study 7 (metastatic gastric cancer), of the 294 patients treated with Herceptin 108 (37%) were
535 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or
536 effectiveness were observed.

537

538 **10 OVERDOSAGE**

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

541

542 **11 DESCRIPTION**

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

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

553

554 **12 CLINICAL PHARMACOLOGY**

555 **12.1 Mechanism of Action**

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

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

563 **12.2 Pharmacokinetics**

564 The pharmacokinetics of trastuzumab were studied in women with metastatic breast cancer. Short
565 duration intravenous infusions of 10 to 500 mg Herceptin once weekly demonstrated dose-dependent
566 pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level.
567 The half-life averaged 2 and 12 days at the 10 and 500 mg dose levels, respectively. The volume of
568 distribution of trastuzumab was approximately that of serum volume (44 mL/kg). At the highest
569 weekly dose studied (500 mg), mean peak serum concentrations were 377 mcg/mL.

570 In studies using an initial dose of 4 mg/kg followed by a weekly dose of 2 mg/kg, a mean half-life
571 of 6 days (range 1–32 days) was observed. Between weeks 16 and 32, trastuzumab serum
572 concentrations reached a steady state with mean trough and peak concentrations of approximately
573 79 mcg/mL and 123 mcg/mL, respectively.

574 In a study of women receiving adjuvant therapy for breast cancer, a mean half-life of trastuzumab
575 of 16 days (range: 11–23 days) was observed after an initial dose of 8 mg/kg followed by a dose of
576 6 mg/kg every three weeks. Between weeks 6 and 37, trastuzumab serum concentrations reached a
577 steady-state with mean trough and peak concentrations of 63 mcg/mL and 216 mcg/mL,
578 respectively.

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

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

587 Data suggest that the disposition of trastuzumab is not altered based on age or serum creatinine
588 (≤ 2.0 mg creatinine/dL).

589

590 **13 NONCLINICAL TOXICOLOGY**

591 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

592 Herceptin has not been tested for carcinogenic potential.

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

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

601 **13.2 Animal Toxicology and/or Pharmacology**

602 *Reproductive Toxicology Studies*

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

610

611 14 CLINICAL STUDIES

612 14.1 Adjuvant Breast Cancer

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

618 *Studies 1 and 2*

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

625 Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by
626 paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin).
627 In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m² and cyclophosphamide
628 600 mg/m². Paclitaxel was administered either weekly (80 mg/m²) or every 3 weeks (175 mg/m²)
629 for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in
630 Study 2. Herceptin was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a
631 dose of 2 mg/kg weekly for a total of 52 weeks. Herceptin treatment was permanently discontinued
632 in patients who developed congestive heart failure, or persistent/recurrent LVEF decline [*see Dosage*
633 *and Administration (2.2)*]. Radiation therapy, if administered, was initiated after the completion of
634 chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-free
635 survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral
636 breast cancer, other second primary cancer, or death, was the main outcome measure of the
637 combined efficacy analysis.

638 A total of 3752 patients were included in the efficacy analyses. The data from both arms in
639 Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. Of these
640 patients, the median age was 49 years (range, 22–80 years; 6% > 65 years), 84% were white,
641 7% black, 4% Hispanic, and 4% Asian/Pacific Islander. Disease characteristics included 90%
642 infiltrating ductal histology, 38% T1, 91% nodal involvement, 27% intermediate and 66% high
643 grade pathology, and 53% ER+ and/or PR+ tumors. At the time of randomization 53% of the
644 population were to receive paclitaxel on a weekly regimen, and the remainder were to receive a
645 q3 week schedule of paclitaxel.

646 *Study 3*

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

653 Patients were randomized (1:1) upon completion of definitive surgery, and at least four cycles of
654 chemotherapy to receive no additional treatment (n = 1693) or 1 year of Herceptin treatment
655 (n = 1693). Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients
656 with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator

657 discretion. Herceptin was administered with an initial dose of 8 mg/kg followed by subsequent
658 doses of 6 mg/kg once every three weeks for a total of 52 weeks. The main outcome measure was
659 disease-free survival (DFS), defined as in Studies 1 and 2.

660 Among the 3386 patients randomized to the two treatment arms, the median age was 49 years
661 (range 21–80), 83% were Caucasian, and 13% were Asian. Disease characteristics: 94% infiltrating
662 ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32% node negative, and in 11% of
663 patients, nodal status was not assessable due to prior neo-adjuvant chemotherapy.
664 Ninety-six percent (1055/1098) of patients with node-negative disease had high-risk features:
665 among the 1098 patients with node-negative disease, 49% (543) were ER– and PgR–, and 47%
666 (512) were ER and/or PgR + and had at least one of the following high-risk features: pathological
667 tumor size greater than 2 cm, Grade 2–3, or age < 35 years. Prior to randomization, 94% of patients
668 had received anthracycline-based chemotherapy regimens.

669 *Study 4*

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

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

688 Among the 3222 patients randomized, the median age was 49 (range 22 to 74 years; 6%
689 ≥65 years). Disease characteristics included 54% ER+ and/or PR+ and 71% node positive. Prior to
690 randomization, all patients underwent primary surgery for breast cancer.

691

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^e</u>				
AC→TH (n=1872)	133	0.48 ^a (0.39, 0.59) p=< 0.0001 ^b	62	0.67 p=NS ^d
AC→T (n = 1880)	261		92	
<u>Study 3</u>				
Chemo→ Herceptin (n =1693)	127	0.54 (0.44, 0.67) p=< 0.0001 ^c	31	0.75 p=NS ^d
Chemo→ Observation (n = 1693)	219		40	
<u>Study 4^f</u>				
TCH (n=1075)	134	0.67 (0.54 – 0.84) p=0.0006 ^{b,g}	56	
AC→TH (n=1074)	121	0.60 (0.48 – 0.76) p=< 0.0001 ^{b,g}	49	
AC→T (n=1073)	180		80	

CI = confidence interval.

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

^b stratified log-rank test.

^c log-rank test.

^d NS= non-significant.

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

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

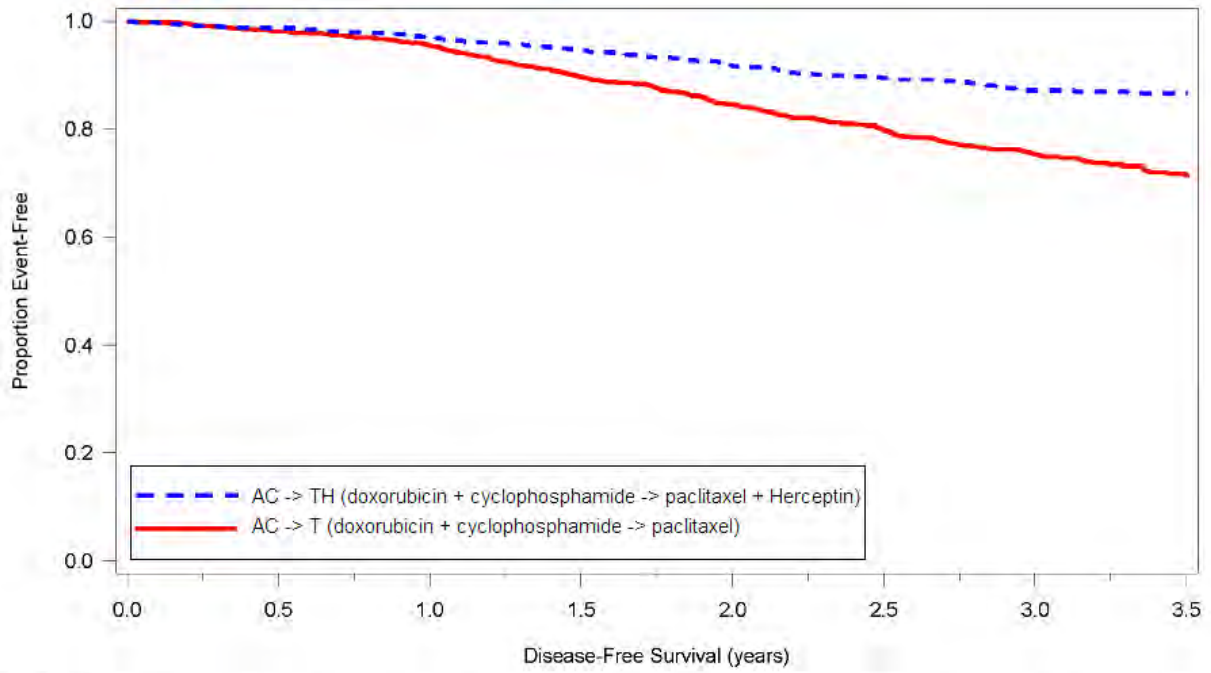
^g A two-sided alpha level of 0.025 for each comparison.

692

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

701
702
703

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

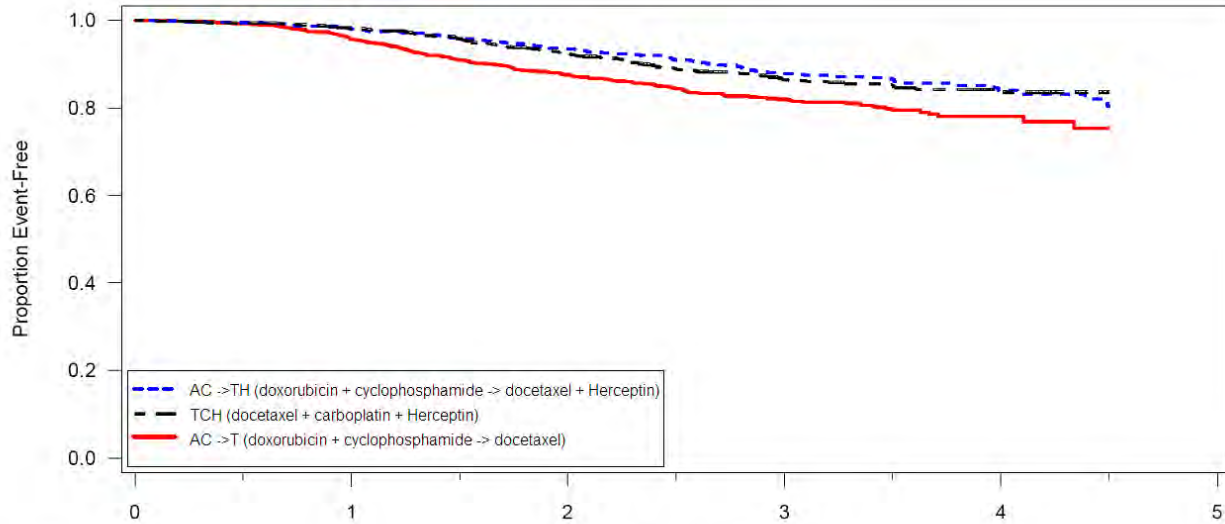


Number at risk								
AC -> T	1880	1490	1159	926	689	534	375	195
AC -> T + H	1872	1529	1240	997	764	575	426	239

704
705

706
707
708

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



	Disease-Free Survival (years)			
Number at risk	0	1	2	3
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.

709
710
711
712
713
714
715
716
717
718

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

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

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

719

720 14.2 Metastatic Breast Cancer

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

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

728 Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with
729 metastatic breast cancer who had not been previously treated with chemotherapy for metastatic
730 disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+,
731 or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were
732 eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or
733 in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly
734 doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the
735 adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m² over 3 hours every 21 days for at
736 least six cycles); for all other patients, chemotherapy consisted of anthracycline plus
737 cyclophosphamide (AC: doxorubicin 60 mg/m² or epirubicin 75 mg/m² plus 600 mg/m²
738 cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to
739 receive chemotherapy alone in this study received Herceptin at the time of disease progression as
740 part of a separate extension study.

741 Based upon the determination by an independent response evaluation committee the patients
742 randomized to Herceptin and chemotherapy experienced a significantly longer median time to
743 disease progression, a higher overall response rate (ORR), and a longer median duration of response,
744 as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin
745 and chemotherapy also had a longer median survival (see Table 9). These treatment effects were

746 observed both in patients who received Herceptin plus paclitaxel and in those who received
 747 Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.
 748

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

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

^b Assessed by an independent Response Evaluation Committee.

^c Kaplan-Meier Estimate.

^d log-rank test.

^e χ^2 -test.

749
 750 Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients
 751 with the highest level of HER2 protein overexpression (3+) (see [Table 10](#)).
 752

Table 10
Treatment Effects in Study 5 as a
Function of HER2 Overexpression or Amplification

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

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

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

753

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

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

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

767 **14.3 Metastatic Gastric Cancer**

768 The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine
769 (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or
770 gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial,
771 594 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine
772 (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic
773 vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes
774 vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil).
775 All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients
776 were also required to have adequate cardiac function (e.g., LVEF > 50%).

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

779 cisplatin was administered at a dose of 80 mg/m² Day 1 every 3 weeks for 6 cycles as a 2 hour IV
 780 infusion. On both study arms capecitabine was administered at 1000 mg/m² dose orally twice daily
 781 (total daily dose 2000 mg/m²) for 14 days of each 21 day cycle for 6 cycles. Alternatively continuous
 782 intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m²/day from Day 1
 783 through Day 5 every three weeks for 6 cycles.

784 The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were
 785 Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1;
 786 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these
 787 patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant
 788 therapy, and 2% had received prior radiotherapy.

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

794

Table 11
 Study 7: Overall Survival in ITT Population

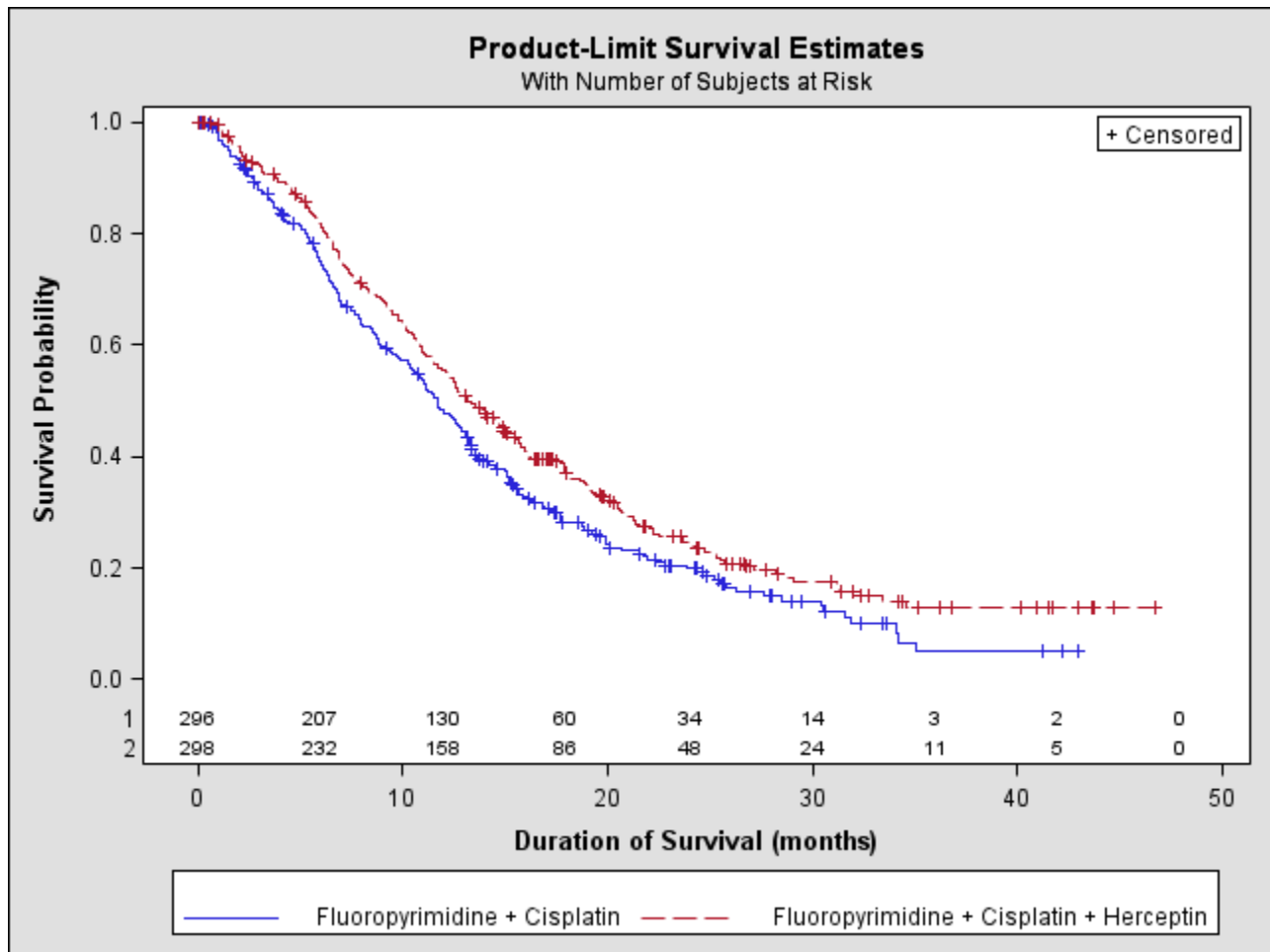
	FC Arm N=296	FC + H Arm N=298
<u>Definitive (Second Interim) Overall Survival</u>		
No. Deaths (%)	184 (62.2%)	167 (56.0%)
Median	11.0	13.5
95% CI (mos.)	(9.4, 12.5)	(11.7, 15.7)
Hazard Ratio		0.73
95% CI		(0.60, 0.91)
p-value*, two-sided		0.0038
<u>Updated Overall Survival</u>		
No. Deaths (%)	227 (76.7%)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

795

796
797

Figure 6
Updated Overall Survival in Patients with Metastatic Gastric Cancer (Study 7)



798
799
800
801
802

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

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

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

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

803

804 **16 HOW SUPPLIED/STORAGE AND HANDLING**

805 **16.1 How Supplied**

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

810 **16.2 Stability and Storage**

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

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

820 **17 PATIENT COUNSELING INFORMATION**

- 821 • Advise patients to contact a health care professional immediately for any of the following: new
822 onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face,
823 palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness
824 [*see Boxed Warning: [Cardiomyopathy](#)*].
- 825 • Advise pregnant women and women of childbearing potential that Herceptin exposure can
826 result in fetal harm [*see Warnings and Precautions (5.6) and Use in Specific Populations*
827 *(8.1)*].
- 828 • Advise women of childbearing potential to use effective contraceptive methods during
829 treatment and for a minimum of six months following Herceptin [*see Warnings and*
830 *Precautions (5.6)*].
- 831 • Encourage women who are exposed to Herceptin during pregnancy to enroll in MotHER- the
832 Herceptin Pregnancy Registry [*see Pregnancy (8.1)*].
- 833

HERCEPTIN[®] [trastuzumab]

Manufactured by:

Genentech, Inc.

1 DNA Way

South San Francisco, CA 94080-4990

4851301

Initial US Approval: Sept. 1998

Revision Date: October 2010

©2010 Genentech, Inc.