

- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

- 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 Storage
- 17 PATIENT COUNSELING INFORMATION**

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

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

Cardiomyopathy

Administration of trastuzumab products can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens.

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

Infusion Reactions; Pulmonary Toxicity

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

Embryo Fetal Toxicity

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

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

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

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

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

1.2 Metastatic Breast Cancer

HERZUMA is indicated:

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

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

1.3 Metastatic Gastric Cancer

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

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

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

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

2.2 Recommended Doses and Schedules

- **Do not administer as an intravenous push or bolus. Do not mix HERZUMA with other drugs.**

- **Do not substitute HERZUMA (trastuzumab-pkrb) for or with ado-trastuzumab emtansine.**

Adjuvant Treatment, Breast Cancer:

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

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

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

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

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

Metastatic Treatment, Breast Cancer:

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

Metastatic Gastric Cancer:

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

2.3 Important Dosing Considerations

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

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

Infusion Reactions

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

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

Cardiomyopathy

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

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

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

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

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

2.4 Preparation for Administration

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

420 mg Multiple-dose vial

Reconstitution

Reconstitute each 420 mg vial of HERZUMA with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multiple-dose solution containing 21 mg/mL trastuzumab-pkrb that delivers 20 mL (420 mg trastuzumab-pkrb). 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 powder of HERZUMA, which has a cake-like appearance. The stream of diluent should be directed into the cake. The reconstituted vial yields a solution for multiple-dose use, containing 21 mg/mL trastuzumab-pkrb.
- 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 HERZUMA in the refrigerator at 2°C to 8°C (36°F to 46°F); discard unused HERZUMA after 28 days. If HERZUMA is reconstituted with SWFI without preservative, use immediately and discard any unused portion. **Do not freeze.**

Dilution

- Determine the dose (mg) of HERZUMA [see *Dosage and Administration (2.2)*]. Calculate the volume of the 21 mg/mL reconstituted HERZUMA 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.
- The solution of HERZUMA for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours prior to use. **Do not freeze.**

150 mg Single-dose vial

Reconstitution

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

Use appropriate aseptic technique when performing the following reconstitution step:

- Using a sterile syringe, slowly inject the 7.4 mL of SWFI (not supplied) into the vial containing the lyophilized powder of HERZUMA, which has a cake-like appearance. The stream of diluent should be directed into the cake. The reconstituted vial yields a solution for single-dose use, containing 21 mg/mL trastuzumab-pkrb.
- 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.
- Use the HERZUMA solution immediately following reconstitution with SWFI, as it contains no preservative and is intended for single-dose only. If not used immediately, store the reconstituted HERZUMA solution for up to 24 hours at 2°C to 8°C (36°F to 46°F); discard any unused HERZUMA after 24 hours. **Do not freeze.**

Dilution

- Determine the dose (mg) of HERZUMA [see *Dosage and Administration (2.2)*].
- Calculate the volume of the 21 mg/mL reconstituted HERZUMA 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.
- The solution of HERZUMA for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours prior to use. Discard after 24 hours. This storage time is additional to the time allowed for the reconstituted vials. **Do not freeze.**

3 DOSAGE FORMS AND STRENGTHS

- For injection: 150 mg of HERZUMA as a white to pale yellow lyophilized powder in a single-dose vial
- For injection: 420 mg of HERZUMA as a white to pale yellow lyophilized powder in a multiple-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [see *Boxed Warning: Cardiomyopathy*]. Trastuzumab products 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 trastuzumab products as a single agent or in combination therapy compared with those not receiving trastuzumab products. The highest absolute incidence occurs when a trastuzumab product is administered with an anthracycline.

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

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

Cardiac Monitoring

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

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

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

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

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

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

- Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal abnormalities, and neonatal death [*see Warnings and Precautions (5.3)*]
- Glomerulopathy [*see Adverse Reactions (6.1)*]
- Immune thrombocytopenia
- Tumor lysis syndrome (TLS): Cases of possible TLS have been reported in patients treated with trastuzumab. Patients with significant tumor burden (e.g. bulky metastases) may be at a higher risk. Patients could present with hyperuricemia, hyperphosphatemia, and acute renal failure which may represent possible TLS. Providers should consider additional monitoring and/or treatment as clinically indicated.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Trastuzumab products can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death [*see Data*]. Apprise the patient of the potential risks to a fetus. There are clinical considerations if a trastuzumab product is used in a pregnant woman or if a patient becomes pregnant within 7 months following the last dose of a trastuzumab product [*see Clinical Considerations*].

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Human Data

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

Animal Data

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

8.2 Lactation

Risk Summary

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

Data

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of HERZUMA.

Contraception

Females

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

8.4 Pediatric Use

The safety and effectiveness of trastuzumab products in pediatric patients have not been established.

8.5 Geriatric Use

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

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

10 OVERDOSAGE

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

11 DESCRIPTION

Trastuzumab-pkrb is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab-pkrb is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture.

HERZUMA (trastuzumab-pkrb) for injection is a sterile, white to pale yellow, preservative-free lyophilized powder with a cake-like appearance, for intravenous administration.

Each multiple-dose vial of HERZUMA delivers 420 mg trastuzumab-pkrb, 839 mg α,α -trehalose dihydrate, 9.5 mg L-histidine HCl, 6.1 mg L-histidine, and 1.7 mg polysorbate 20. Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution containing 21 mg/mL trastuzumab-pkrb that delivers 20 mL (420 mg trastuzumab-pkrb), at a pH of approximately 6. If

HERZUMA is reconstituted with SWFI without preservative, the reconstituted solution is considered single-dose.

Each single-dose vial of HERZUMA delivers 150 mg trastuzumab-pkrb, 299.6 mg α,α -trehalose dihydrate, 3.4 mg L-histidine HCl, 2.2 mg L-histidine, and 0.6 mg polysorbate 20. Reconstitution with 7.4 mL of sterile water for injection (SWFI) yields a solution containing 21 mg/mL trastuzumab-pkrb that delivers 7.15 mL (150 mg trastuzumab-pkrb), at a pH of approximately 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Trastuzumab products are mediators of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, trastuzumab product-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

12.2 Pharmacodynamics

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

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

Population PK based simulations indicate that following discontinuation of trastuzumab, concentrations in at least 95% of breast cancer patients and MGC patients will decrease to

approximately 3% of the population predicted steady-state trough serum concentration (approximately 97% washout) by 7 months [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1, 8.3)*].

Table 7: Population Predicted Cycle 1 PK Exposures (Median with 5th – 95th Percentiles) in Breast Cancer and MGC Patients

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

Table 8: Population Predicted Steady State PK Exposures (Median with 5th – 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	C _{min,ss} ^a (µg/mL)	C _{max,ss} ^b (µg/mL)	AUC _{ss, 0-21 days} (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	47.4 (5 to 115)	179 (107 to 309)	1794 (673 to 3618)	12	0.173 to 0.283
	MGC	274	32.9 (6.1 to 88.9)	131 (72.5 to 251)	1338 (557 to 2875)	9	0.189 to 0.337
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	66.1 (14.9 to 142)	109 (51.0 to 209)	1765 (647 to 3578)	12	0.201 to 0.244

^a Steady-state trough serum concentration of trastuzumab

^b Maximum steady-state serum concentration of trastuzumab

Specific Populations

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

Drug Interaction Studies

There have been no formal drug interaction studies performed with trastuzumab products in humans. Clinically significant interactions between trastuzumab and concomitant medications used in clinical trials have not been observed.

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

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

Cisplatin and capecitabine: 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 trastuzumab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Trastuzumab products have not been tested for carcinogenic potential.

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

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

14 CLINICAL STUDIES

14.1 Adjuvant Breast Cancer

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

Studies 1 and 2

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

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

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

Study 3

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

Study 3 was designed to compare one and two years of three-weekly trastuzumab treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). Patients were randomized (1:1:1) upon completion of definitive surgery, and at least four cycles of chemotherapy to receive no

additional treatment, or one year of trastuzumab treatment or two years of trastuzumab treatment. Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator discretion. Trastuzumab was administered with an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every three weeks. The main outcome measure was Disease-Free Survival (DFS), defined as in Studies 1 and 2.

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

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

Study 4

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

Patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus trastuzumab (AC-TH), or docetaxel and carboplatin plus trastuzumab (TCH). In both the AC-T and AC-TH arms, doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² were administered every 3 weeks for four cycles; docetaxel 100 mg/m² was administered every 3 weeks for four cycles. In the TCH arm, docetaxel 75 mg/m² and carboplatin (at a target AUC of 6 mg/mL/min as a 30- to 60-minute infusion) were administered every 3 weeks for six cycles. Trastuzumab was administered weekly (initial dose of 4 mg/kg followed by weekly dose of 2 mg/kg) concurrently with either T or TC, and then every 3 weeks (6 mg/kg) as monotherapy for a total of 52 weeks.

Radiation therapy, if administered, was initiated after completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-Free Survival (DFS) was the main outcome measure.

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

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

Table 9: Efficacy Results from Adjuvant Treatment of Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	DFS Hazard ratio (95% CI) p-value	Deaths (OS events)	OS Hazard ratio p-value
<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^f</u>				
Chemo→ Trastuzumab (n = 1693)	127	0.54 (0.44, 0.67) p < 0.0001 ^g	31	0.75 p = NS ^h
Chemo→ Observation (n = 1693)	219		40	
<u>Study 4ⁱ</u>				
TCH (n = 1075)	134	0.67 (0.54 – 0.84) p = 0.0006 ^{e, j}	56	
AC→TH (n = 1074)	121	0.60 (0.48 – 0.76) p < 0.0001 ^{e, i}	49	
AC→T (n = 1073)	180		80	

CI = confidence interval

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

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

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

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

^e stratified log-rank test.

^f At definitive DFS analysis with median duration of follow-up of 12.6 months in the one-year trastuzumab treatment arm.

^g log-rank test.

^h NS = non-significant.

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

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

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

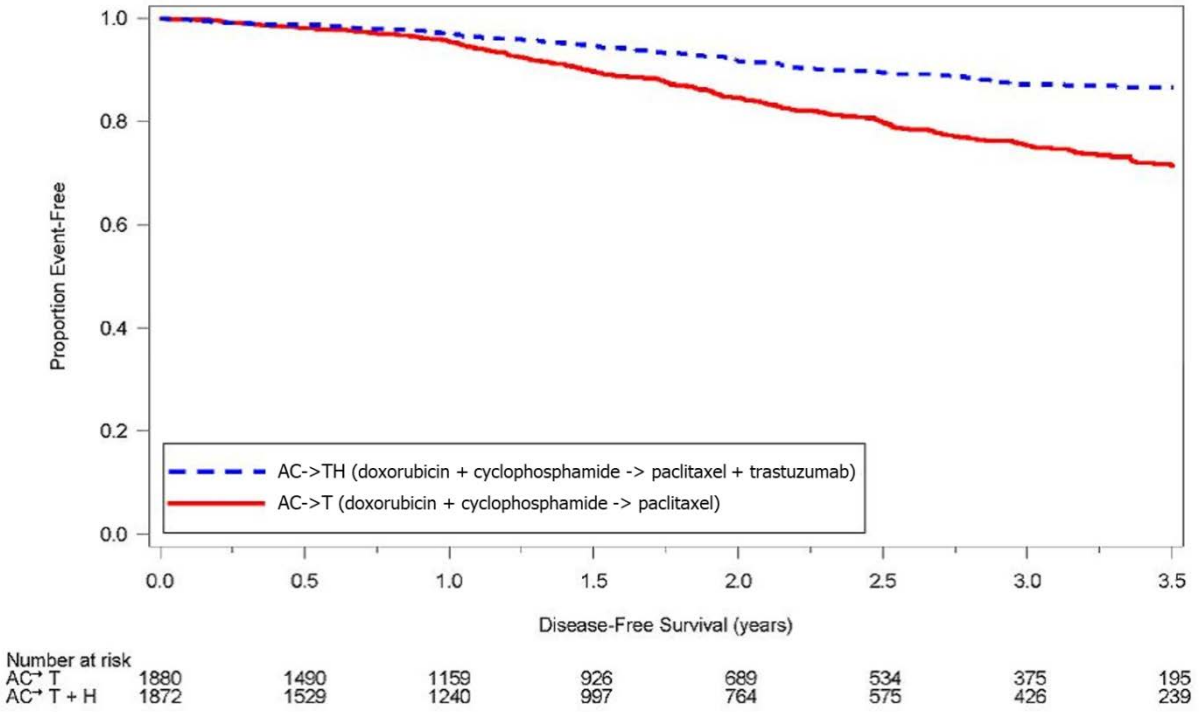


Figure 5: Duration of Overall Survival in Patients with Adjuvant Treatment of Breast Cancer (Studies 1 and 2)

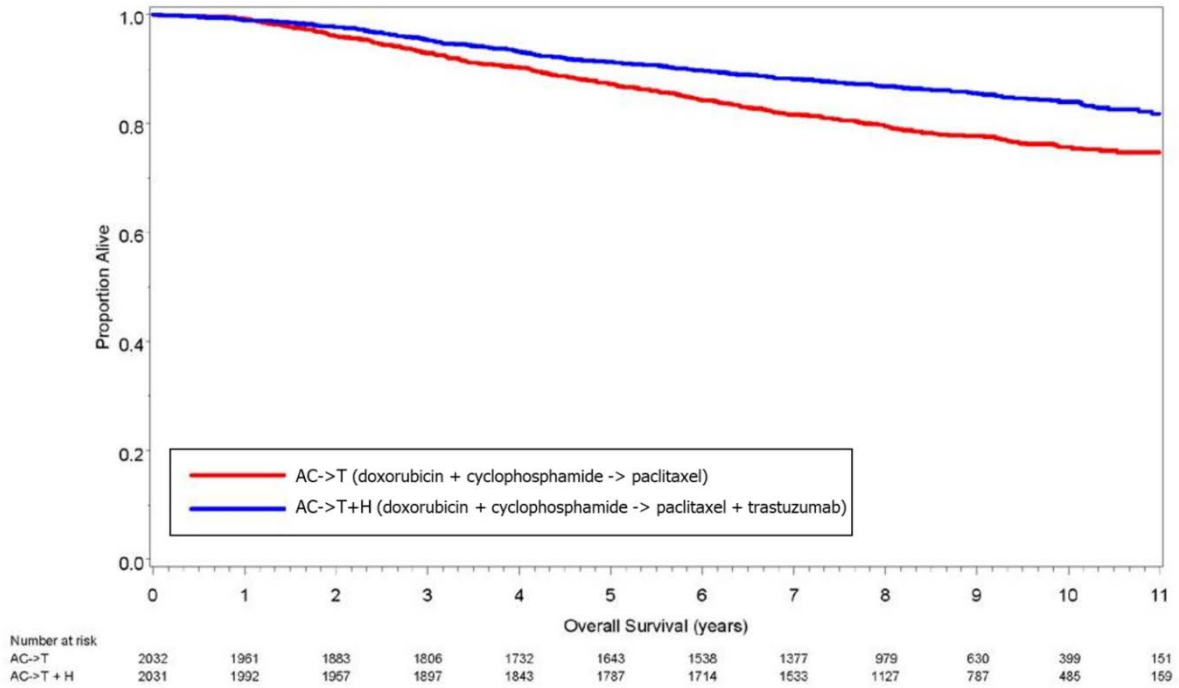
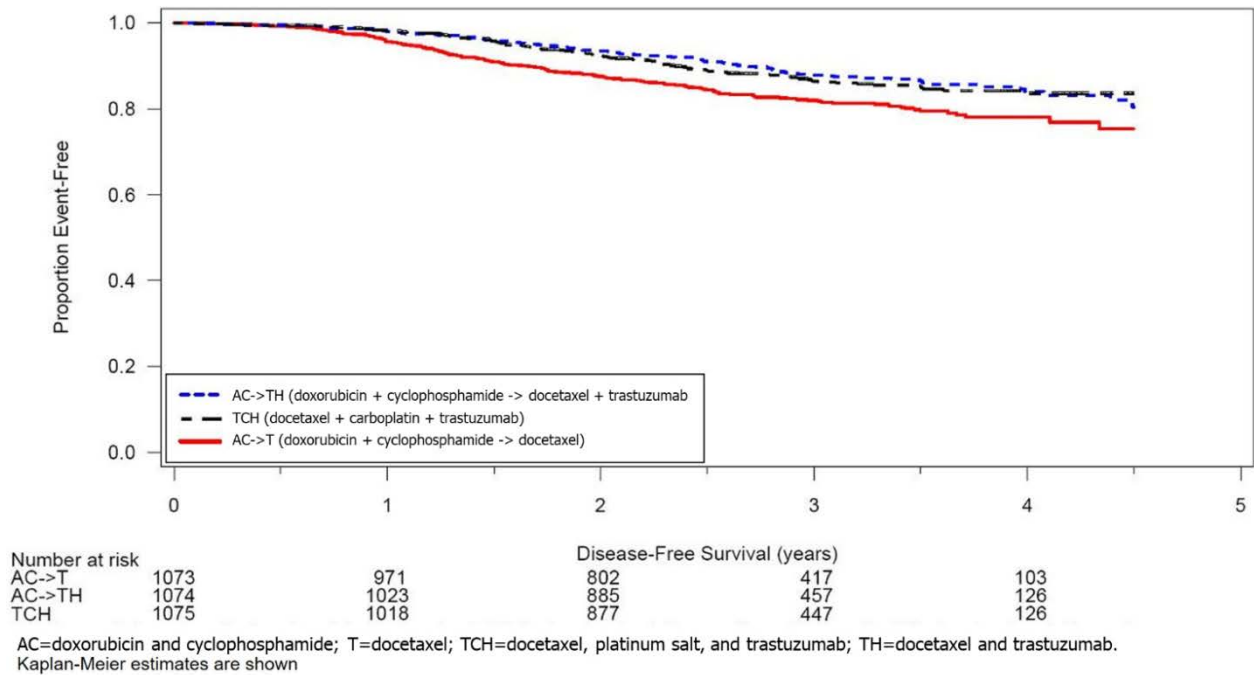


Figure 6: Duration of Disease-Free Survival in Patients with Adjuvant Treatment of Breast Cancer (Study 4)



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

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

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

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

^c Median follow-up duration of 12.6 months in the one-year trastuzumab treatment arm.

14.2 Metastatic Breast Cancer

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

Previously Untreated Metastatic Breast Cancer (Study 5)

Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or in combination with trastuzumab given intravenously as a 4 mg/kg loading dose

followed by weekly doses of trastuzumab at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m² over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m² or epirubicin 75 mg/m² plus 600 mg/m² cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to receive chemotherapy alone in this study received trastuzumab at the time of disease progression as part of a separate extension study.

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

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

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Trastuzumab + All Chemotherapy (n = 235)	All Chemotherapy (n = 234)	Trastuzumab + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Trastuzumab + AC ^a (n = 143)	AC (n = 138)
Primary Endpoint						
<u>Median 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 Response 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 Duration (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 (mos)</u> ^c	25.1	20.3	22.1	18.4	26.8	21.4

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Trastuzumab + All Chemotherapy (n = 235)	All Chemotherapy (n = 234)	Trastuzumab + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Trastuzumab + AC ^a (n = 143)	AC (n = 138)
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.

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

Table 12: Treatment Effects in Study 5 as a Function of HER2 Overexpression or Amplification

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

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

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

Previously Treated Metastatic Breast Cancer (Study 6)

Trastuzumab was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative

treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of trastuzumab at 2 mg/kg IV.

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

14.3 Metastatic Gastric Cancer

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

On the trastuzumab-containing arm, trastuzumab was administered as an IV infusion at an initial dose of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms, cisplatin was administered at a dose of 80 mg/m² Day 1 every 3 weeks for 6 cycles as a 2 hour IV infusion. On both study arms, capecitabine was administered at 1000 mg/m² dose orally twice daily (total daily dose 2000 mg/m²) for 14 days of each 21 day cycle for 6 cycles. Alternatively, continuous intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m²/day from Day 1 through Day 5 every three weeks for 6 cycles.

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

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

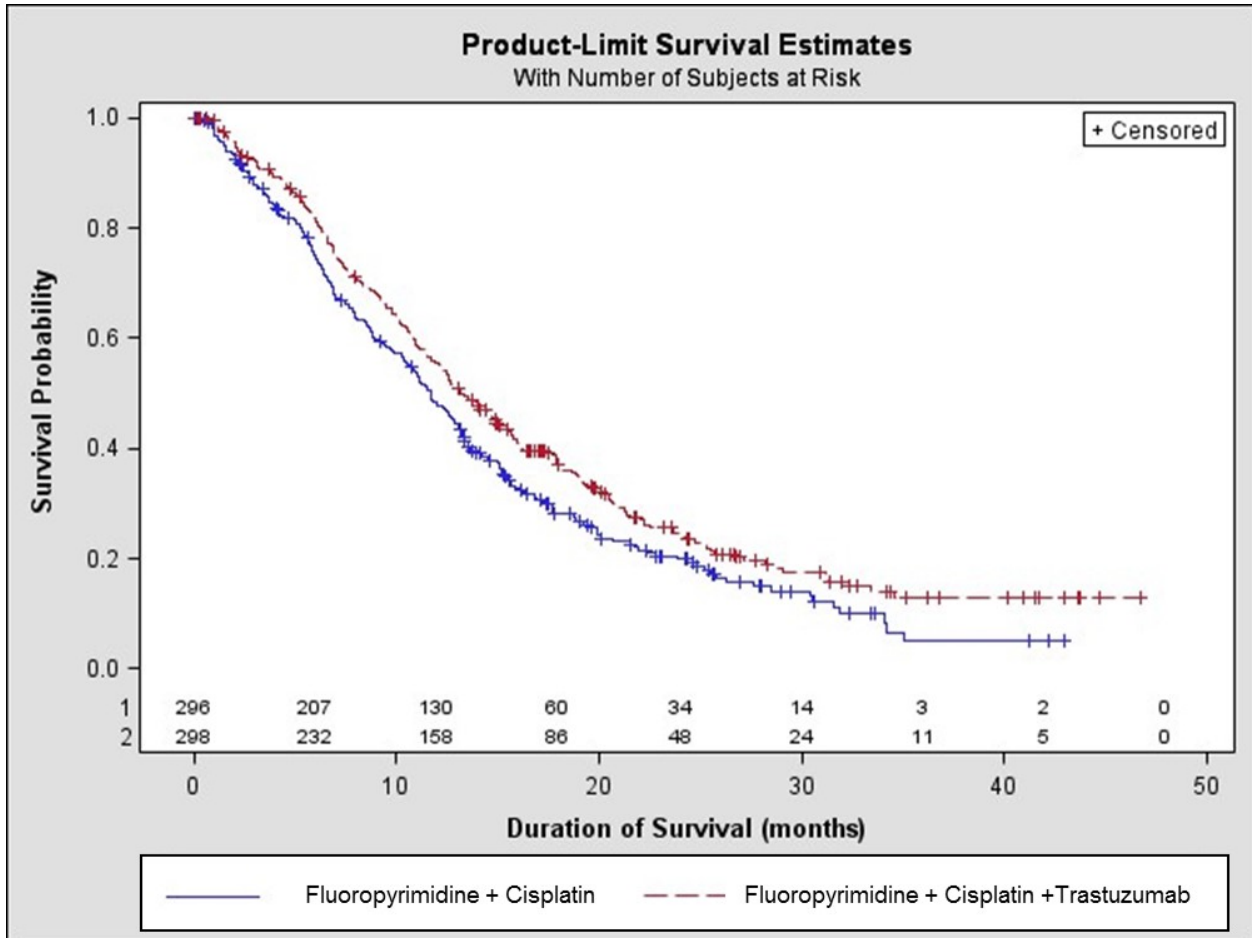
Table 13: Study 7: Overall Survival in ITT Population

	FC Arm N = 296	FC + H Arm N = 298
<u>Definitive (Second Interim) Overall Survival</u>		
No. Deaths (%)	184 (62.2%)	167 (56.0%)

	FC Arm N = 296	FC + H Arm N = 298
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.

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



An exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein overexpression (IHC) testing is summarized in Table 14.

Table 14: Exploratory Analyses by HER2 Status Using Updated Overall Survival Results

	FC (N = 296)^a	FC + H (N = 298)^b
<u>FISH+ / IHC 0, 1+ subgroup (N=133)</u>		
No. Deaths / n (%)	57/71 (80%)	56/62 (90%)
Median OS Duration (mos.)	8.8	8.3
95% CI (mos.)	(6.4, 11.7)	(6.2, 10.7)
Hazard ratio (95% CI)	1.33 (0.92, 1.92)	
<u>FISH+ / IHC2+ subgroup (N=160)</u>		
No. Deaths / n (%)	65/80 (81%)	64/80 (80%)

	FC (N = 296)^a	FC + H (N = 298)^b
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 trastuzumab-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 trastuzumab arm with FISH-, IHC3+ and 8 patients on chemotherapy arm, 8 patients on trastuzumab arm with FISH status unknown, IHC 3+.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

420 mg Multiple-dose vial NDC 63459-305-47

HERZUMA (trastuzumab-pkrb) for Injection 420 mg/vial is supplied in a multiple-dose vial as a white to pale yellow lyophilized sterile powder, under vacuum. Each carton contains one multiple-dose vial (420 mg/vial) of HERZUMA and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.

150 mg Single-dose vial NDC 63459-303-43

HERZUMA (trastuzumab-pkrb) for Injection 150 mg/vial is supplied in a single-dose vial as a white to pale yellow lyophilized sterile powder, under vacuum. Each carton contains one single-dose vial (150 mg/vial) of HERZUMA.

16.2 Storage

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

17 PATIENT COUNSELING INFORMATION

Cardiomyopathy

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [*see Boxed Warning: Cardiomyopathy*].

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential that HERZUMA exposure during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of HERZUMA [*see Use in Specific Populations (8.3)*].

HERZUMA[®] [trastuzumab-pkrb]

Manufactured by:

CELLTRION, Inc.

23, Academy-ro,
Yeonsu-gu, Incheon
22014, Republic of Korea
U.S. License No. 1996

HERZUMA[®] is a registered trademark of CELLTRION, Inc.

Marketed by:

Teva Pharmaceuticals USA, Inc.

North Wales, PA 19454