

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103792Orig1s5311

LABELING

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

Dosage and Administration (2) 03/2014
Warnings and Precautions, Cardiomyopathy (5.1) 03/2014

INDICATIONS AND USAGE

Herceptin is a HER2/neu receptor antagonist indicated for:

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

DOSAGE AND ADMINISTRATION

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

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

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.1)

Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 52 weeks, or

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

Metastatic HER2-Overexpressing Breast Cancer (2.1)

- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.

Metastatic HER2-overexpressing Gastric Cancer (2.1)

- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- 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)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

- 1.1 Adjuvant Breast Cancer
- 1.2 Metastatic Breast Cancer
- 1.3 Metastatic Gastric Cancer

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Doses and Schedules
- 2.2 Dose Modifications
- 2.3 Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Cardiomyopathy
- 5.2 Infusion Reactions
- 5.3 Embryo-Fetal Toxicity
- 5.4 Pulmonary Toxicity
- 5.5 Exacerbation of Chemotherapy-Induced Neutropenia
- 5.6 HER2 Testing

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity
- 6.3 Post-Marketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

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

14 CLINICAL STUDIES

- 14.1 Adjuvant Breast Cancer
- 14.2 Metastatic Breast Cancer
- 14.3 Metastatic Gastric Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 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, EMBRYO-FETAL** 3 **TOXICITY, and PULMONARY TOXICITY**

4 **Cardiomyopathy**

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

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

12 **Infusion Reactions; Pulmonary Toxicity**

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

19 **Embryo-Fetal Toxicity**

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

24 1 INDICATIONS AND USAGE

25 1.1 Adjuvant Breast Cancer

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

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

32 1.2 Metastatic Breast Cancer

33 Herceptin is indicated:

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

38 1.3 Metastatic Gastric Cancer

39 Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the
40 treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction
41 adenocarcinoma, who have not received prior treatment for metastatic disease.
42

43 2 DOSAGE AND ADMINISTRATION

44 2.1 Recommended Doses and Schedules

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

48 *Adjuvant Treatment, Breast Cancer:*

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

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

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

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

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

62 [*see Dose Modifications (2.2)*]

63 *Metastatic Treatment, Breast Cancer:*

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

67 *Metastatic Gastric Cancer*

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

71 2.2 Dose Modifications

72 *Infusion Reactions*

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

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

77 *Cardiomyopathy*

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

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

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

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

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

2.3 Preparation for Administration

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

Reconstitution

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

Use appropriate aseptic technique when performing the following reconstitution steps:

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

Dilution

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

3 DOSAGE FORMS AND STRENGTHS

440 mg lyophilized powder per multi-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

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

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

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

Withhold Herceptin for $\geq 16\%$ absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and $\geq 10\%$ absolute decrease in LVEF from pretreatment

136 values [see *Dosage and Administration (2.2)*]. The safety of continuation or resumption of
137 Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been
138 studied.

139 *Cardiac Monitoring*

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

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

148 In Study 1, 15% (158/1031) of patients discontinued Herceptin due to clinical evidence of
149 myocardial dysfunction or significant decline in LVEF after a median follow-up duration of
150 8.7 years in the AC-TH arm. In Study 3, the number of patients who discontinued Herceptin due to
151 cardiac toxicity was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) patients in the TCH arm
152 (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068)
153 patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy
154 phase) discontinued Herceptin due to cardiac toxicity.

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

162

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

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

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

^b Anthracycline (doxorubicin) and cyclophosphamide.

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

163

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.

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

5.2 Infusion Reactions

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

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

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.

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.

5.3 Embryo-Fetal Toxicity

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)*].

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

198 pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and
199 pulmonary fibrosis. Such events can occur as sequelae of infusion reactions [*see Warnings and*
200 *Precautions (5.2)*]. Patients with symptomatic intrinsic lung disease or with extensive tumor
201 involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

202 **5.5 Exacerbation of Chemotherapy-Induced Neutropenia**

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

208 **5.6 HER2 Testing**

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

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

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

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

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

232

233 **6 ADVERSE REACTIONS**

234

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

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

241

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

246 left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity [*see Dosage and*
247 *Administration (2.2)*].

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

255 **6.1 Clinical Trials Experience**

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

259 *Adjuvant Breast Cancer Studies*

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

263 The data summarized in Table 3 below, from Study 3, reflect exposure to Herceptin in
264 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18.
265 Among the 3386 patients enrolled in Study 3, the median age was 49 years (range: 21 to 80 years),
266 83% of patients were Caucasian, and 13% were Asian.
267

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 (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^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 (0.06%)	0 (0%)
<u>Infections</u>		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	39 (3%)	13 (0.8%)
<u>Immune System Disorders</u>		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

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

^b Higher level grouping term.

269

270 The safety data from Studies 1 and 2 were obtained from 3655 patients, of whom 2000 received
271 Herceptin; the median treatment duration was 51 weeks. The median age was 49 years (range:
272 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian.

273 In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5
274 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The
275 following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater
276 among patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone: fatigue
277 (29.5% vs. 22.4%), infection (24.0% vs. 12.8%), hot flashes (17.1% vs. 15.0%), anemia (12.3% vs.
278 6.7%), dyspnea (11.8% vs. 4.6%), rash/desquamation (10.9% vs. 7.6%), leukopenia (10.5% vs.
279 8.4%), neutropenia (6.4% vs. 4.3%), headache (6.2% vs. 3.8%), pain (5.5% vs. 3.0%), edema (4.7%
280 vs. 2.7%) and insomnia (4.3% vs. 1.5%). The majority of these events were Grade 2 in severity.

281 In Study 2, data collection was limited to the following investigator-attributed treatment-related
282 adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic
283 toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes,
284 motor neuropathy, sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during
285 chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of
286 Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving Herceptin plus
287 chemotherapy as compared to chemotherapy alone: arthralgia (12.2% vs. 9.1%), nail changes
288 (11.5% vs. 6.8%), dyspnea (2.4% vs. 0.2%), and diarrhea (2.2% vs. 0%). The majority of these
289 events were Grade 2 in severity.

290 Safety data from Study 4 reflect exposure to Herceptin as part of an adjuvant treatment regimen
291 from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TCH: n=1056].
292 The overall median treatment duration was 54 weeks in both the AC-TH and TCH arms.
293 The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including
294 weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy
295 period. Among these patients, the median age was 49 years (range 22 to 74 years). In Study 4, the
296 toxicity profile was similar to that reported in Studies 1, 2, and 3 with the exception of a low
297 incidence of CHF in the TCH arm.

298 *Metastatic Breast Cancer Studies*

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

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

308 Among the 352 patients treated in single agent studies (213 patients from Study 6), the median
 309 age was 50 years (range 28–86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in
 310 other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed
 311 by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months
 312 and ≥ 12 months were 31% and 16%, respectively.
 313

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

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

314

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.

315

316 *Metastatic Gastric Cancer*

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

320 chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was
 321 administered at 80 mg/m² on Day 1 and the fluoropyrimidine was administered as either
 322 capecitabine 1000 mg/m² orally twice a day on Days 1–14 or 5-fluorouracil 800 mg/m²/day as a
 323 continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day
 324 cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin
 325 infusions administered was eight.
 326

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

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

327

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

331 *Cardiomyopathy*

332 Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant
333 treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months
334 (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and
335 2, 7.9 years in the AC-T arm, 8.3 years in the AC-TH arm. In Studies 1 and 2, 6% of all randomized
336 patients with post-AC LVEF evaluation were not permitted to initiate Herceptin following
337 completion of AC chemotherapy due to cardiac dysfunction (LVEF < LLN or ≥ 16 point decline in
338 LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of
339 new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and
340 paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients
341 receiving Herceptin monotherapy compared to observation in Study 3 (see Table 6, Figures 1 and 2).
342 The per-patient incidence of new-onset cardiac dysfunction, as measured by LVEF, remained similar
343 when compared to the analysis performed at a median follow-up of 2.0 years in the AC-TH arm.
344 This analysis also showed evidence of reversibility of left ventricular dysfunction, with 64.5% of
345 patients who experienced symptomatic CHF in the AC-TH group being asymptomatic at latest
346 follow-up, and 90.3% having full or partial LVEF recovery.

347

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

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

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

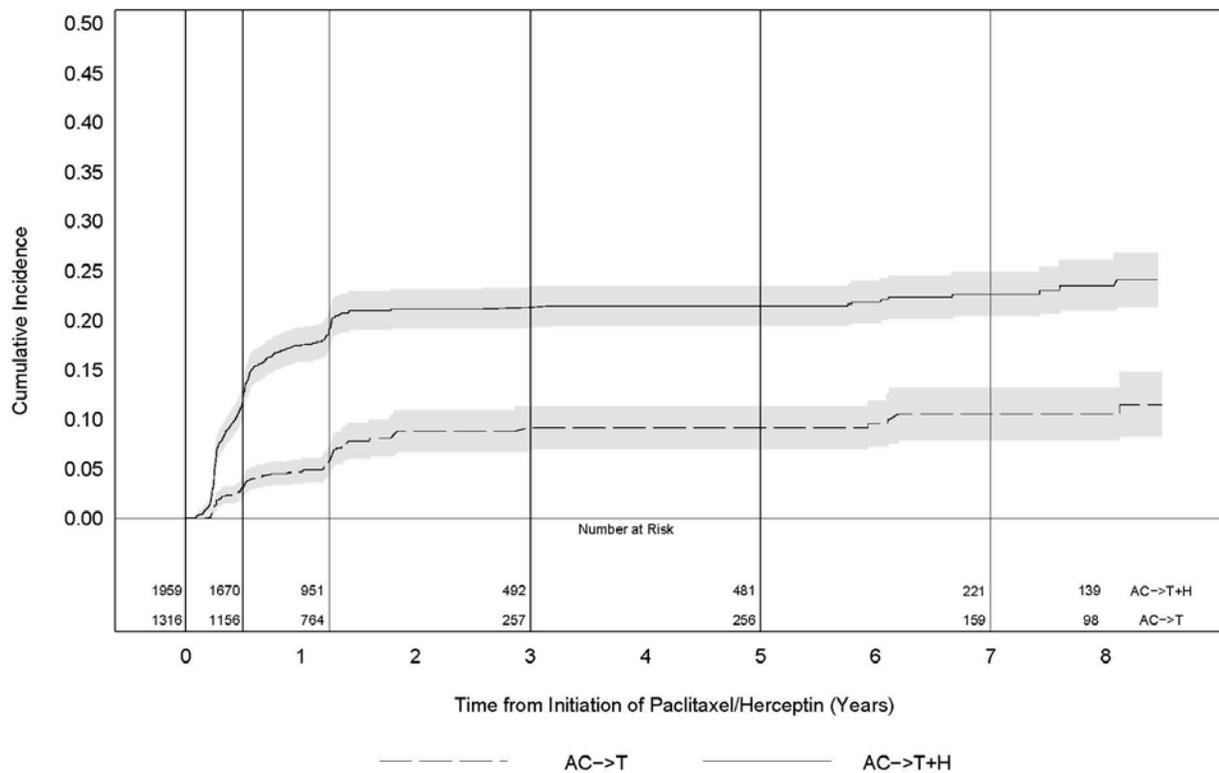
^b Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

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

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

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

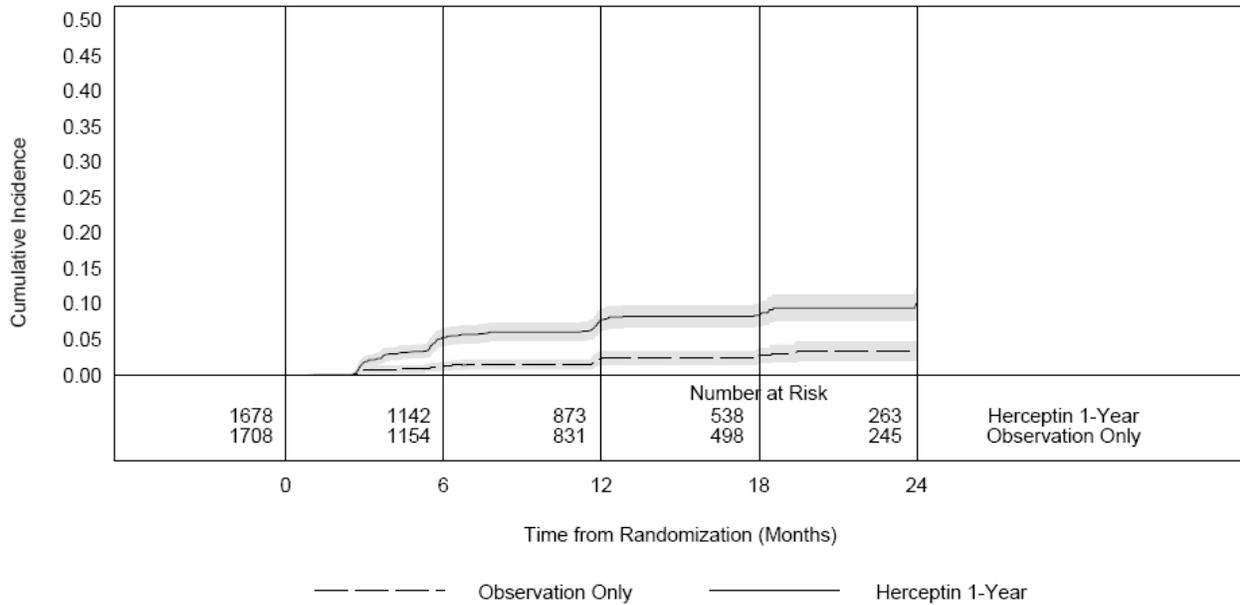


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Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

357
358
359
360

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



361

Time 0 is the date of randomization.

362

363

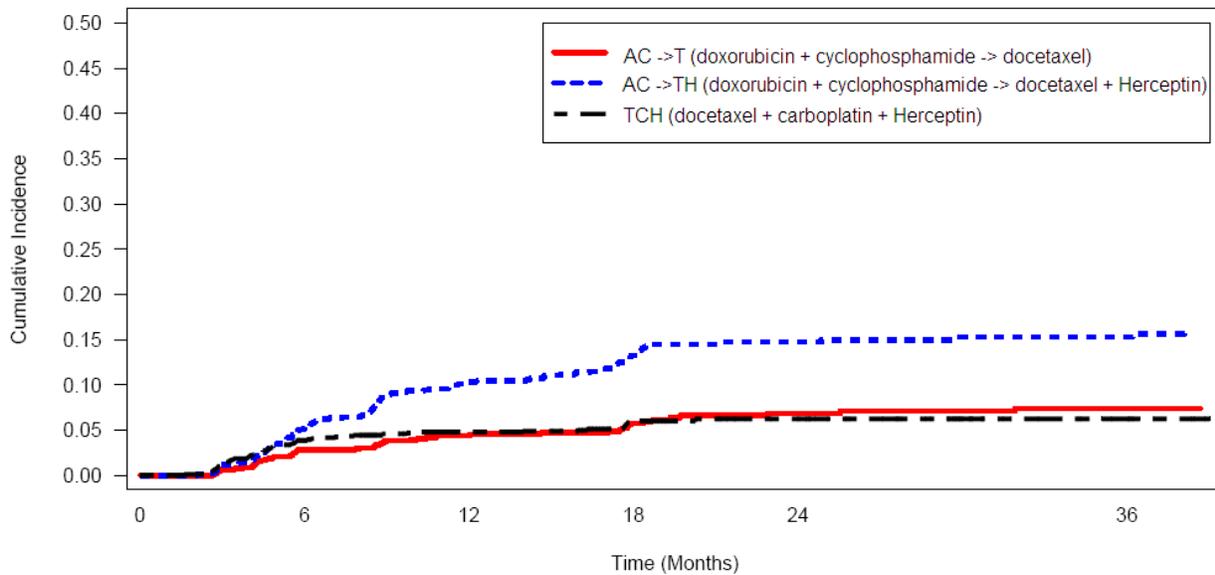
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Figure 3
Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



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

368

Time 0 is the date of randomization.

369

370

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

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

379 *Infusion Reactions*

380 During the first infusion with Herceptin, the symptoms most commonly reported were chills and
381 fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with
382 acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of
383 Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity was required in
384 $< 1\%$ of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at
385 tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and
386 asthenia. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9%
387 of patients, on second or subsequent Herceptin infusions administered as monotherapy or in
388 combination with chemotherapy, respectively. In the post-marketing setting, severe infusion
389 reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

390 *Anemia*

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

399 *Neutropenia*

400 In randomized controlled clinical trials in the adjuvant setting, the incidence of selected
401 NCI-CTC Grade 4–5 neutropenia (1.7% vs. 0.8% [Study 2]) and of selected Grade 2–5 neutropenia
402 (6.4% vs. 4.3% [Study 1]) were increased in patients receiving Herceptin and chemotherapy
403 compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients
404 with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and
405 of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in
406 combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7
407 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone
408 arm, the incidence of NCI CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile
409 neutropenia 5.1% compared to 2.8%.

410 *Infection*

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

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

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

422 *Pulmonary Toxicity*

423 *Adjuvant Breast Cancer*

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

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

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

436 *Metastatic Breast Cancer*

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

443 *Thrombosis/Embolism*

444 In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher
445 in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies
446 (2.6% vs. 1.5% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]).

447 *Diarrhea*

448 Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC
449 Grade 2–5 diarrhea (6.7% vs. 5.4% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (2.2% vs. 0%
450 [Study 2]), and of Grade 1–4 diarrhea (7% vs. 1% [Study 3]) were higher in patients receiving
451 Herceptin as compared to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher
452 [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH
453 vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single
454 agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased
455 incidence of diarrhea was observed in patients receiving Herceptin in combination with
456 chemotherapy for treatment of metastatic breast cancer.

457 *Renal Toxicity*

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

463 In the postmarketing setting, rare cases of nephrotic syndrome with pathologic evidence of
464 glomerulopathy have been reported. The time to onset ranged from 4 months to approximately
465 18 months from initiation of Herceptin therapy. Pathologic findings included membranous

466 glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications
467 included volume overload and congestive heart failure.

468 **6.2 Immunogenicity**

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

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

480 **6.3 Post-Marketing Experience**

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

- 484 • Infusion reaction [*see Warnings and Precautions (5.2)*]
 - 485 • Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal
486 abnormalities, and neonatal death [*see Warnings and Precautions (5.3)*]
 - 487 • Glomerulopathy [*see Adverse Reactions (6.1)*]
- 488

489 **7 DRUG INTERACTIONS**

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

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

499

500 **8 USE IN SPECIFIC POPULATIONS**

501 **8.1 Pregnancy: Category D** [*see Warnings and Precautions (5.3), Nonclinical Toxicology* 502 *(13.2)*]

503 Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing
504 reports of Herceptin during pregnancy resulted in cases of oligohydramnios and of
505 oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and
506 neonatal death.

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

511 Monitor women exposed to Herceptin during pregnancy for oligohydramnios. If oligohydramnios
512 occurs, perform fetal testing that is appropriate for gestational age and consistent with community

513 standards of care. The efficacy of IV hydration in management of oligohydramnios due to Herceptin
514 exposure is not known.

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

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

525 **8.3 Nursing Mothers**

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

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

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

538 **8.4 Pediatric Use**

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

540 **8.5 Geriatric Use**

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

551 In Study 7 (metastatic gastric cancer), of the 294 patients treated with Herceptin 108 (37%) were
552 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or
553 effectiveness were observed.

554 **10 OVERDOSAGE**

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

558

559 **11 DESCRIPTION**

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

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

571 **12 CLINICAL PHARMACOLOGY**

572 **12.1 Mechanism of Action**

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

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

580 **12.2 Pharmacokinetics**

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

587 In studies using an initial dose of 4 mg/kg followed by a weekly dose of 2 mg/kg, a mean half-life
588 of 6 days (range 1–32 days) was observed. Between weeks 16 and 32, trastuzumab serum
589 concentrations reached a steady state with mean trough and peak concentrations of approximately
590 79 mcg/mL and 123 mcg/mL, respectively.

591 In a study of women receiving adjuvant therapy for breast cancer, a mean half-life of trastuzumab
592 of 16 days (range: 11–23 days) was observed after an initial dose of 8 mg/kg followed by a dose of
593 6 mg/kg every three weeks. Between weeks 6 and 37, trastuzumab serum concentrations reached a
594 steady-state with mean trough and peak concentrations of 63 mcg/mL and 216 mcg/mL,
595 respectively.

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

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

604 Data suggest that the disposition of trastuzumab is not altered based on age or serum creatinine
605 (≤ 2.0 mg creatinine/dL).

606

607 13 NONCLINICAL TOXICOLOGY

608 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

609 Herceptin has not been tested for carcinogenic potential.

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

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

618 13.2 Animal Toxicology and/or Pharmacology

619 *Reproductive Toxicology Studies*

620 Reproductive toxicology studies have been conducted in cynomolgus monkeys at doses up to 25
621 times the weekly recommended human dose of 2 mg/kg Herceptin and have revealed no evidence of
622 impaired fertility or harm to the fetus. However, HER2 protein expression is high in many
623 embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died
624 in early gestation. Placental transfer of trastuzumab was detected at Caesarean section in offspring
625 from pregnant cynomolgus monkeys dosed during the early (Days 20–50 of gestation) or late (Days
626 120–150 of gestation) fetal development periods.

627

628 14 CLINICAL STUDIES

629 14.1 Adjuvant Breast Cancer

630 The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2
631 overexpressing breast cancer, were evaluated in an integrated analysis of two randomized,
632 open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final
633 overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of
634 3386 women, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study
635 4).

636 *Studies 1 and 2*

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

643 Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by
644 paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin).
645 In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m² and cyclophosphamide
646 600 mg/m². Paclitaxel was administered either weekly (80 mg/m²) or every 3 weeks (175 mg/m²)
647 for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in
648 Study 2. Herceptin was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a
649 dose of 2 mg/kg weekly for a total of 52 weeks. Herceptin treatment was permanently discontinued
650 in patients who developed congestive heart failure, or persistent/recurrent LVEF decline [*see Dosage*
651 *and Administration (2.2)*]. Radiation therapy, if administered, was initiated after the completion of
652 chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. The primary
653 endpoint of the combined efficacy analysis was Disease-free survival (DFS), defined as the time

654 from randomization to recurrence, occurrence of contralateral breast cancer, other second primary
655 cancer, or death. The secondary endpoint was overall survival (OS).

656 A total of 3752 patients were included in the joint efficacy analysis of the primary endpoint of
657 DFS following a median follow-up of 2.0 years in the AC→paclitaxel + Herceptin arm. The
658 pre-planned final OS analysis from the joint analysis included 4063 patients and was performed
659 when 707 deaths had occurred after a median follow-up of 8.3 years in the AC→paclitaxel +
660 Herceptin arm. The data from both arms in Study 1 and two of the three study arms in Study 2 were
661 pooled for efficacy analyses. The patients included in the primary DFS analysis had a median age of
662 49 years (range, 22–80 years; 6% > 65 years), 84% were white, 7% black, 4% Hispanic, and 4%
663 Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1,
664 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or
665 PR+ tumors. Similar demographic and baseline characteristics were reported for the efficacy
666 evaluable population, after 8.3 years of median follow-up in the AC→paclitaxel + Herceptin arm.

667 *Study 3*

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

674 Patients were randomized (1:1) upon completion of definitive surgery, and at least four cycles of
675 chemotherapy to receive no additional treatment (n = 1693) or 1 year of Herceptin treatment
676 (n = 1693). Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients
677 with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator
678 discretion. Herceptin was administered with an initial dose of 8 mg/kg followed by subsequent
679 doses of 6 mg/kg once every three weeks for a total of 52 weeks. The main outcome measure was
680 disease-free survival (DFS), defined as in Studies 1 and 2.

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

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

690 *Study 4*

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

698 Patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by
699 docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus Herceptin
700 (AC-TH), or docetaxel and carboplatin plus Herceptin (TCH). In both the AC-T and AC-TH arms,
701 doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² were administered every 3 weeks for

702 four cycles; docetaxel 100 mg/m² was administered every 3 weeks for four cycles. In the TCH arm,
703 docetaxel 75 mg/m² and carboplatin (at a target AUC of 6 mg/mL/min as a 30- to 60-minute
704 infusion) were administered every 3 weeks for six cycles. Herceptin was administered weekly
705 (initial dose of 4 mg/kg followed by weekly dose of 2 mg/kg) concurrently with either T or TC, and
706 then every 3 weeks (6 mg/kg) as monotherapy for a total of 52 weeks. Radiation therapy, if
707 administered, was initiated after completion of chemotherapy. Patients with ER+ and/or PR+ tumors
708 received hormonal therapy. Disease-free survival (DFS) was the main outcome measure.

709 Among the 3222 patients randomized, the median age was 49 (range 22 to 74 years; 6%
710 ≥65 years). Disease characteristics included 54% ER+ and/or PR+ and 71% node positive. Prior to
711 randomization, all patients underwent primary surgery for breast cancer.

712 The results for DFS for the integrated analysis of Studies 1 and 2, Study 3, and Study 4 and OS
713 results for the integrated analysis of Studies 1 and 2, and Study 3 are presented in Table 7. For
714 Studies 1 and 2, the duration of DFS following a median follow-up of 2.0 years in the AC→TH arm,
715 is presented in Figure 4, and the duration of OS after a median follow-up of 8.3 years in the
716 AC→TH arm is presented in Figure 5. The duration of DFS for Study 4 is presented in Figure 6.
717 Across all four studies, at the time of definitive DFS analysis, there were insufficient numbers of
718 patients within each of the following subgroups to determine if the treatment effect was different
719 from that of the overall patient population: patients with low tumor grade, patients within specific
720 ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients >65 years of
721 age. For Studies 1 and 2 the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74). At 8.3 years of median
722 follow-up [AC→TH], the survival rate was estimated to be 86.9% in the AC→TH arm and 79.4% in
723 the AC→T arm. The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age,
724 hormone receptor status, number of positive lymph nodes, tumor size and grade, and
725 surgery/radiation therapy, was consistent with the treatment effect in the overall population. In
726 patients ≤ 50 years of age (n=2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in
727 patients > 50 years of age (n=1866), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the
728 subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive)
729 (n=2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with
730 hormone receptor-negative disease (ER-negative and PR-negative) (n=1830), the hazard ratio for OS
731 was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤2 cm (n=1604), the
732 hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size >2
733 cm (n=2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80).

734

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

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

CI = confidence interval.

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

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

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

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

^e stratified log-rank test.

^f log-rank test.

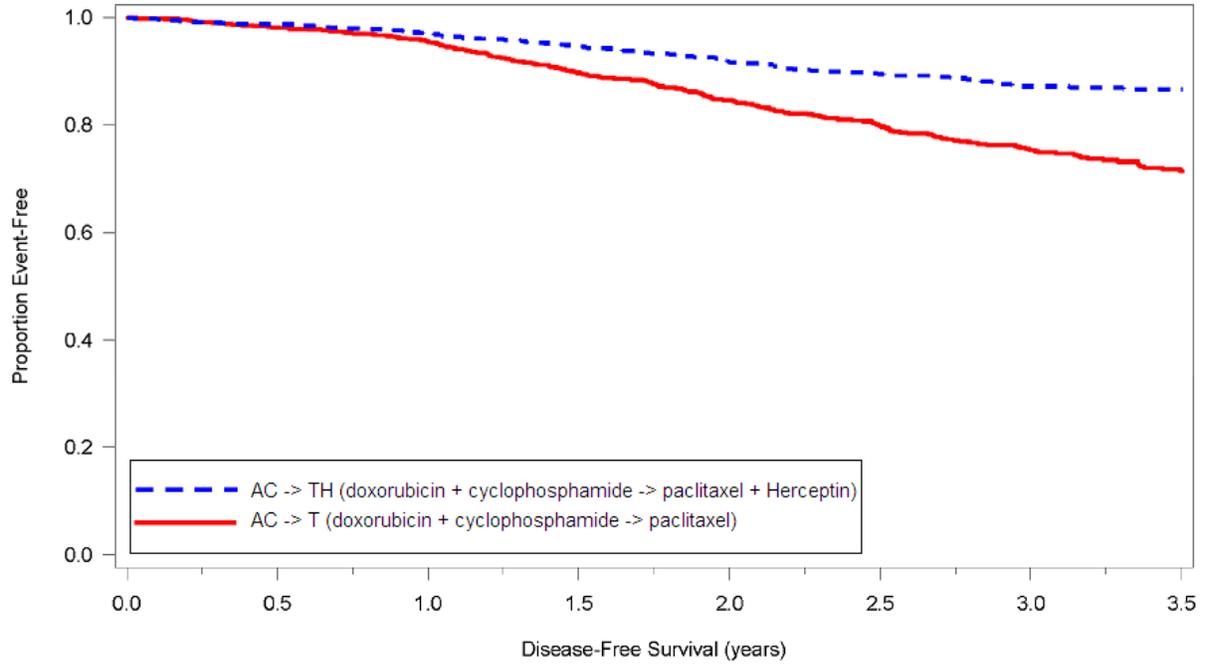
^g NS= non-significant.

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

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

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738

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

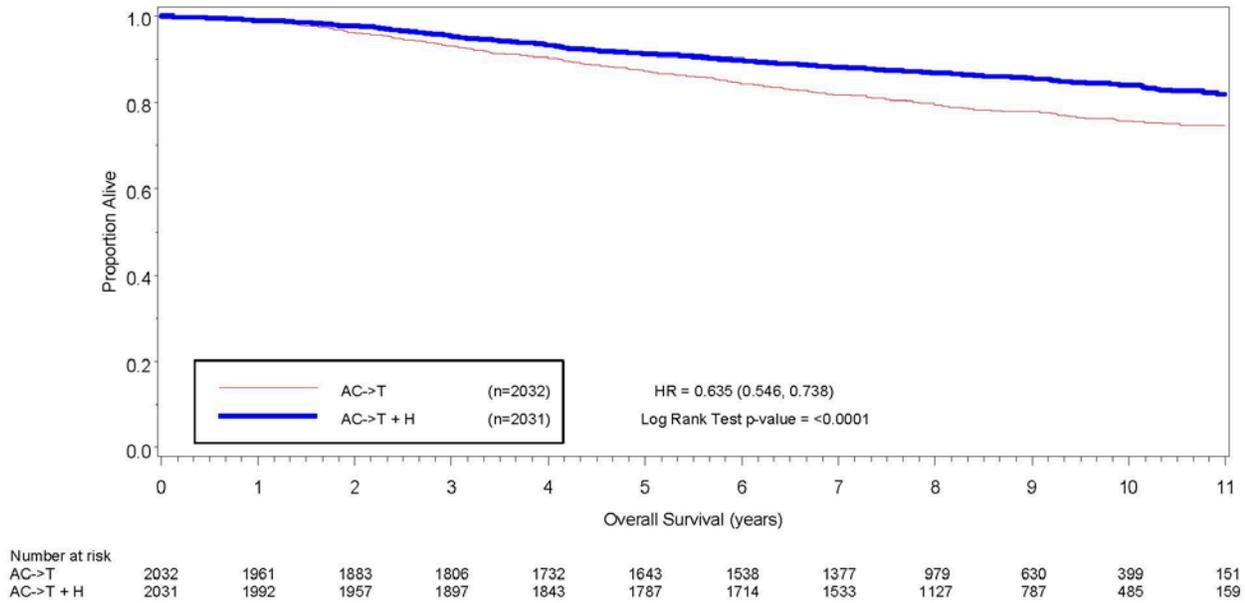


Number at risk								
AC -> T	1880	1490	1159	926	689	534	375	195
AC -> T + H	1872	1529	1240	997	764	575	426	239

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740

741
742
743
744

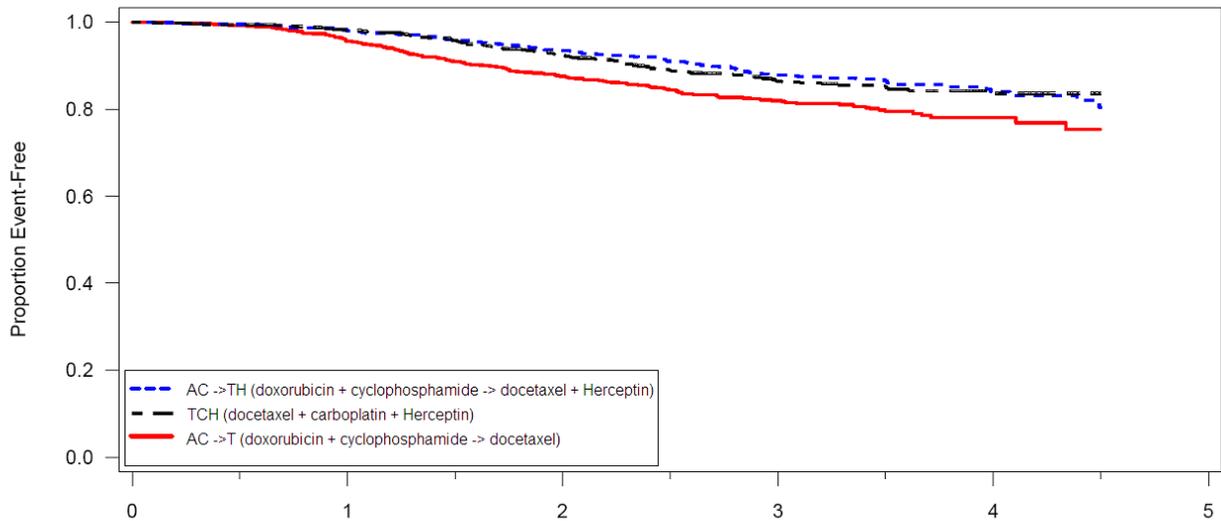
Figure 5
Duration of Overall Survival in Patients with
Adjuvant Treatment of Breast Cancer (Studies 1 and 2)



A=doxorubicin; C=cyclophosphamide; H=Herceptin; T=paclitaxel;
An event was defined as death from any cause at any time during the study.
Kaplan-Meier estimates are shown.
The strata were study, intended paclitaxel schedule, number of positive nodes and hormone receptor status.
Source: Biostatistics\abbycat\pdm\immuno\her2\abcjoint\finalos\programs\g_dur output (g_dur_os_bt)
Database(Data Received in 2013)
Joint Analysis Final Overall Survival : Generated 17.JUL.13 13:33 Page 1 of 1
Datasets (pateff)

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746
747
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749

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



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

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

750
751

752 Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were
 753 conducted for patients in Studies 2 and 3, where central laboratory testing data were available.
 754 The results are shown in Table 8. The number of events in Study 2 was small with the exception of
 755 the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions
 756 cannot be drawn regarding efficacy within other subgroups due to the small number of events.
 757 The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the
 758 IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups.
 759

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+.

760

761 14.2 Metastatic Breast Cancer

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

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

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

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

782 Based upon the determination by an independent response evaluation committee the patients
 783 randomized to Herceptin and chemotherapy experienced a significantly longer median time to
 784 disease progression, a higher overall response rate (ORR), and a longer median duration of response,
 785 as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin
 786 and chemotherapy also had a longer median survival (see Table 9). These treatment effects were
 787 observed both in patients who received Herceptin plus paclitaxel and in those who received
 788 Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.
 789

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.

790

791 Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients
 792 with the highest level of HER2 protein overexpression (3+) (see Table 10).
 793

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.

794

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

796 Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial
797 (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following
798 one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had
799 received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for
800 metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue.
801 Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin at
802 2 mg/kg IV.

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

808 **14.3 Metastatic Gastric Cancer**

809 The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine
810 (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or
811 gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial,
812 594 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine
813 (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic
814 vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes
815 vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil).
816 All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients
817 were also required to have adequate cardiac function (e.g., LVEF > 50%).

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

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

825 The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were
 826 Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1;
 827 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these
 828 patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant
 829 therapy, and 2% had received prior radiotherapy.

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

835

Table 11
 Study 7: Overall Survival in ITT Population

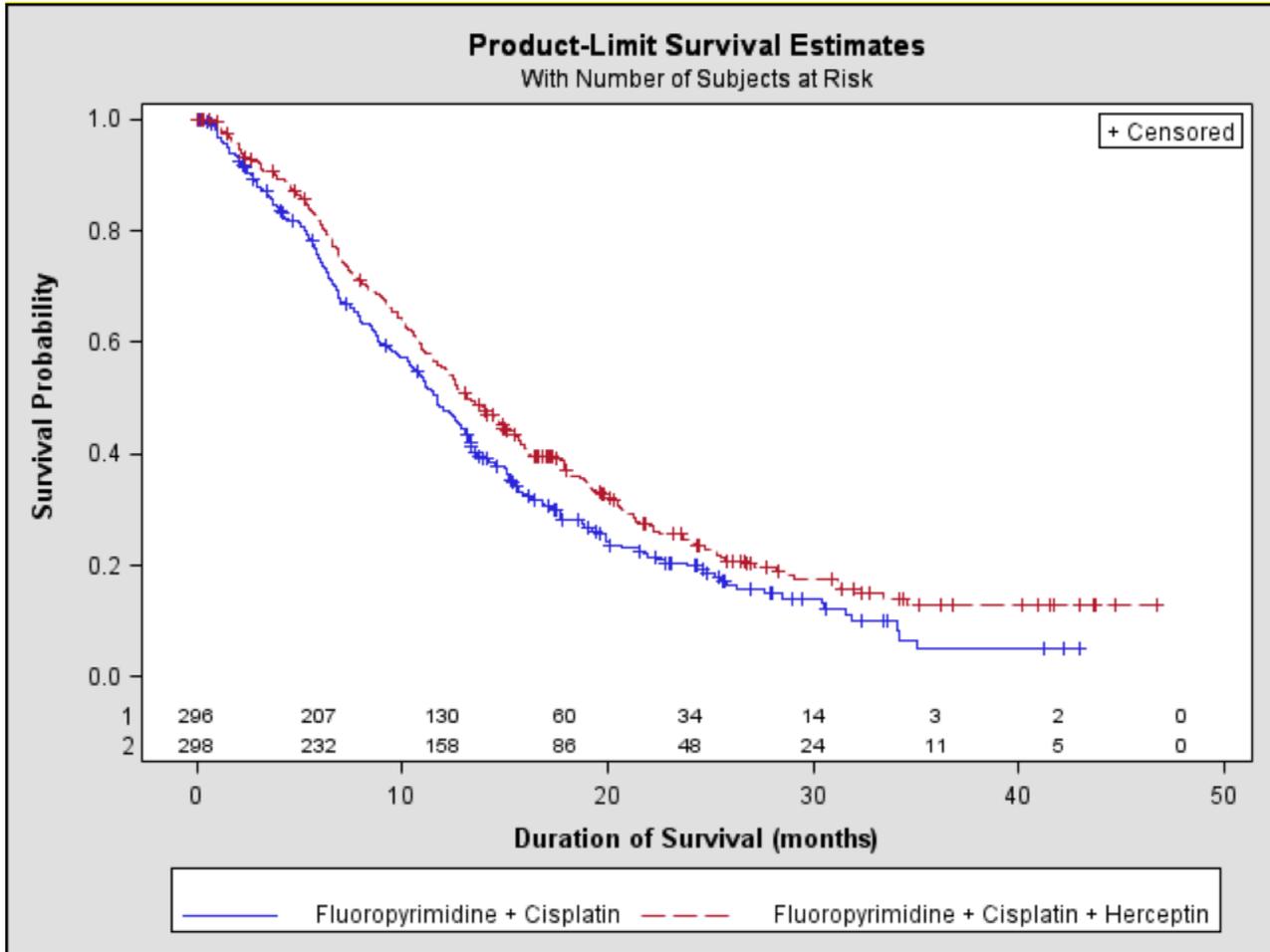
	FC Arm N=296	FC + H Arm N=298
<u>Definitive (Second Interim) Overall Survival</u>		
No. Deaths (%)	184 (62.2%)	167 (56.0%)
Median	11.0	13.5
95% CI (mos.)	(9.4, 12.5)	(11.7, 15.7)
Hazard Ratio	0.73	
95% CI	(0.60, 0.91)	
p-value*, two-sided	0.0038	
<u>Updated Overall Survival</u>		
No. Deaths (%)	227 (76.7%)	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 7
Updated Overall Survival in Patients with Metastatic Gastric Cancer (Study 7)



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

844

845 **16 HOW SUPPLIED/STORAGE AND HANDLING**

846 **16.1 How Supplied**

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

851 **16.2 Stability and Storage**

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

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

861 **17 PATIENT COUNSELING INFORMATION**

- 862 • Advise patients to contact a health care professional immediately for any of the following: new
863 onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face,
864 palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness
865 [*see Boxed Warning Cardiomyopathy*].
- 866 • Advise pregnant women and women of childbearing potential that Herceptin exposure can
867 result in fetal harm [*see Warnings and Precautions (5.3) and Use in Specific Populations*
868 (8.1)].
- 869 • Advise women of childbearing potential to use effective contraceptive methods during
870 treatment and for a minimum of six months following Herceptin [*see Warnings and*
871 *Precautions (5.3)*].
- 872 • Advise nursing mothers treated with Herceptin to discontinue nursing or discontinue Herceptin,
873 taking into account the importance of the drug to the mother [*see Use in Specific Populations*
874 (8.3)].
- 875 • Encourage women who are exposed to Herceptin during pregnancy to enroll in MotHER- the
876 Herceptin Pregnancy Registry (1-800-690-6720) [*see Warnings and Precautions (5.3) and Use*
877 *in Specific Populations (8.1)*].
- 878

HERCEPTIN[®] [trastuzumab]

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

Initial US Approval: September 1998

Revision Date: March 2014

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/s/

AMNA IBRAHIM
03/07/2014