PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrOGIVRI®

(trastuzumab)

Sterile Powder for Intravenous Infusion Only

150 mg trastuzumab/vial
440 mg trastuzumab/vial

Pharmaceutical standard professed

Antineoplastic Agent

Manufactured by:

Biosimilar Collaborations Ireland Limited

Unit 35/36, Grange Parade, Baldoyle Industrial Estate,

Dublin 13, DUBLIN Ireland D13 R20R

Distributed by:

BGP Pharma ULC

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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration	06/2022
1 Indications, 2 Contraindications, 4 Dosage and Administration, 6 Dosage Form, Strengths, Composition and Packaging, 7 Warnings and Precautions, 8 Adverse Reactions, 9 Drug Interactions, 14 Clinical Trials – updated for the use of combination treatment with Pertuzumab	10/2021
8.4 Post Market Adverse Reactions Table updated to as per the Herceptin PM dated May 7, 2020	10/2021

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OGIVRI® (trastuzumab) is a biosimilar biologic drug (biosimilar) to HERCEPTIN®.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Indications have been granted on the basis of similarity between OGIVRI and the reference biologic drug HERCEPTIN.

OGIVRI (trastuzumab) is indicated for:

Early Breast Cancer (EBC)
OGIVRI (trastuzumab) is indicated for the treatment of patients with early stage breast cancer with ECOG 0-1 status, whose tumours overexpress HER2,

- following surgery and after chemotherapy
- following adjuvant chemotherapy consisting of doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.

For detailed information on the inclusion criteria for the clinical trials of trastuzumab in EBC according to the TNM (Tumour, Node, Metastasis) classification system, see Part II: 14.4 Clinical Trials – Reference Biologic Drug section.

Based on the analysis of the HERA trial, the benefit of the adjuvant treatment with trastuzumab for low risk patients not given adjuvant chemotherapy are unknown.

The comparative efficacy and safety between different chemotherapy regimens (i.e. concurrent versus sequential, anthracycline containing versus non-anthracycline containing) was not studied.

Metastatic Breast Cancer (MBC)
OGIVRI is indicated for the treatment of patients with MBC whose tumours overexpress HER2.

The benefits of treatment with OGIVRI in patients who do not overexpress HER2 (HER2 overexpression 0 as determined by a validated immunohistochemical (IHC) test or who exhibit lower-level overexpression (HER2 overexpression 1+ as determined by a validated IHC test, and the subgroup of patients with HER2 overexpression 2+ as determined by a validated IHC test that corresponds to 1+ scoring by the investigative clinical trial assay), are unclear (see 7 WARNINGS AND PRECAUTIONS: Selection of Patients / Diagnostic Tests).

OGIVRI can be used in combination with pertuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. For information on the use of OGIVRI in combination with pertuzumab and docetaxel, consult the Product Monograph for pertuzumab.

Metastatic Gastric Cancer (MGC)
OGIVRI in combination with capecitabine or intravenous 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

OGIVRI should only be administered to patients with MGC whose tumours have HER2 overexpression as defined by IHC2+ confirmed by FISH+, or IHC 3+ as determined by an accurate and validated assay.

1.1 Pediatrics

The safety and effectiveness of OGIVRI in pediatric patients (< 18 years of age) have not been established.

1.2 Geriatrics

The reported clinical experience is not adequate to determine whether older patients respond differently to OGIVRI treatment than younger patients (see 7 WARNINGS AND PRECAUTIONS, Geriatrics).

2 CONTRAINDICATIONS

- OGIVRI (trastuzumab) is contraindicated in patients with known hypersensitivity to trastuzumab, Chinese Hamster Ovary (CHO) cell proteins, or to any ingredient in the formulation, including any non-medicinal ingredient, or any component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- When using in combination with pertuzumab and docetaxel, consult Product Monographs for pertuzumab and docetaxel for further information on these drugs.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

There is a risk of medication errors between OGIVRI (trastuzumab) and KADCYLA® (trastuzumab emtansine). In order to minimize this risk, check the vial labels to ensure that the drug being prepared and administered is OGIVRI (trastuzumab) and not KADCYLA® (trastuzumab emtansine). OGIVRI should be prescribed using both the trade name and non-proprietary name (see 4 DOSAGE AND ADMINISTRATION, Dosing Considerations).

Cardiotoxicity
OGIVRI (trastuzumab) can result in the development of ventricular dysfunction and congestive heart failure. In the adjuvant treatment setting, the incidence of cardiac dysfunction was higher in patients who received trastuzumab plus chemotherapy versus chemotherapy alone. An increase in the incidence of symptomatic and asymptomatic cardiac events was observed when trastuzumab was

administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin. The incidence was more marked when trastuzumab was administered concurrently with a taxane than when administered sequentially to a taxane. In the metastatic setting, the incidence and severity of cardiac dysfunction was particularly high in patients who received trastuzumab concurrently with anthracyclines and cyclophosphamide (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Evaluate left ventricular function in all patients prior to and during treatment with OGIVRI (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Infusion Reactions; Pulmonary Toxicity

OGIVRI administration can result in serious infusion reactions and pulmonary toxicity. Fatal infusion reactions have been reported. In most cases, symptoms occurred during or within 24 hours of administration of trastuzumab. OGIVRI infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinue OGIVRI for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome (see 7 WARNINGS AND PRECAUTIONS).

Embryo-Fetal Toxicity

Exposure to OGIVRI during pregnancy can result in impairment of fetal renal growth and/or renal function impairment resulting in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, intrauterine growth retardation and neonatal death (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

4 DOSAGE AND ADMINISTRATION

Trastuzumab intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only. If an alternate route of administration is required, other trastuzumab products offering such an option should be used.

4.1 Dosing Considerations

There is a risk of medication errors between OGIVRI (trastuzumab) and KADCYLA® (trastuzumab emtansine). In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is OGIVRI (trastuzumab) and not KADCYLA® (trastuzumab emtansine). Ensure that the recommended OGIVRI (trastuzumab) dose is administered (see 4 Recommended Dose and Dosage Adjustment section).

OGIVRI should be prescribed using both the trade name and non-proprietary name. Do not substitute OGIVRI for or with KADCYLA® (trastuzumab emtansine).

When using in combination with pertuzumab and docetaxel for treatment of patients with HER-2-positive metastatic breast cancer, consult Product Monographs for pertuzumab and docetaxel for further information, such as dose adjustment, sequence of administration of each medication and duration of treatment.

Trastuzumab intravenous infusion should be administered by a healthcare provider prepared to manage anaphylaxis and an emergency kit should be available.

4.2 Recommended Dose and Dosage Adjustment

Early Breast Cancer (EBC)
3-Weekly Schedule: The recommended initial loading dose is 8 mg/kg OGIVRI (trastuzumab) administered as a 90-minute infusion. The recommended maintenance dose is 6 mg/kg OGIVRI 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion. **Do not administer as an IV push or bolus** (see Preparation for Administration)

Weekly schedule: As a weekly regimen, the recommended initial loading dose of OGIVRI is 4 mg/kg followed by 2 mg/kg every week. See 14.4 Clinical Trials– Reference Biological Drug section for chemotherapy combination dosing.

Metastatic Breast Cancer (MBC)
Weekly schedule: The recommended initial loading dose is 4 mg/kg OGIVRI administered as a 90-minute infusion. The recommended weekly maintenance dose is 2 mg/kg OGIVRI and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. OGIVRI may be administered in an outpatient setting. **Do not administer as an IV push or bolus** (see Preparation for Administration).

Metastatic Gastric Cancer (MGC)
3-Weekly Schedule: The recommended initial loading dose is 8 mg/kg OGIVRI administered as a 90-minute infusion. The recommended maintenance dose is 6 mg/kg OGIVRI 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion. **Do not administer as an IV push or bolus** (see Preparation for Administration)

Duration of Treatment
Patients with MBC or MGC should be treated with OGIVRI until progression of disease or unmanageable toxicity.

Patients with EBC should be treated for 1 year or until disease recurrence or unmanageable toxicity, whichever occurs first (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular). Extending treatment in EBC beyond one year is not recommended (see 14.4 Clinical Trials - Reference Biological Drug, Early Breast Cancer (EBC), HERA).

Dose Modification
If the patient develops an infusion-related reaction (IRR), the infusion rate of OGIVRI IV may be slowed or interrupted.

No reductions in the dose of trastuzumab were made during clinical trials. Patients may continue therapy with trastuzumab during periods of reversible, chemotherapy-induced myelosuppression, but

they should be monitored carefully for complications of neutropenia during this time. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

Table 1 depicts the criteria for permanent discontinuation of trastuzumab for cardiac dysfunction in pivotal studies in adjuvant breast cancer.

Table 1
Criteria for Permanent Discontinuation for Cardiac Dysfunction in Pivotal Studies in Adjuvant Breast Cancer

STUDY	If Symptomatic CHF	If Held for Asymptomatic LVEF Decrease (per algorithm used in each study protocol)
HERA	required	required if trastuzumab held for 2 consecutive cycles
NSABP B-31, NCCTG N9831 and BCIRG-006	required	required if trastuzumab held for 2 consecutive cycles, or for 3 intermittent cycles; investigator may choose to discontinue permanently sooner

Dose Holding

Monitoring of Cardiac Function (also see 7 WARNINGS AND PRECUATIONS, Cardiovascular, Cardiotoxicity)

Table 2
Recommendations for Continuation or Withdrawal of Trastuzumab Therapy in Asymptomatic Patients Based on Serial Measurements of Left Ventricular Ejection Fraction (LVEF)[a]
(Adapted from the Canadian Consensus Guidelines*)

Relationship of LVEF to LLN	Asymptomatic decrease in LVEF from baseline		
	≤ 10 percentage points	10–15 percentage points	≥ 15 percentage points
Within radiology facility's normal limits	Continue Trastuzumab	Continue Trastuzumab	Hold Trastuzumab and repeat MUGA or ECHO after 4 weeks
1–5 percentage points below LLN	Continue Trastuzumab [b]	Hold Trastuzumab and repeat MUGA or ECHO after 4 weeks [b,c]	Hold Trastuzumab and repeat MUGA or ECHO after 4 weeks [c,d]
≥6 percentage points below LLN	Continue Trastuzumab and repeat MUGA or ECHO after 4 weeks[d]	Hold Trastuzumab and repeat MUGA or ECHO after 4 weeks [c,d]	Hold Trastuzumab and repeat MUGA or ECHO after 4 weeks [c,c]

[a] Based on NSABP B-31 trial protocol. Modified to include recommendations for cardiology consultation or treatment of cardiac dysfunction (or both) when appropriate, as indicated in the subsequent footnotes.
[b] Consider cardiac assessment and initiation of angiotensin converting-enzyme inhibitor therapy.
[c] After two holds, consider permanent discontinuation of Trastuzumab.
[d] Initiate angiotensin converting-enzyme inhibitor therapy and refer to cardiologist. LLN = lower limit of normal; MUGA = multiple-gated acquisition scan; ECHO = echocardiography.

**Source: Mackey JR, Clemons M, Côté MA, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. Curr Oncol. 2008 Jan;15(1):24-35.*

For the frequency of cardiac monitoring see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Cardiotoxicity.

Health Canada has not authorized an indication for pediatric use (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

4.3 Reconstitution

Table 3 - Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Concentration per mL
150 mg/vial	7.2 mL of Sterile Water for Injection (SWFI)	21 mg/mL
440 mg/vial	20 mL of BWFI	21 mg/mL

Preparation for Administration

Use appropriate aseptic technique. Each vial of OGIVRI 150 mg/vial should be reconstituted with 7.2 mL of Sterile Water for Injection (SWFI) (not supplied), to yield a single-dose solution containing 21 mg/mL trastuzumab. Each vial of OGIVRI 440 mg/vial should be reconstituted with 20 mL of BWFI, containing 1.1% benzyl alcohol, as supplied, to yield a multi-dose solution containing 21 mg/mL trastuzumab. Immediately upon reconstitution with BWFI, the vial of OGIVRI must be labelled in the area marked "Do not use after:" with the future date that is 28 days from the date of reconstitution.

If the patient has a known hypersensitivity to benzyl alcohol, OGIVRI must be reconstituted with Sterile Water for Injection (SWFI) (see 7 WARNINGS AND PRECAUTIONS). OGIVRI **which has been reconstituted with SWFI must be used immediately from a microbiological point of view and no later than 10 days after reconstitution. Any unused portion should be discarded. Use of other reconstitution diluents should be avoided**.

OGIVRI should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted OGIVRI may result in problems with the amount of OGIVRI that can be withdrawn from the vial.

Reconstitution:

150 mg/vial

1. Using a sterile syringe, slowly inject 7.2 mL of Sterile Water for Injection (SWFI) (not supplied) in the vial containing the lyophilized OGIVRI directing the stream into the lyophilized cake.

2. Swirl vial gently to aid reconstitution. **Do not shake.**

440 mg/vial

1. Using a sterile syringe, slowly inject 20 mL of Bacteriostatic Water for Injection in the vial containing the lyophilized OGIVRI directing the stream into the lyophilized cake.

2. Swirl vial gently to aid reconstitution. **Do not shake.**

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted OGIVRI results in a colorless to pale yellow transparent solution and should be essentially free of visible particles.

Determine the volume in mL of OGIVRI solution needed:

Weekly Schedule: based on a loading dose of 4 mg trastuzumab/kg body weight or a maintenance dose of 2 mg trastuzumab/kg body weight.

$$\textbf{Volume}\ (\text{mL}) = \frac{[\textbf{Body Weight}\ (\text{kg}) \times \textbf{Dose}\ (4\ \text{mg/kg for loading}\ \textbf{OR}\ 2\ \text{mg/kg for maintenance})]}{21\ \text{mg/mL (concentration of reconstituted solution)}}$$

3-Weekly Schedule: based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent 3 weekly dose of 6 mg trastuzumab/kg body weight:

$$\textbf{Volume}\ (\text{mL}) = \frac{[\textbf{Body Weight}\ (\text{kg}) \times \textbf{Dose}\ (8\ \text{mg/kg for loading}\ \textbf{OR}\ 6\ \text{mg/kg for maintenance})]}{21\ \text{mg/mL (concentration of reconstituted solution)}}$$

Withdraw the appropriate volume of solution calculated from the vial and add it to an infusion bag containing 250 mL of 0.9% sodium chloride, USP. **Dextrose (5%) solution should not be used** since it causes aggregation of the protein. To mix the solution and avoid foaming, invert the bag gently. The reconstituted preparation results in a colourless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discolouration prior to administration. No incompatibilities between OGIVRI and polyvinylchloride, polypropylene, polyethylene or polyolefin bags have been observed.

4.4 Administration

Weekly Schedule: Treatment may be administered in an outpatient setting by administration of a 4 mg/kg loading dose of OGIVRI by intravenous (IV) infusion over 90 minutes. **Do not administer as an IV push or bolus**. Patients should be observed for fever and chills or other infusion associated symptoms. Serious adverse reactions to infusions of trastuzumab including dyspnea, hypotension, hypertension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress have been reported infrequently (also see 8 ADVERSE REACTIONS). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

If prior infusion was well tolerated, subsequent weekly doses of 2 mg/kg OGIVRI may be administered over 30 minutes (see Recommended Dose and Dosage Adjustment). Patients should still be observed for fever and chills or other infusion-associated symptoms (see 8 ADVERSE REACTIONS).

3-Weekly Schedule: Treatment may be administered in an outpatient setting by administration of a 8 mg/kg loading dose of OGIVRI by intravenous (IV) infusion over 90 minutes. **Do not administer as an IV push or bolus**. Patients should be observed for fever and chills or other infusion associated symptoms (see 8 ADVERSE REACTIONS). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

If prior infusion was well tolerated, subsequent 3-weekly doses of 6 mg/kg OGIVRI may be administered over 30 minutes (see Recommended Dose and Dosage Adjustment). Patients should still be observed for fever and chills or other infusion-associated symptoms (see 8 ADVERSE REACTIONS).

OGIVRI should not be mixed or diluted with other drugs. Infusions of OGIVRI should not be administered or mixed with dextrose solutions.

4.5 Missed Dose

Weekly schedule: If the patient has missed a dose of OGIVRI by one week or less, then the usual maintenance dose (2 mg/kg) should be given as soon as possible (do not wait until the next planned cycle). Subsequent maintenance OGIVRI doses of 2 mg/kg should be administered 7 days later according to the weekly schedule.

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

3-Weekly Schedule: If the patient has missed a dose of OGIVRI by one week or less, then the usual maintenance dose (6 mg/kg) should be administered as soon as possible (do not wait until the next planned cycle). Subsequent maintenance OGIVRI doses of 6 mg/kg should be administered 21 days later according to the 3-weekly schedule.

If the patient has missed a dose of OGIVRI by more than one week, a re-loading dose of OGIVRI should be administered (8 mg/kg over approximately 90 minutes) as soon as possible. Subsequent maintenance OGIVRI doses of 6 mg/kg should be administered 21 days later according to the 3-weekly schedule.

5 OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 500 mg (10 mg/kg) have not been tested.

Ensure that the recommended OGIVRI (trastuzumab) dose and NOT KADCYLA® (trastuzumab emtansine) dose is administered. For information on the risk of KADCYLA® overdose due to medication errors, see KADCYLA® Product Monograph.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of OGIVRI, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
for Intravenous Infusion	Lyophilized Powder 150 mg trastuzumab/vial 440 mg trastuzumab/vial	L-histidine, L-histidine HCl monohydrate, PEG-3350/macrogol 3350, D-sorbitol. It also contains hydrochloric acid and sodium hydroxide to adjust the pH. **Note:** The Sterile Water for Injection (SWFI) for dilution of the 150 mg/vial is not supplied. The Bacteriostatic Water for Injection (BWFI) supplied with trastuzumab 440 mg/vial contains 1.1% benzyl alcohol (see 7 WARNINGS AND PRECAUTIONS).

Composition:
OGIVRI (trastuzumab) is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration.

150 mg/vial
Each vial of OGIVRI contains 150 mg trastuzumab, 2.16 mg L-histidine, 3.36 mg L-histidine HCl monohydrate, 33.6 mg PEG 3350/macrogol 3350, and 115.2 mg D - sorbitol. It also contains sodium hydroxide and hydrochloric acid to adjust the pH. Reconstitution with 7.2 mL of Sterile Water for Injection (SWFI) (not supplied), yields a single-dose solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.

440 mg/vial
Each vial of OGIVRI contains 440 mg trastuzumab, 6.34 mg L-histidine, 9.9 mg L-histidine HCl monohydrate, 98.6 mg PEG 3350/macrogol 3350, and 337.9 mg D-sorbitol. It also contains sodium hydroxide and hydrochloric acid to adjust the pH. Reconstitution with 20 mL of the supplied BWFI, containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.

Availability:
150 mg/vial

OGIVRI is supplied as a lyophilized, sterile powder containing 150 mg trastuzumab per vial under vacuum.

Each carton contains one vial of 150 mg OGIVRI.

440 mg/vial
OGIVRI is supplied as a lyophilized, sterile powder containing 440 mg trastuzumab per vial under vacuum.

BWFI is supplied as a 20 mL vial of sterile solution containing 1.1% benzyl alcohol as an antimicrobial preservative.

Each carton contains one vial of 440 mg OGIVRI and one 20 mL vial of BWFI containing 1.1% benzyl alcohol.

Description
OGIVRI (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody directed against the extracellular domain of the human epidermal growth factor receptor 2 (HER2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. OGIVRI binds to HER2 protein on the surface of cancer cells and inhibits their proliferation and survival.

7 WARNINGS AND PRECAUTIONS

Please see the 3 Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General
Therapy with OGIVRI should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

When using in combination with pertuzumab and docetaxel, consult Product Monographs for pertuzumab and docetaxel for further information on these drugs.

Selection of Patients / Diagnostic Tests

Early Breast Cancer (EBC)/Metastatic Breast Cancer (MBC)

Trastuzumab should only be used in patients whose tumors overexpress HER2 as determined by immunohistochemistry. CICH or FISH testing for HER2 status also may be used, provided that the testing is done in experienced laboratories that have validated the test.
To ensure accurate and reproducible results, the protocol described in the package insert of an appropriate diagnostic test needs to be strictly followed. However, based on the current scientific knowledge, no standard test can be recommended at this time. There is no standard method of staining and no standard for the type of antibodies used. The grading for overexpression is subjective, and the signal may fade with time on stored slides.

The test method for HER2 overexpression used to determine eligibility of patients for inclusion in the MBC clinical trials employed immunohistochemical staining for HER2 of fixed material from tissue biopsy using the murine monoclonal antibodies CB11 and 4D5. Patients classified as staining 2+ or 3+ were included, while those staining 0 or 1+ were excluded. Greater than 70% of patients enrolled exhibited 3+ overexpression. The data suggest that beneficial effects were greater among those patients with higher levels of overexpression of HER2.

In the studies, an investigative clinical trial assay was employed which utilized a 0 to 3+ scale. The degree of HER2 overexpression indicated by different test methods may not correlate with that used as the eligibility criterion for inclusion in the clinical trials. For example, the validated immunohistochemical (IHC) test also utilizes a scale of 0 to 3+. A reading of 3+ with a validated IHC test is likely to correspond to that of a 2+ or 3+ with the investigative clinical trial assay. A 2+ reading with a validated IHC test would likely incorporate a significant number of patients who were scored as 1+ by the investigative clinical trial assay. These patients (1+) would not have met the inclusion criteria. Test methods having increased sensitivity, relative to the investigative clinical trial assay, may alter the benefit-to-risk ratio compared to that seen in the clinical trials. In deciding which patients should receive trastuzumab, the risk of cardiac dysfunction (see 7 WARNINGS and PRECAUTIONS) must be weighed against the potential benefits of treatment, especially for those not in the high range of HER2 overexpression.

For inclusion criteria in terms of HER2 expression in clinical trials in EBC, see 14.4 Clinical Trials – Reference Biologic Drug section.

Early Breast Cancer:
The safety of the various combination chemotherapy regimens prior to trastuzumab therapy was not separately analyzed in the HERA trial. The data provided in the Product Monograph reflects the safety and efficacy of trastuzumab for the recommended 1 year treatment duration.

Benzyl Alcohol: Benzyl alcohol, used as a preservative in BWFI, has been associated with toxicity in neonates and children up to 3 years old. For patients with a known hypersensitivity to benzyl alcohol (the preservative in BWFI), reconstitute OGIVRI with Sterile Water for Injection (SWFI). **Use SWFI-reconstituted OGIVRI immediately and discard the vial** (see 4 DOSAGE AND ADMINISTRATION).

Cardiovascular
Cardiotoxicity: Administration of OGIVRI can result in the development of ventricular dysfunction and congestive heart failure. In the adjuvant treatment setting, the incidence of cardiac dysfunction was higher in patients who received trastuzumab plus chemotherapy versus chemotherapy alone. In patients with EBC, an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when trastuzumab was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin. The incidence was more marked when trastuzumab was administered concurrently with a taxane than when administered sequentially to a taxane. In the metastatic setting, the incidence and severity of cardiac dysfunction were particularly high in patients who received trastuzumab concurrently with anthracyclines and cyclophosphamide. The incidence of cardiac adverse events was also higher in patients with previous exposure to anthracyclines based on post-marketing data.

Because the half-life of trastuzumab, using a population pharmacokinetic method, is approximately 28.5 days (95% CI, 25.5 - 32.8 days), trastuzumab may persist in the circulation for approximately 24 weeks (range: 22-28 weeks) after stopping treatment with trastuzumab. Since the use of an anthracycline during this period could possibly be associated with an increased risk of cardiac dysfunction, a thorough assessment of the risks versus the potential benefits is recommended in addition to careful cardiac monitoring. If possible, physicians should avoid anthracycline based therapy while trastuzumab persists in the circulation.

Patients who receive OGIVRI either as a component of adjuvant treatment or as a treatment for metastatic HER2 positive breast cancer may experience signs and symptoms of cardiac dysfunction such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S_3 gallop, or reduced ejection fraction. Cardiac dysfunction associated with therapy with OGIVRI may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke. Left ventricular function should be evaluated in all patients prior to and during treatment with OGIVRI. If left ventricular ejection fraction (LVEF) drops 10 ejection points from baseline and/or to below 50%, OGIVRI should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of OGIVRI should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. The scientific basis of cardiac dysfunction has been incompletely investigated in pre-clinical studies.

Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction and in EBC, in those patients with an LVEF of 55% or less. Candidates for treatment with OGIVRI as part of adjuvant treatment for operable breast cancer or for MBC, especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo thorough baseline cardiac assessment including history and physical exam, electrocardiogram (ECG) and either 2D echocardiogram or multiple gated acquisition (MUGA) scan. A careful risk-benefit assessment should be made before deciding to treat with OGIVRI. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of OGIVRI. In patients with EBC who receive anthracycline containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of OGIVRI, or longer if a continued decrease of LVEF is observed. Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g., every 6-8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy unless the benefits for the individual patient are deemed to outweigh the risks.

If symptomatic cardiac failure develops during therapy with OGIVRI, it should be treated with the standard medications for this purpose. Discontinuation of OGIVRI should be strongly considered in patients who develop clinically significant congestive heart failure. In the MBC clinical trials, approximately two-thirds of patients with cardiac dysfunction were treated for cardiac symptoms, most patients responded to appropriate medical therapy (which may include one or more of the following: diuretics, angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II receptor blockers, or cardiac glycosides) often including discontinuation of trastuzumab. The safety of continuation or resumption of OGIVRI in patients who have previously experienced cardiac toxicity has not been prospectively studied.

Early Breast Cancer (EBC)
OGIVRI and anthracyclines should not be given concurrently in the adjuvant treatment setting.

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low level of baseline and declining LVEF (< 55%), low LVEF prior to or following the initiation of paclitaxel treatment, trastuzumab treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving trastuzumab after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of trastuzumab and a high body mass index (BMI > 25 kg/m^2).

In EBC, the following patients were excluded from the HERA, JA (NSABP B-31 and NCCTG N9831) and BCIRG006 trials there are no data about the benefit risk balance, and therefore treatment cannot be recommended in such patients:

- history of myocardial infarction (MI),
- angina pectoris requiring medication,
- history of or present CHF (NYHA II –IV),
- other cardiomyopathy,
- cardiac arrhythmia requiring medication,
- clinically significant cardiac valvular disease,
- poorly controlled hypertension (hypertension controlled by standard medication eligible) and
- clinically significant pericardial effusion.

The safety of continuation or resumption of OGIVRI in patients who have previously experienced cardiac toxicity has not been prospectively studied. According to the narrative reports of cardiac events, about half of the events had resolved completely by the time of the interim analysis. Please see Table 6 below.

For patients with EBC, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of OGIVRI. In patients who receive anthracycline containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of OGIVRI, or longer if a continued decrease of LVEF is observed.

A high index of clinical suspicion is warranted for discontinuing treatment in the setting of cardiopulmonary symptoms. Close monitoring of cardiac function should be carried out for all patients and adequate treatment for CHF should be administered regardless of the discontinuation of OGIVRI therapy. Please see Table 2 in 4 DOSAGE AND ADMINISTRATION: Dose Holding, Monitoring of Cardiac Function, for information on continuation and discontinuation of OGIVRI based on interval LVEF assessments.

HERA
In the HERA trial, cardiac monitoring (electrocardiogram [ECG], left ventricular ejection fraction [LVEF], signs/symptoms and cardiac questionnaire) was performed at baseline and regularly throughout the study. The assessment schedule for cardiac monitoring was at Months 3 and 6 and then every 6 months until month 36 (3 years from the date of therapy) and in Month 60 (5 years from the date of therapy). In

addition, LVEF was measured at 48 months (4 years from the date of therapy) and followed up every 12 months from Year 6 to Year 10.

When trastuzumab was administered after completion of adjuvant chemotherapy, New York Heart Association (NYHA) class III-IV heart failure was observed in 0.6% of patients in the 1-Year arm after a median follow-up of 12 Months.

Table 5a Absolute Numbers and Rates of Cardiac Endpoints in HERA (Median follow-up of 12 Months)

HERA study	**Observation** n (%) N=1708	**Trastuzumab** n (%) N=1678
Primary cardiac endpoint	1 (0.1%)	10 (0.6%)
Secondary cardiac endpoint	9 (0.5%)	51 (3.0%)
Total "cardiac endpoints"	10 (0.6%)	61 (3.6%)

Table 5b Absolute Numbers and Rates of Cardiac Endpoints in HERA (Median follow-up of 8 Years)

HERA study	**Observation** n (%) N=1744	**Trastuzumab** 1 year arm n (%) N=1682
Primary cardiac endpoint	2 (0.1%)	14 (0.8%)
Events after 1 year	0 (0.0%)	1 (0.1%)
Secondary cardiac endpoint	15 (0.9%)	78 (4.6%) (69 – excluding patients with primary endpoint)
Events after 1 year	7 (0.4%)	14 (0.8%) (13 – excluding patients with primary endpoint)
Total "cardiac endpoints"	17 (1.0%)	83 (4.9%)

Table 6a Median Time to Return to Baseline LVEF/ Stabilizations of LVEF in the HERA Trial (Median follow-up of 8 years) - Primary Cardiac Endpoint

HERA study	Primary Cardiac Endpoint	
	Observation (n = 2)	**Trastuzumab** 1-year (n=14)
Return to baseline LVEF	0	11 (79%)
Median time to return to baseline LVEF	-	218 d
Stabilization of LVEF	0	5 (36%)

Table 6b Median Time to Return to Baseline LVEF/ Stabilizations of LVEF in the HERA Trial (Median Follow-up of 8 Years) - Secondary Cardiac Endpoint

HERA study	Secondary Cardiac Endpoint (excluding patients with primary cardiac endpoint)	
	Observation (n = 15)	**Trastuzumab** 1-year (n=69)
Return to baseline LVEF	10 (67%)	60 (87%)
Median time to return to baseline LVEF	189 d	240 d
Stabilization of LVEF	4 (27%)	18 (26%)

A significant drop in left ventricular ejection fraction (LVEF) is defined as an absolute decrease of 10 EF points or more from baseline and to below 50%, measured by MUGA scan or echocardiogram.

A **primary cardiac endpoint** was defined as the occurrence at any time after randomization but prior to any new therapy for recurrent disease of symptomatic congestive heart failure of NYHA class III or IV, confirmed by a cardiologist and a significant drop in LVEF, or cardiac death.

A **secondary cardiac endpoint** was defined as asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) cardiac dysfunction with a significant LVEF drop. In addition, events which did not meet the above criteria for a secondary cardiac endpoint but which in the opinion of the Cardiac Advisory Board should be classed as secondary cardiac endpoints were included.

After a median follow-up of 3.6 years the incidences of severe CHF, symptomatic CHF and at least one significant LVEF decrease (an absolute decline of at least 10% from baseline LVEF and to less than 50%) after 1 year of trastuzumab therapy was 0.8%, 1.9% and 9.8%, respectively.

After a median follow-up of 8 years the incidence of severe CHF (NYHA III & IV) in the trastuzumab 1 year treatment arm was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%. At least one LVEF assessment was missing for 20.8% of patients in the observation only arm and 32.0% of patients in the trastuzumab 1-year arm. During the follow-up until

month 60, at least one LVEF assessment was missed for 18.0% of patients in the observation only arm and 17.9% of patients in the trastuzumab 1-year arm.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥50% after the event) was evident for 71.4% of trastuzumab-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of patients. Approximately 17% (14/83) of cardiac endpoints occurred after completion of trastuzumab in the trastuzumab 1-year arm.

Joint Analysis: NSABP B-31 and NCCTG N9831

Cardiac dysfunction adverse events were defined in both B-31 and N9831 as symptomatic cardiac events and asymptomatic LVEF events. Symptomatic cardiac events were reviewed and confirmed by the cardiac committee of each study and included the occurrence of symptomatic congestive heart failure with objective findings and confirmation by imaging, deaths due to cardiac causes (CHF, MI, or documented primary arrhythmia) and probable cardiac deaths (sudden death without documented etiology). Asymptomatic LVEF events were defined as absolute drop in LVEF ≥10% to < 55% or an absolute drop in LVEF of ≥5% to below the institution's lower limit of normal (LLN). In Study B-31, 15.5% of patients discontinued trastuzumab due to asymptomatic LVEF decrease (12.2%), CHF (2.2%) or Cardiac diagnosis other than CHF (1.1%) in the trastuzumab + chemotherapy arm; no patients in the chemotherapy alone arm discontinued treatment for these reasons. In all analyses the rate of cardiac dysfunction was higher in patients in the trastuzumab + chemotherapy arm compared with those in the chemotherapy alone arm. From the paclitaxel baseline to the six month, nine month and eighteen month assessment, the average change in LVEF was more pronounced in the trastuzumab + chemotherapy arm (-4.2%, -5.1% and -3.1% in the trastuzumab + chemotherapy alone arm, respectively versus -0.5%, -0.4% and -0.9% in the chemotherapy alone arm, respectively).

Table 7
Joint Analysis: (NSABP B-31 and NCCTG N9831)
The Incidence and Type of Cardiac Events (Median Duration of More Than 8 Years
Safety Follow up)

	B31		N9831		B-31+N9831	
	AC→T (n=889)	**AC→T + H (n=1031)**	**AC→T (n =766)**	**AC→T + H (n=969)**	**AC→T (n =1655)**	**AC→T + H (n=2000)**
Symptomatic CHF (non-death)	11 (1.2%)	38 (3.7%)	5 (0.7%)	24 (2.5%)	16 (1.0%)[a]	62 (3.1%)[b]
Cardiac death	2 (0.2%)[c]	1 (0.1%)	3 (0.4%)	1 (0.1%)	5 (0.3%)[c]	2 (0.1%)
Death due to CHF, MI, or primary arrhythmia	0 (0.0%)	0 (0.0%)	2 (0.3%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Sudden death without documented etiology	2 (0.2%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	3 (0.2%)	1 (0.1%)
Any cardiac or asymptomatic LVEF events	270 (30.4%)	401 (38.9%)	209 (27.3%)	367 (37.9%)	479 (28.9%)	768 (38.4%)
Drop in LVEF of 10 points compared with baseline to below 55*	236 (26.5%)	376 (36.5%)	184 (24.0%)	340 (35.1%)	420 (25.4%)	716 (35.8%)
Drop in LVEF of 5 points compared with baseline to below the lower limit of normal*	161 (18.1%)	267 (25.9%)	127 (16.6%)	238 (24.6%)	288 (17.4%)	505 (25.3%)

A = doxorubicin; C = cyclophosphamide; CHF = congestive heart failure; H = trastuzumab; LVEF = left ventricular ejection fraction; MI = myocardial infarction; T = paclitaxel.

*Asymptomatic LVEF per protocol events at any time after AC initiation: 1. Drop in LVEF of 10 points compared with AC baseline LVEF to below 55. or 2. Drop in LVEF of 5 points compared with AC baseline LVEF to below the lower limit of normal.

** In the joint analysis safety population, the median duration of follow-up was 8.1 years for the AC→T + H group and 8.5 years for the AC→T group

[a] 16 AC→T patients had adjudicated and confirmed symptomatic CHF out of the 62 possible CHF patients reviewed by the study committees.

[b] 62 AC→T + H patients had adjudicated and confirmed symptomatic CHF out of the 135 possible CHF patients reviewed by the study committees.

[c] A patient received AC→T in study B-31; not included here and had "emphysema" listed on autopsy.

At 3 years, the cardiac event rate in patients receiving AC→TH (doxorubicin plus cyclophosphamide followed by paclitaxel + trastuzumab) was estimated at 3.2%, compared with 0.9% in AC→T treated patients. Between 5 and 7 years of follow-up, an additional patient in each treatment group experienced a cardiac event; the cardiac event rate at 9 years follow-up in patients receiving AC→TH was estimated at 3.2%, compared with 1.0% in AC→T treated patients.

Table 8 summarizes the follow-up information for 84 patients (52 from Study B-31 and 32 from study N9831) for whom symptomatic CHF was adjudicated and confirmed by the study committee.

Table 8
Joint Analysis (NSABP B-31 and NCCTG N9831)
Follow-Up of Symptomatic CHF Events (Median Duration of More Than 8 Years* Safety Follow up)
(Patients from the Joint Safety Population with Symptomatic CHF Confirmed by Study Committee)

	B-31		N9831		Joint Analysis	
	AC→T (n=11)	AC→T +H (n=38)	AC→T (n =5)	AC→T + H (n=24)	AC→T (n =6)	AC→T +H (n =62)
Months from onset to first overall recovery						
N	4	22	0	9	4	31
Mean (SD)	10.1 (2.2)	21.5 (11.1)	NA	10.5 (8.6)	10.1 (2.2)	18.3 (11.5)
Median	10.2	16.9	NA	6.6	10.2	14.5
Range	8–12	9–50	NA	3–31	8–12	3–50
Current overall recovery status						
Recovery (LVEF ≥50% and no symptoms)	3 (27.3%)	8 (21.1%)	(0.0%)	7 (29.2%)	3 (18.8%)	15 (24.2%)
No recovery (LVEF <50% or symptoms)	2 (18.2%)	7 (18.4%)	3 (60.0%)	6 (25.0%)	5 (31.3%)	13 (21.0%)
Unknown	6 (54.5%)	23 (60.5%)	2 (40.0%)	11 (45.8%)	8 (50.0%)	34 (54.8%)

A = doxorubicin; C = cyclophosphamide; H = trastuzumab; LVEF = left ventricular ejection fraction; SD = standard deviation; T = paclitaxel;
* = In the joint analysis safety population, the median duration of follow-up was 8.1 years for the AC→T + H group and 8.5 years for the AC→T group.

Following initiation of paclitaxel therapy, 344 patients treated with AC→TH (18.5%) experienced an LVEF percentage decrease of **≥** 10 points from paclitaxel baseline to < 50 points, compared with 82 patients treated with AC→T (7.0%) at a median follow-up of 8.1 years for the AC→TH group. The per patient incidence of new onset cardiac dysfunction, after initiation of paclitaxel therapy, as determined by LVEF, remained unchanged compared to the analysis performed at a median follow up of 2.0 years in the AC→TH group.

An independent clinical review was performed on 62 patients with symptomatic congestive heart failure in the trastuzumab + chemotherapy arm to assess treatment and resolution status. Most patients were treated with oral medications commonly used to manage congestive heart failure. Complete or partial LVEF recovery was documented in 56 patients (90.3%), with complete recovery in 17 of these patients (27.4%) and partial recovery in 39 of these patients (62.9%), compared to 6 patients (9.7%) experiencing no recovery**.** This analysis also showed evidence of reversibility of left ventricular dysfunction in 64.5% of patients who experienced a symptomatic CHF in the AC→TH group being asymptomatic at the latest follow up.

Risk factors for a cardiac event included trastuzumab treatment, increased age, prior or current use of anti-hypertensive medications and low LVEF prior to or following the initiation of paclitaxel treatment. In the trastuzumab + chemotherapy arm, the risk of a cardiac event increased with the number of these

risk factors present. In study B-31, there was no association between the incidence of cardiac events and either radiation to the left side of the chest or smoking.

BCIRG006

In Study BCIRG006, cardiac events were defined as congestive heart failure (CHF; grade 3 or 4 cardiac left ventricular function [CLVF], per the NCI-CTC, v 2.0), grade 3 or 4 cardiac arrhythmia, grade 3 or 4 cardiac ischemia/infarction, cardiac death and serious adverse events with cardiac etiology not pre-defined as a cardiac event in the protocol but assessed as being a significant cardiac event by the Independent Cardiac Review Panel (ICRP). Asymptomatic LVEF events were defined as an absolute decline in LVEF value of >15 % from baseline to a value that was below the institution's lower limit of normal (LLN). [Note: asymptomatic LVEF events defined in HERA as: a drop in LVEF of at least 10 EF points from baseline and to below 50%, and in the JA as: absolute drop in LVEF ≥10% to < 55% or an absolute drop in LVEF of ≥5% to below the institution's LLN.]

Table 9 summarizes symptomatic cardiac events reported at any time during the study.

Table 9
Symptomatic Cardiac Events per the Independent Cardiac Review Panel (ICRP) Occurring at Any Time During the Study (Safety Population)
5 Year Follow Up

Event Type	AC→T (n=1041)	AC→TH (n=1077)	TCH (n=1056)
CHF (Grade 3/4 CLVF)	6 (0.6%)	20 (1.9%)	4 (0.4%)
Grade 3/4 cardiac ischemia/infarction	0	3 (0.3%)	2 (0.2%)
Grade 3/4 arrhythmia	6 (0.6%)	3 (0.3%)	6 (0.6%)
Cardiac death	0	0	0
Any symptomatic cardiac event	10 (1.0%)	25 (2.3%)	12 (1.1%)

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; CHF = congestive heart failure; CLVF = cardiac left ventricular function; TCH = docetaxel, carboplatin, and trastuzumab.

At 5.5 years, the rates of symptomatic cardiac or LVEF events were 1.0%, 2.3%, and 1.1% in the AC→T (doxorubicin plus cyclophosphamide, followed by docetaxel), AC→TH (doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab), and TCH (docetaxel, carboplatin and trastuzumab) treatment arms, respectively. For symptomatic CHF (Grade 3 - 4), the 5-year rates were 0.6%, 1.9%, and 0.4% in the AC→T, AC→TH, and TCH treatment arms, respectively. The overall risk of developing symptomatic cardiac events was similar for patients in AC→T and TCH arms. There was an increased risk of developing a symptomatic cardiac event for patients in the AC→TH arm, where the cumulative rate of symptomatic cardiac or LVEF events was 2.3% compared to approximately 1% in the two comparator arms (AC→T and TCH, respectively).

In BCIRG006 study, 155 patients treated with AC→TH (14.4%) experienced an LVEF decrease of ≥ 10% from baseline to < 50%, compared with 79 (7.6%) patients treated with AC→T and 63 (6.0%) patients treated with TCH.

Table 10 presents the incidence of symptomatic and asymptomatic LVEF events.

Table 10 Asymptomatic and Symptomatic LVEF Declines by Baseline Events, Using the Same Assessment Method as Baseline (Safety Population) 5 Year Follow Up			
Event Type	**AC→T (n =1041)**	**AC→TH (n =1077)**	**TCH (n =1056)**
Absolute decline of >15% from baseline and to a value below the LLN	50 (4.8%)	111 (10.3%)	42 (4.0%)
Absolute decline of >10% from baseline and to a value <50%	71 (6.8%)	137 (12.7%)	50 (4.7%)
Symptomatic and/or asymptomatic decline of >15%, below the LLN	56 (5.4%)	128 (11.9%)	57 (5.4%)
AC-T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC-TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab); ANC = absolute neutrophil count; LLN = lower limit of normal; TCH = docetaxel, carboplatin, and trastuzumab.			

Metastatic Breast Cancer (MBC)

OGIVRI and anthracyclines should not be given concurrently in the MBC setting.

In particular, moderate to severe cardiac dysfunction has been observed in MBC patients treated with trastuzumab in combination with an anthracycline (doxorubicin or epirubicin) and cyclophosphamide (see 8 ADVERSE REACTIONS). The clinical status of patients in the trials who developed congestive heart failure were classified for severity using the New York Heart Association classification system (I-IV[a] where IV is the most severe level of cardiac failure) (see Table 11).

Table 11 Incidence and Severity of Cardiac Dysfunction in Metastatic Breast Cancer Patients					
	trastuzumab + Anthracycline + cyclophosphamide[b]	**Anthracycline + cyclophosphamide[b]**	**trastuzumab + Paclitaxel[b]**	**Paclitaxel[b]**	**trastuzumab[a] Alone**
	(n=143)	**(n= 135)**	**(n= 91)**	**(n= 95)**	**(n= 338)**
Any Cardiac Dysfunction	27%	7%	12%	1%	4%
Class III-IV	16%	3%	2%	1%	3%

[a] Single agent studies H0551g, H0649g and H0650g.

[a] New York Heart Association Functional Classification
Class I: Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

[b] Randomized Phase III study comparing chemotherapy plus trastuzumab to chemotherapy alone, where chemotherapy is either anthracycline/cyclophosphamide or paclitaxel.

In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic heart failure was 2.2% in patients receiving trastuzumab and docetaxel, compared with 0% in patients receiving docetaxel alone. In the MBC trials, the probability of cardiac dysfunction was highest in patients who received trastuzumab concurrently with anthracyclines. The MBC data suggest that advanced age may increase the probability of cardiac dysfunction.

Pre-existing cardiac disease or prior cardiotoxic therapy (e.g., anthracycline or radiation therapy) to the chest may decrease the ability to tolerate therapy with OGIVRI; however, the data is not adequate to evaluate correlation between cardiac dysfunction observed with trastuzumab and these factors in patients with HER2 positive MBC.

Driving and Operating Machinery
Trastuzumab has a minor influence on the ability to drive and use machines. Dizziness and somnolence may occur during treatment with trastuzumab. Patients experiencing infusion-related symptoms should be advised not to drive or use machines until symptoms resolve completely.

Hematologic
Exacerbation of Chemotherapy-Induced Neutropenia: In randomized, controlled clinical trials in both adjuvant and MBC designed to assess the impact of the addition of trastuzumab on chemotherapy, the per-patient incidences of moderate to severe neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy compared with those receiving chemotherapy alone.

Using NCI-CTC criteria, in the adjuvant HERA trial, 0.4% of patients treated with trastuzumab experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

In the adjuvant studies, NSABP B-31 and NCCTG N9831, there were 6 deaths due to septicemia or severe neutropenia. Five deaths occurred on the chemotherapy alone arm: 2 patients died of pneumonia with febrile neutropenia and 3 patients died of septicemia. One death occurred on the trastuzumab + chemotherapy arm and the patient died of infection/neutropenic fever with lung infiltrates. All except 2 septicemia deaths occurred during protocol treatment period.

In the post-marketing setting in MBC, deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving trastuzumab and myelosuppressive chemotherapy, although in controlled MBC clinical trials (pre- and post-marketing), the incidence of septic death was not significantly increased.

The pathophysiologic basis for exacerbation of neutropenia has not been determined; the effect of trastuzumab on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated. If neutropenia occurs, the appropriate management should be instituted as per local practice/guidelines and the labelled instructions for chemotherapy agents should be followed with regard to dose interruption or dose reduction (see 4 DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment, Dose Modification).

Hypersensitivity Reactions Including Anaphylaxis, Infusion-Associated Reactions and Pulmonary Events

Administration of OGIVRI can result in severe hypersensitivity reactions (including anaphylaxis), infusion reactions and pulmonary events. In rare cases, these reactions have been fatal. See discussion below.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with OGIVRI after experiencing a severe reaction. Trastuzumab has been re-administered to some patients who fully recovered from a previous severe reaction. Prior to re-administration of trastuzumab the majority of these patients were prophylactically treated with pre-medications including antihistamines and/or corticosteroids. While some of these patients tolerated retreatment, others had severe reactions again despite the use of prophylactic pre-medications.

Hypersensitivity Reactions Including Anaphylaxis: Severe hypersensitivity reactions have been infrequently reported in patients treated with trastuzumab. Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. The onset of symptoms generally occurred during an infusion, but there have also been reports of symptom onset after the completion of an infusion. Reactions were most commonly reported in association with the initial infusion. In HERA 1 observation and 10 trastuzumab treated patients experienced hypersensitivity. Eight out of the 10 events were considered related to trastuzumab treatment. The incidence of allergic reactions in the Joint Analysis (chemotherapy alone versus trastuzumab + chemotherapy: 3.6% versus 3.1% in study B-31 and 1.1% versus 0.3% in study N9831) was comparable between the two treatment arms in both studies. In study BCIRG006, the incidence of allergic reactions according to the NCI-CTC v 2.0 classification was 9.4%, 12.3% and 14.9% in AC→T, AC→TH and TCH arms, respectively.

Infusional administration of OGIVRI should be interrupted in all patients with severe hypersensitivity reactions. In the event of a hypersensitivity reaction, appropriate medical therapy should be administered, which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Infusion-Related Reactions (IRRs): IRRs are known to occur with trastuzumab. Pre-medication may be used to reduce risk of occurrence of IRRs.

Serious IRRs to infusions of trastuzumab including dyspnea, hypotension, hypertension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, supraventricular tachyarrhythmia and urticaria have been reported (see 8 ADVERSE REACTIONS). Patients should be observed for IRRs. Interruption of an IV infusion may help control such symptoms and the infusion may be resumed when symptoms abate. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists and corticosteroids (see 8 ADVERSE REACTIONS). The appropriate management of patients with uncontrolled hypertension or history of hypertension should be considered prior to infusion with OGIVRI.

These severe reactions were usually associated with the first infusion of trastuzumab and generally occurred during or immediately following the infusion. For some patients, symptoms later worsened and led to further pulmonary complications. Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than six hours after the start of the infusion of trastuzumab. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if those symptoms occur. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients who are experiencing dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with OGIVRI.

Pulmonary Events: Severe pulmonary events leading to death have been reported with the use of trastuzumab in the adjuvant breast cancer clinical studies and the post-marketing MBC setting. These events may occur as part of an infusion-related reaction or with a delayed onset (See Infusion-Related Reactions subsection of 7 WARNINGS AND PRECAUTIONS), and were reported to occur at varying latencies, from within 24 hours to over 30 days, since the start of treatment with trastuzumab. Cases of interstitial lung disease (which often present with dyspnea) including lung infiltrates, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, respiratory insufficiency, acute respiratory distress syndrome, and pneumonia have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients with dyspnea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with OGIVRI.

Other severe events reported rarely in the post-marketing MBC setting include pneumonitis and pulmonary fibrosis. All of the confirmed cases of pulmonary fibrosis received to date are characterized by one or more significant confounding factors including pre-existing lung disease and prior/concomitant chemotherapy such as cyclophosphamide. However, a causal relationship between OGIVRI and pulmonary fibrosis cannot be excluded.

Immune
Immunogenicity:
Samples for assessment of human anti-human antibody (HAHA) were not collected in studies of adjuvant breast cancer. Of 903 patients that have been evaluated in the MBC trials, human anti-human antibody (HAHA) to trastuzumab was detected in 1 patient, who had no allergic manifestations.

Respiratory
Refer to Pulmonary Events subsection of 7 WARNINGS AND PRECAUTIONS.

Thrombosis/Embolism
Thrombosis/embolism has been observed in patients who receive trastuzumab + chemotherapy in both the adjuvant and metastatic treatment setting, and in rare cases, has been fatal (see 8 ADVERSE REACTIONS section).

7.1 Special Populations

7.1.1 Pregnant Women

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg trastuzumab and have revealed no evidence of impaired fertility or harm to the fetus (see 15 NON-CLINICAL TOXICOLOGY, Reproductive Toxicity). However, when assessing the risk of reproductive toxicity in humans, it is important to consider the significance of the rodent form of the HER2 receptor in normal embryonic development and the embryonic death in mutant mice lacking this receptor. Placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (days 120-150 of gestation) fetal development period was observed.

OGIVRI can cause fetal harm when administered to a pregnant woman. In the post-marketing setting, cases of impairment of fetal renal growth and/or renal function impairment, intrauterine growth retardation and skeletal abnormalities in association with oligohydramnios during the second and third trimesters, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab. Also, the causal role of trastuzumab cannot be excluded nor confirmed in two cases of interventricular septal defects reported in infants exposed to trastuzumab in utero. In 1 of these 2 cases, spontaneous closure of the defect occurred 9 months postpartum. No follow up information regarding closure of the defect was available in the second case. HER 2 is known to be expressed in many embryonic tissues. Women of childbearing potential should be advised to use effective contraception during treatment with OGIVRI and for at least 7 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with OGIVRI, close monitoring by a multidisciplinary team is desirable.

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

Animal reproduction studies revealed no evidence of impaired fertility or harm to the fetus. Because animal reproduction studies are not always predictive of human response, trastuzumab should not be used during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

7.1.2 Breast-feeding

A study conducted in lactating cynomolgus monkeys at doses 25 times the weekly human maintenance dose of 2 mg/kg trastuzumab demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. It is not known whether OGIVRI is excreted in human milk. As human IgG is excreted in human milk, and the potential for absorption and harm to the infant is unknown, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of trastuzumab and the importance of the drug to the mother.

7.1.3 Pediatrics

The safety and effectiveness of OGIVRI in pediatric patients below the age of 18, have not been established.

7.1.4 Geriatrics (> 65 years of age)

Trastuzumab has been administered in clinical studies to 386 patients who were 65 years of age or over (253 in the adjuvant treatment and 133 in MBC treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared with younger patients in both those receiving treatment for metastatic disease and those receiving adjuvant therapy in Studies NSABP B-31 and NCCTG N9831, and BCIRG006. Age ≥ 60 years was associated with increased risk of shorter time to first symptomatic cardiac event in study BCIRG-006 (based on 35 cardiac events in 2066 patients) (for the definition of cardiac events in each study see 7 WARNINGS AND PRECAUTIONS, Cardiotoxicity, Early Breast Cancer). Limitations in data collection and differences in study design of the 4 studies of trastuzumab in adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of trastuzumab in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (as measured by ORR, TTP, OS, and DFS) of trastuzumab treatment in older patients differ from those observed in patients <65 years of age, for either treatment of metastatic disease or adjuvant treatment of EBC.

In ToGA (BO18255) study in MGC, of the 294 patients treated with trastuzumab, 108 (37%) were 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or effectiveness were observed.

The risk of hematologic toxicities (leukopenia and thrombocytopenia) may be increased in geriatric patients.

Data suggest that the disposition of trastuzumab is not altered based on age (see 10 CLINICAL PHARMACOLOGY: Pharmacokinetics). In clinical studies, geriatric patients (≥ 65 years of age) did not receive reduced doses of trastuzumab.

Metastatic Gastric Cancer (MGC)

OGIVRI should only be administered to patients with MGC whose tumours have HER2 overexpression as determined by validated immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) testing. The testing should be done in experienced laboratories that have validated the test.

Patients are eligible for OGIVRI treatment if they demonstrate strong HER2 protein overexpression, defined by a 3+ score by IHC, or a 2+ score by IHC and a positive FISH result.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The adverse drug reaction profiles reported in clinical studies that compared OGIVRI to the reference

biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Early Breast Cancer (EBC)

HERA
(adjuvant sequential: use of OGIVRI following surgery and after chemotherapy)

Please see 7 WARNINGS AND PRECAUTIONS: Cardiovascular/Cardiotoxicity/Early Breast Cancer - Tables 5a, Table 5b, Table 6a and Table 6b for a description of the absolute numbers and rates of cardiac endpoints in HERA as well as the median time to return to baseline LVEF/ stabilizations of LVEF in the HERA trial.

The HERA trial is a randomised, open label study in patients with HER2 positive EBC. Table 12 displays adverse events which were reported after 8 years of median follow up in ≥ 1% of patients, by study treatment.

Table 12
Adverse Events Reported in ≥ 1% of HERA Study Patients, by Study Treatment
Final Analysis After 8 years of Median Follow Up
According to MedDRA v 15.0 Classification

Adverse Event Term	Observation Only	Trastuzumab 1 year
	N = 1744	N = 1682
	No. (%)	No. (%)
Blood and Lymphatic System Disorders		
Anemia	4 (<1)	15 (<1)
Cardiac Disorders		
Cardiac Failure Congestive	19 (1)	93 (6)*
Palpitations	20 (1)	73 (4)
Tachycardia	5 (<1)	25 (1)
Ear and Labyrinth Disorders		
Vertigo	14 (<1)	33 (2)
Tinnitus	6 (<1)	7 (<1)
Eye Disorders		
Conjunctivitis	7 (<1)	21 (1)
Vision blurred	6 (<1)	16 (<1)
Lacrimation Increased	1 (<1)	12 (<1)

Table 12 Adverse Events Reported in ≥ 1% of HERA Study Patients, by Study Treatment Final Analysis After 8 years of Median Follow Up According to MedDRA v 15.0 Classification		
Adverse Event Term	**Observation Only**	**Trastuzumab 1 year**
	N = 1744	**N = 1682**
	No. (%)	**No. (%)**
Gastrointestinal Disorders		
Diarrhea	23 (1)	156 (9)
Nausea	37 (2)	134 (8)
Vomiting	17 (<1)	76 (5)
Constipation	27 (2)	55 (3)
Abdominal Pain	25 (1)	60 (4)
Abdominal Pain Upper	30 (2)	45 (3)
Dyspepsia	14 (<1)	42 (2)
Stomatitis	1 (<1)	33 (2)
Gastritis	17 (<1)	27 (2)
Hemorrhoids	8 (<1)	18 (1)
Mouth Ulceration	2 (<1)	13 (<1)
General Disorders and Administration Site Conditions		
Fatigue	83 (5)	198 (12)
Edema Peripheral	64 (4)	114 (7)
Pyrexia	12 (<1)	119 (7)
Asthenia	42 (2)	102 (6)
Chills	1 (<1)	101 (6)
Chest Pain	36 (2)	65 (4)
Influenza Like Illness	7 (<1)	51 (3)
Pain	24 (1)	23 (1)
Spinal Pain	21 (1)	21 (1)
Chest Discomfort	6 (<1)	27 (2)
Axillary Pain	17 (<1)	18 (1)
Edema	10 (<1)	23 (1)
Mucosal Inflammation	1 (<1)	18 (1)
Malaise	1 (<1)	18 (1)
Immune System Disorders		
Seasonal Allergy	6 (<1)	14 (<1)
Infections and Infestations#		
Nasopharyngitis	65 (4)	192 (11)
Influenza	17 (<1)	95 (6)
Upper Respiratory Tract Inflection	31 (2)	53 (3)
Urinary Tract Infection	19 (1)	54 (3)
Rhinitis	11 (<1)	44 (3)

Table 12 Adverse Events Reported in ≥ 1% of HERA Study Patients, by Study Treatment Final Analysis After 8 years of Median Follow Up According to MedDRA v 15.0 Classification		
Adverse Event Term	**Observation Only**	**Trastuzumab 1 year**
	N = 1744	**N = 1682**
	No. (%)	**No. (%)**
Bronchitis	25 (1)	36 (2)
Cystitis	15 (<1)	28 (2)
Sinusitis	7 (<1)	36 (2)
Pharyngitis	12 (<1)	33 (2)
Herpes Zoster	14 (<1)	31 (2)
Lower Respiratory Tract Infection	14 (<1)	17 (1)
Gastroenteritis	10 (<1)	9 (<1)
Oral Herpes	5 (<1)	15 (<1)
Cellulitis	6 (<1)	14 (<1)
Vaginal Infection	10 (<1)	13 (<1)
Ear Infection	6 (<1)	9 (<1)
Localised Infection	-	18 (1)
Injury, Poisoning and Procedural Complications		
Confusion	12 (<1)	13 (<1)
Investigations		
Ejection Fraction Decreased	11 (<1)	64 (4)
Weight Increased	23 (1)	42 (2)
Weight Decreased	10 (<1)	10 (<1)
Metabolism and Nutrition Disorders		
Decreased Appetite	17 (<1)	25 (1)
Hypercholesterolemia	15 (<1)	16 (<1)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	148 (8)	223 (13)
Back Pain	105 (6)	145 (9)
Pain in Extremity	73 (4)	94 (6)
Musculoskeletal Pain	66 (4)	75 (4)
Myalgia	28 (2)	86 (5)
Muscle Spasms	13 (<1)	68 (4)
Bone Pain	31 (2)	54 (3)
Musculoskeletal Chest Pain	37 (2)	43 (3)
Osteoporosis	29 (2)	30 (2)
Neck Pain	18 (1)	29 (2)
Osteoarthritis	18 (1)	28 (2)
Osteopenia	12 (<1)	19 (1)
Musculoskeletal Stiffness	8 (<1)	14 (<1)

Table 12 Adverse Events Reported in ≥ 1% of HERA Study Patients, by Study Treatment Final Analysis After 8 years of Median Follow Up According to MedDRA v 15.0 Classification		
Adverse Event Term	**Observation Only**	**Trastuzumab 1 year**
	N = 1744	**N = 1682**
	No. (%)	**No. (%)**
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)		
Contralateral Breast Cancer	10 (<1)	23 (1)
Uterine Letomyoma	7 (<1)	9 (<1)
Nervous System Disorders		
Headache	73 (4)	199 (12)
Dizziness	39 (2)	80 (5)
Paraesthesia	21 (1)	42 (2)
Hypoaesthesia	15 (<1)	25 (1)
Lethargy	8 (<1)	20 (1)
Migraine	3 (<1)	15 (<1)
Peripheral Sensory Neuropathy	6 (<1)	14 (<1)
Pregnancy, Puerperium and Perinatal Conditions		
Pregnancy	11 (<1)	22 (1)
Psychiatric Disorders		
Depression	59 (3)	87 (5)
Insomnia	49 (3)	94 (6)
Anxiety	32 (2)	56 (3)
Sleep Disorder	5 (<1)	13 (<1)
Renal and Urinary Disorders		
Dysuria	3 (<1)	20 (1)
Reproductive System and Breast Disorders		
Breast Pain	26 (1)	36 (2)
Vaginal Haemorrhage	20 (1)	23 (1)
Vulvovaginal Dryness	16 (<1)	23 (1)
Breast Mass	22 (1)	17 (1)
Vaginal Discharge	9 (<1)	15 (<1)
Endometrial Hyperplasia	13 (<1)	17 (1)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	61 (3)	116 (7)
Dyspnoea	46 (3)	81 (5)
Oropharnygeal Pain	14 (<1)	40 (2)
Epistaxis	3 (<1)	29 (2)
Dyspnoea Exertional	16 (<1)	32 (2)
Rhinorrhoea	5 (<1)	27 (2)
Nasal Dryness	1 (<1)	25 (1)
Asthma	7 (<1)	9 (<1)

Table 12 Adverse Events Reported in ≥ 1% of HERA Study Patients, by Study Treatment Final Analysis After 8 years of Median Follow Up According to MedDRA v 15.0 Classification		
Adverse Event Term	**Observation Only**	**Trastuzumab 1 year**
	N = 1744	**N = 1682**
	No. (%)	**No. (%)**
Skin and Subcutaneous Tissue Disorders		
Rash	25 (1)	98 (6)
Onychoclasis	2 (<1)	53 (3)
Nail Disorder	2 (<1)	52 (3)
Pruritus	14 (<1)	58 (3)
Dry Skin	4 (<1)	22 (1)
Erythema	8 (<1)	39 (2)
Alopecia	6 (<1)	18 (1)
Scar Pain	18 (1)	21 (1)
Eczema	9 (<1)	19 (1)
Hyperhidrosis	10 (<1)	17 (1)
Urticaria	4 (<1)	13 (<1)
Acne	3 (<1)	17 (1)
Vascular Disorders		
Hot Flush	129 (7)	163 (10)
Hypertension	61 (3)	104 (6)
Lymphoedema	69 (4)	80 (5)
Flushing	10 (<1)	14 (<1)
Hypotension	4 (<1)	14 (<1)

Multiple occurrences of the same adverse even in one individual counted only once.
*69 out of the total 93 Cardiac Failure Congestive events reported in the 1-year trastuzumab arm occurred within 365 days from randomization.
Serious adverse reactions of cellulitis and erysipelas were also reported in the HERA study.

In HERA, after a median follow-up of 12 months, 1 observation and 10 trastuzumab treated patients experienced hypersensitivity. Eight out of the 10 events were considered related to trastuzumab treatment.

In total, in the trastuzumab 1 year arm, 124 patients (7%) withdrew from trastuzumab treatment due to adverse events, and 2 patients (<1%) withdrew from the post-treatment follow-up phase due to adverse events, based on the withdrawal criteria in the HERA study protocol.

Please see Tables 6a and 6b in 7 WARNINGS AND PRECAUTIONS: Cardiovascular, Cardiotoxicity, Early Breast Cancer for information on the median time to return to baseline LVEF and stabilizations of LVEF after 8 years of median follow up in the HERA trial.

Joint Analysis –NSABP Study B-31 and NCCTG Study N9831
(adjuvant concurrent: use of Trastuzumab in combination with paclitaxel)

Cardiac failure/dysfunction, pulmonary events, and exacerbation of chemotherapy-induced neutropenia were the most serious adverse reactions in the two randomized, controlled adjuvant breast cancer studies (NSABP study B-31 and NCCTG study N9831, see 14 CLINICAL STUDIES). Please refer to 7 WARNINGS AND PRECAUTIONS section for detailed description of these reactions and Table 7 for a description of the incidence and type of cardiac events seen in the Joint Analysis.

Adverse events according to the National Cancer Institute - Common Terminology Criteria NCI-CTC v 2.0 classification occurring at a frequency of > 1% for NSABP-B31 and NCCTG N9831, are summarized in Tables 13 and 14 respectively.

Table 13
Adverse Events of Any Grade with Incidence ≥ 1% in Study B-31
(Final Analysis after Median Follow-up of 8.1 years in the AC - T+H Group) According to NCI-CTC v 2.0 Classification

Adverse Event Term[a]	AC - T (n = 885)			AC - T + H (n = 1030)		
	Any Grade	Grades 3–4	Grade 5	Any Grade	Grades 3–4	Grade 5
Allergy/immunology						
Allergic reaction*	33 (3.7%)	10 (1.1%)	(0.0%)	35 (3.4%)	12 (1.2%)	(0.0%)
Allergic rhinitis	11 (1.2%)	(0.0%)	(0.0%)	29 (2.8%)	(0.0%)	(0.0%)
Blood/bone marrow						
Hemoglobin (HGB)*	156 (17.6%)	27 (3.1%)	(0.0%)	209 (20.3%)	33 (3.2%)	(0.0%)
Leukocytes (total WBC)	152 (17.2%)	95 (10.7%)	(0.0%)	201 (19.5%)	103 (10.0%)	(0.0%)
Lymphopenia	43 (4.9%)	27 (3.1%)	(0.0%)	54 (5.2%)	31 (3.0%)	(0.0%)
Neutrophils/ granulocytes	112 (12.7%)	88 (9.9%)	(0.0%)	134 (13.0%)	107 (10.4%)	(0.0%)
Platelets	22 (2.5%)	11 (1.2%)	(0.0%)	23 (2.2%)	12 (1.2%)	(0.0%)
Cardiovascular (general)						
Cardiac-left ventricular function*	47 (5.3%)	7 (0.8%)	(0.0%)	151 (14.7%)	35 (3.4%)	(0.0%)
Edema	26 (2.9%)	1 (0.1%)	(0.0%)	50 (4.9%)	(0.0%)	(0.0%)
Hypertension	6 (0.7%)	4 (0.5%)	(0.0%)	25 (2.4%)	17 (1.7%)	(0.0%)
Thrombosis/embolism*	24 (2.7%)	23 (2.6%)	(0.0%)	39 (3.8%)	35 (3.4%)	(0.0%)
Constitutional symptoms						
Fatigue*	323 (36.5%)	54 (6.1%)	(0.0%)	426 (41.4%)	58 (5.6%)	(0.0%)
Fever (in the absence of neutropenia)*	21 (2.4%)	2 (0.2%)	(0.0%)	38 (3.7%)	7 (0.7%)	(0.0%)
Sweating (diaphoresis)	10 (1.1%)	(0.0%)	(0.0%)	19 (1.8%)	(0.0%)	(0.0%)
Weight gain	5 (0.6%)	1 (0.1%)	(0.0%)	14 (1.4%)	3 (0.3%)	(0.0%)
Dermatology/skin						
Alopecia	285 (32.2%)	3 (0.3%)	(0.0%)	354 (34.4%)	2 (0.2%)	(0.0%)

Table 13
Adverse Events of Any Grade with Incidence ≥ 1% in Study B-31
(Final Analysis after Median Follow-up of 8.1 years in the AC - T+H Group) According to NCI-CTC v 2.0 Classification

Adverse Event Term[a]	AC - T (n = 885)			AC - T + H (n = 1030)		
	Any Grade	Grades 3–4	Grade 5	Any Grade	Grades 3–4	Grade 5
Nail changes	10 (1.1%)	(0.0%)	(0.0%)	30 (2.9%)	1 (0.1%)	(0.0%)
Pruritus	18 (2.0%)	1 (0.1%)	(0.0%)	18 (1.7%)	3 (0.3%)	(0.0%)
Radiation dermatitis	20 (2.3%)	3 (0.3%)	(0.0%)	31 (3.0%)	10 (1.0%)	(0.0%)
Rash/desquamation*	88 (9.9%)	12 (1.4%)	(0.0%)	130 (12.6%)	6 (0.6%)	(0.0%)
Skin-other	14 (1.6%)	2 (0.2%)	(0.0%)	25 (2.4%)	2 (0.2%)	(0.0%)
Wound-infectious	7 (0.8%)	4 (0.5%)	(0.0%)	15 (1.5%)	8 (0.8%)	(0.0%)
Endocrine						
Hot flashes/flushes	157 (17.7%)	2 (0.2%)	(0.0%)	197 (19.1%)	(0.0%)	(0.0%)
Gastrointestinal						
Anorexia*	71 (8.0%)	12 (1.4%)	(0.0%)	64 (6.2%)	11 (1.1%)	(0.0%)
Constipation*	81 (9.2%)	7 (0.8%)	(0.0%)	123 (11.9%)	5 (0.5%)	(0.0%)
Dehydration	22 (2.5%)	7 (0.8%)	(0.0%)	28 (2.7%)	5 (0.5%)	(0.0%)
Diarrhea without prior colostomy*	83 (9.4%)	23 (2.6%)	(0.0%)	112 (10.9%)	26 (2.5%)	(0.0%)
Dyspepsia	46 (5.2%)	2 (0.2%)	(0.0%)	51 (5.0%)	2 (0.2%)	(0.0%)
GI-other	14 (1.6%)	2 (0.2%)	(0.0%)	24 (2.3%)	4 (0.4%)	(0.0%)
Nausea*	309 (34.9%)	70 (7.9%)	(0.0%)	356 (34.6%)	69 (6.7%)	(0.0%)
Stomatitis/pharyngitis*	151 (17.1%)	6 (0.7%)	(0.0%)	179 (17.4%)	10 (1.0%)	(0.0%)
Taste disturbance (dysgeusia)	13 (1.5%)	(0.0%)	(0.0%)	25 (2.4%)	(0.0%)	(0.0%)
Vomiting*	232 (26.2%)	66 (7.5%)	(0.0%)	247 (24.0%)	64 (6.2%)	(0.0%)
Hemorrhage						
Vaginal bleeding	4 (0.5%)	(0.0%)	(0.0%)	18 (1.8%)	(0.0%)	(0.0%)
Hepatic						
SGOT (AST) (serum glutamic oxaloacetic transaminase)*	18 (2.0%)	6 (0.7%)	(0.0%)	27 (2.6%)	5 (0.5%)	(0.0%)
SGPT (ALT) serum glutamic pyruvic transaminase *	26 (2.9%)	5 (0.6%)	(0.0%)	33 (3.2%)	5 (0.5%)	(0.0%)
Infection/febrile neutropenia						
Febrile neutropenia*	42 (4.7%)	42 (4.7%)	(0.0%)	39 (3.8%)	39 (3.8%)	(0.0%)
Infection*	246 (27.8%)	124 (14.0%)	3 (0.3%)	341 (33.1%)	140 (13.6%)	(0.0%)
Lymphatics						
Lymphatics	9 (1.0%)	(0.0%)	(0.0%)	25 (2.4%)	(0.0%)	(0.0%)
Metabolic/laboratory						
Hyperglycemia	118 (13.3%)	46 (5.2%)	(0.0%)	139 (13.5%)	49 (4.8%)	(0.0%)

Table 13
Adverse Events of Any Grade with Incidence ≥ 1% in Study B-31
(Final Analysis after Median Follow-up of 8.1 years in the AC - T+H Group) According to NCI-CTC v 2.0 Classification

Adverse Event Term[a]	AC - T (n = 885)			AC - T + H (n = 1030)		
	Any Grade	Grades 3–4	Grade 5	Any Grade	Grades 3–4	Grade 5
Hypoglycemia	6 (0.7%)	2 (0.2%)	(0.0%)	12 (1.2%)	6 (0.6%)	(0.0%)
Musculoskeletal						
Joint, muscle, bone-other	11 (1.2%)	2 (0.2%)	(0.0%)	19 (1.8%)	2 (0.2%)	(0.0%)
Neurology						
Ataxia (incoordination)	1 (0.1%)	(0.0%)	(0.0%)	11 (1.1%)	2 (0.2%)	(0.0%)
Dizziness/lightheadedness	30 (3.4%)	5 (0.6%)	(0.0%)	36 (3.5%)	6 (0.6%)	(0.0%)
Insomnia	35 (4.0%)	2 (0.2%)	(0.0%)	60 (5.8%)	6 (0.6%)	(0.0%)
Mood alteration-anxiety/agitation	44 (5.0%)	5 (0.6%)	(0.0%)	46 (4.5%)	9 (0.9%)	(0.0%)
Mood alteration-depression	56 (6.3%)	10 (1.1%)	(0.0%)	71 (6.9%)	11 (1.1%)	(0.0%)
Neuropathy-motor*	45 (5.1%)	17 (1.9%)	(0.0%)	51 (5.0%)	16 (1.6%)	(0.0%)
Neuropathy-sensory*	203 (22.9%)	59 (6.7%)	(0.0%)	235 (22.8%)	43 (4.2%)	(0.0%)
Syncope (fainting)	8 (0.9%)	8 (0.9%)	(0.0%)	12 (1.2%)	12 (1.2%)	(0.0%)
Ocular/visual						
Dry Eye	13 (1.5%)	(0.0%)	(0.0%)	9 (0.9%)	(0.0%)	(0.0%)
Tearing (watery eyes)	6 (0.7%)	(0.0%)	(0.0%)	12 (1.2%)	(0.0%)	(0.0%)
Vision-blurred vision	11 (1.2%)	(0.0%)	(0.0%)	22 (2.1%)	(0.0%)	(0.0%)
Pain						
Abdominal pain or cramping	25 (2.8%)	12 (1.4%)	(0.0%)	24 (2.3%)	6 (0.6%)	(0.0%)
Arthralgia (joint pain)*	273 (30.8%)	57 (6.4%)	(0.0%)	329 (31.9%)	68 (6.6%)	(0.0%)
Bone pain	46 (5.2%)	14 (1.6%)	(0.0%)	60 (5.8%)	11 (1.1%)	(0.0%)
Chest pain	14 (1.6%)	4 (0.5%)	(0.0%)	36 (3.5%)	4 (0.4%)	(0.0%)
Headache*	80 (9.0%)	20 (2.3%)	(0.0%)	127 (12.3%)	30 (2.9%)	(0.0%)
Myalgia (muscle pain)*	293 (33.1%)	83 (9.4%)	(0.0%)	362 (35.1%)	65 (6.3%)	(0.0%)
Neuropathic pain	11 (1.2%)	4 (0.5%)	(0.0%)	20 (1.9%)	6 (0.6%)	(0.0%)
Pain-other	50 (5.6%)	10 (1.1%)	(0.0%)	78 (7.6%)	10 (1.0%)	(0.0%)
Pulmonary						
Cough	9 (1.0%)	1 (0.1%)	(0.0%)	32 (3.0%)	2 (0.2%)	(0.0%)
Dyspnea (shortness of breath)	63 (7.1%)	21 (2.4%)	(0.0%)	144 (14.0%)	24 (2.3%)	(0.0%)
Pulmonary-other	7 (0.8%)	3 (0.3%)	(0.0%)	15 (1.5%)	4 (0.4%)	(0.0%)
Renal/genitourinary						
Dysuria (painful urination)	9 (1.0%)	1 (0.1%)	(0.0%)	11 (1.1%)	1 (0.1%)	(0.0%)

Table 13
Adverse Events of Any Grade with Incidence ≥ 1% in Study B-31
(Final Analysis after Median Follow-up of 8.1 years in the AC - T+H Group) According to NCI-CTC v 2.0 Classification

Adverse Event Term[a]	AC - T (n = 885)			AC - T + H (n = 1030)		
	Any Grade	Grades 3–4	Grade 5	Any Grade	Grades 3–4	Grade 5
Urinary frequency/urgency	7 (0.8%)	3 (0.3%)	(0.0%)	11 (1.1%)	2 (0.2%)	(0.0%)
Vaginitiis (not due to infection)	10 (1.1%)	1 (0.1%)	(0.0%)	4 (0.4%)	1 (0.1%)	(0.0%)
Sexual/reproductive function						
Irregular menses (change from baseline)	35 (4.0%)	27 (3.1%)	(0.0%)	44 (4.3%)	37 (3.6%)	(0.0%)
Vaginal dryness	12 (1.4%)	(0.0%)	(0.0%)	26 (2.5%)	1 (0.1%)	(0.0%)

[a] NCIC CTC terminology

A = doxorubicin; C = cyclophosphamide; GI = gastrointestinal; H = trastuzumab; T = paclitaxel; WBC = white blood cell.

Note: Only Grade 3–5 events, treatment-related Grade 2 events, Grade 2–5 cardiac left ventricular dysfunction, and Grade 2–5 dyspnea were collected during and 3 months following protocol treatment.

The term "febrile neutropenia" refers to febrile neutropenia with no evidence of infection; decreased neutrophils were not intended to be collected.

* Adverse event term is itemized on the Adverse Event CRF.

Table 14
Adverse Events of Any Grade with Incidence ≥ 1% in Study N9831
(Final Analysis after Median Follow-up of 8.1 years in the AC - T+H Group) According to NCI-CTC v 2.0 Classification

Adverse Event Term[a]	AC - T (n = 766)			AC - T + H (n = 969)		
	Any Grade	Grades 3–4	Grade 5	Any Grade	Grades 3–4	Grade 5
Allergy/immunology						
Allergic reaction*	9 (1.2%)	9 (1.2%)	(0.0%)	3 (0.3%)	3 (0.3%)	(0.0%)
Blood/bone marrow						
Leukocytes (total WBC)*	59 (7.7%)	58 (7.6%)	1 (0.1%)	82 (8.5%)	82 (8.5%)	(0.0%)
Neutrophils/granulocytes*	209 (27.3%)	208 (27.2%)	1 (0.1%)	286 (29.5%)	286 (29.5%)	(0.0%)
Cardiovascular (arrhythmia)						
Palpitations	12 (1.6%)	(0.0%)	(0.0%)	15 (1.5%)	(0.0%)	(0.0%)
Cardiovascular (general)						
Cardiac-ischemia/infarction*	9 (1.2%)	7 (0.9%)	(0.0%)	13 (1.3%)	7 (0.7%)	(0.0%)
Cardiac-left ventricular function*	73 (9.5%)	1 (0.1%)	(0.0%)	219 (22.6%)	21 (2.2%)	(0.0%)
Edema	8 (1.0%)	(0.0%)	(0.0%)	15 (1.5%)	(0.0%)	(0.0%)
Hypertension	7 (0.9%)	3 (0.4%)	(0.0%)	12 (1.2%)	6 (0.6%)	(0.0%)

Table 14
Adverse Events of Any Grade with Incidence ≥ 1% in Study N9831
(Final Analysis after Median Follow-up of 8.1 years in the AC - T+H Group) According to NCI-CTC v 2.0 Classification

Adverse Event Term[a]	AC - T (n = 766)			AC - T + H (n = 969)		
	Any Grade	Grades 3–4	Grade 5	Any Grade	Grades 3–4	Grade 5
Thrombosis/embolism*	22 (2.9%)	20 (2.6%)	2 (0.3%)	18 (1.9%)	18 (1.9%)	(0.0%)
Constitutional symptoms						
Fatigue*	34 (4.4%)	34 (4.4%)	(0.0%)	41 (4.2%)	41 (4.2%)	(0.0%)
Dermatology/skin						
Nail changes*	50 (6.5%)	(0.0%)	(0.0%)	116 (12.0%)	(0.0%)	(0.0%)
Gastrointestinal						
Diarrhea without prior colostomy*	5 (0.7%)	5 (0.7%)	(0.0%)	33 (3.4%)	33 (3.4%)	(0.0%)
Nausea*	40 (5.2%)	40 (5.2%)	(0.0%)	53 (5.5%)	53 (5.5%)	(0.0%)
Vomiting*	39 (5.1%)	39 (5.1%)	(0.0%)	36 (3.7%)	36 (3.7%)	(0.0%)
Infection/febrile neutropenia						
Febrile neutropenia*	33 (4.3%)	32 (4.2%)	1 (0.1%)	57 (5.9%)	57 (5.9%)	(0.0%)
Infection*	38 (5.0%)	38 (5.0%)	(0.0%)	71 (7.3%)	70 (7.2%)	1 (0.1%)
Metabolic/laboratory						
Hyperglycemia	14 (1.8%)	14 (1.8%)	(0.0%)	9 (0.9%)	9 (0.9%)	(0.0%)
Neurology						
Neuropathy-motor*	38 (5.0%)	8 (1.0%)	(0.0%)	42 (4.3%)	13 (1.3%)	(0.0%)
Neuropathy-sensory*	132 (17.2%)	29 (3.8%)	(0.0%)	174 (18.0%)	46 (4.7%)	(0.0%)
Pain						
Arthralgia (joint pain)*	75 (9.8%)	10 (1.3%)	(0.0%)	133 (13.7%)	18 (1.9%)	(0.0%)
Chest pain	5 (0.7%)	1 (0.1%)	(0.0%)	13 (1.3%)	5 (0.5%)	(0.0%)
Myalgia (muscle pain)*	62 (8.1%)	10 (1.3%)	(0.0%)	110 (11.4%)	10 (1.0%)	(0.0%)
Pulmonary						
Dyspnea (shortness of breath)	3 (0.4%)	3 (0.4%)	(0.0%)	29 (3.0%)	24 (2.5%)	(0.0%)
Pneumonitis/Pulmonary infiltrates*	8 (1.0%)	7 (0.9%)	1 (0.1%)	10 (1.0%)	9 (0.9%)	(0.0%)

[a] NCIC CTC terminology

A = doxorubicin; AE = adverse event; C = cyclophosphamide; H = trastuzumab; T = paclitaxel; WBC = white blood cell.

Note: Only treatment-related Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic toxicities, Grade 1–5 cardiac toxicities, as well as Grade 2–5 arthralgia, myalgia, nail changes, neuropathy–motor, and neuropathy–sensory adverse events were collected during the treatment period. During the post-treatment follow-up period, only Grade 3–5 cardiac ischemia/infarction, thrombosis/embolism, pneumonitis/pulmonary infiltrates, and lymphatic events were collected.

*Adverse event term is itemized on the Adverse Event CRF.

BCIRG-006
(adjuvant concurrent: use of Trastuzumab in combination with docetaxel)

Adverse events according to the National Cancer Institute - Common Terminology Criteria NCI-CTC v 2.0 classification occurring at a frequency of ≥ 1% for study BCIRG-006 are summarized in Table 15. For adverse events that could not be classified according to the NCI-CTC, the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) coding dictionary was used (see Table 16).

Table 15
Adverse Events of Any Grade with Incidence ≥ 1% in Study BCIRG-006
(5 Year Follow Up) According to NCI-CTC v 2.0 Classification

	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
NCI-CTC term	**AC→T (n=1041)**	**AC→T (n=1041)**	**AC→TH (n=1077)**	**AC→TH (n=1077)**	**TCH (n=1056)**	**TCH (n=1056)**
Allergy/immunology						
Allergic reaction/ hypersensitivity (including drug fever)	98 (9.4%)	12 (1.2%)	133 (12.3%)	19 (1.8%)	157 (14.9%)	28 (2.7%)
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	83 (8.0%)	(0.0%)	138 12.8%)	(0.0%)	97 (9.2%)	(0.0%)
Auditory/hearing						
Earache (otalgia)	32 (3.1%)	(0.0%)	30 (2.8%)	(0.0%)	17 (1.6%)	(0.0%)
Inner ear/hearing	26 (2.5%)	1 (0.1%)	33 (3.1%)	(0.0%)	34 (3.2%)	1 (0.1%)
Blood/bone marrow						
Neutrophils/granulocytes (ANC/AGC)	23 (2.2%)	21 (2.0%)	34 (3.2%)	24 (2.2%)	20 (1.9%)	19 (1.8%)
Cardiovascular (general)						
Cardiac left ventricular function	30 (2.9%)	6 (0.6%)	81 (7.5%)	22 (2.0%)	27 (2.6%)	1 (0.1%)
Edema	30 (2.9%)	(0.0%)	37 (3.4%)	(0.0%)	33 (3.1%)	1 (0.1%)
Hypertension	37 (3.6%)	12 (1.2%)	52 (4.8%)	23 (2.1%)	61 (5.8%)	33 (3.1%)
Hypotension	20 (1.9%)	1 (0.1%)	31 (2.9%)	(0.0%)	19 (1.8%)	2 (0.2%)
Pericardial effusion/ pericarditis	14 (1.3%)	(0.0%)	19 (1.8%)	(0.0%)	17 (1.6%)	1 (0.1%)
Phlebitis (superficial)	14 (1.3%)	(0.0%)	22 (2.0%)	(0.0%)	9 (0.9%)	(0.0%)
Thrombosis/embolism	17 (1.6%)	16 (1.5%)	21 (1.9%)	19 (1.8%)	30 (2.8%)	28 (2.7%)
Cardiovascular (arrhythmia)						
Palpitations	73 (7.0%)	(0.0%)	88 (8.2%)	(0.0%)	96 (9.1%)	(0.0%)
Sinus tachycardia	46 (4.4%)	4 (0.4%)	44 (4.1%)	1 (0.1%)	55 (5.2%)	(0.0%)
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	11 (1.1%)	5 (0.5%)	8 (0.7%)	4 (0.4%)	10 (0.9%)	5 (0.5%)
Constitutional symptoms						
Fatigue (lethargy,	858 (82.4%)	70 (6.7%)	905 (84.0%)	80 (7.4%)	879	76 (7.2%)

Table 15 Adverse Events of Any Grade with Incidence ≥ 1% in Study BCIRG-006 (5 Year Follow Up) According to NCI-CTC v 2.0 Classification						
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
NCI-CTC term	**AC→T (n=1041)**	**AC→T (n=1041)**	**AC→TH (n=1077)**	**AC→TH (n=1077)**	**TCH (n=1056)**	**TCH (n=1056)**
malaise, asthenia)					(83.2%)	
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 109/l)	144 (13.8%)	2 (0.2%)	170 (15.8%)	5 (0.5%)	115 (10.9%)	6 (0.6%)
Rigors, chills	53 (5.1%)	(0.0%)	86 (8.0%)	(0.0%)	75 (7.1%)	(0.0%)
Sweating (diaphoresis)	68 (6.5%)	(0.0%)	66 (6.1%)	(0.0%)	72 (6.8%)	(0.0%)
Weight gain	205 (19.7%)	10 (1.0%)	253 (23.5%)	6 (0.6%)	255 (24.1%)	9 (0 .9%)
Weight loss	82 (7.9%)	2 (0.2%)	100 (9.3%)	2 (0.2%)	69 (6.5%)	3 (0.3%)
Dermatology/skin						
Alopecia	1025 (98.5%)	(0.0%)	1060 (98.4%)	(0.0%)	1016 (96.2%)	2 (0.2%)
Bruising (in absence of grade 3 or 4 thrombocytopenia)	17 (1.6%)	(0.0%)	17 (1.6%)	(0.0%)	25 (2.4%)	(0.0%)
Dry skin	74 (7.1%)	(0.0%)	96 (8.9%)	(0.0%)	60 (5.7%)	(0.0%)
Flushing	46 (4.4%)	(0.0%)	56 (5.2%)	(0.0%)	76 (7.2%)	(0.0%)
Hand-foot skin reaction	85 (8.2%)	20 (1.9%)	77 (7.1%)	15 (1.4%)	30 (2.8%)	(0.0%)
Injection site reaction	64 (6.1%)	3 (0.3%)	61 (5.7%)	1 (0.1%)	78 (7.4%)	2 (0.2%)
Nail changes	512 (49.2%)	(0.0%)	472 (43.8%)	(0.0%)	302 (28.6%)	(0.0%)
Pigmentation changes (e.g., vitiligo)	65 (6.2%)	(0.0%)	67 (6.2%)	(0.0%)	48 (4.5%)	(0.0%)
Pruritus	29 (2.8%)	(0.0%)	34 (3.2%)	1 (0.1%)	51 (4.8%)	1 (0.1%)
Radiation dermatitis	187 (18.0%)	5 (0.5%)	192 (17.8%)	9 (0.8%)	242 (22.9%)	8 (0.8%)
Rash/desquamation	295 (28.3%)	18 (1.7%)	369 (34.3%)	14 (1.3%)	348 (33.0%)	9 (0.9%)
Wound- infectious	22 (2.1%)	4 (0.4%)	33 (3.1%)	6 (0.6%)	38 (3.6%)	9 (0.9%)
Wound Non-infectious	6 (0.6%)	(0.0%)	11 (1.0%)	(0.0%)	17 (1.6%)	(0.0%)
Gastrointestinal						
Anorexia	222 (21.3%)	6 (0.6%)	224 (20.8%)	5 (0.5%)	238 (22.5%)	6 (0.6%)
Constipation	396 (38.0%)	8 (0.8%)	389 (36.1%)	15 (1.4%)	351 (33.2%)	6 (0.6%)

Table 15 Adverse Events of Any Grade with Incidence ≥ 1% in Study BCIRG-006 (5 Year Follow Up) According to NCI-CTC v 2.0 Classification						
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
NCI-CTC term	**AC→T (n=1041)**	**AC→T (n=1041)**	**AC→TH (n=1077)**	**AC→TH (n=1077)**	**TCH (n=1056)**	**TCH (n=1056)**
Dehydration	30 (2.9%)	5 (0.5%)	39 (3.6%)	4 (0.4%)	42 (4.0%)	5 (0.5%)
Diarrhea patients without colostomy:	447 (42.9%)	32 (3.1%)	548 (50.9%)	60 (5.6%)	660 (62.5%)	57 (5.4%)
Dyspepsia/ heartburn	205 (19.7%)	5 (0.5%)	262 (24.3%)	3 (0.3%)	254 (24.1%)	5 (0.5%)
Dysphagia, esophagitis, odynophagia (painful swallowing)	45 (4.3%)	2 (0.2%)	45 (4.2%)	(0.0%)	37 (3.5%)	1 (0.1%)
Flatulence	19 (1.8%)	(0.0%)	23 (2.1%)	(0.0%)	20 (1.9%)	(0.0%)
Gastritis	17 (1.6%)	(0.0%)	35 (3.2%)	1 (0.1%)	22 (2.1%)	(0.0%)
Mouth dryness	85 (8.2%)	(0.0%)	54 (5.0%)	(0.0%)	37 (3.5%)	(0.0%)
Mucositis	22 (2.1%)	1 (0.1%)	26 (2.4%)	2 (0.2%)	21 (2.0%)	1 (0.1%)
Nausea	911 (87.5%)	62 (6.0%)	946 (87.8%)	61 (5.7%)	864 (81.8%)	51 (4.8%)
Proctitis	29 (2.8%)	(0.0%)	34 (3.2%)	(0.0%)	39 (3.7%)	(0.0%)
Salivary gland changes	11 (1.1%)	(0.0%)	9 (0.8%)	(0.0%)	7 (0.7%)	(0.0%)
Sense of smell	14 (1.3%)	(0.0%)	18 (1.7%)	(0.0%)	8 (0.8%)	(0.0%)
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	681 (65.4%)	37 (3.6%)	717 (66.6%)	31 (2.9%)	562 (53.2%)	15 (1.4%)
Taste disturbance (dysgeusia)	298 (28.6%)	(0.0%)	304 (28.2%)	(0.0%)	320 (30.3%)	(0.0%)
Vomiting	577 (55.4%)	65 (6.2%)	616 (57.2%)	72 (6.7%)	434 (41.1%)	37 (3.5%)
Hemorrhage						
Epistaxis	63 (6.1%)	(0.0%)	140 (13.0%)	(0.0%)	170 (16.1%)	4 (0.4%)
Rectal bleeding/hematochezia	23 (2.2%)	(0.0%)	36 (3.3%)	1 (0.1%)	28 (2.7%)	1 (0.1%)
Vaginal bleeding	34 (3.3%)	2 (0.2%)	24 (2.2%)	2 (0.2%)	24 (2.3%)	1 (0.1%)
Endocrine						
Hot flashes/flushes	356 (34.2%)	1 (0.1%)	379 (35.2%)	2 (0.2%)	349 (33.0%)	(0.0%)
Infection/febrile neutropenia						
Catheter-related infection	18 (1.7%)	7 (0.7%)	30 (2.8%)	14 (1.3%)	26 (2.5%)	8 (0.8%)
Febrile neutropenia (fever of unknown origin	97 (9.3%)	96 (9.2%)	117 (10.9%)	117 (10.9%)	100 (9.5%)	100 (9.5%)

Table 15 Adverse Events of Any Grade with Incidence ≥ 1% in Study BCIRG-006 (5 Year Follow Up) According to NCI-CTC v 2.0 Classification						
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
NCI-CTC term	**AC→T (n=1041)**	**AC→T (n=1041)**	**AC→TH (n=1077)**	**AC→TH (n=1077)**	**TCH (n=1056)**	**TCH (n=1056)**
without clinically or microbiologically documented infection) (ANC < 1.0 x 109/l, fever 38.5°c)						
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia	119 (11.4%)	116 (11.1%)	131 (12.2%)	129 (12.0%)	118 (11.2%)	118 (11.2%)
Infection with unknown ANC	122 (11.7%)	120 (11.5%)	120 (11.1%)	117 (10.9%)	87 (8.2%)	86 (8.1%)
Infection without neutropenia	241 (23.2%)	33 (3.2%)	326 (30.3%)	50 (4.6%)	248 (23.5%)	37 (3.5%)
Lymphatics						
Lymphatics	68 (6.5%)	(0.0%)	71 (6.6%)	3 (0.3%)	81 (7.7%)	2 (0.2%)
Metabolic/laboratory						
Hyperglycemia	80 (7.7%)	18 (1.7%)	81 (7.5%)	12 (1.1%)	79 (7.5%)	20 (1.9%)
Hypokalemia	17 (1.6%)	2 (0.2%)	22 (2.0%)	4 (0.4%)	24 (2.3%)	6 (0.6%)
Hypomagnesemia	5 (0.5%)	(0.0%)	(0.0%)	(0.0%)	12 (1.1%)	1 (0.1%)
Musculoskeletal						
Muscle weakness (not due to neuropathy)	36 (3.5%)	2 (0.2%)	36 (3.3%)	3 (0.3%)	30 (2.8%)	(0.0%)
Neurology						
Cognitive disturbance/ learning problems	10 (1.0%)	(0.0%)	8 (0.7%)	(0.0%)	3 (0.3%)	(0.0%)
Confusion	10 (1.0%)	(0.0%)	9 (0.8%)	2 (0.2%)	6 (0.6%)	(0.0%)
Dizziness/lightheadedness	113 (10.9%)	6 (0.6%)	151 (14.0%)	7 (0.6%)	129 (12.2%)	4 (0.4%)
Insomnia	234 (22.5%)	1 (0.1%)	278 (25.8%)	5 (0.5%)	252 (23.9%)	3 (0.3%)
Memory loss	37 (3.6%)	(0.0%)	34 (3.2%)	1 (0.1%)	31 (2.9%)	1 (0.1%)
Mood alteration- anxiety agitation	133 (12.8%)	8 (0.8%)	126 11.7%)	5 (0.5%)	101 (9.6%)	4 (0.4%)
Mood alteration- depression	108 (10.4%)	4 (0.4%)	135 (12.5%)	13 (1.2%)	122 (11.6%)	6 (0.6%)
Neuropathy-motor	55 (5.3%)	4 (0.4%)	68 (6.3%)	8 (0.7%)	45 (4.3%)	3 (0.3%)
Neuropathy-sensory	511 (49.1%)	25 (2.4%)	542 (50.3%)	25 (2.3%)	384 (36.4%)	8 (0.8%)

Table 15 Adverse Events of Any Grade with Incidence ≥ 1% in Study BCIRG-006 (5 Year Follow Up) According to NCI-CTC v 2.0 Classification						
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
NCI-CTC term	**AC→T (n=1041)**	**AC→T (n=1041)**	**AC→TH (n=1077)**	**AC→TH (n=1077)**	**TCH (n=1056)**	**TCH (n=1056)**
Syncope (fainting)	20 (1.9%)	20 (1.9%)	20 (1.9%)	20 (1.9%)	19 (1.8%)	19 (1.8%)
Vertigo	16 (1.5%)	(0.0%)	37 (3.4%)	3 (0.3%)	28 (2.7%)	6 (0.6%)
Pain						
Abdominal pain or cramping	184 (17.7%)	7 (0.7%)	215 (20.0%)	8 (0.7%)	237 (22.4%)	8 (0.8%)
Arthralgia (joint pain)	436 (41.9%)	34 (3.3%)	497 (46.1%)	35 (3.2%)	313 (29.6%)	15 (1.4%)
Bone pain	188 (18.1%)	17 (1.6%)	224 (20.8%)	10 (0.9%)	141 (13.4%)	3 (0.3%)
Chest pain (non-cardiac and non-pleuritic)	59 (5.7%)	1 (0.1%)	79 (7.3%)	7 (0.6%)	72 (6.8%)	3 (0.3%)
Headache	307 (29.5%)	11 (1.1%)	316 (29.3%)	16 (1.5%)	304 (28.8%)	7 (0.7%)
Myalgia (muscle pain)	551 (52.9%)	54 (5.2%)	600 (55.7%)	57 (5.3%)	412 (39.0%)	19 (1.8%)
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	18 (1.7%)	1 (0.1%)	16 (1.5%)	2 (0.2%)	10 (0.9%)	1 (0.1%)
Pulmonary						
Cough	189 (18.2%)	3 (0.3%)	204 (18.9%)	3 (0.3%)	143 (13.5%)	(0.0%)
Dyspnea (shortness of breath)	229 (22.0%)	12 (1.2%)	264 (24.5%)	30 (2.8%)	227 (21.5%)	23 (2.2%)
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	10 (1.0%)	1 (0.1%)	12 (1.1%)	1 (0.1%)	11 (1.0%)	1 (0.1%)
Ocular/visual						
Conjunctivitis	94 (9.0%)	5 (0.5%)	112 10.4%)	1 (0.1%)	43 (4.1%)	(0.0%)
Dry eye	44 (4.2%)	(0.0%)	53 (4.9%)	(0.0%)	30 (2.8%)	(0.0%)
Tearing (watery eyes)	213 (20.5%)	(0.0%)	258 (24.0%)	3 (0.3%)	124 (11.7%)	(0.0%)
Vision- blurred vision	35 (3.4%)	(0.0%)	51 (4.7%)	2 (0.2%)	55 (5.2%)	(0.0%)
Renal/genitourinary						
Dysuria (painful urination)	25 (2.4%)	(0.0%)	48 (4.5%)	(0.0%)	56 (5.3%)	1 (0.1%)

Table 15
Adverse Events of Any Grade with Incidence ≥ 1% in Study BCIRG-006
(5 Year Follow Up) According to NCI-CTC v 2.0 Classification

	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
NCI-CTC term	**AC→T (n=1041)**	**AC→T (n=1041)**	**AC→TH (n=1077)**	**AC→TH (n=1077)**	**TCH (n=1056)**	**TCH (n=1056)**
Incontinence	3 (0.3%)	(0.0%)	10 (0.9%)	1 (0.1%)	15 (1.4%)	(0.0%)
Urinary frequency/urgency	26 (2.5%)	(0.0%)	34 (3.2%)	(0.0%)	25 (2.4%)	(0.0%)
Vaginitis (not due to infection)	17 (1.6%)	(0.0%)	16 (1.5%)	(0.0%)	14 (1.3%)	1 (0.1%)
Sexual/reproductive function						
Irregular menses (change from baseline)	372 (35.7%)	283 (27.2%)	349 (32.4%)	262 (24.3%)	383 (36.3%)	283 (26.8%)
Libido	6 (0.6%)	(0.0%)	9 (0.8%)	(0.0%)	11 (1.0%)	(0.0%)
Vaginal dryness	33 (3.2%)	(0.0%)	44 (4.1%)	(0.0%)	49 (4.6%)	(0.0%)

A=doxorubicin; C=cyclophosphamide; H=trastuzumab; T =docetaxel; C (in TCH)=carboplatin
Note: In the BCIRG-006 study, all grade hematological and non-hematological AEs, and cardiac AEs were collected, as well as laboratory data.

Table 16
Adverse Events of Any Grade with Incidence ≥ 1% in Study BCIRG-006
(5 Year Follow Up) According to COSTART Classification

	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
COSTART term	**AC→T (n=1041)**	**AC→T (n=1041)**	**AC→TH (n=1077)**	**AC→TH (n=1077)**	**TCH (n=1056)**	**TCH (n=1056)**
Body as a whole						
Accidental injury	19 (1.8%)	2 (0.2%)	18 (1.7%)	1 (0.1%)	20 (1.9%)	3 (0.3%)
Back pain	83 (8.0%)	3 (0.3%)	133 (12.3%)	12 (1.1%)	97 (9.2%)	5 (0.5%)
Chest pain	13 (1.2%)	1 (0.1%)	14 (1.3%)	(0.0%)	10 (0.9%)	1 (0.1%)
Cyst	13 (1.2%)	1 (0.1%)	12 (1.1%)	1 (0.1%)	13 (1.2%)	1 (0.1%)
Face edema	12 (1.2%)	(0.0%)	16 (1.5%)	(0.0%)	12 (1.1%)	(0.0%)
Fever	32 (3.1%)	7 (0.7%)	30 (2.8%)	2 (0.2%)	22 (2.1%)	4 (0.4%)
Flu syndrome	33 (3.2%)	(0.0%)	33 (3.1%)	(0.0%)	29 (2.7%)	(0.0%)
Injection site pain	23 (2.2%)	(0.0%)	39 (3.6%)	(0.0%)	40 (3.8%)	1 (0.1%)
Neck pain	14 (1.3%)	1 (0.1%)	13 (1.2%)	(0.0%)	16 (1.5%)	(0.0%)
Pain	228 (21.9%)	5 (0.5%)	257 (23.9%)	8 (0.7%)	208 (19.7%)	3 (0.3%)
Cardiac adverse events (body as a whole)						
Chest pain	7 (0.7%)	(0.0%)	16 (1.5%)	(0.0%)	16 (1.5%)	(0.0%)
Cardiac adverse events (cardiovascular system)						
Cardiomegaly	7 (0.7%)	(0.0%)	18 (1.7%)	(0.0%)	9 (0.9%)	(0.0%)

Table 16
Adverse Events of Any Grade with Incidence ≥ 1% in Study BCIRG-006
(5 Year Follow Up) According to COSTART Classification

	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
COSTART term	**AC→T (n=1041)**	**AC→T (n=1041)**	**AC→TH (n=1077)**	**AC→TH (n=1077)**	**TCH (n=1056)**	**TCH (n=1056)**
Cardiovascular disorder	16 (1.5%)	1 (0.1%)	25 (2.3%)	(0.0%)	16 1.5%)	1 (0.1%)
Hemorrhage	19 (1.8%)	(0.0%)	11 (1.0%)	2 (0.2%)	9 (0.9%)	2 (0.2%)
Tachycardia	7 (0.7%)	(0.0%)	18 (1.7%)	(0.0%)	14 (1.3%)	2 (0.2%)
Digestive system						
Anorexia	14 (1.3%)	(0.0%)	12 (1.1%)	(0.0%)	16 (1.5%)	(0.0%)
Dyspepsia	7 (0.7%)	(0.0%)	10 (0.9%)	(0.0%)	17 (1.6%)	(0.0%)
Esophagitis	20 (1.9%)	2 (0.2%)	8 (0.7%)	(0.0%)	12 (1.1%)	(0.0%)
Flatulence	16 (1.5%)	(0.0%)	24 (2.2%)	(0.0%)	22 (2.1%)	(0.0%)
Gum hemorrhage	1 (0.1%)	(0.0%)	14 (1.3%)	(0.0%)	5 (0.5%)	(0.0%)
Rectal disorder	17 (1.6%)	(0.0%)	23 (2.1%)	1 (0.1%)	28 (2.7%)	2 (0.2%)
Hemic and lymphatic system						
Lymphedema	21 (2.0%)	(0.0%)	23 (2.1%)	1 (0.1%)	28 (2.7%)	(0.0%)
Metabolic and nutritional disorders						
Edema	4 (0.4%)	(0.0%)	6 (0.6%)	(0.0%)	13 (1.2%)	(0.0%)
Peripheral edema	349 (33.5%)	4 (0.4%)	395 (36.7%)	4 (0.4%)	346 (32.8%)	2 (0.2%)
Musculoskeletal system						
Arthralgia	19 (1.8%)	(0.0%)	20 (1.9%)	(0.0%)	24 (2.3%)	1 (0.1%)
Joint disorder	9 (0.9%)	(0.0%)	7 (0.6%)	1 (0.1%)	10 (0.9%)	1 (0.1%)
Osteoporosis	6 (0.6%)	(0.0%)	11 (1.0%)	1 (0.1%)	12 (1.1%)	1 (0.1%)
Nervous system						
Hypertonia	6 (0.6%)	(0.0%)	11 (1.0%)	(0.0%)	16 (1.5%)	(0.0%)
Leg cramps	8 (0.8%)	(0.0%)	13 (1.2%)	(0.0%)	7 (0.7%)	(0.0%)
Neuropathy	8 (0.8%)	1 (0.1%)	10 (0.9%)	(0.0%)	9 (0.9%)	2 (0.2%)
Twitching	7 (0.7%)	(0.0%)	13 (1.2%)	(0.0%)	26 (2.5%)	(0.0%)
Respiratory system						
Pharyngitis	71 (6.8%)	(0.0%)	83 (7.7%)	(0.0%)	55 (5.2%)	2 (0.2%)
Rhinitis	111 (10.7%)	1 (0.1%)	142 (13.2%)	1 (0.1%)	108 (10.2%)	(0.0%)
Sinusitis	18 (1.7%)	(0.0%)	21 (1.9%)	1 (0.1%)	22 (2.1%)	1 (0.1%)
Skin and appendages						
Acne	11 (1.1%)	(0.0%)	28 (2.6%)	(0.0%)	33 (3.1%)	(0.0%)
Herpes simplex	20 (1.9%)	1 (0.1%)	27 (2.5%)	4 (0.4%)	19 (1.8%)	1 (0.1%)
Nail disorder	11 (1.1%)	(0.0%)	5 (0.5%)	(0.0%)	3 (0.3%)	(0.0%)
Pruritus	10 (1.0%)	(0.0%)	16 (1.5%)	1 (0.1%)	16 (1.5%)	(0.0%)
Skin and appendages						
Rash	38 (3.7%)	1 (0.1%)	55 (5.1%)	(0.0%)	42 (4.0%)	1 (0.1%)
Skin disorder	6 (0.6%)	(0.0%)	13 (1.2%)	(0.0%)	11 (1.0%)	(0.0%)

Table 16 Adverse Events of Any Grade with Incidence ≥ 1% in Study BCIRG-006 (5 Year Follow Up) According to COSTART Classification						
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
COSTART term	**AC→T (n=1041)**	**AC→T (n=1041)**	**AC→TH (n=1077)**	**AC→TH (n=1077)**	**TCH (n=1056)**	**TCH (n=1056)**
Special senses						
Abnormal vision	9 (0.9%)	(0.0%)	14 (1.3%)	(0.0%)	13 (1.2%)	(0.0%)
Conjunctivitis	17 (1.6%)	(0.0%)	10 (0.9%)	(0.0%)	2 (0.2%)	(0.0%)
Eye pain	16 (1.5%)	(0.0%)	15 (1.4%)	(0.0%)	16 (1.5%)	(0.0%)
Urogenital system						
Breast pain	53 (5.1%)	(0.0%)	57 (5.3%)	1 (0.1%)	61 (5.8%)	2 (0.2%)
Leukorrhea	16 (1.5%)	(0.0%)	26 (2.4%)	(0.0%)	19 (1.8%)	(0.0%)

The toxicity profile of trastuzumab in all four adjuvant trials appears to be similar. Cardiac dysfunction is the main concern with OGIVRI treatment (see 7 WARNINGS AND PRECAUTIONS).

Metastatic Breast Cancer (MBC)

In clinical trials conducted prior to marketing, a total of 958 patients received trastuzumab alone or in combination with chemotherapy. Data in Table 18 are based on the experience with the recommended dosing regimen for trastuzumab in the randomized controlled clinical trial in 234 patients who received trastuzumab in combination with chemotherapy and the open-label study of trastuzumab as a single agent in 213 patients with HER2-overexpressing MBC.

Table 17 Adverse Events Occurring in ≥ 1% of Patients in Study H0649g (up to First Disease Progression on Study)	
Adverse event term	**Single Agent (n=213)**
Body as a whole	
Abdomen enlarged	3 (1.4%)
Abdominal pain	47 (22.1%)
Accidental injury	12 (5.6%)
Allergic reaction	4 (1.9%)
Ascites	9 (4.2%)
Asthenia	100 (46.9%)
Back pain	44 (20.7%)
Carcinoma	9 (4.2%)
Cellulitis	3 (1.4%)
Chest pain	46 (21.6%)
Chills	76 (35.7%)
Chills and fever	7 (3.3%)
Face edema	4 (1.9%)

Table 17 Adverse Events Occurring in ≥ 1% of Patients in Study H0649g (up to First Disease Progression on Study)	
Adverse event term	**Single Agent (n=213)**
Fever	83 (39.0%)
Flu syndrome	24 (11.3%)
Headache	56 (26.3%)
Infection	42 (19.7%)
Injection site inflammation	3 (1.4%)
Injection site pain	4 (1.9%)
Malaise	7 (3.3%)
Moniliasis	4 (1.9%)
Mucous membrane disorder	4 (1.9%)
Neck pain	11 (5.2%)
Neoplasm	4 (1.9%)
Pain	105 (49.3%)
Pelvic pain	8 (3.8%)
Procedure	4 (1.9%)
Sepsis	3 (1.4%)
Cardiovascular	
Cardiovascular disorder	3 (1.4%)
Congestive heart failure	4 (1.9%)
Heart arrest	3 (1.4%)
Hemorrhage	3 (1.4%)
Hypertension	4 (1.9%)
Hypotension	5 (2.3%)
Migraine	4 (1.9%)
Palpitation	4 (1.9%)
Tachycardia	13 (6.1%)
Vascular disorder	8 (3.8%)
Vasodilatation	16 (7.5%)
Digestive	
Anorexia	28 (13.1%)
Constipation	27 (12.7%)
Diarrhea	57 (26.8%)
Dry mouth	6 (2.8%)
Dyspepsia	17 (8.0%)
Dysphagia	5 (2.3%)
Flatulence	10 (4.7%)
Gastroenteritis	3 (1.4%)
Gastrointestinal disorder	4 (1.9%)
Hepatic failure	4 (1.9%)
Jaundice	6 (2.8%)

Table 17 Adverse Events Occurring in ≥ 1% of Patients in Study H0649g (up to First Disease Progression on Study)	
Adverse event term	**Single Agent (n=213)**
Liver tenderness	7 (3.3%)
Mouth ulceration	4 (1.9%)
Nausea	79 (37.1%)
Nausea and vomiting	16 (7.5%)
Oral moniliasis	4 (1.9%)
Rectal disorder	4 (1.9%)
Stomatitis	9 (4.2%)
Vomiting	60 (28.2%)
Hemic and lymphatic	
Anemia	9 (4.2%)
Ecchymosis	7 (3.3%)
Hypochromic anemia	3 (1.4%)
Leukopenia	7 (3.3%)
Lymphadenopathy	3 (1.4%)
Lymphedema	4 (1.9%)
Metabolic and nutritional disorders	
Dehydration	5 (2.3%)
Edema	17 (8.0%)
Hypercalcemia	3 (1.4%)
Hypokalemia	8 (3.8%)
Hypomagnesemia	3 (1.4%)
Peripheral edema	21 (9.9%)
Serum glutamic pyruvic transaminase (SGPT) increased	3 (1.4%)
Weight gain	4 (1.9%)
Weight loss	7 (3.3%)
Musculoskeletal	
Arthralgia	13 (6.1%)
Bone pain	18 (8.5%)
Joint disorder	3 (1.4%)
Leg cramps	14 (6.6%)
Myalgia	16 (7.5%)
Myasthenia	6 (2.8%)
Nervous	
Abnormal gait	5 (2.3%)
Amnesia	3 (1.4%)
Anxiety	28 (13.1%)
Circumoral paresthesia	3 (1.4%)
Confusion	4 (1.9%)

Table 17 Adverse Events Occurring in ≥ 1% of Patients in Study H0649g (up to First Disease Progression on Study)	
Adverse event term	**Single Agent (n=213)**
Convulsion	4 (1.9%)
Depression	16 (7.5%)
Dizziness	28 (13.1%)
Hypertonia	9 (4.2%)
Insomnia	35 (16.4%)
Nervousness	6 (2.8%)
Neuropathy	4 (1.9%)
Paralysis	3 (1.4%)
Paresthesia	19 (8.9%)
Peripheral neuritis	4 (1.9%)
Somnolence	15 (7.0%)
Speech disorder	3 (1.4%)
Thinking abnormal	3 (1.4%)
Tremor	4 (1.9%)
Vertigo	3 (1.4%)
Respiratory	
Asthma	13 (6.1%)
Bronchitis	7 (3.3%)
Cough increased	60 (28.2%)
Dyspnea	49 (23.0%)
Epistaxis	12 (5.6%)
Laryngitis	3 (1.4%)
Lung disorder	17 (8.0%)
Pharyngitis	28 (13.1%)
Pleural effusion	19 (8.9%)
Pneumonia	3 (1.4%)
Pneumothorax	4 (1.9%)
Rhinitis	33 (15.5%)
Sinusitis	25 (11.7%)
Voice alteration	6 (2.8%)
Skin and appendages	
Acne	4 (1.9%)
Alopecia	3 (1.4%)
Dry skin	4 (1.9%)
Herpes simplex	5 (2.3%)
Herpes zoster	4 (1.9%)
Nail disorder	4 (1.9%)
Pruritus	24 (11.3%)
Rash	30 (14.1%)

Table 17 Adverse Events Occurring in ≥ 1% of Patients in Study H0649g (up to First Disease Progression on Study)	
Adverse event term	**Single Agent (n=213)**
Skin benign neoplasm	3 (1.4%)
Skin ulcer	3 (1.4%)
Sweating	8 (3.8%)
Urticarial	4 (1.9%)
Special senses	
Abnormal vision	3 (1.4%)
Amblyopia	9 (4.2%)
Conjunctivitis	5 (2.3%)
Diplopia	4 (1.9%)
Ear disorder	5 (2.3%)
Ear pain	5 (2.3%)
Taste perversion	5 (2.3%)
Urogenital	
Breast carcinoma	11 (5.2%)
Breast pain	15 (7.0%)
Dysuria	8 (3.8%)
Hematuria	3 (1.4%)
Urinary frequency	7 (3.3%)
Urinary tract infection	7 (3.3%)
Vaginitis	4 (1.9%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Body as a whole				
Abdomen enlarged	2 (1.4%)	1 (0.7%)	1 (1.1%)	1 (1.1%)
Abdominal pain	33 (23.1%)	25 (18.5%)	31 (34.1%)	21 (22.1%)
Abscess	2 (1.4%)	1 (0.7%)	(0.0%)	(0.0%)
Accidental injury	13 (9.1%)	6 (4.4%)	12 (13.2%)	3 (3.2%)
Allergic reaction	6 (4.2%)	3 (2.2%)	7 (7.7%)	2 (2.1%)
Anaphylactoid reaction	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Ascites	3 (2.1%)	6 (4.4%)	(0.0%)	3 (3.2%)
Asthenia	78 (54.5%)	74 (54.8%)	56 (61.5%)	54 (56.8%)
Back pain	39 (27.3%)	21 (15.6%)	33 (36.3%)	29 (30.5%)
Carcinoma	6 (4.2%)	12 (8.9%)	7 (7.7%)	6 (6.3%)
Cellulitis	2 (1.4%)	3 (2.2%)	3 (3.3%)	5 (5.3%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Chest pain	29 ((20.3%)	28 (20.7%)	27 (29.7%)	26 (27.4%)
Chest pain substernal	3 (2.1%)	(0.0%)	(0.0%)	1 (1.1%)
Chills	50 (35.0%)	15 (11.1%)	38 (41.8%)	4 (4.2%)
Chills and fever	3 (2.1%)	1 (0.7%)	5 (5.5%)	4 (4.2%)
Cyst	2 (1.4%)	(0.0%)	1 (1.1%)	(0.0%)
Face edema	2 (1.4%)	(0.0%)	4 (4.4%)	6 (6.3%)
Facial pain	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Fever	80 (55.9%)	45 (33.3%)	43 (47.3%)	22 (23.2%)
Flu syndrome	17 (11.9%)	8 (5.9%)	11 (12.1%)	5 (5.3%)
Headache	63 (44.1%)	42 (31.1%)	33 (36.3%)	27 (28.4%)
Hydrocephalus	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Hypothermia	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Immune system disorder	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Infection	67 (46.9%)	41 (30.4%)	42 (46.2%)	26 (27.4%)
Infection site edema	3 (2.1%)	1 (0.7%)	2 (2.2%)	(0.0%)
Injection site hemorrhage	1 (0.7%)	1 (0.7%)	1 (1.1%)	(0.0%)
Injection site hypersensitivity	1 (0.7%)	(0.0%)	(0.0%)	1 (1.1%)
Injection site inflammation	12 (8.4%)	3 (2.2%)	3 (3.3%)	2 (2.1%)
Injection site pain	8 (5.6%)	4 (3.0%)	4 (4.4%)	5 (5.3%)
Injection site reaction	6 (4.2%)	1 (0.7%)	6 (6.6%)	1 (1.1%)
Lab test abnormal	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Le syndrome	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Malaise	4 (2.8%)	7 (5.2%)	3 (3.3%)	4 (4.2%)
Moniliasis	3 (2.1%)	3 (2.2%)	1 (1.1%)	1 (1.1%)
Mucous membrane disorder	31 (21.7%)	25 (18.5%)	10 (11.0%)	7 (7.4%)
Neck pain	15 (10.5%)	11 (8.1%)	8 (8.8%)	5 (5.3%)
Neck rigidity	3 (2.1%)	(0.0%)	(0.0%)	3 (3.2%)
Necrosis	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Neoplasm	5 (3.5%)	3 (2.2%)	3 (3.3%)	1 (1.1%)
Pain	82 (57.3%)	56 (41.5%)	55 (60.4%)	58 (61.1%)
Pelvic pain	1 (0.7%)	2 (1.5%)	4 (4.4%)	2 (2.1%)
Photosensitivity reaction	2 (1.4%)	(0.0%)	(0.0%)	(0.0%)
Procedure	11 (7.7%)	5 (3.7%)	5 (5.5%)	2 (2.1%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Radiation injury	(0.0%)	2 (1.5%)	1 (1.1%)	2 (2.1%)
Reaction unevaluable	14 (9.8%)	9 (6.7%)	4 (4.4%)	2 (2.1%)
Sepsis	10 (7.0%)	9 (6.7%)	4 (4.4%)	1 (1.1%)
Sudden death	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Angina pectoris	3 (2.14%)	(0.0%)	(0.0%)	(0.0%)
Arrhythmia	1 (0.7%)	2 (1.5%)	(0.0%)	2 (2.1%)
Atrial fibrillation	(0.0%)	1 (0.7%)	1 (1.1%)	2 (2.1%)
Atrial flutter	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Bradycardia	1 ((0.7%)	1 (0.7%)	(0.0%)	(0.0%)
Cardiomegaly	2 (1.4%)	1 (0.7%)	(0.0%)	(0.0%)
Cardiomyopathy	10 (7.0%)	2 (1.5%)	1 (1.1%)	(0.0%)
Cardiovascular disorder	3 (2.1%)	7 (5.2%)	3 (3.3%)	1 (1.1%)
Cerebrovascular accident	1 (0.7%)	1 (0.7%)	(0.0%)	(0.0%)
Congestive heart failure	17 (11.9%)	2 (1.5%)	2 (2.2%)	1 (1.1%)
Deep thrombophlebitis	4 (2.8%)	1 (0.7%)	1 (1.1%)	1 (1.1%)
Electrocardiogram abnormal	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Endocarditis	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Heart arrest	(0.0%)	1 (0.7%)	1 (1.1%)	2 (2.1%)
Heart failure	1(0.7%)	1 (0.7%)	2 (2.2%)	(0.0%)
Hemorrhage	2 (1.4%)	1 (0.7%)	3 (3.3%)	(0.0%)
Hypertension	5 (3.5%)	4 (3.0%)	5 (5.5%)	4 (4.2%)
Hypotension	10 (7.0%)	5 (3.7%)	2 (2.2%)	3 (3.2%)
Left heart failure	14 (9.8%)	7 (5.2%)	5 (5.5%)	(0.0%)
Migraine	(0.0%)	2 (1.5%)	1 (1.1%)	3 (3.2%)
Myocardial ischemia	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Pallor	7 (4.9%)	2 (1.5%)	1 (1.1%)	2 (2.1%)
Palpitation	8 (5.6%)	5 (3.7%)	4 (4.4%)	2 (2.1%)
Pericardial effusion	1 (0.7%)	1 (0.7%)	(0.0%)	(0.0%)
Peripheral vascular disorder	(0.0%	(0.0%)	2 (2.2%)	3 (3.2%)
Phlebitis	3 (2.1%)	1 (0.7%)	1 (1.1%)	1 (1.1%)
Postural hypotension	4 (2.8%)	2 (1.5%)	1 (1.1%)	1 (1.1%)
Pulmonary embolus	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Shock	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Sinus bradycardia	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Syncope	4 (2.8%)	3 (2.2%)	4 (4.4%)	3 (3.2%)
Tachycardia	14 (9.8%)	7 (5.2%)	11 (12.1%)	4 (4.2%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Thrombophlebitis	2 (1.4%)	2 (1.5%)	(0.0%)	(0.0%)
Thrombosis	3 (2.1%)	(0.0%)	2 (2.2%)	(0.0%)
Varicose vein	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Vascular disorder	9 (6.3%)	7 (5.2%)	2 (2.2%)	2 (2.1%)
Vasodilatation	25 (17.5%)	22 (16.3%)	20 (22.0%)	19 (20.0%)
Ventricular fibrillation	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Ventricular tachycardia	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Digestive				
Abnormal stools	2 (1.4%)	1 (0.7%)	2 (2.2%)	(0.0%)
Anorexia	44 (30.8%)	35 (25.9%)	22 (24.2%)	15 (15.8%)
Cheilitis	1 (0.7%)	1 (0.7%)	1 (1.1%)	(0.0%)
Cholelithiasis	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Cirrhosis of liver	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Colitis	3 (2.1%)	(0.0%)	(0.0%)	1 (1.1%)
Constipation	51 (35.7%)	38 (28.1%)	23 (25.3%)	26 (27.4%)
Diarrhea	64 (44.8%)	34 (25.2%)	41 (45.1%)	28 (29.5%)
Dry mouth	9 (6.3%)	12 (8.9%)	7 (7.7%)	5 (5.3%)
Dyspepsia	32 (22.4%)	27 (20.0%)	16 (17.6%)	15 (15.8%)
Dysphagia	11 (7.7%)	5 (3.7%)	3 (3.3%)	2 (2.1%)
Eructation	2 (1.4%)	(0.0%)	(0.0%)	(0.0%)
Esophageal stenosis	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Esophageal ulcer	1 (0.7%)	(0.0%)	(0.0%)	1 (1.1%)
Esophagitis	2 (1.4%)	8 (5.9%)	(0.0%)	2 (2.1%)
Fecal impaction	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Fecal incontinence	(0.0%)	1 (0.7%)	3 (3.3%)	(0.0%)
Flatulence	5 (3.5%)	8 (5.9%)	1 (1.1%)	5 (5.3%)
Gastritis	3 (2.1%)	4 (3.0%)	3 (3.3%)	(0.0%)
Gastroenteritis	2 (1.4%)	5 (3.7%)	2 (2.2%)	(0.0%)
Gastrointestinal carcinoma	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Gastrointestinal disorder	7 (4.9%)	5 (3.7%)	5 (5.5%)	2 (2.1%)
Gastrointestinal hemorrhage	3 (2.1%)	2 (1.5%)	2 (2.2%)	2 (2.1%)
Gingivitis	4 (2.8%)	2 (1.5%)	2 (2.2%)	(0.0%)
Glossitis	3 (2.1%)	2 (1.5%)	(0.0%)	(0.0%)
Gum hemorrhage	3 (2.1%)	(0.0%)	(0.0%)	(0.0%)
Hematemesis	1 (0.7%)	1 (0.7%)	1 (1.1%)	1 (1.1%)
Hepatic failure	(0.0%)	1 (0.7%)	1 (1.1%)	3 (3.2%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Hepatic neoplasia	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Hepatitis	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Hepatomegaly	2 (1.4%)	1 (0.7%)	3 (3.3%)	1 (1.1%)
Hepatosplenomegaly	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Ileus	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Increased appetite	(0.0%)	(0.0%)	2 (2.2%)	1 (1.1%)
Increased salivation	3 (2.1%)	(0.0%)	(0.0%)	(0.0%)
Intestinal obstruction	(0.0%)	1 (0.7%)	(0.0%)	1 (1.1%)
Jaundice	(0.0%)	1 (0.7%)	1 (1.1%)	4 (4.2%)
Liver damage	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Liver function tests abnormal	2 (1.4%)	(0.0%)	(0.0%)	1 (1.1%)
Liver tenderness	1 (0.7%)	2 (1.5%)	2 (2.2%)	1 (1.1%)
Melena	(0.0%)	1 (0.7%)	1 (1.1%)	1 (1.1%)
Mouth ulceration	17 (11.9%)	19 (14.1%)	4 (4.4%)	1 (1.1%)
Nausea	109 (76.2%)	107 (79.3%)	46 (50.5%)	46 (48.4%)
Nausea and vomiting	26 (18.2%)	12 (8.9%)	13 (14.3%)	11 (11.6%)
Oral moniliasis	5 (3.5%)	6 (4.4%)	4 (4.4%)	6 (6.3%)
Periodontal abscess	1 (0.7%)	(0.0%)	3 (3.3%)	(0.0%)
Pseudomembranous colitis	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Rectal disorder	10 (7.0%)	8 (5.9%)	6 (6.6%)	(0.0%)
Rectal hemorrhage	6 (4.2%)	1 (0.7%)	4 (4.4%)	1 (1.1%)
Stomach ulcer	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Stomatitis	43 (30.1%)	42 (31.1%)	9 (9.9%)	7 (7.4%)
Tenesmus	4 (2.8%)	1 (0.7%)	(0.0%)	(0.0%)
Thirst	3 (2.1%)	1 (0.7%)	(0.0%)	1 (1.1%)
Tongue discoloration	1 (0.7%)	(0.0%)	(0.0%)	(0.0%
Tongue disorder	2 (1.4%)	7 (5.2%)	1 (1.1%)	(0.0%)
Tooth discoloration	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Tooth disorder	2 (1.4%)	1 (0.7%)	1 (1.1%)	(0.0%)
Ulcerative stomatitis	1 (0.7%)	2 (1.5%)	(0.0%)	2 (2.1%)
Vomiting	76 (53.1%)	66 (48.9%)	34 (37.4%)	27 (28.4%)
Endocrine				
Cushings syndrome	1 (0.7%)	4 (3.0%)	(0.0%)	1 (1.1%)
Diabetes mellitus	1 (0.7%)	1 (0.7%)	(0.0%)	(0.0%)
Goiter	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Hyperthyroidism	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Hypothyroidism	3 (2.1%)	1 (0.7%)	(0.0%)	(0.0%)
Thyroiditis	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Hemic and lymphatic				
Acute leukemia	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Anemia	50 (35.0%)	34 (25.2%)	13 (14.3%)	9 (9.5%)
Bleeding time increased	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Coagulation disorder	(0.0%)	(0.0%)	1 (1.1%)	1 (1.1%)
Ecchymosis	9 (6.3%)	3 (2.2%)	7 (7.7%)	2 (2.1%)
Hemolytic anemia	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Hypochromic anemia	8 (5.6%)	1 (0.7%)	2 (2.2%)	2 (2.1%)
Leukocytosis	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Leukopenia	74 (51.7%)	45 (33.3%)	22 (24.2%)	16 (16.8%)
Lymphadenopathy	6 (4.2%)	4 (3.0%)	2 (2.2%)	1 (1.1%)
Lymphangitis	1 (0.7%)	(0.0%)	(0.0%)	1 (1.1%)
Lymphedema	8 (5.6%)	4 (3.0%)	3 (3.3%)	1 (1.1%)
Marrow depression	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Myeloid maturation arrest	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Pancytopenia	5 (3.5%)	3 (2.2%)	2 (2.2%)	1 (1.1%)
Petechia	3 (2.1%)	1 (0.7%)	1 (1.1%)	(0.0%)
Purpura	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Thrombocythemia	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Thrombocytopenia	16 (11.2%)	12 (8.9%)	3 (3.3%)	3 (3.2%)
Thromboplastin increased	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Metabolic and nutritional disorders				
Acidosis	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Alkaline phosphatase increased	1 (0.7%)	(0.0%)	(0.0%)	1 (1.1%)
Bilirubinemia	(0.0%)	1 (0.7%)	1 (1.1%)	(0.0%)
Cachexia	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Creatinine increased	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Dehydration	15 (10.5%)	5 (3.7%)	8 (8.8%)	9 (9.5%)
Edema	16 (11.2%)	7 (5.2%)	9 (9.9%)	8 (8.4%)
Electrolyte abnormality	(0.0%)	2 (1.5%)	(0.0%)	(0.0%)
Glucose tolerance decreased	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Gout	1 (0.7%)	1 (0.7%)	(0.0%)	(0.0%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Growth retarded	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Healing abnormal	4 (2.8%)	(0.0%)	1 (1.1%)	2 (2.1%)
Hypercalcemia	(0.0%)	1 (0.7%)	3 (3.3%)	6 (6.3%)
Hypercholesteremia	1 (0.7%)	1 (0.7%)	(0.0%)	(0.0%)
Hyperglycemia	2 (1.4%)	4 (3.0%)	2 (2.2%)	2 (2.14%)
Hyperkalemia	(0.0%)	(0.0%)	3 (3.3%)	2 (2.1%)
Hypernatremia	(0.0%)	(0.0%)	1 (1.1%)	1 (1.1%)
Hyperuricemia	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Hypervolemia	(0.0%)	2 (1.5%)	(0.0%)	(0.0%)
Hypocalcemia	2 (1.4%)	1 (0.7%)	1 (1.1%)	(0.0%)
Hypoglycemia	1 (0.7%)	1 (0.7%)	(0.0%)	3 (3.2%)
Hypokalemia	18 (12.6%)	6 (4.4%)	2 (2.2%)	3 (3.2%)
Hypomagnesemia	3 (2.1%)	1 (0.7%)	1 (1.1%)	(0.0%)
Hyponatremia	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Hypophosphatemia	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Hypoproteinemia	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Lactic dehydrogenase increased	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
NPN increased	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Peripheral edema	29 (20.3%)	23 (17.0%)	20 (22.0%)	19 (20.0%)
SGOT (serum glutamic oxaloacetic transaminase) increased	(0.0%)	1 (0.7%)	2 (2.2%)	3 (3.2%)
serum glutamic pyruvic transaminase (SGPT) increased	(0.0%)	(0.0%)	2 (2.2%)	1 (1.1%)
Weight gain	4 (2.8%)	3 (2.2%)	2 (2.2%)	2 (2.1%)
Weight loss	12 (8.4%)	8 (5.9%)	7 (7.7%)	5 (5.3%)
musculoskeletal				
Arthralgia	12 (8.4%)	13 (9.6%)	34 (37.4%)	20 (21.1%)
Arthritis	3 (2.1%)	(0.0%)	4 (4.4%)	1 (1.1%)
Bone disorder	(0.0%)	1 (0.7%)	1 (1.1%)	(0.0%)
Bone necrosis	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Bone pain	10 (7.0%)	9 (6.7%)	22 (24.2%)	17 (17.9%)
Joint disorder	5 (3.5%)	2 (1.5%)	2 (2.2%)	3 (3.2%)
Leg cramps	6 (4.2%)	3 (2.2%)	5 (5.5%)	2 (2.1%)
Myalgia	19 (13.3%)	17 (12.6%)	35 (38.5%)	34 (35.8%)
Myasthenia	4 (2.8%)	8 (5.9%)	6 (6.6%)	8 (8.4%)
Myopathy	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Myositis	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Osteoporosis	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Pathological fracture	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Rheumatoid arthritis	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Tendinous contracture	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Tenosynovitis	(0.0%)	(0.0%)	2 (2.2%)	(0.0%)
Twitching	1 (0.7%)	1 (0.7%)	(0.0%)	2 (2.1%)
Nervous				
Abnormal dreams	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Abnormal gait	3 (2.1%)	4 (3.0%)	7 (7.7%)	4 (4.2%)
Agitation	2 (1.4%)	2 (1.5%)	(0.0%)	(0.0%)
Amnesia	3 (2.1%)	4 (3.0%)	2 (2.2%)	1 (1.1%)
Anxiety	26 (18.2%)	19 (14.1%)	17 (18.7%)	14 (14.7%)
Ataxia	2 (1.4%)	3 (2.2%)	6 (6.6%)	4 (4.2%)
Brain edema	2 (1.4%)	2 (1.5%)	1 (1.1%)	(0.0%)
Circumoral paresthesia	1 (0.7%)	1 (0.7%)	2 (2.2%)	1 (1.1%)
Coma	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Confusion	8 (5.6%)	(0.0%)	3 (3.3%)	6 (6.3%)
Convulsion	1 (0.7%)	(0.0%)	2 (2.2%)	3 (3.2%)
Depression	28 (19.6%)	16 (11.9%)	11 (12.1%)	12 (12.6%)
Dizziness	34 (23.8%)	24 (17.8%)	20 (22.0%)	23 (24.2%)
Dystonia	2 (1.4%)	(0.0%)	(0.0%)	(0.0%)
Emotional lability	3 (2.1%)	1 (0.7%)	2 (2.2%)	(0.0%)
Euphoria	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Extraphyramidal syndrome	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Foot drop	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Guillain barre syndrome	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Hallucinations	2 (1.4%)	(0.0%)	1 (1.1%)	2 (2.1%)
Hyperesthesia	3 (2.1%)	(0.0%)	2 (2.2%)	3 (3.2%)
Hyperkinesia	2 (1.4%)	(0.0%)	3 (3.3%)	2 (2.1%)
Hypertonia	11 (7.7%)	3 (2.2%)	10 (11.0%)	3 (3.2%)
Hypesthesia	1 (0.7%)	1 (0.7%)	1 (1.1%)	3 (3.2%)
Hypokinesia	(0.0%)	1 (0.7%)	2 (2.2%)	(0.0%)
Incoordination	2 (1.4%)	(0.0%)	1 (1.1%)	3 (3.2%)
Insomnia	42 (29.4%)	21 (15.6%)	23 (25.3%)	12 (12.6%)
Meningitis	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Movement disorder	(0.0%)	3 (2.2%)	1 (1.1%)	1 (1.1%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Nervousness	6 (4.2%)	5 (3.7%)	4 (4.4%)	2 (2.1%)
Neuralgia	3 (2.1%)	1 (0.7%)	1 (1.1%)	2 (2.1%)
Neuropathy	5 (3.5%)	6 (4.4%)	12 (13.2%)	5 (5.3%)
Neurosis	1 (0.7%)	1 (0.7%)	(0.0%)	(0.0%)
Nystagmus	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Paranoid reaction	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Paraplegia	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Parasthesia	24 (16.8%)	15 (11.1%)	43 (47.3%)	37 (38.9%)
Peripheral neuritis	3 (2.1%)	3 (2.2%)	21 (23.1%)	15 (15.8%)
Reflexes decreased	(0.0%)	1 (0.7%)	3 (3.3%)	1 (1.1%)
Reflexes increased	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Sleep disorder	2 (1.4%)	1 (0.7%)	1 (1.1%)	(0.0%)
Somnolence	15 (10.5%)	20 (14.8%)	9 (9.9%)	9 (9.5%)
Speech disorder	3 (2.1%)	1 (0.7%)	2 (2.2%)	2 (2.1%)
Thinking abnormal	5 (3.5%)	1 (0.7%)	3 (3.3%)	1 (1.1%)
Tremor	5 (3.5%)	2 (1.5%)	4 (4.4%)	4 (4.2%)
Vertigo	4 (2.8%)	3 (2.2%)	3 (3.3%)	2 (2.1%)
Weakness	(0.0%)	2 (1.5%)	(0.0%)	1 (1.1%)
Respiratory				
Apnea	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Asthma	6 (4.2%)	5 (3.7%)	5 (5.5%)	2 (2.1%)
Bronchitis	2 (1.4%)	5 (3.7%)	6 (6.6%)	2 (2.1%)
Carcinoma of lung	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Cough increased	62 (43.4%)	38 (28.1%)	38 (41.8%)	21 (22.1%)
Dry nasal	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Dyspnea	60 (42.0%)	33 (24.4%)	25 (27.5%)	25 (26.3%)
Epistaxis	10 (7.0%)	8 (5.9%)	16 (17.6%)	4 (4.2%)
Hemoptysis	1 (0.7%)	(0.0%)	2 (2.2%)	(0.0%)
Hiccup	4 (2.8%)	1 (0.7%)	(0.0%)	(0.0%)
Hyperventilation	3 (2.1%)	1 (0.7%)	1 (1.1%)	(0.0%)
Hypoxia	4 (2.8%)	1 (0.7%)	(0.0%)	5 (5.3%)
Laryngismus	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Laryngitis	(0.0%)	(0.0%)	3 (3.3%)	1 (1.1%)
Larynx edema	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Lung disorder	12 (8.4%)	4 (3.0%)	7 (7.7%)	7 (7.4%)
Lung edema	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Pharyngitis	43 (30.1%)	25 (18.5%)	20 (22.0%)	13 (13.7%)
Pleural disorder	(0.0%)	(0.0%)	2 (2.2%)	1 (1.1%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Pleural effusion	9 (6.3%)	4 (3.0%)	6 (6.6%)	5 (5.3%)
Pneumonia	9 (6.3%)	4 (3.0%)	2 (2.2%)	2 (2.1%)
Pneumothorax	2 (1.4%)	2 (1.5%)	(0.0%)	(0.0%)
Respiratory disorder	3 (2.1%)	(0.0%)	1 (1.1%)	(0.0%)
Rhinitis	31 (21.7%)	21 (15.6%)	20 (22.0%)	5 (5.3%)
Sinusitis	18 (12.6%)	8 (5.9%)	19 (20.9%)	7 (7.4%)
Sputum change	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Sputum increased	1 (0.7%)	2 (1.5%)	(0.0%)	1 (1.1%)
Vocal cord paralysis	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Voice alteration	5 (3.5%)	(0.0%)	4 (4.4%)	3 (3.2%)
Skin and appendages				
Acne	4 (2.8%)	1 (0.7%)	10 (11.0%)	3 (3.2%)
Alopecia	83 (58.0%)	80 (59.3%)	51 (56.0%)	53 (55.8%)
Contact dermatitis	(0.0%)	(0.0%)	2 (2.2%)	1 (1.1%)
Cutaneous moniliasis	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Dry skin	1 (0.7%)	7 (5.2%)	4 (4.4%)	4 (4.2%)
Eczema	2 (1.4%)	(0.0%)	(0.0%)	(0.0%)
Exfoliative dermatitis	2 (1.4%)	1 (0.7%)	3 (3.3%)	2 (2.1%)
Fungal dermatitis	6 (4.2%)	5 (3.7%)	3 (3.3%)	(0.0%)
Furunculosis	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Herpes simplex	10 (7.0%)	11 (8.1%)	11 (12.1%)	3 (3.2%)
Herpes zoster	4 (2.8%)	4 (3.0%)	4 (4.4%)	2 (2.1%)
Maculopapular rash	2 (1.4%)	3 (2.2%)	3 (3.3%)	1 (1.1%)
Melanosis	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Nail disorder	6 (4.2%)	5 (3.7%)	4 (4.4%)	1 (1.1%)
Pruritus	11 (7.7%)	8 (5.9%)	13 (14.3%)	12 (12.6%)
Psoriasis	1 (0.7%)	2 (1.5%)	(0.0%)	(0.0%)
Purpuric rash	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Pustular rash	1 (0.7%)	(0.0%)	(0.0%)	1 (1.1%)
Rash	38 (26.6%)	23 (17.0%)	35 (38.5%)	17 (17.9%)
Seborrhea	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Skin discoloration	7 (4.9%)	3 (2.2%)	2 (2.2%)	1 (1.1%)
Skin disorder	3 (2.1%)	1 (0.7%)	2 (2.2%)	1 (1.1%)
Skin hypertrophy	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Skin melanoma	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Skin nodule	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Skin ulcer	8 (5.6%)	6 (4.4%)	3 (3.3%)	1 (1.1%)
Subcutaneous nodule	1 (0.7%)	1 (0.7%)	(0.0%)	(0.0%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Sweating	13 (9.1%)	10 (7.4%)	7 (7.7%)	3 (3.2%)
Urticaria	2 (1.4%)	(0.0%)	1 (1.1%)	1 (1.1%)
Vesiculobullous rash	1 (0.7%)	1 (0.7%)	3 (3.3%)	1 (1.1%)
Special senses				
Abnormal vision	11 (7.7%)	3 (2.2%)	6 (6.6%)	3 (3.2%)
Amblyopia	8 (5.6%)	5 (3.7%)	5 (5.5%)	6 (6.3%)
Blepharitis	(0.0%)	2 (1.5%)	(0.0%)	(0.0%)
Blindness	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Cataract specified	1 (0.7%)	(0.0%)	1 (1.1%)	(0.0%)
Conjunctivitis	12 (8.4%)	9 (6.7%)	6 (6.6%)	2 (2.1%)
Corneal lesion	(0.0%)	2 (1.5%)	1 (1.1%)	(0.0%)
Deafness	2 (1.4%)	3 (2.2%)	(0.0%)	2 (2.1%)
Diplopia	1 (0.7%)	2 (1.5%)	1 (1.1%)	2 (2.1%)
Dry eyes	3 (2.1%)	1 (0.7%)	1 (1.1%)	1 (1.1%)
Ear disorder	2 (1.4%)	2 (1.5%)	1 (1.1%)	1 (1.1%)
Ear pain	4 (2.8%)	1 (0.7%)	3 (3.3%)	1 (1.1%)
Eye disorder	1 (0.7%)	2 (1.5%)	(0.0%)	(0.0%)
Eye hemorrhage	1 (0.7%)	1 (0.7%)	(0.0%)	1 (1.1%)
Eye pain	1 (0.7%)	2 (1.5%)	2 (2.2%)	(0.0%)
Glaucoma	(0.0%)	1 (0.7%)	1 (1.1%)	(0.0%)
Hyperacusis	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Keratitis	(0.0%)	(0.0%)	1 (1.1%)	(0.0%)
Lacrimation disorder	7 (4.9%)	12 (8.9%)	3 (3.3%)	(0.0%)
Otitis media	3 (2.1%)	2 (1.5%)	3 (3.3%)	(0.0%)
Parosmia	1 (0.7%)	2 (1.5%)	1 (1.1%)	(0.0%)
Photophobia	(0.0%)	2 (1.5%)	1 (1.1%)	(0.0%)
Ptosis	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Retinal artery occlusion	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Retinal disorder	1 (0.7%)	1 (0.7%)	(0.0%)	(0.0%)
Strabismus	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Taste loss	2 (1.4%)	(0.0%)	(0.0%)	3 (3.2%)
Taste perversion	16 (11.2%)	18 (13.3%)	5 (5.5%)	3 (3.2%)
Tinnitus	2 (1.4%)	2 (1.5%)	2 (2.2%)	2 (2.1%)
Vestibular disorder	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Visual field defect	1 (0.7%)	(0.0%)	3 (3.3%)	(0.0%)
Vitreous disorder	2 (1.4%)	(0.0%)	1 (1.1%)	(0.0%)
Urogenital				
Acute kidney failure	(0.0%)	(0.0%)	1 (1.1%)	1 (1.1%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Albuminuria	2 (1.4%)	(0.0%)	1 (1.1%)	(0.0%)
Amenorrhea	2 (1.4%)	5 (3.7%)	1 (1.1%)	(0.0%)
Breast carcinoma	6 (4.2%)	3 (2.2%)	2 (2.2%)	5 (5.3%)
Breast enlargement	1 (0.7%)	1 (0.7%)	(0.0%)	1 (1.1%)
Breast neoplasm	3 (2.14%)	2 (1.5%)	1 (1.1%)	(0.0%)
Breast pain	8 (5.6%)	7 (5.2%)	2 (2.2%)	6 (6.3%)
Cystitis	1 (0.7%)	3 (2.2%)	1 (1.1%)	1 (1.1%)
Dysmenorrhea	(0.0%)	(0.0%)	(0.0%)	2 (2.1%)
Dyspareunia	1 (0.7%)	1 (0.7%)	(0.0%)	(0.0%)
Dysuria	6 (4.2%)	7 (5.2%)	3 (3.3%)	3 (3.2%)
Fibrocystic breast	2 (1.4%)	(0.0%)	(0.0%)	(0.0%)
Hematuria	3 (2.1%)	2 (1.5%)	2 (2.2%)	1 (1.1%)
Hydronephrosis	2 (1.4%)	1 (0.7%)	(0.0%)	(0.0%)
Kidney failure	1 (0.7%)	(0.0%)	(0.0%)	1 (1.1%)
Kidney function abnormal	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Kidney pain	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Leukorrhea	6 (4.2%)	1 (0.7%)	(0.0%)	1 (1.1%)
Mastitis	3 (2.1%)	1 (0.7%)	2 (2.2%)	(0.0%)
Menopause	3 (2.1%)	(0.0%)	(0.0%)	(0.0%)
Menorrhagia	(0.0%)	1 (0.7%)	1 (1.1%)	2 (2.1%)
Menstrual disorder	(0.0%)	(0.0%)	(0.0%)	1 (1.1%)
Metrorrhagia	3 (2.1%)	1 (0.7%)	2 (2.2%)	(0.0%)
Nocturia	1 (0.7%)	1 (0.7%)	(0.0%)	(0.0%)
Oliguria	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Papanicolau smear suspicious	(0.0%)	1 (0.7%)	(0.0%)	(0.0%)
Polyuria	(0.0%)	1 (0.7%)	1 (1.1%)	(0.0%)
Urinary frequency	5 (3.5%)	8 (5.9%)	1 (1.1%)	1 (1.1%)
Urinary incontinence	7 (4.9%)	1 (0.7%)	2 (2.2%)	1 (1.1%)
Urinary retention	2 (1.4%)	(0.0%)	(0.0%)	1 (1.1%)
Urinary tract disorder	1 (0.7%)	1 (0.7%)	1 (1.1%)	1 (1.1%)
Urinary tract infection	19 (13.3%)	9 (6.7%)	17 (18.7%)	13 (13.7%)
Urinary urgency	1 (0.7%)	1 (0.7%)	2 (2.2%)	(0.0%)
Urination impaired	1 (0.7%)	(0.0%)	(0.0%)	(0.0%)
Urine abnormality	2 (1.4%)	1 (0.7%)	1 (1.1%)	(0.0%)
Vaginal hemorrhage	(0.0%)	2 (1.5%)	1 (1.1%)	2 (2.1%)
Vaginal moniliasis	9 (6.3%)	2 (1.5%)	2 (2.2%)	1 (1.1%)

Table 18 Adverse Events Occurring in ≥ 1% of Patients in Study H0648g (up to First Disease Progression on Study)				
Adverse Event Term	**Trastuzumab + AC (N=143)**	**AC Alone (N=135)**	**Trastuzumab + Paclitaxel (N=91)**	**Paclitaxel Alone (N=95)**
Vaginitis	7 (4.9%)	8 (5.9%)	5 (5.5%)	1 (1.1%)

Other Serious Adverse Events
The following other serious adverse events occurred in at least one of the 958 patients treated with trastuzumab in the MBC clinical trials conducted prior to market approval:

Body as a Whole: abdomen enlarged, allergic reaction, anaphylactoid reaction, ascites, carcinoma, cellulitis, chills and fever, death, dermatomyositis, hydrocephalus, necrosis, neoplasm, pelvic pain, radiation injury, sepsis, malaise
Cardiovascular: atrial fibrillation, cardiomyopathy, cardiovascular disorder, cerebrovascular accident, deep thrombophlebitis, heart arrest, heart failure, hemorrhage, hypotension, pericardial effusion, pulmonary embolus, thrombophlebitis, thrombosis, syncope, shock, supraventricular tachycardia, vascular disorder, ventricular arrhythmia
Digestive: colitis, dysphagia, esophageal hemorrhage, esophageal ulcer, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, hematemesis, hepatic coma, hepatic failure, hepatic neoplasia, hepatitis, hepatomegaly, ileus, intestinal obstruction, liver tenderness, pancreatitis, peptic ulcer hemorrhage, pseudomembranous colitis, rectal hemorrhage
Endocrine: hypothyroidism
Hematological: acute leukemia, coagulation disorder, lymphangitis, marrow depression, myeloid maturation arrest, pancytopenia
Metabolic: bilirubinemia, growth retardation, hypercalcemia, hyponatremia, hypoglycemia, hypomagnesemia, weight loss
Musculoskeletal: pathologic fracture, bone necrosis, myopathy
Nervous: ataxia, CNS neoplasia, confusion, convulsion, grand mal convulsion, manic reaction, thinking abnormal
Respiratory: apnea, asthma, hypoxia, laryngitis, lung disorder, lung edema, pleural effusion, pneumonia, pneumothorax, respiratory disorder
Skin: herpes zoster, skin ulceration, dry skin
Special Senses: amblyopia, deafness, retinal artery occlusion
Urogenital: breast carcinoma, breast neoplasm, cervical cancer, hematuria, hemorrhagic cystitis, hydronephrosis, kidney failure, kidney function abnormal, pyelonephritis, vaginal hemorrhage

When using in combination with pertuzumab and docetaxel, consult Product Monographs for pertuzumab and docetaxel for further information on these drugs.

Metastatic Gastric Cancer (MGC)
The ToGA trial (BO18255) is a randomised, open-label multicentre, phase III study of trastuzumab in combination with a fluoropyrimidine (FP) and cisplatin versus chemotherapy alone in patients with HER2 positive MGC. There were only 3.4% of patients in each treatment group with locally advanced cancer. The majority of patients had metastatic disease.

The adverse drug reactions that occurred with the incidence of at least 1% in the ToGA (BO18255) study are presented in Table 19.

Table 19
Adverse Drug Reactions With Incidence Rate ≥ 1% in ToGA (BO18255)

	FP/Cisplatin (FP) N = 290 No. (%)	**Trastuzumab/FP/Cisplatin (H+FP) N = 294 No. (%)**
Blood and lymphatic system disorders		
Neutropenia	165 (57)	157 (53)
Anemia	61 (21)	81 (28)
Thrombocytopenia	33 (11)	47 (16)
Febrile neutropenia	8 (3)	15 (5)
Leukopenia	11 (4)	11 (4)
Cardiac disorders		
Palpitations	2 (<1)	6 (2)
Ear and labyrinth disorders		
Deafness	1 (<1)	8 (3)
Eye disorders		
Lacrimation increased	2 (<1)	5 (2)
Gastrointestinal disorders		
Nausea	184 (63)	197 (67)
Vomiting	134 (46)	147 (50)
Diarrhea	80 (28)	109 (37)
Constipation	93 (32)	75 (26)
Stomatitis	43 (15)	72 (24)
Abdominal pain	42 (14)	46 (16)
Abdominal pain upper	15 (5)	27 (9)
Dyspepsia	16 (6)	18 (6)
Hemorrhoids	3 (1)	5 (2)
Abdominal discomfort	3 (1)	3 (1)
Dry mouth	2 (<1)	4 (1)

Table 19 Adverse Drug Reactions With Incidence Rate ≥ 1% in ToGA (BO18255)		
	FP/Cisplatin (FP) N = 290 No. (%)	**Trastuzumab/FP/Cisplatin (H+FP) N = 294 No. (%)**
General disorders and administration site conditions		
Fatigue	82 (28)	102 (35)
Asthenia	53 (18)	55 (19)
Pyrexia	36 (12)	54 (18)
Mucosal inflammation	18 (6)	37 (13)
Edema	25 (9)	22 (7)
Edema peripheral	12 (4)	17 (6)
Chills	-	23 (8)
Chest pain	4 (1)	8 (3)
Malaise	6 (2)	6 (2)
Pain	4 (1)	5 (2)
Infusion related reaction	-	3 (1)
Hepatobiliary disorders		
Hepatic function abnormal	3 (1)	3 (1)
Infections and infestations		
Nasopharyngitis	17 (6)	37 (13)
Upper respiratory tract infection	10 (3)	15 (5)
Pneumonia	2 (<1)	9 (3)
Cystitis	1 (<1)	5 (2)
Pharyngitis	2 (<1)	4 (1)
Respiratory tract infection	3 (1)	3 (1)
Infection	2 (<1)	3 (1)
Influenza	1 (<1)	4 (1)
Immune system disorders		
Hypersensitivity	3 (1)	6 (2)
Injury, poisoning and procedural complications		
Contusion	2 (<1)	3 (1)
Investigations		
Weight decreased	40 (14)	69 (23)
Hemoglobin decreased	2 (<1)	7 (2)
Platelet count decreased	6 (2)	1 (<1)
Neutrophil count decreased	3 (1)	3 (1)
Metabolism and nutrition disorders		
Anorexia	133 (46)	135 (46)
Hyperkalaemia	3 (1)	-
Musculoskeletal and connective tissue disorders		
Back pain	15 (5)	12 (4)

Table 19 Adverse Drug Reactions With Incidence Rate ≥ 1% in ToGA (BO18255)		
	FP/Cisplatin (FP) N = 290 No. (%)	**Trastuzumab/FP/Cisplatin (H+FP) N = 294 No. (%)**
Pain in extremity	7 (2)	4 (1)
Arthralgia	2 (<1)	7 (2)
Musculoskeletal pain	4 (1)	5 (2)
Myalgia	3 (1)	4 (1)
Muscular weakness	3 (1)	2 (<1)
Muscle spasms	1 (<1)	3 (1)
Musculoskeletal chest pain	3 (1)	1 (<1)
Neck pain	1 (<1)	3 (1)
Nervous system disorders		
Dizziness	28 (10)	31 (11)
Peripheral sensory neuropathy	24 (8)	23 (8)
Neuropathy peripheral	21 (7)	24 (8)
Dysgeusia	14 (5)	28 (10)
Headache	19 (7)	14 (5)
Paraesthesia	9 (3)	9 (3)
Lethargy	8 (3)	6 (2)
Peripheral motor neuropathy	6 (2)	8 (3)
Tremor	5 (2)	3 (1)
Renal and urinary disorders		
Renal impairment	39 (13)	47 (16)
Nephropathy toxic	12 (4)	18 (6)
Renal failure acute	2 (<1)	3 (1)
Renal failure	1 (<1)	3 (1)
Respiratory, thoracic and mediastinal disorders		
Cough	17 (6)	19 (6)
Dyspnea	16 (6)	9 (3)
Epistaxis	9 (3)	13 (4)
Rhinorrhea	2 (<1)	6 (2)
Psychiatric disorders		
Insomnia	20 (7)	24 (8)
Depression	5 (2)	4 (1)
Anxiety	5 (2)	3 (1)
Sleep disorder	3 (1)	2 (<1)
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia syndrome	64 (22)	75 (26)
Alopecia	27 (9)	32 (11)
Rash	12 (4)	16 (5)

Table 19 Adverse Drug Reactions With Incidence Rate ≥ 1% in ToGA (BO18255)		
	FP/Cisplatin (FP) N = 290 No. (%)	**Trastuzumab/FP/Cisplatin (H+FP) N = 294 No. (%)**
Nail disorder	6 (2)	13 (4)
Dry skin	4 (1)	10 (3)
Pruritus	3 (1)	8 (3)
Urticaria	3 (1)	3 (1)
Vascular disorders		
Hypertension	7 (2)	11 (4)
Hypotension	6 (2)	6 (2)

Adverse Events of Special Interest
The following subsections provide additional detail regarding adverse reactions observed in clinical trials in EBC, MBC, MGC, or post-marketing experience.

Cardiac (EBC and MBC)
For a description of cardiac toxicities see 7 WARNINGS AND PRECAUTIONS.

Cardiac (Metastatic Gastric Cancer)
In the ToGA (BO18255) study, at screening, the median LVEF value was 64% (range 48%-90%) in the FP arm and 65% (range 50%-86%) in the FP+H arm. At baseline, a LVEF value of 50% or more (measured by ECHO or MUGA) was required at study entry.

The majority of the LVEF decreases noted in ToGA (BO18255) were asymptomatic, with the exception of one patient in the trastuzumab -containing arm whose LVEF decrease coincided with cardiac failure.

Table 20 Summary of LVEF Change from Baseline ToGA (BO18255)		
LVEF Decrease: Lowest Post-screening Value	**FP/Cisplatin (N = 290) (% of patients in each treatment arm)**	**Trastuzumab/FP/ Cisplatin (N = 294) (% of patients in each treatment arm)**
*LVEF decrease of ≥ 10% to a value of <50%	1.1%	4.6%
Absolute Value <50%	1.1%	5.9%
*LVEF decrease of ≥ 10% to a value of ≥ 50%	11.8%	16.5%

*Only includes patients whose method of assessment at that visit is the same as at their initial assessments (F + C, n = 187 and H +FC, n = 237)

Table 21 Cardiac Adverse Events ToGA (BO18255)		
	FP/Cisplatin (N = 290) (% of patients in each treatment arm)	**Trastuzumab/FP/ Cisplatin (N = 294) (% of patients in each treatment arm)**
Total Cardiac Events	6%	6%
≥ Grade 3 NCI-CTC AE V3.0	*3%	**1%

* 9 patients experienced 9 Events
** 4 patients experienced 5 Events

Infusion-Associated Symptoms
During the first infusion with trastuzumab, chills and/or fever are observed commonly in patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, asthenia and hypertension. The symptoms are usually mild to moderate in severity, and occur infrequently with subsequent infusions of trastuzumab. The symptoms can be treated with an analgesic/antipyretic such as meperidine or acetaminophen, or an antihistamine such as diphenhydramine (see 4 DOSAGE AND ADMINISTRATION). Interruption of the infusion was infrequent. Some adverse reactions to infusions of trastuzumab including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress can be serious and potentially fatal (see 7 WARNINGS AND PRECAUTIONS).

Hematological Toxicity
In a randomized controlled clinical trial in MBC (H0648g), WHO Grade 3 or 4[b] hematological toxicity was observed in 63% of patients treated with trastuzumab and an anthracycline plus cyclophosphamide compared to an incidence of 62% in patients treated with anthracycline/cyclophosphamide combination without trastuzumab. There was an increase in WHO Grade 3 or 4 hematological toxicity in patients treated with the combination of trastuzumab and paclitaxel compared with patients receiving paclitaxel alone (34% vs. 21%).

In a randomized, controlled trial in patients with MBC conducted in the post-marketing setting, hematological toxicity was also increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using NCI-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with trastuzumab plus docetaxel (23% versus 17% for patients treated with docetaxel alone), see 7 WARNINGS AND PRECAUTIONS.

Anemia and Leukopenia
In a randomized controlled clinical trial in MBC, an increased incidence of anemia and leukopenia was observed in the treatment group receiving trastuzumab and chemotherapy (26.9% and 41%), especially in the trastuzumab and AC subgroup (35.0% and 51.7%), compared with the treatment group receiving

[b] WHO Grade 3 Hematological Toxicity: Hemoglobin – 6.5-7.9 g/100 mL, 65-79 g/L, 4.0-4.9 mmol/L, Leukocytes (1000/mm3) – 1.0-1.9, Granulocytes (1000/mm3) – 0.5-0.9, Platelets (1000/mm3) – 25-49.
WHO Grade 4 Hematological Toxicity: Hemoglobin – <6.5 g/100 mL, <65 g/L, <4.0 mmol/L, Leukocytes (1000/mm3) – <1.0, Granulocytes (1000/mm3) – <0.5, Platelets (1000/mm3) – <25.

chemotherapy alone (18.7% and 26.5%). The majority of these cytopenic events were mild or moderate in intensity, reversible, and none resulted in discontinuation of therapy with trastuzumab.

Hematologic toxicity is infrequent following the administration of trastuzumab as a single agent, with an incidence of Grade 3 toxicities for WBC, platelets, hemoglobin all < 1%. No Grade 4 toxicities were observed.

In Study B-31, the incidence of grade 3 to 5 anemia was comparable between the trastuzumab + chemotherapy and the chemotherapy alone arm (3.2% versus 3.1%). The incidence of grade 3 to 5 leukopenia was lower in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone (10.0% versus 10.7%).

In Study N9831, the incidence of grade 3 to 5 anemia was comparable between the trastuzumab + chemotherapy and the chemotherapy alone arm (0.2% versus 0.0%). The incidence of grade 3 to 5 leukopenia was higher in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone (8.5% versus 7.7%).

In Study BCIRG006 the incidence of grade 3 or 4 anemia according to the NCI-CTC v 2.0 classification was comparable between the AC-T arm (4.4%) and the AC-TH arm (4.9%). The TCH arm had a higher incidence of grade 3 or 4 anemia (8.3%) as would be expected from the known toxicity profile of carboplatin. The incidence of grade 3 or 4 leukopenia according to the NCI-CTC v 2.0 classification (52.7% AC-T, 61.5% AC-TH, and 49.9% TCH) was similar in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone.

Thrombocytopenia
In HERA study in EBC, the incidence of thrombocytopenia (0.1% vs. 0.06%) was comparable between patients randomized to trastuzumab + chemotherapy and those randomized to chemotherapy alone.

In study B-31 in EBC, the incidence of thrombocytopenia (2.2% in the AC→TH arm vs. 2.5% in the AC→T arm) was lower in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone.

In study N9831 in EBC, the incidence of thrombocytopenia (0% in the AC→TH arm vs. 0.3% in the AC→T arm) was lower in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone.

In study BCIRG-006 in EBC, the incidence of grade 3 or 4 thrombocytopenia (5.6% in the AC→T arm, 6.8% in the AC→TH arm) was higher in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone. The incidence of grade 3 or 4 thrombocytopenia in the TCH arm (9.8%) was higher as would be expected from the known toxicity profile of carboplatin.

Neutropenia
In HERA study in EBC, the incidence of neutropenia (0.4% vs. 0.2%) was higher in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone.

In Study B-31 in EBC, the incidence of febrile neutropenia (3.8% in the AC→TH arm vs. 4.7% in the AC→T arm) was lower in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone. The incidence of neutropenia (grade 3-5) (10.4% in the AC→TH arm vs. 9.9% in the AC→T arm) was higher in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone.

In Study N9831 in EBC, the incidence of febrile neutropenia (5.9% in the AC→TH arm vs. 4.3% in the AC→T arm) was higher in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone. The incidence of neutropenia (grade 3-5) (29.5% in the AC→TH arm vs. 27.3% in the AC→T arm) was higher in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone.

In Study BCIRG-006, the incidence of febrile neutropenia according to NCI-CTC v 2.0 classification (10.9% in the AC→TH arm, 9.6% in the TCH arm, and 9.3% in the AC→T arm) was comparable between patients randomized to trastuzumab + chemotherapy and with those randomized to chemotherapy alone. The incidence of grade 3 or 4 neutropenia according to the NCI-CTC v 2.0 classification (72.5% in the AC→TH arm, 67.0% in the TCH arm, and 64.6% in the AC→T arm) was comparable between patients randomized to trastuzumab + chemotherapy and with those randomized to chemotherapy alone.

Infection
In three studies in EBC, the incidence of infection was higher in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone (HERA: 29% vs. 12%; B-31: 32% AC→TH vs. 28% AC→T; N9831: 7.3% AC→TH vs. 4.7% AC→T).

In study BCIRG-006 in EBC, the overall incidence of infection (all grades) was higher with the addition of trastuzumab 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 clinical trial in MBC, an increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, was observed in patients receiving trastuzumab in combination with chemotherapy.

In the ToGA (BO18255) study in MGC, infections and infestations were reported in 20 % of patients in the FP arm vs. 32% in the FP+H arm. The major contributors to the higher incidence of infections and infestations in the trastuzumab arm were nasopharyngitis (6% in the FP arm vs. 13% in the FP+H arm) and upper respiratory tract infection (3% vs. 5%).

Hypersensitivity Reactions Including Anaphylaxis and Pulmonary Events
In HERA study, there were 4 cases of interstitial pneumonitis in trastuzumab-treated patients compared to none in the control arm.

The incidence of allergic reactions (chemotherapy alone versus trastuzumab+ chemotherapy: 3.7% versus 3.4% in study B-31 and 1.2% versus 0.3% in study N9831) was comparable between the two treatment arms in both studies.

The incidence of pulmonary events in the original analysis for adjuvant studies (16.1% versus 7.8% in

study B-31 and 4.1% versus 1.4% in study N9831) was higher in patients randomized to trastuzumab + chemotherapy versus chemotherapy alone. The most common pulmonary event was dyspnea. The majority of these events were mild to moderate in intensity. Fatal pulmonary events were reported in 4 patients in the trastuzumab + chemotherapy arm. Only 1 of these patients actually received trastuzumab. The cause of death in these 4 patients was cardio-respiratory arrest, bronchopneumonia, respiratory insufficiency, and pneumonia accompanied by neutropenic fever. Pneumonitis/lung infiltrates were reported in 20 patients who participated in either adjuvant clinical trial. Twelve of these 20 patients had received trastuzumab + chemotherapy. The etiology of pneumonitis/lung infiltrates was possible hypersensitivity/inflammation reaction (n= 4), pneumonia (n=5), radiation therapy toxicity (n=1) ad unknown etiology (n= 2).

In the most recent safety update for the NSABP B-31 and NCCTG N9831 Joint Analysis report (median follow-up of 8.1 years for the AC→TH group and 8.5 years for the AC→T group), the incidences of pulmonary adverse events reported in study B-31 were 17.5% in the AC→T + H group and 8.5% in the AC→T group. Likewise, the incidences of pulmonary adverse events reported in study N9831 were 4.0% in the AC→T + H group and 1.7% in the AC→T group. These results confirm the results from the original analysis, which showed a higher rate of pulmonary events in the trastuzumab patients. Dyspnea remained the most common pulmonary adverse event reported in both studies. Dyspnea can be a result of cardiac left ventricular dysfunction.

Pneumonitis/pulmonary infiltrates were reported in 26 patients in both studies (7 in study B-31, 18 in study N9831) and17 of these patients were in the AC→T + H group. All 7 patients in study B-31 were in the AC→T + H group, and 10 of the patients in study N9831 were in the AC→T + H group. There were 8 patients with this adverse event in study N9831 in the AC→T group.

In study BCIRG006, the incidence of allergic reactions according to the NCI-CTC v 2.0 classification was 9.4%, 12.3% and 14.9% in AC→T, AC→TH and TCH arms, respectively.

Among women receiving trastuzumab for treatment of MBC in a randomized controlled clinical trial, the incidence of pulmonary toxicity was also increased in patients randomized to trastuzumab + chemotherapy compared with those randomized to chemotherapy alone (e.g. dyspnea 36.3% vs. 25.2%, lung disorder 8.1% vs. 4.8%, lung edema 0.4% vs. 0%, pleural effusion 6.4% vs. 3.9%).

In the post-marketing setting, severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary adverse events have been reported. These events include anaphylaxis, angioedema, bronchospasm, hypotension, hypoxia, dyspnea, lung infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome (see 7 WARNINGS AND PRECAUTIONS).

Thrombosis/Embolism

In study BCIRG-006, the incidence of all grades thrombosis/embolism according to the NCI-CTC v 2.0 classification was higher in patients receiving trastuzumab in combination with docetaxel and carboplatin (TCH) (3.2%) compared to the AC→TH group (2.0%) and AC→T group (1.7%). The incidence of thrombosis/embolism, grade 3 (deep vein thrombosis, requiring anticoagulant) and grade 4 (embolic event including pulmonary embolism) combined, was higher in patients receiving trastuzumab in

combination with docetaxel and carboplatin (TCH) (2.7%) compared to the AC→TH group (1.8%) and AC→T group (1.5%).

In study B-31, thrombosis/embolism (all grades) was reported in 3.8% of patients randomized to trastuzumab + chemotherapy versus 2.7% of patients randomized to the chemotherapy alone arm. In study N9831, thrombosis/embolism (all grades) was reported in 1.9% of patients randomized to trastuzumab + chemotherapy versus 2.9% of patients randomized to chemotherapy alone.

The incidence of thrombotic adverse events was also higher in patients receiving trastuzumab and chemotherapy compared to chemotherapy alone in a randomized clinical trial in MBC setting (2.1% vs. 0%).

Diarrhea
Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC (v 2.0) Grade 3-5 diarrhea (2.5% vs. 2.6% [B-31]) and of NCI-CTC Grade 3-5 diarrhea (3.4% vs. 0.7% [N9831]), and of Grade 1-4 diarrhea (7% vs. 1% [HERA]) were commonly higher in patients receiving trastuzumab as compared to controls. In BCIRG006 study, the incidence of Grade 3-4 diarrhea was higher [5.6% AC-TH, 5.4% TCH vs. 3.1% AC-T] and of Grade 1-4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving trastuzumab.

Of patients treated with trastuzumab as a single agent for the treatment of MBC, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in patients receiving trastuzumab in combination with chemotherapy.

In the ToGA (BO18255) study in MGC, 109 patients (37%) participating in the trastuzumab-containing treatment arm versus 80 patients (28%) in the comparator arm experienced any grade diarrhea. Using NCI-CTCAE v3.0 severity criteria, the percentage of patients experiencing grade ≥ 3 diarrhea was 4% in the FP arm vs. 9% in the FP+H arm.

Hepatic and Renal Toxicity
In a randomized controlled clinical trial in MBC, WHO Grade 3 or 4[c] hepatic toxicity was observed in 6% of patients treated with trastuzumab and an anthracycline plus cyclophosphamide compared with an incidence of 8% in patients treated with anthracycline/cyclophosphamide combination without trastuzumab. Hepatic toxicity was less frequently observed among patients receiving trastuzumab and paclitaxel than among patients receiving paclitaxel (7% vs. 15%).

WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of trastuzumab as a single agent. This toxicity was associated with progression of disease in the liver in 60% of these patients.

[c] WHO Grade 3 Hepatic Toxicity: Bilirubin – 5.1-10 x N, Transaminases (ASAT/ALAT) – 5.1-10 x N, Alkaline Phosphatase – 5.1-10 x N, where N is the upper limit of normal of population under study.
WHO Grade 4 Hepatic Toxicity: Bilirubin – >10 x N, Transaminases (ASAT/ALAT) – >10 x N, Alkaline Phosphatase – >10 x N, where N is the upper limit of normal of population under study.

The toxicity grading scale used for HERA, NSABP B-31, NCCTG N9831, and BCIRG-006 studies in the adjuvant treatment of EBC was the NCI-CTC v 2.0. The definitions for grade 3 and 4 elevations of serum creatinine were: grade 3 (> 3.0 to 6.0 X ULN) and grade 4 (> 6.0 X ULN).

The frequencies of grade 3-4 elevated serum creatinine reported in each study are shown, by treatment arm in Table 22.

Table 22
Frequencies of Grade 3-4 Elevated Serum Creatinine in Studies of the Adjuvant Treatment of Early Breast Cancer

Study	Treatment Arm		Grade 3-4 Serum Creatinine Elevation	
	Regimen	N	N	%
HERA	observation only	1708	0	0.0
	1-year trastuzumab	1678	0	0.0
NSABP B-31	AC→T	885	1	0.1
	AC→TH	1030	0	0.0
NCCTG N9831	AC→T	766	0	0.0
	AC→TH	969	0	0.0
BCIRG-006	AC→T	1041	6	0.6
	AC→TH	1077	3	0.3
	TCH	1056	1	0.1

A higher incidence of renal impairment (13% in the FP arm vs. 16% in the FP+H arm) and toxic nephropathy (4% in the FP arm vs. 6% in the FP+H arm) was reported in the ToGA (BO18255) trial in MGC using NCI-CTCAE (v 3.0) criteria. Grade ≥3 renal toxicity was higher in patients receiving trastuzumab than those in the chemotherapy alone arm (3% and 2% respectively).

NCI-CTCAE (v 3.0) grade ≥3 adverse events in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was reported in 1% of patients receiving trastuzumab compared to <1% in patients in the chemotherapy alone arm.

Blood and Lymphatic System Disorders
In the ToGA (BO18255) study in MGC, the total percentages of patients who experienced an AE of ≥ grade 3 NCI-CTC AE v3.0 categorized under the SOC of Blood and Lymphatic System Disorders were 38% in the FP arm and 40% in the FP + H arm.

Table 23
Blood and Lymphatic System Disorders SOC: The Most Frequently Reported AEs of Grade ≥ 3 With Incidence Rate ≥ 1%

	FP/Cisplatin (N = 290) (% of patients in each treatment arm)	Trastuzumab/FP/ Cisplatin (N = 294) (% of patients in each treatment arm)
Neutropenia	30%	27%
Anaemia	10%	12%

Table 23 Blood and Lymphatic System Disorders SOC: The Most Frequently Reported AEs of Grade ≥ 3 With Incidence Rate ≥ 1%		
	FP/Cisplatin (N = 290) (% of patients in each treatment arm)	**Trastuzumab/FP/ Cisplatin (N = 294) (% of patients in each treatment arm)**
Febrile Neutropenia	3%	5%
Thrombocytopenia	3%	5%
Leukopenia	<1%	2%

8.3 Less Common Clinical Trial Adverse Reactions

Early Breast Cancer (EBC)

HERA
(adjuvant sequential: use of OGIVRI following surgery and after chemotherapy)

Listing of Adverse Events with Incidence Rate of < 1% in Study B-31
(Final analysis after median follow-up of 8.1 years in the AC - T+H group)

Allergy/immunology: allergy-other, autoimmune reaction
Auditory/hearing: hearing-other, inner ear/hearing, middle ear/hearing
Blood/bone marrow: hematologic-other, hemolysis, transfusion: platelets, transfusion: pRBC (packed red blood cells)
Cardiovascular (arrhythmia): arrythmia-other, nodal/junctional arrythmia/dysrhythmia, palpitations, sinus tachycardia, supraventricular arrhythmias*, vasovagal episode, ventricular arrhythmia,
Cardiovascular (general): cardiac troponin I (cTnI), cardiac-ischemia/infarction*, circulatory or cardiac-other, hypotension, pericardial effusion/pericarditis, peripheral arterial ischemia, phlebitis (superficial), visceral arterial ischemia (non-myocardial),
Coagulation: coagulation-other, prothrombin time (PT)
Constitutional symptoms: constitutional symptoms-other, rigors/chills*, weight loss
Dermatology/skin: bruising (in absence of thrombocytopenia), dermatitis, dry skin, erythema multiforme, flushing, hand-foot skin reaction, injection site reaction, pigmentation changes, urticaria (hives, welts, wheals), wound non-infectious
Endocrine: endocrine-other, feminization of male, hypothyroidism, syndrome of inappropriate anti-diuretic hormone (SIADH)
Gastrointestinal: colitis, duodenal ulcer, dysphagia, dysphagia-esophageal, flatulence, gastric ulcer, gastritis, mouth dryness, mucositis due to radiation, pancreatitis, proctitis, salivary gland changes, sense of smell
Hemorrhage: CNS hemorrhage/bleeding, epistaxis, hematuria*, hemorrhage/bleeding without thrombocytopenia, melena/GI bleeding, petechiae/purpura, rectal bleeding/hematochezia,
Hepatic: alkaline phosphatase*, bilirubin*, GGT (gamma-glutamyl transpeptidase), hepatic enlargement, hepatic-other, hypoalbuminemia
Infection/febrile neutropenia: catheter-related infection
Lymphatics: lymphatics-other

Metabolic/laboratory: amylase, CPK (creatinine phosphokinase), hypocalcemia, hypokalemia, hypercholesterolemia, hyperkalemia, hypertriglyceridemia, hypomagnesemia, hyponatremia, hypophosphatemia, lipase, metabolic-other
Musculoskeletal: arthritis, muscle weakness, osteonecrosis
Neurology: arachnoiditis/meningismus/radiculitis, CNS cerebrovascular ischemia*, confusion, cognitive disturbance/learning problems, delusions, depressed level of consciousness, extrapyramidal/involuntary movement/, restlessness, leukoencephalopathy, memory loss, neurologic-other, neuropathy-cranial, personality/behavioral, seizure(s), speech impairment, tremor, vertigo
Not coded: raw term unknown
Ocular/visual: cataract, glaucoma, conjunctivitis, ocular-other, vision-double vision (diplopia), vision-flashing lights/floaters, vision-photophobia
Pain: dysmenorrhea, dyspareunia, earache (otalgia), pain due to radiation, pelvic pain, pleuritic pain, rectal or perirectal pain (proctalgia), tumour pain
Pulmonary: acute respiratory distress syndrome (ARDS), hypoxia, pleural effusion (non-malignant), pneumonitis/pulmonary infiltrates, pneumothorax, pulmonary fibrosis, voice changes/stridor/larynx
Radiation morbidity: radiation-other
Renal/genitourinary: bladder spasms, creatinine, incontinence, proteinuria, renal failure, renal/genitourinary-other, ureteral obstruction
Sexual/reproductive function: libido, sexual/reproductive function-other
***AE term is itemized on the AE CRF.**

Listing of Adverse Events with Incidence Rate of < 1% in Study N9831
(Final analysis after median follow-up of 8.1 years in the AC - T+H group)

Auditory/hearing: inner ear/hearing
Blood/bone marrow: bone marrow cellularity, hemoglobin (HGB)*, platelets*, transfusion: platelets, transfusion: pRBCS (packed red blood cells)
Cardiovascular (arrhythmia): arrythmia-other, sinus bradycardia, sinus tachycardia**,** supraventricular arrhythmias, vasovagal episode, ventricular arrhythmia
Cardiovascular (general): circulatory or cardiac-other, hypotension, pericardial effusion/pericarditis, phlebitis (superficial), visceral arterial ischemia (non-myocardial)
Constitutional symptoms: fever (in the absence of neutropenia), rigors/chills, weight gain, weight loss
Dermatology/skin: dermatitis, erythema multiforme, hand-foot skin reaction, injection site reaction, photosensitivity, radiation dermatitis, rash/desquamation, skin other, wound-infectious
Endocrine: endocrine-other, hypothyroidism, syndrome of inappropriate anti-diuretic hormone (SIADH)
Gastrointestinal: anorexia, colitis, constipation, dehydration, diarrhea with prior colostomy*, dyspepsia, GI-other, ileus, stomatitis/pharyngitis*
Hemorrhage: CNS hemorrhage/bleeding, hemorrhage/bleeding with thrombocytopenia
Hepatic: SGOT (AST) (serum glutamic oxaloacetic transaminase), SGPT (ALT) serum glutamic pyruvic transaminase
Lymphatics: lymphatics*
Metabolic/laboratory: hypoglycemia, hypokalemia, hyponatremia
Musculoskeletal: arthritis
Neurology: ataxia (incoordination), CNS cerebrovascular ischemia, confusion, dizziness/lightheadedness, hallucinations, insomnia, memory loss, mood alteration-anxiety/agitation, mood alteration-depression, speech impairment, syncope (fainting)

Ocular/visual: conjunctivitis
Pain: abdominal pain or cramping, bone pain, dyspareunia, headache, neuropathic pain, pain-other, pleuritic pain
Pulmonary: acute respiratory distress syndrome (ARDS), apnea, cough, FEV1, hypoxia, pleural effusion (non-malignant), pulmonary fibrosis, pulmonary-other
Renal/genitourinary: dysuria (painful urination), fistula or genitourinary fistula, renal failure, renal/genitourinary-other, urinary frequency/urgency
Sexual/reproductive function: irregular menses (change from baseline)
*****AE term is itemized on the AE CRF.

Listing of Adverse Events with Incidence Rate of < 1% in in Study BCIRG-006 (5 Year Follow Up) According to NCI-CTC Classification v 2.0

Allergy/immunology: vasculitis
Auditory/hearing: external auditory canal
Blood/bone marrow: leukocytes (total WBC), platelets, transfusion: platelets, transfusion: pRBCS (packed red blood cells)
Cardiovascular (general): CNS cerebrovascular ischemia, hypertension, hypotension, phlebitis (superficial), thrombosis/embolism, cardiac- ischemia/infarction, edema, myocarditis
Cardiovascular (arrhythmia): sinus tachycardia, vasovagal episode, conduction abnormality/ atrioventricular heart block, sinus bradycardia, ventricular arrhythmia (PVCs/bigeminy/trigeminy/ventricular tachycardia)
Dermatology/skin: photosensitivity, radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port), urticaria (hives, welts, wheals).
Gastrointestinal: colitis, duodenal ulcer (requires radiographic or endoscopic documentation), dysphagia- esophageal related to radiation, gastric ulcer (requires radiographic or endoscopic documentation), dyspepsia/heartburn
Hemorrhage: hematemesis, hematuria (in the absence of vaginal bleeding), hemoptysis, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, melena/GI bleeding, petechiae/purpura (hemorrhage/bleeding into skin or mucosa)
Hepatic: alkaline phosphatase, bilirubin, GGT (gamma - glutamyl transpeptidase), hepatic pain, hypoalbuminemia, SGOT (AST) (serum glutamic oxaloacetic transaminase), SGPT (ALT) (serum glutamic pyruvic transaminase)
Endocrine: cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae), hypothyroidism
Metabolic/laboratory: hypercalcemia, hypercholesterolemia, hyperkalemia, hypernatremia, hypertriglyceridemia, hyperuricemia, hypocalcemia, hypoglycemia, hyponatremia
Musculoskeletal: arthritis, myositis (inflammation/damage of muscle)
Neurology: arachnoiditis/meningismus/radiculitis, ataxia (incoordination), depressed level of consciousness,
extrapyramidal/involuntary movement/ restlessness, hallucinations, mood alteration- euphoria, neuropathy-cranial, personality/behavioral, seizure(s), speech impairment (e.g., dysphasia or aphasia)
Ocular/visual: cataract, glaucoma, middle ear/hearing, vision- double vision (diplopia), vision- flashing lights/floaters, vision- night blindness (nyctalopia), vision-photophobia

Pain: dysmenorrhea, dyspareunia, pain due to radiation, pelvic pain, pleuritic pain, pain due to radiation, rectal or perirectal pain (proctalgia), chest pain (non-cardiac and non-pleuritic)
Pulmonary: apnea, FEV1, hiccoughs (hiccups, singultus), pleural effusion (non-malignant), pulmonary fibrosis, pneumonitis/pulmonary infiltrates, pneumothorax, dyspnea (shortness of breath)
Renal/genitourinary: bladder spasms, creatinine, proteinuria, renal failure, urinary retention, urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)

Listing of Adverse Events with Incidence Rate of < 1% in in Study BCIRG-006 (5 Year Follow Up) According to COSTART Classification

Body as a whole: abdomen enlarged, abdominal pain, abscess, aggravation reaction, allergic reaction, ascites, asthenia, body odor, cellulitis, chest pain substernal, chills, collagen disorder, granuloma, halitosis, headache, hernia, hormone level altered, hydrocephalus, hypothermia, immune system disorder, infection, infection fungal, infection parasitic, injection site edema, injection site hemorrhage, injection site inflammation, injection site reaction, lab test abnormal, malaise, mucous membrane disorder, neck rigidity, necrosis, neoplasm, pelvic pain, peritonitis, photosensitivity reaction, radiation injury, rheumatoid arthritis, scleroderma, viral infection
Cardiac adverse events (body as a whole): chest pain substernal, face edema, pain, angina pectoris
Cardiovascular system: aortic stenosis, aphthous stomatitis, arrhythmia, arteriosclerosis, bigeminy, bradycardia, bundle branch block, cardiomyopathy, cardiospasm, cardiovascular disorder, carotid occlusion, cerebrovascular accident, cheilitis, congestive heart failure, coronary artery disorder, coronary occlusion, dyspnea, electrocardiogram abnormal, endocarditis, extrasystoles, heart arrest, heart failure, heart malformation, hyperkinesia, hyperlipemia, hypokinesia, hypotension, hypertonia, left heart failure, myocardial ischemia, pallor, palpitation, pericarditis, peripheral vascular disorder, spider angioma, supraventricular extrasystoles, supraventricular tachycardia, syncope, T inverted, tachycardia, thrombophlebitis, varicose vein, vascular anomaly, vascular disorder, venous pressure increased, ventricular extrasystoles, peripheral edema
Digestive system: cholecystitis, cholelithiasis, cirrhosis of liver, colitis, constipation, diarrhea, dysphagia, eructation, esophageal hemorrhage, fecal incontinence, gamma glutamyl transpeptidase increased, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gingivitis, glossitis, hepatitis, hepatomegaly, increased appetite, jaundice, liver function tests abnormal, liver necrosis, liver tenderness, melena, mouth ulceration, nausea, oral moniliasis, perforated stomach ulcer, periodontal abscess, proctitis, rectal hemorrhage, sialadentitis, stomach atony, stomatitis, tongue discoloration, tongue disorder, tongue edema, tooth disorder, tooth malformation, vomiting
Endocrine system: diabetes mellitus, endocrine disorder, goiter, hyperthyroidism, thyroid disorder
Hemic and lymphatic system: aplastic anemia, ecchymosis, hemolysis, hypochromic anemia, leukopenia, lymphadenopathy, macrocytic anemia, myeloproliferative disorder, pancytopenia, petechia, purpura, thrombocytopenia
Metabolic and nutritional disorders: acidosis, albuminuria, bun increased, electrolyte abnormality, enzymatic abnormality, generalized edema, healing abnormal, hypercalcemia, hypercholesteremia, hyperlipemia, hypoglycemia, hypophosphatemia, hypoproteinemia, hypovelemia, lactic dehydrogenase increased, liver fatty deposit, respiratory alkalosis, thirst, uremia, weight loss
Musculoskeletal system: arthritis, arthrosis, bone disorder, bone pain, bursitis, generalized spasm, myalgia, myasthenia, myositis, osteomyelitis, tendinous contracture, tenosynovitis

Nervous system: abnormal dreams, abnormal gait, agitation, amnesia, anxiety, ataxia, CNS stimulation, coma, delirium, depression, dizziness, dry mouth, dysautonomia, emotional liability, facial paralysis, grand mal convulsion, hyperesthesia, hyperkinesia, hypesthesia, hypokinesia, ileus, incoordination, increased salivation, myelitis, myoclonus, nervousness, neuralgia, nystagmus, paresthesia, peripheral neuritis, reflexes decreased, somnolence, thinking abnormal, tremor, trismus, vasodilatation, apnea
Respiratory system: asthma, atelectasis, bronchitis, cough increased, dyspnea, hemoptysis, hiccup, hyperventilation, hypoxia, laryngismus, laryngitis, larynx edema, lung disorder, lung edema, lung fibrosis, pleural disorder, pneumonia, pneumothorax, respiratory disorder, sputum increased, application site reaction
Skin and appendages: dry skin, eczema, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis, hair disorder, herpes zoster, hirsutism, ichthyosis, maculopapular rash, psoriasis, pustular rash, skin benign neoplasm, skin carcinoma, skin discoloration, skin granuloma, skin hypertrophy, skin nodule, skin ulcer, sweating, vesiculobullous rash
Special senses: abnormality of accommodation, blepharitis, blindness, conjunctival edema, corneal lesion, deafness, ear disorder, extraocular palsy, eye disorder, eye hemorrhage, glaucoma, keratitis, lacrimation disorder, mydriasis, ophthalmitis, otitis media, parosmia, ptosis, pupillary disorder, refraction disorder, retinal vascular disorder, taste loss, taste perversion, tinnitus, vestibular disorder, vitreous disorder
Urogenital system: amenorrhea, breast carcinoma, breast enlargement, breast neoplasm, cervix disorder, cervix neoplasm, cystitis, dysmenorrhea, dyspareunia, dysuria, endometrial disorder, endometrial hyperplasia, female lactation, genital edema, kidney function abnormal, kidney pain, mastitis, menopause, menorrhagia, menstrual disorder, metrorrhagia, nocturia, oliguria, ovarian disorder, polyuria, ruptured uterus, toxic nephropathy, unintended pregnancy, urethritis, urinary frequency, urinary incontinence, urinary tract disorder, urinary tract infection, urine abnormality, uterine disorder, uterine fibroids enlarged, uterine hemorrhage, uterine neoplasm, vaginal hemorrhage, vaginal moniliasis, vaginitis, vulvovaginal disorder, vulvovaginitis

Metastatic Gastric Cancer (MGC)

Listing 1: Adverse Drug Reactions With Incidence Rate < 1% in ToGA (BO18255)

Cardiac disorders: arrhythmia, atrial fibrillation, atrial flutter, bradycardia, cardiac failure, left ventricular dyfunction
Eye disorders: dry eye
Gastrointestinal disorders: abdominal pain lower, haemorrhoidal haemorrhage, lip swelling
General disorders and administration site conditions: influenza like illness, mucous membrane disorder
Hepatobiliary disorders: hepatic failure, hepatitis toxic, hepatotoxicity, jaundice
Infections and infestations: bronchitis, cellulitis, herpes zoster, lower respiratory tract infection, lung infection, neutropenic sepsis, paronychia, rhinitis, sepsis, sinusitis, urinary tract infection
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased,
Blood potassium increased, blood pressure decreased, ejection fraction decreased, gamma-glutamyltransferase increased, transaminases increased, white blood cell count decreased
Metabolism and nutrition disorders: decreased appetite, fluid retention
Musculoskeletal and connective tissue disorders: arthritis, joint swelling

Nervous system disorders: neurotoxicity, paresis, somnolence, toxic neuropathy
Renal and urinary disorders: renal disorder
Respiratory, thoracic and mediastinal disorders: acute respiratory distress syndrome, hypoxia, pharyngeal edema, pleural effusion, pneumonitis
Skin and subcutaneous tissue disorders: acne, dermatitis, erythema, hyperhidrosis, rash macular, rash papular, rash pruritic

8.4 Post-Market Adverse Reactions

Table 24
Adverse Reactions Reported in the Post-Marketing Setting

System organ class	Adverse reaction
Infections and infestations	Cystitis
	Neutropenic sepsis
Blood and lymphatic system disorders	Hypoprothrombinemia
	Immune thrombocytopenia
Immune system disorders	Anaphylactoid reaction
	Anaphylactic reaction
	Anaphylactic shock
Metabolism and nutrition disorders	Tumour lysis syndrome
Eye disorders	Madarosis
Cardiac disorders	Cardiogenic shock
	Tachycardia
	Pericardial effusion
Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Oxygen saturation decreased
	Respiratory failure
	Interstitial lung disease
	Lung infiltration
	Acute respiratory distress syndrome
	Respiratory distress
	Pulmonary fibrosis
	Hypoxia
	Laryngeal oedema
Hepatobiliary disorders	Hepatocellular injury
Renal and urinary disorders	Glomerulonephropathy
	Renal failure
Pregnancy, puerperium and perinatal conditions	Pulmonary hypoplasia
	Renal hypoplasia
	Oligohydramnios

Adverse Events
Table 25 below indicates adverse events that have been reported in patients who have received trastuzumab.

Table 25 Adverse Events	
System organ class	**Adverse Event**
Infections and infestations	Meningitis
	Bronchitis
Blood and lymphatic system disorders	Leukaemia
Nervous system disorders	Cerebrovascular disorder
	Lethargy
	Coma
Ear and labyrinth disorders	Vertigo
Respiratory, Thoracic and Mediastinal system disorders	Hiccups
	Dyspnoea exertional
Gastrointestinal system disorders	Gastritis
	Pancreatitis
Hepatobiliary disorders	Hepatic failure
Musculoskeletal and connective tissue disorders	Musculoskeletal pain
Renal and urinary disorders	Dysuria
Reproductive system and breast disorders	Breast pain
General disorders and administration site conditions	Chest discomfort

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

There have been no formal drug interaction studies performed with trastuzumab in humans.

9.4 Drug-Drug Interactions

Strong evidence for clinically significant interactions with concomitant medications used in clinical studies has not been observed. However, administration of paclitaxel in combination with trastuzumab resulted in a two-fold decrease in clearance of trastuzumab in a non-human primate study. In one clinical study, an apparent 1.5-fold increase in serum levels of trastuzumab was seen when trastuzumab was administered with paclitaxel. However, this observation could not be confirmed using a population pharmacokinetic approach (see 10 CLINICAL PHARMACOLOGY: I Pharmacokinetics).

A population pharmacokinetic method using data from phase I, phase II and pivotal phase III studies, was used to estimate the steady state pharmacokinetics in patients administered trastuzumab at a loading dose of 4 mg/kg followed by a 2 mg/kg maintenance dose administered weekly. The administration of concomitant chemotherapy (either anthracycline/ cyclophosphamide or paclitaxel) did not appear to influence the pharmacokinetics of trastuzumab.

Experience from phase III clinical trials suggests that there is a potential drug interaction between trastuzumab and anthracycline chemotherapy. However, the clinical pharmacokinetic profile of

doxorubicin or epirubicin in the presence of trastuzumab has not been described to date, and the exact nature of this potential interaction has yet to be described.

When using in combination with pertuzumab and docetaxel, consult Product Monographs for pertuzumab and docetaxel for further information on these drugs.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG1 isotype that contains human framework regions with complementarity-determining regions of a murine anti-p185 HER2 antibody that binds to human HER2.

The HER2 (or c-erbB2) proto-oncogene or c-erbB2 encodes for a single transmembrane spanning, receptor-like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. HER2 protein overexpression is observed in 25%-30% of primary breast cancers. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8% to 34.0% for IHC and 7.1% to 42.6% for FISH A consequence of HER2 gene amplification is an increase in HER2 protein expression on the surface of these tumour cells, which results in a constitutively-activated HER2 protein. Studies indicate that patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. HER2 protein overexpression can be determined using an immunohistochemistry-based assessment of fixed tumour blocks, ELISA techniques on tissue or serum samples or Fluorescence *In Situ* Hybridisation (FISH) technology. N.B., to date, only data derived from immunohistochemistry staining is relevant to treatment with trastuzumab (see 7 WARNINGS AND PRECAUTIONS: Selection of Patients).

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

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

10.2 Pharmacokinetics

The pharmacokinetics of trastuzumab have been studied in breast cancer patients with metastatic disease. In phase I studies, short duration intravenous infusions of 10, 50, 100, 250 and 500 mg once weekly in patients demonstrated dose-dependent pharmacokinetics at doses below 100 mg. Mean half-lives increased and clearance decreased with increasing dose level. The half-life of trastuzumab averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively.

Early Breast Cancer (EBC)/Metastatic Breast Cancer (MBC)

A population pharmacokinetic method, using data from phase I, phase II and pivotal phase III studies, was used to estimate the steady state pharmacokinetics in patients administered trastuzumab at a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg. In this assessment, the typical clearance of trastuzumab was 0.225 L/day and the typical volume of distribution was 2.95 L, with a corresponding terminal half-life of 28.5 days (95% confidence interval, 25.5 - 32.8 days). The inter-patient variability in clearance and volume of distribution was 43% and 29% (co-efficient of variation), respectively. These values are lower than those estimated from the base model. Steady state weekly AUC of 578 mg•day/L, peak concentrations of 110 mg/L and trough concentrations of 66 mg/L should be reached by 143 days, or approximately 20 weeks. It should be noted that these values represent free and dimer complexes of trastuzumab as the assay utilized was unable to detect the trimer complex. Trastuzumab may persist in the circulation for approximately 24 weeks (range: 22-28 weeks, based on a 6-fold terminal elimination half-life value) (see 7 WARNINGS AND PRECAUTIONS: Cardiovascular, Cardiotoxicity).

EBC patients administered an initial loading dose of 8 mg/kg followed by a three weekly maintenance dose of 6 mg/kg achieved steady state (see Table 26 below). These concentrations were comparable to those reported previously in patients with MBC.

Table 26 Summary of Trastuzumab Pharmacokinetic Parameters for Patients Enrolled into the Trastuzumab 1-year Treatment Group (sampled PK Population)

PK Parameter	Cycle 18 (Trastuzumab 1-year arm)
Mean ± SD (n)	
Cmax (µg/mL)	225 ± 30 (30)
Concentration – Day 21* (µg/mL)	68.9 ± 14 (28)
Concentration – Day 42 (µg/mL)	30.7 ± 14 (28)
AUC0-21d (day•µg/mL)	2260 ± 340 (28)
AUC0-42d (day•µg/mL)	3270 ± 560 (28)
Half-life (day)	18.8 ± 7.2 (29)

* Day 21 concentration was calculated by linear interpolation from concentrations observed in patients on Days 14 and 28.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the serum of some patients with HER2- overexpressing tumours. Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations of trastuzumab, however, with weekly dosing, most patients with elevated shed antigen levels achieved target serum concentrations by week 6. Levels of shed antigen were only determined at baseline in the

clinical trials. As a result, the available data are too limited to adequately characterize the interrelationship of HER2 overexpression and serum shed antigen concentrations.

Data suggest that the disposition of trastuzumab is not altered based on age or serum creatinine (up to 2.0 mg/dL or 176.8 µmol/L). No formal interaction studies have been performed.

Metastatic Gastric Cancer (MGC)

A population pharmacokinetic method, using data from the Phase III study ToGA (BO18255), was used to estimate the steady state pharmacokinetics in patients with MGC administered trastuzumab 3-weekly at a loading dose of 8 mg/kg followed by a 3-weekly maintenance dose of 6 mg/kg. In this assessment, the typical clearance of trastuzumab was 0.378 L/day and the typical volume of distribution was 3.91 L, with a corresponding equilibrium half-life of 12.2 days. The median predicted steady-state AUC values (over a period of 3 weeks at steady state) is equal to 1030 mg•day/L, the median steady-state Cmax is equal to 128 mg/L and the median steady-state Cmin values is equal to 23 mg/L. Steady state concentrations should be reached by 49 days, (four equilibrium half lives) or approximately 7 weeks.

Trastuzumab clearance in MGC patients is higher than that in MBC patients, leading to lower AUC, Cmax and Cmin at steady-state.

The estimated equilibrium half life of trastuzumab was 12.2 days in the ToGA (BO18255) trial and 26.3 days for studies BO15935 and WO16229 (in MBC). The lower value in the ToGA (BO18255) trial was due to the increase in clearance in the MGC patients.

11 STORAGE, STABILITY AND DISPOSAL

Vials of OGIVRI (trastuzumab) are stable at 2°C - 8°C prior to reconstitution until the expiry date shown on the vial.

Unopened vials of OGIVRI may be removed from refrigeration and stored up to 25°C for a single period of up to 3 months. Once OGIVRI is removed from refrigeration and stored up to 25°C, discard after 3 months. A discard date field is provided on the carton to record the discard date.

A vial of OGIVRI 440 mg/vial reconstituted with BWFI, containing 1.1% benzyl alcohol, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2°C - 8°C, and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved Sterile Water for Injection (SWFI) (not supplied) is used, the reconstituted solution of OGIVRI has been shown to be physically and chemically stable up to 10 days at 2°C - 8°C; however, from the microbiological perspective, the reconstituted solution should be used immediately, and any unused portion must be discarded. **Do not freeze OGIVRI that has been reconstituted.**

The solution of OGIVRI for infusion diluted in polyvinylchloride, polypropylene, polyethylene, or polyolefin bags containing 0.9% Sodium Chloride Injection, USP, when reconstituted with BWFI, is stable for up to 24 hours at 2°C - 8°C. If reconstituted with SWFI, the infusion solution has been shown to be physically and chemically stable for 60 days at 2°C - 8°C or up to 24 hours at temperatures up to 30°C prior to use.

However, from a microbiological point of view, the reconstituted solution (if SWFI is used) and the infusion solution of OGIVRI should be used immediately since they contain no effective preservative. The product is not intended to be stored after reconstitution and dilution unless this has taken place under controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

12 SPECIAL HANDLING INSTRUCTIONS

Disposal of syringes/sharps

The following procedures should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Dispose of the full container or waste material according to local requirements.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location. Local requirements should be followed for the disposal process of unused/expired medicines.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

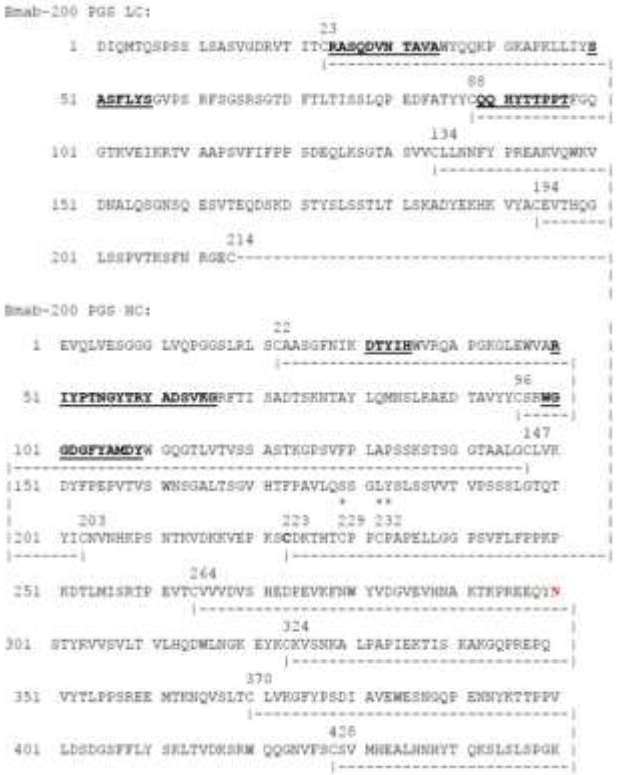
Proper name: Trastuzumab

Chemical name: humanized anti-HER2 monoclonal antibody

Molecular formula and molecular mass: $C_{6460}H_{9972}N_{1724}O_{2014}S_{44}$

The relative molecular mass of intact trastuzumab drug substance (including post-translational modification and excluding C terminal lysine) is approximately 148054±15 Daltons.

Structural formula:



--- indicates disulphide bond

Underline bold indicates complementarity-determining regions

Cysteine (C) 229 & 232 marked with asterisks (*) are involved in inter-heavy chain disulphide bond formation.

HC: **N**300 = glycosylation site.

*representation is with C-terminal lysine and without post-translational modification

C450 K is removed due to expression in CHO cells and carboxypeptidase B enzyme treatment during the cell culture process.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Pivotal Studies

Clinical studies conducted to support similarity between OGIVRI and the reference biologic drug included:

- A comparative pharmacokinetic (PK) study MYL-Her-1001 (2-way crossover design) in healthy male volunteers.
- A comparative pharmacokinetic (PK) study MYL-Her-1002 (parallel design) in healthy male subjects.
- A comparative efficacy and safety study MYL-Her-3001 in patients with untreated HER2-positive metastatic breast cancer (MBC).

An overview of the study design(s) and demographic characteristics of patients enrolled in each clinical study are presented in Table 27.

Table 27 - Summary of trial design and patient demographics

Study #	Trial Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)
Pivotal Studies				
MYL-Her-1001	Single-center, single-dose, 2-period, randomized, double-blind, 2-way crossover study to assess the bioequivalence, safety, and tolerability of OGIVRI versus EU-Herceptin in healthy volunteers	OGIVRI, EU-Herceptin 8 mg/kg single dose IV Single IV dose administered over 90 min	Healthy male subjects 22 randomized; 22 dosed; 19 completed	28 years (18-45)
MYL-Her-1002	Single-center, single-dose, randomized, double-blind, 3-arm parallel-group study to assess the bioequivalence of OGIVRI versus EU-Herceptin, OGIVRI versus US-Herceptin, as well as EU-Herceptin versus US-Herceptin in healthy volunteers	OGIVRI, EU-Herceptin, US-Herceptin 8 mg/kg single dose IV Single IV dose administered over 90 min	Healthy male subjects 132 randomized; 132 dosed; 121 completed~~/~~	31.9 years (19-55)

Study #	Trial Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)
MYL-Her-3001	A multicenter, double-blind, randomized, parallel-group study to compare the efficacy and safety of OGIVRI plus docetaxel or paclitaxel (i.e., taxane) versus EU-Herceptin plus a taxane in patients with HER2-positive metastatic breast cancer	OGIVRI, EU-Herceptin 8 mg/kg loading dose followed by 6 mg/kg maintenance, every 3 weeks for 8 cycles IV Part 1 (OGIVRI or EU-Herceptin in combination with taxane): 24 weeks (Weeks 1-24) Part 2 (OGIVRI or EU-Herceptin monotherapy): 24 weeks (Weeks 25-48)	Female patients with HER2+ MBC 500 randomized; 493 treated; 356 completed Part 1; 214 completed Part 2	OGIVRI: 54.3 years (26-79) EU-Herceptin: 52.9 years (26-82)

14.2 Comparative Bioavailability Studies

14.2.1 Pharmacokinetics

When comparing PK parameters of OGIVRI versus trastuzumab (EU), the point estimate for the C_{max} was 94.2%, and the 90% confidence intervals (CIs) for the geometric means for AUC_{last} were fully contained within the pre-defined bounds of 80.0% to 125.0%.

Table 28: Analyses of PK Parameters (from measured data) Study MYL-Her-1001

Parameters (unit)	Geometric LS Mean		LS Mean Ratio	90% CI of Ratio
	OGIVRI N=19	EU-Trastuzumab N=19		
AUC_{last} (µg·h/mL)	45212	47243	95.7%	90.5% - 101.2%
AUC_{inf} (µg·h/mL)	45266	47294	95.7%	90.5% - 101.2%
C_{max} (µg/mL)	165.4	175.6	94.2%	
T_{max} (h)	1.5^	1.5^		
$T_{1/2}$ (h)	173.8	177.8		
$T_{1/2}$ (days)	7.2	7.4		

^median

When comparing PK parameters of OGIVRI versus trastuzumab (EU), the point estimate for the C_{max} was 104.0%, and the 90% CIs for the geometric means for AUC_{last} were fully contained within the pre-defined bounds of 80.0% to 125.0%.

Table 29: Analyses of PK Parameters (from measured data): Study MYL-Her-1002

Parameters (unit)	Geometric LS Mean			LS Mean Ratio EU	90% CI of Ratio EU	LS Mean Ratio US	90% CI of Ratio US	LS Mean Ratio US/EU	90% CI of Ratio US/EU
	OGIVRI N=42	EU-Trastuzumab N=41	US-Trastuzumab N=37						
AUC_{last} (µg·h/mL)	49029	50690	51377	96.7%	90.9%-102.9%	95.4%	89.5%-101.7%	101.4%	95.1% - 108.1%
AUC_{inf} (µg·h/mL)	49200	50927	51756	96.6%	90.8%-102.8%	95.1%	89.2%-101.4%	101.6%	95.3% - 108.4%
C_{max} (µg/mL)	205.4	197.6	203.5	104.0%		101.0%		103.0%	
T_{max} (h)	2.552	2.389	2.332						
$T_{1/2}$ (h)	154.8	165.9	170.0						
$T_{1/2}$ (days)	6.5	6.9	7.1						

14.2.2 Comparative Safety and Efficacy
Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

Efficacy

MYL-Her-3001
The comparative clinical efficacy and safety study MYL-Her-3001 was designed to rule out any clinically meaningful differences between OGIVRI and EU-approved Herceptin. The study included female patients with histologically confirmed diagnosis of metastatic breast cancer, and who had not received prior systemic therapy in the metastatic disease setting, and who had HER2 gene amplification as confirmed by fluorescent in situ hybridization (FISH), or HER2-overexpression by immunohistochemistry (defined as IHC3+, or IHC2+ with FISH confirmation).

The demographic profile was similar in the OGIVRI group versus the Herceptin group with respect to height, weight, race, and body surface area. With regards to age, the mean age in the Herceptin group and in the OGIVRI group was 52.9 years and 54.3 years, respectively. The percentage of patients who were <50 years of age in the Herceptin group was 37.7% versus 32.2 in the OGIVRI group.

Comparability between OGIVRI and trastuzumab was demonstrated since the two-sided 95% confidence interval of the risk ratio in ORR at week 24 was entirely contained within the pre-defined equivalence interval of [0.81 to 1.24].

Table 30: Best Overall Response Rate (ORR) at Week 24 and Ratio of Best ORR (ITT1 Population; Study MYL-Her-3001)

Response		OGIVRI + Taxane (N = 230)	Herceptin + Taxane (N = 228)
Complete response (CR)	n (%)	3 (1.3)	0 (0.0)
Partial response (PR)	n (%)	157 (68.3)	146 (64.0)
Stable disease (SD)	n (%)	48 (20.9)	49 (21.5)
Progressive disease (PD)	n (%)	9 (3.9)	20 (8.8)
N/E	n (%)	13 (5.7)	13 (5.7)
Overall response rate	n (%)	160 (69.6)	146 (64.0)
95% CI		(63.62, 75.51)	(57.81, 70.26)
Ratio OGIVRI:Herceptin		1.09	
95% CI		(0.954, 1.237)	

CI: confidence interval, ITT: intent-to-treat, N/E: not evaluable
Objective response was defined as confirmed CR or PR according to RECIST Version 1.1 based on central tumor evaluation.

14.3 Immunogenicity

Study MYL-Her-3001
In Study MYL-Her-3001, the immunogenicity of OGIVRI and Herceptin was assessed by measuring the ADA levels in blood samples collected at baseline (pre-infusion) and at Days 43, 85, 127, 169, 253, and 337 during each treatment period. Among all patients who tested positive for ADAs at least once at any timepoint post-baseline regardless of the ADA result at baseline, the overall ADA rate was 3.9% (9/247) in the OGIVRI arm and 4.4% (10/246) in the Herceptin arm. Titers were low in both arms across all timepoints.

14.4 Clinical Trials - Reference Biologic Drug

Early Breast Cancer (EBC)
In the adjuvant treatment setting, trastuzumab was investigated in 4 large multicentre, randomised, trials:

- The HERA study was designed to compare one year of three-weekly trastuzumab treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable).

- The NSAPB B31 and NCCTG N9831 studies that comprise the Joint Analysis were designed to investigate the clinical utility of combining trastuzumab treatment with paclitaxel following AC chemotherapy in HER2 positive EBC following surgery. Additionally, the NCCTG N9831 study investigated adding trastuzumab sequentially after AC-paclitaxel chemotherapy in patients with HER2 positive EBC following surgery.

- The BCIRG-006 study was designed to investigate combining trastuzumab treatment with docetaxel either following AC chemotherapy, or in combination with docetaxel and carboplatin in patients with HER2 positive EBC following surgery.

The comparative efficacy and safety between different chemotherapy regimens (i.e. concurrent versus sequential, anthracycline containing versus non-anthracycline containing) was not studied.

Eligible patients in the four studies included women with operable, non-metastatic adenocarcinoma of the breast whose tumours overexpressed HER2 and who had either node-positive or high-risk node-negative disease. Definitions used in each protocol are shown in Table 32.

Table 32
Eligible Populations in EBC Studies, by TNM Categories[a]

STUDY	AJCC TNM Version	T	N	M	Comment
HERA	Staging Manual 5th edition (1997)	≥T1c, T2, T3, pT4	N0, N1, N2, N3	M0	Prior (neo)adjuvant chemotherapy required. Prior radiotherapy required for nodal (axillary, internal mammary) or pT4 disease.
NSABP B-31	Staging Manual 5th edition (1997) *updated May 2003 to:* Staging Manual 6th edition (2002)	clinical T1, T2, T3 *updated May 2003 to:* T1, T2, T3 (clinical and pathologic)	cN0, cN1 *updated May 2003 to:* cN0, cN1 and pN1, pN2a, pN3a	M0	No prior chemotherapy or radiotherapy permitted. Whole breast irradiation required during study; partial breast or internal mammary radiation prohibited.
NCCTG N9831	Staging Manual 5th edition (1997)	T1, T2, T3	pN1, pN2 (minimum 1/6 nodes)	M0	No prior chemotherapy or radiotherapy permitted. Breast + regional lymphatic irradiation during study, per radiotherapist.
		T1c (ER-/PR-only), T2, T3	pN0 (minimum sentinel node or 1/6 nodes)		
BCIRG-006	Staging Manual 5th edition (1997) [not specified in protocol]	T1, T2, T3	pN1, pN2 (minimum 1/6 nodes)	M0	No prior chemotherapy or radiotherapy permitted. Breast + regional lymphatic irradiation during study, per radiotherapist.
		≥T2, or ER-/PR-, or nuclear Grade 2-3, or age <35 yrs	pN0 (minimum sentinel node or 1/6 nodes)		

[a] Required for all studies: (1) invasive adenocarcinoma on histologic examination; (2) complete excision of primary tumour with tumour-free margins on histologic examination of specimens from definitive surgery; and (3) HER2 positive tumour

HERA

In the adjuvant setting, trastuzumab was investigated in HERA, a multicentre, randomised, trial designed to compare one and two years of three-weekly trastuzumab treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a comparison of two years trastuzumab treatment versus one year trastuzumab treatment was performed, with the objective to assess the superiority of two years of trastuzumab treatment relative to one year of trastuzumab treatment. Breast tumour specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH) as determined at a central laboratory.

Patients assigned to receive trastuzumab were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for either one or two years. One year of trastuzumab treatment was defined as 12 calendar months of treatment from day 1 of first administration and 18 infusions maximum. Two years of trastuzumab treatment were defined as 24 calendar months of treatment from day 1 of first administration and 35 infusions maximum.

The efficacy results from the HERA trial are summarized in Table 33. Please see 8 ADVERSE REACTIONS and 7 WARNINGS AND PRECAUTIONS: Cardiovascular/Cardiotoxicity/Early Breast Cancer for a summary of the HERA safety information.

Table 33
Efficacy Results from the HERA Trial:
Results at 12 months* and 8 years of median follow-up**

	Median follow-up 12 months		**Median follow-up 8 years**	
Parameter	**Observation N=1693**	**Trastuzumab 1 Year N = 1693**	**Observation N=1697*** **	**Trastuzumab 1 Year N=1702*** **
Disease-free survival (DFS)				
- No. patients with event	219 (12.9%)	127 (7.5%)	570 (33.6%)	471 (27.7%)
- No. patients without event	1474 (87.1%)	1566 (92.5%)	1127 (66.4%)	1231 (72.3%)
P-value versus Observation	<0.0001			
Hazard Ratio versus Observation	0.54		0.76	
Adjusted (99.9%) Confidence Interval****	(0.38, 0.78)			
Recurrence-free survival				
- No. patients with event	208 (12.3%)	113 (6.7%)	506 (29.8%)	399 (23.4%)
- No. patients without event	1485 (87.7%)	1580 (93.3%)	1191 (70.2%)	1303 (76.6%)
Hazard Ratio versus Observation	0.51		0.73	

Table 33 Efficacy Results from the HERA Trial: Results at 12 months* and 8 years** of median follow-up				
	Median follow-up 12 months		**Median follow-up 8 years**	
Parameter	**Observation N=1693**	**Trastuzumab 1 Year N = 1693**	**Observation N=1697*** **	**Trastuzumab 1 Year N=1702*** **
Distant disease-free survival				
- No. patients with event	184 (10.9%)	99 (5.8%)	488 (28.8%)	399 (23.4%)
- No. patients without event	1508 (89.1%)	1594 (94.6%)	1209 (71.2%)	1303 (76.6%)
Hazard Ratio versus Observation	0.50		0.76	
Overall survival (death)				
- No. patients with event	40 (2.4%)	31 (1.8%)	350 (20.6%)	278 (16.3%)
- No. patients without event	1653 (97.6%)	1662 (98.2%)	1347 (79.4%)	1424 (83.7%)
Hazard Ratio versus Observation	0.75		0.76	

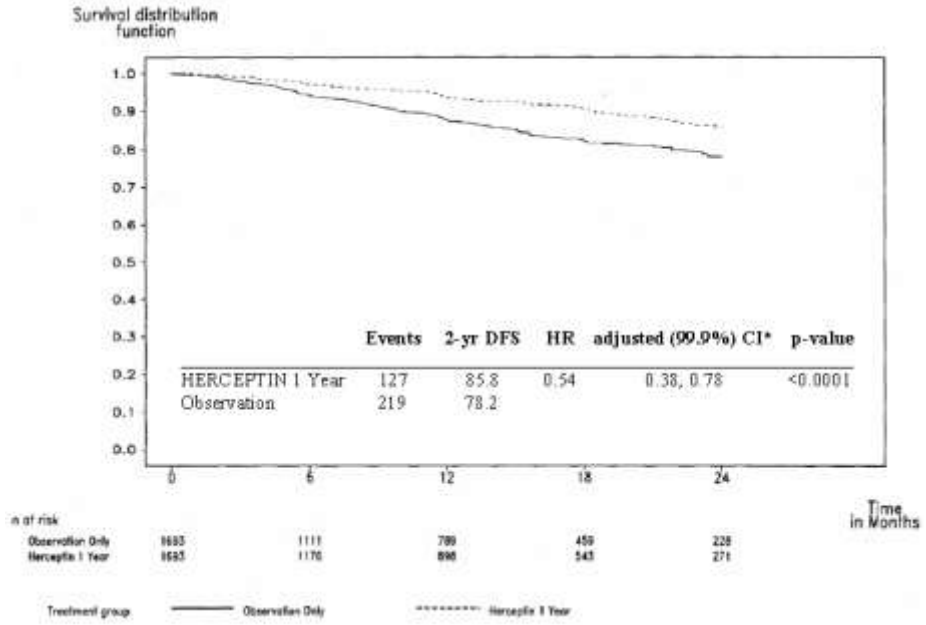
*Co-primary endpoint of DFS of 1 year vs observation met the pre-defined statistical boundary of 0.0010.
**Final analysis (including crossover of 52% of patients from the observation arm to trastuzumab).
***There is a discrepancy in the overall sample size due to a small number of patients who were randomized after the cut-off date for the 12-month median follow-up analysis.
**** Adjusted (both for the interim analysis and the 2 comparisons of each trastuzumab arm (1 year and 2 years) vs. observation) confidence interval presented, to reflect the stopping boundary of p≤ 0.0010 of the comparison trastuzumab 1 year vs. observation. The interval represents the 99.9% confidence interval.

The efficacy results from the interim efficacy analysis crossed the protocol pre-specified statistical boundary of 0.0010 for the comparison of 1-year of trastuzumab vs. observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 0.54 (adjusted 99.9% CI: 0.38, 0.78) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8% vs. 78.2%) in favour of the trastuzumab arm. Please see Figure 1.

A final analysis was performed after a median follow-up of 8 years, which showed that 1 year trastuzumab treatment is associated with a 24% risk reduction compared to observation only (HR = 0.76, unadjusted 95% CI: 0.67, 0.86). This translates into an absolute benefit in terms of an 8 year disease free survival rate of 6.4% in favour of 1 year trastuzumab treatment.

In this final analysis, superiority of 2 years trastuzumab treatment over 1 year trastuzumab treatment could not be demonstrated (DFS HR in the intent to treat (ITT) population of 2 years vs 1 year = 0.99 (unadjusted 95% CI: 0.87, 1.13), p-value = 0.90 and OS HR = 0.98 (unadjusted 95% CI: 0.83, 1.15); p-value = 0.78). The rate of secondary cardiac endpoints was increased in the 2-year treatment arm (8.1% vs 4.6% in the 1-year treatment arm). More patients experienced at least one grade 3 or 4 adverse event in the 2-year treatment arm (20.4%) compared with the 1-year treatment arm (16.3%).

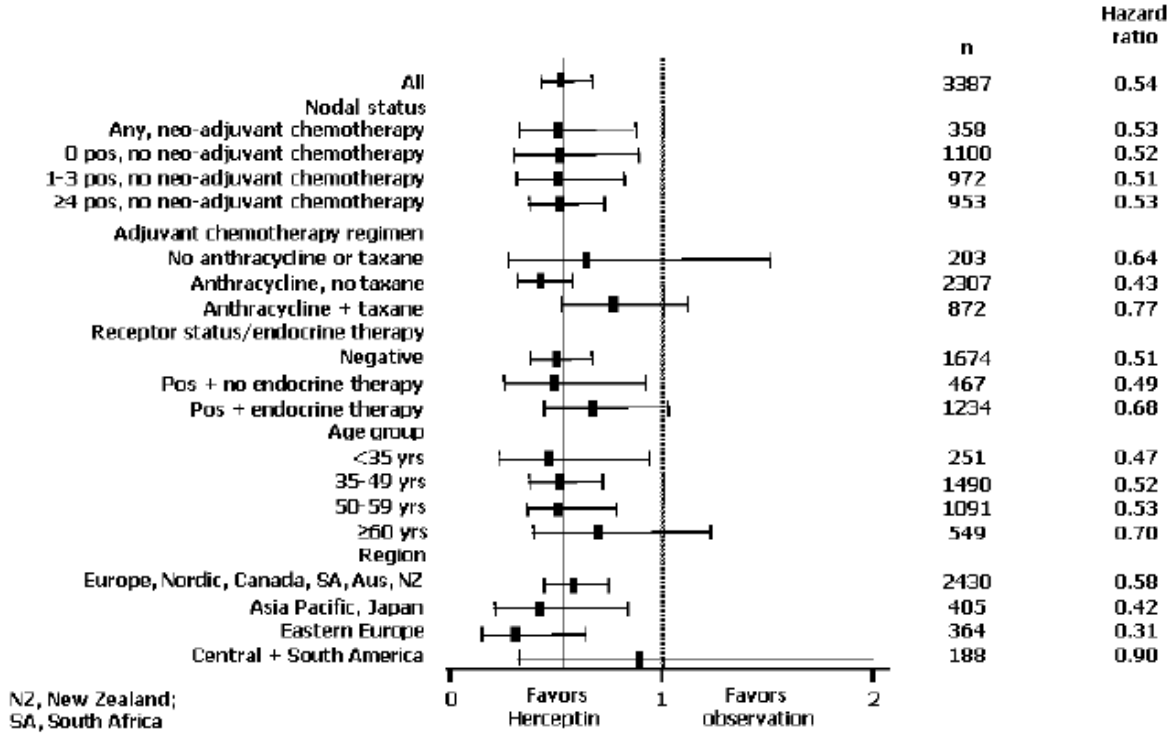
Figure 1
Kaplan-Meier curve of Disease Free survival
(After a Median Follow-up of 12 Months)



*Adjusted (both for the interim analysis and the 2 comparisons of each trastuzumab arm (1 year and 2 years) vs. observation) confidence interval presented, to reflect the stopping boundary of p≤ 0.0010 of the comparison trastuzumab 1year vs. observation. The interval represents the 99.9% confidence interval.

The benefit in disease-free survival was seen in all subgroups analysed (Please see Figure 2).

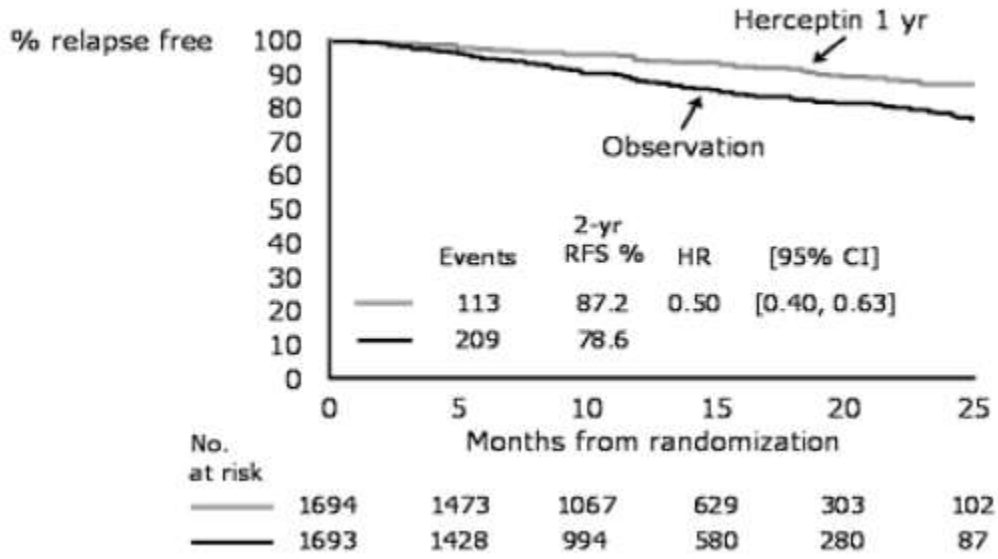
Figure 2
Risk Ratios and 95% Confidence Intervals for Disease-Free Survival by Subgroup
(After a Median Follow-up of 12 Months)



Note: 95%-CIs are not adjusted for multiple testing.

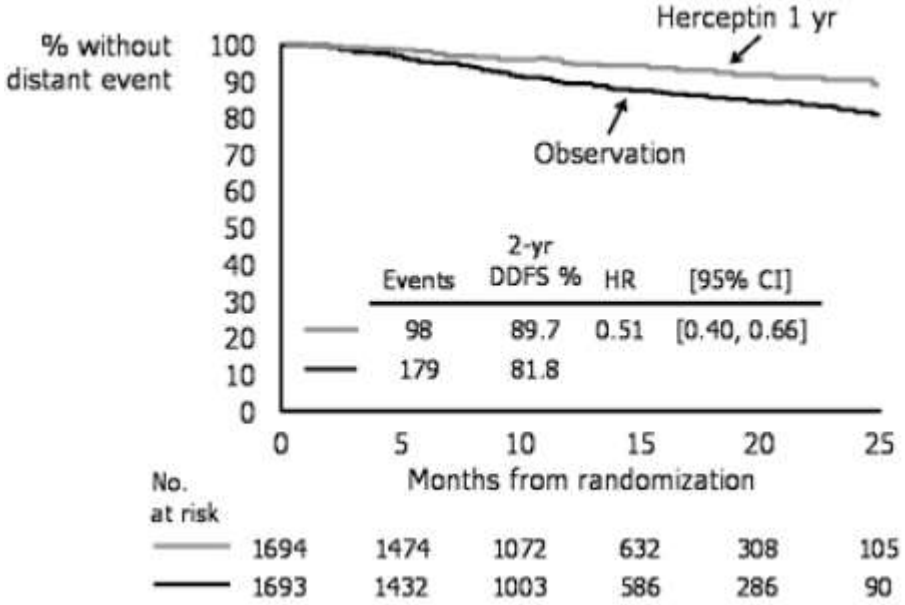
Twenty-one (1.2%) patients in the trastuzumab arm and 16 (0.9) patients in the observation had CNS metastases as first site of relapse.

Figure 3
Kaplan-Meier Curve of Recurrence-Free Survival
(After a Median Follow-up of 12 Months)



Note: 95%-CI is not adjusted for multiple testing.

Figure 4
Kaplan-Meier Curve of Distant-Disease-Free Survival
(After a Median Follow-up of 12 Months)



Note: 95%-CI is not adjusted for multiple testing.

Joint Analysis: NSABP B-31 and NCCTG N9831

Two cooperative group trials, NSABP B-31 and NCCTG N9831, evaluated the efficacy of incorporating trastuzumab into standard adjuvant systemic therapy in women with early stage, HER2 positive breast cancer. Breast tumour 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 (N9831) or was required to be performed at a reference laboratory (B-31). Patients were randomized to receive doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or doxorubicin and cyclophosphamide followed by paclitaxel plus trastuzumab (AC→T + H). In both trials patients received four cycles (3 weeks per cycle) of doxorubicin, at 60 mg/m^2 IV push, concurrently with IV cyclophosphamide at 600 mg/m^2 over 20–30 minutes. Paclitaxel was administered weekly (80mg/m^2) or every 3 weeks (175mg/m^2) for a total of 12 weeks in NSABP B-31; paclitaxel was administered weekly (80mg/m^2) for 12 weeks in NCCTG N9831. Trastuzumab was administered at a loading dose of 4 mg/kg load followed by 2 mg/kg IV weekly. Trastuzumab commenced with paclitaxel and continued for a total of 52 weeks in both trials. Disease-free survival was the pre-specified primary endpoint of the combined efficacy analysis of these studies.

A total of 3752 patients were evaluable for analysis of efficacy at the time of the definitive disease-free survival analysis. Median follow-up from the time of randomization was 1.8 years for the chemotherapy alone arm and 2.0 years for the trastuzumab + chemotherapy arm for both studies combined. Efficacy results are presented in Table 34 and Figure 5. For the primary endpoint, disease-free survival, addition of trastuzumab to chemotherapy reduced the risk of a first event by 52%. Please see 8 ADVERSE REACTIONS and 7 WARNINGS AND PRECAUTIONS: Cardiovascular/Cardiotoxicity/Early Breast Cancer for a summary of the Joint Analysis safety information.

Table 34: Joint Analysis: NSABP B-31 and NCCTG N9831 Efficacy Results at the Time of the Definitive Disease-Free Survival Analysis* (ITT population)

	AC→T[a] n=1880	**AC→T+ trastuzumab [a] n=1872**		
	No. with Event	**No. with Event**	**Hazard Ratio [b] (95% CI)**	**p-value [c]**
Disease-free survival (DFS)	261	133	0.48 (0.39–0.59)	< 0.0001
Overall survival (OS)	92	62	0.67	NS[d]

CI = confidence interval.

Disease-free survival was defined as the time from randomization to recurrence, contralateral breast cancer or other second primary cancer, or death, whichever occurred first. Overall survival was defined as the time from randomization to death.

* at median duration of follow up of 1.8 years for the patients in the AC→T arm and 2.0 years for patients in the AC→TH arm

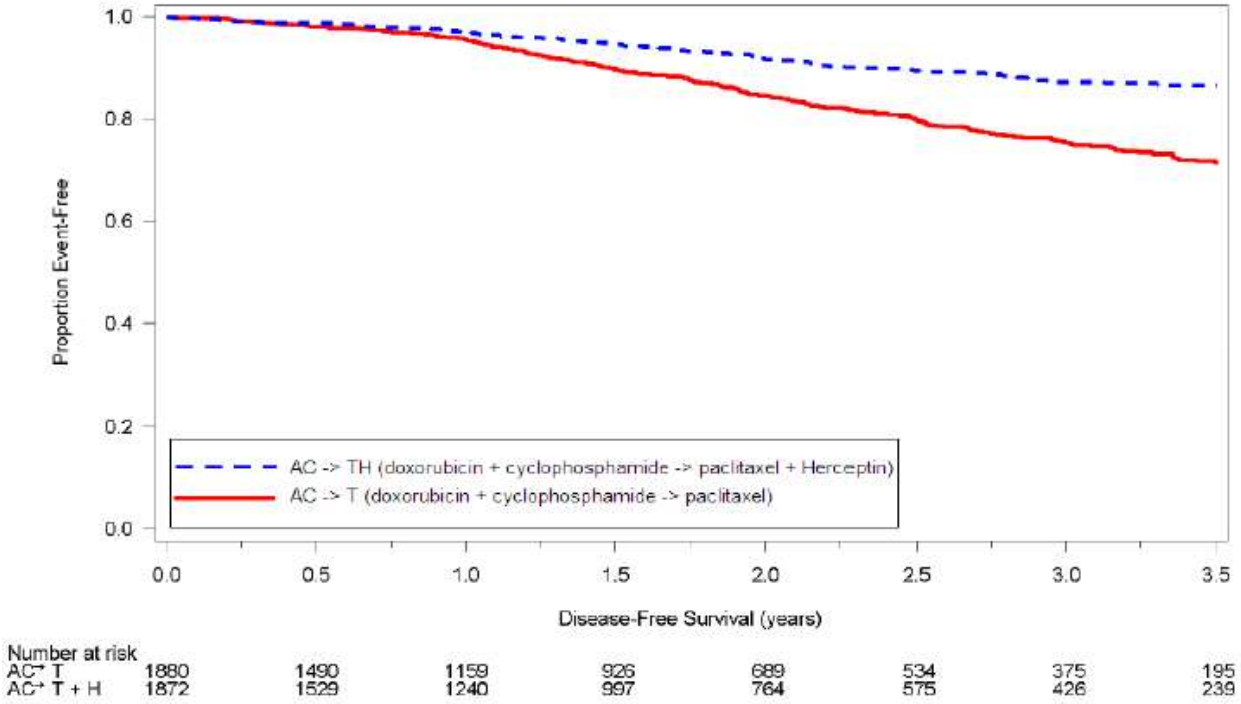
[a] NSABP B-31 and NCCTG N9831 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus trastuzumab (AC→TH).

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

c stratified log-rank test.

d NS=non-significant.

Figure 5 **Duration of Disease-Free Survival in Patients from the Joint Analysis: NSABP B-31 and NCCTG N9831**



There were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect was different from that of the overall patient population: Black, Hispanic, Asian/Pacific Islander patients, node-negative high-risk patients, and patients > 65 years of age.

The pre-planned final analysis of overall survival (OS) from the joint analysis of studies NSABP B-31 and NCCTG N9831 was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC→T+H group). Treatment with AC→T+H resulted in a statistically significant improvement in OS compared with AC→T (stratified HR=0.64; 95.1% CI [0.55, 0.74]; log-rank p-value < 0.0001); formal boundary for statistical significance p-value=0.0245). At 8 years, the survival rate was estimated to be 86.9% in the AC→T+H arm and 79.4% in the AC→T arm, an absolute benefit of 7.4% (refer to Figure 6).

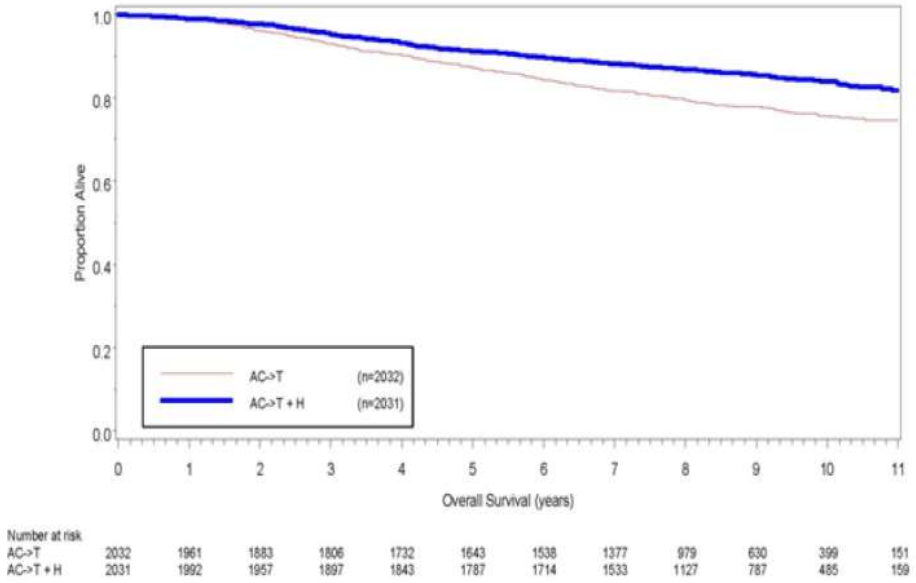
The final OS results from the joint analysis of studies NSABP B-31 and NCCTG N9831 are summarized in Table 35.

Table 35: Final Overall Survival Analysis from the Joint Analysis: NSABP B-31 and NCCTG N9831

	AC→T[a] n=2032	AC→T+ trastuzumab [a] n=2031		
	No. with Event	**No. with Event**	**Hazard Ratio (95.1% CI)**	**p-value**
Overall Survival	418 (20.6%)	289 (14.2%)	0.64 (0.55–0.74)	< 0.0001

[a] NSABP B-31 and NCCTG N9831 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus trastuzumab (AC→TH).

Figure 6 Duration of Overall Survival in Patients from the Joint Analysis: NSABP B-31 and NCCTG N9831



Disease-Free Survival (DFS) analysis was also performed at the final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831. The updated DFS analysis results showed a similar DFS benefit compared to the definitive primary DFS analysis.

<u>BCIRG-006</u>

In the BCIRG006 study, patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by docetaxel (AC→T), doxorubicin and cyclophosphamide followed by docetaxel plus trastuzumab (AC→TH), or docetaxel and carboplatin plus trastuzumab (TCH). 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.

In the AC→T arm, doxorubicin 60 mg/m^2 IV was administered in combination with cyclophosphamide 600 mg/m^2 IV on an every 3 week basis for 4 cycles followed by docetaxel 100 mg/m^2 as 1 hour IV infusion on an every 3 week basis for 4 cycles.

In the AC→TH arm, every 3 weeks for four cycles, patients in the AC→TH arm received 60 mg/m^2 doxorubicin as a 5- to 15-minute intravenous (IV) bolus injection followed by 600 mg/m2 IV cyclophosphamide as a 5- to 60-minute IV bolus injection. Three weeks after the last treatment with AC (i.e., on Day 1 of Cycle 5), a 4-mg/kg trastuzumab loading dose was administered as a 90-minute IV infusion. Beginning on Day 8 of Cycle 5, 2 mg/kg trastuzumab was administered as a 30-minute IV infusion every week. Docetaxel 100 mg/m2 was administered as a 1-hour IV infusion every 3 weeks for four cycles, beginning on Day 2 of Cycle 5 and then on Day 1 of all subsequent cycles. Beginning 3 weeks after the last treatment with docetaxel, 6 mg/kg trastuzumab was administered as a 30-minute IV infusion every 3 weeks.

In the TCH arm, patients received a 4-mg/kg trastuzumab loading dose as a 90-minute IV infusion on Day 1 of Cycle 1. Beginning on Day 8 of Cycle 1, 2 mg/kg trastuzumab was administered as a 30-minute IV infusion every week. Every 3 weeks for six cycles, beginning on Day 2 of Cycle 1 and then on Day 1 of all subsequent cycles, 75 mg/m2 docetaxel was administered as a 1-hour IV infusion, followed by carboplatin at a target area under the concentration–time curve of 6 mg/mL/min as a 30- to 60-minute IV infusion (the dose of carboplatin was calculated using a modified Calvert formula). Beginning 3 weeks after the last treatment with chemotherapy, 6 mg/kg trastuzumab was administered as a 30-minute IV infusion every 3 weeks.

Trastuzumab in combination with docetaxel and carboplatin (TCH) is a non-anthracycline containing regimen and therefore testing of this regimen in study BCIRG006 offered the possibility to evaluate formally a less cardiotoxic regimen for the adjuvant treatment of early stage HER2 positive breast cancer.

Breast tumour specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory.

The efficacy results from the BCIRG006, the primary endpoint of disease-free survival and the secondary endpoint of overall survival, are summarized in the following tables:

Table 36
Overview of Efficacy Analyses BCIRG006 AC→T versus AC→TH

Parameter	AC→T (N=1073)	AC→TH (N=1074)	p-value vs AC→T (log-rank)	Hazard Ratio vs AC→T** (95% CI)
Disease-free survival No. patients with event	195	134	<0.0001	0.61 (0.44, 0.85)*
Overall survival (Death)*** No. patients with event	80	49	***	0.58 (0.40, 0.83)

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; CI = confidence interval
*The 95% CI is the repeated confidence interval (RCI) adjusted by multiple interim looks.
** Hazard ratio was estimated by Cox regression stratified by number of positive nodes and hormonal receptor status.
***Secondary endpoint

Table 37 Overview of Efficacy Analyses BCIRG006 AC→T versus TCH				
Parameter	**AC→T (N=1073)**	**TCH** (N=1074)	**p-value vs AC→T (log-rank)**	**Hazard Ratio vs AC→T** (95% CI)**
Disease-free survival No. patients with event	195	145	0.0003	0.67 (0.49,0.92)*
Overall survival (Death)*** No. patients with event	80	56	***	0.66 (0.47, 0.93)

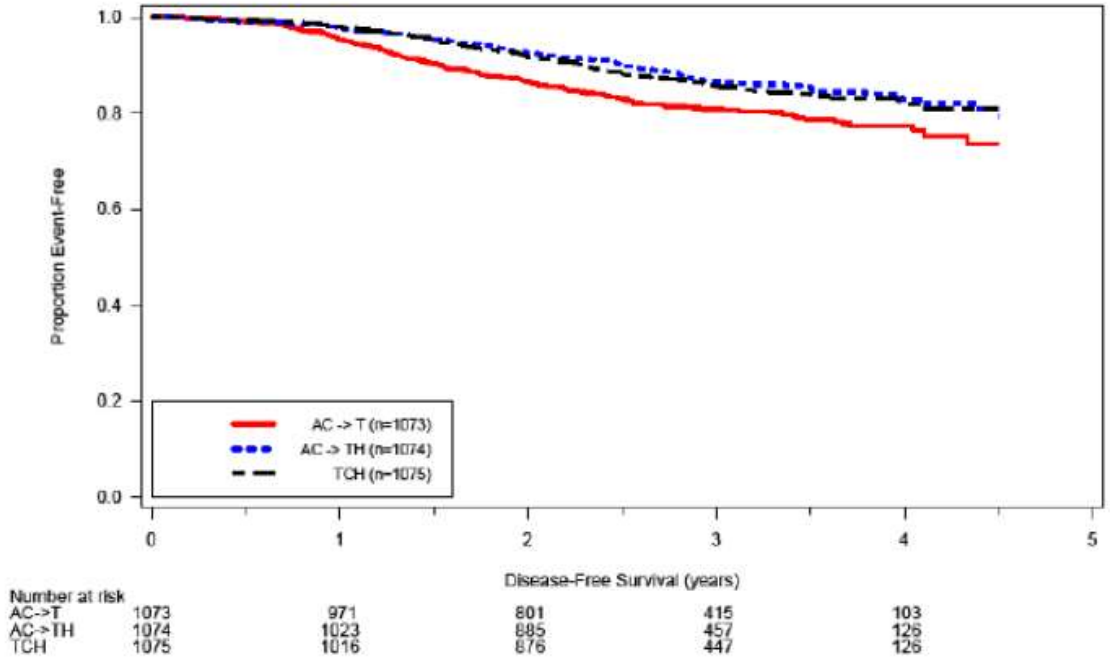
AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; TCH = docetaxel, carboplatin and trastuzumab; CI = confidence interval

*The 95% CI is the repeated confidence interval (RCI) adjusted by multiple interim looks.

** Hazard ratio was estimated by Cox regression stratified by number of positive nodes and hormonal receptor status.

***Secondary endpoint

Figure 7
Duration of Disease-Free Survival in Patients from BCIRG-006



AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel
AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab
TCH = docetaxel, carboplatin and trastuzumab

Metastatic Breast Cancer (MBC)

The safety and efficacy of trastuzumab were studied in a multicenter, randomized, controlled clinical trial conducted in 469 patients with HER2- overexpressing MBC who had not been previously treated with chemotherapy for metastatic disease. Patients were eligible if they had 2+ or 3+ levels of overexpression (based on a 0 to 3+ scale) by immunohistochemical assessment of tumour tissue

performed by a central testing lab. Eligible patients were randomized to receive chemotherapy alone or in combination with trastuzumab given intravenously as a 4 mg/kg loading dose followed by weekly doses of trastuzumab at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/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). Compared with patients in the AC subgroups (n=281), patients in the paclitaxel subgroups (n=188) were more likely to have had the following: poor prognostic factors (premenopausal status, estrogen or progesterone receptor negative tumours, positive lymph nodes), prior therapy (adjuvant chemotherapy, myeloablative chemotherapy, radiotherapy), and a shorter disease-free interval.

Compared with patients randomized to chemotherapy alone, the patients randomized to trastuzumab and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a higher one-year survival rate. These treatment effects were observed both in patients who received trastuzumab plus paclitaxel and in those who received trastuzumab plus AC, however the magnitude of the effects was greater in the paclitaxel subgroup. The degree of HER2 overexpression was a predictor of treatment effect.

The results of the study are discussed in Table 38.

Table 38
Phase III Clinical Efficacy in First-Line Treatment

	Combined Results		***Paclitaxel Subgroup***		***AC Subgroup***	
	trastuzumab + Chemotherapy (n=235)	**Chemotherapy (n=234)**	**trastuzumab + Paclitaxel (n=92)**	**Paclitaxel (n=96)**	**trastuzumab + AC[a] (n=143)**	**AC (n=138)**
Primary Endpoint						
Time to Progression[b,c]						
Median (months)	7.6	4.6	6.9	3.0	8.1	6.1
95% confidence interval	(7.0, 9.4)	(4.4, 5.4)	(5.3, 9.9)	(2.1, 4.3)	(7.3, 9.9)	(4.9, 7.1)
p-value	0.0001		0.0001		0.0003	
Secondary Endpoints						
Overall Response Rate[b]						
Rate (percent)	48	32	42	16	52	43
95% confidence interval	(42, 55)	(26, 38)	(32, 52)	(8, 23)	(44, 61)	(34, 51)
p-value	0.0002		< 0.0001		0.1038	
Duration of Response[b,c]						
Median (months)	9.3	5.9	11.0	4.4	9.1	6.5
95% confidence interval	(8.0, 11.0)	(5.5, 7.0)	(8.2, >19.8)	(3.9, 5.3)	(7.2, 11.0)	(5.8, 8.0)
p-value	0.0001		0.0001		0.0025	
1-Year Survival[c]						
Percent alive	78	67	72	60	83	72

Table 38 Phase III Clinical Efficacy in First-Line Treatment						
	Combined Results		***Paclitaxel Subgroup***		***AC Subgroup***	
	trastuzumab + Chemotherapy (n=235)	**Chemotherapy (n=234)**	**trastuzumab + Paclitaxel (n=92)**	**Paclitaxel (n=96)**	**trastuzumab + AC[a] (n=143)**	**AC (n=138)**
p-value	0.0080		0.0975		0.0415	

a AC = anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
b Assessed by an independent Response Evaluation Committee.
c Kaplan-Meier Estimate

Trastuzumab was also studied as a single agent in a multicentre, open-label, single-arm clinical trial 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, 68% had received prior adjuvant chemotherapy, 32% had one and 68% had received two prior chemotherapy regimens for metastatic disease, and 26% 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. The ORR (complete response + partial response), as determined by an independent Response Evaluation Committee, was 15% (with 8 patients having a complete response and 26 patients with a partial response) with a median survival of 13 months. Complete responses were observed only in patients with disease limited to skin and lymph nodes. The degree of HER2 overexpression was a predictor of treatment effect.

For information on clinical studies with Trastuzumab in combination with pertuzumab and docetaxel, consult the Product Monograph for pertuzumab.

Metastatic Gastric Cancer (MGC)
ToGA (BO18255)
Study ToGA (BO18255) was an open-label randomized multicentre, international Phase III study of trastuzumab in combination with a fluoropyrimidine (FP) and cisplatin versus chemotherapy alone in patients with inoperable locally advanced or recurrent and/or metastatic HER2 positive adenocarcinoma of the stomach or gastro-esophageal junction. Eligibility for inclusion required patients to be HER2 positive as determined by either HER2 protein overexpression (IHC) or HER2 gene amplification (FISH), performed by a central laboratory.

At the time of conducting the ToGA (BO18255) trial, the combination of 5-FU or capecitabine and cisplatin was considered to be a standard of care in Canada.

Table 39 Summary of Demographic Data		
	FP/ Cisplatin (FP) N = 290	**Trastuzumab/ FP/ Cisplatin (H+FP) N = 294**
Sex		
Male	218 (75%)	226 (77%)
Female	72 (25%)	68 (23%)
Race		
Black	2 (<1%)	1 (<1%)
Caucasian	105 (36%)	115 (39%)
Oriental	158 (54%)	151 (51%)
Other	25 (9%)	27 (9%)
Age in years		
Mean	58.5	59.4
SD	11.22	10.75
Median	59.0	61.0
Min-Max	21-82	23-83
Weight in kg		
Mean	63.17	62.08
SD	13.034	12.594
Median	60.30	61.45
Min-Max	28.0-105.0	35.0-110.0
Height in cm		
Mean	166.4	166.3
SD	8.85	8.26
Median	167.0	166.0
Min-Max	128-190	146-198

The efficacy results from the ToGA (BO18255) study are summarized in tables 39-41. Patients were recruited to the trial who were previously untreated for HER2 positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction not amenable to curative therapy. The primary endpoint was overall survival which was defined as the time from the date of randomization to the date of death from any cause. At the time of the analysis a total of 349 randomized patients had died: 182 patients (62.8%) in the control arm and 167 patients (56.8%) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer.

The addition of trastuzumab to capecitabine/5-FU and cisplatin resulted in a clinically relevant and statistically significant improvement in the primary endpoint of overall survival (p = 0.0046, Log Rank test). The median survival time was 11.1 months with capecitabine/5-FU and cisplatin and 13.8 months with trastuzumab + capecitabine/5-FU and cisplatin. The risk of death was decreased by 26% (Hazard Ratio [HR] 0.74 95% CI [0.60-0.91]) for patients in the trastuzumab arm compared to the capecitabine/5-FU arm. The results are considered by the study's independent data monitoring committee as the definitive outcome of the study.

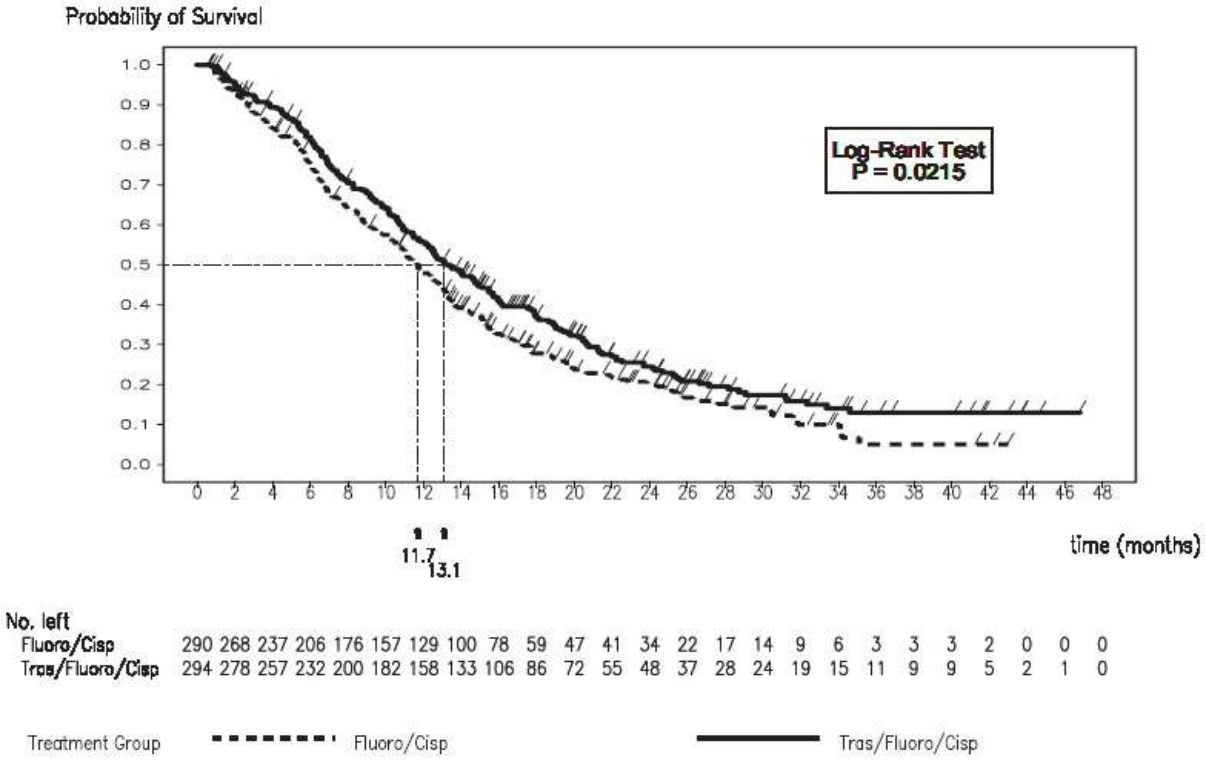
One year after the clinical cutoff date of the definitive efficacy and safety second interim analysis, updated overall survival analysis demonstrated that 446 patients had died: 225 patients (78%) in the control arm and 221 patients (75%) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer. The median survival time was 11.7 months with capecitabine/5-FU and cisplatin and 13.1 months with trastuzumab + capecitabine/5-FU and cisplatin. The risk of death was decreased by 20% (Hazard Ratio [HR] 0.80 repeated CI [0.661, 0.978]) for patients in the trastuzumab arm compared to the capecitabine/5-FU and cisplatin arm (see Table 40 and Figure 8).

Table 40
Summary of Overall Survival Results From Study ToGA (BO18255) Full Analysis Set

Analysis	**Overall Survival, Median months**		**HR CI*** **	**p-value**
	FP N =290	**(H+FP) N = 294**		
2nd Interim Efficacy and Safety Analysis*	11.1	13.8	0.74 (0.573, 0.950)	0.0046
Updated OS Analysis**	11.7	13.1	0.80 (0.661, 0.978)	0.0215

FP: Fluoropyrimidine/cisplatin
H+FP: trastuzumab + fluoropyrimidine/cisplatin
*The OS results presented in the first row of Table 40 are the results from the second efficacy interim analysis (clinical data cut off date: January 7, 2009). The OS results reviewed by the Independent Data Monitoring Committee (IDMC) from the second interim analysis based on 348 deaths crossed the pre specified statistical boundary of 0.0188 (p=0.0048) and were the definitive outcome of study ToGA (BO18255).
**The OS results presented in the second row of Table 40 are the results from the updated OS analysis one year after the clinical cutoff date of the definitive efficacy and safety second interim analysis.
*** For the purposes of maintaining confidence intervals at an overall 95% level for the multiple looks at the survival data, repeated confidence intervals (RCIs) for the hazard ratio for OS were calculated.

Figure 8
Kaplan-Meier Curve for Overall Survival*



*The Kaplan-Meier curves for the OS are the results from the updated OS analysis one year after the clinical cutoff date of the definitive efficacy and safety second interim analysis.

In trial ToGA (BO18255), post hoc subgroup analyses indicate that a positive treatment effect was limited to tumours with higher levels of HER2 protein (IHC 2+ /FISH+ and IHC 3+). At the time of the second interim efficacy and safety analysis, the median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR 0.65 (95% CI 0.51-0.83) (see Table 41).

Table 41
Overall Survival Results by HER2 Status – IHC 0, IHC 1+ versus IHC 3+, IHC 2+/FISH+ (Full Analysis Set)

Subgroup		FP			H+FP				
		Patients per group	N Events	Median time	Patients per group	N Events	Media n time	HR	95% CI for HR
All		290	182	11.1	294	167	13.8	0.74	[0.60; 0.91]
HER2 Results	FISH+/IHC0 or 1+ FISH- or + or no result/IHC2+ or 3+	70 218	45 136	8.7 11.8	61 228	43 120	10.0 16.0	1.07 0.65	[0.70; 1.62] [0.51; 0.83]

A total of 233 patients [40%] received previous treatments for gastric cancer, which included adjuvant chemotherapy, radiotherapy, and/or surgery: 130 patients [44%] in the FP + H arm and 103 patients

[36%] in the FP arm. A total of 351 patients [60%] did not receive previous treatments for gastric cancer. Of these, there were 164 patients [56%] in the FP + H arm and 187 patients [64%] in the FP arm (see Table 42).

Table 42
Analysis Of Overall Survival By Prior Gastric Cancer Treatment: Full Analysis Set

	FP			H+FP			Hazard Ratio[a] (95% CI)
	Patient per Group	Events	Median OS (mo)	Patient per Group	Events	Median OS (mo)	0.74 (0.60, 0.91)
All	290	182	11.1	294	167	13.8	
Prior treatment for gastric cancer							0.67 (0.51, 0.88)
No	187	123	10.2	164	101	12.6	0.88 (0.62, 1.25)
Yes	103	59	13.5	130	66	14.6	

[a] Relative to fluoropyrimidine/cisplatin; based on unstratified analysis.

The results for the primary endpoint of the study ToGA (BO18255), overall survival, were supported by the improvements in the secondary efficacy parameters of PFS, time to progression, overall response rate, and duration of response. At the time of the second interim efficacy and safety analysis, for the FP + H arm versus the FP arm, median PFS was 6.7 months versus 5.5 months; median time to progression was 7.1 months versus 5.6 months; overall response rate was 47.3% (139/294) versus 34.5% (100/290); and median duration of response was 6.9 months versus 4.8 months.

15 NON-CLINICAL TOXICOLOGY

The trastuzumab toxicology program addressed issues of species specificity, chronic administration, coadministration with chemotherapeutic agents, manufacturing process optimization, and changes in formulation.

Trastuzumab is specific for the human $p185^{HER2}$ receptor and does not bind the corresponding rodent receptor ($p185^{neu}$). The *in vitro* tissue binding profile of trastuzumab to monkey tissues demonstrated that the monkey was an appropriate model for comprehensive toxicity testing.

Acute Toxicity Studies: In acute dose studies, trastuzumab was well tolerated and produced no evidence of systemic toxicity at any dose tested, including the highest dose that could be delivered of a 5 mg/mL formulation. Intravenous administration of trastuzumab as a single dose of 94 mg/kg (mice), or 47-50 mg/kg (monkeys), produced no findings of toxicologic significance in any parameter evaluated.

Bridging studies conducted in monkeys to evaluate the safety and pharmacokinetics of trastuzumab, produced by optimization of the manufacturing process including a cell line change (from H2 to H13), revealed no evidence of acute toxicity or changes in pharmacokinetic disposition in monkeys. Trastuzumab produced from a subsequent manufacturing scale up and formulation change

(lyophilization) resulted in comparable pharmacokinetic profiles in monkeys and had no effect on safety endpoints.

The findings from the acute toxicity studies with trastuzumab are summarized in Table 45.

Multidose Toxicity Studies: In multiple-dose studies, trastuzumab was well tolerated and produced no evidence of systemic toxicity at any dose tested, including the highest dose that could be delivered of 25 mg/kg. Intravenous administration of trastuzumab as multiple intravenous doses in monkeys of up to 25 mg/kg given weekly for 26 weeks, or twice-weekly for up to 12 weeks, produced no findings of toxicologic significance in any parameter evaluated.

Some isolated changes in ECG, which followed no apparent pattern, were observed in the multiple intravenous doses study in monkeys, dosed up to 25 mg/kg weekly for 26 weeks. The following is a summary of the electrocardiographic findings that were statistically significant in this study from control. In female monkeys, at weeks 5 and 21, the Q-T interval for the 5 mg/kg dose was 0.22 seconds (Vehicle 0.18 seconds) and for the 25 mg/kg dose was 0.23 seconds (Vehicle 0.18 seconds). In male monkeys, at weeks 9 and 17, the Q-T interval for the 1 mg/kg dose was 0.16 seconds (Vehicle 0.21 seconds) and for the 25 mg/kg dose was 0.04 seconds (Vehicle 0.03 seconds). The heart rate, at week 17, for the 5 and 25 mg/kg dose, was 145 and 160 beats/minute, respectively (Vehicle 183 beats/minute). There were no statistically significant electrocardiographic findings in female monkeys at weeks 9, 13, 17 and 26, and in male monkeys at weeks 5, 13, 21 and 26. In male monkeys during the recovery phase (weeks 30 and 34), the heart rate for the 25 mg/kg dose was 190 beats/minute (Vehicle 160 beats/minute) and 180 beats/minute (Vehicle 200 beats/minute), respectively; while the Q-T interval was 0.19 seconds (Vehicle 0.22 seconds) and 0.23 seconds (Vehicle 0.19 seconds), respectively. In female monkeys, at weeks 30 and 34, the heart rate was 190 beats/minute (Vehicle 210 beats/minute) and 140 beats/minute (Vehicle 180 beats/minute), respectively; while the Q-T interval was 0.22 seconds (Vehicle 0.17 seconds) and 0.26 seconds (Vehicle 0.21 seconds), respectively for the 25 mg/kg dose.

Although, administration of trastuzumab was associated with a mild reduction in heart rate in some male monkeys receiving 5 or 25 mg/kg, this was not considered toxicologically significant since bradycardia was not present in these monkeys. There was no toxicological significance of the aberrant ventricular complexes seen in monkeys treated with trastuzumab since these were not seen broadly in all treated monkeys. Occasional abnormal complexes may be observed in normal animals.

The findings from the multidose toxicity studies with trastuzumab are summarized in Table 46.

Special Toxicity Studies: Specific toxicity studies performed with trastuzumab included: issue cross-reactivity studies in human and monkey tissue, immunogenicity, drug interaction, and local tolerance studies, *in vitro* hemolytic potential/blood compatibility studies, and a systemic toxicity study in mice with the formulation component trehalose. Details from these studies are provided in Table 47.

No gross or histopathologic changes were observed in tissues which demonstrated trastuzumab binding in the tissue cross-reactivity studies.

In addition, trehalose, a component of the lyophilized formulation, produced no evidence of clinical or

anatomical toxicity when given daily to mice at intravenous doses of up to 1 g/kg. Single dose drug interaction studies in which 1.5 mg/kg trastuzumab (lower than the recommended dose) was administered intravenously with single doses of doxorubicin, cyclophosphamide, paclitaxel, or the combination of doxorubicin and cyclophosphamide, did not show any significant alterations in disposition profiles of trastuzumab, or any of the chemotherapeutic agents, that might suggest possible safety or efficacy concerns. In local tolerance studies conducted in rabbits, no gross or histopathologic evidence of irritative potential was noted following intravenous administration of the liquid or lyophilized trastuzumab formulations at a concentration of 5 mg/mL. Both the liquid and lyophilized formulations are compatible with whole blood, serum, and plasma obtained from humans and monkeys.

Table 45: Overall Summary of Nonclinical Acute Toxicity Studies with Trastuzumab

Study No.	Study Type	Species/ Strain	No./Sex/ Group	Route of Admin.	Dose (mg/kg)	Lot No.	Estimated Safety Factor		Study Duration
							Body Weight Ratio	AUC_A/ AUC_H	
91-629-1450	Acute Single Dose (GLP)	Mouse/Crl: CD-1® (ICR) BR/VAF/ PlusTM	5/M 5/F	IV	0 9.4 47 94	M3-RD175	--- 4.7x NA 47x	--- 2.8x NA 19x	At least 2 weeks
Comments: Trastuzumab was well tolerated and the no observable effect level (NOEL) after a single intravenous bolus injection of trastuzumab was 94.0 mg/kg in mice.									
91-640-1450	Acute Single Dose (GLP)	Monkey/ Rhesus	2/M 2/F	IV	0 4.7 23.5 47	M3-RD175	--- 2.4x NA 24x	--- 1x NA 12x	At least 2 weeks
Comments: Trastuzumab was well tolerated and the no observable effect level (NOEL) after a single intravenous bolus injection of trastuzumab was 47.0 mg/kg in rhesus monkeys.									
94-173-1450[a]	Acute Single Dose (GLP)	Monkey/ Rhesus	2/M 2/F	IV	0 5 50 50	M3-RD319 A9806AX	--- 2.5x 2.5x 2.5x	--- NA NA NA	At least 2 weeks
Comments: A single intravenous dose of trastuzumab H13 or trastuzumab H2 up to 50 mg/kg was well tolerated and produced no adverse effects in rhesus monkeys.									
94-436-1450[b]	Acute single Dose (GLP)	Monkey/ Rhesus	4/F	IV	1.5 1.5	M3-RD319 C9802AX	0.8x 0.8x	NA NA	30 days
Comments: The single intravenous administration of trastuzumab (H13-1K) or trastuzumab (H13-12K) at a dose level of 1.5 mg/kg was well tolerated and produced no test material-related differential effects on toxicity parameters in female rhesus monkeys.									

Table 46: Overall Summary of Nonclinical Acute Toxicity Studies with Trastuzumab

Study No.	Study Type	Species/ Strain	No./Sex/ Group	Route of Admin.	Dose (mg/kg)	Lot No.	Estimated Safety Factor		Study Duration
							Body Weight Ratio	AUC_A/ AUC_H	
95-490-1450[c]	Acute Single Dose (GLP)	Monkey/ Rhesus	6/F	IV	1.5 1.5	M4-RD494 C9807AX	0.8x 0.8x	NA NA	11 weeks
Comments: This crossover study was conducted to provide serum samples from rhesus monkeys following single intravenous bolus injections of trastuzumab (single dose liquid formulation) and trastuzumab (multi-dose lyophilized formulation) to compare their pharmacokinetic profiles. All animals survived the study, and no test material-related overt clinical signs of toxicity were observed. Furthermore, there were no statistically significant or otherwise notable differences between the two groups that might be attributed to the different formulations.									

IV=Intravenous

[a] This study was conducted to support a liquid formulation process change from trastuzumab H2 to trastuzumab H13.

[b] This study was conducted to support the clinical use of trastuzumab produced by a scaled-up manufacturing process, trastuzumab (H13-12K)

[c] This study was conducted to support the clinical use of lyophilized trastuzumab.

Table 47: Overall Summary of Nonclinical Multidose Toxicity Studies with Trastuzumab

Study No.	Study Type	Species/ Strain	No./Sex/ Group	Route of Admin.	Dose (mg/kg)	Lot No.	Estimated Safety Factor		Study Duration
							Body Weight Ratio	AUC_A/ AUC_H	
91-667-1450	Multidose (GLP)	Monkey/ Rhesus	4-6/M 4-6/F	IV	0 2.35 11.75 23.5	--- 2.4x 12x 24x	--- 2x 11x 21x	8 weeks	At least 2 weeks
Comments: Intravenous bolus injections of trastuzumab at doses of up to 23.5 mg/kg were well tolerated when administered twice weekly for approximately 4 weeks.									
94-455-1450	Multidose (GLP)	Monkey/ Cynomolgus	4-6/M 4-6/F	IV	0 1 5 25	--- 0.5x 2.5x 13x	--- 0.3x 3x 14x	8 months	At least 2 weeks
Comments: Intravenous bolus injections of trastuzumab up to 25 mg/kg were well-tolerated and produce no evidence of toxicity when administered to cynomolgus monkeys once a week for approximately 6 months. However, some changes in ECG were noted at various times (Refer to the TOXICOLOGY - Multidose Toxicity Studies discussion section.									
97-333-1450	Multidose (GLP)	Monkey/ Cynomolgus	4-6/M 4-6/F	IV	0 1 5 25	--- 1x 5x 25x	--- NA NA NA	5 months	At least 2 weeks
Comments: Based on preliminary evaluation of the results of this study, administration of trastuzumab produced no apparent adverse effects on male or female cynomologus monkeys at doses up to 25 mg/kg.									

IV=Intravenous, NA=not available.

Table 48: Overall Summary of Nonclinical Multidose Toxicity Studies with Trastuzumab

Study No.	Study Type	Species/ Strain	No./Sex/ Group	Route of Admin.	Dose (mg/kg)	Lot No.	Estimated Safety Factor		Study Duration
							Body Weight Ratio	AUC_A/ AUC_H	
91-663-1450	Tissue Cross-Reactivity (GLP)	Human Tissue	NA	NA	2.5 µg/mL 50 µg/mL	0.02x[a] 0.04x[a]	NA NA	NA	At least 2 weeks
Comments: Humanized antibody trastuzumab defects an antigen that has a restricted distribution in epithelial cells and carcinomas. Murine antibody muMab 4D5 reacts in normal tissues paralleling the patterns observed for trastuzumab. Differences in staining may reflect methodological conditions employed to detect these two antibodies. The patterns of immunoreactivities observed in human tumours are almost identical for these two antibodies.									
91-686-1450	Tissue Cross-Reactivity (GLP)	Monkey/Rhesus Tissue	NA	NA	2.5 mg/mL 0.79 mg/mL	20x[a] 6x[a]	NA NA	NA	
Comments: muMab 4D5 detected an antigen in nerve and epithelial cells of various normal tissues. The pattern of staining observed with humanized trastuzumab was similar in distribution, but inconsistent and less intense. The differences in staining observed between trastuzumab and muMab 4D5 may be attributed to methodological differences in detection of the two antibodies. The results indicated that rhesus monkey expresses an antigen which is recognized by monoclonal antibodies to p185HER2.									
92-458-1450[b]	Multidose Immunogenicity (GLP)	Monkey/ Cynomolgus	3/F	IV	5.0 5.0 5.0 5.0	2.5 x 2.5 x 2.5 x 2.5 x	2.9 x 2.5 x 1.9 x 1.0 x	6 months	
Comments: Weekly administration of 5.0 mg/mL of the test material, trastuzumab (high glutamine variant), trastuzumab (low glutamine variant) and trastuzumab (arginine variant) or muMab 4D5 in cynomologus monkeys was well tolerated. Trastuzumab, trastuzumab (high glutamine variant), trastuzumab (low glutamine variant), and trastuzumab (arginine variant) were not immunogenic based on expected pharmacokinetics and a lack of antibody response, whereas muMab 4D5 was considered immunogenic in the cynomolgus monkey.									
93-446-1450[c]	Follow-Up Immunogenicity (GLP)	Monkey/ Cyomolgus	3/F	IV	5.0 5.0	2.5x 2.5x	NA NA	2 weeks	
Comments: An intravenous challenge dose of 5.0 mg/kg of trastuzumab (high glutamine variant) or trastuzumab (low glutamine variant) was well tolerated and was not immunogenic as measured by antibody formation in female cynomolgus monkeys.									

Table 49: Overall Summary of Nonclinical Multidose Toxicity Studies with Trastuzumab

Study No.	Study Type	Species/ Strain	No./Sex/ Group	Route of Admin.	Dose (mg/kg)	Lot No.	Estimated Safety Factor		Study Duration
							Body Weight Ratio	AUC_A/ AUC_H	
94-241-1450	Single-Dose Drug Interaction (GLP)	Monkey/Rhesus	3/F	IV	1.5	0.8x	NA	3 weeks	At least 2 weeks
Comments: A single intravenous injection of trastuzumab liquid formulation (at doses that approximate the human clinical dose on a body weight basis), when given alone or in combination with Adriamycin® or Taxol®, or when given in combination of Adriamycin® or Cytoxan®, was well tolerated and produced no evidence of systemic toxicity.									
91-639-1450	Acute Local Tolerance (GLP)	Rabbit/Hra: (NZW) SPF	9/F	IV	0 1.9	--- 1x	--- NA	7 days	
Comments: The test material and excipient formulations are not considered to be locally irritating following a single bolus intravenous administration in rabbits.									
95-502-1450	Acute Local Torerance (GLP)	Rabbit/Hra: (NZW) SPF	IV IV SC SC	0 5 mg/mL 50 mg/mL 100 mg/mL	--- 1x 9.5x 19x	--- NA NA NA	7 days	6 months	
Comments: Administration of trastuzumab given as a single intravenous bolus injection following reconstitution with 1.1% benzyl alcohol and dilution with saline to a concentration of 5 mg/mL, or given as a single subcutaneous injection following reconstitution with 1.1% benzyl alcohol to a concentration of 100 mg/mL, or dilution with saline to 50 mg/mL is well-tolerated in rabbits and produces no evidence of local irritation attributable to the test material.									
91-668-1450	Hemolytic Potential Blood Compatibility (GLP)	Monkey/Rhesus and Human blood and plasma	NA	NA	4.7 mg/mL	38x[a]	NA	NA	
Comments: Trastuzumab (at a concentration of 4.7 mg/mL) and excipient trastuzumab did not cause hemolysis of human or rhesus monkey erythrocytes and were compatible with human and rhesus monkey serum and plasma.									

Adriamycin is a registered Trade-Mark of Pharmacia & Upjohn S.P.A.
Taxol is a registered Trade-Mark of Bristol-Myers Squibb Company
Cytoxan is a registered Trade-Mark of Mead Johnson & Company

Table 50: Overall Summary of Nonclinical Multidose Toxicity Studies with Trastuzumab

Study No.	Study Type	Species/ Strain	No./Sex/ Group	Route of Admin.	Dose (mg/kg)	Lot No.	Estimated Safety Factor		Study Duration
							Body Weight Ratio	AUC_A/ AUC_H	
95-501-1450	Hemolytic Potential Blood Compatibility (GLP)	Monkey/Rhesus and Human blood and plasma	NA	NA	5 mg/mL	41x[a]	NA	NA	At least 2 weeks
Comments: Trastuzumab (at a concentration of 5 mg/mL) and trastuzumab vehicle (diluted to a concentration equivalent to a 5 mg/mL trastuzumab concentration) did not cause hemolysis of rhesus monkey or human erythrocytes and are compatible with rhesus monkey and human serum and plasma.									
96-014-1450	Multidose (GLP) with Trehalose	Mouse/Crl: CD1® (ICR)BRVAF/ Plus®	10/M 10/F	IV	0 10 100 1000	--- 35x[d] 350x[d] 3500x[d]	- NA NA NA	2 weeks	
Comments: Daily intravenous administration of trehalose for 2 weeks was well tolerated and produced no adverse effects at doses up to and including 1000 mg/kg in male and female mice.									

IV=Intravenous, NA=not available, SC=Subcutaneous, IP=Intraperitoneal

[a] Animals were not dosed so AUC ratios cannot be calculated, however the ratio of concentration applied *in vitro* to tissues/maximum average concentration observed in human circulation (123 µg/mL) is presented here.
[b] The immunogenic potential to two trastuzumab (H2) preparations, containing high or low levels of glutamine variant, and an arginine variant-containing trastuzumab preparation, was compared to the immunogenic potential of the murine counterpart antibody, muMAb 4D5.
[c] This study was conducted to further assess the immunogenic potential of the presence of glutamine variant in trastuzumab (H2). A single challenge dose was administered to those monkeys (in Study 92-458-1450) that had received 6 months of weekly injections of the high or low glutamine variant-containing trastuzumab (H2) preparations.
[d] The ratio of trehalose dose/projected final trastuzumab formulation trehalose dose (~2 mg/kg) is presented here.
® registered Trademarks of their respective owners

Reproductive Toxicity: The results of reproductive toxicity studies conducted in female cynomolgus monkeys given trastuzumab as daily intravenous injections for 4 days followed by twice-weekly administration for the duration of the dosing period revealed no alterations in menstrual cyclicity or sex hormone profiles, and no trastuzumab-related embryotoxicity or effects on fetal development. Pregnancy did not appear to affect maternal exposure to trastuzumab.

When trastuzumab was administered during the period of organogenesis, fetal serum trastuzumab concentrations ranged from 10%-19% of maternal values. Administration during the last trimester was associated with trastuzumab fetal serum concentrations of approximately 33% of maternal concentrations. The difference in fetal serum trastuzumab concentrations obtained in the early and late gestational periods may be attributable to the time between trastuzumab administration and maternal/fetal blood sampling (e.g., samples were obtained 50 days, early gestational study, or 2 days, late gestational study, after the final trastuzumab administration). However, an increase in fetal/maternal serum concentration ratio is consistent with an increase in immunoglobulin transfer rate observed as gestation progresses in both humans and in nonhuman primates. Compared to serum concentrations, trastuzumab was detected at relatively low levels in the milk of lactating monkeys. Trastuzumab detected in the milk of lactating monkeys had no effect on neonatal growth and development from birth to one month of age when study was terminated. A summary of the reproduction studies conducted with trastuzumab is provided in Table 51.

Carcinogenicity: Trastuzumab has not been tested for its carcinogenic potential.

Mutagenicity: Trastuzumab has not been associated with any evidence of mutagenic potential in a mouse micronucleus test, a bacterial mutation test, or in a chromosomal aberration assay in human lymphocytes. These studies are summarized in Table 52.

Table 51: Overall Summary of Nonclinical Reproduction Studies with Trastuzumab

Study No.	Study Type	Species/ Strain	No./Sex/ Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor		Study Duration
						Body Weight Ratio	AUC_A/ AUC_H	
95-038-1450	Fertility valuation (GLP)	Monkey/ Cynomolgus	6/F	IV	0 1 5 25	--- 1x 5x 25x	--- 8.0xa 2.2xa 1.6xa	7 Menstrual Cycles
Comments: Intravenous administration of trastuzumab at dose levels of 1, 5, and 25 mg/kg during three menstrual cycles was not associated with signs of toxicity, alterations in menstrual cyclicity, or in sex hormone profiles.								
95-039-1450	Embryo-Fetal Development (GLP)	Monkey/ Cynomolgus	12/F	IV	0 1 5 25	--- 1x 5x 25x	--- 7.2x[a] 2.2x[a] 1.8x[a]	100 days
Comments: Intravenous administration of trastuzumab at doses of 1, 5, and 25 mg/kg on Days 20, 21, 22, 23, 27, 30, 34, 37, 41, 44, 47, and 50 of gestation was well tolerated and did not elicit maternal toxicity, embryotoxicity, or teratogenicity. However, five maternal deaths occurred in this study. Two pregnant monkeys, one in the 1.0 mg/kg group and one in the vehicle control group, died without delivery or abortion and were therefore replaced. Three subsequent maternal deaths, two in the 1.0 mg/kg dose group and one in the 25 mg/kg dose group, occurred following abortion of the fetus. The deaths were attributed to the presence of a retroviral infection within the animal colony and not to administration of trastuzumab.								
95-238-1450	Late Gestation Placental Transfer (GLP)	Monkey/ Cynomolgus	8/F	IV	25	25x	1.7x	7 months
Comments: Administration of trastuzumab at an intravenous bolus dose of 25 mg/kg during the period of late gestation and lactation did not elicit maternal, fetal, or neonatal toxicity.								

IV=Intravenous

[a] Sparse pharmacokinetic sampling precludes direct calculation of AUC ratios, however, the ratio of dose-adjusted steady-state trough concentrations of animal/human are presented here.

Table 52: Overall Summary of Nonclinical Mutagenicity Studies with Trastuzumab

Study No.	Study Type	Species/ Strain	No./Sex/ Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor		Study Duration
						Body Weight Ratio	AUC_A/ AUC_H	
98-024-1450	*In Vivo* Micronucleus (GLP)	Mouse/ICR/ (CRj: CD-1,SPF)	6/M	IV	0 29.5 59 118	--- 15x 30x 59X	--- NA NA NA	24 hours
Comments: Trastuzumab was found to be negative for causing clastogenic damage as measured by micronucleus induction for the bone marrow cells of male ICR mice.								
94-382-1450	Mutagenicity (GLP)	*Salmonella typhimurium E. coli*	NA	NA	0-5000 µg/mL	--- 41xa	--- NA	NA
Comments: Trastuzumab was unable to induce mutation in 4 strains of *Salmonella typhimurium* and 2 strains of *E. coli,* when tested at concentrations up to 5000 µg/mL in the absence of a rat liver metabolic activation system (S-9), and 3750 µg/mL in its presence, with treatments performed using a "treat and plate" protocol. All trastuzumab treatments of the test strains, both in the absence and in the presence of S-9, failed to produce a statistically significant increase in revertant numbers when the data were analysed at the 1% level using Dunnett's test. This study was therefore considered to have provided no evidence of trastuzumab mutagenic activity.								
97-101-1450	Cytogenicity (GLP)	Human Lymphocytes	NA	NA	0-5000 µg/mL	--- 41xa	--- NA	NA
Comments: Trastuzumab was considered negative for inducing chromosomal aberrations in human whole blood lymphocytes when treated with trastuzumab at doses up to and including 5000 µg/mL with and without metabolic activation. These results were verified in independently conducted confirmatory trials.								

IV=Intravenous, NA=not applicable.

[a] Animals were not dosed so AUC ratios cannot be calculated, however the ratio of concentration examined *in vitro*/maximum average concentration observed in human circulation (123 µg/mL) is presented here.

15.1 Comparative Non-Clinical Pharmacology and Toxicology

15.1.1 Comparative Non-Clinical Pharmacodynamics

***In vitro* Studies**

Non-clinical Pharmacokinetics:
A comparative pharmacokinetic (PK) study of OGIVRI and Herceptin was performed in cynomolgus monkeys (MYL-HER-PC-02). Each cynomolgus monkey received a single-dose of 25 mg/kg of OGIVRI or Herceptin intravenously. This PK study showed that serum concentrations of Herceptin and OGIVRI declined in a bi-phasic manner with similar geometric mean apparent $t_{1/2}$ greater than 9 days. The systemic availability of OGIVRI (vs Herceptin) was 79.7% based on AUC0-∞ and 78.2% based on Cmax.

15.1.2 Comparative Toxicology

Multi-dose Toxicity Study:

Table 31: Overall Summary of Nonclinical Multi-dose Toxicity Study Comparing OGIVRI and Herceptin

Study Number	Study Type	Species/Strain	Group/ Description	No./Sex	Dose (mg/kg/ week)	Method of Administration/ Duration
MYL-Her2-PC-03	GLP-Compliant Repeat-dose toxicity and toxicokinetics	Cynomolgus monkey (*Macaca fascicularis)*	1/Control	3/M, 3/F	0	Intravenous infusion over 30 minutes/Once per week for 5 weeks
			2/Herceptin	3/M, 3/F	25	
			3/OGIVRI	3/M, 3/F	25	
			4/Herceptin	3/M, 3/F	50	
			5/OGIVRI	3/M, 3/F	50	

Once weekly intravenous administration of OGIVRI or Herceptin at 25 or 50 mg/kg/week to cynomolgus monkeys for 5 weeks was well tolerated and did not cause any drug-related clinical signs, injection site skin reactions or changes in body weight, food consumption, ECG, haematology, clinical chemistry, urinalysis, organ weights or histopathology.

Based on the absence of findings a NOEL of 50 mg/kg/week was determined for both OGIVRI and Herceptin. There were no notable differences between OGIVRI and Herceptin for either toxicokinetic or toxicological endpoints.

Special Toxicity Studies: Local tolerance was assessed in the single-dose PK and repeat-dose toxicity studies in cynomolgus monkeys. Erythema and desquamation were reported at the injection sites for OGIVRI and Herceptin.

16 SUPPORTING PRODUCT MONOGRAPHS

1. HERCEPTIN Product Monograph, Hoffmann-La Roche Limited, Control No. 235646, Date of Revision May 7, 2020

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrOGIVRI® (Oh-Give-ree)
(trastuzumab)
Sterile Powder for Intravenous Infusion

BREAST CANCER

Read this carefully before you start taking OGIVRI and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about OGIVRI.

OGIVRI is a biosimilar biologic drug (biosimilar) to the reference biologic drug HERCEPTIN®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

Serious Warnings and Precautions

Medication Errors
There is a risk of medication errors between OGIVRI (trastuzumab) and KADCYLA® (trastuzumab emtansine). Verify with the healthcare provider that the recommended OGIVRI (trastuzumab) dose and NOT KADCYLA® (trastuzumab emtansine) dose is used.

Cardiotoxicity (harm to the heart)
OGIVRI can result in the development of heart problems including heart failure. The appearance of heart failure can be delayed and can occur after treatment with OGIVRI is completed. The incidence of cardiac dysfunction was higher in patients who received Trastuzumab plus chemotherapy versus chemotherapy alone, with higher risk when Trastuzumab was administered together with a taxane following an anthracycline and cyclophosphamide. In patients with breast cancer that has spread to other parts or organs of the body, the incidence and severity of cardiac dysfunction was particularly high in patients who received Trastuzumab at the same time as anthracyclines and cyclophosphamide.

You should have your heart function evaluated by your doctor before and during treatment with OGIVRI.

Infusion Reactions; Lung Problems
Some patients have had serious infusion reactions and lung problems; infusion reactions causing death have been reported. In most cases, these reactions occurred during or within 24 hours of receiving Trastuzumab. Your OGIVRI infusion should be temporarily stopped if you have shortness of breath or very low blood pressure. Your doctor will monitor you until these symptoms go away. If you have a severe allergic reaction, swelling, lung problems, inflammation of the lung, or severe shortness of breath, your doctor may need to completely stop your OGIVRI treatment.

Toxicity to Fetus (Unborn Baby)
OGIVRI can cause harm to the fetus (unborn baby), in some cases death of the fetus, when taken by a pregnant woman. Women who could become pregnant need to use effective birth control methods during OGIVRI treatment and for at least 7 months after treatment with OGIVRI. Nursing mothers treated with OGIVRI should discontinue nursing or discontinue OGIVRI.

What is OGIVRI used for?

- OGIVRI is a cancer medicine that must be prescribed by a doctor.
- OGIVRI is used to slow down the growth of specific breast cancer cells that produce large amounts of HER2 protein. It is used only for patients whose tumours are growing more rapidly than normal because of a genetic problem in the cells. This occurs in about 25 to 30% of breast cancer tumours.
- If your doctor has prescribed pertuzumab and chemotherapy drug docetaxel in combination with OGIVRI you should also read the leaflet for these medications.
- OGIVRI is also approved for the treatment of gastric cancer (a separate Consumer Information insert provides information on the use of OGIVRI in gastric cancer).

How does OGIVRI work?

- Our bodies have a natural defense system against cancer cells. When cancer cells appear, our bodies respond by making special proteins called antibodies. The antibodies attach to other proteins on the growing tumour cells. Researchers studied this to learn how to create antibodies that help with cancer treatment.
- Antibodies are now made that can target tumours to try to control the growth of cancer.
- OGIVRI belongs to a family of medicines called monoclonal antibodies. It is an antibody that targets the HER2 protein to stop its activity. It attaches to the HER2 receptor on the cancer cell. When it is in place, it works to stop the growth of the cancer cells and may destroy them.

When OGIVRI should be used:

- Patients whose breast cancer tumour cells produce large amounts of the HER2 protein can use OGIVRI.
- OGIVRI is used for certain patients with early breast cancer following surgery and after chemotherapy OR following surgery and with taxane chemotherapy as well as for patients to whom breast cancer has spread to other parts or organs of the body.

What are the ingredients in OGIVRI?

Medicinal ingredients: The medicinal ingredient in OGIVRI is trastuzumab. Each vial of OGIVRI contains 150 mg/vial or 440 mg/vial trastuzumab.

Non-medicinal ingredients: L-histidine, L-histidine HCl monohydrate, PEG-3350/macrogol 3350, and sorbitol. It also contains sodium hydroxide and hydrochloric acid to adjust the pH. The Bacteriostatic Water for Injection supplied with OGIVRI 440 mg/vial contains benzyl alcohol.

OGIVRI comes in the following dosage forms:

OGIVRI is a sterile, powder that will be reconstituted and given as an intravenous (IV) infusion.

Do not use OGIVRI if:

Do not use OGIVRI if you are allergic to trastuzumab, Chinese Hamster Ovary (CHO) cell proteins, or any component of this product (see "What are the ingredients in OGIVRI").

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OGIVRI. Talk about any health conditions or problems you may have, including if you:

- you have ever had a bad reaction to OGIVRI, benzyl alcohol, or any of the inactive ingredients;
- you are allergic to other medicines, food and dyes;
- you are taking any other medicines, including those not prescribed by your doctor;

- you have any other illness or diseases, such as heart problems, heart disease, breathing problems or lung disease; the risk of heart problems may be increased in geriatric patients in both early breast cancer and breast cancer that has spread to other parts or organs of the body; the risk of lung disease may increase if you have taken chemotherapy drugs which are toxic for the lungs;
- you have already been treated with chemotherapy drugs (especially anthracyclines such as doxorubicin, epirubicin or related drugs such as mitoxantrone) or radiation therapy;
- you are pregnant, plan to become pregnant or are breast-feeding a child. Please note that a reduction in the amount of [amniotic] fluid that surrounds the developing fetus within the amniotic sac has been observed in pregnant women receiving OGIVRI;
- you have difficulty breathing at rest.

This information will help your doctor and you decide whether you should use OGIVRI and what extra care may need to be taken while you are on the medication.

Other warnings you should know about:

Driving and using machines:
OGIVRI has a minor influence on the ability to drive a car or operate machines. Dizziness and sleepiness may occur during treatment with OGIVRI. If you experience unwanted effects related to the infusion (such as itching, wheezing, dizziness, racing heart) you should not drive or operate machinery until symptoms resolve completely**.**

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with OGIVRI:
Formal drug interaction studies with Trastuzumab have not been done in humans. Important interactions with other medications were not seen during clinical trials with Trastuzumab.

How to take OGIVRI:
The hospital pharmacy will prepare OGIVRI so it can be used.

If you are sensitive to benzyl alcohol, the OGIVRI powder should be mixed with Sterile Water for Injection (SWFI).

Your doctor has prescribed OGIVRI after carefully studying your condition. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours.

Verify with the healthcare provider that the recommended OGIVRI (trastuzumab) dose and NOT KADCYLA® (trastuzumab emtansine) dose is used.

Usual dose:
The usual dose of OGIVRI depends on your body weight. Your doctor will calculate the dose for you. How long you need to take OGIVRI will depend on your response to the treatment. Your doctor will check your response regularly and decide how many treatments you will receive.

A Registered Nurse in the hospital or outpatient clinic will give you OGIVRI at regular intervals determined by your physician. OGIVRI is not taken by mouth, but given through an intravenous line. An intravenous line, or IV, is a thin, plastic tube with a needle placed in a vein in your hand or arm. When OGIVRI is given intravenously, it is called an infusion.

Your first infusion of OGIVRI will take about 90 minutes. If you tolerate this infusion well, your next infusions may be given in less time, usually about 30 minutes.

Overdose:

If you think you have taken too much OGIVRI, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

For information on the risk of KADCYLA® overdose due to medication errors, see the KADCYLA® Product Monograph.

Missed Dose:
If you miss a dose, your doctor will advise you on when your next administration of OGIVRI will be.

What are possible side effects from using OGIVRI?
These are not all the possible side effects you may feel when taking OGIVRI. If you experience any side effects not listed here, contact your healthcare professional.

Unwanted effects are possible with all medicines. Talk to your doctor, nurse or pharmacist if you are worried about side effects or find them very bothersome, and report any new or continuing symptoms to your doctor immediately. Your doctor will be able to tell you what to do and may be able to help you with these side effects.

Some unwanted effects happen during the first infusion or shortly after it is completed. The effects usually do not last long but may need treatment. The infusion may be stopped, and may be restarted and/or given over a longer time.

These unwanted effects related to the infusion may include:

- Itching
- Wheezing
- Dizziness
- Racing heart

Giving certain medications before the next infusion of OGIVRI may prevent these unwanted effects.

In clinical studies, the most common unwanted effects were fever and chills, nausea, vomiting, diarrhea, pain, and headache. The symptoms can easily be treated. Giving certain medications before OGIVRI can prevent some unwanted effects.

Less common unwanted effects are:

- Shortness of breath and water retention, which are symptoms of heart problems. These are caused by an effect on the heart muscle that reduces the strength of the pumping action of the

heart. This unwanted effect is more common in women who have previously had anthracycline chemotherapy (e.g. doxorubicin, epirubicin). Heart failure as a result of OGIVRI treatment can vary in severity and may require treatment with heart medications and/or OGIVRI treatment may need to be stopped.
- Shortness of breath, fatigue, or a racing heart, which are symptoms of anemia. This is caused by a temporary decrease in the number of red blood cells.
- A temporary decrease in the number of white blood cells may increase your risk of infection and diarrhea.

Difficulty breathing, fatigue and weight loss are commonly seen with lung disease.

Call your doctor immediately if you notice any of the following:
- Shortness of breath;
- Increased cough;
- Swelling of the legs as a result of water retention;
- Diarrhea – if you have an extra four bowel movements each day or any diarrhea at night;
- Symptoms of infection that include:
  - fever: a temperature of 38°C or greater
  - sore throat
  - cough
  - any redness or swelling
  - pain when you pass urine
- Symptoms of an allergic reaction
  - closing of the throat
  - swelling of lips and tongue
  - hives
  - rash
  - dizziness
  - fast heartbeat

What are possible side effects from using OGIVRI?
These are not all the possible side effects you may have when taking OGIVRI. If you experience any side effects not listed here, tell your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
MOST COMMON (≥10%)			
Diarrhea Where you have an extra four bowel movements each day or any diarrhea at night		√	
LESS COMMON ***(≥1 AND ≤10%)***			
Heart problems: Symptoms include shortness of breath, water retention (swelling of		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
the lower legs)			
Anemia (reduced number of red blood cells of the blood): Symptoms include: shortness of breath, racing heart, dizziness, light headedness		√	
Reduced number of white blood cells may lead to an increase chance of infection: Symptoms of infection include: fever (temperature above 38ºc or 101ºf), chills, sore throat, cough, any redness or swelling, pain when you pass your urine		√	
Lung problems: Symptoms include shortness of breath, wheezing or coughing		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- The hospital pharmacy will store OGIVRI in a refrigerator. OGIVRI can be at room temperature when the infusion is given.
- Unopened vials of OGIVRI may be removed from refrigeration and stored up to 25°C for a single period of up to 3 months. Once OGIVRI is removed from refrigeration and stored up to 25°C, discard after 3 months. A discard date field is provided on the carton to record the discard date.
- Keep out of reach and sight of children.

If you want more information about OGIVRI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the importer's website www.mylan.ca, or by calling 1-844-596-9526.

This leaflet was prepared by Biosimilar Collaborations Ireland Limited (BCIL)

Last Revised: May 15, 2023

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrOGIVRI® (Oh-Give-ree)
(trastuzumab)
Sterile Powder for Intravenous Infusion

GASTRIC CANCER

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OGIVRI can result in the development of heart problems including heart failure. The appearance of heart failure can be delayed and can occur after treatment with OGIVRI is completed. The incidence of cardiac dysfunction was higher in patients who received Trastuzumab plus chemotherapy versus chemotherapy alone, with higher risk when Trastuzumab was administered together with a taxane following an anthracycline and cyclophosphamide. In patients with breast cancer that has spread to other parts or organs of the body, the incidence and severity of cardiac dysfunction was particularly high in patients who received Trastuzumab at the same time as anthracyclines and cyclophosphamide.

You should have your heart function evaluated by your doctor before and during treatment with OGIVRI.

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Toxicity to Fetus (Unborn Baby)
OGIVRI can cause harm to the fetus (unborn baby), in some cases death of the fetus, when taken by a pregnant woman. Women who could become pregnant need to use effective birth control methods during OGIVRI treatment and for at least 7 months after treatment with OGIVRI. Nursing mothers treated with OGIVRI should discontinue nursing or discontinue OGIVRI.

What is OGIVRI used for?

- OGIVRI is a cancer medicine that must be prescribed by a doctor.
- OGIVRI is used for certain patients with gastric cancer that has spread to other parts or organs of the body to slow down the growth of specific gastric cancer cells that produce large amounts of HER2 protein
- OGIVRI is used in combination with chemotherapy (capecitabine or intravenous 5-fluorouracil and in combination with cisplatin) for the treatment of gastric cancer that has spread to other parts or organs of the body.
- OGIVRI is also approved for the treatment of breast cancer (a separate Consumer Information insert provides information on the use of OGIVRI in breast cancer)

How does OGIVRI work?

- Our bodies have a natural defense system against cancer cells. When cancer cells appear, our bodies respond by making special proteins called antibodies. The antibodies attach to other proteins on the growing tumour cells. Researchers studied this to learn how to create antibodies that help with cancer treatment.
- Antibodies are now made that can target tumours to try to control the growth of cancer.
- OGIVRI belongs to a family of medicines called monoclonal antibodies. It is an antibody that targets the HER2 protein to stop its activity. It attaches to the HER2 receptor on the cancer cell. When it is in place, it works to stop the growth of the cancer cells and may destroy them.

When OGIVRI should be used:

- Patients whose gastric cancer tumour cells produce large amounts of the HER2 protein can use OGIVRI.
- OGIVRI is used in combination with chemotherapy (capecitabine or intravenous 5-fluorouracil and cisplatin) for the treatment of gastric cancer that has spread to other parts or organs of the body in patients that have not received prior anti-cancer treatment for their disease.

What are the ingredients in OGIVRI?

Medicinal ingredients: The medicinal ingredient in OGIVRI is trastuzumab. Each vial of OGIVRI contains 150 mg/vial or 440 mg/vial trastuzumab.

Non-medicinal ingredients: L-histidine, L-histidine HCl monohydrate, PEG-3350/macrogol 3350, and sorbitol. It also contains sodium hydroxide and hydrochloric acid to adjust the pH. The Bacteriostatic Water for Injection supplied with OGIVRI 440 mg/vial contains benzyl alcohol.

OGIVRI comes in the following dosage forms:

OGIVRI is a sterile, powder that will be reconstituted and given as an intravenous (IV) infusion.

Do not use OGIVRI if:

Do not use OGIVRI if you are allergic to trastuzumab, Chinese Hamster Ovary (CHO) cell proteins, or any component of this product (see "What are the ingredients in OGIVRI").

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OGIVRI. Talk about any health conditions or problems you may have, including if you:

- you have ever had a bad reaction to OGIVRI, benzyl alcohol, or any of the inactive ingredients;
- you are allergic to other medicines, food and dyes;
- you are taking any other medicines, including those not prescribed by your doctor;

- you have any other illness or diseases, such as heart problems, heart disease, breathing problems or lung disease;
- you are pregnant, plan to become pregnant or are breast-feeding a child. Please note that a reduction in the amount of [amniotic] fluid that surrounds the developing fetus within the amniotic sac has been observed in pregnant women receiving OGIVRI;
- you have difficulty breathing at rest.

This information will help your doctor and you decide whether you should use OGIVRI and what extra care may need to be taken while you are on the medication.

Other warnings you should know about:

Driving and using machines
OGIVRI has a minor influence on the ability to drive a car or operate machines. Dizziness and sleepiness may occur during treatment with OGIVRI. If you experience unwanted effects related to the infusion (such as itching, wheezing, dizziness, racing heart) you should not drive or operate machinery until symptoms resolve completely**.**

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with OGIVRI:
Formal drug interaction studies with Trastuzumab have not been done in humans. Important interactions with other medications were not seen during clinical trials with Trastuzumab.

How to take OGIVRI:
The hospital pharmacy will prepare OGIVRI so it can be used.

If you are sensitive to benzyl alcohol, the OGIVRI powder should be mixed with Sterile Water for Injection (SWFI).

Verify with the healthcare provider that the recommended OGIVRI (trastuzumab) dose and NOT KADCYLA® (trastuzumab emtansine) dose is used.

Usual dose:
The usual dose of OGIVRI depends on your body weight. Your doctor will calculate the dose for you. How long you need to take OGIVRI will depend on your response to the treatment. Your doctor will check your response regularly and decide how many treatments you will receive.

A Registered Nurse in the hospital or outpatient clinic will give you OGIVRI at regular intervals determined by your physician. OGIVRI is not taken by mouth, but given through an intravenous line. An intravenous line, or IV, is a thin, plastic tube with a needle placed in a vein in your hand or arm. When OGIVRI is given intravenously, it is called an infusion.

Your first infusion of OGIVRI will take about 90 minutes. If you tolerate this infusion well, your next infusions may be given in less time, usually about 30 minutes.

Overdose:

If you think you have taken too much OGIVRI, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

For information on the risk of KADCYLA® overdose due to medication errors, see the KADCYLA® Product Monograph.

Missed Dose:
If you miss a dose, your doctor will advise you on when your next administration of OGIVRI will be.

What are possible side effects from using OGIVRI?
These are not all the possible side effects you may feel when taking OGIVRI. If you experience any side effects not listed here, contact your healthcare professional.

Unwanted effects are possible with all medicines. Talk to your doctor, nurse or pharmacist if you are worried about side effects or find them very bothersome, and report any new or continuing symptoms to your doctor immediately. Your doctor will be able to tell you what to do and may be able to help you with these side effects.

Some unwanted effects happen during the first infusion or shortly after it is completed. The effects usually do not last long but may need treatment. The infusion may be stopped, and may be restarted and/or given over a longer time.

These unwanted effects related to the infusion may include:

- Itching
- Wheezing
- Dizziness
- Racing heart

Giving certain medications before the next infusion of OGIVRI may prevent these unwanted effects.

In the main clinical study in gastric cancer, the most common unwanted effects which are known to be associated with both the chemotherapy drugs used in the study and with trastuzumab administration were:

- stomach disorders such as nausea, vomiting, diarrhea and constipation
- blood disorders such as neutropenia (reduced number of white blood cells) anemia (reduced number of red blood cells) and thrombocytopenia (reduced number of platelet cells (colorless blood cells that play an important role in blood clotting)).

Call your doctor immediately if you notice any of the following:

- Shortness of breath;
- Increased cough;
- Swelling of the legs as a result of water retention;
- Diarrhea – if you have an extra four bowel movements each day or any diarrhea at night;

- Symptoms of infection that include:
    - fever: a temperature of 38°C or greater
    - sore throat
    - cough
    - any redness or swelling
    - pain when you pass urine
- Symptoms of an allergic reaction
    - closing of the throat
    - swelling of lips and tongue
    - hives
    - rash
    - dizziness
    - fast heartbeat

What are possible side effects from using OGIVRI?
These are not all the possible side effects you may have when taking OGIVRI. If you experience any side effects not listed here, tell your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
LESS COMMON *(≥1 AND ≤10%)*			
Stomach problems - Diarrhea, - Vomiting -Difficulty swallowing.		√	
Blood disorders - Reduced number of white blood cells leading to increased chance of infection; fever.		√	
Infections - Infection of the lungs (pneumonia) Symptoms may include symptoms of a cold followed by high fever.		√	
General Disorders - Fever		√	
Metabolism Disorders - Anorexia		√	
Kidney problems -Kidneys fail to function adequately Symptoms may include: decreased or normal urine output, fluid retention, causing swelling in your legs, ankles or feet, drowsiness shortness of breath, fatigue.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- The hospital pharmacy will store OGIVRI in a refrigerator. OGIVRI can be at room temperature when the infusion is given.
- Unopened vials of OGIVRI may be removed from refrigeration and stored up to 25°C for a single period of up to 3 months. Once OGIVRI is removed from refrigeration and stored up to 25°C, discard after 3 months. A discard date field is provided on the carton to record the discard date.
- Keep out of reach and sight of children.

If you want more information about OGIVRI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the importer's website www.mylan.ca, or by calling: 1-844-596-9526.

This leaflet was prepared by Biosimilar Collaborations Ireland Limited (BCIL)

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