DOSING AND ADMINISTRATION GUIDE

Herceptin HYLECTA™

trastuzumab and hyaluronidase-oysk

INJECTION FOR SUBCUTANEOUS USE | 600 mg/10,000 units

This guide provides dosing and administration guidelines for Herceptin HYLECTA™ (trastuzumab and hyaluronidase-oysk).

INDICATIONS:

Adjuvant Breast Cancer

HERCEPTIN HYLECTA (trastuzumab and hyaluronidase-oysk) is indicated for adjuvant treatment of adults with HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature*) breast cancer:

- As part of a treatment regimen containing doxorubicin, cyclophosphamide and either paclitaxel or docetaxel
- 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 trastuzumab

*High-risk is defined as ER/PR-positive with one of the following features: tumor size >2 cm, age <35 years, or tumor grade 2 or 3.

Metastatic Breast Cancer

HERCEPTIN HYLECTA is indicated in adults:

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- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

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BOXED WARNINGS and Additional Important Safety Information

Cardiomyopathy

- **HERCEPTIN HYLECTA administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving HERCEPTIN HYLECTA with anthracycline-containing chemotherapy regimens.**
- **Evaluate left ventricular function in all patients prior to and during treatment with HERCEPTIN HYLECTA. Discontinue HERCEPTIN HYLECTA treatment in patients receiving adjuvant therapy and withhold HERCEPTIN HYLECTA in patients with metastatic disease for clinically significant decrease in left ventricular function**

Pulmonary Toxicity

- **HERCEPTIN HYLECTA administration can result in serious and fatal pulmonary toxicity. Symptoms usually occur during or within 24 hours of HERCEPTIN HYLECTA administration. Discontinue HERCEPTIN HYLECTA for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Monitor patients until symptoms completely resolve**

Embryo-Fetal Toxicity

- **Exposure to HERCEPTIN HYLECTA 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**

Please see additional Important Safety Information throughout, and on pages 12-15, and the accompanying full Prescribing Information, including BOXED WARNINGS, on pages 17-47 for Herceptin HYLECTA and on pages 48-85 for Herceptin.

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Herceptin®
trastuzumab
21 mg/mL INJECTION FOR INTRAVENOUS USE

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Infusion Reactions; Pulmonary Toxicity

- **Herceptin administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of Herceptin administration. Interrupt Herceptin infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome**

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IMPORTANT SAFETY INFORMATION FOR HERCEPTIN HYLECTA (CONT'D)

- Exacerbation of chemotherapy-induced neutropenia has also occurred
- Hypersensitivity and severe Administration-Related Reactions (ARRs) including anaphylaxis, have been reported with HERCEPTIN HYLECTA. Serious and fatal reactions have been reported after treatment with intravenous trastuzumab products

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Herceptin HYLECTA™
trastuzumab and hyaluronidase-oysk
INJECTION FOR SUBCUTANEOUS USE | 600 mg/10,000 units

Key dosing and administration differences between Herceptin HYLECTA and Herceptin[1,2]

	HERCEPTIN HYLECTA	HERCEPTIN
Vial configurations	Vial with a light blue cap Supplied in 600 mg trastuzumab and 10,000 units hyaluronidase per 5 mL in single-dose vials	Vial with a red cap Supplied in single-dose 150 mg vials
Dosing	Fixed-dose	Weight-based dose
Preparation	No dilution required (ready-to-use solution)	Reconstitution and dilution required
Administration	**Subcutaneous injection**	**Intravenous infusion**
Vial storage & stability	Store Herceptin HYLECTA vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Once removed from the refrigerator, Herceptin HYLECTA must be administered within 4 hours and should not be kept above 30°C (86°F)	Store Herceptin vials in the refrigerator at 2ºC-8ºC (36ºF-46ºF) until time of reconstitution

Herceptin HYLECTA is for subcutaneous use only. Herceptin HYLECTA has different dosage and administration instructions than intravenous trastuzumab products. Do not administer intravenously. Do not substitute Herceptin HYLECTA for or with ado-trastuzumab emtansine.

Additional Storage Information for Herceptin HYLECTA

- Herceptin HYLECTA should be a clear-to-opalescent and colorless-to-yellowish liquid. Do not use vial if particulates or discoloration is present
- Store Herceptin HYLECTA vials in the original carton to protect them from light
- **Do not freeze or shake**

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Herceptin HYLECTA™ dosing regimens for eligible patients with HER2+ breast cancer[1]

Fixed dose: 600 mg trastuzumab and 10,000 units hyaluronidase

Adjuvant Breast Cancer:

- Treat with Herceptin HYLECTA for 52 weeks or until disease recurrence, whichever occurs first
- Extending treatment in adjuvant breast cancer beyond 1 year is not recommended

Metastatic Breast Cancer (MBC):

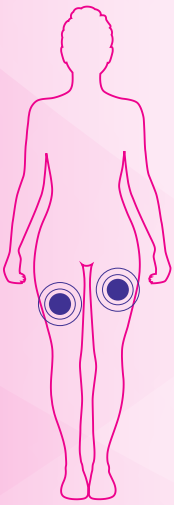
- Treat with Herceptin HYLECTA until progression of disease

NO loading dose

NO dose adjustments for patient body weight or for different concomitant chemotherapy regimens are required

~2-5 minutes

Doses should be administered subcutaneously over approximately 2-5 minutes once every 3 weeks



The injection site should be alternated between the left and right thigh

- New injections should be given at least 2.5 cm from the old previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard, or areas where there are moles or scars
- Other products administered subcutaneously should preferably be injected at different sites

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Herceptin HYLECTA administration[1]

- Prepare the dosing syringe in controlled and validated aseptic conditions
  - After the solution of Herceptin HYLECTA is withdrawn from the vial and into the syringe, replace the transfer needle with a syringe closing cap and label it with a peel-off sticker
  - If the syringe containing Herceptin HYLECTA is not used immediately, it can be stored for up to 24 hours in the refrigerator (2°C to 8°C) and subsequently for up to 4 hours at room temperature (20°C to 25°C). Don't shake or freeze

- Use with commercially available hypodermic needles
  - To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration followed by volume adjustment to 5 mL
- Herceptin HYLECTA is compatible with polypropylene and polycarbonate syringe material and stainless steel transfer and injection needles

Additional dosing considerations for Herceptin HYLECTA

- If a dose is missed, administer the next dose (ie, the missed dose) as soon as possible. The interval between subsequent Herceptin HYLECTA doses should not be <3 weeks
- To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin HYLECTA and not ado-trastuzumab emtansine or intravenous trastuzumab
- Herceptin HYLECTA should be administered by a healthcare professional
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use vial if particulates or discoloration is present. Discard any unused portion remaining in the vial

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Important clinical information[1]

Patient observation

No specific monitoring window following Herceptin HYLECTA™ administration

- Closely monitor patients for systemic hypersensitivity reactions, especially during the first administration of Herceptin HYLECTA
- Permanently discontinue use of Herceptin HYLECTA in patients who experience anaphylaxis or severe hypersensitivity reactions
  - Medications to treat such reactions, as well as emergency equipment, should be available for immediate use
  - For patients experiencing reversible Grade 1 or 2 hypersensitivity reactions, consider pre-medication with an analgesic, antipyretic, or an antihistamine prior to readministration of Herceptin HYLECTA

Adverse reactions

The incidence of administration-related reactions was 39%, with Grade ≥3 ARRs reported in 1% of patients treated with Herceptin HYLECTA

- Injection-site reactions (ISRs) were reported for 20% of patients receiving Herceptin HYLECTA
- The most common ISRs were injection-site erythema (7%) and injection-site pain (6%)
- All ISRs were Grade 1 or 2, except for one (<1%) Grade 3 injection site discomfort
- Most common adverse reactions (≥10%) for Herceptin HYLECTA are fatigue, arthralgia, diarrhea, injection site reaction, upper respiratory tract infection, rash, myalgia, nausea, headache, edema, flushing, pyrexia, cough, and pain in extremity

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Important clinical information[1] (cont'd)

Guidelines for cardiomyopathy (all indications)[1]

- Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin HYLECTA and at regular intervals during treatment. Withhold Herceptin HYLECTA dosing for at least 4 weeks for either of the following:
  - ≥16% absolute decrease in LVEF from pretreatment values
  - LVEF below institutional limits of normal and ≥10% absolute decrease in LVEF from pretreatment values
- Herceptin HYLECTA may be resumed if, within 4-8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%
- Permanently discontinue Herceptin HYLECTA for a persistent (>8 weeks) LVEF decline or for suspension of Herceptin HYLECTA dosing on more than 3 occasions for cardiomyopathy

Drugs interactions - Anthracyclines

- Patients who receive anthracycline after stopping Herceptin HYLECTA may be at increased risk of cardiac dysfunction because of Herceptin HYLECTA's estimated long washout period. If possible, avoid anthracycline-based therapy for up to 7 months after stopping Herceptin HYLECTA. If anthracyclines are used, carefully monitor the patient's cardiac function

Contact your Genentech representative to learn more or visit HerceptinHYLECTA.com

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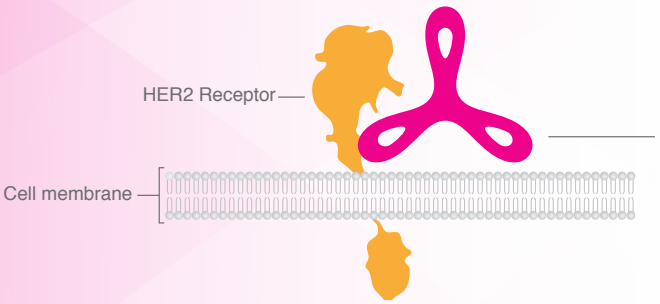
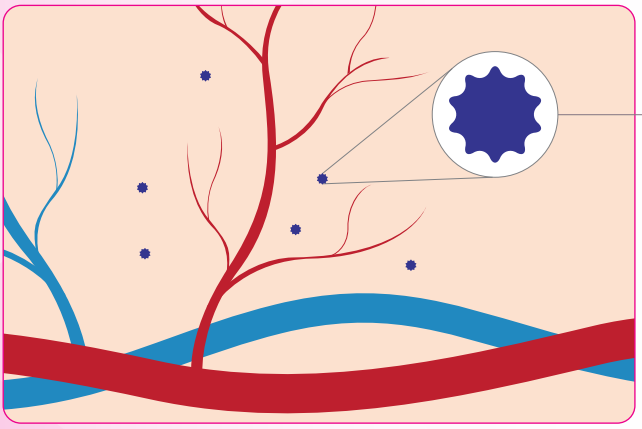
What is Herceptin HYLECTA™?[1]

Herceptin HYLECTA is a combination of trastuzumab and hyaluronidase



Trastuzumab is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the HER2 protein.



Hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously

IMPORTANT SAFETY INFORMATION (CONT'D)

Most Common Adverse Reactions

- **Adjuvant Breast Cancer:** Most common adverse reactions for HERCEPTIN HYLECTA are fatigue, arthralgia, diarrhea, injection site reaction, upper respiratory tract infection, rash, myalgia, nausea, headache, edema, flushing, pyrexia, cough, and pain in extremity.
- **Metastatic Breast Cancer (based on intravenous trastuzumab):** The most common adverse reactions are fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash.

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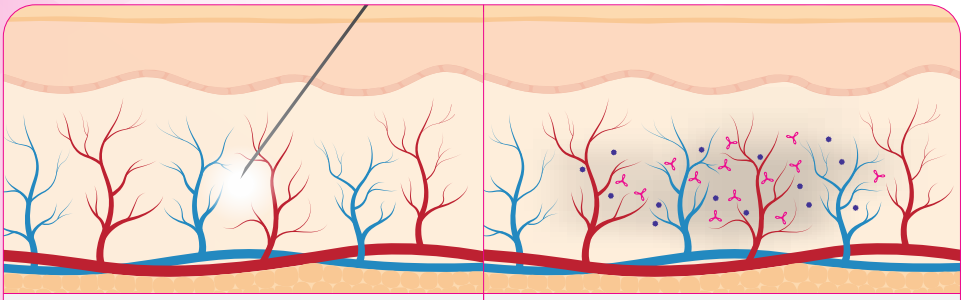
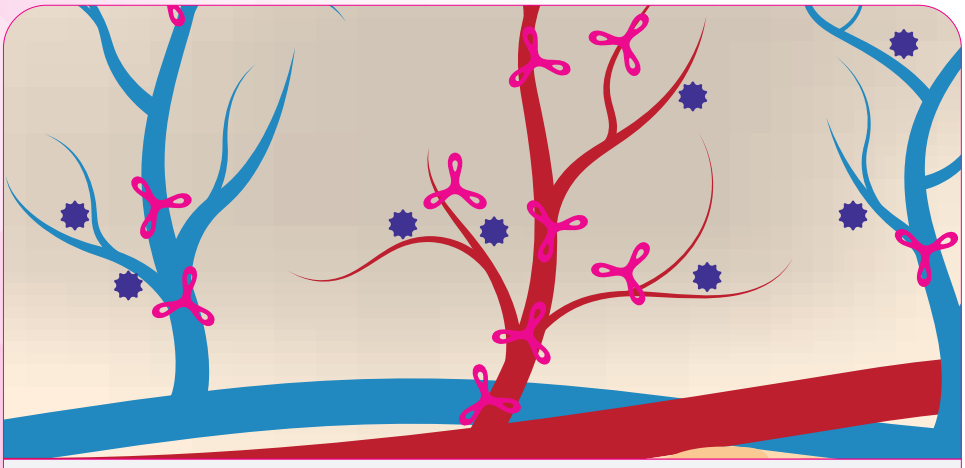
Herceptin HYLECTA: same antibody as Herceptin® (trastuzumab), delivered subcutaneously with hyaluronidase[1]

Proposed MOA



- Herceptin HYLECTA is administered by subcutaneous injection into the thigh
- Hyaluronidase increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan, based on preclinical studies



- In the doses administered, hyaluronidase in Herceptin HYLECTA acts transiently and locally
- The effects of hyaluronidase are reversible, and permeability of the subcutaneous tissue is restored within 28 to 48 hours
- Hyaluronidase has been shown to increase the absorption rate of trastuzumab into the systemic circulation, based on animal studies

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Embryo-Fetal Toxicity

- **Exposure to HERCEPTIN HYLECTA 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**

Cardiomyopathy and Cardiac Monitoring

- **HERCEPTIN HYLECTA administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving HERCEPTIN HYLECTA with anthracycline-containing chemotherapy regimens. In a pivotal adjuvant trastuzumab trial, one patient who developed CHF died of cardiomyopathy**
- **Discontinue HERCEPTIN HYLECTA treatment in patients receiving adjuvant therapy and withhold HERCEPTIN HYLECTA in patients with metastatic disease for clinically significant decrease in left ventricular function**
- **Evaluate cardiac function prior to and during treatment. For adjuvant therapy, also evaluate cardiac function after completion of HERCEPTIN HYLECTA**

IMPORTANT SAFETY INFORMATION (CONT'D)

- Monitor frequently for decreased left ventricular function during and after HERCEPTIN HYLECTA treatment. Monitor more frequently if HERCEPTIN HYLECTA is withheld for significant left ventricular cardiac dysfunction

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- **Exposure to HERCEPTIN HYLECTA during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death**
- Verify the pregnancy status of females of reproductive potential prior to the initiation of HERCEPTIN HYLECTA
- Advise pregnant women and females of reproductive potential that exposure to HERCEPTIN HYLECTA during pregnancy or within 7 months prior to conception can result in fetal harm
- Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of HERCEPTIN HYLECTA
- If HERCEPTIN HYLECTA is administered during pregnancy, or if a patient becomes pregnant while receiving HERCEPTIN HYLECTA or within 7 months following the last dose of HERCEPTIN HYLECTA, healthcare providers and patients should immediately report HERCEPTIN HYLECTA exposure to Genentech at 1-888-835-2555

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- **HERCEPTIN HYLECTA administration can result in serious and fatal pulmonary toxicity,** which includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis.
- Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity
- Discontinue HERCEPTIN HYLECTA in patients experiencing pulmonary toxicity

Exacerbation of Chemotherapy-Induced Neutropenia

- In randomized, controlled clinical trials with intravenous trastuzumab, the per-patient incidences of NCI-CTC Grade 3-4 neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone

Hypersensitivity and Administration-Related Reactions

- Severe administration-related reactions (ARRs), including hypersensitivity and anaphylaxis, have been reported with HERCEPTIN HYLECTA. Patients experiencing dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a severe or of a fatal ARR.
- Serious and fatal reactions have been reported after treatment with intravenous trastuzumab products
- Closely monitor patients for systemic hypersensitivity reactions, especially during the first administration. Permanently discontinue HERCEPTIN HYLECTA in patients who experience anaphylaxis or severe hypersensitivity reactions.

  Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

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You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

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- If Herceptin is administered during pregnancy, or if a patient becomes pregnant while receiving Herceptin or within 7 months following the last dose of Herceptin, healthcare providers and patients should immediately report Herceptin exposure to Genentech at 1-888-835-2555

Pulmonary Toxicity

- **Herceptin administration can result in serious and fatal pulmonary toxicity,** which includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions
- Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity
- Discontinue Herceptin in patients experiencing pulmonary toxicity

Exacerbation of Chemotherapy-Induced Neutropenia

- In randomized, controlled clinical trials, the per-patient incidences of NCI-CTC Grade 3-4 neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone

Most Common Adverse Reactions

- The most common adverse reactions associated with Herceptin use were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

For additional Important Safety Information see the Herceptin full Prescribing Information, including BOXED WARNINGS on pages 48-85.

Herceptin HYLECTA™

trastuzumab and hyaluronidase-oysk

INJECTION FOR SUBCUTANEOUS USE | 600 mg/10,000 units

Financial resources

Helping patients access their Genentech medicine

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This Oncology Co-pay Assistance Program ("Program") is valid ONLY for patients with commercial (private or non-governmental) insurance who have a valid prescription for a Food and Drug Administration (FDA)-approved indication of a Genentech medicine. Patients using Medicare, Medicaid or any other federal or state government programs (collectively, "Government Programs") to pay for their Genentech medicine are not eligible.

Under the Program, the patient may be required to pay a co-pay. The final amount owed by a patient may be as little as $0 for the Genentech medicine (see Program specific details available at the Program website). The total patient out-of-pocket cost is dependent on the patient's health insurance plan. The Program assist with the cost of the Genentech medicine only. It does not assist with the cost of other medicines, procedures or office visit fees. After reaching the maximum annual Program benefit amount, the patient will be responsible for all remaining out-of-pocket expenses. The Program benefit amount cannot exceed the patient's out-of-pocket expenses for the Genentech medicine.

All participants are responsible for reporting the receipt of all Program benefits as required by any insurer or by law. The Program is only valid in the United States and U.S. Territories, is void where prohibited by law and shall follow state restrictions in relation to AB-rated generic equivalents (e.g., MA, CA) where applicable. No party may seek reimbursement for all or any part of the benefit received through the Program. The value of the Program is intended exclusively for the benefit of the patient. The funds made available through the Program may only be used to reduce the out-of-pocket costs for the patient enrolled in the Program. The Program is not intended for the benefit of third parties, including without limitation third party payers, pharmacy benefit managers, or their agents. If Genentech determines that a third party has implemented a program that adjusts patient cost-sharing obligations based on the availability of support under the Program and/or excludes the assistance provided under the Program from counting towards the patient's deductible or out-of-pocket cost limitations, Genentech may impose a per fill cap on the cost- sharing assistance available under the Program. Submission of true and accurate information is a requirement for eligibility and Genentech reserves the right to disqualify patients who do not comply from Genentech programs. Genentech reserves the right to rescind, revoke or amend the Program without notice at any time. Additional terms and conditions apply. Please visit the Co-pay Program website for the full list of Terms and Conditions.

Please see additional Important Safety Information throughout, and on pages 12-15, and the accompanying full Prescribing Information, including BOXED WARNINGS, on pages 17-47 for Herceptin HYLECTA and on pages 48-85 for Herceptin for Herceptin HYLECTA™ and Herceptin®.

References: 1. Herceptin HYLECTA Prescribing Information. Genentech, Inc. 2024.

2. Herceptin Prescribing Information. Genentech, Inc. 2024.

Genentech

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 M-US-00007526(v3.0). 11/24

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HERCEPTIN HYLECTA safely and effectively. See full prescribing information for HERCEPTIN HYLECTA.

HERCEPTIN HYLECTA® (trastuzumab and hyaluronidase-oysk) injection, for subcutaneous use
Initial U.S. Approval: 2019

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

See full prescribing information for complete boxed warning.

Cardiomyopathy: HERCEPTIN HYLECTA can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue HERCEPTIN HYLECTA for cardiomyopathy. (2.4, 5.1)

Pulmonary Toxicity: Discontinue HERCEPTIN HYLECTA for anaphylaxis, angioedema, interstitial pneumonitis or acute respiratory distress syndrome. (5.3)

Embryo-Fetal Toxicity: Exposure to HERCEPTIN HYLECTA during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception. (5.2, 8.1, 8.3)

RECENT MAJOR CHANGES

Dosage and Administration, Evaluation and Testing Before Initiating HERCEPTIN HYLECTA (2.1)	06/2024

INDICATIONS AND USAGE

HERCEPTIN HYLECTA is a combination of trastuzumab, a HER2/neu receptor antagonist, and hyaluronidase, an endoglycosidase, indicated in adults for:

- The treatment of HER2-overexpressing breast cancer. (1.1, 1.2)

Select patients for therapy based on an FDA-approved companion diagnostic for trastuzumab. (1, 2.2)

DOSAGE AND ADMINISTRATION

For subcutaneous use only. HERCEPTIN HYLECTA has different dosage and administration instructions than intravenous trastuzumab products.

Do not administer intravenously. (2.3)

Do not substitute HERCEPTIN HYLECTA for or with ado-trastuzumab emtansine. (2.3)

Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1, 2.2)

The recommended dose of HERCEPTIN HYLECTA is 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) administered subcutaneously over approximately 2-5 minutes once every three weeks. (2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 600 mg trastuzumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL) solution in a single-dose vial. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- Exacerbation of Chemotherapy-Induced Neutropenia. (5.4, 6.1)
- Hypersensitivity and Administration-Related Reactions (ARRs): Severe ARRs, including anaphylaxis, have been reported with HERCEPTIN HYLECTA. Monitor patients for systemic hypersensitivity reactions. Permanently discontinue HERCEPTIN HYLECTA in patients who experience anaphylaxis or severe hypersensitivity reactions. (5.5)

ADVERSE REACTIONS

Adjuvant Breast Cancer

- Most common adverse reactions (≥10%) for HERCEPTIN HYLECTA are fatigue, arthralgia, diarrhea, injection site reaction, upper respiratory tract infection, rash, myalgia, nausea, headache, edema, flushing, pyrexia, cough, and pain in extremity. (6.1)

Metastatic Breast Cancer (based on intravenous trastuzumab)

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

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of HERCEPTIN HYLECTA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Cardiomyopathy

HERCEPTIN HYLECTA administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving HERCEPTIN HYLECTA with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with HERCEPTIN HYLECTA. Discontinue HERCEPTIN HYLECTA treatment in patients receiving adjuvant therapy and withhold HERCEPTIN HYLECTA in patients with metastatic disease for clinically significant decrease in left ventricular function *[see Dosage and Administration (2.4) and Warnings and Precautions (5.1)]*.

Pulmonary Toxicity

HERCEPTIN HYLECTA administration can result in serious and fatal pulmonary toxicity. Symptoms usually occur during or within 24 hours of HERCEPTIN HYLECTA administration. Discontinue HERCEPTIN HYLECTA for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome *[see Warnings and Precautions (5.3, 5.5)]*. Monitor patients until symptoms completely resolve.

Embryo-Fetal Toxicity

Exposure to HERCEPTIN HYLECTA 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 (5.2) and Use in Specific Populations (8.1, 8.3)]*.

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

HERCEPTIN HYLECTA is indicated for adjuvant treatment of adults with 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 trastuzumab *[see Dosage and Administration (2.2)]*.

1.2 Metastatic Breast Cancer

HERCEPTIN HYLECTA is indicated in adults:

- 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 trastuzumab *[see Dosage and Administration (2.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Evaluation and Testing Before Initiating HERCEPTIN HYLECTA

Verify the pregnancy status of females of reproductive potential prior to the initiation of HERCEPTIN HYLECTA *[see Use in Specific Populations (8.1, 8.3)]*.

2.2 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 cancer 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.

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.

2.3 Recommended Dosage

HERCEPTIN HYLECTA is for subcutaneous use only. HERCEPTIN HYLECTA has different dosage and administration instructions than intravenous trastuzumab products. Do not administer intravenously.

Do not substitute HERCEPTIN HYLECTA for or with ado-trastuzumab emtansine.

The recommended dose of HERCEPTIN HYLECTA is 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) administered subcutaneously over approximately 2-5 minutes once every three weeks.

No loading dose is required. No dose adjustments for patient body weight or for different concomitant chemotherapy regimens are required.

Duration of treatment

Patients with adjuvant breast cancer should be treated with HERCEPTIN HYLECTA for 52 weeks or until disease recurrence, whichever occurs first; extending treatment in adjuvant breast cancer beyond one year is not recommended.

Patients with metastatic breast cancer (MBC) should be treated with HERCEPTIN HYLECTA until progression of disease.

Missed Dose

If one dose is missed, it is recommended to administer the next 600 mg/10,000 units dose (i.e. the missed dose) as soon as possible. The interval between subsequent HERCEPTIN HYLECTA doses should not be less than three weeks.

2.4 Dosage Modification for Adverse Reactions

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

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

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

HERCEPTIN HYLECTA may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%.

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

2.5 Administration and Storage

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is HERCEPTIN HYLECTA and not ado-trastuzumab emtansine or intravenous trastuzumab.

HERCEPTIN HYLECTA should be administered by a healthcare professional.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use vial if particulates or discoloration is present. Discard any unused portion remaining in the vial.

HERCEPTIN HYLECTA is for single use only. The 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) solution is a ready to use solution for injection which does not need to be diluted.

To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration followed by volume adjustment to 5 mL. HERCEPTIN HYLECTA is compatible with polypropylene and polycarbonate syringe material and stainless steel transfer and injection needles.

Prepare the dosing syringe in controlled and validated aseptic conditions. After the solution of HERCEPTIN HYLECTA is withdrawn from the vial and into the syringe, replace the transfer needle with a syringe closing cap. Label the syringe with the peel-off sticker.

Administration

The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard, or areas where there are moles or scars. During the treatment course with HERCEPTIN HYLECTA other medicinal products for subcutaneous administration should preferably be injected at different sites. The dose should be administered subcutaneously over approximately 2 to 5 minutes.

Storage

If the syringe containing HERCEPTIN HYLECTA is not used immediately, then the syringe can be stored in the refrigerator (2°C to 8°C) for up to 24 hours and subsequently at room temperature (20°C to 25°C) for up to 4 hours. Protect from light. Do not shake or freeze.

3 DOSAGE FORMS AND STRENGTHS

HERCEPTIN HYLECTA is a colorless to yellowish, clear to opalescent solution for subcutaneous injection:

- Injection: 600 mg trastuzumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL) in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

HERCEPTIN HYLECTA can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death *[see Boxed Warning: Cardiomyopathy]*. HERCEPTIN HYLECTA can also cause asymptomatic decline in LVEF.

There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving trastuzumab as a single agent or in combination therapy compared with those not receiving trastuzumab. The highest absolute incidence occurs when trastuzumab is administered with an anthracycline. The incidence of symptomatic myocardial dysfunction for intravenous trastuzumab and HERCEPTIN HYLECTA was similar in clinical trials *[see Adverse Reactions (6)]*.

Withhold HERCEPTIN HYLECTA for ≥16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥10% absolute decrease in LVEF from pretreatment values *[see Dosage and Administration (2.4)]*. The safety of continuation or resumption of HERCEPTIN HYLECTA in patients with HERCEPTIN HYLECTA induced left ventricular cardiac dysfunction has not been studied.

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

Cardiac Monitoring

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

- Baseline LVEF measurement immediately prior to initiation of HERCEPTIN HYLECTA
- LVEF measurements every 3 months during and upon completion of HERCEPTIN HYLECTA
- Repeat LVEF measurement at 4 week intervals if HERCEPTIN HYLECTA is withheld for significant left ventricular cardiac dysfunction *[see Dosage and Administration (2.4)]*
- LVEF measurements every 6 months for at least 2 years following completion of HERCEPTIN HYLECTA as a component of adjuvant therapy.

HERCEPTIN HYLECTA

In the HannaH study, the overall percentage of patients with at least one cardiac disorder was similar in both study arms: 15% (44/297) of patients in the HERCEPTIN HYLECTA arm and 14% (42/298) of patients in the intravenous trastuzumab arm. The most frequent cardiac adverse reactions were left ventricular dysfunction [3.4% (10/297) and 4.0% (12/298)], tachycardia [2% (6/297) and 3% (9/298)] and palpitations [2% (6/297) and 1.3% (4/298)] in the HERCEPTIN HYLECTA arm and the intravenous trastuzumab arm, respectively. The incidence of cardiac failure and congestive cardiac failure was 1% (3/297) in the HERCEPTIN HYLECTA arm and <1% (1/298) in the intravenous trastuzumab arm. The proportion of patients in each treatment arm with a significant decrease in LVEF defined as a drop of ≥10% points to an LVEF of <50% was comparable between treatment arms [3.8% (11/297) in the HERCEPTIN HYLECTA arm and 4.2% (12/298) in the intravenous trastuzumab arm]. In patients with lower body weights (<59 kg, the lowest body weight quartile) the fixed-dose used in the HERCEPTIN HYLECTA arm was not associated with an increased risk of cardiac events or significant drop in LVEF.

In the SafeHER study, in patients treated with HERCEPTIN HYLECTA, 17% (323/1864) reported a cardiac disorder during the treatment period. Decreased ejection fraction, reported in 4.5% (84/1864) of the patients was the most frequently reported cardiac disorder. Congestive cardiac failure was reported in <1% (10/1864) of patients and <1% (4/1864) of patients reported cardiac failure during the treatment period. One patient reported congestive cardiac failure during the follow-up period. Six percent (111/1864) of the patients treated with HERCEPTIN HYLECTA had an LVEF <50% with a decrease of ≥10 points in LVEF from baseline.

Trastuzumab (intravenous formulation):

In study NSABP B31 (NCT00004067), 15% (158/1031) of patients discontinued intravenous 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 arm. In the HERA study (one-year intravenous trastuzumab treatment; NCT00045032), the number of patients who discontinued intravenous trastuzumab due to cardiac toxicity at

12.6 months median duration of follow-up was 2.6% (44/1678). In the BCIRG006 study (NCT00021255), a total of 2.9% (31/1056) of patients in the TCH arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) of patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued intravenous trastuzumab due to cardiac toxicity.

Among 64 patients receiving adjuvant chemotherapy (studies NSABP B31 and NCCTG N9831; NCT00005970) who developed congestive heart failure (CHF), 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 ≥ 50%) and no symptoms on continuing medical management at the time of last follow-up. Incidence of CHF is presented in Table 1. The safety of continuation or resumption of intravenous trastuzumab in patients with trastuzumab-induced left ventricular cardiac dysfunction has not been studied.

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

		Incidence of **Congestive Heart Failure % (n)**	
Study	Regimen	Intravenous Trastuzumab	Control
NSABP B31 & NCCTG N9831[*]	AC[†]→paclitaxel + intravenous trastuzumab	3.2% (64/2000) [‡]	1.3% (21/1655)
HERA[§]	Chemotherapy → intravenous trastuzumab	2% (30/1678)	0.3% (5/1708)
BCIRG006	AC[†]→docetaxel + intravenous trastuzumab	2% (20/1068)	0.3% (3/1050)
BCIRG006	Docetaxel + carboplatin + intravenous trastuzumab	0.4% (4/1056)	0.3% (3/1050)

[*] Median follow-up duration for studies NSABP B31 and NCCTG N9831 combined was 8.3 years in the AC→ paclitaxel+Herceptin arm.
[†] Anthracycline (doxorubicin) and cyclophosphamide.
[‡] Includes 1 patient with fatal cardiomyopathy and 1 patient with sudden death without documented etiology.
[§] Includes NYHA II-IV and cardiac death at 12.6 months median duration of follow-up in the one-year intravenous trastuzumab arm.

In the HERA study (one-year intravenous trastuzumab treatment), at a median follow-up duration of 8 years, the incidence of severe CHF (NYHA III & IV) was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Table 2
Incidence of Cardiac Dysfunction* in Metastatic Breast Cancer Studies

		Incidence			
		NYHA I–IV		NYHA III–IV	
Study	Event	Intravenous Trastuzumab	Control	Intravenous Trastuzumab	Control
H0648g (AC)†	Cardiac Dysfunction	28%	7%	19%	3%
H0648g (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
H0649g	Cardiac Dysfunction‡	7%	N/A	5%	N/A

*Congestive heart failure or significant asymptomatic decrease in LVEF.
†Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
‡Includes 1 patient with fatal cardiomyopathy.

In the BCIRG006 study, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the intravenous trastuzumab containing regimens [AC-TH: 0.3% (3/1068) and TCH: 0.2% (2/1056)] as compared to none in AC-T.

5.2 Embryo-Fetal Toxicity

HERCEPTIN HYLECTA 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 oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

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

5.3 Pulmonary Toxicity

HERCEPTIN HYLECTA can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

5.4 Exacerbation of Chemotherapy-Induced Neutropenia

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

5.5 Hypersensitivity and Administration-Related Reactions

Severe administration-related reactions (ARRs), including hypersensitivity and anaphylaxis, have been reported with HERCEPTIN HYLECTA. Patients experiencing dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a severe or of a fatal ARR.

In the HannaH and SafeHER trials, 9% and 4.2% of patients experienced Grade 1-4 hypersensitivity and anaphylaxis, respectively. Grade 3-4 hypersensitivity and anaphylactic reactions occurred in 1% and <1% of the patients treated with HERCEPTIN HYLECTA, respectively. In the SafeHER trial, 2 patients required permanent treatment discontinuation with HERCEPTIN HYLECTA (1 patient due to a hypersensitivity reaction and 1 patient due to anaphylaxis). Serious and fatal reactions have been reported after treatment with intravenous trastuzumab products.

Closely monitor patients for systemic hypersensitivity reactions, especially during the first administration. Permanently discontinue HERCEPTIN HYLECTA in patients who experience anaphylaxis or severe hypersensitivity reactions. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. For patients experiencing reversible Grade 1 or 2 hypersensitivity reactions, consider pre-medication with an analgesic, antipyretic, or an antihistamine prior to readministration of HERCEPTIN HYLECTA *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

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

- Cardiomyopathy *[see Warnings and Precautions (5.1)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.2)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.3)]*
- Exacerbation of Chemotherapy-Induced Neutropenia *[see Warnings and Precautions (5.4)]*
- Hypersensitivity and Administration-Related Reactions *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

The safety of HERCEPTIN HYLECTA administered subcutaneously has been established in the HannaH and SafeHER studies conducted in patients with HER2 overexpressing breast cancer. The safety of intravenous trastuzumab has been established in studies H0648g and H0649g conducted in patients with HER2 overexpressing metastatic breast cancer.

Adjuvant Breast Cancer

HannaH

HannaH was a randomized, open-label study to compare the pharmacokinetics, efficacy, and safety of HERCEPTIN HYLECTA compared to intravenous trastuzumab in women with HER2-positive breast cancer. Patients randomized to the HERCEPTIN HYLECTA arm received a dose of 600 mg HERCEPTIN HYLECTA every 3 weeks throughout the treatment phase. Patients were treated for 8 cycles in combination with chemotherapy (docetaxel followed by 5FU, epirubicin and cyclophosphamide), then underwent surgery, and continued HERCEPTIN HYLECTA to complete 18 cycles of therapy. The median age of patients was 50 (range: 25-81 years), all patients were female, and a majority of patients were white (67%). The median number of HERCEPTIN HYLECTA cycles received was 18 (range 1-18).

The most common adverse reactions of any grade (occurring in ≥10% of patients) with HERCEPTIN HYLECTA were alopecia (63%), nausea (49%), ARRs (48%), neutropenia (44%), diarrhea (34%), asthenia (25%), fatigue (24%), vomiting (23%), myalgia (21%), decreased appetite (20%), stomatitis (19%), arthralgia (18%), headache (17%), rash (16%), constipation (14%), radiation skin injury (14%), pyrexia (12%), cough (12%), anemia (11%), dyspnea (11%), incision site pain (11%), peripheral sensory neuropathy (11%), leukopenia (10%), mucosal inflammation (10%), hot flush (10%), upper respiratory tract infection (10%).

The most common Grade ≥3 adverse reactions (occurring in >1% of patients) in the HERCEPTIN HYLECTA arm were neutropenia (30%), febrile neutropenia (6%), leukopenia (4%), diarrhea (3%), hypertension (2%), irregular menstruation (2%), alopecia (1%), nausea (1%), granulocytopenia (1%), vomiting (1%), amenorrhea (1%), and cellulitis (1%). Adverse reactions leading to interruption of any study drug in the HERCEPTIN HYLECTA arm occurred in 34% of patients; 31% of patients had these events during the neoadjuvant phase of the study with concurrent chemotherapy and 9% of patients had these events during the adjuvant phase. Overall, the most common (≥ 1%) were neutropenia (21%), leukopenia (2.4%), ALT increase (1.7%), pyrexia (1.7%), anemia (1%), bronchitis (1%), and left ventricular dysfunction (1%). Adverse reactions that led to discontinuation of any study drug in the HERCEPTIN HYLECTA arm (>1 patient) were left ventricular dysfunction (2%).

The incidence of ARRs in the HERCEPTIN HYLECTA arm was 48% and was 37% in the intravenous trastuzumab arm. Five (2%) patients in the HERCEPTIN HYLECTA arm experienced a Grade 3 ARR. Three of the events in the HERCEPTIN HYLECTA arm occurred on the day of study drug administration when docetaxel treatment was administered concurrently. The most commonly reported ARRs in the HERCEPTIN HYLECTA arm (≥5% of patients) were rash, pruritus, erythema, cough and dyspnea. Grade 1 and 2 injection-site reactions (ISRs) occurred in 10% of patients in the HERCEPTIN HYLECTA arm. The most common ISRs were injection-site pain and injection-site erythema.

The data in Table 3 were obtained from the HannaH trial for adverse reactions that occurred in ≥ 5% of the patients treated with HERCEPTIN HYLECTA.

Table 3
Adverse Reactions[*] (≥ 5% Incidence) Reported in HannaH

Adverse Reactions	HERCEPTIN HYLECTA 600 mg n=297		Intravenous Trastuzumab (loading dose: 8 mg/kg; maintenance dose: 6 mg/kg) n=298	
	All Grades %	Grades 3 to 5 %	All Grades %	Grades 3 to 5 %
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Alopecia[*,†]	63	1.3	63	1.7
Rash[*,†]	26	< 1	26	-
Nail Disorder[*,†]	14	-	14	< 1
Pruritus[*,†]	9	-	9	-
Skin Discoloration[*]	9	-	8	-
Erythema[*]	7	< 1	3	-
GASTROINTESTINAL DISORDERS				
Nausea	49	1.3	49	1.3
Diarrhea[*,†]	34	2.7	37	2.7
Vomiting[†]	23	1	23	1.7
Stomatitis[*]	21	< 1	18	< 1
Abdominal Pain[*,†]	14	-	14	< 1
Dyspepsia	11	-	10	-
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue[*,†]	46	< 1	49	2
Edema[*,†]	14	-	15	-
Pyrexia[*]	13	1	12	< 1
Mucosal Inflammation[†]	10	< 1	13	-
Pain[*,†]	5	-	8	< 1
Injection Site Reaction[*,‡]	10	-	< 1	-
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Neutropenia[†]	44	30	47	34
Leukopenia[*,†]	11	5	16	8
Anemia[*,†]	12	< 1	14	1
Febrile Neutropenia[*]	6	6	4	4

Table 3
Adverse Reactions* (≥ 5% Incidence) Reported in HannaH

Adverse Reactions	HERCEPTIN HYLECTA 600 mg n=297		Intravenous Trastuzumab (loading dose: 8 mg/kg; maintenance dose: 6 mg/kg) n=298	
	All Grades %	Grades 3 to 5 %	All Grades %	Grades 3 to 5 %
INFECTIONS AND INFESTATIONS				
Upper Respiratory Tract Infection*,†	24	1	27	< 1
Urinary Tract Infection*,†	4	-	8	< 1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Myalgia*	21	-	19	< 1
Arthralgia*,†	18	-	21	< 1
Back Pain*	11	1	9	1
Pain in Extremity	10	-	9	< 1
Pain*,†	8	< 1	9	-
Bone Pain	6	< 1	3.4	-
NERVOUS SYSTEM DISORDERS				
Neuropathy Peripheral*	20	-	15	-
Headache*	17	< 1	15	< 1
Dizziness*	10	< 1	9	< 1
Dysgeusia*	10	-	8	-
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Incision Site Complication*	11	-	8	< 1
Pain*	6	-	5	< 1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Cough*	12	< 1	8	-
Dyspnea*,†	7	-	8	-
Epistaxis	6	-	6	-
Nasal Inflammation / Discomfort*,†	5	-	7	-
VASCULAR DISORDERS				
Flushing*	14	< 1	13	< 1
Hypertension*	8	2.4	5	< 1
METABOLISM AND NUTRITION DISORDERS				
Decreased Appetite	20	< 1	20	< 1
INVESTIGATIONS				
Liver Function Analysis Abnormal*,†	6	1	9	1.7
CARDIAC DISORDERS				
Arrhythmia*†	5	-	5	< 1
IMMUNE SYSTEM DISORDERS				
Hypersensitivity*,†	7	1	7	1.3

* Contains grouped terms

† The HannaH trial was not designed to demonstrate a statistically significant difference in adverse reaction rates between HERCEPTIN HYLECTA and intravenous trastuzumab.

‡ Injection Site Reaction includes terms for injection related reaction and injection site joint pain, bruising, dermatitis, discoloration, discomfort, erythema, extravasation, fibrosis, hematoma, hemorrhage, hypersensitivity, induration, inflammation, irritation, macule, mass, nodule, edema, pallor, paraesthesia, pruritus, rash, reaction, swelling, ulcer, vesicles and warmth.

SafeHER

SafeHER was a prospective, two-cohort, non-randomized, multi-center, multinational, open-label study to assess the safety of HERCEPTIN HYLECTA in patients with operable HER2-positive breast cancer. In SafeHER, 1864

patients were enrolled and treated with 600 mg of HERCEPTIN HYLECTA administered subcutaneously once every three weeks for 18 cycles.

The median age of patients was 54 (range: 20-88 years), 99.8% were female, and a majority were white (76%). A majority of the patients received HERCEPTIN HYLECTA concurrently with a chemotherapy regimen (58%). The median number of HERCEPTIN HYLECTA cycles administered was 18 and the median duration of HERCEPTIN HYLECTA exposure was 11.8 months. The median duration of follow-up was 23.7 months.

During the treatment period, the most common adverse reactions of any grade (occurring in ≥10% of patients) were ARRs (39%), diarrhea (21%), fatigue (21%), arthralgia (21%), nausea (15%), myalgia (14%), headache (13%), asthenia (12%), pain in extremity (11%), cough (11%), pyrexia (11%), hot flush (10%), and rash (10%). The most common Grade ≥3 adverse reactions (occurring in >1% of patients) were neutropenia (4%), febrile neutropenia (2%), hypertension (2%), leukopenia (1%), and diarrhea (1%). Adverse reactions that led to study drug discontinuation (≥0.5% of patients) were ejection fraction decreased (2%) and left ventricular dysfunction (1%).

The incidence of ARRs was 39%, with Grade ≥3 ARRs reported in 1% of patients treated with HERCEPTIN HYLECTA. The most frequently reported Grade ≥3 ARRs were dyspnea (<1%), cough (<1%), erythema (<1%), rash (<1%), and drug hypersensitivity (<1%). ISRs were reported in 20% of patients treated with HERCEPTIN HYLECTA. The most common ISRs were injection-site erythema (7%) and injection-site pain (6%). All ISRs were Grade 1 or 2, except for one (<1%) Grade 3 injection site discomfort.

The data in Table 4 were obtained from the SafeHER trial for adverse reactions that occurred in ≥5% of the patients treated with HERCEPTIN HYLECTA.

Table 4
Adverse Reactions* (≥ 5% Incidence) Reported in SafeHER

Adverse Reactions *,†	HERCEPTIN HYLECTA 600 mg (once every 3 weeks) n=1864	
	All Grades %	Grades 3 to 5 %
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue*	33	< 1
Injection Site Reaction*,‡	20	< 1
Edema*	12	< 1
Pyrexia*	11	< 1
Pain*	8	< 1
Mucosal Inflammation	6	< 1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia*	21	< 1
Myalgia*	17	< 1
Pain in Extremity	11	< 1
Back Pain*	8	< 1
Pain*	7	< 1
GASTROINTESTINAL DISORDERS		
Diarrhea*	21	1
Nausea	15	< 1
Abdominal Pain*	10	< 1
Constipation	9	< 1
Stomatitis*	8	< 1
Vomiting	7	< 1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash*	17	< 1
Nail Disorder*	10	< 1

Table 4
Adverse Reactions* (≥ 5% Incidence) Reported in SafeHER

Adverse Reactions *,†	HERCEPTIN HYLECTA 600 mg (once every 3 weeks) n=1864	
	All Grades %	Grades 3 to 5 %
Alopecia*	9	< 1
Erythema*	9	< 1
Pruritus*	6	-
INFECTIONS AND INFESTATIONS		
Upper Respiratory Tract Infection*	19	< 1
Urinary Tract Infection*	6	< 1
Viral Infection*	5	-
NERVOUS SYSTEM DISORDERS		
Neuropathy Peripheral*	14	< 1
Headache*	13	< 1
Dizziness*	6	< 1
Paresthesia	6	< 1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough*	11	< 1
Dyspnea*	8	< 1
Epistaxis	6	-
Nasal Inflammation/Discomfort*	6	-
VASCULAR DISORDERS		
Flushing*	12	< 1
Hypertension*	8	2
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia*	8	< 1
Neutropenia	6	4
PSYCHIATRIC DISORDERS		
Insomnia*	7	< 1

* Contains grouped terms
† Includes adverse reactions reported throughout study treatment and follow-up.
‡ ISR includes injection related reaction and injection site joint pain, bruising, dermatitis, discoloration, discomfort, erythema, extravasation, fibrosis, hematoma, hemorrhage, hypersensitivity, induration, inflammation, irritation, macule, mass, nodule, edema, pallor, paresthesia, pruritus, rash, reaction, swelling, ulcer, vesicles and warmth.

Metastatic Breast Cancer (based on intravenous trastuzumab)

The data below reflect exposure to intravenous trastuzumab in one randomized, open-label study, H0648g, of chemotherapy with (n=235) or without (n=234) intravenous trastuzumab in patients with metastatic breast cancer, and one single-arm study (H0649g; n=222) in patients with metastatic breast cancer. Data in Table 5 are based on H0648g and H0649g.

Among the 464 patients treated in H0648g, the median age was 52 years (range: 25–77 years). Eighty-nine percent were white, 5% black, 1% Asian, and 5% other racial/ethnic groups. All patients received 4 mg/kg initial dose of intravenous trastuzumab followed by 2 mg/kg weekly. The percentages of patients who received intravenous trastuzumab treatment for ≥ 6 months and ≥ 12 months were 58% and 9%, respectively.

Among the 352 patients treated in single agent studies (213 patients from H0649g), the median age was 50 years (range 28–86 years), 86% were white, 3% were black, 3% were Asian, and 8% in other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of intravenous trastuzumab followed by 2 mg/kg weekly. The percentages of patients who received intravenous trastuzumab treatment for ≥ 6 months and ≥ 12 months were 31% and 16%, respectively.

Table 5
Adverse Reactions (≥ 5%) in the Intravenous Trastuzumab Arm (H0648g and H0649g)

	Intravenous trastuzumab [a] n = 352 %	Intravenous trastuzumab + Paclitaxel n = 91 %	Paclitaxel n = 95 %	Intravenous trastuzumab + AC[b] n = 143 %	AC[b] n = 135 %
General					
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
Gastrointestinal					
Nausea	33	51	9	76	77
Diarrhea	25	45	29	45	26
Vomiting	23	37	28	53	49
Anorexia	14	24	16	31	26
Nausea and vomiting	8	14	11	18	9
Respiratory					
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
Skin					
Rash	18	38	18	27	17
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	< 1
Nervous					
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

[a] Data for Herceptin single agent were from 4 studies, including 213 patients from H0649g.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

Table 6
Adverse Reactions (≥ 5%) of Patients in the Intravenous Trastuzumab Arm (H0648g and H0649g) (*continued*)

	Intravenous trastuzumab [a] n = 352 %	Intravenous trastuzumab + Paclitaxel n = 91 %	Paclitaxel n = 95 %	Intravenous trastuzumab + AC[b] n = 143 %	AC[b] n = 135 %
Neuropathy	1	13	5	4	4
Metabolic					
Peripheral edema	10	22	20	20	17
Edema	8	10	8	11	5
Cardiovascular					
Congestive heart failure	7	11	1	28	7
Tachycardia	5	12	4	10	5
Musculoskeletal					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9
Urogenital					
Urinary tract infection	5	18	14	13	7
Blood and Lymphatic					
Anemia	4	14	9	36	26
Leukopenia	3	24	17	52	34

[a] Data for Herceptin single agent were from 4 studies, including 213 patients from H0649g.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

6.2 Postmarketing Experience

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

- Administration-related reaction *[see Warnings and Precautions (5.5)]*
- Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal abnormalities, and neonatal death *[see Warnings and Precautions (5.2)]*
- 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

Anthracyclines

Patients who receive anthracycline after stopping HERCEPTIN HYLECTA may be at increased risk of cardiac dysfunction because of HERCEPTIN HYLECTA's estimated long washout period *[see Clinical Pharmacology (12.3)]*. If possible, avoid anthracycline-based therapy for up to 7 months after stopping HERCEPTIN HYLECTA. If anthracyclines are used, closely monitor the patient's cardiac function.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Pharmacovigilance Program

There is a pregnancy pharmacovigilance program for HERCEPTIN HYLECTA. If HERCEPTIN HYLECTA is administered during pregnancy, or if a patient becomes pregnant while receiving HERCEPTIN HYLECTA or within 7 months following the last dose of HERCEPTIN HYLECTA, health care providers and patients should immediately report HERCEPTIN HYLECTA exposure to Genentech at 1-888-835-2555.

Risk Summary

HERCEPTIN HYLECTA can cause fetal harm when administered to a pregnant woman. In post-marketing reports and published literature, 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 HERCEPTIN HYLECTA is used in a pregnant woman or if a patient becomes pregnant within 7 months following the last dose of HERCEPTIN HYLECTA *[see Clinical Considerations]*.

The 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 HERCEPTIN HYLECTA during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal/neonatal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

In post-marketing reports and published literature, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence. Fetal manifestations included 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 most reported cases, amniotic fluid index increased after use of trastuzumab was stopped. In reported cases where Herceptin therapy was resumed after amniotic index improved, oligohydramnios recurred.

Animal Data

HERCEPTIN HYLECTA for subcutaneous injection contains trastuzumab and hyaluronidase *[see Description (11)]*.

Trastuzumab:

In studies where intravenous 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.

Hyaluronidase:

In an embryo-fetal study, mice have been dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase (recombinant human) at dose levels up to 2,200,000 U/kg, which is >7,200 times higher than the human dose. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is >1,200 times higher than the human dose.

In a peri-and post-natal reproduction study, mice have been dosed daily by subcutaneous injection, with hyaluronidase (recombinant human) from implantation through lactation and weaning at dose levels up to 1,100,000 U/kg, which is >3,600 times higher than the human dose. The study found no adverse effects on sexual maturation, learning and memory or fertility of the offspring.

8.2 Lactation

Risk Summary

There is no information regarding the presence of trastuzumab or hyaluronidase 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 HERCEPTIN HYLECTA treatment and any potential adverse effects on the breastfed child from HERCEPTIN HYLECTA or from the underlying maternal condition. This consideration should also take into account the trastuzumab 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 intravenous trastuzumab). 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 HERCEPTIN HYLECTA.

Contraception

Females

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

8.4 Pediatric Use

The safety and effectiveness of HERCEPTIN HYLECTA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the HannaH and SafeHER studies treated with HERCEPTIN HYLECTA, 19% were 65 and over, while 4.7% were 75 and over.

In patients receiving intravenous trastuzumab, the risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients, in both those receiving treatment for adjuvant therapy or metastatic disease. Other differences in safety or effectiveness were not observed between elderly patients and younger patients.

11 DESCRIPTION

HERCEPTIN HYLECTA is a combination of trastuzumab and hyaluronidase. Trastuzumab 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 is produced by recombinant DNA technology in

a mammalian cell (Chinese Hamster Ovary) culture. Trastuzumab has a molecular weight of approximately 148 kDa.

Hyaluronidase (recombinant human) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is a glycosylated single-chain protein produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hyaluronidase (recombinant human) has a molecular weight of approximately 61 kDa.

HERCEPTIN HYLECTA (trastuzumab and hyaluronidase) injection is a sterile, preservative-free, colorless to yellowish, clear to opalescent solution supplied in single-dose vials for subcutaneous administration.

HERCEPTIN HYLECTA is supplied as 600 mg trastuzumab and 10,000 units hyaluronidase per 5 mL in single-dose vials. Each mL of solution contains trastuzumab (120 mg), hyaluronidase (2,000 units), L-histidine (0.39 mg), L-histidine hydrochloride monohydrate (3.67 mg), L-methionine (1.49 mg), polysorbate 20 (0.4 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

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

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

Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan. In the doses administered, hyaluronidase in HERCEPTIN HYLECTA acts transiently and locally.

The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

Hyaluronidase has been shown to increase the absorption rate of a trastuzumab product into the systemic circulation when given in the subcutis of Göttingen Minipigs.

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

Trastuzumab exposure following subcutaneous administration of HERCEPTIN HYLECTA 600 mg every 3 weeks as compared to intravenous trastuzumab 8 mg/kg loading dose, 6 mg/kg maintenance every 3 weeks in the HannaH Study is shown in Table 6. The pharmacokinetic (PK) results for the co-primary endpoint, C_{trough} pre-dose Cycle 8, showed non-inferiority of HERCEPTIN HYLECTA (78.7 mcg/mL) compared to intravenous trastuzumab (57.8 mcg/mL), with a geometric mean ratio of 1.3 (90% CI: 1.2–1.4).

A population PK model with parallel linear and nonlinear elimination from the central compartment was constructed using pooled HERCEPTIN HYLECTA and intravenous trastuzumab pharmacokinetic (PK) data from HannaH to describe the observed trastuzumab PK concentrations following HERCEPTIN HYLECTA subcutaneous administration and intravenous trastuzumab administration. Population PK predicted trastuzumab exposure are shown in Table 6.

Following subcutaneous administration of HERCEPTIN HYLECTA, trastuzumab concentrations were approximately at steady-state after the Cycle 7 dose with < 15% increase in concentration up to Cycle 13. The mean C_{trough} at the pre-dose Cycle 18 in HERCEPTIN HYLECTA arm is similar to that of Cycle 13, suggesting no further increase after Cycle 13. The mean C_{max} was 32% lower, and the mean $AUC_{0\text{-}21\ days}$ following the Cycle 7 dose and Cycle 12 dose was approximately 10% and 20% higher, respectively, in the HERCEPTIN HYLECTA arm than in the intravenous trastuzumab arm.

Table 7
Trastuzumab Exposure (median with 5th-95th Percentiles) following Subcutaneous Administration of HERCEPTIN HYLECTA or Intravenous Trastuzumab

Trastuzumab Exposure		HERCEPTIN HYLECTA	Intravenous Trastuzumab
C_{trough} (mcg/mL)	Cycle 1	28.2 (14.8–40.9)	29.4 (5.8–59.5)
	Cycle 7	75.0 (35.1–123)	47.4 (5–114.7)
C_{max} (mcg/mL)	Cycle 1	79.3 (56.1–109)	178 (117–291)
	Cycle 7	149 (86.1–214)	179 (107–309)
$AUC_{0\text{-}21\ days}$ (mcg/mL•day)	Cycle 1	1065 (718–1504)	1373 (736–2245)
	Cycle 7	2337 (1258–3478)	1794 (673–3618)

General PK parameters of trastuzumab following subcutaneous administration of HERCEPTIN HYLECTA are shown in Table 7. Trastuzumab is estimated to reach concentrations that are < 1 mcg/mL by 7 months in at least 95% patients.

Table 8
PK parameters of Trastuzumab following Subcutaneous Administration of HERCEPTIN HYLECTA*

Absorption	
Absolute Bioavailability	0.77 (13)
First-order absorption rate, ka (day^{-1})	0.4 (2.92)†
T_{max} (day)	3 (1-14)‡
Distribution	
Volume of Central Compartment (L)	2.9 (19.1)
Elimination	
Linear Elimination Clearance (L/day)	0.11 (30)
Non-linear Elimination V_{max} (mg/day)	11.9 (19.9)†
Non-linear Elimination K_m (mg/L)	33.9 (38.6)†

* Parameters represented as geometric mean (%CV) unless otherwise specified
† Residual standard error
‡ Median (range)

Specific Populations

Body weight showed a statistically significant influence on PK. In patients with a body weight < 51 kg, mean steady state AUC of trastuzumab was about 80% higher after HERCEPTIN HYLECTA than after intravenous trastuzumab treatment, whereas in the highest BW group (> 90 kg) AUC was 20% lower after HERCEPTIN

HYLECTA than after intravenous trastuzumab treatment. However, no body weight based dose adjustments are needed, as the exposure changes are not considered clinically relevant.

Drug Interaction Studies

There have been no formal drug interaction studies performed with trastuzumab 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 intravenous 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 BO18255, the pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered in combination with intravenous trastuzumab.

12.6 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to HERCEPTIN HYLECTA and intravenous trastuzumab in the study described below with the incidence of antibodies in other studies or to other products may be misleading.

In the HannaH study, at a median follow-up exceeding 60 months, the incidence of treatment-induced/enhanced anti-trastuzumab antibodies was 10% (30/296) in patients treated with intravenous trastuzumab and 16% (47/295) in patients receiving HERCEPTIN HYLECTA. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2/30 patients in the intravenous trastuzumab arm and 3/47 patients in the HERCEPTIN HYLECTA arm. The incidence of treatment-induced/enhanced anti-recombinant human hyaluronidase antibodies was 21% (62/295) in the HERCEPTIN HYLECTA arm. None of the patients who tested positive for anti-recombinant human hyaluronidase antibodies tested positive for neutralizing antibodies.

The clinical relevance of the development of anti-trastuzumab or anti-recombinant human hyaluronidase antibodies after treatment with HERCEPTIN HYLECTA is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

HERCEPTIN HYLECTA contains trastuzumab and hyaluronidase.

Trastuzumab has not been tested for carcinogenicity 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 intravenous trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels.

Hyaluronidases are found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase. In addition, when hyaluronidase (recombinant human) was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, which is > 670 times higher than the human dose, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

14 CLINICAL STUDIES

The comparability between HERCEPTIN HYLECTA administered subcutaneously and intravenous trastuzumab was established in the HannaH study. The HannaH study was conducted in patients with HER2 overexpressing breast cancer in the neoadjuvant and adjuvant settings with co-primary endpoints of pathological complete response (pCR) and the PK endpoint of C_{trough} at cycle 7 *[see Clinical Pharmacology (12.3)]*.

14.1 Adjuvant Breast Cancer

HERCEPTIN HYLECTA

HannaH

The HannaH study (NCT00950300) was a randomized, multicenter, open-label, clinical trial in 596 patients with HER2-positive operable or locally advanced breast cancer (LABC), including inflammatory breast cancer. HER2-positivity was defined as IHC 3+ or ISH+. Patients were randomized to receive 8 cycles of either HERCEPTIN HYLECTA or intravenous trastuzumab concurrently with chemotherapy (docetaxel followed by 5FU, epirubicin and cyclophosphamide), followed by surgery and continued therapy with HERCEPTIN HYLECTA or intravenous trastuzumab as treated prior to surgery, for an additional 10 cycles, to complete 18 cycles of therapy. HannaH was designed to demonstrate non-inferiority of treatment with HERCEPTIN HYLECTA versus intravenous trastuzumab based on co-primary PK and efficacy outcomes (trastuzumab C_{trough} at pre-dose Cycle 8, and pCR rate at definitive surgery, respectively) *[see Clinical Pharmacology 12.3]*. EFS and OS were among other outcomes evaluated in this study. The majority of patients were white (69%) and the median age was 50 years (range: 24-81).

The analysis of the efficacy co-primary outcome, pCR, defined as absence of invasive neoplastic cells in the breast, resulted in rates of 45.4% (95% CI: 39.2, 51.7) in the HERCEPTIN HYLECTA arm and 40.7% (95% CI: 34.7, 46.9) in the intravenous trastuzumab arm.

Table 9:
Summary of Pathological Complete Response (pCR) (HannaH)

	HERCEPTIN HYLECTA (n=260)	Intravenous Trastuzumab (n=263)
pCR (absence of invasive neoplastic cells in breast [ypT0/is])	118 (45.4%)	107 (40.7%)
Exact 95% CI for pCR Rate*	(39.2; 51.7)	(34.7; 46.9)
Difference in pCR (SC minus IV arm)	4.70	
95% CI for Difference in pCR†	(-4.0; 13.4)	

*CI for one sample binomial using Pearson-Clopper method
†Approximate 95% CI for difference of two rates using Hauck-Anderson method

With a median follow-up exceeding 70 months, no difference in EFS and OS was observed in the final analysis between patients who received intravenous trastuzumab and those who received HERCEPTIN HYLECTA.

SafeHER
The SafeHER study (NCT01566721) was a prospective, two-cohort, non-randomized, multinational, open-label study designed to assess the overall safety and tolerability of HERCEPTIN HYLECTA with chemotherapy in 1864 patients with HER2-positive breast cancer. The secondary objectives include the evaluation of DFS and OS. HER2-positivity was defined as IHC 3+ or ISH+. Patients received a fixed dose of 600 mg HERCEPTIN HYLECTA every 3 weeks for a total of 18 cycles throughout the study. HERCEPTIN HYLECTA treatment was initiated either sequentially with chemotherapy, concurrently with chemotherapy, or without adjuvant chemotherapy, or in combination with neoadjuvant chemotherapy followed by trastuzumab therapy. The majority of treated patients were white (76%) and the median age was 54 years (range: 20-88).

In the primary safety analysis (median follow-up 23.7 months), no new safety signals were identified for HERCEPTIN HYLECTA. Safety and tolerability results, including in lower weight patients, were consistent with the known safety profile for HERCEPTIN HYLECTA and intravenous trastuzumab.

In the ITT population (n=1867), 126 patients (7%) had a DFS event (recurrence, contralateral invasive breast cancer or death) and 28 patients (1.5%) had an OS event at the time of clinical cut-off.

Intravenous Trastuzumab
The safety and efficacy of intravenous 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 NSABP B31 and NCCTG N9831) with a total of 4063 women at the protocol-specified final overall survival analysis, a third randomized, open-label, clinical trial (HERA Study) with a total of 3386 women at definitive DFS analysis for 1-year intravenous trastuzumab treatment versus observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study BCIRG006).

Studies NSABP B31 and NCCTG N9831
In Studies NSABP B31 and NCCTG N9831, 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 NCCTG N9831) or was required to be performed at a reference laboratory (Study NSABP B31). 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 intravenous trastuzumab (AC→paclitaxel + intravenous trastuzumab).

In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. Paclitaxel was administered either weekly (80 mg/m^2) or every 3 weeks (175 mg/m^2) for a total of 12 weeks in Study NSABP B31; paclitaxel was administered only by the weekly schedule in Study NCCTG N9831. Intravenous 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. Intravenous 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 major efficacy outcome of the combined efficacy analysis was DFS, defined as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second primary cancer, or death. An additional efficacy outcome measure was OS.

A total of 3752 patients were included in the joint efficacy analysis of DFS following a median follow-up of 2.0 years in the AC→paclitaxel + intravenous 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 + intravenous trastuzumab arm. The data from both arms in Study NSABP B31 and two of the three study arms in Study NCCTG N9831 were pooled for efficacy analyses. The patients included in the 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.

HERA Study

In the HERA Study, 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.

Patients were randomized (1:1:1) upon completion of definitive surgery, and at least 4 cycles of chemotherapy to receive no additional treatment, or 1 year of intravenous trastuzumab treatment or 2 years of intravenous 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. Intravenous trastuzumab was administered with an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every 3 weeks. The major efficacy outcome measure was DFS, defined as in Studies NSABP B31 and NCCTG N9831.

HERA was designed to compare 1 and 2 years of three-weekly intravenous trastuzumab treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). A protocol specified interim efficacy analysis comparing one-year intravenous trastuzumab treatment to observation was performed at a median follow-up duration of 12.6 months in the intravenous trastuzumab. Among the 3386 patients randomized to the observation (n = 1693) and intravenous trastuzumab one-year (n = 1693) treatment arms, the median age was 49 years (range 21–80), 83% were White, 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 > 2 cm, Grade 2–3, or age < 35 years. Prior to randomization, 94% of patients had received anthracycline-based chemotherapy regimens.

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

BCIRG006 Study

In the BCIRG006 Study, 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 intravenous trastuzumab (AC-TH), or docetaxel and carboplatin plus intravenous trastuzumab (TCH). In both the AC-T and AC-TH arms, doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 were administered every 3 weeks for four cycles; docetaxel 100 mg/m^2 was administered every 3 weeks for four cycles. In the TCH arm, docetaxel 75 mg/m^2 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. Intravenous 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. DFS was the major efficacy outcome measure.

Among 3222 patients, the median age was 49 (range 22 to 74 years; 6% ≥ 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 NSABP B31 and NCCTG N9831, HERA, and BCIRG006 and OS results for the integrated analysis of Studies NSABP B31 and NCCTG N9831, and HERA are presented in Table 10. For Studies NSABP B31 and NCCTG N9831, the duration of DFS following a median follow-up of 2.0 years in the AC→TH arm is presented in Figure 1, and the duration of OS after a median follow-up of 8.3 years in the AC→TH arm is presented in Figure 2. The duration of DFS for BCIRG006 is presented in Figure 3. For Studies NSABP B31 and NCCTG N9831, the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74). At 8.3 years of median follow-up [AC→TH], the survival rate was estimated to be 86.9% in the AC→TH arm and 79.4% in the AC→T arm. The final OS analysis results from Studies NSABP B31 and NCCTG N9831 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 ≤ 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 ≤ 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 10
Efficacy Results from Adjuvant Treatment of Breast Cancer
(Studies NSABP B31, NCCTG N9831, HERA, and BCIRG006)

	DFS events	DFS Hazard ratio (95% CI) p-value	Deaths (OS events)	OS Hazard ratio p-value
Studies NSABP B31 and NCCTG N9831[*]				
AC→TH (n = 1872)[†] (n = 2031)[‡]	133[†]	0.48[†,§] (0.39, 0.59) p< 0.0001[¶]	289[‡]	0.64[‡,§] (0.55, 0.74) p< 0.0001[¶]
AC→T (n = 1880)[†] (n = 2032)[‡]	261[†]		418[‡]	
HERA[#]				
Chemo→ Intravenous trastuzumab (n = 1693)	127	0.54 (0.44, 0.67) p< 0.0001[Þ]	31	0.75 p = NS[ß]
Chemo→ Observation (n = 1693)	219		40	
BCIRG006[à]				
TCH (n = 1075)	134	0.67 (0.54 – 0.84) p=0.0006[¶,è]	56	
AC→TH (n = 1074)	121	0.60 (0.48 – 0.76) p< 0.0001[¶,à]	49	
AC→T (n = 1073)	180		80	

CI = confidence interval.

[*] Studies NSABP B31 and NCCTG N9831 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus intravenous trastuzumab (AC→TH).

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

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

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

[¶] stratified log-rank test.

[#] At definitive DFS analysis with median duration of follow-up of 12.6 months in the one-year intravenous trastuzumab treatment arm.

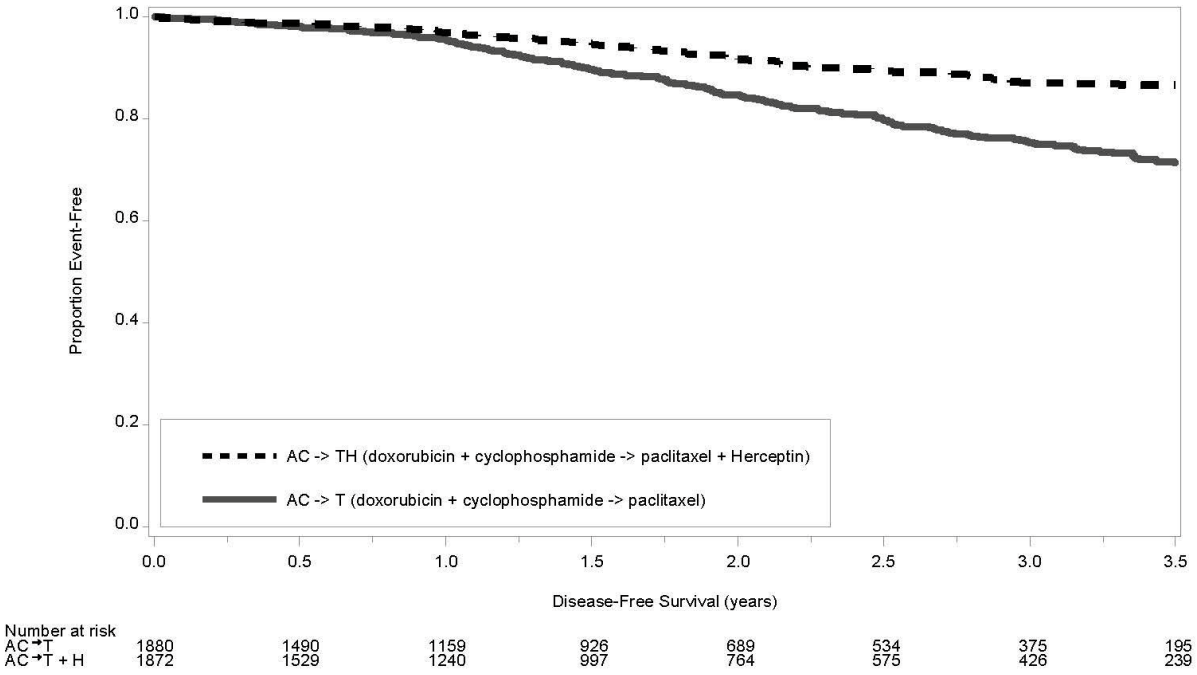
[Þ] log-rank test.

[ß] NS = non-significant.

[à] BCIRG006 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus intravenous trastuzumab (AC→TH); docetaxel and carboplatin plus intravenous trastuzumab (TCH).

[è] A two-sided alpha level of 0.025 for each comparison.

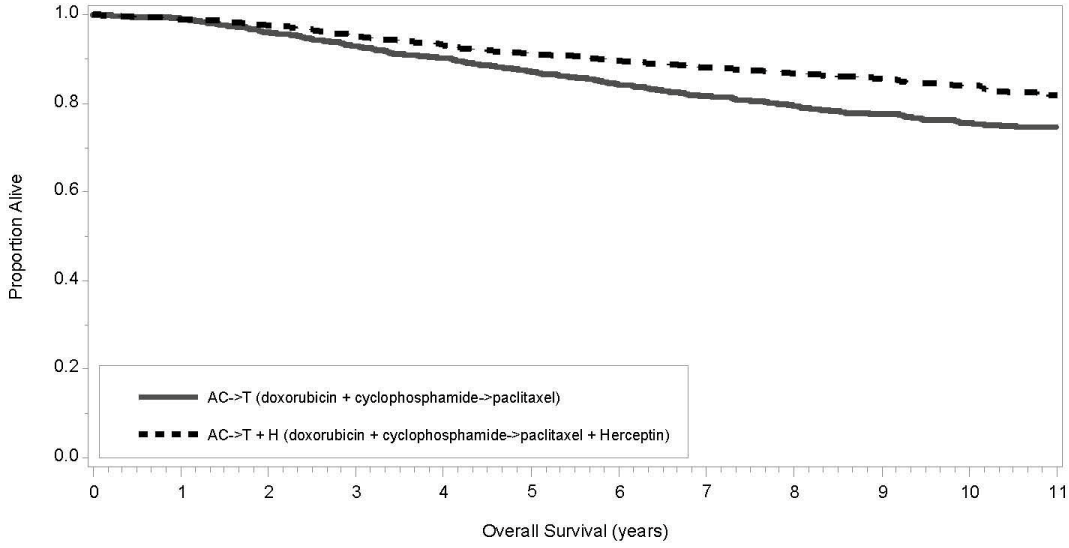
Figure 1
Duration of Disease-Free Survival in Patients with Adjuvant Treatment of Breast Cancer (Studies NSABP B31 and NCCTG N9831)



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

Figure 2

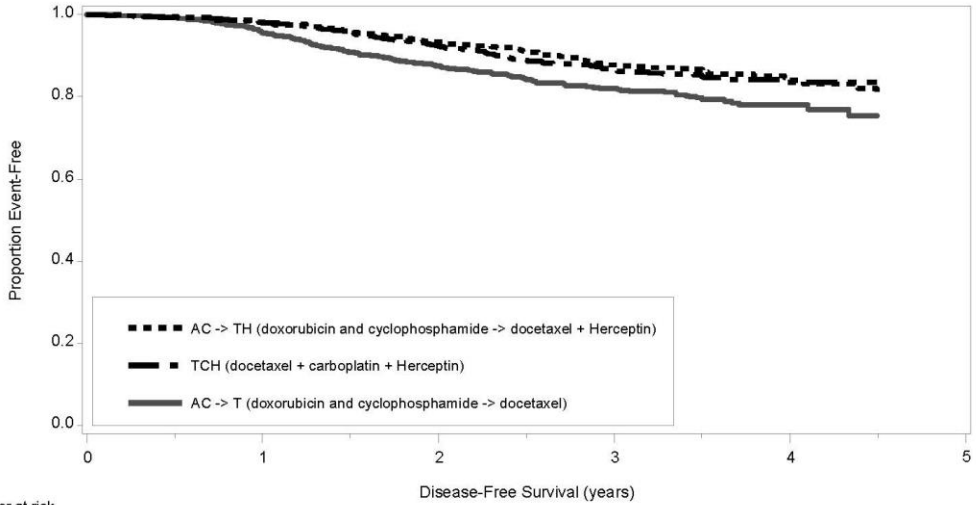
Duration of Overall Survival in Patients with Adjuvant Treatment of Breast Cancer (Studies NSABP B31 and NCCTG N9831)



Number at risk												
AC->T	2032	1961	1883	1806	1732	1643	1538	1377	979	630	399	151
AC->T + H	2031	1992	1957	1897	1843	1787	1714	1533	1127	787	485	159

Figure 3

Duration of Disease-Free Survival in Patients with Adjuvant Treatment of Breast Cancer (BCIRG006)



Number at risk					
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.

Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Study NCCTG N9831 and HERA, where central laboratory testing data were available. The results are shown in Table 11. The number of events in Study NCCTG N9831 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 HERA was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH+/IHC unknown subgroups.

Table 11
Treatment Outcomes in Study NCCTG N9831 and HERA for Patients with HER2 Overexpression or Amplification

	Study NCCTG N9831		HERA*	
HER2 Assay Result†	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‡	0.53 (0.20, 1.42)
IHC unknown / FISH (+)	—	—	724	0.59 (0.38, 0.93)

* Median follow-up duration of 12.6 months in the one-year intravenous trastuzumab treatment arm.
† IHC by HercepTest, FISH by PathVysion (HER2/CEP17 ratio ≥ 2.0) as performed at a central laboratory.
‡ All cases in this category in HERA were IHC 2+.

14.2 Metastatic Breast Cancer

Intravenous Trastuzumab

The safety and efficacy of intravenous trastuzumab in the treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (H0648g, n=469 patients) and an open-label single agent clinical trial (H0649g, n=222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had level 2 or 3 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 (H0648g)

H0648g 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. 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 intravenous trastuzumab at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 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/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles).

Sixty-five percent of patients randomized to receive chemotherapy alone in this study received intravenous 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 intravenous trastuzumab and chemotherapy experienced a significantly longer time to disease progression (TTP), a higher overall response rate (ORR), and a longer median duration of response as compared with patients randomized to chemotherapy alone. Patients randomized to intravenous trastuzumab and chemotherapy also had a longer median overall survival (OS) (see Table 12). These treatment effects were observed both in patients who received intravenous trastuzumab plus paclitaxel and in those who received intravenous trastuzumab plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.

Table 12:
H0648g: Efficacy Results in First-Line Treatment for Metastatic Breast Cancer

	Combined Results		**Paclitaxel Subgroup**		**AC Subgroup**	
	Intravenous Trastuzumab + All Chemo-therapy (n=235)	All Chemo-therapy (n=234)	Intravenous Trastuzumab + Paclitaxel (n=92)	Paclitaxel (n=96)	Intravenous Trastuzumab + AC* (n=143)	AC (n=138)
Time to Disease Progression (TTP)						
Median (months)†,‡	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§	< 0.0001		< 0.0001		0.002	
Overall Response Rate (ORR)†						
Events (n)	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value¶	< 0.001		< 0.001		0.10	
Duration of Response (DoR)						
Median (months)†,‡	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
Overall Survival (OS)						
Median (months)‡	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§	0.05		0.17		0.16	

* AC=Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
† Assessed by an independent Response Evaluation Committee.
‡ Kaplan-Meier Estimate.
§ log-rank test.
¶ $\chi 2$-test.

Data from H0648g suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 13).

Table 13:
Treatment Effects in H0648g as a Function of HER2 Overexpression or Amplification

HER2 Assay Result	Number of Patients (N)	Relative Risk * for Time to Disease Progression (95% CI)	Relative Risk * for Mortality (95% CI)
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)
FISH (+) †	325	0.44 (0.34, 0.57)	0.70 (0.53, 0.91)
FISH (–) †	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)

*The relative risk represents the risk of progression or death in the trastuzumab plus chemotherapy arm versus the chemotherapy arm.
† FISH testing results were available for 451 of the 469 patients enrolled on study.

Previously Treated Metastatic Breast Cancer (Study H0649g)
Intravenous trastuzumab was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study H0649g) in patients with HER2 overexpressing MBC 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 Patient Experience

The PrefHER study (NCT01401166) was a randomized, multi-center, two-arm, cross-over trial conducted in 240 patients with HER2-positive breast cancer undergoing neoadjuvant or adjuvant treatment. One hundred twenty-one patients in arm A received 4 cycles of HERCEPTIN HYLECTA followed by 4 cycles of intravenous trastuzumab and 119 patients in arm B received 4 cycles of intravenous trastuzumab followed by 4 cycles of HERCEPTIN HYLECTA. Both arms received a total of 18 cycles. After Cycle 8, 199 of 231 patients (86%) reported preferring subcutaneous administration of HERCEPTIN HYLECTA over intravenous trastuzumab and the most common reason cited was administration required less time (179/231) in the clinic. After Cycle 8, 29 out of 231 patients (13%) reported preferring intravenous trastuzumab over HERCEPTIN HYLECTA and the most common reason was fewer local injection reactions. Three out of 231 patients (1%) had no preference for the route of administration. Nine out of 240 (3.8%) withdrew from treatment prior to completion of Cycle 8 and did not complete the post-study preference questionnaire.

16 HOW SUPPLIED/STORAGE AND HANDLING

HERCEPTIN HYLECTA (trastuzumab and hyaluronidase-oysk) injection for subcutaneous use supplied as a sterile, preservative-free, colorless to yellowish, clear to opalescent solution in a single-dose vial. The following configuration is available:

Individually packaged single-dose vials:

- HERCEPTIN HYLECTA 600 mg/10,000 units (NDC: 50242-077-01) providing 600 mg trastuzumab and 10,000 units hyaluronidase per 5 mL.

Store HERCEPTIN HYLECTA vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake. Once removed from the refrigerator, HERCEPTIN HYLECTA must be administered within 4 hours and should not be kept above 30°C (86°F).

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 Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity *[see Warnings and Precautions (5.2)]*

- Advise pregnant women and females of reproductive potential that HERCEPTIN HYLECTA 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 HERCEPTIN HYLECTA *[see Use in Specific Populations (8.3)]*.
- Advise women who are exposed to HERCEPTIN HYLECTA during pregnancy or who become pregnant within 7 months following the last dose of HERCEPTIN HYLECTA that there is a pregnancy pharmacovigilance program that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to Genentech *[see Use in Specific Populations (8.1)]*.

Hypersensitivity and Administration-Related Reactions

- Advise patients to contact their healthcare provider immediately and to report any symptoms of hypersensitivity and administration-related reactions including dizziness, nausea, chills, fever, vomiting, diarrhea, urticaria, angioedema, breathing problems, or chest pain *[see Warnings and Precautions (5.5)]*.

HERCEPTIN HYLECTA® [trastuzumab and hyaluronidase-oysk]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License No. 1048

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) for injection, for intravenous use
Initial U.S. Approval: 1998

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY
See full prescribing information for complete boxed warning.

Cardiomyopathy: Herceptin can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy. (2.5, 5.1)

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

Embryo-Fetal Toxicity: Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.3)

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Evaluation and Testing Before Initiating Herceptin (2.1)	06/2024

----------INDICATIONS AND USAGE----------

Herceptin is a HER2/neu receptor antagonist indicated in adults 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)

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin (1, 2.2).

----------DOSAGE AND ADMINISTRATION----------

For intravenous (IV) infusion only. Do not administer as an IV push or bolus. Herceptin has different dosage and administration instructions than subcutaneous trastuzumab products. (2.3)
Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan. (2.3)
Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1, 2.2)

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.2)
Administer at either:

- Initial dose of 4 mg/kg over 90 minutes IV infusion, then 2 mg/kg over 30 minutes IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel and carboplatin). One week after the last weekly dose of Herceptin, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy, 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 (2.3)

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

Metastatic HER2-Overexpressing Gastric Cancer (2.3)

- 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----------

- For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Exacerbation of Chemotherapy-Induced Neutropenia. (5.5, 6.1)

----------ADVERSE REACTIONS----------

Adjuvant Breast Cancer

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

Metastatic Breast Cancer

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

Metastatic Gastric Cancer

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

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----------

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of Herceptin (8.3).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Cardiomyopathy

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

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and withhold Herceptin in patients with metastatic disease for clinically significant decrease in left ventricular function *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)].*

Infusion Reactions; Pulmonary Toxicity

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

Embryo-Fetal Toxicity

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

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

Herceptin is indicated in adults 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 Herceptin *[see Dosage and Administration (2.2)]*.

1.2 Metastatic Breast Cancer

Herceptin is indicated in adults:

- 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 Herceptin *[see Dosage and Administration (2.2)]*.

1.3 Metastatic Gastric Cancer

Herceptin is indicated in adults, 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 Herceptin *[see Dosage and Administration (2.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Evaluation and Testing Before Initiating Herceptin

Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin and at regular intervals during treatment. *[see Boxed Warning, Dosage and Administration (2.5), Warnings and Precautions (5.1)]*.

Verify the pregnancy status of females of reproductive potential prior to the initiation of Herceptin *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.2 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.

2.3 Recommended Dosage

- **Herceptin is for intravenous infusion only. Do not administer as an intravenous push or bolus.**
- **Herceptin has different dosage and administration instructions than subcutaneous trastuzumab products.**
- **Do not mix Herceptin with other drugs.**
- **Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan.**

Adjuvant Treatment of Breast Cancer

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

During and following paclitaxel, docetaxel, or docetaxel/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 Herceptin, administer Herceptin 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.

- Extending adjuvant treatment beyond one year is not recommended *[see Adverse Reactions (6.1)]*.

Metastatic Breast Cancer

- Administer Herceptin, 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 Herceptin 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.

2.4 Important Dosing Considerations

Missed Dose

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

If the patient has missed a dose of Herceptin by more than one week, a re-loading dose of Herceptin should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; once every three week schedule: 8 mg/kg) as soon as possible. Subsequent Herceptin 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 once every three week schedules, respectively.

2.5 Dosage Modifications for Adverse Reactions

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 Herceptin 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 Herceptin and at regular intervals during treatment. Withhold Herceptin dosing for at least 4 weeks for either of the following:

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

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

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

2.6 Preparation Instructions

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 or fam-trastuzumab deruxtecan.

150 mg Single-dose vial

Reconstitution

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

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject 7.4 mL of SWFI (not supplied) into the vial containing the lyophilized powder of Herceptin, 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.
- 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 Herceptin 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 Herceptin solution for up to 24 hours at 2°C to 8°C (36°F to 46°F); discard any unused Herceptin after 24 hours. **Do not freeze.**

Dilution

- Determine the dose (mg) of Herceptin *[see Dosage and Administration (2.3)]*.
- Calculate the volume of the 21 mg/mL reconstituted Herceptin solution needed.
- Withdraw this amount from the vial using a sterile needle and syringe 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 Herceptin 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 white to pale yellow lyophilized powder in a single-dose 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 ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values *[see Dosage and Administration (2.5)]*. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied. Patients who receive anthracycline after stopping Herceptin may also be at increased risk of cardiac dysfunction *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

Cardiac Monitoring

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

- Baseline LVEF measurement immediately prior to initiation of Herceptin
- LVEF measurements every 3 months during and upon completion of Herceptin
- Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction *[see Dosage and Administration (2.43)]*
- LVEF measurements every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy.

In NSABP B31, 15% (158/1031) of patients discontinued Herceptin due to clinical evidence of myocardial dysfunction or significant decline in LVEF after a median follow-up duration of 8.7 years in the AC-TH arm. In HERA (one-year Herceptin treatment), the number of patients who discontinued Herceptin due to cardiac toxicity at 12.6 months median duration of follow-up was 2.6% (44/1678). In BCIRG006, a total of 2.9% (31/1056) of patients in the TCH arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) of patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued Herceptin due to cardiac toxicity.

Among 64 patients receiving adjuvant chemotherapy (NSABP B31 and NCCTG N9831) 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 ≥ 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 Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

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

		Incidence of Congestive Heart Failure % (n)	
Study	**Regimen**	**Herceptin**	**Control**
NSABP B31 & NCCTG N9831[a]	AC[b]→Paclitaxel+Herceptin	3.2% (64/2000)[c]	1.3% (21/1655)
HERA[d]	Chemotherapy → Herceptin	2% (30/1678)	0.3% (5/1708)
BCIRG006	AC[b]→Docetaxel+Herceptin	2% (20/1068)	0.3% (3/1050)
BCIRG006	Docetaxel+Carboplatin+Herceptin	0.4% (4/1056)	0.3% (3/1050)

[a] Median follow-up duration for NSABP B31 & NCCTG N9831 combined was 8.3 years in the AC→paclitaxel+Herceptin arm.
[b] Anthracycline (doxorubicin) and cyclophosphamide.
[c] Includes 1 patient with fatal cardiomyopathy and 1 patient with sudden death without documented etiology.
[d] Includes NYHA II-IV and cardiac death at 12.6 months median duration of follow-up in the one-year Herceptin arm.

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

Table 2: Incidence of Cardiac Dysfunction[a] in Metastatic Breast Cancer Studies

		Incidence			
		NYHA I–IV		NYHA III–IV	
Study	**Event**	**Herceptin**	**Control**	**Herceptin**	**Control**
H0648g (AC)[b]	Cardiac Dysfunction	28%	7%	19%	3%
H0648g (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
H0649g	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 BCIRG006, 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 post-marketing 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.

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

5.4 Pulmonary Toxicity

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

5.5 Exacerbation of Chemotherapy-Induced Neutropenia

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

6 ADVERSE REACTIONS

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

- Cardiomyopathy *[see Warnings and Precautions (5.1)]*
- Infusion Reactions *[see Warnings and Precautions (5.2)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.4)]*
- Exacerbation of Chemotherapy-Induced Neutropenia *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

The most common adverse reactions in patients receiving Herceptin in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of Herceptin treatment include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity *[see Dosage and Administration (2.5)]*.

In the metastatic gastric cancer setting, the most common adverse reactions (≥ 10%) that were increased (≥ 5% difference) in the Herceptin arm as compared to the chemotherapy alone arm were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia.

The most common adverse reactions which resulted in discontinuation of treatment on the Herceptin-containing arm in the absence of disease progression were infection, diarrhea, and febrile neutropenia.

Adjuvant Breast Cancer

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

HERA

Table 3 reflects exposure to Herceptin in 1678 patients in HERA; the median treatment duration was 51 weeks and median number of infusions was 18 *[see Clinical Studies (14.1)]*.

Table 3: Adverse Reactions (≥1%) in HERA (All Grades)[a]

Adverse Reactions	Herceptin (n = 1678) %	Observation (n = 1708) %
Nervous System		
Headache	10	3
Paresthesia	2	0.6
Musculoskeletal		
Arthralgia	8	6
Back pain	5	3
Myalgia	4	1
Bone pain	3	2
Muscle spasm	3	0.2
Infections		
Nasopharyngitis	8	3
Urinary tract infection	3	0.8
Gastrointestinal		
Diarrhea	7	1
Nausea	6	1
Vomiting	3.5	0.6
Constipation	2	1
Dyspepsia	2	0.5
Upper abdominal pain	2	1
General		
Pyrexia	6	0.4
Peripheral edema	5	2
Chills	5	0
Asthenia	4.5	2
Influenza-like illness	2	0.2
Respiratory Thoracic Mediastinal		
Cough	5	2
Influenza	4	0.5
Dyspnea	3	2
URI	3	1
Rhinitis	2	0.4
Pharyngolaryngeal pain	2	0.5
Sinusitis	2	0.3
Epistaxis	2	0.06
Cardiac		
Hypertension	4	2
Dizziness	4	2
Ejection fraction decreased	3.5	0.6
Palpitations	3	0.7
Cardiac arrhythmias[b]	3	1
Cardiac failure (congestive)	2	0.3
Skin & Subcutaneous Tissue		
Rash	4	0.6
Nail disorders	2	0
Pruritus	2	0.6

[a] The incidence of Grade 3 or higher adverse reactions was <1% in both arms for each listed term.

[b] Higher level grouping term.

Clinically relevant adverse reactions in < 1% of patients who received Herceptin in HERA included hypersensitivity (0.6%), cardiac failure (0.5%), cardiac disorder (0.3%), interstitial pneumonitis (0.2%), pulmonary hypertension (0.2%), ventricular disorder (0.2%), autoimmune thyroiditis (0.3%), and sudden death (0.06%).

Adjuvant Treatment of Breast Cancer with Herceptin Beyond One Year

Extending adjuvant treatment beyond one year is not recommended *[see Dosage and Administration (2.2)]*. In HERA, a comparison of Herceptin administered once every 3 weeks for two years versus one year was performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year Herceptin compared to the 1-year Herceptin treatment arm (8.1% versus 4.6%, respectively). More patients experienced at least one adverse reaction of Grade 3 or higher in the 2-year Herceptin treatment arm (20.4%) compared with the one-year Herceptin treatment arm (16.3%).

NSABP B31 and NCCTG N9831

The safety data from NSABP B31 and NCCTG N9831 were obtained from 3655 patients, of whom 2000 received Herceptin; the median treatment duration was 51 weeks *[see Clinical Studies (14.1)]*.

In NSABP B31, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone: fatigue (29.5% vs. 22.4%), infection (24.0% vs. 12.8%), hot flashes (17.1% vs. 15%), anemia (12.3% vs. 6.7%), dyspnea (11.8% vs. 4.6%), rash/desquamation (10.9% vs. 7.6%), leukopenia (10.5% vs. 8.4%), neutropenia (6.4% vs. 4.3%), headache (6.2% vs. 3.8%), pain (5.5% vs. 3%), edema (4.7% vs. 2.7%), and insomnia (4.3% vs. 1.5%). The majority of these events were Grade 2 in severity.

In NCCTG N9831, data collection was limited to the following investigator-attributed treatment-related adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes, motor neuropathy, and sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (12.2% vs. 9.1%), nail changes (11.5% vs. 6.8%), dyspnea (2.4% vs. 0.2%), and diarrhea (2.2% vs. 0%). The majority of these events were Grade 2 in severity.

BCIRG006

Safety data from BCIRG006 reflect exposure to Herceptin as part of an adjuvant treatment regimen from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TCH: n=1056]. The overall median treatment duration was 54 weeks in both the AC-TH and TCH arms. The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including weekly infusions during the chemotherapy phase and once every three week dosing in the monotherapy period *[see Clinical Studies (14.1)]*. In BCIRG006, the toxicity profile was similar to that reported in Studies NSABP B31, NCCTG N9831, and HERA with the exception of a lower incidence of CHF in the TCH arm.

Metastatic Breast Cancer Studies

The safety of Herceptin was evaluated in one randomized, open-label study (H0648g) of chemotherapy with (n = 235) or without (n = 234) intravenous trastuzumab in patients with metastatic breast cancerand in one single-arm study (H0649g); in patients with metastatic breast cancer (n=222) *[see Clinical Studies (14.1)]*. Patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. In H0648g, 58% of patients received Herceptin for ≥ 6 months

and 9% received Herceptin ≥ 12 months, respectively. In H0649g, 31% of patients received Herceptin for ≥ 6 months and 16% received Herceptin for ≥ 12 months, respectively.

Table 4 shows the adverse reactions (≥ 5%) in patients from H0648g and H0649g.**Table 4: Adverse Reactions[3] (5%) in the Herceptin Arms in H0648g and H0649g**

	Herceptin[a] n = 352 %	Herceptin + Paclitaxel n = 91 %	Paclitaxel n = 95 %	Herceptin + AC[b] n = 143 %	AC[b] n = 135 %
General					
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
Gastrointestinal					
Nausea	33	51	9	76	77
Diarrhea	25	45	29	45	26
Vomiting	23	37	28	53	49
Anorexia	14	24	16	31	26
Nausea and vomiting	8	14	11	18	9
Respiratory					
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
Skin					
Rash	18	38	18	27	17
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	< 1
Nervous					
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
Metabolic					
Peripheral edema	10	22	20	20	17
Edema	8	10	8	11	5
Cardiovascular					
Congestive heart failure	7	11	1	28	7

Tachycardia	5	12	4	10	5

Table 4: Adverse Reactions (≥ 5%) in the Herceptin Arms in H0648g and H0649g *(continued)*

	Herceptin[a] n = 352 %	Herceptin + Paclitaxel n = 91 %	Paclitaxel n = 95 %	Herceptin + AC[b] n = 143 %	AC[b] n = 135 %
Musculoskeletal					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9
Urogenital					
Urinary tract infection	5	18	14	13	7
Blood and Lymphatic					
Anemia	4	14	9	36	26
Leukopenia	3	24	17	52	34

[a] Data for Herceptin single agent were from 4 studies, including 213 patients from H0649g.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

Metastatic Gastric Cancer

The safety of Herceptin was evaluated in patients with previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma in an open label, multi-center trial (ToGA) *[see Clinical Studies (14.3)]*. Patients were randomized (1:1) to receive Herceptin in combination with cisplatin and a fluoropyrimidine (FC+H) (n=294) or chemotherapy alone (FC) (n=290) Patients in the Herceptin plus chemotherapy arm received Herceptin 8 mg/kg administered on Day 1 (prior to chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was administered at 80 mg/m^2 on Day 1 and the fluoropyrimidine was administered as either capecitabine 1000 mg/m^2 orally twice a day on Days 1–14 or 5-fluorouracil 800 mg/m^2/day as a continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day cycles. Median duration of Herceptin treatment was 21 weeks and the median number of Herceptin infusions administered was eight.

Table 5: Adverse Reactions (All Grades ≥ 5% or Grade 3-4 ≥ 1% between Arms) in ToGA

Adverse Reactions	Herceptin +FC (N = 294) %		FC (N = 290) %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Investigations				
Neutropenia	78	34	73	29
Hypokalemia	28	10	24	6
Anemia	28	12	21	10
Thrombocytopenia	16	5	11	3
Blood and Lymphatic System Disorders				
Febrile Neutropenia	—	5	—	3
Gastrointestinal Disorders				
Diarrhea	37	9	28	4

Adverse Reactions	Herceptin +FC (N = 294) %		FC (N = 290) %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Stomatitis	24	1	15	2
Dysphagia	6	2	3	< 1
General				
Fatigue	35	4	28	2
Fever	18	1	12	0
Mucosal Inflammation	13	2	6	1
Chills	8	<1	0	0
Metabolism and Nutrition Disorders				
Weight Decrease	23	2	14	2
Infections and Infestations				
Upper Respiratory Tract Infections	19	0	10	0
Nasopharyngitis	13	0	6	0
Renal and Urinary Disorders				
Renal Failure and Impairment	18	3	15	2
Nervous System Disorders				
Dysgeusia	10	0	5	0

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

Cardiomyopathy

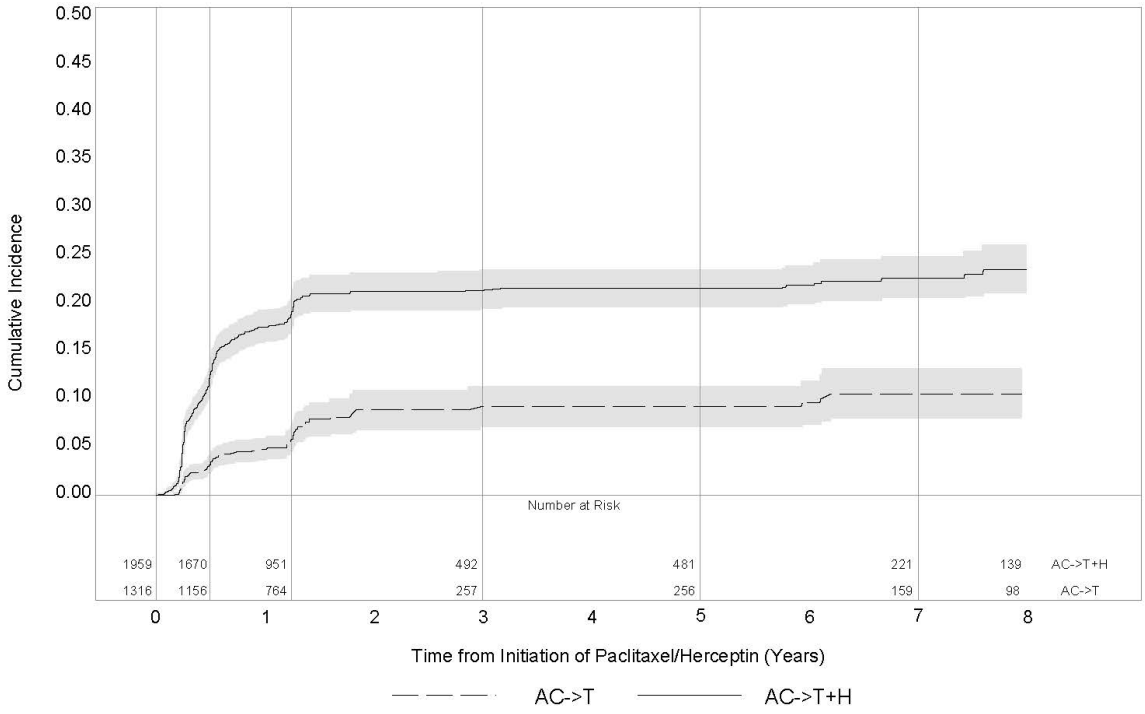
Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In HERA, the median duration of follow-up was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in NSABP B31 and NCCTG N9831, 7.9 years in the AC-T arm, 8.3 years in the AC-TH arm. Following initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel alone in NSABP B31 and NCCTG N9831, and in patients receiving one-year Herceptin monotherapy compared to observation in HERA (see Table 6, Figures 1 and 2). The incidence of new-onset cardiac dysfunction, as measured by LVEF, remained similar when compared to the analysis performed at a median follow-up of 2.0 years in the AC-TH arm. This analysis showed evidence of reversibility of left ventricular dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC-TH group being asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.

Table 6: Myocardial Dysfunction (by LVEF) in Studies 1, 2, 3 and 4 [a]

Study and Arm	LVEF < 50% and Decrease from Baseline			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)
HERA[d]					
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)
BCIRG006[e]					
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)

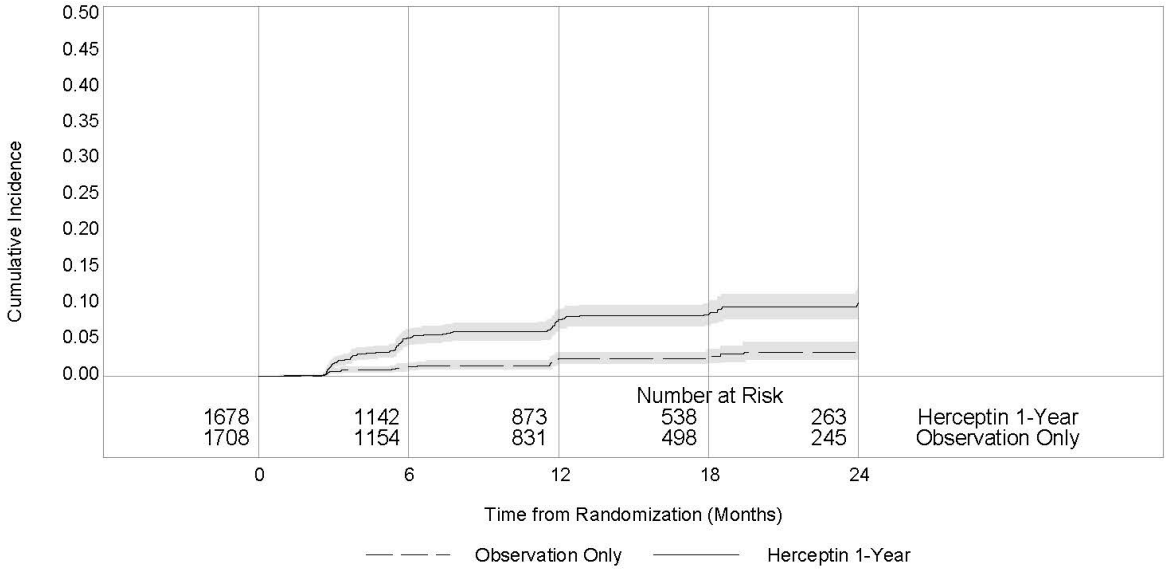
[a] For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For BCIRG006, events are counted from the date of randomization.
[b] NSABP B31 and NCCTG N9831 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).
[c] Median duration of follow-up for NSABP B31 and NCCTG N9831 combined was 8.3 years in the AC→TH arm.
[d] Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.
[e] BCIRG006 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

Figure 1
NSABP B31 and NCCTG N9831: 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



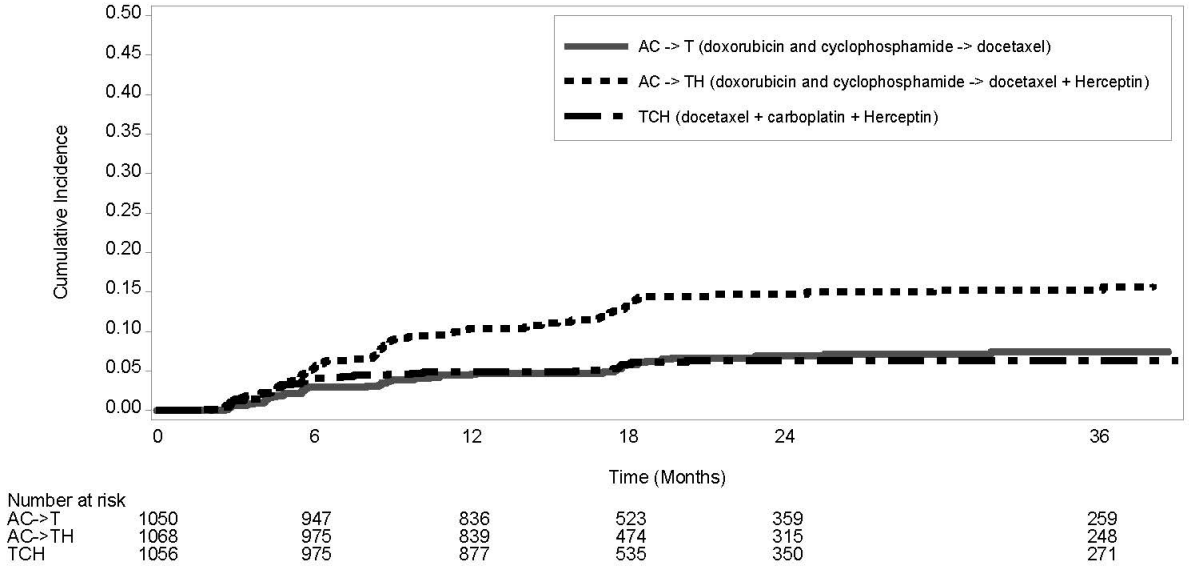
Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

Figure 2
HERA: 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



Time 0 is the date of randomization.

Figure 3
BCIRG006: 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



Time 0 is the date of randomization.

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

In ToGA, 5% of patients in the Herceptin plus chemotherapy arm compared to 1.1% of patients in the chemotherapy alone arm had LVEF value below 50% with a ≥10% absolute decrease in LVEF from pretreatment values.

Infusion Reactions

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

Anemia

In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [H0648g]), of selected NCI-CTC Grade 2−5 anemia (12.3% vs. 6.7% [NSABP B31]), and of anemia requiring transfusions (0.1% vs. 0 patients [NCCTG N9831]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. Following the administration of Herceptin as a single agent (H0649g), the incidence of NCI-CTC Grade 3 anemia was < 1%. In ToGA (metastatic gastric cancer), on the Herceptin containing arm as compared to the chemotherapy alone arm, the overall incidence of anemia was 28% compared to 21% and of NCI-CTC Grade 3/4 anemia was 12.2% compared to 10.3%.

Neutropenia

In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTC Grade 4–5 neutropenia (1.7% vs. 0.8% [NCCTG N9831]) and of selected Grade 2–5 neutropenia (6.4% vs. 4.3% [NSABP B31]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In ToGA (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone arm, the incidence of NCI-CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile neutropenia 5.1% compared to 2.8%.

Infection

The overall incidences of infection (46% vs. 30% [H0648g]), of selected NCI-CTC Grade 2–5 infection/febrile neutropenia (24.3% vs. 13.4% [NSABP B31]) and of selected Grade 3–5 infection/febrile neutropenia (2.9% vs. 1.4% [NCCTG N9831]) were higher in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. The most common site of infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract.

In BCIRG006, the overall incidence of infection was higher with the addition of Herceptin to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC Grade 3–4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms.

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

Pulmonary Toxicity

Adjuvant Breast Cancer

Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC Grade 2–5 pulmonary toxicity (14.3% vs. 5.4% [NSABP B31]) and of selected NCI-CTC Grade 3–5 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4% vs. 0.9% [NCCTG N9831]) was higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The most common pulmonary toxicity was dyspnea (NCI-CTC Grade 2–5: 11.8% vs. 4.6% [NSABP B31]; NCI-CTC Grade 2–5: 2.4% vs. 0.2% [NCCTG N9831]).

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

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

Metastatic Breast Cancer

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

Thrombosis/Embolism

In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies (2.6% vs. 1.5% [NSABP B31], 2.5% and 3.7% vs. 2.2% [BCIRG006] and 2.1% vs. 0% [H0648g]).

Diarrhea

Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC Grade 2–5 diarrhea (6.7% vs. 5.4% [NSABP B31]) and of NCI-CTC Grade 3–5 diarrhea (2.2% vs. 0% [NCCTG N9831]), and of Grade 1–4 diarrhea (7% vs. 1% [HERA; one-year Herceptin treatment at 12.6 months median duration of follow-up]) were higher in patients receiving Herceptin as compared to controls. In BCIRG006, the incidence of Grade 3–4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer.

Renal Toxicity

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

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

6.2 Post-Marketing Experience

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

- Infusion reaction *[see Warnings and Precautions (5.2)]*
- 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 Herceptin. 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

Anthracyclines

Patients who receive anthracycline after stopping Herceptin may be at increased risk of cardiac dysfunction because of trastuzumab's estimated long washout period *[see Clinical Pharmacology (12.3)]*. If possible, avoid anthracycline-based therapy for up to 7 months after stopping Herceptin. If anthracyclines are used, closely monitor the patient's cardiac function.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Pharmacovigilance Program

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

Risk Summary

Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports and published literature, use of Herceptin 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 Herceptin is used in a pregnant woman or if a patient becomes pregnant within 7 months following the last dose of Herceptin *[see Clinical Considerations]*.

The 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 Herceptin during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal/neonatal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

In post-marketing reports and published literature, use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence. Fetal manifestations included pulmonary hypoplasia, skeletal abnormalities, and neonatal death. These case reports described oligohydramnios in pregnant women who received Herceptin either alone or in combination with chemotherapy. In most reported cases, amniotic fluid index increased after Herceptin was stopped. In reported cases where Herceptin therapy was resumed after amniotic index improved, 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 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 Herceptin treatment and any potential adverse effects on the breastfed child from Herceptin or from the underlying maternal condition. This consideration should also take into account the trastuzumab 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 Herceptin). 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 Herceptin.

Contraception

Females

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Herceptin 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 H0648g and H0649g, or adjuvant therapy in NSABP B31 and NCCTG N9831. Limitations in data collection and differences in study design of the 4 studies of Herceptin in adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of Herceptin 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 Herceptin treatment in older patients is different from that observed in patients < 65 years of age for metastatic disease and adjuvant treatment.

In ToGA (metastatic gastric cancer), of the 294 patients treated with Herceptin, 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.

11 DESCRIPTION

Trastuzumab 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 is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture.

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

Each single-dose vial of Herceptin delivers 150 mg trastuzumab, 136.2 mg α,α-trehalose dihydrate, 3.4 mg L-histidine HCl monohydrate, 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 that delivers 7.15 mL (150 mg trastuzumab), 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. Herceptin has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Herceptin is a mediator of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, Herceptin-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

Herceptin exposure-response relationships and the time course of pharmacodynamic responses are not fully characterized.

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 was evaluated in a pooled population pharmacokinetic (PK) model analysis of 1,582 subjects with primarily breast cancer and metastatic gastric cancer (MGC) receiving intravenous Herceptin. 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 once every three week schedule compared to the weekly schedule of Herceptin, 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 Herceptin cycle and at steady state exposure are described in Tables 7 and 8, respectively.

Population PK based simulations indicate that following discontinuation of Herceptin, concentrations in at least 95% of breast cancer 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)	$AUC_{0\text{-}21days}$ (µg.day/mL)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	29.4 (5.8 - 59.5)	178 (117 - 291)	1373 (736 - 2245)
	MGC	274	23.1 (6.1 - 50.3)	132 (84.2 - 225)	1109 (588 - 1938)
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	37.7 (12.3 - 70.9)	88.3 (58 - 144)	1066 (586 - 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)	$AUC_{ss,\ 0\text{-}21\ days}$ (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 - 115)	179 (107 - 309)	1794 (673 - 3618)	12	0.173 - 0.283
	MGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 - 2875)	9	0.189 - 0.337
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	66.1 (14.9 - 142)	109 (51.0 - 209)	1765 (647 - 3578)	12	0.201 - 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 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 Herceptin in humans. Clinically significant interactions between Herceptin 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 Herceptin 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 ToGA, the pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered in combination with Herceptin.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of HERCEPTIN or of other trastuzumab products.

Among 903 women with metastatic breast cancer, human anti human antibody (HAHA) to Herceptin was detected in one patient using an enzyme linked immunosorbent assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast cancer.

The clinical relevance of the development of anti-trastuzumab antibodies after treatment with HERCEPTIN is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Herceptin has 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 Herceptin in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, open-label, clinical trials (NSABP B31 and NCCTG N9831) with a total of 4063 women at the protocol-specified final overall survival analysis, a third randomized, open-label, clinical trial (HERA) with a total of 3386 women at definitive Disease-Free Survival analysis for one-year Herceptin treatment versus observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (BCIRG006).

NSABP B31 and NCCTG N9831

In NSABP B31 and NCCTG N9831, 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 (NCCTG N9831) or was required to be performed at a reference laboratory (NSABP B31). 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 Herceptin (AC→paclitaxel + Herceptin). In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. Paclitaxel was administered either weekly (80 mg/m^2) or every 3 weeks (175 mg/m^2) for a total of 12 weeks in NSABP B31; paclitaxel was administered only by the weekly schedule in NCCTG N9831. Herceptin 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. Herceptin treatment was permanently discontinued in patients who developed congestive heart failure, or persistent/recurrent LVEF decline *[see Dosage and Administration (2.5)]*. Radiation therapy, if administered, was initiated after the completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. The major efficacy outcome measure 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. An additional efficacy outcome measure was overall survival (OS).

A total of 3752 patients were included in the joint efficacy analysis of DFS following a median follow-up of 2.0 years in the AC→paclitaxel + Herceptin 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 + Herceptin arm. The data from both arms in NSABP B31 and two of the three study arms in NCCTG N9831 were pooled for efficacy analyses.

The patients included in the 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.

HERA

In HERA, 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.

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 Herceptin treatment or two years of Herceptin 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. Herceptin was administered with an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every three weeks. The major efficacy outcome measure was Disease-Free Survival (DFS), defined as in NSABP B31 and NCCTG N9831.

HERA was designed to compare one and two years of once every three week Herceptin treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). A protocol specified interim efficacy analysis comparing one-year Herceptin treatment to observation was performed at a median follow-up duration of 12.6 months in the Herceptin arm.

Among the 3386 patients randomized to the observation (n = 1693) and Herceptin one-year (n = 1693) treatment arms, the median age was 49 years (range 21–80), 83% were White, 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 DFS results comparing observation to one-year Herceptin treatment were disclosed, a prospectively planned analysis that included comparison of one year versus two years of Herceptin treatment at a median follow-up duration of 8 years was performed. Based on this analysis, extending Herceptin treatment for a duration of two years did not show additional benefit over treatment for one year [Hazard Ratios of two-years Herceptin versus one-year Herceptin 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].

BCIRG006

In BCIRG006, 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 Herceptin (AC-TH), or docetaxel and carboplatin plus Herceptin (TCH). In both the AC-T and AC-TH arms, doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 were administered every 3 weeks for four cycles; docetaxel 100 mg/m^2 was administered every 3 weeks for four cycles. In the TCH arm, docetaxel 75 mg/m^2 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. Herceptin 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 major efficacy outcome measure.

Among 3222 patients, the median age was 49 (range 22 to 74 years; 6% ≥ 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 NSABP B31 and NCCTG N9831, HERA, and BCIRG006 and OS results for the integrated analysis of NSABP B31 and NCCTG N9831, and HERA are presented in Table 9. For NSABP B31 and NCCTG N9831, the duration of DFS following a median follow-up of 2.0 years in the AC→TH arm is presented in Figure 4, and the duration of OS after a median follow-up of 8.3 years in the AC→TH arm is presented in Figure 5. The duration of DFS for BCIRG006 is presented in Figure 6. For NSABP B31 and NCCTG N9831, the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74). At 8.3 years of median follow-up [AC→TH], the survival rate was estimated to be 86.9% in the AC→TH arm and 79.4% in the AC→T arm. The final OS analysis results from NSABP B31 and NCCTG N9831 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 ≤ 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 ≤ 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 (NSABP B31 and NCCTG N9831, HERA, and BCIRG006)

	DFS events	DFS Hazard ratio (95% CI) p-value	Deaths (OS events)	OS Hazard ratio p-value
NSABP B31 and NCCTG N9831[a]				
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]	
HERA[f]				
Chemo→ Herceptin (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	
BCIRG006[i]				
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] NSABP B31 and NCCTG N9831 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] At definitive DFS analysis with median duration of follow-up of 12.6 months in the one-year Herceptin treatment arm.

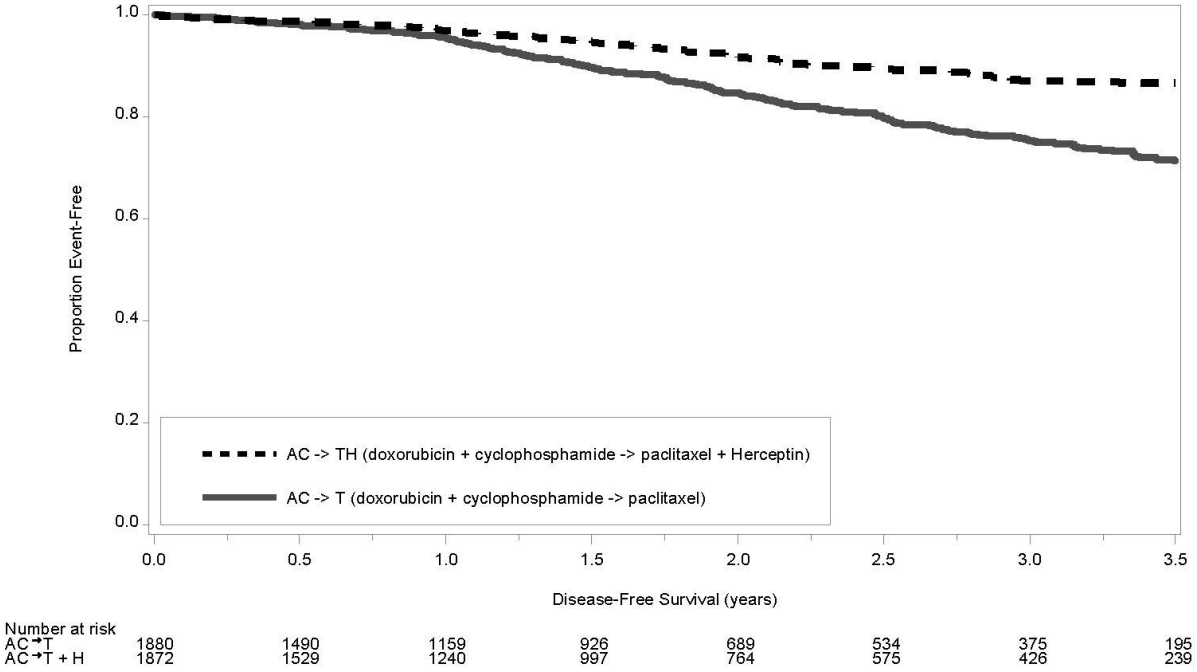
[g] log-rank test.

[h] NS = non-significant.

[i] BCIRG006 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

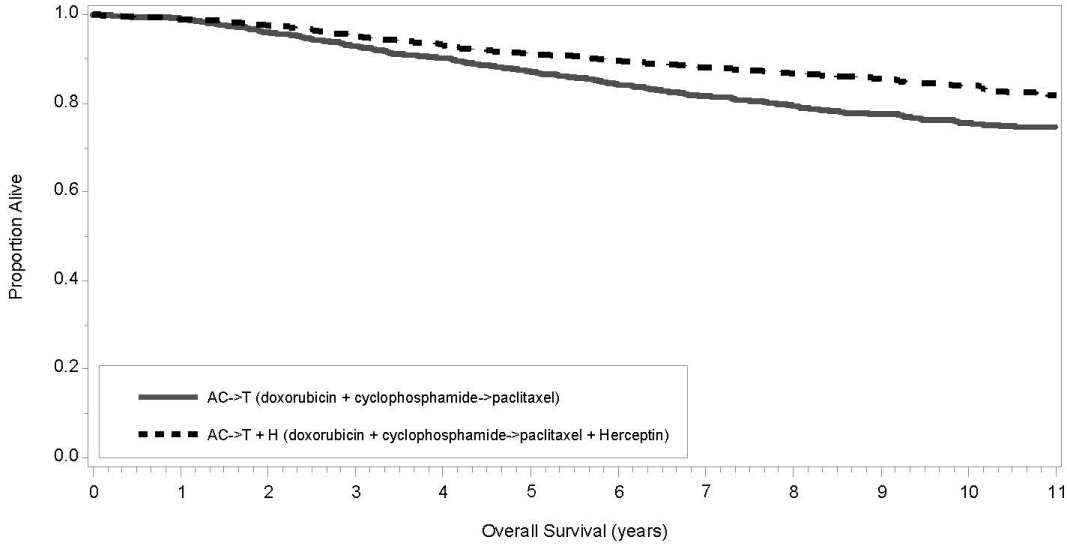
[j] A two-sided alpha level of 0.025 for each comparison.

Figure 4: Duration of Disease-Free Survival in Patients with Adjuvant Treatment of Breast Cancer (NSABP B31 and NCCTG N9831)



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

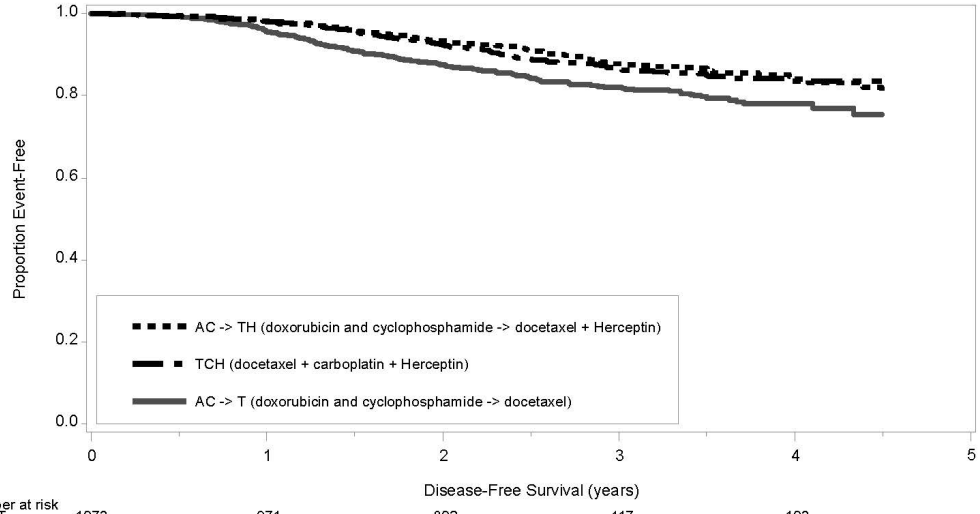
Figure 5: Overall Survival in Patients with Adjuvant Treatment of Breast Cancer (NSABP B31 and NCCTG N9831)



Number at risk

AC->T	2032	1961	1883	1806	1732	1643	1538	1377	979	630	399	151
AC->T + H	2031	1992	1957	1897	1843	1787	1714	1533	1127	787	485	159

Figure 6: Disease-Free Survival in Patients with Adjuvant Treatment of Breast Cancer (BCIRG006)



Number at risk

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.

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 NCCTG N9831 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 HERA was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH+/IHC unknown subgroups.

Table 10: DFS in NCCTG N9831 and HERA for Patients with HER2 Overexpression or Amplification

	NCCTG N9831		HERA[c]	
HER2 Assay Result[a]	**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 ≥ 2.0) as performed at a central laboratory.
[b] All cases in this category in HERA were IHC 2+.
[c] Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

14.2 Metastatic Breast Cancer

The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (H0648g, n = 469 patients) and an open-label, single agent clinical trial (H0649g, 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 (H0648g)

H0648g 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 Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 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/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to receive chemotherapy alone in this study received Herceptin 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 Herceptin and chemotherapy experienced a significantly longer median time to disease progression (TTP), a higher overall response rate (ORR), and a longer median duration of response (DoR) as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin and chemotherapy also had a longer median overall survival (OS) (see Table 11). These treatment effects were observed both in patients who received Herceptin plus paclitaxel and in those who received Herceptin plus AC; however, the magnitude of the effects was greater in the paclitaxel subgroup.

Table 11: H0648g: Efficacy Results in First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC[a] 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[a] (n = 138)
Time to Disease Progression (TTP)						
Median (months)[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	
Overall Response Rate (ORR)[b]						
Events (n)	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	
Duration of Response (DoR)						
Median (months)[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
Overall Survival (OS)						
Median (months)[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] $\chi 2$-test.

Data from H0648g 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 H0648g 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.

Previously Treated Metastatic Breast Cancer (H0649g)

Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial (H0649g) 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 Herceptin 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 Herceptin in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (ToGA). In this open-label, multi-center trial, 594 patients were randomized 1:1 to Herceptin 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 Herceptin-containing arm, Herceptin 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/m^2 Day 1 every 3 weeks for 6 cycles as a 2 hour IV infusion. On both study arms, capecitabine was administered at 1000 mg/m^2 dose orally twice daily

(total daily dose 2000 mg/m^2) 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/m^2/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 ToGA 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.

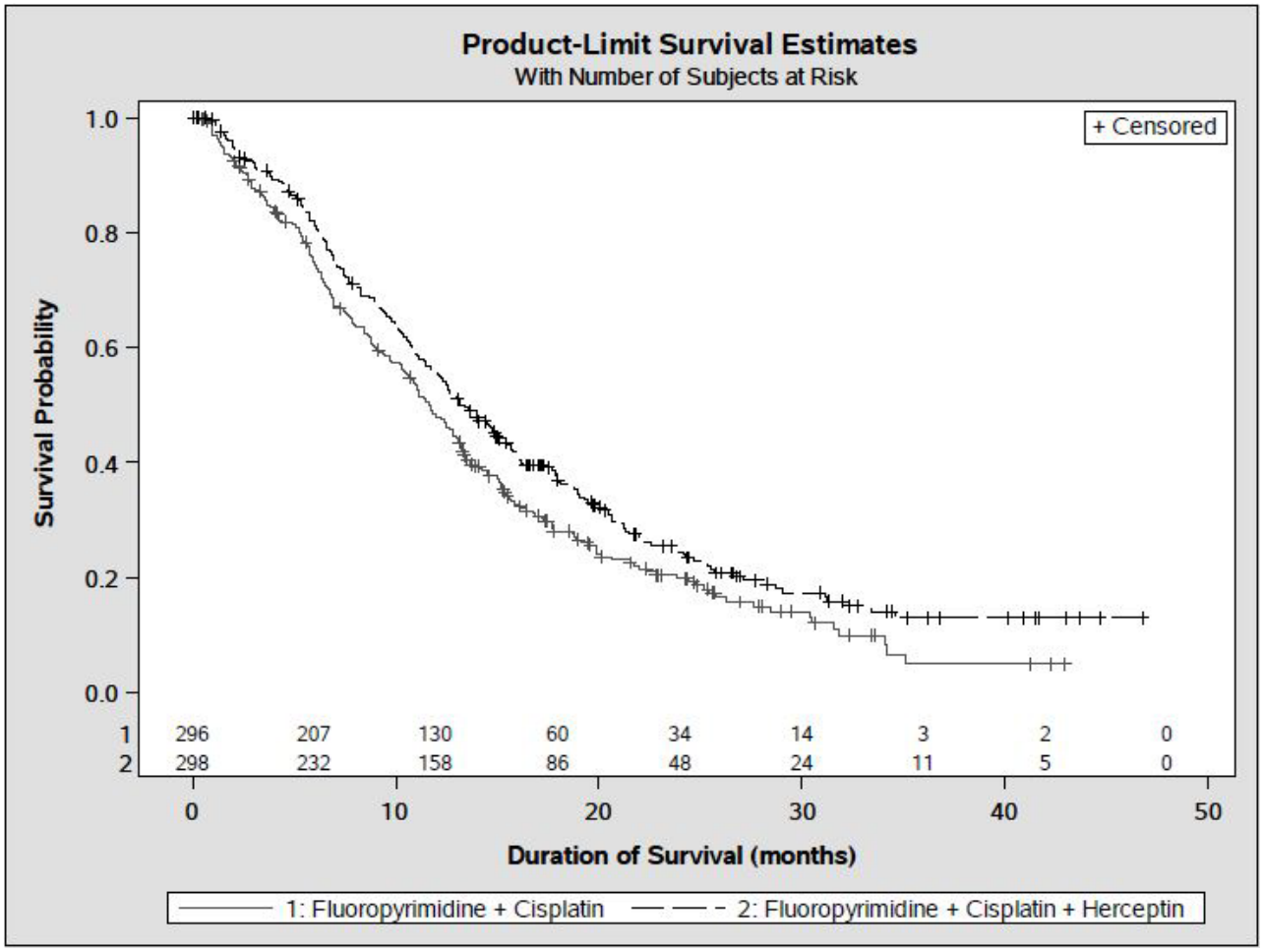
Table 13: Overall Survival in ToGA (ITT Population)

	FC[a] + Herceptin Arm N = 298	**FC[a] Arm N = 296**
Overall Survival (interim analysis)		
N (%)	167 (56.0%)	184 (62.2%)
Median (months)	13.5	11.0
95% CI	(11.7, 15.7)	(9.4, 12.5)
Hazard Ratio	0.73	
95% CI	(0.60, 0.91)	
p-value[b]	0.0038	
Overall Survival (updated)		
N (%)	221 (74.2%)	227 (76.7%)
Median (months)	13.1	11.7
95% CI	(11.9, 15.1)	(10.3, 13.0)
Hazard Ratio	0.80	
95% CI	(0.67, 0.97)	

a FC = capecitabine vs. 5-fluorouracil

b Two sided p-value comparing with the nominal significance level of 0.0193.

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



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]
FISH+ / IHC 0, 1+ subgroup (N=133)		
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)	
FISH+ / IHC2+ subgroup (N=160)		
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)	
FISH+ or FISH- / IHC3+[c] subgroup (N=294)		
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+.

16 HOW SUPPLIED/STORAGE AND HANDLING

150 mg Single-dose vial

Herceptin (trastuzumab) for injection 150 mg/vial is supplied in a single-dose vial as a preservative-free, white to pale yellow lyophilized sterile powder, under vacuum. Available in a carton containing one single-dose vial (NDC 50242-132-01) and a carton containing 10 single-dose vials (NDC 50242-132-10).

Store Herceptin 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 Herceptin 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 women who are exposed to Herceptin during pregnancy or who become pregnant within 7 months following the last dose of Herceptin that there is a pregnancy pharmacovigilance program that monitor pregnancy outcomes. Encourage these patients to report their pregnancy to Genentech *[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 Herceptin *[see Use in Specific Populations (8.3)]*.

HERCEPTIN® [trastuzumab]

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