

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**BLA 103792/5187/5189**

***Trade Name:*** Herceptin

***Generic Name:*** trastuzumab

***Sponsor:*** Genentech, Inc.

***Approval Date:*** May 22, 2008

***Indications:*** Part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel, for adjuvant treatment of HER2 over-expressing, node-positive or high-risk node-negative, breast cancer. As part of a treatment regimen containing docetaxel and carboplatin, for the adjuvant treatment of HER2 over-expressing, node-positive or high-risk node-negative, breast cancer.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**BLA 103792/5187/5189**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**BLA 103792/5187/5189**

**APPROVAL LETTER**



Our STNs: BL 103792/5187 and 103792/5189

MAY 22 2008

Genentech, Incorporated  
Attention: Todd W. Rich, M.D.  
Vice President  
Clinical and Commercial Regulatory Affairs  
1 DNA Way, MS #242  
South San Francisco, CA 94080-4990

Dear Dr. Rich:

Your request to supplement your biologics license application for trastuzumab (Herceptin) to expand the breast cancer indication as follows has been approved:

- Herceptin, as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel, for the adjuvant treatment of HER2 over-expressing, node-positive or high-risk node-negative, breast cancer (BL 103792/5187).
- Herceptin, as part of a treatment regimen containing docetaxel and carboplatin, for the adjuvant treatment of HER2 over-expressing, node-positive or high-risk node-negative, breast cancer (BL 103792/5189).

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for these supplements because necessary studies are impossible or highly impracticable. HER2 over-expressing, node-positive or high-risk node-negative, breast cancer does not occur in pediatric patients.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biologic product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Herceptin was first approved in 1998 as a single agent for HER2 over-expressing metastatic breast cancer, in patients who have received one or more chemotherapy regimens for metastatic disease. It was also approved in combination with paclitaxel for the first-line treatment of HER2 over-expressing metastatic breast cancer. The label for Herceptin has a black box warning concerning cardiomyopathy. Now, however, Herceptin is being approved as a component of two novel adjuvant treatment regimens for patients with HER2 over-expressing, node-positive or high-risk node-negative, breast cancer following surgical resection, and our recent analysis of the data in your supplements indicate the need to assess the long-term cardiovascular risks of Herceptin in these new treatment situations. Our new analysis of available scientific data indicates that the long-term incidence and severity of the known serious risk of cardiovascular toxicity associated with Herceptin may be different with the use of this drug in new combination with these adjuvant chemotherapy regimens. In addition, based on new information associated with the fact that Herceptin will now be indicated for use with Carboplatin, we are concerned that the use of Herceptin with Carboplatin may cause a drug-drug interaction (DDI) that could affect the pharmacokinetics of one or the other of the two drugs, creating an unexpected serious risk.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of cardiovascular toxicity in the new patient population and when the drug is used in combination with other therapies, or assess the potential for an unexpected serious risk associated with an effect on pharmacokinetics from the use of Herceptin in combination with Carboplatin.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess either this known serious risk or the potential for this unexpected serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this known serious risk or the potential for this unexpected serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing clinical trials of Herceptin:

1. To provide an update of cardiac safety from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 5 years of follow-up. The update will include analysis of per-protocol defined cardiac events, changes in LVEF measurements, and narratives for any patients who developed a new per-protocol defined symptomatic cardiac event.

The timetable you submitted on April 24, 2008, states that you will conduct this trial according to the following schedule:

Completion of 5-year follow-up:  
Final Report Submission:

June 30, 2009  
March 31, 2010

2. To perform a DDI trial in metastatic cancer patients to evaluate the impact of Herceptin on Carboplatin pharmacokinetics and to evaluate the impact of Carboplatin on Herceptin pharmacokinetics. Herceptin concentrations in the DDI trial will be compared to clinical pharmacokinetic data from clinical trials BO16348, BO15935, and WO16229.

The timetable you submitted on May 13, 2008, states that you will conduct this trial according to the following schedule:

Protocol submission:	March 31, 2009
Study Initiation:	September 30, 2009
Final report submission:	January 31, 2013

We acknowledge your written commitment to complete a drug-drug interaction (DDI) trial as described in your May 13, 2008, electronic correspondence (email).

Submit the protocol for continued assessment of cardiac safety and your DDI trial protocol to your IND 4517 with a cross-reference letter to your BLA, STN 103792. Submit all final report(s) to your BLA, STN 103792.

Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

You are required to report periodically to FDA on the status of these postmarketing clinical trials pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 601.70. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with Herceptin.

**POSTMARKETING STUDY COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 601.70.**

We acknowledge your written commitment to provide additional information on the ongoing BCIRG006 study as described in your April 24, 2008, letter as outlined below:

3. To provide an update of efficacy from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 10 years of follow-up, with an interim update of efficacy at 5-years of follow-up.

The timetable you submitted on April 24, 2008, states that you will conduct this trial according to the following schedule:

Completion of 5-year follow-up: 5-year DFS and OS update	June 30, 2009 March 31, 2010
Completion of 10-year follow-up Final report submission (10-year DFS and OS update)	June 30, 2014 March 31, 2015.

Submit the protocol to your IND 4517, with a cross-reference letter to your BLA, STN 103792. Submit all final report(s) to your BLA, STN 103792. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

- Postmarketing Commitment Protocol
- Postmarketing Commitment - Final Report
- Postmarketing Correspondence
- Annual Status Report of Postmarketing Commitments

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (<http://www.fda.gov/cder/pmc/default.htm>). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see <http://www.fda.gov/cder/guidance/5569fnl.htm>) for further information.

### **CONTENT OF LABELING**

Within 21 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions "Product Correspondence – Final SPL for approved STN BL 103792/5187 and 103792/5189." In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

This information will be included in your biologics license application file.

If you have any questions, call Monica L. Hughes, M.S., RPM, at 301-796-2320.

Sincerely,



Patricia Keegan, M.D.  
Director  
Division of Biologic Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure: Package Insert Labeling

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**BLA 103792/5187/5189**

**OTHER ACTION LETTERS**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STNs: BL 103792/5187 and 103792/5189

**AUG 28 2007**

Genentech, Incorporated  
Attention: Todd W. Rich, M.D.  
Vice President, Clinical and Commercial Regulatory Affairs  
1 DNA Way, MS #242  
South San Francisco, CA 94080-4990

Dear Dr. Rich:

This letter is in regard to your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your supplements dated June 28, 2007, and June 29, 2007, for Trastuzumab (Herceptin) to determine their acceptability for filing. Under 21 CFR 601.2(a) we have filed your supplements today. The review classification for each of these applications is Standard. Therefore, the user fee goal date for STN 103792/5187 is April 28, 2008, and the user fee goal for STN 103792/5189 is May 4, 2008. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

During our filing review, we identified the following potential review issue:

- The labeling provided did not incorporate the drug interaction results obtained from clinical study JP16003: Pharmacokinetic Study of RO45-2317 (Trastuzumab) in Combination with Docetaxel in HER2-overexpressing Metastatic Breast Cancer. Please submit revised labeling as an amendment to both to STN 103792/5187 and 103792/5189.

We are providing the above comment to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplement. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements.

We acknowledge receipt of your request for a waiver of pediatric studies for these applications for pediatric patients less than 18 years of age.

We also have the following comments and requests for additional information:

1. We are aware that, under the direction of the principal investigator for the BCIRG 006 study, patients' tumor specimens were assessed for Topo IIa gene amplification and exploratory analyses of the relevance of Topo IIa gene status was investigated. We request that Genentech provide the following information in an amendment to STNs 103792/5187 and 103792/5189:
  - a. A detailed description of the assay methodology, including qualification data, utilized to determine Topo IIa gene amplification.
  - b. A supplemental electronic database that includes Topo IIa gene amplification results, where obtained, for each patient enrolled in BCIRG 006. The database should be organized such that it can be merged with safety and efficacy datasets contained in the supplements.
  - c. The results of exploratory analyses of efficacy and safety data as a function of Topo IIa gene status.
2. On August 1, 2007, FDA communicated, via email, to Genentech a request for the conversion of adverse event information obtained in the BCIRG 006 study from COSTART to the MedDRA v.10 format. We acknowledge your August 15, 2007, response:

“Consistent with agreements conveyed during the 18 April 2007 BCIRG pre-sBLA, the following is an excerpt from FDA meeting minutes pertaining to the version of AE coding:

Additional 18-April-2007 FDA Meeting Requests:

- FDA asked for clarification on the AE coding, whether MedDRA was used. GNE confirmed that MedDRA was not used, and that the same coding approach was used for AE and cardiac adverse events, in which all (>95%) were reported based on NCI-CTC v.2 and those with terms not existing per NCI-CTC were coded based on COSTART. AEs were summarized either NCI-CTC v.2 terms or COSTART preferred terms. In addition, GNE clarified that two safety datasets will be presented in the sBLA, one for non-cardiac adverse events and one for cardiac adverse events.

As requested within the 18 April 2007 pre-sBLA teleconference, on 7 May 2007, Genentech provided sample datasets and a brief description of the adverse event collection, classification, and grading that was conducted for Study BCIRG.006.

Based on our prior discussion as well as having provided the sample safety dataset as requested, we propose that the adverse event dataset be accepted as submitted. At this juncture, we are unable to provide a remapped version of the BCIRG.006 AE study terms to MedDRA v.10 in a timeframe that would be useful for the Agency's supplement review."

Please note that, in order to permit a consistent assessment of safety data and evaluate safety signals of Herceptin across recently submitted supplements, we will undertake to convert adverse event data coded in COSTART or NCI-CTC to MedDRA higher level terms, using the raw text term provided in the 103792/5187 and 103792/5189 supplements to map to the appropriate MedDRA term.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Erik Laughner, M.S., at (301) 796-1393.

Sincerely,



Patricia Keegan, M.D.  
Director  
Division of Biologic Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 103792/5189

AUG 01 2007

Genentech, Incorporated  
Attention: Todd Rich, M.D.  
Vice President  
Clinical and Commercial Regulatory Affairs  
1 DNA Way, MS #242  
South San Francisco, CA 94080-4990

Dear Dr. Rich:

We have received your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

STN	Name of Biological Product
BL 103792/5189	Trastuzumab / Herceptin

**Reason for the submission:** To expand the indication for Herceptin, as part of a treatment regimen containing docetaxel and carboplatin, for the adjuvant treatment of HER2 overexpressing, node-positive, or high-risk node-negative breast cancer.

**Date of Supplement:** June 29, 2007

**Date of Receipt:** July 5, 2007

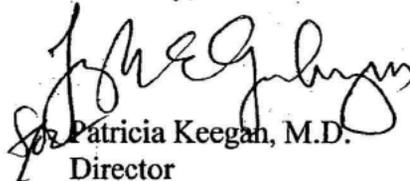
We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Erik Laughner, M.S., at (301) 796-1393.

Sincerely,

A handwritten signature in black ink, appearing to read 'Patricia Keegan', is written over the printed name.

Dr. Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**BLA 103792/5187/5189**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use Herceptin safely and effectively. See full prescribing information for Herceptin.

**HERCEPTIN® (trastuzumab)**  
**Intravenous Infusion**  
**Initial U.S. Approval: 1998**

**WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, and PULMONARY TOXICITY**  
*See full prescribing information for complete boxed warning*  
**Cardiomyopathy:** Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy. (5.1, 2.2)  
**Infusion reactions, Pulmonary toxicity:** Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

**RECENT MAJOR CHANGES**

Indications and Usage, Adjuvant Treatment of Breast Cancer (1.1)	05/2008
Dosage and Administration, Recommended Doses and Schedules (2.1)	05/2008
Dosage and Administration, Dose Modifications (2.2)	05/2008
Warnings and Precautions, Cardiomyopathy (5.1)	05/2008
Warnings and Precautions, Interstitial Pneumonitis (5.4)	01/2008
Warnings and Precautions, Embryo-Fetal Toxicity (5.6)	01/2008

**INDICATIONS AND USAGE**

Herceptin is a HER2/neu receptor antagonist indicated for the treatment of HER2 overexpressing breast cancer (1.1, 1.2).

**DOSAGE AND ADMINISTRATION**

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

**Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.1)**

Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 52 weeks.
- Or, initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 90 minutes IV infusion every three weeks for 52 weeks.

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING – CARDIOMYOPATHY, INFUSION REACTIONS, PULMONARY TOXICITY**

**1 INDICATIONS AND USAGE**

- 1.1 Adjuvant Breast Cancer
- 1.2 Metastatic Breast Cancer

**2 DOSAGE AND ADMINISTRATION**

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- 2.2 Dose Modifications
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- 6.2 Immunogenicity
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**Metastatic HER2-Overexpressing Breast Cancer (2.1)**

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

**DOSAGE FORMS AND STRENGTHS**

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

**CONTRAINDICATIONS**

- None. (4)

**WARNINGS AND PRECAUTIONS**

- Cardiomyopathy (5.1, 6.1)
- Infusion Reactions (5.2, 6.1)
- Pulmonary Toxicity (5.4, 6.1)
- Exacerbation of Chemotherapy-Induced Neutropenia (5.3, 6.1)
- HER2 testing should be performed by laboratories with demonstrated proficiency. (5.5)
- May cause oligohydramnios and fetal harm when administered to a pregnant woman. Pregnancy registry available (1-800-690-6720). (5.6, 8.1)

**ADVERSE REACTIONS**

**Adjuvant Breast Cancer**

- Adverse reactions (≥2% higher incidence with Herceptin-containing treatment compared with control treatment) are fatigue, infection, neutropenia, anemia, myalgia, dyspnea, rash/desquamation, headache, diarrhea, and nausea. (6.1)

**Metastatic Breast Cancer**

- Adverse reactions (≥ 15% incidence with Herceptin monotherapy or ≥5% with Herceptin/ paclitaxel) are nausea, fever, infection, rash, increased cough, vomiting, diarrhea, headache, and anemia. (6.1)

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2008

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## FULL PRESCRIBING INFORMATION

### **WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, and PULMONARY TOXICITY**

#### **Cardiomyopathy**

Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF and decreased LVEF. The incidence and severity of left ventricular cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and strongly consider discontinuation of Herceptin treatment in patients with metastatic breast cancer for clinically significant decrease in left ventricular function. [see *Warnings and Precautions (5.1) and Dosage and Administration (2.2)*]

#### **Infusion Reactions; Pulmonary Toxicity**

Herceptin 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 Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinue Herceptin for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. [see *Warnings and Precautions (5.2, 5.4)*]

## 1 INDICATIONS AND USAGE

### 1.1 Adjuvant Breast Cancer

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

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

### 1.2 Metastatic Breast Cancer

Herceptin is indicated:

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Doses and Schedules

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

#### *Adjuvant Treatment, Breast Cancer:*

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

- During and following paclitaxel, docetaxel, or docetaxel/carboplatin:
- Initial dose of 4mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
  - One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30-60 minutes every three weeks.

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

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

[see *Dose Modification (2.2)*]

#### *Metastatic Treatment, Breast Cancer:*

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

## 2.2 Dose Modifications

#### *Infusion Reactions*

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

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

#### *Cardiomyopathy*

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

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

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

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

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

## 2.3 Preparation for Administration

#### *Reconstitution*

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

Use appropriate aseptic technique when performing the following reconstitution steps:

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

#### *Dilution*

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

## 3 DOSAGE FORMS AND STRENGTHS

440 mg lyophilized powder per multi-use vial.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cardiomyopathy

Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death

[see Boxed Warning: Cardiomyopathy]. Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

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

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

#### Cardiac Monitoring

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

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

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

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

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

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

<sup>a</sup> Includes 1 patient with fatal cardiomyopathy.

<sup>b</sup> Anthracycline (doxorubicin) and cyclophosphamide

**Table 2**

Incidence of Cardiac Dysfunction<sup>a</sup> in Metastatic Breast Cancer Studies

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

<sup>a</sup> Congestive heart failure or significant asymptomatic decrease in LVEF.

<sup>b</sup> Anthracycline (doxorubicin or epirubicin) and cyclophosphamide

<sup>c</sup> Includes 1 patient with fatal cardiomyopathy.

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

#### 5.2 Infusion Reactions

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

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

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

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

#### 5.3 Exacerbation of Chemotherapy-Induced Neutropenia

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

#### 5.4 Pulmonary Toxicity

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

#### 5.5 HER2 Testing

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown. Assessment for HER2 overexpression and of HER2 gene amplification should be performed by

laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay procedures, and failure to include appropriate controls for assay validation, can lead to unreliable results.

Several FDA-approved commercial assays are available to aid in the selection of patients for Herceptin therapy. These include HercepTest™ and Pathway® HER-2/neu (IHC assays) and PathVysion® and HER2 FISH pharmDx™ (FISH assays). Users should refer to the package inserts of specific assay kits for information on the validation and performance of each assay.

Limitations in assay precision (particularly for the IHC method) and in the direct linkage between assay result and overexpression of the Herceptin target (for the FISH method) make it inadvisable to rely on a single method to rule out potential Herceptin benefit. A negative FISH result does not rule out HER2 overexpression and potential benefit from Herceptin. Treatment outcomes for metastatic breast cancer (Study 5) as a function of IHC and FISH testing are provided in Table 9. Treatment outcomes for adjuvant breast cancer (Studies 2 and 3) as a function of IHC and FISH testing are provided in Table 7.

#### HER2 Protein Overexpression Detection Methods

HER2 protein overexpression can be established by measuring HER2 protein using an IHC method. HercepTest®, one test approved for this use, was assessed for concordance with the Clinical Trial Assay (CTA), using tumor specimens collected and stored independently from those obtained in Herceptin clinical studies in women with metastatic breast cancer. Data are provided in the package insert for HercepTest®.

#### HER2 Gene Amplification Detection Method

The presence of HER2 protein overexpression and gene amplification are highly correlated, therefore the use of FISH to detect gene amplification may be employed for selection of patients appropriate for Herceptin therapy. PathVysion®, one test approved for this use, was evaluated in an exploratory, retrospective assessment of available CTA 2+ or 3+ tumor specimens collected as part of patient screening for clinical studies in metastatic breast cancer (Studies 5 and 6). Data are provided in the package insert for PathVysion®.

#### 5.6 Embryo-Fetal Toxicity (Pregnancy Category D)

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

#### 6 ADVERSE REACTIONS

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

- Cardiomyopathy [see Warnings and Precautions (5.1)]
- Infusion reactions [see Warnings and Precautions (5.2)]
- Exacerbation of chemotherapy-induced neutropenia [see Warnings and Precautions (5.3)]
- Pulmonary toxicity [see Warnings and Precautions (5.4)]

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

#### 6.1 Clinical Trials Experience

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

##### Adjuvant Breast Cancer Studies

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

The data summarized in Table 3 below, from Study 3, reflect exposure to Herceptin in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18. Among the 3386 patients enrolled in

Study 3, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

**Table 3**  
Adverse Reactions for Study 3, All Grades<sup>a</sup>:

MedDRA (v. 7.1) Adverse Event Preferred Term	1 Year Herceptin (n= 1678)	Observation (n=1708)
<b>Cardiac</b>		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias <sup>b</sup>	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
<b>Respiratory Thoracic Mediastinal Disorders</b>		
Nasopharyngitis	135 (8%)	43 (3%)
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
<b>Gastrointestinal Disorders</b>		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
<b>Musculoskeletal &amp; Connective Tissue Disorders</b>		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
<b>Nervous System Disorders</b>		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
<b>Skin &amp; Subcutaneous Tissue Disorders</b>		
Rash	70 (4%)	10 (.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritis	40 (2%)	10 (0.6%)
<b>General Disorders</b>		
Pyrexia	100 (6%)	6 (0.4%)

**Table 3 (cont'd)**  
Adverse Reactions for Study 3, All Grades<sup>a</sup>:

MedDRA (v. 7.1) Adverse Event Preferred Term	1 Year Herceptin (n= 1678)	Observation (n=1708)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Aesthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (.06%)	0 (0%)
<b>Infections</b>		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	39 (3%)	13 (0.8%)
<b>Immune System Disorders</b>		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

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

<sup>b</sup> Higher level grouping term.

The data from Studies 1 and 2 were obtained from 3206 patients enrolled, of which 1635 patients received Herceptin; the median treatment duration was 50 weeks. The median age was 49.0 years (range: 24-80); 84% of patients were White, and 7% were Black, 4% were Hispanic, and 4% were Asian.

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

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

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

#### Metastatic Breast Cancer Studies

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

Among the 464 patients treated in Study 5, the median age was 52 years (range: 25-77 years). Eighty-nine percent were White, 5% Black, 1% Asian and 5% other racial/ethnic groups. All patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who

received Herceptin treatment for ≥6 months and ≥12 months were 58% and 9%, respectively.

Among the 352 patients treated in single agent studies (213 patients from Study 6), the median age was 50 years (range 28-86 years), 100% had breast cancer, 86% were White, 3% were Black, 3% were Asian, and 8% in other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥6 months and ≥12 months were 31% and 16%, respectively.

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

	Single Agent <sup>a</sup> n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC <sup>b</sup> n = 143	AC <sup>b</sup> Alone n = 135
<b>Body as a Whole</b>					
Pain	47	61	62	57	42
Asthenia	42	62	57	54	55
Fever	36	49	23	56	34
Chills	32	41	4	35	11
Headache	26	36	28	44	31
Abdominal pain	22	34	22	23	18
Back pain	22	34	30	27	15
Infection	20	47	27	47	31
Flu syndrome	10	12	5	12	6
Accidental injury	6	13	3	9	4
Allergic reaction	3	8	2	4	2
<b>Cardiovascular</b>					
Tachycardia	5	12	4	10	5
Congestive heart failure	7	11	1	28	7
<b>Digestive</b>					
Nausea	33	51	9	76	77
Diarrhea	25	45	29	45	26
Vomiting	23	37	28	53	49
Nausea and vomiting	8	14	11	18	9
Anorexia	14	24	16	31	26
<b>Heme &amp; Lymphatic</b>					
Anemia	4	14	9	36	26
Leukopenia	3	24	17	52	34
<b>Metabolic</b>					
Peripheral edema	10	22	20	20	17
Edema	8	10	8	11	5
<b>Musculoskeletal</b>					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9
<b>Nervous</b>					
Insomnia	14	25	13	29	15
Dizziness	13	22	24	24	18

**Table 4 (cont'd)**  
Per-Patient Incidence of Adverse Reactions Occurring in  $\geq 5\%$  of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6) (Percent of Patients)

	Single Agent <sup>a</sup> n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC <sup>b</sup> n = 143	AC <sup>b</sup> Alone n = 135
Paresthesia	9	48	39	17	11
Depression	6	12	13	20	12
Peripheral neuritis	2	23	16	2	2
Neuropathy	1	13	5	4	4
<b>Respiratory</b>					
Cough increased	26	41	22	43	29
Dyspnea	22	27	26	42	25
Rhinitis	14	22	5	22	16
Pharyngitis	12	22	14	30	18
Sinusitis	9	21	7	13	6
<b>Skin</b>					
Rash	18	38	18	27	17
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	< 1
<b>Urogenital</b>					
Urinary tract infection	5	18	14	13	7

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

<sup>b</sup> Anthracycline (doxorubicin or epirubicin) and cyclophosphamide

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

**Cardiomyopathy**

Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and 2, 23 months in the AC-T arm, 24 months in the AC-TH arm. In Studies 1 and 2, 6% of patients were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF <50% or  $\geq 15$  point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients receiving Herceptin monotherapy compared to observation in Study 3 (see Table 5, Figures 1 and 2).

**Table 5<sup>a</sup>**  
Per-patient Incidence of New Onset Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

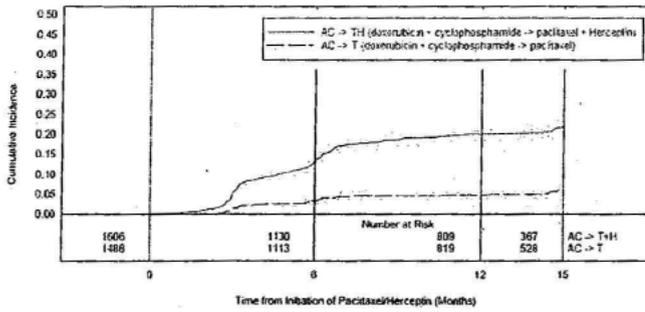
	LVEF <50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF <50%	$\geq 10\%$ decrease	$\geq 16\%$ decrease	<20% and $\geq 10\%$	$\geq 20\%$
<b>Studies 1 &amp; 2<sup>b</sup></b>					
AC→TH (n=1606)	22.8% (366)	18.3% (294)	11.7% (188)	33.4% (536)	9.2% (148)
AC→T (n=1488)	9.1% (136)	5.4% (81)	2.2% (33)	18.3% (272)	2.4% (36)
<b>Study 3</b>					
Herceptin (n=1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n=1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
<b>Study 4<sup>c</sup></b>					
TCH (n=1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n=1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n=1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

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

<sup>b</sup> Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)

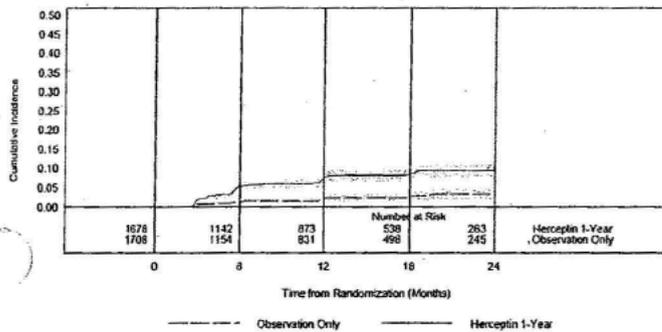
<sup>c</sup> Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH)

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



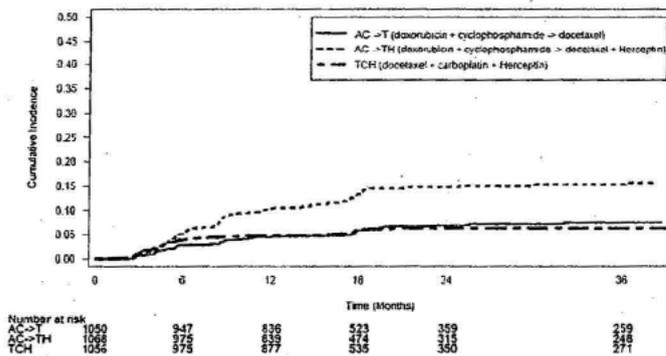
Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

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



Time 0 is the date of randomization.

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



Time 0 is the date of randomization.

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

#### Infusion Reactions

During the first infusion with Herceptin, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in

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

#### Anemia

In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]), of selected NCI-CTC Grade 2–5 anemia (12.5% vs. 6.6% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. Following the administration of Herceptin as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was < 1%.

#### Neutropenia

In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTC Grade 4–5 neutropenia (2% vs. 0.7% [Study 2]) and of selected Grade 2–5 neutropenia (7.1% vs. 4.5% [Study 1]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

#### Infection

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

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

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

#### Pulmonary Toxicity

##### Adjuvant Breast Cancer

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

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

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

##### Metastatic Breast Cancer

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

### Thrombosis/Embolism

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

### Diarrhea

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

### Glomerulopathy

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

### 6.2 Immunogenicity

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

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

### 6.3 Post-Marketing Experience

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

- Infusion reaction [see *Warnings and Precautions* (5.2)]
- Oligohydramnios [see *Warnings and Precautions* (5.6)]
- Glomerulopathy

## 7 DRUG INTERACTIONS

In clinical studies, administration of paclitaxel in combination with Herceptin resulted in a 1.5-fold increase in trastuzumab serum levels [see *Clinical Pharmacology* (12)].

In drug interaction studies, the pharmacokinetics of docetaxel and paclitaxel were not altered when each was administered in combination with Herceptin.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

**Teratogenic Effects: Category D** [see *Warnings and Precautions* (5.6)]

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

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

Women using Herceptin during pregnancy should be monitored for oligohydramnios. If oligohydramnios occurs, fetal testing should be done that is appropriate for gestational age and consistent with community standards of

care. Additional intravenous (IV) hydration has been helpful when oligohydramnios has occurred following administration of other chemotherapy agents, however the effects of additional IV hydration with Herceptin treatment are not known.

Reproduction studies in cynomolgus monkeys at doses up to 25 times the recommended weekly human dose of 2 mg/kg trastuzumab have revealed no evidence of harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation. Placental transfer of trastuzumab during the early (Days 20–50 of gestation) and late (Days 120–150 of gestation) fetal development period was observed in monkeys. [See *Nonclinical Toxicology* (13.2)]

Because animal reproduction studies are not always predictive of human response, Herceptin should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

### Registry

Pregnant women with breast cancer who are using Herceptin are encouraged to enroll in the Cancer and Childbirth Registry: phone 1-800-690-6720.

### 8.3 Nursing Mothers

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

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

Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from Herceptin, 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.

### 8.4 Pediatric Use

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

### 8.5 Geriatric Use

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

## 10 OVERDOSAGE

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

## 11 DESCRIPTION

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

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal

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

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

## 12.2 Pharmacokinetics

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

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

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

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

Data suggest that the disposition of trastuzumab is not altered based on age or serum creatinine ( $\leq 2.0$  mg creatinine/dL).

Mean serum trough concentrations of trastuzumab, when administered in combination with paclitaxel, were consistently elevated approximately 2-fold as compared with serum concentrations of trastuzumab when used in combination with anthracycline plus cyclophosphamide. In clinical studies in HER2+ metastatic breast cancer where Herceptin was administered in combination with paclitaxel, in combination with docetaxel, or in combination with paclitaxel and doxorubicin, Herceptin did not appear to alter the plasma concentrations of these chemotherapeutic agents, or the metabolites that were analyzed.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Herceptin has not been tested for carcinogenic potential.

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

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

### 13.2 Animal Toxicology and/or Pharmacology

#### Reproductive Toxicology Studies

Reproductive toxicology studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg Herceptin and have revealed no evidence of impaired fertility or harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation. Placental transfer of Herceptin during the early (Days 20-50 of gestation) and late (Days 120-150 of gestation) fetal development period was observed in monkeys.

## 14 CLINICAL STUDIES

### 14.1 Adjuvant Breast Cancer

The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer, were evaluated in an

integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 3752 women, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4).

#### Studies 1 and 2

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

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

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

#### Study 3

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

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

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

#### Study 4

In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory. Patients

were required to have either node-positive disease, or node-negative disease with at least one of the following high-risk features: ER/PR-negative, tumor size > 2 cm, age < 35 years, or histologic and/or nuclear Grade 2 or 3.

Patients with a history of CHF, myocardial infarction, Grade 3 or 4 cardiac arrhythmia, angina requiring medication, clinically significant valvular heart disease, poorly controlled hypertension (diastolic > 100 mmHg), any T4 or N2 or known N3 or M1 breast cancer were not eligible.

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

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

**Table 6**  
Efficacy Results from Adjuvant Treatment of Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	Hazard ratio (95% CI) p value	Deaths	Hazard ratio p value
<b>Studies 1 + 2<sup>c</sup></b>				
AC→TH (n=1872)	133	0.48 <sup>a</sup> (0.39, 0.59) p<0.0001 <sup>b</sup>	62	0.67 p=NS <sup>d</sup>
AC→T (n=1880)	261		92	
<b>Study 3</b>				
Chemo→ Herceptin (n=1693)	127	0.54 (0.44, 0.67) p<0.0001 <sup>e</sup>	31	0.75 p=NS <sup>d</sup>
Chemo→ Observation (n=1693)	219		40	
<b>Study 4<sup>f</sup></b>				
TCH (n=1075)	134	0.67 (0.54 - 0.84) p=0.0006 <sup>b,g</sup>	56	
AC→TH (n=1074)	121	0.60 (0.48 - 0.76) p<0.0001 <sup>b,g</sup>	49	
AC→T (n=1073)	180		80	

CI = confidence interval.

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

<sup>b</sup> stratified log-rank test.

<sup>c</sup> log-rank test.

<sup>d</sup> NS = non-significant.

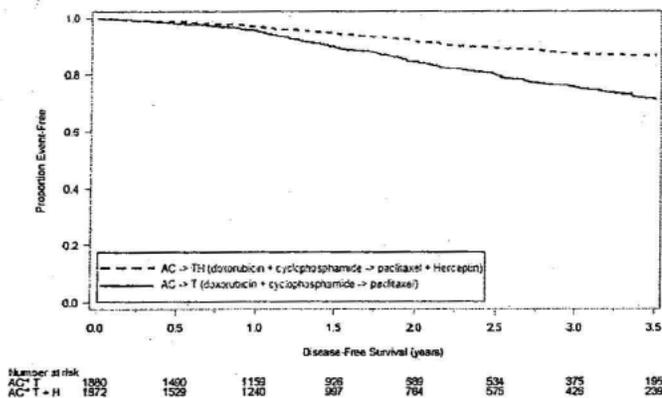
<sup>e</sup> Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)

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

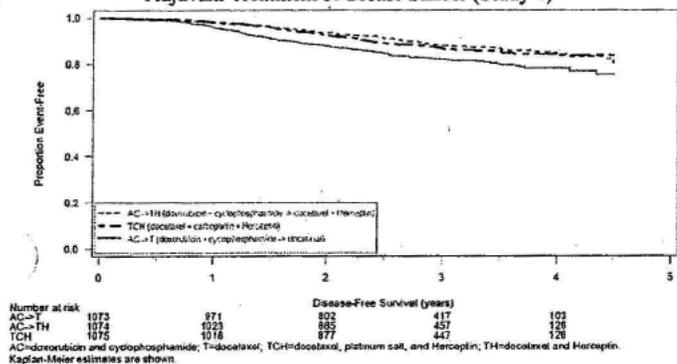
<sup>g</sup> A two-sided alpha level of 0.025 for each comparison

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

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



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



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

**Table 7**  
Treatment Outcomes in Studies 2 and 3 as a Function of HER2 Overexpression or Amplification

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

<sup>a</sup> IHC by HercepTest, FISH by PathVysion (HER2/CEP17 ratio ≥ 2.0) as performed at a central laboratory.

<sup>b</sup> All cases in this category in Study 3 were IHC 2+.

#### 14.2 Metastatic Breast Cancer

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

##### Previously Untreated Metastatic Breast Cancer (Study 5)

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

Based upon the determination by an independent response evaluation committee the patients randomized to Herceptin and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), and a longer median duration of response, as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin and chemotherapy also had a longer median survival (see Table 8). These treatment effects were observed both in patients who received Herceptin plus paclitaxel and in those who received Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.

**Table 8**  
Study 5: Efficacy Results in  
First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Herceptin + All Chemo-therapy (n = 235)	All Chemo-therapy (n = 234)	Herceptin + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Herceptin + AC <sup>a</sup> (n = 143)	AC (n = 138)
<b>Primary Endpoint</b>						
Median TTP(mos) <sup>b,c</sup>	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
p-value <sup>d</sup>	< 0.0001		< 0.0001		0.002	
<b>Secondary Endpoints</b>						
Overall Response Rate <sup>b</sup>	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value <sup>e</sup>	< 0.001		< 0.001		0.10	
Median Resp Duration (mos) <sup>b,c</sup>	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% quartile	6, 15	4, 8	5, 11	4, 7	6, 15	4, 8
Med Survival (mos) <sup>f</sup>	25.1	20.3	22.1	18.4	26.8	21.4
95% CI	22, 30	17, 24	17, 29	13, 24	23, 33	18, 27
p-value <sup>d</sup>	0.05		0.17		0.16	

<sup>a</sup> AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

<sup>b</sup> Assessed by an independent Response Evaluation Committee.

<sup>c</sup> Kaplan-Meier Estimate.

<sup>d</sup> log-rank test.

<sup>e</sup>  $\chi^2$ -test.

Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 9).

**Table 9**  
Treatment Effects in Study 5 as a  
Function of HER2 Overexpression or Amplification

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

<sup>a</sup> FISH testing results were available for 451 of the 469 patients enrolled on study.

<sup>b</sup> The relative risk represents the risk of progression or death in the Herceptin plus chemotherapy arm versus the chemotherapy arm.

*Previously Treated Metastatic Breast Cancer (Study 6)*

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

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

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How Supplied**

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

**16.2 Stability and Storage**

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

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

**17 PATIENT COUNSELING INFORMATION**

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [see *Boxed Warning: Cardiomyopathy*].
- Advise women with reproductive potential to use effective contraceptive methods during treatment and for a minimum of six months following Herceptin [see *Pregnancy (8.1)*].
- Encourage pregnant women who are using Herceptin to enroll in the Cancer and Childbirth Registry [see *Pregnancy (8.1)*].

**HERCEPTIN<sup>®</sup> [trastuzumab]**

Manufactured by:

Genentech, Inc.

4839800

1 DNA Way

South San Francisco, CA 94080-4990

©2006 Genentech, Inc.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**BLA 103792/5187/5189**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	May 5, 2008
<b>From</b>	Patricia Keegan, M.D. <i>P. Keegan</i> 5-5-08
<b>Subject</b>	Division Director Summary Review
<b>BLA Supplement #</b>	STN BL 103792/5187
<b>Applicant Name</b>	Genentech, Inc.
<b>Date of Submission</b>	June 29, 2007
<b>PDUFA Goal Date</b>	April 28, 2008
<b>Proprietary Name / Established (USAN) Name</b>	Herceptin® / trastuzumab
<b>Dosage Forms / Strength</b>	Lyophilized powder for reconstitution and intravenous infusion (b) (4) mg vial
<b>Proposed Indication(s)</b>	"As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive, (b) (4) breast cancer"
<b>Action</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Katherine Fedenko
Statistical Review	Yuan-Li Shen
Pharmacology Toxicology Review	None
CMC Review/OBP Review	Wendy Weinberg
Microbiology Review	None
Clinical Pharmacology Review	None
DDMAC	Carole Broadnax
DSI	None
CDTL Review	None
OSE/DMETS	None
OSE/DDRE	None
OSE/DSRCS	None

OND=Office of New Drugs  
 DDMAC=Division of Drug Marketing, Advertising and Communication  
 OSE= Office of Surveillance and Epidemiology  
 DMETS=Division of Medication Errors and Technical Support  
 DSI=Division of Scientific Investigations  
 DDRE= Division of Drug Risk Evaluation  
 DSRCS=Division of Surveillance, Research, and Communication Support  
 CDTL=Cross-Discipline Team Leader

# Signatory Authority Review Template

## 1. Introduction

These two supplements were based on different investigational arms of a single, three-arm, multinational, randomized, open-label clinical trial, BCIRG 006. The trial was conducted in 3222 women with HER-2 gene amplified, surgically resected localized breast cancer, receiving post-resection adjuvant chemotherapy, with equal allocation (1:1:1) to the control arm (combination anthracycline-cyclophosphamide followed by docetaxel) and the two trastuzumab-containing investigational arms. The primary objective of the trial was to determine whether the addition of Herceptin<sup>®</sup> (trastuzumab) to a standard adjuvant regimen (sequential anthracycline /cyclophosphamide followed by docetaxel) or given in combination with a non-anthracycline-containing chemotherapy regimen (carboplatin plus docetaxel) resulted in improved disease-free survival. The key secondary objective was determination of the incidence and severity of trastuzumab-induced cardiotoxicity. The trial was initiated and conducted by the Breast Cancer International Research Group (BCIRG), an independent cooperative oncology group, rather than the applicant and not originally intended to support labeling claims for trastuzumab. After initiation of the trial, Genentech reached agreement with BCIRG to provide the results of the study under an agreed-upon post-marketing commitment to characterize Herceptin-induced cardiomyopathy when given following anthracycline exposure and when given to an anthracycline-naïve patient population.

The trial was monitored by a DSMB, which released the results following the second interim analysis of efficacy which crossed a pre-specified boundary, demonstrating a significantly superior and clinically important prolongation in relapse-free survival in each of the trastuzumab-containing regimens as compared to the control.

Specific areas to be discussed in this review are

- The use of a single trial to demonstrate safety and efficacy in support for this extended labeling claim
- Standardization of the definition of disease-free survival and use of an alternate definition of DFS as the primary outcome measure by FDA
- Need for additional follow-up to characterize long-term efficacy (disease-free survival) and safety (overall survival, late onset cardiomyopathy)

## 2. Background

Herceptin (trastuzumab) is a humanized monoclonal antibody that binds specifically and with high affinity to the extracellular domain of HER2 (epidermal growth factor receptor 2 protein), resulting in inhibition of binding of the HER2 ligand to its receptor and inhibition of stimulatory effects.

Trastuzumab was approved on Sept. 25, 1998, in combination with paclitaxel, for treatment patients with HER2 overexpressing breast cancer who had received no prior chemotherapy for metastatic disease. The approval was based on a randomized, open-label study of 469 women receiving either cyclophosphamide plus doxorubicin or paclitaxel chemotherapy and patients were randomized (1:1) to receive chemotherapy alone or in combination with trastuzumab. The study demonstrated a clinically significant improvement in time-to-progression, overall response rate, longer response duration, and higher one-year survival rates among patients randomized to trastuzumab plus chemotherapy. The trial also demonstrated an increased risk of congestive heart failure; the magnitude of this risk was greater among patients receiving trastuzumab with cyclophosphamide and doxorubicin and represented an unacceptable risk in light of the benefits, leading to approval of trastuzumab only for use in combination with paclitaxel. The approval was supported by a single arm study of single agent trastuzumab (H0649g). This study demonstrated evidence of durable objective responses with single agent trastuzumab in 222 patients with HER2 overexpressing metastatic breast cancer, following treatment with 1-2 prior cytotoxic chemotherapy regimens.

On Dec. 11, 2001, product labeling was revised to include updated survival data from the first-line breast cancer study.

On August 28, 2002, product labeling was revised to include the Vysis PathVysion HER2 DNA probe for detection of gene amplification as a method to select patients for trastuzumab therapy.

On (b) (4), labeling claims were expanded to include an indication for trastuzumab as part of a treatment regimen containing doxorubicin, cyclophosphamide and paclitaxel, for the adjuvant treatment of patients with HER2 overexpressing, node-positive breast cancer.

On January 18, 2008, labeling was expanded to include a new dose and schedule for trastuzumab when administered as part of an anthracycline containing chemotherapy regimen for the adjuvant treatment of HER2 overexpressing, node-positive or high risk node negative, breast cancer.

The current supplement is based on the results of the BCIRG study, which was submitted to an IND held by sanofi aventis for Taxotere (docetaxel). Sanofi Aventis was granted an expanded labeling claim for Taxotere for use with doxorubicin and cyclophosphamide as adjuvant treatment of operable, node-positive breast cancer on August 18, 2004. The regimen used to support this claim was docetaxel 75 mg/m<sup>2</sup>, in combination with doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup>, administered every three weeks for six cycles.

Genentech, Inc. did not meet with FDA to discuss the acceptability of the trial design in support of labeling claims for trastuzumab prior to study initiation. However, Genentech notified FDA of their intent to provide the results of the BCIRG 006 trial to further characterize the cardiotoxicity of trastuzumab in their PMC annual report, STN BL 103792/5170 submitted on November 28, 2006. In this report, Genentech identified use of BCIRG 006 as a replacement for a previously identified study intended to fulfill one aspect of PMC #6, as described in the approval letter for STN BL 103792/0.

The BCIRG 006 trial initiated accrual in March 2001 and the last patient was enrolled in September 2003. On March 17, 2005, the fourth protocol amendment modified the statistical analysis plan to require three interim analyses for DFS, when 300, 450, and 650 DFS events and a final analysis at 900 DFS events (the original protocol required one interim analysis at 654 events and a final analysis at 1308 events). The first interim analysis was conducted with a data cut-off date of June 30, 2005; although the boundary was crossed for the ACT vs. ACTH comparison (and possibly for the ACT vs. TCH comparison depending upon the interpretation of the method of adjustment) that trial continued until the second interim analysis was conducted following 474 events with a data cut-off date of November 1, 2006.

A pre-sBLA teleconference was held with Genentech on April 18, 2007, as described in Genentech's meeting minutes with clarifications from FDA on May 30, 2007. The following key agreements were reached:

- Since two claims are sought, separate applications must be submitted in support of inclusion of the ACTH regimen and TCH regimen in product labeling.
- The results of the first and second interim analyses would be provided; results of the second interim analysis would be provided as descriptive information in product labeling and the results of the first interim analysis would be used for inference purposes in labeling.
- [REDACTED] (b) (4) [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]
- A separate application would be submitted in support of partial fulfillment of PMC #6 under the STN BL 103792/0 approval letter, containing or cross-referencing data from BCIRG intended to fulfill a portion of the PMC regarding cardiotoxicity in Herceptin-treatment, anthracycline naïve patients. *[Note- an amendment identified as a clinical study report for PMC #6 was not submitted during the review of this application]*

### 3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. As noted by Dr. Weinberg in her review, the BCIRG 006 study relied on both FDA-licensed Herceptin manufactured at Genentech, and EU-approved Herceptin manufactured by Roche at their facility in Penzberg, Germany. The comparability of the Genentech- and Roche-manufactured Herceptin was reviewed under STN BL 103792/5175. [REDACTED] (b) (4) [REDACTED]

[REDACTED], results of physicochemical and biological assessments support sufficient comparability to rely on the Roche material in this study for expansion of Genentech's Herceptin license. There are no CMC outstanding issues which would preclude approval.

## 4. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology or toxicology studies were submitted in support of this supplemental application. No additional nonclinical studies, besides those contained in the original application or agreed-upon post-marketing commitments, were required to make a determination of safety and efficacy in support of the expanded labeling claims.

## 5. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology or biopharmaceutics data were submitted in support of this supplemental application. The pharmacokinetic profile of the dose and schedule of trastuzumab utilized in this application has been adequately characterized in prior supplements. In addition, the drug-drug interactions between trastuzumab and commonly prescribed antineoplastic agents (doxorubicin, paclitaxel, and docetaxel) were investigated under PMC #8 associated with the original approval of trastuzumab. The final study report for Study JP16003, submitted to BL STN 103792/5177, assessed interactions between docetaxel and trastuzumab. The analysis of these data, which was incorporated into product labeling, Clinical Pharmacology section, approved with STN BL 103792/5175, described this information and noted that there were no significant interactions observed between trastuzumab and docetaxel. There were no safety signals identified in the review of these supplements which required further exploration of drug-drug interactions in order to establish the safety and effectiveness of the proposed dose, however Genentech should conduct drug-drug interaction studies as a post-marketing commitment, and as proposed during the April 18, 2007 pre-sBLA meeting.

## 6. Clinical Microbiology

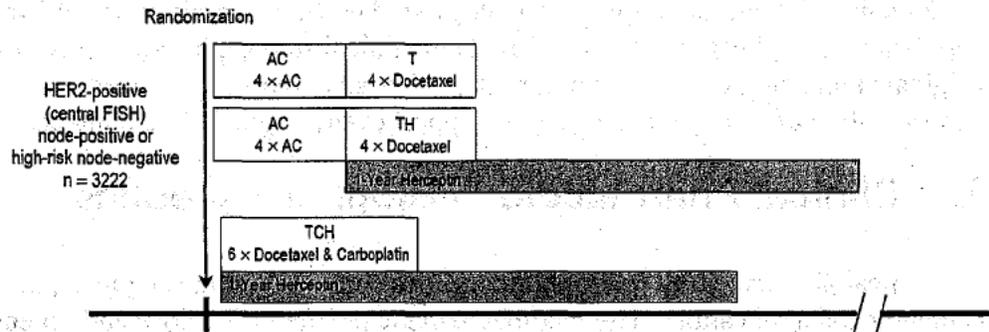
Clinical microbiology data are not required for, or applicable to the review of, this product for this indication.

## 7. Clinical/Statistical-Efficacy

(b) (4)

BCIRG 006 represents the fourth such trial and the results of this trial, using different background chemotherapy regimens than the previous three studies (NSABP B31, NCCTG N9831, and HERA), demonstrated that the addition of trastuzumab to a regimen of cyclophosphamide and anthracycline followed by docetaxel (ACTH) resulted in superior disease-free survival as compared cyclophosphamide and anthracycline followed by docetaxel (ACT). The effects on DFS, whether as defined by the investigators or as defined by FDA, were robust and similar in magnitude to that observed in the previous adjuvant trials.

The treatment regimens (ACT, ACTH, and TCH) are displayed in the following figure



AC=doxorubicin plus cyclophosphamide; AC→T=four cycles of AC followed by four cycles of docetaxel every 3 weeks; AC→TH=same chemotherapy regimen with the addition of 52 weeks of Herceptin starting concurrently with docetaxel and continuing as monotherapy; FISH=fluorescence in situ hybridization; T=docetaxel; TCH=docetaxel every 3 weeks concurrently with Herceptin, followed by Herceptin monotherapy.

The study population was limited to patients with HER2 gene amplification by FISH, high-risk node-negative (29%) or node-positive (71%) breast cancer. The population had a median age of 49 years, with 6% of patients  $\geq 65$  years of age. Racial/ethnic data were not collected.

The primary outcome measure in this supplement resulted from the pair-wise comparison of results from the 1073 patients randomized to the control (ACT) arm with that of 1074 patients randomized to the ACTH arm. The basis for approval of weekly trastuzumab in combination with 4 cycles of anthracycline and cyclophosphamide followed by 4 cycles of docetaxel, followed by trastuzumab every three weeks for a total of one year of therapy (ACTH) is based on evidence of superior disease-free survival as compared to the same combination chemotherapy regimen (ACT) without trastuzumab. With a median follow-up of 36 months, patients randomized to TCH demonstrated a significantly longer disease-free survival as compared to the those randomized to the control regimen of doxorubicin and cyclophosphamide followed by docetaxel (hazard ratio 0.61 [95% CI: 0.49, 0.76],  $p < 0.0001$  stratified log-rank test). The treatment effect was also present across relevant prognostic subgroups. An unplanned analysis of overall survival, provided at FDA's request for assessment of safety, did not raise safety concerns. An evaluation of survival for efficacy is premature based on the limited number of events.

One specific issue with this trial, as identified by FDA at the pre-BLS submission meeting, was the definition of the composite endpoint, disease-free survival. The medical officer undertook a review of prior approvals for adjuvant treatment of breast cancer. While there are exceptions, in the majority of approvals, the term disease-free survival included the following as events: ipsilateral or contralateral invasive breast cancer, distant metastatic breast cancer, and death. In a few prior approvals, non-breast second primary cancers were also included as "disease" events, which was also the case in the BCIRG protocol-defined DFS composite endpoint. The justification for inclusion of non-breast cancer second primaries was concern for detection of hormonally-induced cancers (e.g., uterine) or chemotherapy-induced cancers

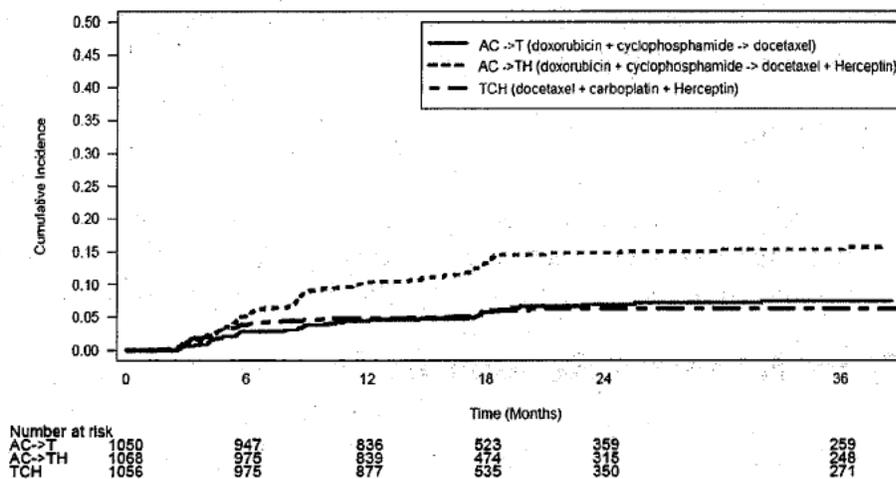
(e.g., secondary acute non-lymphocytic leukemia and myelodysplastic syndromes) which might offset the benefits of an effect on breast cancer recurrence. FDA considered these non-breast, second primary cancers to be toxic events rather than measures of clinical benefit; for consistency with the majority of approvals and the reasons just discussed, FDA excluded non-breast second primary cancers from the primary determination of efficacy.

## 8. Safety

Although not conducted with an intent to support expanded labeling claims, the size of the ACTH treatment group (1068 patients in the ACTH group and 1044 patients in the control group) was sufficient to identify new safety signals and the trial was designed to characterize the cardiotoxicity of the ACTH regimen through serial monitoring for subclinical cardiomyopathy over an 18 month period, which encompassed the treatment period and short-term post-treatment effects.

The most serious adverse reaction due to Herceptin is cardiomyopathy. The incidence of symptomatic congestive heart failure is higher (2.1% vs. 0.3%) in the ACTH group compared to the control group. In evaluation of time-to-decline in left ventricular ejection fraction, there is a higher incidence of clinically significant decline in LVEF appearing at 6 months and stabilizing at approximately 18 months as compared to that observed in the control group. These data are displayed in the figure below, reproduced from the physician package insert.

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



Time 0 is the date of randomization.

The following non-cardiac adverse events adverse reactions NCI CTC grades 1-4 occurring in  $\geq 5\%$  of subjects at a higher incidence in the ACTH group as compared to controls were: diarrhea (51% vs. 43%), infection (44% vs. 38%), maculopapular rash (34% vs. 28%),

dyspepsia (25% vs. 20%), rhinitis (25% vs. 28%), and epistaxis (13% vs. 6%). thrombotic events NCI CTC grades 1-4 (2.5% vs. 2.2%) and NCI CTC grade 3-4 neutropenia (71% vs. 63%).

An assessment of post-marketing reports was conducted during the review period of this application and the findings of this review were included in product labeling with the approval of STN BL 103702/5175. The new safety information included reports of oligohydramnios in women receiving Herceptin during pregnancy, resulting in an agreed-upon commitment to collect additional data in a cancer-pregnancy registry and inclusion in product labeling of signals of arrhythmias and interstitial pneumonitis.

Due to the lack of long-term cardiac safety information with the combination of trastuzumab when administered following cyclophosphamide and doxorubicin, and in combination and following docetaxel, FDA required that follow-up information on cardiac toxicity, both clinical cardiac events as defined in the BCIRG 006 protocol and results of protocol-mandated left ventricular ejection fraction measurements up to 36 months post-randomization, be collected, analyzed, and provided to FDA.

## **9. Advisory Committee Meeting**

An advisory committee was not convened because the application did not raise new issues with regard to the safety or efficacy of trastuzumab as a component of adjuvant therapy for breast cancer. The findings that patients receiving an adjuvant treatment regimen consisting of a combination multi-agent chemotherapy, hormonal therapy where appropriate, and trastuzumab have longer disease-free survival is consistent with prior studies. The effects on DFS are clinically important in magnitude and statistically robust. The risks of trastuzumab in this setting are considered acceptable and well-defined in the short-term.

## **10. Pediatrics**

The indication for which expanded labeling claims are sought, i.e., HER2 over-expressing, node-positive or high-risk node negative, breast cancer does not occur in children. Therefore, no studies are required or requested to be conducted in pediatric patients.

## **11. Other Relevant Regulatory Issues**

There are no other unresolved relevant regulatory issues. Regulatory issues considered in the review of these supplements include the following:

- DSI audits were not requested because the data in these supplements expand on prior supplemental applications in patients receiving adjuvant chemotherapy for HER2 over-expressing breast cancer and are consistent with these findings. The review of datasets when compared to primary records where provided, did not suggest the presence of fraud or misconduct, indicating a need for a directed audit. In addition, from the size of the

study and number of subjects enrolled per site, it was not possible for one or a limited number of sites to substantially affect study results. A total of 433 centers in 43 countries enrolled patients in this study. The number of centers by country ranged from one center (Bosnia, Cyprus, Greece, Sweden, and Switzerland) to 177 centers (United States).

- **Financial Disclosure:** An assessment of financial conflicts of interest was conducted. Based on the large number of study sites and small proportion of study patients contributed by any single study site, sites with potential conflicts would have had limited ability to influence the overall study results.
- **DDMAC consultative advice:** The recommendations of the DDMAC reviewer were incorporated during revisions to the final product labeling.

## **12. Labeling**

Based on a review by OSE staff within the past year, product labeling was revised and additional requests for agreed-upon post-marketing commitments were generated to address outstanding safety signals under the supplement (STN BL 103792/5175) approved January 18, 2008. Review of STN BL 103792/5175 overlapped with the review timeframes for the current supplement and no additional consultation with OSE was considered needed at this time.

All outstanding issues regarding revisions to physician labeling were resolved by the time of approval. Major revisions to product labeling included:

- Revision of the adjuvant breast cancer subsections of the Indications and Usage, Dosage and Administration, and Clinical Experience sections to include the TCH regimen, directions for use, and clinical efficacy data supporting this expanded indication.
- Revision to the Cardiomyopathy subsections of the Warnings and Precautions and the Adverse Reactions sections to include the following safety information
  - Incidence of symptomatic cardiotoxicity, including ischemic cardiac events with the TCH regimen
  - Clarification of the recommended cardiac monitoring program during trastuzumab use for metastatic and for adjuvant breast cancer treatment
  - Time-to-development of cardiomyopathy as determined by changes in left ventricular ejection fraction.
- Description of the study population and exposure data from the BCIRG 006 study and summary statement regarding non-cardiac adverse reaction information under the Clinical Trials Experience of the Adverse Reactions section, specifically regarding infections, diarrhea, and thrombosis/embolism.

- Update of the Geriatric Use subsection of the Use in Specific Populations section to include elderly patients enrolled in BCIRG 006.

- [REDACTED] (b) (4)

- [REDACTED] (b) (4)

- [REDACTED] (b) (4)

### 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment

Both clinical and statistical reviewers recommended approval of this application. The combination of trastuzumab to an anthracycline-containing adjuvant chemotherapy results in improved DFS with an acceptable increase in cardiotoxicity given the magnitude of the benefit, as compared to the same regimen without trastuzumab.

- Recommendation for Postmarketing Risk Management Activities

Given the short duration of follow-up, the applicant is required to provide a complete evaluation of cardiotoxicity after all patients have been followed for 5 years and have completed the serial cardiac monitoring (LVEF assessment) portion of the trial.

- Recommendation for other Postmarketing Study Commitments

Given the short duration of follow-up for both DFS and OS, the applicant has agreed to provide analyses of the durability of the effects of TCH on DFS and overall survival (OS), as compared to ACT, with 5 and 10 years of follow-up. These data are not necessary to confirm clinical benefit but will provide information on the durability of the effect on DFS and establish whether there is an effect on OS at a time when a sufficient number of events have occurred to perform an analysis.

## Summary Review for Regulatory Action

<b>Date</b>	May 5, 2008
<b>From</b>	Patricia Keegan, M.D. <i>P. Keegan 5-5-08</i>
<b>Subject</b>	Division Director Summary Review
<b>BLA Supplement #</b>	BL STN 103792/5189
<b>Applicant Name</b>	Genentech
<b>Date of Submission Receipt</b>	July 5, 2007
<b>PDUFA Goal Date</b>	May 4, 2008
<b>Proprietary Name / Established (USAN) Name</b>	Herceptin® / trastuzumab
<b>Dosage Forms / Strength</b>	Lyophilized powder for reconstitution and intravenous infusion (b) (4) mg vial
<b>Proposed Indication(s)</b>	"As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer"
<b>Action</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Patricia Cortazar
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 CDTL=Cross-Discipline Team Leader

# Signatory Authority Review Template

## 1. Introduction

This supplement is based on comparisons of safety and efficacy of one of two investigational arms with an active control treatment regimen within a single, three-arm, multinational, randomized, open-label clinical trial, Protocol BCIRG 006. The BCIRG 006 trial enrolled 3222 women with HER-2 gene amplified, surgically resected localized breast cancer, receiving post-resection adjuvant chemotherapy, with equal allocation (1:1:1) to the control arm (combination anthracycline-cyclophosphamide followed by docetaxel) and the two trastuzumab-containing investigational arms. For the purposes of this supplemental application, the primary objective of the trial was determine whether the addition of Herceptin® (trastuzumab) given in combination with a non-anthracycline-containing chemotherapy regimen (carboplatin and docetaxel) resulted in improved disease-free survival. The key secondary objective was determination of the incidence and severity of trastuzumab-induced cardiotoxicity as compared to the background rate observed with an anthracycline-containing adjuvant regimen. The trial was initiated and conducted by the Breast Cancer International Research Group (BCIRG), a independent cooperative oncology group, rather than the applicant and was not originally intended to support labeling claims for trastuzumab. After initiation of the trial, Genentech reached agreement with BCIRG to provide the results of the study under an agreed-upon post-marketing commitment to characterize Herceptin-induced cardiomyopathy when given following anthracycline exposure and when given to an anthracycline-naïve patient population.

The trial was monitored by a DSMB, which released the results following the second interim analysis of efficacy which crossed a pre-specified boundary, demonstrating a significantly superior and clinically important prolongation in disease-free survival in each of the trastuzumab-containing regimens as compared to the control.

Specific areas to be discussed in this review are

- The use of a single trial to demonstrate safety and efficacy in support for this extended labeling claim
- Trial design considerations which precluded a direct assessment of the contribution of Herceptin to the carboplatin/docetaxel regimen
- Standardization of the definition of disease-free survival and use of an alternate definition of DFS as the primary outcome measure by FDA
- Need for additional follow-up to characterize long-term efficacy (disease-free survival) and safety (overall survival, late onset cardiomyopathy)

## 2. Background

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On Dec. 11, 2001, product labeling was revised to include updated survival data from the first-line breast cancer study.

On August 28, 2002, product labeling was revised to include the Vysis PathVysion HER2 DNA probe for detection of gene amplification as a method to select patients for trastuzumab therapy.

On (b) (4) labeling claims were expanded to include an indication for trastuzumab as part of a treatment regimen containing doxorubicin, cyclophosphamide and paclitaxel, for the adjuvant treatment of patients with HER2 overexpressing, node-positive breast cancer.

On January 18, 2008, labeling was expanded to include a new dose and schedule for trastuzumab when administered as part of an anthracycline containing chemotherapy regimen for the adjuvant treatment of HER2 overexpressing, node-positive or high risk node negative, breast cancer.

The current supplement is based on the results of the BCIRG study, which was submitted to an IND held by sanofi aventis for Taxotere (docetaxel). Sanofi Aventis was granted an expanded labeling claim for Taxotere for use with doxorubicin and cyclophosphamide as adjuvant treatment of operable, node-positive breast cancer on August 18, 2004. The regimen used to support this claim was docetaxel 75 mg/m<sup>2</sup>, in combination with doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup>, administered every three weeks for six cycles.

Genentech, Inc. did not meet with FDA to discuss the acceptability of the trial design in support of labeling claims for trastuzumab prior to study initiation. However, Genentech notified FDA of their intent to provide the results of the BCIRG 006 trial to further characterize the cardiotoxicity of trastuzumab in their PMC annual report, STN BL 103792/5170 submitted on November 28, 2006. In this report, Genentech identified use of BCIRG 006 (b) (4) to fulfill one aspect of PMC #6, as described in the approval letter for STN BL 103792/0.

The BCIRG 006 trial initiated accrual in March 2001 and the last patient was enrolled in September 2003. On March 17, 2005, the fourth protocol amendment modified the statistical analysis plan to require three interim analyses for DFS, when 300, 450, and 650 DFS events and a final analysis at 900 DFS events (the original protocol required one interim analysis at 654 events and a final analysis at 1308 events). The first interim analysis was conducted with a data cut-off date of June 30, 2005; although the boundary was crossed for the ACT vs. ACTH comparison (and possibly for the ACT vs. TCH comparison depending upon the interpretation of the method of adjustment) that trial continued until the second interim analysis was conducted following 474 events with a data cut-off date of November 1, 2006.

A pre-sBLA teleconference was held with Genentech on April 18, 2007, as described in Genentech's meeting minutes with clarifications from FDA on May 30, 2007. The following key agreements were reached:

- Since two claims are sought, separate applications must be submitted in support of inclusion of the ACTH regimen and TCH regimen in product labeling.
- The results of the first and second interim analyses would be provided; results of the second interim analysis would be provided as descriptive information in product labeling and the results of the first interim analysis would be used for inference purposes in labeling.

(b) (4)

- Genentech agreed to conduct drug-drug interactions studies for trastuzumab and carboplatin as a post-marketing commitment.
- A separate application would be submitted in support of partial fulfillment of PMC #6 under the STN BL 103792/0 approval letter, containing or cross-referencing data from BCIRG intended to fulfill a portion of the PMC regarding cardiotoxicity in Herceptin-treatment, anthracycline naïve patients. *[Note- an amendment identified as a clinical study report for PMC #6 was not submitted during the review of this application]*

### 3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. As noted by Dr. Weinberg in her review, the BCIRG 006 study relied on both FDA-licensed Herceptin manufactured at Genentech, and EU-approved Herceptin manufactured by Roche at their facility in Penzberg, Germany. The comparability of the Genentech- and Roche-manufactured Herceptin was reviewed under STN BL 103792/5175.

(b) (4)

results of physicochemical and biological assessments support sufficient comparability to rely on the Roche material in this study for expansion of Genentech's Herceptin license. There are no CMC outstanding issues which would preclude approval.

## 4. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology or toxicology studies were submitted in support of this supplemental application. No additional nonclinical studies, besides those contained in the original application or agreed-upon post-marketing commitments, were required to make a determination of safety and efficacy in support of the expanded labeling claims.

## 5. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology or biopharmaceutics data were submitted in support of this supplemental application. The pharmacokinetic profile of the dose and schedule of trastuzumab utilized in this application has been adequately characterized in prior supplements. In addition, the drug-drug interactions between trastuzumab and commonly prescribed antineoplastic agents (i.e., doxorubicin, paclitaxel, and docetaxel) were investigated under PMC #8 associated with the original approval of trastuzumab. The final study report for Study JP16003, submitted to BL STN 103792/5177, assessed interactions between docetaxel and trastuzumab. The analysis of these data, which was incorporated into product labeling, Clinical Pharmacology section, approved with STN BL 103792/5175, described this information and noted that there were no significant interactions observed between trastuzumab and docetaxel. There were no safety signals identified in the review of these supplements which required further exploration of drug-drug interactions in order to establish the safety and effectiveness of the proposed dose, however Genentech should conduct drug-drug interaction studies as a post-marketing commitment, and as proposed during the April 18, 2007 pre-sBLA meeting.

## 6. Clinical Microbiology

Clinical microbiology data are not required for, or applicable to the review of, this product for this indication.

## 7. Clinical/Statistical-Efficacy

(b) (4)

BCIRG 006 represents the fourth such trial and the results of this trial, using different background chemotherapy regimens than the previous three studies (NSABP B31, NCCTG N9831, and HERA), demonstrated that the addition of trastuzumab to carboplatin and docetaxel (TCH) results in superior disease-free survival as compared to a standard anthracycline/taxane-containing (ACT) regimen. The effects on DFS, whether as defined by the investigators or as defined by FDA, were robust and similar in magnitude to that observed in the previous adjuvant trials.

The primary outcome measure in this supplement resulted from the pair-wise comparison of results from the 1073 patients randomized to the control arm with that of 1075 patients randomized to the TCH arm. The basis for approval of trastuzumab as a component of the docetaxel, carboplatin, and trastuzumab (TCH) adjuvant regimen is based on evidence of superior disease-free survival as compared to a standard, anthracycline-taxane based, non-trastuzumab-containing regimen. With a median follow-up of 36 months, patients randomized to TCH demonstrated a significantly longer disease-free survival as compared to those randomized to the control regimen of doxorubicin and cyclophosphamide followed by docetaxel (hazard ratio 0.67 [95% CI: 0.54, 0.84],  $p=0.0006$  stratified log-rank test, unadjusted for pairwise comparisons). The treatment effect was also present across relevant prognostic subgroups. An unplanned analysis of overall survival, provided at FDA's request for assessment of safety, did not raise safety concerns. An evaluation of survival for efficacy is premature based on the limited number of events.

One major flaw with regard to the design of this trial is that the effect of trastuzumab, when given in combination with carboplatin and docetaxel, was not isolated. The applicant, at FDA's request, provided literature references containing the results of randomized studies which taken in aggregate, served to evaluate the contribution of the different components of the three drug regimen (trastuzumab, carboplatin, and docetaxel). The evaluation of the contribution of trastuzumab to docetaxel/carboplatin rests primarily on the following information:

- 1) In Study M77001, a randomized (1:1), multicenter study in 198 women receiving first-line therapy for HER2 overexpressing, metastatic breast cancer, the combination of docetaxel and trastuzumab demonstrated superior overall response rates, time-to-disease progression, and overall survival as compared to women receiving docetaxel alone.
- 2) In Study BCIRG 007, a randomized (1:1) multicenter study in 263 women receiving first-line therapy for HER2 overexpressing, metastatic breast cancer, the addition of carboplatin to docetaxel (75 mg/m<sup>2</sup> q 3wks) and trastuzumab did not significantly improve time-to-progression, survival, or response rates as compared to docetaxel (100 mg/m<sup>2</sup> q3wks) and trastuzumab alone.

Based on these studies, the contribution of trastuzumab to docetaxel yields superior results (M77001), while the addition of carboplatin to trastuzumab and a modestly reduced dose of docetaxel was not superior to docetaxel and trastuzumab alone (BCIRG 007) and the study was not adequate to establish equivalence of the 3-drug to the 2-drug regimen. Thus, in addition to the M77001 results, the approval is based on the totality of the effect of the TCH regimen against the ACT regimen, an accepted adjuvant combination chemotherapy regimen for women with high-risk breast cancer.

An additional issue was the definition of the composite endpoint, disease-free survival. The medical officer undertook a review of prior approvals for adjuvant treatment of breast cancer. While there are exceptions, in the majority of approvals, the term disease-free survival included the following as events: ipsilateral or contralateral invasive breast cancer, distant

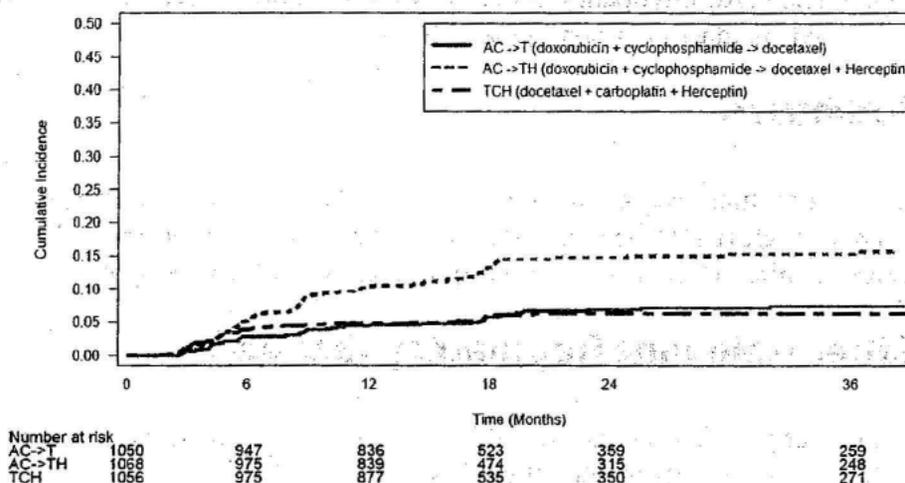
metastatic breast cancer, and death. In a few prior approvals, non-breast second primary cancers were also included as “disease” events, which was also the case in the BCIRG protocol-defined DFS composite endpoint. The justification for inclusion of non-breast cancer second primaries was concern for detection of hormonally-induced cancers (e.g., uterine) or chemotherapy-induced cancers (e.g., secondary acute non-lymphocytic leukemia and myelodysplastic syndromes) which might offset the benefits of an effect on breast cancer recurrence. FDA considered these non-breast second primary cancers to be toxic events rather than measures of clinical benefit; for consistency with the majority of approvals and the reasons just discussed, FDA excluded non-breast second primary cancers from the primary determination of efficacy.

## 8. Safety

Although not conducted with an intent to support expanded labeling claims, the size of the TCH treatment group (1056 patients in the TCH group and 1044 patients in the control group) was sufficient to identify new safety signals and the trial was designed to characterize the cardiotoxicity of the TCH regimen through serial monitoring for subclinical cardiomyopathy over an 18 month period, which encompassed the treatment period and short-term post-treatment effects.

The most serious adverse reaction due to Herceptin is cardiomyopathy. The incidence of NCI-CTC Grade 3 or 4 cardiac ischemia/infarction was higher in the TCH group (0.2%) as compared to the control group, in which no cases of cardiac ischemia/infarction were reported. The incidence of symptomatic congestive heart failure was slightly higher (0.4% vs. 0.3%) in the TCH group compared to the control group. In evaluation of time-to-decline in left ventricular ejection fraction, the curves for the TCH group are similar to that of the control. These data are displayed in the figure below, reproduced from the physician package insert.

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



Time 0 is the date of randomization.

The following adverse reactions occurred at higher incidence in the TCH group as compared to controls: NCI CTC grades 1-4 diarrhea (62% vs. 43%), thrombotic events NCI CTC grades 1-4 (3.7% vs. 2.2%) NCI CTC grade 3-4 neutropenia (66% vs. 63%), and NCI CTC grades 3-4 thrombocytopenia (5% vs. 1%).

An assessment of post-marketing reports was conducted during the review period of this application and the findings of this review were included in product labeling with the approval of STN BL 103702/5175. The new safety information included reports of oligohydramnios in women receiving Herceptin during pregnancy, resulting in an agreed-upon commitment to collect additional data in a cancer-pregnancy registry and inclusion in product labeling of signals of arrhythmias and interstitial pneumonitis.

Due to the lack of long-term cardiac safety information with the combination of carboplatin and docetaxel, FDA required that follow-up information on cardiac toxicity, both clinical cardiac events as defined in the BCIRG 006 protocol and results of protocol-mandated left ventricular ejection fraction measurements up to 36 months post-randomization, be collected, analyzed, and provided to FDA.

## **9. Advisory Committee Meeting**

An advisory committee was not convened because the application did not raise new issues with regard to the safety or efficacy of trastuzumab as a component of adjuvant therapy for breast cancer. The findings that patients receiving an adjuvant treatment regimen consisting of a combination multi-agent chemotherapy, hormonal therapy where appropriate, and trastuzumab have longer disease-free survival is consistent with prior studies. The effects on DFS are clinically important in magnitude and statistically robust. The risks of trastuzumab in this setting are considered acceptable and well-defined in the short-term. In particular, the risks of subclinical cardiomyopathy in the TCH combination appear to be similar to that for ACT, an accepted standard regimen in the U.S. of care.

## **10. Pediatrics**

The indication for which expanded labeling claims are sought, i.e., HER2 over-expressing, node-positive or high-risk node negative, breast cancer does not occur in children. Therefore, no studies are required or requested to be conducted in pediatric patients.

## **11. Other Relevant Regulatory Issues**

There are no other unresolved relevant regulatory issues. Regulatory issues considered in the review of these supplements include the following:

- DSI audits were not requested because the data in these supplements expand on prior supplemental applications in patients receiving adjuvant chemotherapy for HER2 over-expressing breast cancer and are consistent with these findings. The review of datasets when compared to primary records where provided, did not suggest the presence of fraud or misconduct, indicating a need for a directed audit. In addition, from the size of the study and number of subjects enrolled per site, it was not possible for one or a limited number of sites to substantially affect study results. A total of 433 centers in 43 countries enrolled patients in this study. The number of centers by country ranged from one center (Bosnia, Cyprus, Greece, Sweden, and Switzerland) to 177 centers (United States).
- Financial Disclosure: An assessment of financial conflicts of interest was conducted. Based on the large number of study sites and small proportion of study patients contributed by any single study site, sites with potential conflicts would have had limited ability to influence the overall study results.
- DDMAC consultative advice: The recommendations of the DDMAC reviewer were incorporated during revisions to the final product labeling.

## 12. Labeling

Based on a review by OSE staff within the past year, product labeling was revised and additional requests for agreed-upon post-marketing commitments were generated to address outstanding safety signals under the supplement (STN BL 103792/5175) approved January 18, 2008. Review of STN BL 103792/5175 overlapped with the review timeframes for the current supplement and no additional consultation with OSE was considered needed at this time.

All outstanding issues regarding revisions to physician labeling were resolved by the time of approval. Major revisions to product labeling included:

- Revision of the adjuvant breast cancer subsections of the Indications and Usage, Dosage and Administration, and Clinical Experience sections to include the TCH regimen, directions for use, and clinical efficacy data supporting this expanded indication.
- Revision to the Cardiomyopathy subsections of the Warnings and Precautions and the Adverse Reactions sections to include the following safety information
  - Incidence of symptomatic cardiotoxicity, including ischemic cardiac events with the TCH regimen
  - Clarification of the recommended cardiac monitoring program during trastuzumab use for metastatic and for adjuvant breast cancer treatment
  - Time-to-development of cardiomyopathy as determined by changes in left ventricular ejection fraction.

- Description of the study population and exposure data from the BCIRG 006 study and summary statement regarding non-cardiac adverse reaction information under the Clinical Trials Experience of the Adverse Reactions section, specifically regarding infections, diarrhea, and thrombosis/embolism.
- Update of the Geriatric Use subsection of the Use in Specific Populations section to include elderly patients enrolled in BCIRG 006.

(b) (4)



### **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action: Approval
- Risk Benefit Assessment  
Both clinical and statistical reviewers recommended approval of this application. The combination of trastuzumab to non-anthracycline-containing adjuvant chemotherapy results in improved DFS and without additional cardiotoxicity, as compared to the previous standard adjuvant regimen for high-risk breast cancer. Although the contribution of trastuzumab is inferred from other trials, rather than directly tested in this clinical trial, the combination is both effective and reasonably safe.
- Recommendation for Postmarketing Risk Management Activities  
Given the short duration of follow-up, the applicant is required to provide a complete evaluation of cardiotoxicity after all patients have been followed for 5 years and have completed the serial cardiac monitoring (LVEF assessment) portion of the trial.
- Recommendation for other Postmarketing Study Commitments
  - Given the short duration of follow-up for both DFS and OS, the applicant has agreed to provide analyses of the durability of the effects of TCH on DFS and overall survival (OS), as compared to ACT, with 5 and 10 years of follow-up. These data are not necessary to confirm clinical benefit but will provide information on the durability of the effect on DFS and establish whether there is an effect on OS at a time when a sufficient number of events have occurred to perform an analysis.

- As discussed during the April 18, 2007 pre-BLS meeting, drug-drug interaction studies for carboplatin and trastuzumab were not ongoing and should be assessed.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**BLA 103792/5187/5189**

**OFFICER/EMPLOYEE LIST**

**Officer/Employee List**  
**Application: 103792/5189**

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Cortazar, Patricia  
Keegan, Patricia  
Laughner, Erik  
Rothmann, Mark  
Shen, Yuan-Li  
Swann, Patrick  
Weinberg, Wendy

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**BLA 103792/5187/5189**

**MEDICAL REVIEW(S)**

**CLINICAL REVIEW**

Application Type: Prior approval supplement  
Submission Number: BL STN 103792.5187  
Letter Date: June 29, 2007  
PDUFA Goal Date: April 28, 2008

Reviewers Names: Katherine Fedenko, MS, CRNP  
Patricia Cortazar, M.D.

*K. Fedenko 5/2/2008*  
*P Cortazar 5/2/08*  
*P. Lee 5/2/08*

Review Completion Date: May 2, 2008

Established Name: Herceptin® (trastuzumab)  
Therapeutic Class: HER2/neu receptor antagonist  
Applicant: Genentech, Inc.  
Priority Designation: Standard

**Indications:**

“As part of a treatment regimen containing doxorubicin,  
cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-  
overexpressing, node-positive (b) (4) breast cancer”

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Clinical Review  
{Katherine Fedenko, MS, CRNP and Patricia Cortazar, MD }  
{sBLA 103792}  
{Herceptin® (Trastuzumab )}

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## 1 EXECUTIVE SUMMARY

This multidisciplinary medical-statistical review addresses an efficacy supplement to BLA 103792 for use of Herceptin® (trastuzumab) for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer. The original BLA for Herceptin® was approved in 1998 as a single agent for patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Herceptin® was also approved in 1998 in combination with paclitaxel for treatment of patients with metastatic breast cancer whose tumors overexpress HER2 protein and who have not received chemotherapy for their metastatic disease. On November 2006, FDA approved Herceptin® for the adjuvant treatment of patients with HER2 overexpressing, node-positive breast cancer as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel. In this regimen, Herceptin is given concurrently with paclitaxel and then as monotherapy, for a total duration of Herceptin therapy of 52 weeks. On January 2008, Herceptin® was also approved for the adjuvant treatment of patients with HER2 overexpressing, node-positive and high risk node-negative breast cancer, as a single agent for 52 weeks, after completion of surgery, chemotherapy, and radiotherapy (if applicable).

The current supplement presents the results of a randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC-T) with doxorubicin and cyclophosphamide followed by docetaxel plus Herceptin (AC-TH) and docetaxel plus carboplatin plus Herceptin (TCH), as adjuvant treatment in women with HER2 overexpressing, node-positive and high risk node-negative breast cancer.

The applicant submitted data to support two new indications. The sBLA 103792 was reviewed by two medical reviewers. This review, 103792\5187, addresses the following proposed indication, "As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer" sBLA 103792\5189, supports the following proposed indication, "As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer". and was reviewed by Clinical Reviewer, Patricia Cortazar.

### 1.1 Recommendation on Regulatory Action

The Division of Biologic Oncology Products recommends full approval of Herceptin® for the proposed indication:

"As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer".

The efficacy claims in support of this application are based on the results of a single large randomized well controlled trial (BCIRG006) entitled, "A multicenter phase III randomized trial

comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) and with docetaxel, platinum salt and trastuzumab (TCH) in the treatment of node positive and high risk node negative adjuvant patients with operable breast cancer containing the HER2neu alteration.”

The protocol primary endpoint was disease free survival. Secondary endpoints included overall survival and to compare cardiac and non-cardiac toxicity between the 3 arms, in order to determine the safety of Herceptin with these chemotherapy regimens. At the second interim analysis and 36 months of median follow-up, AC→TH, the anthracycline containing arm (Herceptin concurrently with docetaxel) demonstrated a significantly longer disease-free survival as compared to the AC→T (doxorubicin and cyclophosphamide followed by docetaxel) treatment arm.

(b) (4)

The safety profile of doxorubicin and cyclophosphamide followed by docetaxel in combination with Herceptin are consistent with the known toxicities of the four agents and typical antineoplastic therapy. The AC→TH arm appears to have a higher incidence rates of the LVEF related events (e.g. post-baseline LVEF: 50% and significant LVEF drop) as compared to the rates in the AC→T arm.

## 1.2 Recommendation on Postmarketing Actions

### Risk Management Activity

#### Required Phase 4 Commitments

1. Updated efficacy data at 10 years of follow-up from all 3 treatment arms in BCIRG006, with an interim update at 5 years of follow-up

To provide an efficacy update from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled (March 2004) in the trial reaches approximately 10 years of follow-up, with an interim report on the updated efficacy at 5-years of follow-up. It is estimated that the completion of 5-year follow-up will occur in Q2 2009. The DFS and OS update based on 5-year follow-up date will be submitted to the FDA in Q1 2010. It is estimated that the completion of 10-year follow-up will occur in Q2 2014. The updated DFS and OS data will be submitted to the FDA in Q1 2015.

2. Cardiac safety update at 5 years of follow-up from all 3 treatment arms in BCIRG006

To provide an update on cardiac safety from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 5 years of follow-up. The update will include analysis of per-protocol defined cardiac events, changes in LVEF measurements, and narratives for any patients who developed a new per-protocol defined cardiac event. The completion of 5-year follow-up will occur in Q2 2009 and the 5-year cardiac update will be submitted to FDA in Q1 2010.

## Other Phase 4 Requests

### 1.3 Summary of Clinical Findings

#### Brief Overview of Clinical Program

Genentech submitted Study BCIRG006, an multinational randomized, open-label, active-controlled clinical trial, to evaluate Herceptin given either concurrently with a non-anthracycline chemotherapy regimen of docetaxel and carboplatin (TCH) or with docetaxel after completion of doxorubicin and cyclophosphamide (AC→TH) compared with the control arm: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) as adjuvant treatment of HER-2 over-expressing, node-positive and high-risk node-negative patients with operable breast cancer.

Study BCIRG006 was conducted by BCIRG and sponsored by Sanofi-Aventis (under IND 35,555) and Genentech. About 30% of the patients were from the US. The rest of the patients were from Europe, Asia, New Zealand, Australia, Canada and other countries. Patient assignment to treatment was based on a stochastic minimization scheme with center, status of axillary lymph nodes involved and hormonal receptor status as factors. The primary endpoint of this study was disease-free survival and the secondary efficacy endpoints included overall survival and quality of life. The primary comparison of this study was between each of the arms containing Herceptin versus the AC→ T arm using the stratified log-rank test.

#### Efficacy

A total of 3222 patients were randomized into the three treatment arms. The primary efficacy analysis population consisted of all the randomized patients (ITT) according to the randomized treatment. The median follow-up of the study was 36 months. The treatment arms were well balanced for important baseline characteristics (b) (4)

(b) (4)

At the second interim analysis and 36 months of median follow-up AC→TH, the anthracycline containing arm which consisted of Herceptin given concurrently with docetaxel following doxorubicin and cyclophosphamide, demonstrated a significantly longer disease-free survival as compared to the AC→T (doxorubicin and cyclophosphamide followed by docetaxel) treatment arm. The hazard ration of the AC→TH arm versus AC→T arm is 0.60(95% CI=[0.48, 0.76]) with p-value <0.0001 based on stratified log-rank statistic.

The beneficial treatment effect of the AC→TH arm consistently demonstrated in various subgroups and is robust based on several sensitivity analyses.

There were no pre-specified alpha spending, no pre-planned interim analyses and no pre-specified significance levels for overall survival in the protocol. (b) (4)

### Safety

The safety database consists of the following groups: AC→T (n=1050), AC→TH (n=1068), and TCH (n=1056) which included all patients who received at least one dose of study treatment.

Exposure information is provided for the Herceptin containing arms for a total of 2101 subjects (AC→TH n=1045 and TCH n=1056). The median duration (378 days) and the median dose (107.4 mg and 109.5 mg for AC→TH and TCH arm respectively) of Herceptin appear to be comparable between AC→TH and TCH arm.

The clinical safety data were captured in datasets using National Cancer Institute Common toxicity Criteria (NCI-CTC) version 2.0 or COSTART. Key safety findings for study BCIRG 006:

- Treatment emergent sign and symptoms most common were Herceptin toxicity related; congestive heart failure and decreased left ventricular ejection fraction.
- The incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the Herceptin containing regimens: (AC-TH: 0.3% (3/1068) and TCH 0.2% (: 2/1056) as compared to none in AC-T. Incidence of CHF was higher in both Herceptin containing regimens as compared to the control [ACTH (2%) TCH (0.4%) vs. ACT (0.3%)].
- The overall incidence of infection was higher with the addition of Herceptin to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC grade 3-4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms.
- The incidence of thrombotic adverse events was higher in patients receiving Herceptin and chemotherapy compared to chemotherapy alone [AC→TH 2.5% and TCH 3.7% vs. AC→T 2.2%].

- The incidence of Grade 3-4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1-4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin.
- The most common non-cardiac adverse events reported in  $\geq 5\%$  of subjects with a higher between group difference of  $\geq 5\%$  in the Herceptin-containing (ACT versus AC→TH) group were: diarrhea, infection, maculopapular rash, dyspepsia, rhinitis, and epistaxis.
- The most common cardiac adverse events reported in  $\geq 5\%$  of subjects, with a difference of  $\geq 2\%$  in adverse events between ACT and AC→TH were hypertension and left heart failure.

### Dosing Regimen and Administration

The following are the recommended doses and schedules of Herceptin for a total of 52 weeks, for the treatment of adjuvant breast cancer:

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

- Initial dose of 4mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30-60 minutes every three weeks.

(b) (4)



(b) (4)

(b) (4)

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

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

**Renal Impairment**

The sponsor has not performed any renal impairment studies with Herceptin.

**Hepatic Impairment**

The sponsor has not performed any hepatic impairment studies with Herceptin.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Herceptin (Trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG<sub>1</sub> kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2. The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary [CHO]) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Herceptin is supplied in a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. The content of each Herceptin vial is 440 mg Trastuzumab, 400 mg  $\alpha,\alpha$ -trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing 21 mg/mL Trastuzumab, at a pH of approximately 6

### 2.2 Currently Available Treatment for Indications

Approximately 25% of patients with invasive breast cancer have tumors that are HER2-positive, determined by either HER2 protein overexpression or HER2 gene amplification (Slamon et al. 1987, 1989). This characteristic is strongly associated with an unfavorable prognosis regardless of other prognostic factors (Slamon et al. 1987, 1989). Patients with HER2-positive breast cancer have a more aggressive disease course, evidenced by a shortened disease-free interval following adjuvant therapy and inferior overall survival (OS) compared with patients without HER2-amplified cancers (Slamon et al. 1987; Winstanley et al. 1991; Press et al. 1997; Pauletti et al. 2000).

Herceptin was initially studied in the metastatic breast cancer setting. Initial studies were designed to establish the benefits and risks of Herceptin administered either in combination with chemotherapy (Study H0648g) or as a single agent (Study H0649g) to women with HER2 overexpressing metastatic breast cancer. Efficacy and safety data supporting the current licensed indication for Herceptin in HER2 overexpressing MBC were based on two pivotal studies, H0648g and H0649g. In Study H0648g, the addition of Herceptin to chemotherapy for patients with HER2 overexpressing MBC was associated with a longer time to disease progression (median, 7.2 months for the Herceptin + chemotherapy arm vs. 4.5 months for the chemotherapy-alone arm;  $p < 0.0001$ ), a higher objective response rate (45% vs. 29%;  $p < 0.001$ ), a longer duration of objective response (median, 8.3 vs. 5.8 months), and a longer median survival (25.1 vs. 20.3 months;  $p = 0.05$ ).

In view of the survival advantage conferred in the metastatic setting by Herceptin (trastuzumab), four large randomized studies (BCIRG 006, B-31, N9831, and HERA) were designed to evaluate the addition of Herceptin to commonly used adjuvant chemotherapy regimens.

The joint analysis of Studies NSABP B-31 and NCCTG N9831 formed the basis of a previous supplemental Biologics License Application (sBLA) for Herceptin, which was approved on November 2006. The studies were conducted by two major U.S. cooperative groups, the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the North Central Cancer Treatment Group (NCCTG). The NSABP B-31 trial compared doxorubicin and cyclophosphamide followed by paclitaxel every 3 weeks (Arm 1) with the same regimen plus 52 weeks of Herceptin beginning with the first dose of paclitaxel (Arm 2). The NCCTG N9831 study compared three regimens: doxorubicin and cyclophosphamide followed by weekly paclitaxel (Arm A), the same regimen plus 52 weeks of Herceptin initiated concurrently with paclitaxel (Arm C), or the same regimen followed by 52 weeks of Herceptin after paclitaxel (Arm B). Initially, enrollment in both studies was restricted to patients with node-positive disease; however, because of accumulating data on the risk of recurrence in women with node-negative, HER2-positive EBC, the NCCTG protocol was amended to allow the inclusion of high-risk node-negative patients. The addition of Herceptin to standard adjuvant chemotherapy led to a clinically meaningful and statistically significant improvement in DFS. The risk of recurrence among patients who received Herceptin plus chemotherapy was reduced by 52% compared with chemotherapy alone, [HR]:0.48; 95% [CI]: 0.39, 0.59;  $p < 0.0001$ ).

At the HERA study first planned interim analysis (median follow-up of 2 years), results of treatment with Herceptin for 1 year ( $n = 1693$ ) versus observation ( $n = 1694$ ) were reviewed by the Agency. Results of the 1-year analysis of Herceptin versus 2-year analysis were not released by the Independent Data Monitoring Committee (IDMC). Patients in the 1-year Herceptin arm had a 46% reduction in risk of recurrence compared with the observation arm (HR = 0.54; 95% CI: 0.44, 0.67 and a  $p < 0.0001$ ). Similar benefits were observed across important patient subgroups, including patients with node-negative disease. An unplanned survival analysis at the time of the DFS interim did not suggest a worse survival in the Herceptin arm.

The administration of adjuvant chemotherapy to women with early-stage breast cancer is a critical component of optimal treatment, especially for those women with the highest risk for recurrence. Prognostic factors of clinical outcome following systemic therapy for early-stage breast cancer include nodal status, tumor size, tumor histologic type or nuclear grade, and HER2 status (Goldhirsch et al. 2005). However, patients without lymph node involvement (node-negative patients) are also at high risk for recurrence, if at least one of the following conditions is present: tumor size  $> 2$  cm, histologic and/or nuclear Grade 2 or 3, evidence of peri-tumoral vascular invasion, HER2-positive status, or age  $< 35$  years (Goldhirsch et al. 2005). Therefore, women with node-negative, HER2-positive tumors are considered to have a similar risk for recurrence as those with node-positive, HER2-negative tumors (Goldhirsch et al. 2005). HER2-positive status has been shown in two independent analyses to be an independent and unfavorable prognostic factor for DFS in both node-negative and node-positive patients (Andrulis et al. 1998; Sun et al. 2004).

### **2.3 Availability of Proposed Active Ingredient in the United States**

Herceptin was approved by the FDA in 1998 as a single agent for patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Herceptin was also approved in 1998 in combination with paclitaxel for treatment of patients with metastatic breast cancer whose tumors overexpress HER2 protein and who have not received chemotherapy for their metastatic disease.

On November 2006, FDA approved Herceptin for the adjuvant treatment of patients with HER2 overexpressing, node-positive breast cancer as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel. In this regimen, Herceptin is given concurrently with paclitaxel and then as monotherapy, for a total duration of Herceptin therapy of 52 weeks.

On January 2008, Herceptin was approved based on efficacy and safety data from the HERA study, which demonstrated that the administration of Herceptin as a single agent for 52 weeks, after completion of surgery, chemotherapy, and radiotherapy (if applicable).

### **2.4 Important Issues With Pharmacologically Related Products**

There are no commercially available pharmacologically related products. Herceptin is the only US-FDA approved antibody product directed against the HER2 receptor. There is one approved drug, lapatinib (Tykerb), a tyrosine kinase inhibitor that is approved for treatment of HER2-overexpressing metastatic breast cancer that has progressed following Herceptin therapy. However, lapatinib is not pharmacologically related to Herceptin.

### **2.5 Presubmission Regulatory Activity**

The study design of BCIRG006 was not discussed with FDA.

### **2.6 Other Relevant Background Information**

## **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1 CMC (and Product Microbiology, if Applicable)**

The submission contained no new Chemistry, Manufacturing and Controls information. See Wendy Weinberg CMC Review for additional information.

### 3.2 Animal Pharmacology/Toxicology

No new animal pharmacology/toxicology data were submitted with this BLA submission. Given the available extensive clinical experience with Herceptin, animal pharmacology toxicology data is not very useful.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The sBLA consisted of an electronic submission of the BCIRG006 trial, a clinical study report, CRFs and datasets.

### 4.2 Tables of Clinical Studies

BCIRG006 was the only clinical trial submitted to support the Herceptin approval for the two indications. Two supplements were submitted with a single study with two indications under consideration:

“As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer”

“As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer”

### 4.3 Review Strategy

The applicant submitted data to support two new proposed indications. The data were reviewed by two medical reviewers. The data supporting the proposed indication, “As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer” were reviewed by Medical Reviewer, Patricia Cortazar. The data supporting the proposed indication, “As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer” were reviewed by Medical Reviewer, Katherine Fedenko.

### 4.4 Data Quality and Integrity

Because this is the fourth study in the of adjuvant treatment of breast cancer and the BCIRG006 data were consistent with the study results of the previous trials, FDA did not request source data verification and auditing of study sites through FDA’s Division of Scientific Integrity.

#### 4.5 Compliance with Good Clinical Practices

The trials were conducted in compliance with good clinical practices:  
Informed consents were obtained as a routine  
The trials conformed to acceptable ethical standards

#### 4.6 Financial Disclosures

Financial disclosure information submitted by the applicant was reviewed.  
The submitted information seems to be adequate and the reviewer believes it to be in compliance with financial disclosure requirements.

### 5 CLINICAL PHARMACOLOGY

#### 5.1 Pharmacokinetics

The pharmacokinetics of Herceptin were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively. Herceptin's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377 µg/mL.

In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range = 1 to 32 days) was observed. Between Weeks 16 and 32, Herceptin serum concentrations reached a steady state with mean trough and peak concentrations of approximately 79 µg/mL and 123 µg/mL, respectively.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the sera of some patients with HER2 overexpressing tumors.

Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients with metastatic breast cancer had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations. However, with weekly dosing, most patients with elevated shed antigen levels achieved target serum Herceptin concentrations of 20 µg/mL (based on pre-clinical tumor efficacy models) by Week 8.

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

Mean serum trough concentrations of Herceptin, when administered in combination with paclitaxel, were consistently elevated approximately 1.5-fold as compared with serum concentrations of Herceptin used in combination with anthracycline plus cyclophosphamide. In primate studies, administration of Herceptin with paclitaxel resulted in a reduction in Herceptin clearance. Serum levels of Herceptin in combination with cisplatin, doxorubicin, or epirubicin

plus cyclophosphamide did not suggest any interactions; no formal drug interaction studies were performed.

## 5.2 Pharmacodynamics

There were no studies provided in the application which justified the dose and schedule based on pharmacodynamic findings. The mechanism(s) of action of trastuzumab are not well-understood. In previous submissions, a rough correlation between pharmacodynamic effects, specifically the blockade of HER-2 receptor signaling and anti-tumor activity has been identified in preclinical but not in clinical models. No additional data were provided in the application that investigated the pharmacodynamic effects of trastuzumab at the new dose and schedule.

## 5.3 Exposure-Response Relationships

The application did not contain data which addressed exposure-response relationships. The primary efficacy study was conducted at a fixed dose and dose-ranging studies were not provided which could have provided insight into the relationship between dose and efficacy or safety outcomes.

# 6 INTEGRATED REVIEW OF EFFICACY

## 6.1 Indication

BCIRG006 was submitted to support two supplements and two indications:

**“As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer”**

“As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer”  
This medical review will address only the first indication.

### Detailed Review of Study BCIRG 006

“A multicenter phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) and with docetaxel, platinum salt and trastuzumab (TCH) in the treatment of node positive and high risk node negative adjuvant patients with operable breast cancer containing the HER2neu alteration. BCIRG 006”

### *Principal Investigators*

The study was sponsored by Aventis. The following were the study co-chairs:  
Jean-Marc Nabholz, MD  
UCLA School of Medicine  
USA

Dennis Slamon, MD, PhD  
UCLA School of Medicine  
USA

John Crown, MD  
St. Vincent's University Hospital  
Ireland

#### 6.1.1.1 Protocol Milestones:

**Table 1 BCIRG006 Protocol Milestones**

<b>Milestone</b>	<b>Dates</b>
Open for accrual	March 2001
Protocol Original Version	December, 2000
First Patient recruited	March 2001
Last Patient recruited	September 2003
1 <sup>st</sup> Planned interim analysis	June, 2005
2 <sup>nd</sup> Planned interim analysis	November, 2006
Study close to accrual	
Data Cutoff	November, 2006
Study Completion	Ongoing
sBLA submission	June, 2007
clinical study report and datasets submission	June, 2007

#### 6.1.1.2 Objectives:

**Primary:**

To compare disease-free survival after treatment with doxorubicin and cyclophosphamide followed by docetaxel (Taxotere®) (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (Herceptin™) (AC→TH) and with docetaxel in combination with platinum salt and Herceptin (TCH) in the treatment of node positive and high risk node negative adjuvant patients with operable breast cancer containing the HER2neu alteration.

**Secondary:**

The secondary objectives of the study are:

- To compare overall survival between the 3 above mentioned arms.
- To compare cardiac toxicity between the 3 above mentioned arms.
- To compare toxicity and quality of life between the 3 above mentioned arms.
- To evaluate pathologic and molecular markers for predicting efficacy in these patient groups.
- To compare peripheral levels of shed HER2 ECD with FISH determination in predicting outcome to treatment with Herceptin.
- In addition, an independent socioeconomic study was to be conducted in parallel with the clinical study.

## **Study Design**

The protocol design is a Phase III, multicenter, multinational, randomized, non-blinded study comparing the efficacy and safety of doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) and with docetaxel, platinum salt and trastuzumab (TCH) in the treatment of node positive and high risk node negative adjuvant patients with operable breast cancer containing the her2neu alteration. A total of 3,150 patients, 1,050 patients per treatment arm, were to be randomized to either (AC→T), (AC→TH) or (TCH). The randomization was to be centralized and stratified for node status: node negative, node positive 1-3 nodes and node positive  $\geq 4$  nodes, and for hormonal receptor status (estrogen and/or progesterone receptor positive versus negative).

All included patients in each arm will receive a fixed number of cycles of treatment.

The study primary endpoint was disease free survival. A secondary endpoint of the trial was to compare the cardiac toxicity between the 3 arms, in order to determine the safety of Herceptin with these chemotherapy regimens.

### **6.1.1.3 Protocol Amendments:**

Subsequent to study initiation, there were four protocol amendments, as summarized below.

*First amendment* was dated 8 May 2001, after 4 patients had been randomized. This amendment contained the following changes:

- Echocardiography was allowed at study entry (in addition to MUGA scans) for confirmation of a patient's LVEF status.
- Echocardiography guidelines and availability of videotapes of echocardiograms were added upon request.

- An LVEF evaluation was added at 36 months to allow for long-term assessment of cardiac function.
- Clarifications regarding the dosing of carboplatin and Herceptin, were added according to a patient's weight modification.

*Second Amendment* was dated 30 July 2001, after 34 patients had been randomized. This amendment contained the following changes:

- The dosing schedule for Herceptin monotherapy after completion of chemotherapy was modified from once a week to every 3 weeks based on the safety results and pharmacokinetics of Herceptin in two studies in patients with HER2-positive (by IHC or FISH) MBC.
- Guidelines for Herceptin initiation were modified for the AC→TH arm.
- The Herceptin post-infusion observation periods were revised.
- The optional HER2 extracellular domain (ECD) and cardiac biochemical marker sub studies were extended.

*Third amendment* was dated 10 April 2002, after 468 patients had been randomized. This amendment contained the following changes:

- The TCH regimen was modified so that the platinum salt was limited to carboplatin (i.e., cisplatin was no longer allowed), based on updated results from the BCIRG 101 and 102 studies.
- The instructions describing the administration of Herceptin and the dose calculation for carboplatin was clarified.
- Measurement of the follicle-stimulating hormone to luteinizing hormone ratio to assess menopausal status in patients < 55 years old with a history of hysterectomy without bilateral ovariectomy was no longer required.

*Fourth amendment* was dated 17 March 2005, after 3222 patients had been randomized. This amendment contained the following changes:

- Statistical considerations were revised based on the results of BCIRG 001 study:  
The assumed DFS rate at 5 years in the AC→T arm was changed from 55% to 70%.  
The IDMC requested interim efficacy analyses when 300, 450, and 650 DFS events had been observed and a main analysis when 900 DFS events had been observed (the initial protocol called for one interim analysis at 654 events and a final analysis at 1308 events).
- Following a request from the IDMC, one additional cardiac safety analysis was to be conducted when all patients had been observed for at least 9 months.
- The indication for adjuvant hormonal therapy was modified to allow the use of aromatase inhibitors for postmenopausal patients who were ER- or PR-positive, as well as for patients for whom tamoxifen was contraindicated. In addition, the use of letrozole was allowed for patients having completed 5 years of tamoxifen therapy.
- Based on American Society of Clinical Oncology 2002 follow-up guidelines, hematologic and blood chemistry evaluations and chest X-rays were no longer required during the follow-up period.

#### 6.1.1.4 Eligibility Criteria

##### Inclusion Criteria:

The protocol states:

1. Histologically proven breast cancer with an interval between definitive surgery that includes axillary lymph node involvement assessment and registration of less than or equal to 60 days. A central pathology review may be performed post randomization for confirmation of diagnosis and molecular studies. The same block used for HER2neu determination prior to randomization may be used for the central pathology review.
2. Definitive surgical treatment must be either mastectomy with axillary lymph node involvement assessment, or breast conserving surgery with axillary lymph node involvement assessment for operable breast cancer (T1-3, Clinical N0-1, M0). Margins of resected specimen from definitive surgery must be histologically free of invasive adenocarcinoma and/or ductal carcinoma in situ (DCIS). The finding of lobular carcinoma in-situ will not be scored as a positive margin.
3. Patients must be either lymph node positive or high risk node negative. Lymph node positive patients will be defined as patients having invasive adenocarcinoma with at least one axillary lymph node (pN1) showing evidence of tumor among a minimum of six resected lymph nodes. High risk lymph node negative patients will be defined as patients having invasive adenocarcinoma with either 0 (pNo) among a minimum of 6 resected lymph nodes or negative sentinel node biopsy (pNo) AND at least one of the following factors: tumor size > 2 cm, ER and/or PR status is negative, histologic and/or nuclear grade 2-3, or age < 35 years.
4. Tumor must show the presence of the HER2neu gene amplification by Fluorescence In-Situ Hybridization (FISH analysis) in a designated central laboratory.
5. Estrogen and/or progesterone receptor analysis performed on the primary tumor prior to randomization. Results must be known at the time of randomization.
6. Age  $\geq$  18 years and age  $\leq$  70 years. The upper age limit is not meant to be exclusionary but rather is based on the lack of safety data for the TCH regimen in women >70 years of age.
7. Karnofsky Performance status index  $\geq$  80%.
8. Normal cardiac function must be confirmed by LVEF (MUGA scan) and ECG within 3 months prior to registration. The result of the MUGA must be equal to or above the lower limit of normal for the institution.
9. Laboratory requirements: (within 14 days prior to registration)
  - a) Hematology:
    - i Neutrophils  $\geq$  2.0 10<sup>9</sup>/L
    - ii Platelets  $\geq$  100 10<sup>9</sup>/L
    - iii Hemoglobin  $\geq$  10 g/Dl
  - b) Hepatic function:
    - i Total bilirubin < 1 UNL
    - ii ii) ASAT (SGOT) and ALAT (SGPT)  $\leq$  2.5 UNL
    - iii iii) Alkaline phosphatase  $\leq$  5 UNL
    - iv iv) Patients with ASAT and/or ALAT > 1.5 x UNL associated with alkaline phosphatase > 2.5 x UNL are not eligible for the study.

- c) Renal function:
    - i Creatinine  $\leq 175 \mu\text{mol/L}$  (2 mg/dL)
    - ii If limit reached, the calculated creatinine clearance should be  $\geq 60 \text{ mL/min}$ .
  - 10. Complete staging work-up within 3 months prior to registration. All patients will have bilateral mammography, chest Xray (PA and lateral) and/or CT and/or MRI, abdominal ultrasound and/or CT scan and/or MRI, and bone scan. In cases of positive bone scans, bone X-ray evaluation is mandatory to rule out the possibility of metastatic bone scan positivity. Other tests may be performed as clinically indicated.
  - 11. . Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential.
  - 12. . An audiology assessment with normal results will be performed within 3 months of registration. This is only for those centers who have selected cisplatin as their platinum salt of choice for the BCIRG 006 study.
- \* A sample of serum/blood is requested prior to study start, and is to be sent to the central laboratory for detection of shed HER2 ECD.

Exclusion Criteria:

- 1. Prior systemic anticancer therapy for breast cancer (immunotherapy, hormonotherapy, chemotherapy).
- 2. . Prior anthracycline therapy, taxoids (paclitaxel, docetaxel) or platinum salts for any malignancy.
- 3. . Prior radiation therapy for breast cancer.
- 4. Bilateral invasive breast cancer.
- 5. Pregnant, or lactating patients. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures during study treatment (chemotherapy, Herceptin and tamoxifen therapy) and must have negative urine or serum pregnancy test within 7 days prior to registration.
- 6. Any T4 or N2 or known N3 or M1 breast cancer.
- 7. Pre-existing motor or sensory neurotoxicity of a severity  $\geq$  grade 2 by NCI criteria.
- 8. Cardiac disease that would preclude the use of doxorubicin, docetaxel and Herceptin.
  - a) any documented myocardial infarction
  - b) angina pectoris that requires the use of antianginal medication
  - c) any history of documented congestive heart failure
  - d) Grade 3 or Grade 4 cardiac arrhythmia (NCI CTC, version 2.0)
  - e) clinically significant valvular heart disease
  - f) f) patients with cardiomegaly on chest x-ray or ventricular hypertrophy on ECG, unless they demonstrate by MUGA scan within the past 3 months that the LVEF is  $\geq$  the lower limit of normal for the radiology facility;
  - g) g) patients with poorly controlled hypertension i.e. diastolic greater than 100 mm/Hg. (Patients who are well controlled on medication are eligible for entry
  - h) h) patients who currently receive medications (digitalis, beta-blockers, calcium channel-blockers, etc) that alter cardiac conduction, if these medications are administered for cardiac arrhythmia, angina or congestive heart failure. If these medications are administered for other reasons (ie hypertension), the patient will be eligible.

9. Other serious illness or medical condition:
  - a) a) history of significant neurologic or psychiatric disorders including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent
  - b) b) active uncontrolled infection
  - c) c) active peptic ulcer, unstable diabetes mellitus
  - d) d) impaired hearing (only for those patients treated at centers who have selected cisplatin as their platinum salt of choice)
10. Past or current history of neoplasm other than breast carcinoma, except for:
  - a) curatively treated non-melanoma skin cancer
  - b) in situ carcinoma of the cervix
  - c) other cancer curatively treated and with no evidence of disease for at least 10 years
  - d) ipsilateral ductal carcinoma in-situ (DCIS) of the breast
  - e) lobular carcinoma in-situ (LCIS) of the breast
11. Current therapy with any hormonal agent such as raloxifene, tamoxifen, or other selective estrogen receptor modulators (SERMs), either for osteoporosis or prevention. Patients must have discontinued these agents prior to randomization.
12. Chronic treatment with corticosteroids unless initiated > 6 months prior to study entry and at low dose ( $\leq 20$  mg methylprednisolone or equivalent).
13. Concurrent treatment with ovarian hormonal replacement therapy. Prior treatment must be stopped prior to randomization.
14. Definite contraindications for the use of corticosteroids.
15. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry.
16. Concurrent treatment with any other anti-cancer therapy.
17. Male patients.

## Study Therapy

### Dosage schedule

Patients were to be post surgically assigned to receive adjuvant treatment with either:

- AC→T: Doxorubicin  $60 \text{ mg/m}^2$  as an IV bolus in combination with cyclophosphamide  $600 \text{ mg/m}^2$  IV for four cycles. Three weeks after the last course of AC, docetaxel will be given  $100 \text{ mg/m}^2$  as 1 hour IV infusion on day 1 every 3 weeks for 4 cycles.
- AC→TH: Doxorubicin  $60 \text{ mg/m}^2$  IV in combination with cyclophosphamide  $600 \text{ mg/m}^2$  IV on an every 3 week basis for 4 cycles. Three weeks after the last cycle of AC, Herceptin  $4 \text{ mg/kg}$  initial dose by IV infusion over 90 minutes on Day 1 of Cycle 5 will be administered, followed by Herceptin  $2 \text{ mg/kg}$  by IV infusion over 30 minutes weekly starting Day 8; and docetaxel  $100 \text{ mg/m}^2$  administered by IV infusion over 1 hour on Day 2 of Cycle 5, then on day 1 on an every 3 week basis for all subsequent cycles (total 4 cycles of docetaxel). Herceptin to continue weekly for 1 year from date of first administration.

- TCH: Herceptin 4 mg/kg initial dose by IV infusion over 90 minutes on Day 1 of Cycle 1 only, followed by Herceptin 2 mg/kg by IV infusion over 30 minutes weekly starting on Day 8; and docetaxel 75 mg/m<sup>2</sup> administered on Day 2 of Cycle 1, then on day 1 of all subsequent cycles by IV infusion over 1 hour followed by carboplatin at target AUC=6 mg/mL administered by IV infusion over 30-60 minutes or minutes or cisplatin at 75 mg/m<sup>2</sup> by IV infusion over at least one hour (duration of cisplatin infusion as per center's guidelines) repeated every 3 weeks. A total of six cycles of docetaxel and platinum salt will be administered on an every 3 week basis. Herceptin will continue weekly for 1 year from date of first administration.

**Selection of Platinum Salt for the TCH Arm:**

Selection of either carboplatin or cisplatin for use in the TCH arm was at the investigator's discretion. However, a center could select only one platinum salt for all patients randomized to the BCIRG 006 study at their institution, and BCIRG was to be informed of the choice at the time of study initiation. In the case where a patient on cisplatin experiences serious toxicity (s), the investigator may change to carboplatin for remaining cycles.

- Tamoxifen Indication - Each Arm: Tamoxifen 20 mg p.o. daily for 5 years, starting 3 to 4 weeks after the last course of chemotherapy for patients with positive estrogen and/or progesterone receptor status unless there is a contraindication for the use of tamoxifen therapy.
- Radiation Indication - Each Arm: Patients treated with lumpectomy were to undergo postoperative radiation therapy after completion of chemotherapy and resolution of any side effect. Postmastectomy radiation therapy, and ipsilateral nodal radiation therapy, could be used at the discretion of the treating radiation oncologist. This was to be done in a consistent manner according to the guidelines at each institution. Radiation guidelines were to be requested from each institution prior to study start at the institution.
- Each Arm: No more than 8 days should elapse between the date of randomization and the start date of the first cycle of adjuvant chemotherapy.

**Prophylactic premedication:**

- Dexamethasone was to be given as prophylaxis for docetaxel-related hypersensitivity reactions and fluid retention.
- Primary prophylactic use of antibiotics was not allowed in either arm. Prophylactic use of antibiotics was allowed in subsequent chemotherapy cycles for those patients who experienced a serious or life-threatening infection only.
- Primary prophylactic use of G-CSF was not allowed in either arm. Prophylactic G-CSF was to be used in subsequent cycles for those patients who experienced an episode of febrile neutropenia or infection during chemotherapy.
- Antiemetic prophylaxis was mandatory for all patients.
- Hydration TCH – Cisplatin: a minimum of 1 liter intravenous fluid pre-cisplatin and 1 litre intravenous fluid post-cisplatin was required.

**Prophylactic premedication regimen for Docetaxel-related hypersensitivity reactions and fluid**

retention was to be administered for all patients treated with docetaxel. The following premedication regimen included Dexamethasone 8 mg p.o. for total of 6 doses.

1. night before chemotherapy
2. immediately upon waking the morning of chemotherapy
3. one hour before infusion of docetaxel (may be given oral or intravenous)
4. night of chemotherapy
5. morning the day after chemotherapy
6. evening the day after chemotherapy

Dexamethasone 8 mg equivalent could be used

Dexamethasone 8 mg = Methylprednisolone 40 mg = Prednisone 50 mg = Prednisolone 50 mg

Treatment Duration:

AC → T arm: 4 cycles of AC every 3 weeks followed by 4 cycles of single agent docetaxel every 3 weeks was to be administered.

AC → TH arm: 4 cycles of AC every 3 weeks followed by 4 cycles of single agent docetaxel every 3 weeks with weekly Herceptin for 1 year from the time of 1st dose of Herceptin.

TCH arm: 6 cycles of TC every 3 weeks administered with weekly Herceptin for 1 year from the time of 1st dose of Herceptin.

Formulation:

Multidose vial nominally containing 440 mg Herceptin as a lyophilized, sterile powder and one vial of 20 mL Bacteriostatic Water for Injection, USP, 1.1% benzyl alcohol.

**Dose Modifications**

**Cardiac Toxicity**

The table below shows the protocol guidelines for Initiation of Herceptin in AC → TH at the time of MUGA #2.

**Table 2 Parameters for LVEF changes at MUGA # 2**

Absolute change in LVEF between baseline and 3 weeks after last AC cycle (MUGA 2)	Decision regarding initiation of Herceptin treatment
Increase or no change	Initiate Herceptin
Decrease of $\leq 15$ percentage points but at or above the radiology facility's lower limit of normal	Initiate Herceptin
Decrease of $\leq 15$ percentage points and below the radiology facility's lower limit of normal	Administration of Herceptin is prohibited
Decrease of 16 or more percentage points (regardless of the radiology's facility's lower limit of normal)	Administration of Herceptin is prohibited

The following are the protocol guidelines for performing MUGA scan and management of Herceptin in patients who have an asymptomatic decrease in LVEF from baseline (for AC→TH and TCH).

**Asymptomatic Decrease LVEF Percentage Points From Baseline**

RELATIONSHIP OF LVEF TO THE LOWER LIMIT OF NORMAL (LLN)	ABSOLUTE DECREASE OF < 10 PERCENTAGE POINTS	ABSOLUTE DECREASE OF 10 TO 15 PERCENTAGE POINTS	ABSOLUTE DECREASE OF ≥ 16 PERCENTAGE POINTS
Within radiology facility's normal limits	Continue Herceptin	Continue Herceptin	Hold Herceptin and repeat MUGA after 4 weeks
1 to 5 percentage points below the LLN	Continue Herceptin	Hold Herceptin and repeat MUGA after 4 weeks	Hold Herceptin and repeat MUGA after 4 weeks
≥ 6 percentage points below the LLN	Hold Herceptin and repeat MUGA after 4 weeks	Hold Herceptin and repeat MUGA after 4 weeks	Hold Herceptin and repeat MUGA after 4 weeks

Herceptin was to be permanently discontinued following two consecutive "hold" categories. Patients who do develop a symptomatic cardiac toxicity while on active treatment (receiving chemotherapy and/or Herceptin) were to have their treatment discontinued.

*Management of Treatment Arms in case of Cardiac Arrhythmia*

Table 3 Dose modifications for arrhythmias

Treatment Arm	Grade 1	Grade 2	Grade 3 / Grade 4
AC→ T During AC  During Docetaxel	Not necessary to permanently stop doxorubicin if acute dysrhythmias occurring during and shortly after  Stop or slow docetaxel infusion. Subsequent cycles to be done under continuous cardiac monitoring	Hold AC and conduct cardiac evaluation. Based on results, continue AC at Investigator discretion. Docetaxel at discretion of  Hold docetaxel and conduct cardiac evaluation. Based on results, continuation of docetaxel at investigator's discretion.	Discontinue AC. Docetaxel at discretion of investigator if recovery.  Discontinue Docetaxel .
AC→ TH During AC  During Docetaxel and Herceptin	Not necessary to permanently stop doxorubicin if acute dysrhythmias occurring during and shortly after doxorubicin infusion. Monitor often Docetaxel +/-Herceptin may be given.  If during either docetaxel or Herceptin, slow or stop infusion. Subsequent cycles to be done under continuous cardiac monitoring.	Hold AC and conduct cardiac evaluation. Based on results, continue of AC at investigator discretion. Docetaxel +/- Herceptin at discretion of investigator.  Hold Docetaxel and Herceptin. Conduct cardiac evaluation. Continuation of Docetaxel +/- Herceptin at investigator's discretion.	Discontinue AC. Herceptin not permitted. Docetaxel at discretion of investigator if recovery.  Discontinue docetaxel and Herceptin
TCH	If during either docetaxel or Herceptin, slow or stop infusion. Subsequent cycles to be done under continuous cardiac monitoring.	Hold TCH and conduct cardiac evaluation. Based on results, continuation of docetaxel/platinum +/- Herceptin at discretion of investigator.	Discontinue TCH

*Symptomatic Cardiac Left Ventricular Function*

Clinical signs and symptoms suggesting congestive heart failure (dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea,

peripheral edema, etc) was to be confirmed by a decrease in MUGA and a chest X-ray. All CHF events and associated reports were to be reviewed by an independent team of cardiologists. LVEF assessment were to be repeated 4 to 7 days afterwards to confirm a diagnosis of congestive heart failure before considering the patient to come off treatment as per the guidelines in the table below.

**Table 4 Dose modifications for symptomatic CHF.**

Treatment Arm	Grade 3 or 4
AC→ T During AC  During Docetaxel	Discontinue AC when symptoms of heart failure present and diagnosis of CHF confirmed. Docetaxel at discretion of investigator if heart failure adequately controlled.  Docetaxel to continue at discretion of investigator.
AC→ TH During AC  During Docetaxel and Herceptin	Discontinue AC when symptoms of heart failure present and diagnosis of CHF confirmed.  Herceptin not permitted. Docetaxel at discretion of investigator if heart failure adequately controlled.
TCH	Discontinue Herceptin. Docetaxel / platinum at discretion of investigator.

**Cardiac Ischemia / Infarction**

Management of treatment arms in case of cardiac ischemia is shown in the table below.

**Table 5 Dose modifications for cardiac ischemia or infarction.**

Treatment Arm	Grade 1 or 2	Grade 3 or 4
AC→ T During AC	Continue AC with frequent monitoring. Docetaxel may be given with frequent monitoring.	Discontinue AC. Docetaxel at discretion of investigator.
During Docetaxel	Continue docetaxel with frequent monitoring.	Docetaxel to continue at investigator discretion.
AC→ TH During AC	Continue AC with frequent monitoring. Docetaxel +/- Herceptin may be given with frequent monitoring.	Discontinue AC. Herceptin not permitted. Docetaxel at discretion of investigator.
During Docetaxel and Herceptin	If during either Docetaxel or Herceptin, slow or stop infusion. Docetaxel +/- Herceptin to continue with frequent monitoring.	Discontinue Herceptin. Docetaxel to continue at investigator discretion.
TCH	If during either docetaxel or Herceptin, slow or stop infusion. TCH to continue with frequent monitoring.	Discontinue Herceptin. Docetaxel / platinum to continue at investigator discretion.

**Hematological Toxicities**

*Febrile neutropenia* was defined as fever of  $\geq 38.5^{\circ}\text{C}$  or  $101.3^{\circ}\text{F}$  in the presence of neutropenia (where neutropenia is defined as  $\text{ANC} < 1.0 \times 10^9/\text{L}$ ). In case of febrile neutropenia, blood counts must be done every 2 days until recovery of  $\text{ANC} \geq 1.0$  or temperature  $< 38.5^{\circ}\text{C}$ . For all subsequent chemotherapy cycles, prophylactic G-CSF was to be added. Prophylactic antibiotics were not allowed as prophylaxis for febrile neutropenia. In the case of a second febrile neutropenia event, patient were to continue with the prophylactic G-CSF for all subsequent cycles. In addition, all chemotherapeutic drug doses were to be reduced by 20% for all remaining cycles except Herceptin dose. Chemotherapy dose reductions by 20% are as follows:

- Docetaxel Single Agent: from  $100 \text{ mg}/\text{m}^2$  to  $80 \text{ mg}/\text{m}^2$
- Docetaxel in Combination: from  $75 \text{ mg}/\text{m}^2$  to  $60 \text{ mg}/\text{m}^2$
- Doxorubicin: from  $60 \text{ mg}/\text{m}^2$  to  $48 \text{ mg}/\text{m}^2$
- Cyclophosphamide: from  $600 \text{ mg}/\text{m}^2$  to  $480 \text{ mg}/\text{m}^2$
- Carboplatin: from AUC  $6 \text{ mg}/\text{mL}$  to AUC of  $5 \text{ mg}/\text{mL}$
- Cisplatin: from  $75 \text{ mg}/\text{m}^2$  to  $60 \text{ mg}/\text{m}^2$

In the case of a 3rd event, there will be no further dose reduction. Patient were to go off study (into regular follow-up).

*Infection with (or without) neutropenia:*

For severe (Grade 3) or life-threatening (Grade 4) infection during chemotherapy, with or without neutropenia, prophylactic G-CSF and prophylactic antibiotics were to be added to all remaining cycles. Ciprofloxacin was recommended at 500 mg orally twice daily for 10 days starting day 5 of each cycle for remaining chemotherapy cycles.

*Delayed ANC Recovery on Day 21*

Blood counts on day 21

Neutrophils  $\geq 1.5 \times 10^9/L$ : treat on time

Neutrophils  $< 1.5 \times 10^9/L$ : CBC should be repeated every other day till day 35. Proceed with full dose chemotherapy as soon as ANC  $\geq 1.5$ . Add G-CSF remaining cycles if recovery occurred after day 28.

If there is no recovery on day 35, (ANC  $< 1.5 \times 10^9/L$ ), the patient will go off chemotherapy. In arms with Herceptin, Herceptin may continue at the discretion of the investigator

*Thrombocytopenia:*

The following dose adjustments were recommended based on the hematologic counts on the day of or day prior to chemotherapy treatment.

$> 100,000$  (cells/ $\mu$ L): No change

50,000 to 99,000 (cells/ $\mu$ L): If during AC, reduce doxorubicin from 60 to 50 mg/m<sup>2</sup>

If during docetaxel, reduce docetaxel from 100 to 75 mg/m<sup>2</sup>

If during TCH with carboplatin, decrease carboplatin to AUC of 5 mg/mL and docetaxel from 75 to 60 mg/m<sup>2</sup>.

If during TCH, with cisplatin, decrease docetaxel from 75 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup>

$< 50,000$  (cells/ $\mu$ L): Hold for 2 weeks. If after 2 weeks, and no recovery above 50,000, all chemotherapy is permanently discontinued.

If after 2 weeks, recovery  $> 50,000$ , treat with dose reduction above for all subsequent doses.

Herceptin may continue in all cases above.

*Anemia:*

In case of  $\geq$  grade 2 decrease in hemoglobin, treatment with blood transfusion or erythropoietin were to be given. If the next cycle of chemotherapy was due, chemotherapy to be administered if hemoglobin is  $< 10$  g/dL. In case of  $\geq$  grade 3 or 4 decrease in hemoglobin, doses were to be reduced as follows:

With docetaxel as single agent in AC  $\rightarrow$  T and AC  $\rightarrow$  TH, docetaxel dose to be decreased from 100 mg/m<sup>2</sup> to 80 mg/m<sup>2</sup>.

If during TCH with carboplatin, docetaxel to be reduced from 75 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup> and carboplatin reduced from an AUC of 6 mg/mL to an AUC of 5 mg/mL.

If during TCH with cisplatin, docetaxel to be reduced from 75 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup> and cisplatin reduced from 75 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup>.

**Gastrointestinal Toxicity**

*Diarrhea:*

No primary prophylactic treatment for diarrhea was recommended. However, in case of grade 2 to 3 diarrhea, the patient was to be treated with loperamide. For subsequent cycles, give loperamide the day of the first episode of diarrhea, including grade 1. If despite this treatment,

patient still experienced grade 3 or more diarrhea, the following dose reductions were recommended.

In case of diarrhea  $\geq$  grade 3 in the AC segment of AC $\rightarrow$ T or AC  $\rightarrow$ TH, reduce the dose of doxorubicin from 60 to 50 mg/m<sup>2</sup> in the subsequent cycles. If despite dose reduction, diarrhea still occurs at grade  $\geq$ 3, the patient was to go off chemotherapy as per investigator discretion.

Docetaxel (T) Segment in AC $\rightarrow$ T, AC $\rightarrow$ TH, TCH

In case of diarrhea  $\geq$  grade 3 during treatment with docetaxel , reduce the dose of docetaxel from 75 to 60 mg/m<sup>2</sup> (TCH) or from 100 to 75 mg/m<sup>2</sup>

If despite dose reduction diarrhea still occurs at grade  $\geq$ 3, investigator to consider taking patient off study.

#### *Stomatitis:*

In case of grade 3 stomatitis (and/or esophagitis):

AC $\rightarrow$ T or AC $\rightarrow$ TH During AC Segment

Doxorubicin was to be reduced from 60 to 50 mg/m<sup>2</sup>. If despite dose reduction, stomatitis still occurred at grade  $\geq$ 3, doxorubicin was to be reduced from 50 to 40 mg/m<sup>2</sup>. No further dose reduction was planned.

During Docetaxel (+/- Herceptin) Segment

Docetaxel was to be reduced from 100 to 75 mg/m<sup>2</sup>. If despite dose reduction, stomatitis still occurred at grade  $\geq$ 3, docetaxel was to be further reduced from 75 to 60 mg/m<sup>2</sup>. No further dose reduction was planned.

TCH Docetaxel was to be reduced from 75 to 60 mg/m<sup>2</sup>. If despite dose reduction, stomatitis still occurred at grade  $\geq$ 3, docetaxel was to be further reduced from 75 to 60 mg/m<sup>2</sup>. No further dose reduction was planned.

#### **Hepatic Toxicity**

*Bilirubin and impaired liver function tests:*

Docetaxel and doxorubicin doses were to be modified for hepatic toxicity. If docetaxel was delayed due to hepatic toxicity, other drugs being used in combination at that time were also to be delayed and administered when docetaxel was resumed. The same applied for delays with doxorubicin i.e. other drugs being used in combination with doxorubicin were also to be delayed until doxorubicin was resumed.

In the event that bilirubin levels are abnormal during the study, the next cycle was to be delayed by a maximum of two weeks. If no recovery, the patient was to be taken off chemotherapy.

In the event that ASAT and/or ALAT and/or alkaline phosphatase levels were abnormal in the absence of relapse, the following dose modifications were to be applied:

ASAT / ALAT/ Alkaline Phosphatase Values

$\leq 1.5$  x UNL /  $\leq 5$  x UNL: no dose modification

$> 1.5$  x UNL to  $\leq 2.5$  x UNL /  $\leq 2.5$  x UNL: no dose modification

$> 2.5$  x UNL to  $\leq 5$  x UNL /  $\leq 2.5$  x UNL: TCH: Reduce dose of docetaxel from 75 to 60 mg/m<sup>2</sup>

AC $\rightarrow$ T: AC $\rightarrow$ TH Reduce dose of doxorubicin

from 60 to 50 mg/m<sup>2</sup>. Reduce dose of docetaxel from 100 to 75 mg/m<sup>2</sup>

$> 1.5$  x UNL to  $\leq 5$  x UNL /  $> 2.5$  x UNL

to  $\leq 5$  x UNL:TCH: Reduce dose of docetaxel from 75 to 60 mg/m<sup>2</sup>  
AC→T: AC→TH Reduce dose of doxorubicin  
from 60 to 50 mg/m<sup>2</sup>. Reduce dose of docetaxel from 100 to 75 mg/m<sup>2</sup>  
> 5 x UNL / > 5 x UNL: All Arms: Dose delay by a maximum of 2 weeks. If  
no recovery to the above figures, patient was to go off chemotherapy.  
In case of recovery of liver function tests on the following cycle, the dose should be re-escalated  
to the previous dose-level.

**Peripheral neuropathy:**

In case of symptoms or signs experienced by the patient, dose modifications of docetaxel should  
be performed as follows:

Grade 0,1: Each Arm: no change

Grade 2: TCH (carboplatin): Delay carboplatin and docetaxel treatment by maximum of two  
weeks. As soon as patient recovers, treatment was to be continued with the following dose  
recommendations:

If patient recovered to Grade 1 toxicity, dose of docetaxel was to be decreased from 75 to 60  
mg/m<sup>2</sup>.

If grade  $\geq 2$  persisted for > 2 weeks, patient will either go off study or continue with carboplatin  
and Herceptin only.

In case of 2nd episode, the docetaxel dose was to be reduced from 60 to 50 mg/m<sup>2</sup>.

TCH (cisplatin): Delay cisplatin and docetaxel treatment by maximum of two weeks. As soon as  
patient recovers, treatment was to be continued with the following dose recommendations:

If patient recovers to Grade 1 toxicity, dose of docetaxel was to be decreased from 75 to 60  
mg/m<sup>2</sup> and cisplatin from 75 to 60 mg/m<sup>2</sup>.

If patient not recovered to Grade 1 in two weeks, patient was to either go off study or be  
switched to carboplatin.

If grade  $\geq 2$  persists for > 2 weeks, patient will either go off study or be switched to carboplatin.

AC→T and AC→TH:

Delay docetaxel treatment by maximum of two weeks. As soon as patient recovers, treatment  
should continue with the following dose recommendations:

If patient recovers to Grade 1 toxicity, dose of docetaxel will be decreased from 75 to 60 mg/m<sup>2</sup>.

If patient not recovered to Grade 1 in two weeks, patient will go off study.

If grade  $\geq 2$  persists for > 2 weeks, patient will go off study. In case of 2nd episode, reduce dose  
from 75 to 60 mg/m<sup>2</sup>. No further dose reduction was planned.

Grade 3: patient was to go off chemotherapy.

The same guideline also applies for patients with grade 1 neuropathy at baseline.

**Cutaneous reactions:**

Grade 0, 1, 2 Each Arm: no change

Grade 3: maximum two weeks delay until  $\leq$  grade 1 then for subsequent cycles of TCH:

Dose reduction of docetaxel from 75 to 60 mg/m<sup>2</sup>; Second reduction allowed of docetaxel from  
60 to 50 mg/m<sup>2</sup>

AC→T and AC→TH: Dose reduction of docetaxel 100 to 75 mg/m<sup>2</sup>. Second reduction allowed  
of docetaxel from 75 to 60 mg/m<sup>2</sup>.

If no recovery to  $\leq$  grade 1 within two weeks delay, patient was to go off chemotherapy.

**Docetaxel anaphylactoid-type and hypersensitivity reactions:**

The protocol states that in the event that a hypersensitivity reaction occurs despite premedication, it is then very likely to occur within few minutes of start of the first or of the second infusion of docetaxel. Therefore, during the 1st and the 2nd infusions, the infusion was to be given drop by drop for the first 5 minutes, and a careful evaluation of general sense of well being and whenever possible blood pressure and heart rate monitoring was to be performed so that immediate intervention would occur in response to symptoms of an untoward reaction. Facilities and equipment for resuscitation were to be immediately available: antihistamine, corticosteroids, aminophylline, epinephrine.

If a reaction occurred, the specific treatment that could be medically indicated for a given symptom was epinephrine in case of anaphylactic shock and aminophylline in case of bronchospasm. In addition, it was recommended to take the measures listed below:

- Mild symptoms such as localized cutaneous reactions, pruritus, flushing or rash: Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside. Then, complete docetaxel infusion at the initial planned rate.
- Moderate symptoms such as any symptom not listed above (mild symptoms) or below (severe symptoms), such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure (BP)  $>$  80 mm Hg: Stop docetaxel infusion. Give i.v. dexamethasone 10 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent). Resume docetaxel infusion after recovery of symptoms. At subsequent cycles, give i.v. dexamethasone 10 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent) one hour before infusion, in addition to the premedication planned.
- Severe symptoms such as bronchospasm, generalized urticaria, hypotension with systolic BP  $\leq$  80 mm Hg and angioedema: Stop docetaxel infusion. Give i.v. dexamethasone 10 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent), add epinephrine as needed. Whenever possible resume docetaxel infusion within 3 hours after recovery or reinfuse the patient within 72 hours using i.v. dexamethasone 20 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent) one hour prior to resumption of infusion. At the subsequent cycles, dexamethasone (or equivalent) was to be given at 20 mg orally the evening before chemotherapy, the morning of chemotherapy and one hour before docetaxel infusion. Additionally diphenhydramine (or equivalent) was to be given at 50 mg i.v. 1 hour before docetaxel infusion. If a severe reaction recurs, patient will go off chemotherapy.
- Anaphylaxis (NCI grade 4 reaction): No further study drug therapy.

*Herceptin infusion-associated reactions:*

Chills and/or fever are commonly observed in patients during the first Herceptin infusion. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity and occur infrequently with subsequent Herceptin infusions. These symptoms can be treated with an analgesic/antipyretic such as meperidine/pethidine or acetaminophen/paracetamol, or an antihistamine. Some adverse reactions to Herceptin infusion such as dyspnea, hypotension,

wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress, can be serious and potentially fatal. If a grade 3 or 4 toxicity occurs during a Herceptin infusion, the infusion was to be stopped immediately. The patient was to be monitored for a minimum of 1 hour after the infusion was stopped. If an outpatient, the patient must be admitted to the hospital for monitoring if the toxicity does not resolve within 3 hours. Prior to readministration of Herceptin, patients could be prophylactically treated with pre-medications including antihistamines and/or corticosteroids.

*Docetaxel related fluid retention:*

No dose reduction was planned for fluid retention occurred during treatment with docetaxel. Fluid retention treatment was to start when signs and/or symptoms of fluid retention were observed, including weight gain from baseline  $\geq$  grade 1 not otherwise explained.

The following treatment was recommended:

Furosemide 20 mg p.o. o.d. If the symptoms could not be controlled adequately, i.e. worsening of the fluid retention or spread to another area, the dose of furosemide was to be increased to 40 mg. It was recommended, that patients with fluid retention of grade 3 severity should be withdrawn from chemotherapy. In case of difficulty to make a judgment whether an effusion would be disease related or study drug related, the treatment should be continued until progressive disease in other organs is documented.

*Renal Toxicity:*

Cisplatin and carboplatin doses were to be modified for renal toxicity. Dose modifications were based on test results at Day 1 of each cycle. No dose reduction for docetaxel, cyclophosphamide, doxorubicin or Herceptin were to be made for renal toxicity. However, drugs could be delayed if the creatinine was  $> 2$  mg/dL ( $> 175$   $\mu$ mol/L).

**Table 6 Cisplatin and carboplatin modifications for renal toxicity**

Creatinine Clearance mL/min	Carboplatin Dose to be Administered	Cisplatin Dose to be Administered
$\geq 50$ mL/min	AUC 6 mg/mL (regular dose as in protocol)	75 mg/m <sup>2</sup>
49 – 31 mL/min	AUC 5 mg/mL	60 mg/m <sup>2</sup>
$\leq 30$ mL/min	Delay	Delay

*Auditory Toxicity:*

Cisplatin is known to cause high-frequency hearing loss. If Grade 1 hearing loss occurs cisplatin was to be discontinued. Cisplatin was to be replaced with carboplatin.

*Treatment Delays*

Treatment with chemotherapy could be delayed no more than 2 weeks (up to Day 35) to allow recovery from acute toxicity.

Herceptin treatment could continue while chemotherapy was being withheld due to chemotherapy-related toxicity at investigator discretion except for asymptomatic decreases in left ventricular ejection fraction.

**Events which require discontinuing protocol therapy:**

- relapse during treatment
- unacceptable toxicities,
- withdrawn consent,

**Patient Evaluations**

**Pre-therapy evaluations:**

Women selected for entry into the study will also have the following required of them:

Concomitant medications, and their indication, used within one month prior to study entry.

- History, including: diagnosis of breast adenocarcinoma, prior antitumor therapy and outcome, menopausal status, receptor status at diagnosis, general medical history including cardiac history and allergy, concurrent illness and existing signs and symptoms.
- General physical examination including: height and weight, Karnofsky index for performance status/vital signs.
- CBC, differential, platelet count, alkaline phosphatase, SGOT or SGPT, total bilirubin, and serum creatinine tests within 180 days prior to randomization.
- Menopausal Status, for patients  $\leq 55$  years old and having had a hysterectomy without bilateral ovariectomy, FSH and LH.
- HER2 neu assessment, positive by FISH test (BCIRG central lab confirmation).
- Blood sample for detection of HER2 Shed ECD (to BCIRG central lab).
- ER PR status
- Pregnancy test
- Imaging, mandatory for all patients: bilateral mammography, where applicable chest-X-Ray (PA and lateral), CT or MRI, abdominal ultrasound and/or CT scan and/or MRI, bone scan and bone X-ray in case of hot spots in bone scan and other instrumental examinations as indicated.
- ECG and MUGA.
- Completion of required QOL questionnaires (QLQ - C30, BR23 & Euroqol questionnaires).
- Audiometry exam, only for those centers having selected cisplatin as the salt of choice.
- All eligible patients were to be registered with the Breast Cancer International Research Group Registration Officer in the Montreal, Quebec, Canada prior to start of treatment.

**Participants' follow-up:**

All patients during the study were to be evaluated according to the following schedule until they come off chemotherapy.

Clinical Review

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Medical history and laboratory studies:

- A medical history was to be taken at each visit to determine whether any illness, tamoxifen- or raloxifene-related toxicity, fracture, operation, hospital admission, or alteration in protocol regimen has occurred since the previous visit.
- CBC, platelet count, alkaline phosphatase, SGOT or SGPT, total bilirubin, and serum creatinine tests are required annually, as long as the participant is receiving protocol therapy.

Table 7 Protocol Evaluations

Examination	PRESTUDY SCREEN		DURING THERAPY Every 3 weeks	End of Chemo-therapy ****	Follow-up*****
	Completed no more than (time) prior to registration before study entry				
Patient informed consent		X			
History	14 days	X			
Physical examination					
Weight	14 days	X	X*	X	
Performance Status					
Signs and symptoms**	14 days	X	X	X	
Adverse events			X	X	
Concomitant medication***	14 days	X	X	X	
Hematology					
Hemoglobin, WBC, neutrophils, platelets	14 days	X	X†	X	
Biochemistry					
Liver function	14 days	X	X	X	
ASAT/ ALAT	(Liver function tests repeated within 3 days if abnormal)		(within 3 days prior to chemotherapy)		
alkaline phosphatase					
bilirubin					
Renal function	14 days	X	X		
creatinine					
creatinine clearance (if indicated)					
Menopausal Status					
For women ≤ 55 years of age and having had hysterectomy without bilateral ovariectomy	3 months (can be done up to 3 months after registration)	X			
FSH					
LH					
FISH TEST (positive)	before study entry	X			
Serum Sample	At study entry	X	And at recurrence		
ER Status / PR Status	before study entry	X			
Pregnancy test (urine or serum)	7 days	X			
ECG	3 months	X	As clinically indicated		
LVEF	3 months	X	See Section VI		
MUGA scan or echocardiography					
Mammography	3 months	X			
Work up to rule out metastatic disease					
chest-X-ray (PA and lateral) and/or chest CT scan and/or chest MRI	3 months	X			

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Abdominal ultrasound or CT or MRI bone scan and bone X-ray in case of hot spots in bone scan	3 months 3 months	X X			
<b>Audiometry Exam</b> (for patients on cisplatin only)	3 months	X	After cycle 3	X	
<b>Quality of life</b>	14 days	X	Section VIII	X	X
<b>Other investigations</b>	as clinically indicated				

\*Physical exam will be performed at day 1 or -1 of the cycle.

\*\* signs and symptoms will be recorded for baseline in the appropriate CRFs and for ALL other visits in the Clinical Adverse Experience CRF.

\*\*\*Concomitant medication will be recorded for baseline on the appropriate CRFs, and will include all medication used within one month prior to registration. For ALL other visits concomitant medication will be captured ONLY if related to adverse events.

\*\*\*\* The End of Chemotherapy evaluation will be performed at 21 to 28 days after the last dose of chemotherapy (including patients that did not complete all cycles)

\*\*\*\*\* see Table 5 for follow up schedule

*Follow-up After End of Chemotherapy (EOC):*

Because of the difference in duration of chemotherapy treatments between the three arms, the sponsor tried to balance the timing of the follow-up assessments in order to assess efficacy at equivalent intervals.

Follow-up Visit # 1 for

AC→ T was planned 3 months after EOC

AC→ TH was planned 3 months after EOC

TCH was planned 4 ½ months after EOC.

An extra follow-up visit (FUp1a ) was planned 6 weeks after EOC for the TCH arm. The timing of this extra Follow-Up occurs at the timing of the EOC for the AC→T and AC→TH arms.

Physical exam, quality of life, assessment of adverse effects, and MUGA 4 was to be performed at this visit. Timing of follow-up visits were based on EOC and were to be performed according to the following schedule (see Table 5). Clinical follow-up could be more frequent according to the standard of practice at the participating center and at the discretion of the investigator.

**Table 8 Follow-up visit flow chart**

	Physical Exam	Hematology Biochemistry	Mammography	Chest X Ray	QOL	Adverse* Experiences
<b>Year 1 and 2</b>						
3 months	X				X	X
6 months	X	X			X	X
9 months	X				X	X
12 months	X	X	X	X	X	X
15 months	X				X	X
18 months	X	X			X	X
21 months	X				X	X
24 months	X	X	X	X	X	X
<b>Year 3, 4 and 5**</b>						
30 months	X	X				X
36 months	X	X	X	X		X
42 months	X	X				X
48 months	X	X	X	X		X
54 months	X	X				X
60 months	X	X	X	X		X
<b>Year 6, 7, 8, 9, and 10***</b>						
72 months	X	X	X			X
84 months	X	X	X			X
96 months	X	X	X			X
108 months	X	X	X			X
120 months	X	X	X			X

\*\*follow up visits will occur every 6 months

\*\*\*follow up visits will occur every 12 months

**First 2 years: (all patients)**

- every 3 months physical examination and quality of life
- every 6 months hematology and biochemistry in addition to physical examination
- every 12 months mammography and chest X-ray in addition to physical examination, hematology and biochemistry

**1. For patients in the TCH arm:**

A follow-up visit #1 was planned 6 weeks after EOC. The timing of this extra Follow-Up occurred at the timing of the EOC for the AC→T and AC→TH arms. Physical exam, quality of life, assessment of adverse effects, and MUGA 4 were to be performed at this visit.

2. At Follow-Up #1 (corresponds to 9 months from randomization) all arms were to have LVEF assessment (MUGA 5).
3. At Follow-Up #4 (corresponds to 18 months from randomization) all arms were to have LVEF assessment (MUGA 6).
4. Follow-up information on cardiac status were to be collected in the case report form on all patients in the cardiac safety analysis, at baseline, every 6 months for 5 years, and then annually for years 6 to 10.
  - Patients who develop congestive heart failure at any time during the study (either during active treatment or in follow-up), were required to have a repeated LVEF

every 3 months for the first year and every year until the end of follow-up or otherwise as clinically indicated.

- Patients who develop grade 3 or 4 arrhythmias were required to have an ECG during the follow-up every 3 months for the first year, and every year until the end of follow-up or otherwise as clinically indicated.
- Patients who develop grade 3 or 4 ischemia/infarction, were required to have an LVEF and ECG repeated during the follow-up
- every 3 months for the first year, and every year until the end of follow-up or otherwise as clinically indicated.

MUGA scans were required at baseline only. Further assessment of LVEF during active treatment, at completion of chemotherapy or during the follow-up were left to the discretion of the investigator.

Years 3 to 5: (all patients)

- every 6 months physical examination, hematology, biochemistry
- every 12 months mammography and chest X-ray in addition to physical examination, hematology and biochemistry

Years 6 to 10: (all patients)

- every 12 months physical examination, hematology, biochemistry, mammography

Quality of Life assessment were required every 3 months for the first 2 years, then at relapse. An additional Quality of Life assessment was required at the Follow-Up 1a visit in the TCH arm.

Other diagnostic tests (i.e.: abdominal ultrasound and/or CT scan, bone scan) were to be performed only in presence of signs and/or symptoms suggestive of cancer recurrence.

Audiology Exam: an audiology exam were to be performed every 3 months until resolution for patients having received cisplatin and having had a grade 1 or higher hearing loss.

Symptoms and toxicity:

Breast examinations

- A clinical breast examination was to be performed at each follow up visit.
- A bilateral mammogram was required annually.

The results of all breast biopsies and cytologies (including those diagnosed as benign) were to be reported. When the report was either positive or suspicious, all mammogram reports, operative reports, and pathology reports/materials were to be submitted to BCIRG has decided to use this method of identifying patients for entry in to this adjuvant trial. BCIRG will use fluorescence in situ hybridization (FISH) performed in centralized laboratories to select women for this clinical trial.

- Biostatistical Center for medical review.

#### Gynecologic examinations

- All participants who have not had a prior hysterectomy and bilateral salpingo-oophorectomy were to receive a pelvic exam and, as indicated, a pap smear on an annual basis. At each visit, participants were to be questioned about postmenopausal bleeding, bloody discharge, postcoital staining, or any vaginal bleeding.
- Participants who develop postmenopausal bleeding or staining had to undergo gynecologic evaluation, to include endometrial sampling with or without transvaginal ultrasound (TVU). If this evaluation was negative but the bleeding continues, further diagnostic procedures, such as dilatation and curettage, hysteroscopy, or saline infusion sonogram (SIS) are appropriate to rule out a specific endometrial cause of the symptoms. Participants who develop significant menstrual abnormalities and who refuse or do not comply with the recommendation for gynecological evaluation should have their protocol medication discontinued until the conditions have resolved.
- Diagnosis of any cancer or hyperplasia, as well as the results of all endometrial biopsies or cytologies, were to be reported on the event form. Copies of the operative and pathology reports and tumor blocks were to be submitted to the Biostatistical Center for review.

#### Ophthalmic monitoring

- During each follow up visit, participants were to be questioned about visual changes and ophthalmic events (cataracts, retinal changes, corneal opacity, etc).

#### Cardiovascular monitoring

- All cardiovascular events were to be reported. Any indication of arteriosclerotic vascular disease (ASVD), including non-fatal myocardial infarction and death due to ASVD, was to be reported.

#### Fracture monitoring

- All fractures were to be reported, documenting the site, severity, and method of injury. Submission of the x ray report and any additional documentation (hospital summary, operative report, etc.) was also required.

#### Mortality

- All deaths were to be reported to the Biostatistical Center and accompanied by a copy of the death certificate.

#### Follow-up

Patients were to be followed every 3 months for the first two years, every 6 months for years 3 – 5, and then once a year for ten years or until relapse to document:

- Disease-free survival
- Survival
- Further therapy

- Quality of life (for the first two years only)
- Late side effects, including congestive heart failure. This to include chemotherapy, Herceptin and Tamoxifen related toxicities.
- 2nd primary malignancy

In case of disease relapse, 2nd primary malignancy, and/or administration of other systemic cancer therapy other than the study drug, patients were to be followed for:

- Survival
- Congestive Heart Failure

### Criteria for Efficacy Assessment

#### Disease-Free Survival (DFS):

The **primary efficacy endpoint** was a 5 year Disease-Free Survival (DFS). DFS was defined as the interval from the date of randomization to the date of local, regional or metastatic relapse or the date of second primary cancer or death from any cause whichever occurred first.

*Objective Relapse* was defined as any clinical or radiologic evidence of tumor relapse including the central nervous system. Histology or cytological proof of failure were to be obtained, if feasible.

*Local relapse* was defined as evidence of tumor in the breast surgical scar, ipsilateral breast (conservative surgery), or evidence of tumor in the ipsilateral anterior chest wall (mastectomy) or skin or soft tissues within the local area. Histologic or cytologic proof was mandatory.

*Regional relapse* was defined as evidence of tumor in the axillary scar, ipsilateral nodal areas (axillary, internal mammary, and infraclavicular) as well as skin or soft tissues within the regional area. Histologic or cytologic proof was mandatory.

*Distant relapse* was defined as evidence of tumor beyond the local-regional level as previously defined. This included the following:

- 1) lymph nodes not included in the areas defined above (i.e. supraclavicular, contralateral axilla, paratracheal, etc.)
- 2) skin not included in the areas defined above
- 3) liver
- 4) lung
- 5) bone
- 6) central nervous system
- 7) contralateral breast
- 8) other sites not defined above

Histologic or cytologic proof was preferred especially in solitary lesions. Positive bone scans was to be correlated with bone X-ray.

Any new breast malignancy was to be biopsied if possible and blocks sent to the central operational office for confirmation of primary or metastatic status along with pathologic and molecular studies.

The following did not constitute relapse, however, a new evaluation was recommended to evaluate possible extent of disease: 10% or more decrease in baseline Karnofsky performance status and or a single new lesion on bone scan without evidence of lytic disease by radiography or bone scan.

*Second Primary Cancer* was defined as any other histopathologically proven cancer including second invasive primary breast cancer in ipsilateral or contralateral breast. Excluded are non-melanoma skin cancer, in-situ carcinoma of the cervix, and in-situ carcinoma of the breast (LCIS/DCIS).

*Survival* was to be measured from the date of randomization up to the date of death of any cause.

**Reviewer's Comments:**

All cancers other than those of the breast were to be reported on event form. The protocol does not state if a copy of the pathology report and blocks of the tumor were required for review. The protocol does not state if a death certificate was to be submitted or if the patient was in the hospital at the time of death, a discharge summary was required.

A **secondary endpoint** of the study was to compare the cardiac safety of the arms containing Herceptin to the control arm of AC→ T.

**Definitions of Cardiac Toxicity**

**Symptomatic Cardiac Event**

A cardiac event occurred if a patient had a cardiac death, congestive heart failure, grade 3 or grade 4 arrhythmias, or grade 3 or grade 4 ischemia/infarction.

**Cardiac Death:**

Cardiac death was defined as death due to one of the following confirmed congestive heart failure

myocardial infarction

documented primary arrhythmia

probable cardiac death i.e. sudden death without documented etiology

An autopsy was preferred in cases where cause of death has a cardiac etiology.

***Congestive Heart Failure (CHF):***

Clinical signs and symptoms suggesting congestive heart failure (dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc) were to be investigated. The suspicion of congestive heart failure, based on the signs and symptoms had be confirmed by a decrease in MUGA, with a chest X-ray. All CHF events and associated reports needed a reviewed by an independent team of cardiologists. LVEF assessment were to be repeated 4 to 7 days after to confirm a diagnosis of congestive heart failure.

***Cardiac Arrhythmias:***

The NCI Common Toxicity Criteria, version 2.0 were used to classify an arrhythmia as grade 3, which is symptomatic and requiring treatment, or grade 4 which is an arrhythmia considered to be life-threatening e.g. an arrhythmia associated with CHF, hypotension, syncope, shock.

***Cardiac Ischemia / Infarction***

The NCI Common Toxicity Criteria, version 2.0 were used to classify the severity of cardiac ischemia/infarction. Grade 3 ischemia was defined as angina without evidence of infarction. Grade 4 was defined as an acute myocardial infarction.

**Asymptomatic Cardiac Abnormality**

***Asymptomatic decreases in left ventricular ejection fraction (LVEF):***

Clinically significant asymptomatic cardiac abnormality was defined as an absolute decline of LVEF of >15% points from baseline and a value below LLN. A specific monitoring plan was devised for data collection of asymptomatic decreases in left ventricular ejection fraction.

Data on the incidence and degree of LVEF decrease in the first 1,500 patients randomized were to be collected at scheduled time points and reviewed as defined below. All randomized patients will continue with the scheduled MUGAs until results on the first 1,500 patients in the cardiac safety analysis have been completed.

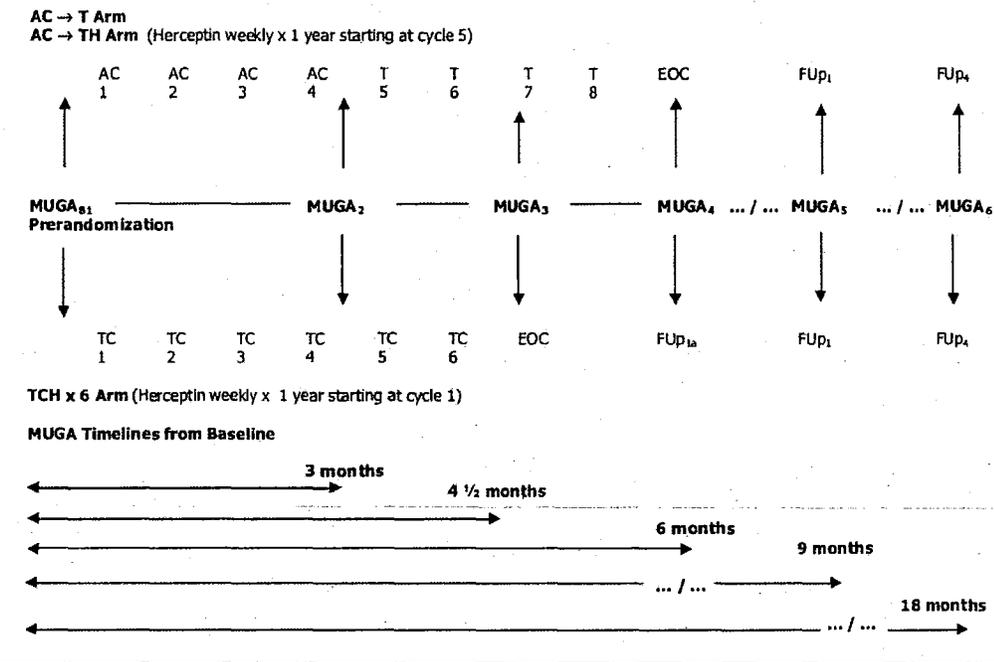
For patients with an asymptomatic decrease in LVEF, the treatment decision with respect to Herceptin and repeat LVEF determinations were to be defined by the measured left ventricular ejection fraction as it relates to the radiology facility's lower limit of normal and the change in LVEF from baseline. Determination of left ventricular ejection fraction were to be performed as outlined in Figure 1 until results from the cardiac safety analysis have been completed. Following completion of the cardiac safety analysis, patients further randomized were only required to have a LVEF determination at baseline, and as clinically indicated in the case of a clinical cardiac event.

**Evaluable Patients for the Cardiac Safety Evaluation**

The first 1,500 patients randomized to the study, with the required normal baseline MUGA, were considered evaluable for the cardiac safety evaluation on an intent-to-treat basis. Scheduled MUGAs have been planned for the first 1,500 randomized patients in order to evaluate asymptomatic changes in left ventricular ejection fraction from baseline. Timing of analyses of cardiac toxicity were to take place when: (1) 100 randomized patients per arm (total

300 patients) (2) 300 randomized patients per arm (total 900 patients), and (3) 500 randomized patients per arm (total 1,500 patients), respectively and on an intent-to-treat basis, have been followed up to and including the timing of MUGA 5. (see Figure 1).  
 The final cardiac analysis was to take place after 1,500 patients (500 patients per arm) have been followed up to and including follow-up visit #1 (9 months post randomization).  
 At each of these analyses, cardiac deaths, congestive heart failure events, grade 3 or 4 arrhythmias, grade 3 or 4 cardiac ischemia / infarction events, and asymptomatic left ventricular decreases were to be reviewed and assessed

Figure 1 Timing of LVEF Determination for patients in the cardiac safety analysis



**Timing of MUGA Evaluations:**

As part of the assessment of cardiac safety of each treatment arm, MUGAs are scheduled as follows for each arm.

- MUGA 1 Pre-randomization, baseline MUGA evaluation within 3 months prior to randomization.
- MUGA 2 was scheduled after the 4th cycle of chemotherapy in each arm. Corresponds to the LVEF determination after completion of AC in the AC→T and AC→TH arm, and after 4 cycles of TC with Herceptin.

- MUGA 3 was scheduled after the 6th cycle of chemotherapy in each arm. It corresponds to the End of Chemotherapy visit evaluation in the TCH arm.
- MUGA 4 was scheduled at 6 months post randomization. It corresponds to the End of Chemotherapy visit in the AC→T and AC→TH arms MUGA 4 corresponds to an extra follow-up visit (FUp1a) 6 weeks after the EOC for the TCH arm.
- MUGA 5 was scheduled 9 months after randomization. Corresponds to follow-up visit # 1, which is exactly 3 months after the EOC in the AC→T and AC→TH arms, and 4 ½ months after the EOC in the TCH arm.
- MUGA 6 The 6th MUGA was scheduled 18 months after randomization

### Criteria for Safety Assessment

All adverse event reporting use NCI Common Toxicity Criteria (CTC) Version 2.0 standards for adverse event (toxicity) grading. Attribution categories were as follows: unrelated, unlikely, possibly, probably, or definitely related to the study drug(s).

*Serious Adverse Event* was defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: 1) death, 2) a life-threatening adverse drug experience, 3) inpatient hospitalization or prolongation of existing hospitalization, or 4) a persistent or significant disability/incapacity, or 5) a congenital anomaly/birth defect.

Congestive heart failure (CHF) is a protocol-defined Serious Adverse Event for this study. CHF was to be reported as a serious adverse event regardless of causality during the observation period and if in the investigator's opinion it was study drug-related, or medically significant during the follow-up period.

*Unexpected Adverse Event* was defined as any adverse drug experience that was not listed in the current product label or investigator's brochure for either tamoxifen or raloxifene. These included events that may have been symptomatically and pathophysiologically related to an event listed but that differed from the event because of greater severity or specificity.

### Endpoints and Statistical Considerations

#### Endpoints:

##### *Primary Endpoint:*

The primary endpoint of the study was the occurrence of Disease Free Survival.

##### *Secondary Endpoints:*

- Overall Survival
- Cardiac Safety
- Non- Cardiac Safety

- Quality of Life

### **Statistical Considerations:**

#### **Sample Size:**

The protocol was to target a sample size of 3,150 (1,050 patients per treatment arm). Power calculations were based on several factors including: 1) the expected disease free survival rate; and 2) the dropout rate for the study.

#### 1) Expected rate of disease free survival:

It is assumed that the proportions of patients who have no axillary lymph node involved (No), 1 to 3 axillary lymph nodes involved (N1-3) and 4 or more axillary lymph nodes involved (N4+) will be approximately 20% , 50% and 30%, respectively.

It is expected that DFS at 5 years of patients receiving AC→T in these three strata, are, respectively equal to about 67%, 57% and 42%. The overall DFS of all patients receiving AC→T will therefore be equal to about 55%. It is of clinical interest to detect a 7% improvement in 5-year DFS (ie an increase from 55% to 62%).

The overall error rate for a false positive outcome ( $\alpha$ ) is set to 5%, using two-sided significance tests. Since the three pairwise treatment comparisons will be of interest in the final analysis, the error rate for each comparison is set at a conservative level of 0.017.

If the 5-year DFS were different from 55%, the trial would have a power of about 80% or higher to detect a difference of 7% between the treatment arms regardless of the 5-year DFS.

The absolute 5-year DFS difference of 7% corresponds to a hazard ratio of 0.807, i.e., a 20% relative reduction in the risk of an event (recurrence or death). The trial will have a power of 96% to detect a 25% relative reduction in the risk of an event, which corresponds to an absolute 5-year DFS difference of about 9%.

With the sample size as stated in the primary endpoint, this trial has 80% power (at a significance level of 0.05) to detect an absolute difference in **overall survival** of approximately 5%. If overall survival at 5 years in the control arm is between 70% and 80%, the detectable difference in one of the experimental arms is between 5.5% and 4.7%, respectively. This translates into a reduction in relative risk between 21% and 26%.

#### 2) Study dropouts

The study assumes that about 3% of the patients will be found ineligible after randomization,

#### **Populations to be Analyzed**

The analysis of DFS and of OS will be performed on the Intent-to-Treat (ITT) population, defined as the population of all randomized patients analyzed in the treatment group they were assigned to. Randomized patients who did not receive chemotherapy will be analyzed in their group of randomization. The analysis of DFS and OS will also be performed on the eligible

patients populations, defined as the ITT population patients less patients who were randomized but were not eligible for the trial according to the inclusion and exclusion criteria.

#### Statistical Methods

The Kaplan-Meier method will be used to estimate DFS and OS. The log rank test, stratified for nodal status (No versus N1-3 versus N4+), for hormonal receptor status (estrogen and/or progesterone receptor positive versus negative), will be used to perform all pair-wise comparisons between the control and the two treatment arms with respect to DFS and OS. All tests of hypotheses will be two-sided. Confidence intervals of the median survival will be calculated using the Simon method.

Cox's proportional hazards regression analysis will be performed for DFS and OS in order to adjust the treatment comparison for the major prognostic factors. These factors include age, menopausal status, type of surgery, histopathological findings, tumor size, pathological markers and molecular markers.

A statistical analysis does not plan to include any center effect in the analyses.

#### Primary analysis plan:

The protocol plan was to perform the definitive analysis when 1,270 events have been observed among eligible patients.

A stratified log-rank test (using the stratification variables from the randomization procedure) was to be used and conclude that one of the treatments was the more effective for reducing the rate of disease free survival if the statistic had a two-sided p-value of less than .05.

#### Interim Analysis and Follow-up Analyses

One interim efficacy analysis was planned after 50% of the expected events (635 events) have been observed. A pragmatic group sequential design, as suggested by Haybittle-Peto, was to be used with a significance level of 0.001 (overall) for interim analyses. At the time of the interim analysis, all patients will likely have been recruited.

Some patients are expected to have a very long disease free survival. Consequently, a 10-year clinical follow-up has been planned. Two confirmatory analyses will be performed: firstly at 8 years and finally at 10 years after the recruitment of the last patient into the trial. The purpose of these follow-up analyses is to update the DFS and OS estimates. All randomized patients will be followed until death or until 10 years after the last patient entry.

#### Cardiac Safety Analysis

One of the secondary endpoints of the study is to compare the cardiac safety of the three treatment arms. At each of the cardiac analyses, cardiac deaths, congestive heart failure events, grade 3 or 4 arrhythmias, grade 3 or 4 cardiac ischemia / infarction events, and asymptomatic left ventricular decreases were to be reviewed and assessed.

Cardiac events which encompass cardiac deaths, congestive heart failure, grade 3 or 4 ischemia, grade 3 or 4 arrhythmias were considered in the statistical analyses below.

The following assumptions were made:

1. The baseline incidence of events (cardiac deaths and congestive heart failure, grade 3 or 4 ischemia, grade 3 or 4 arrhythmias) in the AC→T arm is expected to be 1%
2. A difference of > 4% between the AC→T arm and either of the Herceptin-containing arms, AC→TH and TCH, respectively, were considered unacceptable.

At each analysis, the two-tailed significance level of each interim analysis will be set at 0.05. This level of significance is not adjusted to take repeated analyses into account, and hence it will be merely indicative of a potential increase in incidence that needs to be scrutinized by the IDMC. Assuming a baseline incidence of cardiac deaths and symptomatic cardiac events of 1% in the control arm, the analyses will have approximately the following power to detect a difference of at least 4% in either treatment arm: 40% with 300 patients, 80% with 900 patients, and 95% with 1,500 patients. The statistical power to detect a 4% difference would be slightly higher than these figures should the baseline incidence be lower than 1%, and slightly lower than these figures should the baseline incidence be higher than 1%.

If one of the treatment arms have an unacceptably high incidence of cardiac toxicity, this group will be terminated after data review by the Independent Data Monitoring Committee.

Asymptomatic cardiac abnormalities i.e., asymptomatic decreases in left ventricular ejection fraction, will be part of the cardiac monitoring within the cardiac safety evaluation plan, but will not be evaluated within the cardiac safety analysis above.

Clinically significant asymptomatic cardiac abnormality is an absolute decline of LVEF of >15% % points from baseline and a value below LLN. The asymptomatic decreases will be evaluated as follows:

- For the asymptomatic decreases in left ventricular ejection fraction, at each interval as defined above by accrual of evaluable patients to 100 per arm, 300 and 500 patients, respectively, data collected will be reviewed. Because of lack of data with respect to the significance of an asymptomatic decrease and its relation to the development of clinical congestive heart failure, no unacceptable number will be defined up front. The IDMC will be responsible for determining when the incidence of and/or the degree of asymptomatic decreases has become unacceptable and treatment arm must be discontinued.

#### Populations to be analyzed

The safety analysis will be conducted on all patients who started at least one infusion of the study treatment.

#### Statistical Methods

Adverse events will be compared using two-tailed  $\chi^2$  tests or, when expected counts are low, Fisher's exact test or one of its generalizations. In view of the anticipated large number of statistical tests, p-values will not be interpreted in the usual sense but will be used as a "flagging device" to highlight differences worth further attention. Descriptive statistics will be given on the number of patients in whom the study medication had to be replaced, delayed or

permanently stopped.

**Independent Data Monitoring Committee (IDMC)**

The Independent Data Monitoring Committee (IDMC) was to be composed of three medical oncologists, one statistician, and two cardiologists. These members were to be independent of the trial and familiar with the methodology of oncology trials. The mission of the IDMC was to ensure the ethical conduct of the trial and to protect the safety interests of patients in this study. The IDMC was to be responsible for both review of trial efficacy and safety. In the absence of any major event requiring the meeting of the IDMC members, an annual meeting of the IDMC was to be held.

**Quality of life evaluation**

A quality of life assessment for each arm was a secondary endpoint of the study. Centers participating in the analysis needed to be predefined. Some countries may be unable to participate due to the unavailability of the tools in the patient's first language.

The EORTC cancer-specific and EUROQUOL (ED-5D) general health indexes were chosen in this comparative study. The QLQ-30 (v.3.0) profile questionnaire and the BR-23 module specific to breast cancer were, respectively, 30 and 23 items in a questionnaire format. The EUROQUOL ED-5D is a five question format in addition to a visual analog scale. They were to be self-administered by the patient and completed in accordance with the following schedules.

**Table 9 QOL questionnaire schedule**

	AC→T	AC→TH	TCH
Baseline	Within 14 days prior to randomization	Within 14 days prior to randomization	Within 14 days prior to randomization
Cycles 1, 3 & 5	day -1 to day 1 (before chemotherapy)	day -1 to day 1 (before chemotherapy)	day -1 to day 1 (before chemotherapy)
Cycle 7 AC→T Cycle 7 AC→TH EOC* TCH	day -1 to day 1 (before chemotherapy)	day -1 to day 1 (before chemotherapy)	EOC* Visit
EOC* AC→T EOC* AC→TH Fup1a TCH	EOC* Visit	EOC* Visit	6 weeks after the EOC visit Fup1a visit
Follow-Up	Follow-up Visit every 3 months for the first 2 years	Follow-up Visit every 3 months for the first 2 years	Follow-up Visit every 3 months for the first 2 years
At Relapse	At Relapse Visit	At Relapse Visit	At Relapse Visit

**Reviewer's Comments:**

The protocol does not state the sample size for the quality-of-life monitoring.

## Study Results

### 6.1.1.5 Patient Demographics/ Disposition

#### **Patient Demographics**

The following results are from the sponsor's analyses and tables. This clinical study report summarizes data from the second efficacy interim analysis and a median duration of follow-up of 3 years for all patients.

#### *Enrollment:*

A total of 433 centers in 43 countries enrolled patients in this study. The number of centers by country ranged from one center (Bosnia, Cyprus, Greece, Sweden, and Switzerland) to 177 centers (United States). The number of patients by country ranged from two to 990. The largest enrolling countries were the United States (n = 990; 30.7%), Germany (n = 313; 9.7%), Australia (n = 293; 9.1%) and Poland (n = 260; 8.1%).

Three thousand two hundred twenty two women were enrolled in this study. Between 5 April 2001 and 31 March 2004, patients were randomized into the study as follows: 1073 were randomized to the AC→T arm, 1074 were randomized to the AC→TH arm, and 1075 were randomized to the TCH arm. Of the 3222 randomized, 48 did not receive any study treatment: 28 in the AC→T arm, 2 in the AC→TH arm, and 18 in the TCH arm. One patient was randomized to the AC→T arm but received AC→TH instead, 6 patients were randomized to the AC→TH arm but received AC→T, 1 patient was randomized to the TCH arm but received AC→TH, and 2 patients randomized to the TCH arm received Herceptin but no chemotherapy.

The primary efficacy analysis population consists of all randomized subjects (ITT) according to randomized treatment arm. Patients were considered evaluable for safety if they received any amount of study treatment (chemotherapy or Herceptin) and were analyzed according to treatment received. See table below.

**Table 10 Analysis Population**

	AC→T	AC→TH	TCH	All Patients
ITT Population <sup>a</sup>	1073	1074	1075	3222
untreated	28	2	18	48
Safety Population <sup>b</sup>	1050	1068	1056	3174
Treatment Received				
AC→T <sup>c</sup>	1044	6	0	1050
AC→TH <sup>d</sup>	1	1066	1	1068
TCH <sup>e</sup>	0	0	1056	1056

<sup>a</sup> The efficacy population consists of all randomized patients.

<sup>b</sup> The safety population consists of all treated patients and all analyses were conducted on an "as-treated" basis.

<sup>c</sup> Patients 30857, 31363, 31579, 32022, 32376, and 33197 were randomized to receive AC→TH but did not receive Herceptin.

<sup>d</sup> Patient 31682 was randomized to AC→T but received her first dose of Herceptin during the monotherapy phase of the study. One patient (30344) was randomized to receive TCH but received AC→TH.

<sup>e</sup> Patients 32533 and 32816 received Herceptin but no chemotherapy.

The table below summarizes the treatments received and disposition for all randomized patients. Of the patients randomized to receive AC→T and AC→TH, 97.4% and 99.8% started AC, respectively. Of the patients randomized to receive TCH, 98.1% began chemotherapy. The most frequent reasons for premature discontinuation of chemotherapy in all arms were adverse experiences (AC→T: 4.3%; AC→TH: 4.0%; and TCH: 2.8%) and withdrawal of consent or patient refusal (AC→T: 3.7%; AC→TH: 2.8%; and TCH: 0.9%).

Of the patients randomized to the AC→TH and TCH arms, 96.9% and 98.3%, respectively, received Herceptin concurrent with chemotherapy. The most frequent reasons for discontinuation of Herceptin prior to completion of chemotherapy in the AC→TH arm were Herceptin toxicity (3.3%) and patient refusal and withdrawal of consent (2.1%). The most cited reasons for discontinuation of Herceptin prior to completion of chemotherapy in the TCH arm were patient refusal and withdrawal of consent (1.6%), Herceptin toxicity (1.2%), and adverse experience (1.2%).

Of the patients randomized to AC→TH and TCH arms, 90.6% and 93.9%, respectively, began treatment with Herceptin monotherapy. The most frequent reasons for premature discontinuation of Herceptin monotherapy in both Herceptin-containing arms were significant cardiac disease (AC→TH: 3.8%; TCH: 1.2%) and patient refusal and withdrawal of consent (AC→TH: 2.2%; TCH: 1.1%).

Patients were considered to have "completed" Herceptin therapy if the total duration from first to last Herceptin infusion exceeded 11 months and there was no report of early discontinuation of Herceptin. Of the patients randomized to receive AC→TH and TCH, 74.9% and 84.9% completed the protocol-specified year of Herceptin therapy. Of those randomized to receive AC→TH, 5.9% did not complete the protocol-specified year of Herceptin therapy and no reason for discontinuation was available. Of those randomized to receive TCH, 3.5% did not complete the protocol-specified year of Herceptin therapy and no reason for discontinuation was available.

**Table 11 Patient Disposition**

	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
<b>Entered chemotherapy</b>	<b>1045 (97.4%)</b>	<b>1072 (99.8%)</b>	<b>1055 (98.1%)</b>
Completed <sup>b</sup>	953 (88.8%)	991 (92.3%)	1011 (94.0%)
Did not complete	92 (8.6%)	81 (7.5%)	44 (4.1%)
Death	1 (0.1%)	0 (0.0%)	2 (0.2%)
Breast cancer relapse	5 (0.5%)	4 (0.4%)	1 (0.1%)
Second primary malignancy	0 (0.0%)	1 (0.1%)	0 (0.0%)
Adverse experience	46 (4.3%)	43 (4.0%)	30 (2.8%)
Patient refusal/consent withdrawn	40 (3.7%)	30 (2.8%)	10 (0.9%)
Other <sup>a</sup>	0 (0.0%)	3 (0.3%)	1 (0.1%)
<b>Entered Herceptin during chemotherapy</b>	<b>1 (0.1%)</b>	<b>1041 (96.9%)</b>	<b>1057 (98.3%)</b>
Completed	1 (0.1%)	969 (90.2%)	1008 (93.8%)
Did not complete		72 (6.7%)	49 (4.6%)
Death		0 (0.0%)	2 (0.2%)
Breast cancer relapse		1 (0.1%)	1 (0.1%)
Second primary malignancy		1 (0.1%)	0 (0.0%)
Adverse experience		6 (0.6%)	13 (1.2%)
Herceptin toxicity		35 (3.3%)	13 (1.2%)
Patient refusal/consent withdrawn		23 (2.1%)	17 (1.6%)
Other		3 (0.3%)	3 (0.3%)
Missing		3 (0.3%)	0 (0.0%)
<b>Entered Herceptin monotherapy</b>	<b>1 (0.1%)</b>	<b>973 (90.6%)</b>	<b>1009 (93.9%)</b>
Completed <sup>b</sup>	0 (0.0%)	804 (74.9%)	913 (84.9%)
Not completed/no discontinuation <sup>c</sup>	1 (0.1%)	63 (5.9%)	38 (3.5%)
Did not complete		106 (9.9%)	58 (5.4%)
Death		0 (0.0%)	1 (0.1%)
Breast cancer relapse		8 (0.7%)	7 (0.7%)
Second primary malignancy		1 (0.1%)	2 (0.2%)
Significant cardiac disease		41 (3.8%)	13 (1.2%)
Patient refusal/consent withdrawn		24 (2.2%)	12 (1.1%)
Lost to follow-up		0 (0.0%)	1 (0.1%)
Concomitant therapy <sup>d</sup>		1 (0.1%)	0 (0.0%)
Other		30 (2.8%)	21 (2.0%)
Missing		1 (0.1%)	1 (0.1%)

<sup>a</sup> Other includes "other deviation from protocol" and "other."

<sup>b</sup> Patients whose total duration from initial to final Herceptin infusion was > 11 months were classified as having "completed" Herceptin monotherapy.

<sup>c</sup> Patients whose total duration from initial to final Herceptin infusion was ≤ 11 months and for whom no data on early discontinuation of Herceptin were available were classified as "did not complete but no evidence of discontinuation."

<sup>d</sup> other than anti-tumor therapy

6.1.1.6 Protocol Violations and Deviations:

Seventy seven patients (2.4%) were found to have had at least one major protocol eligibility violation. The most common reasons for ineligibility were no definitive surgery performed, TNM staging not categorized as T1-T3, N0-N1, M0, or margin involvement (n = 25; 0.8%); and primary tumor classified as T4, N2-N3, or M1 (n = 18; 0.6%). There were 12 protocol violations with respect to the requirement of HER2/*neu* positivity by FISH.

**Table 12 BCIRG006 Protocol Violations**

	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Protocol Violations	25 (2.3%)	24 (2.2%)	28 (2.6%)
Definitive surgery not performed or incorrect TNM stage, or margin involvement	6 (0.6%)	5 (0.5%)	14 (1.3%)
Clinical T4, pN2, pN3, or M1	4 (0.4%)	4 (0.4%)	10 (0.9%)
Hematologic, hepatic, and renal function	5 (0.5%)	4 (0.4%)	4 (0.4%)
HER2-negative by FISH a	6 (0.6%)	4 (0.4%)	2 (0.2%)
Ongoing hormonal therapy at time of first infusion	1 (0.1%)	3 (0.3%)	3 (0.3%)
Concurrent treatment with other anti-cancer therapy	2 (0.2%)	2 (0.2%)	3 (0.3%)
Prior systemic anti-cancer therapy for breast cancer	1 (0.1%)	2 (0.2%)	2 (0.2%)
History of or current neoplasm other than breast cancer	2 (0.2%)	1 (0.1%)	2 (0.2%)
Left ventricular function	1 (0.1%)	2 (0.2%)	1 (0.1%)
Cardiac disease precluding use of AC, T, and Herceptin	0 (0.0%)	2 (0.2%)	0 (0.0%)
Preexisting motor or sensory neuron-toxicity NCI-CTC Grade ≥ 2	2 (0.2%)	0 (0.0%)	0 (0.0%)

**Patient Crossover**

Per the protocol, crossover was not allowed. However, a total of 18 patients (30474, 30017, 32852, 33068, 30233, 33123, 30731, 31985, 31688, 32991, 33194, 33101, 32133, 30084, 31174, 31265, 32932, and 32158) from the control arm crossed over to the Herceptin arm.

Patient Characteristics

The demographic characteristics of the ITT population are summarized in the table below.

There were no significant differences between the treatment groups. All patients underwent primary surgery for breast cancer prior to study enrollment. A total of 59.5% of patients in the AC→T arm, 62.8% in the AC→TH arm, and 59.7% in the TCH arm had a mastectomy. Positive HER2 status by FISH performed at the central laboratory was mandatory at the time of enrollment. A total of 99.6% of patients (3209 of 3222) were HER2-positive, as assessed by the central laboratory. There were 12 patients who were HER2 negative per central FISH assessment. Nodal involvement was very similar across the three treatment arms, with 28.8%, 28.5%, and 28.6% of patients having node-negative disease and 13.4%, 11.4%, and 11.3% of patients having ten or more nodes involved in the AC→T, AC→TH, and TCH arms, respectively. Approximately half of the patients were ER-positive and/or PR-positive: Infiltrating ductal carcinoma was the most common histopathologic type in all treatment arms. Most tumors were poorly differentiated and were excised with clear margins.

**Table 13 BCIRG006 Patient Tumor Characteristics**

	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
HER2 status	1072*	1074	1075
Positive	1066 (99.4%)	1070 (99.6%)	1073 (99.8%)
Negative**	6 (0.6%)	4 (0.4%)	2 (0.2%)
Type of surgery			
Mastectomy	638 (59.5%)	674 (62.8%)	642 (59.7%)
Quadrantectomy	270 (25.2%)	255 (23.7%)	268 (24.9%)
Lumpectomy	165 (15.4%)	145 (13.5%)	165 (15.3%)
Detection type			
Sentinel node	113 (13.0%) <sup>4</sup>	112 (13.0%)	115(13.2%)
Axillary dissection	757 (87.1%)	753 (87.2%)	757 (86.9%)
Both	1 (0.1%)	1 (0.1%)	1 (0.1%)
Number of positive nodes			
0	309 (28.8%)	306 (28.5%)	307 (28.6%)
1-3	413 (38.5%)	410 (38.2%)	415 (38.6%)
4-9	207 (19.3%)	236 (22.0%)	232 (21.6%)
10+	144 (13.4%)	122 (11.4%)	121 (11.3%)
Hormone receptor			
ER+ and/or PR+	577 (53.8%)	578 (53.8%)	579 (53.9%)
ER- and PR -	496 (46.2%)	496 (46.2%)	496 (46.1%)
Tumor size (cm)			
≤ 2	439 (40.9%)	411 (38.3%)	429 (39.9%)
> 2	636 (59.3%)	663 (61.5%)	641 (59.7%)
Nuclear Grade			
GX	44 (4.1%)	52 (4.8%)	45 (4.2%)
G1	24 (2.2%)	12 (1.1%)	18 (1.7%)

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G2	301 (28.1%)	321 (29.9%)	300 (27.9%)
G3	701 (65.3%)	688 (64.1%)	709 (66.0%)
G4	3 (0.3%)	1 (0.1%)	3 (0.3%)
Positive Margins	2 (0.2%)	3 (0.3%)	3 (0.3%)
Histologic type			
Infiltrating:			
ductal carcinoma	966 (90.0%)	981 (91.3%)	986 (91.7%)
lobular carcinoma	38 (3.5%)	31 (2.9%)	30 (2.8%)
Other	69 (6.4%)	62 (5.8%)	59 (5.5%)

\* Patient # 30839 was HER2-positive based on local test results not assessed by the central laboratory.

\*\* Patients # 30091, 30104, 30149, 30483, 30948, 31051, 31236, 31253, 31281, 31931, 31980, 32162

GX: not assessable, G1: well differentiated, G2: moderately differentiated, G3: poorly differentiated, G4: undifferentiated

High-risk node-negative patients were defined as those patients having invasive adenocarcinoma with either no axillary lymph nodes showing evidence of tumor or a minimum of six resected lymph nodes, or a negative sentinel node biopsy and at least one of the following factors: tumor size >2 cm, ER- and PR-negative, histologic and/or nuclear grade of 2 or 3, or age < 35 years. The table below summarizes the high risk characteristics of all node-negative patients. For the majority of the patients, the high-risk criterion met was nuclear grade 2 or 3.

**Table 14 High Risk Patient Population**

	AC→T (n = 309)	AC→TH (n = 306)	TCH (n = 307)
Age (yr) <35	22 (7.1%)	19 (6.2%)	26 (8.5%)
ER - and PR -	151 (48.9%)	140 (45.8%)	163 (53.1%)
Nuclear grade 2 or 3			
G2	76 (24.6%)	89 (29.1%)	92 (30.0%)
G3	220 (71.2%)	207 (67.6%)	202 (65.8%)
Tumor size (cm) > 2	153 (49.5%)	158 (51.6%)	152 (49.5%)

**DFS**

**Sponsor's Analysis of time to disease recurrence:**

The *first interim analysis* was conducted after 322 DFS event using a data cut-off date of June 30, 2005. DFS results, using the FEVAL dataset, shows that the comparison of each Herceptin treated arm to the control (AC→TH or TCH versus AC→T) crossed the pre-specified O'Brien Fleming Boundary (nominal  $\alpha=0.0002$ ) and shows significantly lower risk of DFS in the Herceptin treated arms. The hazard ratios based on the Cox's proportional hazards model was 0.49 (with 95% C.I. = [0.37, 0.64], p-value<0.0001) and 0.61 (with 95% C.I. = [0.47, 0.79], p-value=0.00013) for AC→TH versus AC→T and TCH versus AC→T, respectively.

**Table 15 Sponsor's Disease Free Survival – First Interim analysis**

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event	147 (13.7%)	77 (7.2%)	98 (9.1%)
Stratified analysis			
Hazard ratio <sup>a</sup>	NA	0.49	0.61
95% CI	NA	(0.37, 0.65)	(0.47, 0.79)
p-value <sup>b</sup>	NA	0.0000005	0.000153

<sup>a</sup> Relative to AC→T. Estimated using Cox model stratified by number of positive nodes and hormonal receptor status.  
<sup>b</sup> Stratified log-rank p-value.

At data cut-off (November 1, 2006), second interim analysis, and median duration of follow up of 36 months, a total of 474 patients (14.7%) had disease recurrence (including death from any cause). One hundred ninety five of the 1073 patients in the AC→T arm had disease recurrence (18.2%) compared to 134 of the 1074 patients in the AC→TH arm (12.5%) and 145 of the 1075 patients in the TCH arm (13.5%). This difference is equivalent to a 39% reduction in the risk of disease recurrence for AC→TH arm patients (hazard ratio 0.61, [CI]: 0.49, 0.77;  $p<0.0001$ ) relative to the AC→T arm and to a 33% reduction in the risk of disease recurrence for TCH arm patients (hazard ratio 0.67, [CI]: 0.54, 0.83;  $p=0.0003$ ) relative to the AC→T arm. The table below summarizes the recurrence status according to first confirmed event.

**Table 16 Sponsor's Disease Free Survival – Second Interim Analysis**

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
First event <sup>a</sup>	195 (18.2%)	134 (12.5%)	145 (13.5%)
Distant recurrence	141 <sup>a</sup>	89	97
Local/regional recurrence <sup>b</sup>	25	19	26

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Second primary cancer	24 <sup>a</sup>	21	15
Death	5	5	7
Stratified analysis			
Hazard ratio <sup>c</sup>	NA	0.61	0.67
95% CI	NA	(0.49, 0.76 <sup>e</sup> )	(0.54, 0.83)
p-value <sup>d</sup>	NA	< 0.0001	0.0003

a First event modify by the reviewer.

b First event modify by the reviewer. The value is the first event for each patient, either local or regional recurrence.

c Relative to AC→T. Estimated using Cox model stratified by number of positive nodes and hormonal receptor status.

d Stratified log-rank p-value.

e The 95% C.I. for the comparison between AC→TH vs. AC→T was revised by the reviewer. The sponsor's original 95% C.I. is [0.49, 0.77].

The sponsor performed several sensitivity analyses for DFS based on a) FEVAL dataset, b) excluding second primary cancer; c) excluding metastatic disease and HER-2 negative and d) excluding non-breast cancer second primary cancer for comparisons between AC→TH vs. AC→T and TCH vs. AC→T (see the following two tables). All results appear to be consistent with the primary analysis of DFS. The sponsor's analysis for distant recurrence also shows nominally significant results in favor of AC→TH and TCH arm versus AC→T arm.

**Table 17 Sponsor's Sensitivity Analyses for Efficacy Endpoint: AC→T versus AC→TH**

	AC→T (n = 1073)	AC→TH (n = 1074)	Hazard Ratio (95% CI) <sup>a</sup>	P-value <sup>b</sup>
	<u>Number of events</u>			
DFS event	195	134	0.61 (0.49, 0.76)	< 0.0001
Death (OS event)	80	49	0.58 (0.40, 0.83)	0.0024
DFS event (FEVAL)	192	128	0.60 (0.48, 0.75)	< 0.0001
DFS, excluding second primary cancer	179	117	0.58 (0.46, 0.74)	< 0.0001
DFS, excluding non-breast cancer second primary cancer	182	122	0.60 (0.48, 0.76)	< 0.0001
DFS, excluding metastatic disease or who were HER2-negative	194	134	0.61 (0.49, 0.76)	< 0.0001
Distant recurrence	144	95	0.59 (0.46, 0.77)	< 0.0001

a Relative to the AC→T arm. Estimated using Cox regression stratified by number of positive nodes and hormone receptor status.

b Stratified log-rank p-value

**Table 18 Sponsor's Sensitivity Analyses for Efficacy Endpoint: AC→T versus TCH**

	AC→T (n = 1073)	TCH (n = 1075)	Hazard Ratio (95% CI) <sup>a</sup>	P-value <sup>b</sup>
	<b>Number of events</b>			
DFS event	195	145	0.67 (0.54, 0.83)	0.0003
Death (OS event)	80	56	0.66 (0.47, 0.93)	0.0182
DFS event (FEVAL)	192	142	0.67 (0.54, 0.83)	0.0003
DFS, excluding second primary cancer	179	134	0.68 (0.54, 0.85)	0.0006
DFS, excluding non-breast cancer second primary cancer	182	135	0.67 (0.54, 0.84)	0.0005
DFS, excluding metastatic disease or who were HER2-negative	194	144	0.67 (0.54, 0.83)	0.0002
Distant recurrence	144	103	0.65 (0.50, 0.84)	0.0008

DFS = disease-free survival; FEVAL = final evaluation of patients; OS = overall survival.

<sup>a</sup> Relative to the AC→T arm. Estimated using Cox regression stratified by number of positive nodes and hormone receptor status.

<sup>b</sup> Stratified log-rank p-value

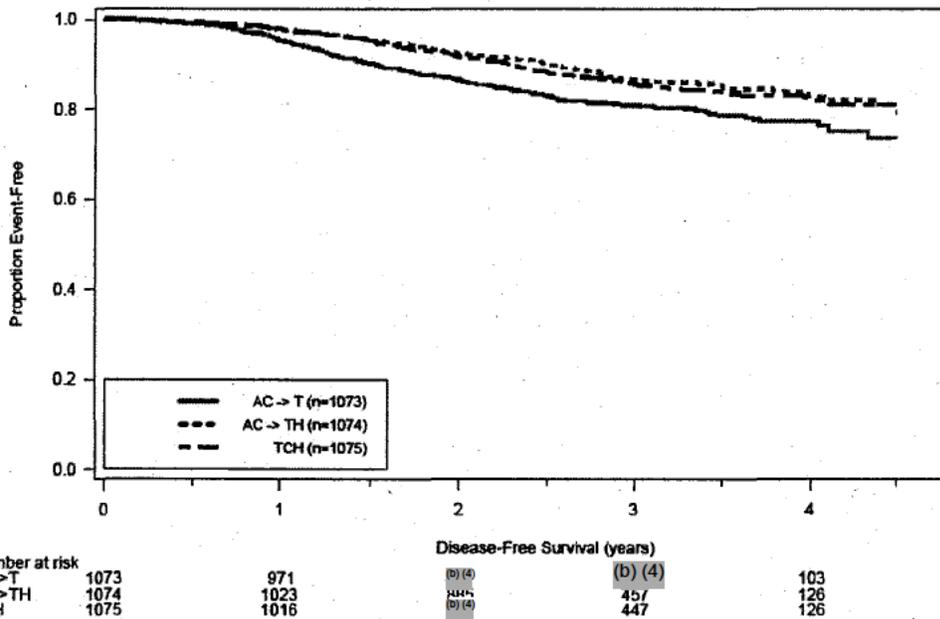


Figure 2 Disease Free Survival All Patients (Sponsor's figure)

**FDA's Analysis of time to disease recurrence:**

FDA does not agree with the protocol's definition of disease-free survival: "the interval from the date of randomization to the date of local, regional or metastatic relapse or the date of second primary cancer or death from any cause whichever occurs first". Currently there is no standard definition of disease free survival. However, FDA had accepted in previous applications the following components of this composite endpoint: local recurrence, distal recurrence, contralateral breast new invasive breast cancer and unrelated deaths. Second primary cancers are considered unrelated to the primary breast cancer and therefore cannot be accepted as an event for disease-free survival.

The FDA analysis of disease-free survival includes the following differences from the sponsor's analysis:

- 2 patients with disease recurrence (patients 30138, 30364) were not counted as events because their locoregional recurrence was not confirmed.
- Patients who had events due to second primary malignancy were not counted as events except except 8 patients (patients 32624, 31961, 30852, 31520, 33184, 31815, 31998, 31420 who had another breast primary tumor and who were counted as DFS events and patients who died who are counted as death events.

- The re-analysis results are similar to the sponsor's results that exclude non-breast secondary primary cancer (the nominal p-values are <0.0001 and 0.0006 for AC→TH versus AC→T and TCH versus AC→T, respectively).

**Table 19 FDA's Analysis of DFS events**

DFS Events	AC→T (n = 1073)	TCH (n = 1075)	AC→TH (n = 1074)
All DFS events	180 (41.4%)	134 (30.8)	121 (27.8)
Distant Recurrence	131 (72.8%)	92 (68.7)	85 (70.3)
Local/Regional	36 (20.0%)	26 (21.5)	31 (23.1)
Deaths	11 (6.1%)	10 (7.5)	5 (4.1)
Second Primary Cancers	Not counted	Not counted)	Not counted)
Hazard ratio <sup>c</sup>	NA	0.67	0.60
95% CI	NA	(0.54, 0.84)	(0.48, 0.76)
p-value <sup>d</sup>	NA	0.0006	< 0.0001

a First event modify by the reviewer.

b First event modify by the reviewer. The value is the first event for each patient, either local or regional recurrence.

c Relative to AC→T. Estimated using Cox model stratified by number of positive nodes and hormonal receptor status.

d Stratified log-rank p-value.

e The 95% C.I. for the comparison between AC→TH vs. AC→T was revised by the reviewer. The sponsor's original 95% C.I. is [0.49, 0.77].

The table bellow shows the different type of second malignancies.  
 Second Malignancies:

**Table 20 Secondary Malignancies:**

	AC→T (n=1073)	AC→TH (n=1074)	TCH (n=1075)	Total (n=3222)
ENDOMETRIUM CANCER	0	1	0	1
LEUKEMIA	3	1	0	4
OTHER	16	12	12	40
OVARIAN CANCER	1	1	1	3
PRIMARY BREAST CANCER RIGHT	3	3	1	7
PRIMARY BREAST CANCER LEFT	1	3	1	5

Forty-two patients had secondary tumors listed in the datasets as "other" malignancies. See table below:

**Table 21 Secondary malignancies listed as "other" in the datasets:**

	AC→T (n=1073)	AC→TH (n=1074)	TCH (n=1075)	Total (n=3222)
OTHER	18	12	12	42
Melanoma	3	0	1	4
colorectal	6	1	2	9
Gastric/gall bladder	1	1	0	2
Squamous/ Basal	1	1	0	2
Brain	1	0	1	2
Renal	1	0	0	1
Lung	0	2	1	3
Liposarcoma	0	1	0	1
DCIS	2	1	1	4
lymphoma	0	3	2	5
Cervix	0	1	2	3
Pancreas	1	0	1	2
Thyroid	2	1	1	4

The following patients had non invasive cancers:

- ACT30293 DCIS Right breast,
- 32861 Right DCIS
- ACTHPatient 31548 had basal cell
- 30643 DCIS Right
- TCH31185, 32148 Carcinoma in situ
- 30479 had DCIS left breast
- 31510 superficial cancer on a sigmoid polyp

Four of five patients had left primary breast cancer and were counted as a DFS event:

- ACT32624 had a primary right breast cancer, the histopathology report of the second left breast primary was invasive carcinoma.
- ACTH30852 had a primary right breast cancer, the histopathology report of the second left breast primary was invasive ductal carcinoma.
- 31520 had a primary right breast cancer, the histopathology report of the second left breast primary was invasive ductal carcinoma.
- 33184 had a primary right breast cancer, the histopathology report of the second left breast primary was invasive ductal carcinoma.

The fifth patient was not counted as a DFS event:

- TCH30942 Had a left quadrantectomy followed by adjuvant radiotherapy for a T1N0M0 breast cancer. The new primary on the left breast was DCIS.

Four at of seven patients who had right primary breast cancer were counted as a DFS event:

- ACT31961 had a primary left breast cancer, the histopathology report of the second right breast primary was invasive ductal carcinoma.
- ACTH31815 had a primary left breast cancer, the histopathology report of the second right breast primary was invasive ductal carcinoma.
- 31998 had a primary left breast cancer, the histopathology report of the second right breast primary was infiltrating tubular carcinoma.
- TCH31420 had a primary left breast cancer, the histopathology report of the second right breast primary was infiltrating ductal carcinoma.

The other three patients were not counted as a DFS event:

- ACT31517 had a primary right breast cancer treated by lumpectomy and radiation. A second right breast cancer diagnosed by stereotactic needle biopsy is not available in the CRF.
- 31594 had a primary left breast cancer, the histopathology report of the second right breast primary is not available in the CRF
- ACTH31179 had a primary left breast cancer, the histopathology report of the second right breast primary was DCIS according to the CRF.

**Table 22 Reviewer’s Summary of the first recurrent events by Event Types – Second Interim Analysis (Study BCIRG006)**

EVENT	AC→T (n= 1073)	AC→TH (n= 1074)	TCH (n= 1075)
Patients with an event	195 (18.2%)	134 (12.5%)	145 (13.5%)
Distant recurrence	141 <sup>a</sup>	89	97
Local/regional recurrence <sup>b</sup>	25	19	26
Second primary cancer	24 <sup>a</sup>	21	15
Death	5	5	7

<sup>a</sup> First event modify by the reviewer.

<sup>b</sup> First event modify by the reviewer. The value is the first event for each patient, either local or regional recurrence.

Most DFS events were distant relapses occurring as multiple liver, bone, and lung lesions. There was a reduction in the number of distant relapses in both Herceptin-containing arms relative to the AC→T arm.

Kaplan-Meier curves for DFS are shown in the figure below. There is little separation

between the curves during the first year after randomization, since < 5% of the patients had a DFS event during that time period. At 3 years, the DFS rate was estimated to be 80.9% (95% CI: 78.3%, 83.5%) in the AC→T arm and 86.7% (95% CI: 84.4, 89) in the AC→TH arm, resulting in an absolute benefit of 5.8%. At 3 years, the DFS rate was estimated to be 85.5% (95% CI: 83.2, 87.9) in the TCH arm, an absolute benefit of 4.6% compared to the AC→T arm. At 4 years, the DFS rate was estimated to be 77.3% (95% CI: 74.1, 80.5) in the AC→T arm and 82.9% in the AC→TH arm (95% CI: 79.6, 86.1), an absolute benefit of 5.6%. At 4 years, the DFS rate was estimated to be 82.0% (95% CI: 78.8, 85.1) in the TCH arm, an absolute benefit of 4.7% compared with the AC→T arm.

Pathological confirmation was mandatory for local relapses, regional relapses, and second primary malignancies. Pathological confirmation was not mandatory (but was preferred) for distant relapses.

The table below shows the patients who experienced at least one DFS event for which pathological confirmation was not obtained. For 13 of these 17 patients, multiple sites of simultaneous relapse were reported, and for all 13 of these patients, the sponsor states that protocol requirements were met for the following reasons:

- For patients who experienced a distant relapse, pathological confirmation was not required for any simultaneous local or regional relapses.
- For patients who experienced multiple simultaneous sites of relapse, pathological confirmation of any of these sites was considered to have fulfilled the protocol requirements.

Only 4 patients did not have pathological confirmation of relapse per protocol and did not fulfill protocol requirements.

- Patient 30138 treated in the TCH arm, experienced a local relapse on 20 OCT2005 in the ipsilateral breast. The diagnosis was made by mammography.
- Patient 30364 treated in the TCH arm experienced a regional relapse on 08 AUG2003 in a lymph node. The diagnosis was made by a chest CT scan.
- Patient 32336 experienced a second primary malignancy on 1 September 2005, described as pancreatic carcinoma. The patient died on (b) (6).
- Patient 32738 experienced a local relapse on 21 May 2005 in the ipsilateral breast. The patient transferred care to another physician. According to the CRF there was pathologic proof of relapse on June 9 2005.

In summary, the protocol requirements for pathological confirmation of local or regional relapse and second primary malignancy were met for 147 of 151 (97.4%) patients who's contributing

**Table 23 Patients for whom pathologic confirmation of local or regional relapse was not obtained**

Patient ID	TX ARM	Date of Event	Type of Event	Pathology Proof	Date of Pathology Proof
30001	TCH	04APR2006	Local relapse Regional relapse	NO YES	04APR2006
30084	AC->T	13JAN2004	Distant relapse Regional relapse	NO NO	
30138	TCH	20OCT2005	Local relapse	NO	
30158	TCH	02JUN2004	Distant relapse Regional relapse	NO NO	
30196	AC->T	25JAN2006	Distant relapse Local relapse Regional relapse	NO NO NO	
30314	AC->TH	11JUL2006	Distant relapse Local relapse	YES NO	29JUN2006
30364	TCH	08AUG2003	Regional relapse	NO	
30415	AC->T	17DEC2003	Local relapse Regional relapse	YES NO	17DEC2003
30420	AC->T	30DEC2002	Distant relapse Local relapse	NO NO	
30950	AC->T	01APR2003	Distant relapse Local relapse	NO NO	
31144	AC->TH	17OCT2006	Distant relapse Local relapse Regional relapse	NO YES NO	14OCT2006
31155	TCH	06OCT2005	Distant relapse Local relapse Regional relapse	NO NO NO	
31700	TCH	29JUN2005	Distant relapse Regional relapse	NO NO	
32336	AC->T	01SEP2005	Second primary malignancy	NO	
32738	AC->TH	21MAY2005	Local relapse	NO	
32797	AC->TH	02DEC2004	Distant relapse Local relapse	NO NO	
33097	AC->TH	08NOV2004	Distant relapse Local relapse	YES NO	08NOV2004

One hundred eighty five patients died in the study. Most of the deaths were due to disease progression.

**Table 24 Reviewer Table: Deaths (ITT population)**

	AC→T (n=1073)	AC→TH (n=1074)	TCH (n=1075)	Total (n=3222)
Deaths	80	49	56	185
Breast Cancer	69	44	47	160
Malignant disease other	6	1	2	9
Other	4	4	5	13
Toxicity	1	0	2	3

For 13 patients death cause was listed as" other:  
Patient 30341, 30365, 31218, and 31549 had an unknown cause of death.  
Patient 32172 died from cranial trauma, acute subdural hematoma.  
Patient 30993 committed suicide.  
Patient 30947 had complications of hypercalcemia.  
Patient 30685 died from sudden death.  
Patient 30422 septic shock.  
Patient 30390 stroke.  
Patient 30345 pneumonia.  
Patient 30248 car accident.  
Patient 30073 pulmonary consolidation, autopsy did not show evidence of relapse.

Three patients died from toxicity:  
Patients 30437 and 30611 treated in the TCH arm died from sepsis.  
Patient 32353 treated in the AC T arm died from sepsis

Nine patients died from malignant disease other than breast cancer:  
AC T:30533 (Rectal ca),  
30649 (leukemia),  
31212 (leukemia),  
32782 (leukemia),  
32336 (pancreatic)  
TCH:32938 (glioblastoma),  
33039 (pancreatic),  
32265 (gastric)  
AC TH :31395 (ovarian)

### **Efficacy Conclusions**

• Results of the protocol-specified **second efficacy interim analysis** demonstrated that Herceptin as part of either an anthracycline-based (AC→TH) or non-anthracycline-based (TCH) adjuvant treatment regimen results in a clinically meaningful and statistically significant improvement in

DFS relative to AC→T irrespective of nodal status. For the primary efficacy endpoint, DFS, the risk of a first event was reduced by 39% (95% confidence interval [CI]: 23, 51;  $p < 0.0001$ ) in the AC→TH arm relative to the AC→T arm. For the primary efficacy endpoint, DFS, the risk of a first event was reduced by 33% (95% CI: 17, 46;  $p = 0.0003$ ) in the TCH arm relative to the AC→T arm.

- The DFS benefit in all clinically important subgroups, including those defined by age, menopausal status, hormone receptor status, nodal status, tumor size, nuclear grade, and surgery or radiation therapy, was consistent with the treatment effect in the overall population.
- There was a clinically meaningful and statistically significant improvement in duration of OS. The risk of death was reduced by 42% (95% CI: 17, 60;  $p = 0.0024$ ) in the AC→TH arm relative to the AC→T arm. Similarly, the risk of death was reduced by 34% (95% CI: 7, 53;  $p = 0.0182$ ) in the TCH arm relative to the AC→T arm.

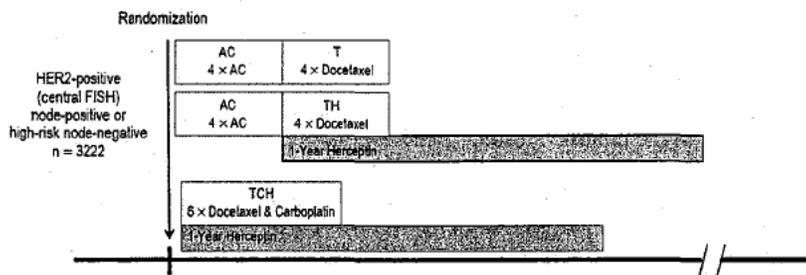
## 7 INTEGRATED REVIEW OF SAFETY

- The incidence of adverse events in Study BCIRG 006 was consistent with the known toxicity profiles of doxorubicin, cyclophosphamide, docetaxel, platinum salts, and Herceptin.
- The 3-year cumulative incidence of all symptomatic cardiac events was 0.5%, 2.36%, and 1.16% in the AC→T, AC→TH, and TCH arms, respectively.
- The 3-year cumulative incidence of symptomatic CHF (Grade 3 or 4 CLVF) events was 0.3%, 2.06%, and 0.4% in the AC→T, AC→TH, and TCH arms, respectively.
- The TCH regimen is a safe and efficacious treatment option with a reduced (relative to AC→TH) incidence of symptomatic cardiac events overall and CHF specifically.
- Decreased on-study LVEF and increased age (>50 years) were identified as key risk factors for development of a symptomatic cardiac event.
- The magnitude of the clinical benefit observed in this trial favors the use of Herceptin in this population of women, who have a high risk for disease recurrence and subsequent death from metastatic breast cancer, including women with high-risk, node-negative HER2-positive early breast cancer.

### 7.1 Methods and Findings

In this application data from 3222 subjects were randomized (1:1:1) either: adriamycin and cyclophosphamide followed by taxotere (AC→T) [control], or adriamycin and cyclophosphamide followed by Herceptin containing regimens of concurrent taxotere and Herceptin (AC→TH), or concurrent taxotere, carboplatin, and Herceptin (TCH). Herceptin containing regimens continued Herceptin post completion of adjuvant chemotherapy for a total

of 52 weeks. The safety population consisted of subjects who received at least one dose of study treatment (AC→T: n = 1050; AC→TH: n = 1068; and TCH: n = 1056).



AC=doxorubicin plus cyclophosphamide; AC→T=four cycles of AC followed by four cycles of docetaxel every 3 weeks; AC→TH=same chemotherapy regimen with the addition of 52 weeks of Herceptin starting concurrently with docetaxel and continuing as monotherapy; FISH=fluorescence in situ hybridization; T=docetaxel; TCH=docetaxel every 3 weeks concurrently with Herceptin, followed by Herceptin monotherapy.

Safety was assessed by evaluating summaries of treatment exposure, adverse events, deaths, symptomatic cardiac events, and asymptomatic declines in LVEF by MUGA scan or echocardiogram, according to treatment received. The safety database was analyzed using COSTART terms and adverse event intensity was coded using NCI CTCAE v. 2.0. The relevant data sources in the application are the clinical study report; pertinent case report forms (CRF's), periodic update safety report (PSUR), case narratives, and data listings were reviewed in order to address specific safety issues. **Error! Reference source not found. 25**, displays the raw and derived datasets reviewed for study BCIRG 006.

The adverse events datasets for BCIRG 006 were structured from four CRF's that captured the following: Clinical adverse events (non-laboratory); febrile neutropenia and infection; Cardiac toxicity monitoring from which included left ventricular ejection fraction (LVEF) and Cardiac Adverse events; and hematology and blood chemistry labs.

**Reviewer's Comment:** The case report forms for the capturing of clinical adverse events and cardiac adverse events for BCIRG 006 was structured as a pre-specified check-list.

**Table 25 Raw and Derived Datasets Reviewed for Study BCIRG 006**

Safety Review	Efficacy Review
AE (Adverse Event)	BCELAP (Breast Cancer Relapse Information)
CARDAE (Cardiac History and Adverse Event Experience)	BCSURG (Breast Cancer Surgery and Diagnosis)
CARDFU (Cardiac Event Report and Follow-up)	CANCERHX (Past or Current History of neoplasm)
CARDIAC (Cardiac Outcome)	CANCERRX ( Anti-Tumor Therapy)
CHMC (Chemistry Lab Test)	DEMOG (Demographics)
CONMED (Concomitant Therapy)	FEVAL (Final Efficacy Evaluation)
DEATH (Death Report)	HORMREC (Hormone Receptor Status)
DXSCAN (Patient Imaging Scan Information)	PATHO (Tumor Pathology Report)
ECHO (Echocardiography Report)	SPMALIG (Second Primary Malignancy)
EKGRAW (Electrocardiogram Report)	SURV (Patient Status Follow-up)
ELIG (Eligibility and Cardiac Disease Criteria)	*ABCFU (Recurrence Analysis File)
HEMC (Hematology lab Test)	*PATEFF (Patient Efficacy Analysis File)
HER2 (Her2neu Screening Information)	
HORMTX (Concomitant Hormonal Treatment)	
HOSP (Inpatient Hospitalization)	
LVEFRAW (Left Ventricular Ejection Fraction)	
TXCHEMO (Chemotherapy Administration)	
TXHER (Herceptin Administration)	
Vital (Vital Signs)	
*CAE (Cardiac Adverse Event Analysis File)	
*EKG (EKG Analysis File)	
*LVEF (LVEF Analysis File)	
*PATEXPO (Study Drug Exposure)	
*PATSAF (Patient Safety Analysis File)	

\* Derived Data

All adverse events reported during the clinical study occurred from the time the subject starts treatment with the study medication (chemotherapy or Herceptin) until 30 days after the last infusion of study treatment. Subjects were evaluated for safety the same whether they received Herceptin containing regimen or not. Safety assessments were divided into during chemotherapy and end of chemotherapy. The schedule of assessments during chemotherapy to end of chemotherapy (EOC) included: physical examinations, labs (hematology and chemistry) every three weeks, and LVEF (MUGA or Echo) all arms after cycle 4, before cycle 5, and Herceptin arms after cycle 6. End of chemotherapy follow-up assessments were also the same across groups. Physical exam every three months for 2.5 years, then every six months up to year five, and then yearly up to year ten. Routine hematology and chemistry exams every six months. Mammography and chest x-ray annually.

Left ventricular ejection fraction measurements occurred at: 3 months after EOC in the AC→T and AC→TH group, and 4.5 months after EOC in the TCH group (corresponds to

follow-up visit 1); Follow-up visit #4 measurements occurred at 12 months EOC for AC→T and AC→TH group, and 13.5 months EOC for the TCH group; and finally at follow-up visit # 10 measurements occurred at 36 months EOC for AC→T and AC→TH group, and 37.5 months EOC for the TCH group. For subjects in the Herceptin groups who developed a decrease in LVEF as a result of Herceptin that required a dose to be held or discontinued and did not have recovery of the LVEF by month 36, were to receive LVEF measurements annually until recovery or until end of follow-up, whichever comes first. Cardiac adverse events reporting occurred; Every 3 months during the first two years of the follow-up period, every 6 months years 3-5, and annually years 6-10.

Adverse events per-event were reproducible by the reviewer using the raw datasets and was comparable to the applicant's table, refer to Table 26. Summary of Per-Event Incidence of non-Laboratory Adverse Events Across Treatment Arms.

**Table 26 Summary of Per-Event Incidence of Non-laboratory Adverse Events Across Treatment Arms**

AE Grade	ACT (n=1050)	ACTH (n=1068)	TCH (n=1056)
1	8594 (17%)	9447 (18%)	8763 (17%)
2	5865 (11%)	6350 (12%)	5294 (10%)
3	1294 (3%)	1385 (3%)	1188 (2%)
4	68 (0.1%)	103 (0.2%)	80 (0.2%)

\*Total # of events across three arms =51666

Early in the review the term “unmapped” was found within the variable “Preferred Term” of the AE dataset refer to Table 27, “Per-Patient Incidence of Non-Laboratory Adverse Events Unmapped”.

Greater than 10% of all non-laboratory adverse event across all three study groups was coded as “unmapped”. The FDA asked the applicant to explain this term. The following response was provided.

“If an investigator verbatim was not classified according to the NCI-CTC version 2.0, then the value of AENCIPT (AE NCI preferred term) was set equal to “unmapped”. Similarly, if an investigator verbatim term was not mapped using the COSTART dictionary, then the value of AEPT (AE COSTART preferred term) was set equal to “unmapped.” In both of the above cases, the value of variable AEBODY (AE COSTART body system) was also set equal to “unmapped.”

The reason for terms being unmapped was two-fold: In most instances, it was because terms were not specific enough to allow for mapping. In other instances, it was because at the time of data cut-off date for the second interim analysis, not all terms had been mapped by the coding group at BCIRG.

In total, 99.4% and 99.8% of all reported non-cardiac and cardiac adverse events, respectively, were coded at the time of the data cut-off date for the second interim analysis. Thus, we believe the submitted data and associated tables provide an adequate characterization of the safety profile for patients in Study BCIRG006”.

**Table 27 Per-Patient Incidence of Non-Laboratory Adverse Events Unmapped**

COSTART	AC→T (n=1050)		AC→TH (n=1068)		TCH (n=1056)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Unmapped	11.9%	1.5%	12.1%	1.7%	12.4%	2.3%

With regard to serious adverse events (SAE), the incidence of non-cardiac events was similar across treatment groups with slightly higher incidence in the Herceptin containing groups. The incidence of SAEs for cardiac events was higher in the Herceptin containing regimens (AC→TH, TCH) compared to the control (ACT). Between Herceptin containing regimens the AC→TH group had a higher incidence of cardiac SAEs compared to the TCH group 5.0% versus 3.5%. Adverse events resulting in discontinuation of chemotherapy was highest in the control group ACT (4.2%) and lowest in the TCH group (2.1%). The incidence of adverse events resulting in discontinuation of Herceptin was similar between ACTH and TCH. Refer to Table 28 , Per-Patient Incidence of Serious Adverse Events.

**Table 28 Per-Patient Incidence of Serious Adverse Events**

	ACT (n=1050)	ACTH (n=1068)	TCH (n=1056)
Any SAE Non-Cardiac	219 (21%)	265 (25%)	256 (24%)
SAE Cardiac	20 (2%)	53 (5%)	37 (3.5%)
AE's Resulting in Death	2 (0.2%)	1 (0.1%)	4 (0.4%)
AE's Resulting in Discontinuation of Chemotherapy	44 (4.2%)	38 (3.6%)	22 (2.1%)
AE's Resulting in Discontinuation of Herceptin	—	14 (1.3%)	12 (1.1%)

The most common non-cardiac adverse events reported in the ACT versus AC→TH group occurring in  $\geq 5\%$  of subjects with a difference between groups of  $\geq 5\%$  were: diarrhea, infection, maculopapular rash, dyspepsia, rhinitis, and epistaxis.

The most common cardiac adverse events reported of any grade with  $\geq 5\%$  in the ACT versus AC→TH group with higher incidence  $\geq 2\%$  in the Herceptin containing arm were: hypertension and left heart failure.

The most common non-cardiac adverse events reported in the ACT versus TCH group occurring in  $\geq 5\%$  of subjects with a difference between groups of  $\geq 5\%$  were: diarrhea, rash, dyspepsia, abdominal pain, epistaxis, and allergic reaction.

The most common cardiac adverse events reported of any grade with  $\geq 5\%$  in the ACT versus TCH group with higher incidence  $\geq 2\%$  in the Herceptin containing arm were: hypertension and palpitations.

The most commonly reported non-cardiac SAEs for the ACT group were: vomiting, stomatitis, nausea, maculopapular rash, cellulitis and neuropathy. For the ACTH group the most commonly reported non-cardiac SAEs were fever, infection, leukopenia, vomiting, diarrhea, nausea and anemia. The TCH group reported the following most common SAEs: fever, infection, vomiting, diarrhea, and leukopenia.

The most commonly reported cardiac SAEs for the ACT group were deep thrombophlebitis, left heart failure, arrhythmia, and tachycardia. For the ACTH group, these were left heart failure, deep thrombophlebitis, myocardial ischemia, and palpitation. The TCH group reported the following most common SAEs: deep thrombophlebitis, myocardial ischemia, arrhythmia, and tachycardia.

The following adverse events resulting in death were reported:

ACT: 30572 Dyspnea, 32354 Infection

ACTH: 32173 "Unmapped"

TCH: 30437 Coma, dehydration, diarrhea, infection, kidney failure, and vomiting.

30611 Infection

30997 Leukopenia, thrombocytopenia

32172 Accidental Injury

**Deaths**

The incidence of all deaths (related and unrelated) was higher in the control arm (78 deaths or 7.4%) in the ACTH arm (48 deaths or 4.5%) and in the TCH arm (55 deaths or 5.2%). The table below shows the different death categories. Most of the patients died from breast cancer. Four patients died from treatment related toxicity: two patients in the TCH arm, 1 patient in the ACTH arm and 1 patient in the ACT arm. There were no cardiac deaths reported in the study treatment arm. Only 1 patient (30685) died from a heart attack but this patient did not receive Herceptin since she was treated in the control arm. The causality of the event is probably unrelated to study drug.

**Table 29 Overall Causes of Death: Safety population**

	ACT (n=1050)	ACTH (n=1068)	TCH (n=1056)
Overall Deaths	78	48	55
Causes			
Breast Cancer	68	43	47
Malignant Disease Other than Breast	5	1	2
Septic Toxicity Due to Chemotherapy	1	1	2
Other	4	4	4

The following table shows the causes of death reported in the “other” category.

**Table 30 Summary of Deaths in Other Category**

	PT #	Death Cause Reported
<b>ACT</b>	30248	Truck Roll Over accident
	30345	Pneumonia
	30685	Sudden Death
	30947	Complications of Hypercalcemia
<b>ACTH</b>	30365	Unknown
	30422	Septic Shock
	31218	Unknown
<b>TCH</b>	31549	Unknown
	30073	Pulmonary Consolidation
	30341	Unknown
	30390	Cerebral Stroke
	32172	Cranial Trauma with Acute Subdural Hematoma

**Other Serious Adverse Events**

Accuracy of coding using NCI-CTC term and COSTART preferred term was verified by a review of AE line listings. Events were then grouped and analyzed by treatment group and other

relevant subgroups. Data listings, CRF's, and narratives were reviewed for cases of particular interest. Finally these data were compared to legacy study data.

In BCIRG006 a serious adverse event was defined as one of the following occurring at any dose that results in: death, life threatening (the subject was at immediate risk of death at the time of the SAE), inpatient hospitalization or prolongation of existing hospitalization, is a congenital anomaly /birth defect, or an important medical event. The definition of SAE used is consistent with 21 CFR 312.32 (a). Serious adverse events were graded according to NCI CTC version 2.0.

The most commonly reported non-cardiac SAEs for the ACT group were: vomiting , stomatitis, nausea, maculopapular rash, cellulitis and neuropathy. For the ACTH group the most common SAEs were: fever, infection, leukopenia, vomiting, diarrhea, nausea and anemia. The TCH group reported the following most common SAEs: fever, infection, vomiting, diarrhea, and leukopenia.

The most commonly reported cardiac SAEs for the ACT group were deep thrombophlebitis, left heart failure, arrhythmia, and tachycardia. For the ACTH group these were left heart failure, deep thrombophlebitis, myocardial ischemia, and palpitation. The TCH group reported the following most common SAEs: deep thrombophlebitis, myocardial ischemia, arrhythmia, and tachycardia.

#### 120 -Day Safety Update

The 120-day safety update for the HERCEPTIN® (trastuzumab) sBLA, originally submitted on 28 June 2007 (STN BL 103792/5187) and 29 June 2007 (STN BL 103892/5189), includes data on patients from Study BCIRG006. Narratives for 8 patients who experienced specified types of adverse events occurring between 1 November 2006 and 31 March 2007 are included in this amendment. The specified adverse events for this update were agreed to by Genentech and the FDA during a teleconference on 18 April 2007 and consist of deaths from causes other than breast cancer; serious adverse events leading to discontinuation of chemotherapy or Herceptin; new symptomatic cardiac events per protocol definition; and updated information (independent cardiac review panel (ICRP)—confirmed or awaiting confirmation) for existing cardiac events submitted in the original sBLA.

#### ACT

4 Deaths;

- patient 31585 pulmonary embolism,
- patient 31377 unspecified second primary malignancy,
- patient 31797 acute myelogenous leukemia
- patient 33090 *update* (death from grade 4 heart failure)

#### ACTH

CHF

- (Grade 3) patient 30471 and 32515

- (Grade 4) patient 33090 lead to Death
- Patient 31758 *update* (CHF grade 3-4)

#### Death

- 30137, automobile accident (b) (6)

### Dropouts and Other Significant Adverse Events

#### 7.1.1.1 Overall profile of dropouts

Per BCIRG 006 clinical study protocol, patients in the Herceptin containing arms who drop out because of chemotherapy related toxicities may continue Herceptin until completion of 1 year or relapse or Herceptin related toxicity (including cardiac safety analysis), whichever comes first. These patients are to be followed in regular follow-up.

The criteria followed in the BCIRG 006 protocol for discontinuation and withdrawal from chemotherapy of Herceptin was: unacceptable toxicity, withdrawal of consent, relapse, second primary malignancy, death, or administration of other systemic cancer treatment other than study drug or Tamoxifen.

The majority of subjects participating in BCIRG 006 completed the chemotherapy and Herceptin portion of treatment. For chemotherapy ACT (91.2%), ACTH (92.4%), and TCH (95.6%) completed, and for the Herceptin containing arms ACTH (90.9%) and TCH (95.4%).

**Table 31 Reasons for Discontinuation of Chemotherapy Treatment for BCIRG 006**

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Began chemotherapy treatment	1050 (100.0%)	1068 (100.0%)	1054 (99.8%)
Completed chemotherapy	958 (91.2%)	987 (92.4%)	1010 (95.6%)
Discontinued chemotherapy	92 (8.8%)	81 (7.6%)	44 (4.2%)
Reason for discontinuation			
Breast cancer relapse	5 (0.5%)	4 (0.4%)	1 (0.1%)
Second primary malignancy	0 (0.0%)	1 (0.1%)	0 (0.0%)
Cardiac adverse event	4 (0.4%)	2 (0.2%)	7 (0.7%)
Non-cardiac adverse event	41 (3.9%)	40 (3.7%)	22 (2.1%)
Withdrawal of consent/refusal	40 (3.8%)	30 (2.8%)	10 (0.9%)
Death	1 (0.1%)	0 (0.0%)	2 (0.2%)
Other <sup>a</sup>	0 (0.0%)	3 (0.3%)	1 (0.1%)

**Table 32 Reasons for Discontinuation of Herceptin Treatment for BCIRG 006**

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Started Herceptin	0 (0.0%)	1043 (97.7%)	1056 (100.0%)
Herceptin therapy completed	NA	971 (90.9%)	1007 (95.4%)
Herceptin therapy discontinued	NA	72 (6.7%)	49 (4.6%)
Reason for discontinuation			
Breast cancer relapse	NA	1 (0.1%)	1 (0.1%)
Second primary malignancy	NA	1 (0.1%)	0 (0.0%)
Adverse experience	NA	6 (0.6%)	13 (1.2%)
Cardiac-related event	NA	1 (0.1%)	5 (0.5%)
Non-cardiac-related event	NA	5 (0.5%)	8 (0.8%)
Consent withdrawn	NA	12 (1.1%)	9 (0.9%)
Death	NA	0 (0.0%)	2 (0.2%)
Required not permitted therapy	NA	0 (0.0%)	0 (0.0%)
Other deviation from protocol	NA	0 (0.0%)	0 (0.0%)
Lost to follow-up	NA	0 (0.0%)	0 (0.0%)
Herceptin toxicity	NA	35 (3.3%)	13 (1.2%)
Patient refusal to continue Herceptin	NA	11 (1.0%)	8 (0.8%)
Other	NA	3 (0.3%)	3 (0.3%)
Missing	NA	3 (0.3%)	0 (0.0%)

During the chemotherapy portion of BCIRG 006, the most common reason for discontinuation of chemotherapy across treatment arms was due to non-cardiac adverse events: ACT (3.9%), ACTH (3.7%), and TCH (2.1%). The second most common reason for discontinuation of chemotherapy was “withdrawal of consent/refusal”: ACT (3.8%), ACTH 2.8%), and TCH (0.9%), Table 31 , Reasons for Discontinuation of Chemotherapy Treatment for BCIRG 006.

During the Herceptin portion of BCIRG 006, the most common reason for discontinuation of Herceptin for the Herceptin containing treatment arms was “Herceptin toxicity”: ACTH (3.3%) , TCH (1.2%). The second most common reason for discontinuation of Herceptin was “consent withdrawn”, Table 32 , Reasons for Discontinuation of Herceptin Treatment for BCIRG 006.

7.1.1.2 Adverse events associated with dropouts

The datasets containing reasons for discontinuation of chemotherapy or Herceptin were located in the TXCHEMO.xpt and TXHER.xpt files. The variables listing reasons for discontinuation categorized adverse events under “adverse experience and “Herceptin toxicity”. Individual adverse experiences and toxicity from Herceptin were not listed. During chemotherapy non-cardiac adverse events was the most common reason for discontinuation with the TCH arm having the least reported. Herceptin toxicity was higher in the ACTH arm (3.3%) versus TCH (1.2%).

7.1.1.3 Other significant adverse events

Symptomatic Cardiac Adverse Event

All adverse experiences related to cardiac toxicities were graded based on NCI-CTC version 2.0. A clinically significant cardiac event was defined in BCIRG 006 as the occurrence of one or more of the following:

- cardiac death (all non-septic deaths due to study treatment will be reviewed)
- grade 3 or 4 cardiac left ventricular ejection fraction (congestive heart failure)
- grade 3 or 4 arrhythmias
- grade 3 or 4 cardiac ischemia / infarction.

The symptomatic grade 3 or 4 cardiac events were confirmed by the Independent Cardiac Review Panel (ICRP).

**Table 33 The Applicant’s Symptomatic Cardiac Events per ICRP Occurring at Any Time during BCIRG 006. (Safety Population)**

Event Type	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
CHF (Grade 3/4 CLVF)	3 (0.3%)	20 (1.9%)	4 (0.4%)
Grade 3/4 cardiac ischemia/infarction	0 (0.0%)	2 (0.2%)	2 (0.2%)
Grade 3/4 arrhythmia	3 (0.3%)	2 (0.2%)	6 (0.6%)
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any symptomatic cardiac event <sup>a</sup>	6 (0.6%)	23 (2.2%)	12 (1.1%)

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

<sup>a</sup> A patient could be included in more than one event type category; therefore, the “any symptomatic cardiac event row” is less the sum of number of events in a given column.

**Table 34 Reviewer's Incidence of Cardiac Events**

	<b>ACT (n=1050)</b>	<b>ACTH (n=1068)</b>	<b>TCH (n=1056)</b>
<b>CHF</b>	4 (0.4%)	20 (2%)	4 (0.4%)
<b>ICRP</b>	2 (0.2%)	8 (0.8%)	4 (0.4%)
<b>Arrythmia</b>	5 (0.5%)	8 (0.8%)	5 (0.5%)
ICRP Grade 3	3 (0.3%)	0 (0%)	1 (0.1%)
ICRP Grade 4	0 (0%)	0 (0%)	0 (0%)
<b>Cardiac Ischemia/Infarction Grade ¾</b>	0 (0%)	3 (0.3%)	2 (0.2%)
ICRP	----	0	1
<b>Cardiac Death</b>	0 (0%)	0 (0%)	0 (0%)

The following narratives support the data for NCI CTC grades 3-5 cardiac ischemia/infarction presented in Table 34, Reviewer's Incidence of Cardiac Events.

Patient No.: 30529

Demographics: 61-year-old female

Treatment Arm: AC→TH

Event: Cardiac ischemia

The patient's concurrent medical conditions included diabetes mellitus treated with glipazide. On 29 April 2002, a baseline echocardiogram revealed an LVEF of 64%, a baseline ECG was within normal limits.

Chemotherapy was completed per the protocol. The last cycle of docetaxel was administered on 16 October 2002. An echocardiogram performed on 5 November 2002 (Cycle 8) revealed an LVEF of 46%. Monotherapy with Herceptin was delayed. An echocardiogram performed on 3 December 2002 (FU1), revealed an LVEF of 57%. On 4 December 2002 (FU1), the patient started Herceptin monotherapy (6 mg/kg) every 3 weeks. The last dose of Herceptin was administered on 23 July 2003 (FU3). An echocardiogram performed on 6 November 2003 (FU4) revealed an LVEF of 68%.

The patient was hospitalized on (b) (6) (FU6) with a serious event of Grade 4 myocardial ischemia. An ECG performed on (b) (6) revealed significant abnormalities. An echocardiogram performed on (b) (6) revealed an LVEF of 53%. Further information on the presenting symptoms, course of hospitalization, and treatment was not reported. The investigator assessed chemotherapy and Herceptin as the most likely cause of the patient's myocardial ischemia. The patient's case was reviewed on an unreported date by an independent cardiac review panel, whose review was inconclusive.

Patient No.: 31978

Demographics: 54-year-old female

Treatment Arm: AC→TH

Event: Cardiac ischemia

A baseline ECG performed on 23 April 2003 was within normal limits. On 21 May 2003, a baseline echocardiogram revealed an LVEF of 80%. The patient received Cycles 1-4 of AC between 23 May 2003 and 28 July 2003. She then received Cycles 5-8 of Herceptin between 18 August 2003 and 3 November 2003 and Cycles 5-8 of docetaxel between 19 August 2003 and 21 October 2003. On 12 November (FU1) 2003, the patient started Herceptin monotherapy (6 mg/kg) every 3 weeks.

On 27 January 2004 (FU1), the patient reported for radiation treatment; an ECG revealed a singular ventricular extrasystole. On 28 January 2004, the patient had an irregular heartbeat during radiation. The patient's vital signs were normal the next day, and she was started on metoprolol in addition to her enalapril. She was hospitalized on (b) (6) with chest pain and hypertension (160/90 mmHg). An ECG revealed a singular ventricular and supraventricular extrasystole with lateral wall ischemia and tachycardia (100 bpm). She was hospitalized on (b) (6) with chest pain and hypertension (160/90 mmHg). An ECG revealed a singular ventricular and supraventricular extrasystole with lateral wall ischemia and tachycardia (100 bpm). The investigator assessed this episode as unrelated to Herceptin; treatment was continued, and the last dose of Herceptin was administered on 9 August 2004 (FU3). The patient's case was reviewed on an unreported date by an independent cardiac review panel, who confirmed the diagnosis of myocardial ischemia.

Treatment Arm: AC→TH

Event: Cardiac ischemia

A baseline ECG performed on 6 August 2003 was within normal limits. On 27 August 2003, a baseline echocardiogram revealed an LVEF of 61%. The patient received Cycles 1-4 of AC between 22 September 2003 and 24 November 2003. She then received Cycles 5-8 of Herceptin between 15 December 2003 and 2 March 2004 and Cycles 5-8 of docetaxel between 16 December 2003 and 18 February 2004. Docetaxel was reduced during Cycle 6 because of non-hematologic toxicity.

During Cycle 5, the patient also experienced palpitations and angina pectoris. An echocardiogram obtained on 5 January 2004 (Cycle 5) showed an LVEF of 59%. An echocardiogram performed on 8 March 2004 (Cycle 8) revealed an LVEF of 79%. Chemotherapy was completed per the protocol. The last cycle of docetaxel was administered on 18 February 2004. On 10 March 2004 (FU1), the patient started Herceptin monotherapy (6 mg/kg) every 3 weeks.

On (b) (6), the patient was admitted to the hospital with retrosternal chest heaviness radiating to the left arm and jaw, with associated diaphoresis and dyspnea. A MUGA scan revealed an LVEF of 55% with no evidence of left ventricular dysfunction. The first ECG showed normal sinus rhythm with some early repolarization; another ECG about 6 hours later revealed ST elevation consistent with an acute infarction. Cardiac catheterization showed 70%-75% occlusion in the left anterior descending coronary artery with flow limitation. Angioplasty

was successfully performed, with stent insertion into the proximal LAD; intracoronary nitroglycerin and intravenous bivalirudin were also administered. She was reported to have experienced a serious event of Grade 4 myocardial ischemia, which improved to Grade 3 in intensity. The myocardial ischemia was reported resolved on (b) (6). The last dose of Herceptin was administered on 30 March 2004, and therapy was discontinued because of concerns over Herceptin cardiotoxicity.

The patient's case was reviewed on an unreported date by an independent cardiac review panel, who diagnosed the patient with Grade 3 myocardial ischemia/infarction.

Patient No.: 30185

Demographics: 43-year-old female

Treatment Arm: TCH

Event: Cardiac ischemia

On 14 November 2001, a baseline MUGA scan revealed an LVEF of 69%. During Cycle 2, the patient experienced chest pain radiating to the left arm that developed into ventricular fibrillation cardiac arrest requiring resuscitation. The patient suffered a 2-minute seizure, anoxic brain injury, and epistaxis. An ECG confirmed an acute anterior myocardial infarction. Chest pain radiating to the left arm that developed into ventricular fibrillation cardiac arrest requiring resuscitation. The patient suffered a 2-minute seizure, anoxic brain injury, and epistaxis. An ECG confirmed an acute anterior myocardial infarction. An echocardiogram performed (b) (6) revealed an LVEF of 40% with regional wall motion abnormalities and mild mitral and tricuspid regurgitation.

The last cycles of docetaxel/cisplatin were administered on 9 January 2002, and the last dose of Herceptin was administered on (b) (6) (Cycle 2). Chemotherapy and Herceptin were discontinued because of the patient's myocardial ischemia.

The patient's case was reviewed on an unreported date by an independent cardiac review panel, which agreed with the diagnosis of acute myocardial infarction but disagreed with the grade of the adverse event. The panel assessed the event as a Grade 4 acute myocardial infarction.

Patient No.: 31944

Demographics: 55-year-old female

Treatment Arm: TCH

Event: Cardiac ischemia

The patient's medical history included surgical carpal tunnel release (2001), and her concurrent medical conditions included Grade 3 hypertension treated with fosinopril, Type 2 diabetes treated with insulin, a Grade 3 cellulitis, and left hip osteoarthritis and sciatica. On 30 April 2003, a baseline MUGA scan revealed an LVEF of 59% and a baseline ECG revealed non-significant abnormalities. MUGA scans performed on 8 August 2003 (Cycle 4) and 6 September 2003 (Cycle 6) revealed LVEFs of 69% and 49%, respectively. On 19 September 2003 (FU1A), the patient started Herceptin (6 mg/kg) every 3 weeks. The patient discontinued tamoxifen because of an unspecified adverse event.

On (b) (6) (FU2), the patient was hospitalized with chest heaviness, bilateral arm discomfort, and a general feeling of malaise. A chest X-ray performed on (b) (6) showed no cardiomegaly or pulmonary consolidation, and an ECG revealed a regular rate (91 bpm), a premature complex of uncertain mechanism, and abnormal T waves in the inferior leads suggestive of ischemia. A coronary angiogram revealed an occlusion in the mid-left circumflex coronary artery, long diffuse disease proximal and severe disease in the mid-right coronary artery, moderate disease in the left anterior diagonal, a larger posteroinferior scar, left ventricular impairment, and inferior and posterior akinesis. These findings were suggestive of an acute myocardial infarction.

The investigator assessed this episode as unrelated to Herceptin. However, further Herceptin therapy was discontinued because of the patient's significant cardiac disease. The last dose of Herceptin was administered on 5 March 2004 (FU2). The patient's case was reviewed on an unreported date by an independent cardiac review panel, who confirmed the diagnosis of inferior myocardial infarction.

The clinical reviewer found an additional case with grade 3 myocardial ischemia/infarction, in the AC→TH group, although reported cause of death was septic shock.

Patient No.: 30422

Demographics: 68-year-old female

Treatment Arm: AC→TH

Events: Cardiac failure left and death resulting from septic shock This patient was diagnosed with a 1.70-cm, ER-negative/PR-negative, poorly differentiated, infiltrating ductal carcinoma of the left breast and underwent a mastectomy and axillary node dissection (eight of 12 axillary nodes were positive) on (b) (6). The central laboratory confirmed HER2-positive status by FISH assay. On 15 March 2002, a baseline echocardiogram revealed an LVEF of 67%, and a baseline ECG was within normal limits. A baseline physical examination performed 26 March 2002 was normal.

The patient received Cycles 1-4 of AC between 26 March 2002 and 29 May 2002. She then received Cycles 5-8 with Herceptin between 19 June 2002 and 11 September 2002 and Cycles 5-8 of docetaxel between 20 June 2002 and 21 August 2002. During Cycles 1-4, the patient experienced non-serious events of alopecia, stomatitis/pharyngitis, fatigue, dysgeusia, nausea, and dry skin. An echocardiogram performed 26 June 2002 revealed an LVEF of 68%. During Cycles 5-8, the patient experienced non-serious events of alopecia, diarrhea, stomatitis/pharyngitis, fatigue, constipation, rash/desquamation, rhinorrhea, dizziness, nausea, dry skin, vomiting, nail changes, pruritus, conjunctivitis, and tearing. Echocardiograms performed 31 July 2002 and 11 September 2002 revealed LVEF values of 50% and 61%, respectively. Chemotherapy was completed per the protocol. The patient's last cycle of docetaxel (Cycle 8) was administered on 21 August 2002. At the end of Cycle 8, on 11 September 2002, the patient started Herceptin monotherapy (6 mg/kg) every 3 weeks.

During FU1, on 3 December 2002, an echocardiogram revealed an LVEF of 51%. On (b) (6) the patient presented with dyspnea, tachycardia, and left arm pain. A chest X-

ray revealed cardiomegaly and pulmonary edema; LVEF by echocardiogram was 20%. Serum troponin was elevated at 1.34 ng/mL (normal, 0.03 ng/mL), and the patient was hypoxemic (pO<sub>2</sub>, 70 mmHg). The patient was treated with furosemide, spironolactone, captopril, enoxaparin, and digoxin. Coronary arteriography performed on (b) (6) revealed no coronary artery deficits. The patient's clinical symptoms had resolved as (b) (6) (FU2); she had a normal ECG and serum troponin level of 0.8 ng/mL. An echocardiogram revealed an LVEF of 50%. She was discharged on spironolactone.

The patient's last dose of Herceptin was administered on 13 November 2002; additional therapy with Herceptin was discontinued because of the patient's decline in cardiac status. Her case was reviewed on an unreported date by an independent cardiac review panel that agreed with the diagnosis of congestive heart failure and also noted a diagnosis of Grade 3 myocardial ischemia/infarction.

As of January 2003, the patient had ongoing asthenia, dyspnea, and chest pressure. An echocardiogram obtained on 8 January 2003 (FU2) revealed an LVEF of 48% with moderate systolic and diastolic dysfunction. Echocardiograms from 30 January 2003, 4 February 2003, and 12 March 2003 (FU2) revealed LVEF values of 30% (with noted severe diastolic and systolic dysfunction), 38%, and 28%, respectively. An echocardiogram performed 30 June 2003 (FU3) revealed an LVEF of 31%; on 16 October 2003 (FU4), LVEF was 44% by echocardiogram. During FU5, the patient was reported to have experienced serious Grade 3 NCI CTC left ventricular dysfunction (mapped to COSTART as "cardiac failure left"), for which she was hospitalized on unreported dates. The event had resolved to Grade 1 left-sided heart failure as of 17 December 2003; an echocardiogram obtained on that date revealed an LVEF of 59%.

Echocardiograms from 8 March 2004 (FU6) and 10 June 2004 (FU7) revealed LVEF values of 58% and 39%, respectively. The patient died of septic shock on (b) (6) no additional details were reported. No autopsy was performed.

**Reviewer Comment's:** The information presented in Table 34 , Reviewer's Incidence of Cardiac Events, cardiac ischemia/infarction grade ¾ will be added to the current Herceptin label..

Congestive heart failure (CHF) was summarized according to three criteria: .

- CHF with signs/symptoms in association with an absolute decrease of LVEF  $\geq$  15% from baseline and below LLN (lower limit of normal) .
- CHF with signs/symptoms in association with an absolute decrease of LVEF  $\geq$  10% from baseline and below LLN.
- CHF with signs/symptoms from a clinical standpoint, regardless of LVEF decline.

Asymptomatic LVEF decline according to the BCIRG 006 protocol, left ventricular ejection fraction was measured at baseline and 3, 4.5, 6, 9, 18 and 42 months after randomization. This schedule was adjusted for each patient according to the actual number of cycles of chemotherapy received. A clinically significant asymptomatic decline in LVEF was defined as an absolute

reduction in LVEF of 15% or more from baseline and a LVEF value of less than the lower limit of normal.

For the primary analysis of the asymptomatic LVEF decline, any LVEF measured with a technique different than the one used at baseline was excluded. An additional analysis was performed based on an absolute decline of 10% or more from baseline in LVEF that is also below 50%.

According to the protocol, a new observed asymptomatic cardiac abnormality would be confirmed by repeat LVEF within 1 month. The confirmation was calculated using a 28 day window for the second evaluation.

Time to the first LVEF decline (defined as the date of randomization to the date of the first LVEF that meets the definition of asymptomatic LVEF decline -- 10% and 15% decline definitions) analyses would be performed. Patients who have not experienced such a decline would be censored at their last LVEF examination.

For time to first clinically significant asymptomatic cardiac event, data from patients not experiencing an event were censored at the earliest date of either the last LVEF assessment or the data cut-off date (1 November 2006). Data from patients with no post-randomization follow-up were censored on Day 1.

**Table 35 Reviewer's Summary of Asymptomatic LVEF Change or Post Baseline Values during BCIRG 006 (Safety Population)**

	AC→T (n = 1050)	AC→TH (n = 1068)	TCH (n = 1056)
Post-baseline LVEF <50%	96(9.14%)	181(16.95%)	90(8.52%)
LVEF < LLN* and ≥15% decrease from baseline	43(4.10%)	109(10.21%)	36(3.41%)
LVEF <50% and ≥10% decrease from baseline	67(6.38%)	141(13.20%)	62(5.87%)
LVEF <50% and ≥16% decrease from baseline	34(3.24%)	104(9.74%)	35(3.31%)
LVEF absolute decrease of ≥10%, <20%	352(33.52%)	470(44.01%)	360(34.09%)
LVEF absolute decrease ≥20%	56(5.33%)	141(13.20%)	66(6.25%)

\*LLN = lower limit of normal.

The summary on all LVEF events are based on events after time of randomization. Based on table 59 of the sponsor's clinical study report, AC→ TH arm shows consistently higher median LVEF drop from 4.5 months up to 42 months (at months 42, the median LVEF changes from baseline are -2.5%, 0% and -1 % for AC→TH, TCH and ACT, respectively). The longer term

effect (longer than 42 months) of the Herceptin + chemotherapy on the change in LVEF can not be determined from the current data.

In the adverse reaction section of the labeling, the sponsor provided a cumulative incidence plots of time to first LVEF decline of  $\geq 10\%$  from baseline and to below 50% with death as the competing events for 2-year periods (based on EL Korn, FJ Dorey. Applications of crude incidence curves. Statistics in Medicine 1992, 11, 813-829). (b) (4)

[Redacted]

The plots show that the cumulative incidence of the significant LVEF drop in AC → TH arm continues to be higher than the other two arms through 42 months., refer to Figure 3.

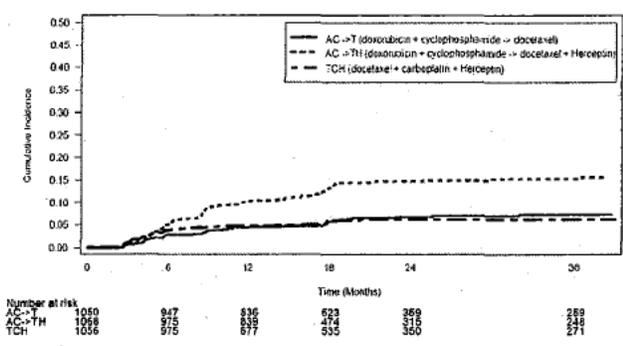


Figure 3 Cumulative Incidence of Time to First LVEF

(b) (4)

Reviewer Comment's: The above figure will be included in the Herceptin label for BCIRG 006.

Deep thrombophlebitis events were reported across all treatment groups in BCIRG 006. The Herceptin containing regimens had a higher incidence of events with particularly highest incidence in the TCH arm (3.7%) versus ACTH (2.5%) and lowest incidence in the control arm ACT (2.2%). Refer to Table 36, Reviewer's Incidence of Deep Thromophlebitis Events.

**Table 36 Reviewer's Incidence of Deep Thromophlebitis Events**

Safety Population	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Deep Thrombophlebitis			
All	23 (2.2%)	27 (2.5%)	39 (3.7%)
Grade 3/4	19 (1.8%)	25 (2.3%)	31 (2.9%)
SAE	7 (0.7%)	11 (1.0%)	14 (1.3%)

**Reviewer Comment's:** The current Herceptin label will contain additional information regarding thrombosis/embolism from BCIRG 006 study (b) (4)

### Common Adverse Events

#### 7.1.1.4 Eliciting adverse events data in the development program

According to the BCIRG 006 protocol, the term adverse event refers to any sign, symptom, illness that appears or worsens in a patient during the period of observation in the clinical study and that may impair the well-being of the patient. The term covers laboratory findings or results of other diagnostic procedures that are considered relevant (e.g., that required unscheduled diagnostic procedures or treatment measures, or resulted in patient withdrawal from the study). All adverse events, including those potentially related to chemotherapy, Herceptin, radiotherapy, and hormonal therapy, were classified and graded according to the NCI-CTC, v2.0. 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 (FDA 1989) (1 = mild, 2 = moderate, 3 = severe, and 4 = life-threatening).

During chemotherapy, evaluation of cardiac and non-cardiac adverse events was to be conducted at each cycle. A final evaluation of cardiac and non-cardiac adverse events was conducted at the end of chemotherapy (EOC) visit, defined as 21 days following the last infusion of chemotherapy. The first follow-up visit was scheduled 3 months following the EOC visit in the AC.T and AC.TH arms and 4.5 months following the EOC visit in the TCH arm. Patients in the TCH arm underwent an additional follow-up visit 6 weeks after the EOC visit to coincide with the EOC visit for the ACT and AC→TH arms. During the first two years of the follow-up period, cardiac adverse event reporting was to be conducted every 3 months. During Years 3–5 of the follow-up period, cardiac adverse event reporting was to be conducted every 6 months. During Years 6–10 of the follow-up period, cardiac adverse event reporting was to be conducted annually. Further evaluation of non-cardiac adverse events was limited to ongoing events deemed possibly or probably related to study treatment at the EOC assessment. The assessment schedule was identical for all three treatment arms throughout the follow-up period. For additional details, see Section 6.1.3.

The adverse events datasets for BCIRG 006 were structured from four CRF's that captured the following: Clinical adverse events (non-laboratory); febrile neutropenia and infection; Cardiac toxicity monitoring from which included left ventricular ejection fraction (LVEF) and Cardiac adverse events; and hematology and blood chemistry labs. All adverse events reported during the clinical study occurred from the time the subject starts treatment with the study medication (chemotherapy or Herceptin) until 30 days after the last infusion of study treatment arm and maximum AE grade. This resulted in a dataset containing one subject per row per AE by maximum grade. The remaining dataset contained only those subjects who experienced at least one AE. These data were then tabulated for the total number of subjects, AE events by grade, and incidence rates per arm. Refer to section 7.1, for overview of AE by intensity and overall incidence of adverse events.

#### 7.1.1.5 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using COSTART terms and NIC-CTC terms. The variables within the datasets had paralleled terms to one another. The safety database of study BCIRG 006, had a total of 3222 subjects broken down into the following; ACT (n=1050), AC→TH (n=1068), and TCH (n=1056). To determine the number of subjects who had an adverse event (AE) at any time during the study, the AE.xpt dataset was grouped patient identifier, COSTART preferred term.

#### 7.1.1.6 Incidence of common adverse events

The most common non-cardiac adverse events reported in  $\geq 5\%$  of subjects with a higher between group difference of  $\geq 5\%$  in the Herceptin-containing (ACT versus AC→TH) group were: diarrhea, infection, maculopapular rash, dyspepsia, rhinitis, and epistaxis.

The most common cardiac adverse events reported in  $\geq 5\%$  of subjects, with a difference of  $\geq 2\%$  in adverse events between ACT and AC→TH were hypertension and left heart failure.

The most common non-cardiac adverse events reported in  $\geq 5\%$  of subjects with a higher between group difference of  $\geq 5\%$  in the Herceptin-containing (ACT versus TCH) group were: diarrhea, rash, dyspepsia, abdominal pain, epistaxis, and allergic reaction.

The most common cardiac adverse events reported of any grade in  $\geq 5\%$  of subjects with a difference of  $\geq 2\%$  in adverse events between ACT and AC→TH were; hypertension and palpitations.

#### 7.1.1.7 Common adverse event tables

##### ACT versus AC→TH

**Table 37 Per Patient Incidence of ACT vs. AC→TH Adverse Events occurring in ≥ 5% of Patients with a Between Group difference in Herceptin Arm ≥ 5%**

COSTART Adverse Event	ACT (n=1050)				ACTH (n=1068)			
	All Grades	%	Grade 3-4	%	All Grades	%	Grade 3-4	%
DIARRHEA	453	43.1	32	3.0	547	51.2	61	5.7
INFECTION	399	38.0	243	23.1	469	43.9	266	24.9
MACULOPAPULAR RASH	298	28.4	18	1.7	365	34.2	14	1.3
DYSPEPSIA	209	19.9	5	0.5	269	25.2	3	0.3
RHINITIS	193	18.4	2	0.2	266	24.9	1	0.1
EPISTAXIS	64	6.1	0	0.0	139	13.0	0	0.0

**Table 38 Table Per Patients Incidence of ACT vs. ACTH Non-Cardiac Adverse Events Occurring in  $\geq 5\%$  of Patients with Between Group difference in Herceptin Arm  $\geq 2\%$**

COSTART Adverse Event	ACT (n=1050)				ACTH (N=1068)			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
MYALGIA	557	53.0	55	5.2	597	55.9	56	5.2
DIARRHEA	453	43.1	32	3.0	547	51.2	61	5.7
ARTHRALGIA	454	43.2	35	3.3	500	46.8	35	3.3
INFECTION	399	38.0	243	23.1	469	43.9	266	24.9
PERIPHERAL EDEMA	362	34.5	4	0.4	397	37.2	4	0.4
MACULOPAPULAR RASH	298	28.4	18	1.7	365	34.2	14	1.3
INSOMNIA	248	23.6	3	0.3	283	26.5	4	0.4
FEVER	235	22.4	103	9.8	270	25.3	122	11.4
DYSPEPSIA	209	19.9	5	0.5	269	25.2	3	0.3
DYSPNEA	235	22.4	12	1.1	267	25.0	30	2.8
RHINITIS	193	18.4	2	0.2	266	24.9	1	0.1
LACRIMATION DISORDER	217	20.7	0	0.0	256	24.0	3	0.3
WEIGHT GAIN	210	20.0	9	0.9	249	23.3	6	0.6
BONE PAIN	197	18.8	18	1.7	229	21.4	9	0.8
ABDOMINAL PAIN	187	17.8	8	0.8	215	20.1	9	0.8
DIZZINESS	113	10.8	6	0.6	151	14.1	7	0.7
ALLERGIC REACTION	106	10.1	12	1.1	139	13.0	19	1.8
EPISTAXIS	64	6.1	0	0.0	139	13.0	0	0.0
BACK PAIN	86	8.2	4	0.4	137	12.8	12	1.1
CHILLS	58	5.5	0	0.0	87	8.1	1	0.1

**Table 39 Per Patient Incidence of ACT vs. ACTH of Cardiac Adverse Events with a Difference of  $\geq 5\%$  in the Herceptin Arm**

COSTART Adverse Event	ACT (n=1050)				ACTH (n=1068)			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
HYPERTENSION	194	18.5	162	15.4	221	20.7	174	16.3
LEFT HEART FAILURE	45	4.3	6	0.6	106	9.9	22	2.1

**Table 40 Per Patient Incidence of All Cardiac Events for ACT Vs. ACTH**

COSTART Adverse Event	ACT (n=1050)				ACTH (n=1068)			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
HYPERTENSION	194	18.5	162	15.4	221	20.7	174	16.3
LEFT HEART FAILURE	45	4.3	6	0.6	106	9.9	22	2.1
PALPITATION	79	7.5	0	0.0	100	9.4	0	0.0
TACHYCARDIA	56	5.3	5	0.5	63	5.9	1	0.1
CARDIOVASCULAR DISORDER	34	3.2	1	0.1	55	5.1	0	0.0
**UNMAPPED**	23	2.2	3	0.3	38	3.6	2	0.2
HYPOTENSION	23	2.2	1	0.1	36	3.4	2	0.2
DEEP THROMBOPHLEBITIS	23	2.2	19	1.8	27	2.5	25	2.3
PHLEBITIS	15	1.4	0	0.0	25	2.3	0	0.0
CARDIOMEGALY	7	0.7	0	0.0	22	2.1	0	0.0
PERICARDIAL EFFUSION	17	1.6	0	0.0	21	2.0	0	0.0
CHEST PAIN	9	0.9	0	0.0	18	1.7	1	0.1
ARRHYTHMIA	18	1.7	5	0.5	17	1.6	4	0.4
SINUS BRADYCARDIA	8	0.8	0	0.0	15	1.4	0	0.0
MYOCARDIAL ISCHEMIA	7	0.7	1	0.1	13	1.2	4	0.4
DYSPNEA	4	0.4	1	0.1	11	1.0	0	0.0
HEART FAILURE	6	0.6	2	0.2	8	0.7	0	0.0
VENTRICULAR ARRHYTHMIA	4	0.4	0	0.0	6	0.6	1	0.1
CARDIOMYOPATHY	0	0.0	0	0.0	5	0.5	1	0.1
SYNCOPE	1	0.1	0	0.0	4	0.4	2	0.2
BUNDLE BRANCH BLOCK	5	0.5	0	0.0	3	0.3	0	0.0
EDEMA	0	0.0	0	0.0	3	0.3	0	0.0
PERIPHERAL EDEMA	0	0.0	0	0.0	3	0.3	0	0.0
SUPRAVENTRICULAR TACHYCARDIA	3	0.3	0	0.0	3	0.3	1	0.1
CORONARY ARTERY DISORDER	1	0.1	1	0.1	2	0.2	0	0.0
ELECTROCARDIOGRAM ABNORMAL	2	0.2	0	0.0	2	0.2	0	0.0
EXTRASYSTOLES	3	0.3	0	0.0	2	0.2	0	0.0
SUPRAVENTRICULAR EXTRASYSTOLES	2	0.2	0	0.0	2	0.2	0	0.0
VASCULAR ANOMALY	0	0.0	0	0.0	2	0.2	0	0.0
VASCULAR DISORDER	0	0.0	0	0.0	2	0.2	0	0.0
VENTRICULAR EXTRASYSTOLES	3	0.3	1	0.1	2	0.2	0	0.0
ANGINA PECTORIS	2	0.2	0	0.0	1	0.1	0	0.0
ATRIAL FIBRILLATION	1	0.1	0	0.0	1	0.1	1	0.1
AV BLOCK	0	0.0	0	0.0	1	0.1	0	0.0
CAROTID OCCLUSION	0	0.0	0	0.0	1	0.1	1	0.1

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COSTART Adverse Event	ACT (n=1050)				ACTH (n=1068)			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
ENDOCARDITIS	0	0.0	0	0.0	1	0.1	1	0.1

EPISTAXIS	0	0.0	0	0.0	1	0.1	0	0.0
HEART MALFORMATION	1	0.1	1	0.1	1	0.1	0	0.0
HYPERKINESIA	1	0.1	0	0.0	1	0.1	0	0.0
HYPERTONIA	0	0.0	0	0.0	1	0.1	0	0.0
HYPOKINESIA	0	0.0	0	0.0	1	0.1	0	0.0
PAIN	0	0.0	0	0.0	1	0.1	0	0.0
PERICARDITIS	0	0.0	0	0.0	1	0.1	0	0.0
T INVERTED	0	0.0	0	0.0	1	0.1	0	0.0
	1	0.1	1	0.1	0	0.0	0	0.0
AORTIC STENOSIS	1	0.1	0	0.0	0	0.0	0	0.0
ARTERIOSCLEROSIS	1	0.1	0	0.0	0	0.0	0	0.0
BIGEMINY	1	0.1	0	0.0	0	0.0	0	0.0
BRADYCARDIA	0	0.0	0	0.0	0	0.0	0	0.0
CEREBRAL ISCHEMIA	0	0.0	0	0.0	0	0.0	0	0.0
CHEST PAIN SUBSTERNAL	1	0.1	0	0.0	0	0.0	0	0.0
CONGESTIVE HEART FAILURE	1	0.1	0	0.0	0	0.0	0	0.0
DYSPEPSIA	0	0.0	0	0.0	0	0.0	0	0.0
DYSTONIA	0	0.0	0	0.0	0	0.0	0	0.0
FACE EDEMA	0	0.0	0	0.0	0	0.0	0	0.0
GLAUCOMA	0	0.0	0	0.0	0	0.0	0	0.0
HEART ARREST	0	0.0	0	0.0	0	0.0	0	0.0
HEART BLOCK	0	0.0	0	0.0	0	0.0	0	0.0
HYPERCHOLESTEREMIA	0	0.0	0	0.0	0	0.0	0	0.0
HYPERLIPEMIA	1	0.1	0	0.0	0	0.0	0	0.0
HYPOTONIA	0	0.0	0	0.0	0	0.0	0	0.0
LEUKOPENIA	1	0.1	0	0.0	0	0.0	0	0.0
MYOCARDIAL INFARCT	0	0.0	0	0.0	0	0.0	0	0.0
MYOCARDITIS	1	0.1	1	0.1	0	0.0	0	0.0
PERIPHERAL VASCULAR DISORDER	0	0.0	0	0.0	0	0.0	0	0.0

**ACT versus TCH**

**Table 41 Per Patient Incidence of ACT vs. TCH Non-Cardiac Adverse Events occurring in ≥ 5% of Patients with a Between Group difference in Herceptin Arm ≥ 5%**

Preferred Term	ACT (n=1050)				TCH (n=1056)			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
DIARRHEA	453	43.1	32	3.0	662	62.7	58	5.5
RASH	219	20.9	4	0.4	282	26.7	9	0.9
DYSPEPSIA	209	19.9	5	0.5	264	25.0	5	0.5
ABDOMINAL PAIN	187	17.8	8	0.8	245	23.2	8	0.8
EPISTAXIS	64	6.1	0	0.0	170	16.1	4	0.4
ALLERGIC REACTION	106	10.1	12	1.1	160	15.2	28	2.7

**Table 42 Per Patients Incidence of ACT vs. TCH Non-Cardiac Adverse Events Occurring in ≥ 5% of Patients with Between Group Difference in Herceptin Arm ≥ 2%**

COSTART Adverse Event	ACT (n=1050)				TCH (n=1056)			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
DIARRHEA	453	43.1	32	3.0	662	62.7	58	5.5
MACULOPAPULAR RASH	298	28.4	18	1.7	347	32.9	9	0.9
RASH	219	20.9	4	0.4	282	26.7	9	0.9
DYSPEPSIA	209	19.9	5	0.5	264	25.0	5	0.5
WEIGHT GAIN	210	20.0	9	0.9	252	23.9	9	0.9
ABDOMINAL PAIN	187	17.8	8	0.8	245	23.2	8	0.8
EPISTAXIS	64	6.1	0	0.0	170	16.1	4	0.4
ALLERGIC REACTION	106	10.1	12	1.1	160	15.2	28	2.7
LYMPHEDEMA	85	8.1	0	0.0	109	10.3	2	0.2
PRURITUS	39	3.7	0	0.0	66	6.3	1	0.1
DYSURIA	26	2.5	0	0.0	57	5.4	1	0.1
ACNE	11	1.0	0	0.0	33	3.1	0	0.0

**Table 43 Table Per Patient Incidence of ACT vs. TCH of Cardiac Adverse Events with a Between Group Difference in Herceptin  $\geq 2\%$**

COSTART Adverse Event	ACT (n=1050)				TCH (n=1068)			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
HYPERTENSION	194	18.5	162	15.4	222	21.0	187	17.7
PALPITATION	79	7.5	0	0.0	102	9.7	0	0.0
**UNMAPPED**	23	2.2	3	0.3	45	4.3	5	0.5

**Table 44 Table Per Patient Incidence of All Cardiac Events for ACT Vs. TCH**

COSTART Adverse Event	ACT				TCH			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
HYPERTENSION	194	18.5	162	15.4	222	21.0	187	17.7
PALPITATION	79	7.5	0	0.0	102	9.7	0	0.0
TACHYCARDIA	56	5.3	5	0.5	71	6.7	2	0.2
**UNMAPPED**	23	2.2	3	0.3	45	4.3	5	0.5
CARDIOVASCULAR DISORDER	34	3.2	1	0.1	40	3.8	1	0.1
DEEP THROMBOPHLEBITIS	23	2.2	19	1.8	39	3.7	31	2.9
LEFT HEART FAILURE	45	4.3	6	0.6	39	3.7	1	0.1
HYPOTENSION	23	2.2	1	0.1	25	2.4	2	0.2
ARRHYTHMIA	18	1.7	5	0.5	18	1.7	7	0.7
CHEST PAIN	9	0.9	0	0.0	17	1.6	1	0.1
PERICARDIAL EFFUSION	17	1.6	0	0.0	17	1.6	0	0.0
CARDIOMEGALY	7	0.7	0	0.0	12	1.1	0	0.0
MYOCARDIAL ISCHEMIA	7	0.7	1	0.1	11	1.0	3	0.3
PHLEBITIS	15	1.4	0	0.0	10	0.9	0	0.0
SINUS BRADYCARDIA	8	0.8	0	0.0	9	0.9	0	0.0
SYNCOPE	1	0.1	0	0.0	8	0.8	1	0.1
DYSPNEA	4	0.4	1	0.1	7	0.7	2	0.2
HEART FAILURE	6	0.6	2	0.2	7	0.7	0	0.0
VENTRICULAR ARRHYTHMIA	4	0.4	0	0.0	7	0.7	1	0.1
BUNDLE BRANCH BLOCK	5	0.5	0	0.0	5	0.5	1	0.1

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COSTART Adverse Event	ACT				TCH			
	All Grades	%	Grades 3-4	%	All Grades	%	Grades 3-4	%
VENTRICULAR EXTRASYSTOLES	3	0.3	1	0.1	4	0.4	0	0.0
ARTERIOSCLEROSIS	1	0.1	0	0.0	3	0.3	0	0.0
AV BLOCK	0	0.0	0	0.0	3	0.3	1	0.1
BIGEMINY	1	0.1	0	0.0	3	0.3	0	0.0
BRADYCARDIA	0	0.0	0	0.0	3	0.3	0	0.0
ELECTROCARDIOGR AM ABNORMAL	2	0.2	0	0.0	3	0.3	0	0.0
	1	0.1	1	0.1	2	0.2	1	0.1
ANGINA PECTORIS	2	0.2	0	0.0	2	0.2	0	0.0
CARDIOMYOPATHY	0	0.0	0	0.0	2	0.2	0	0.0
CORONARY ARTERY DISORDER	1	0.1	1	0.1	2	0.2	1	0.1
EDEMA	0	0.0	0	0.0	2	0.2	0	0.0

EXTRASYSTOLES	3	0.3	0	0.0	2	0.2	0	0.0
SUPRAVENTRICULA R EXTRASYSTOLES	2	0.2	0	0.0	2	0.2	0	0.0
SUPRAVENTRICULA R TACHYCARDIA	3	0.3	0	0.0	2	0.2	0	0.0
AORTIC STENOSIS	1	0.1	0	0.0	1	0.1	1	0.1
CEREBRAL ISCHEMIA	0	0.0	0	0.0	1	0.1	1	0.1
ENDOCARDITIS	0	0.0	0	0.0	1	0.1	0	0.0
GLAUCOMA	0	0.0	0	0.0	1	0.1	1	0.1
HEART ARREST	0	0.0	0	0.0	1	0.1	1	0.1
HYPERCHOLESTERE MIA	0	0.0	0	0.0	1	0.1	0	0.0
HYPERKINESIA	1	0.1	0	0.0	1	0.1	0	0.0
HYPOTONIA	0	0.0	0	0.0	1	0.1	0	0.0
MYOCARDIAL INFARCT	0	0.0	0	0.0	1	0.1	0	0.0
PAIN	0	0.0	0	0.0	1	0.1	0	0.0
VASCULAR ANOMALY	0	0.0	0	0.0	1	0.1	0	0.0
ATRIAL FIBRILLATION	1	0.1	0	0.0	0	0.0	0	0.0
CAROTID OCCLUSION	0	0.0	0	0.0	0	0.0	0	0.0
CHEST PAIN SUBSTERNAL	1	0.1	0	0.0	0	0.0	0	0.0
CONGESTIVE HEART FAILURE	1	0.1	0	0.0	0	0.0	0	0.0

DYSPEPSIA	0	0.0	0	0.0	0	0.0	0	0.0
DYSTONIA	0	0.0	0	0.0	0	0.0	0	0.0
EPISTAXIS	0	0.0	0	0.0	0	0.0	0	0.0
FACE EDEMA	0	0.0	0	0.0	0	0.0	0	0.0
HEART BLOCK	0	0.0	0	0.0	0	0.0	0	0.0
HEART MALFORMATION	1	0.1	1	0.1	0	0.0	0	0.0
HYPERLIPEMIA	1	0.1	0	0.0	0	0.0	0	0.0
HYPERTONIA	0	0.0	0	0.0	0	0.0	0	0.0
HYPOKINESIA	0	0.0	0	0.0	0	0.0	0	0.0
LEUKOPENIA	1	0.1	0	0.0	0	0.0	0	0.0
MYOCARDITIS	1	0.1	1	0.1	0	0.0	0	0.0
PERICARDITIS	0	0.0	0	0.0	0	0.0	0	0.0
PERIPHERAL EDEMA	0	0.0	0	0.0	0	0.0	0	0.0
PERIPHERAL VASCULAR DISORDER	0	0.0	0	0.0	0	0.0	0	0.0
PERIPHERAL VASCULAR DISORDER	0	0.0	0	0.0	0	0.0	0	0.0
T INVERTED	0	0.0	0	0.0	0	0.0	0	0.0
VASCULAR DISORDER	0	0.0	0	0.0	0	0.0	0	0.0

#### 7.1.1.8 Identifying common and drug-related adverse events

Serious adverse events which are probable or definitely due to Herceptin, based on comparison between treatment groups of BCIRG 006 include; congestive heart failure, decreased LVEF, cardiac ischemia/infarction, and deep thrombophlebitis.

The most common non-cardiac adverse events occurring in  $\geq 5\%$  of subjects with a higher between group difference of  $\geq 5\%$  in the in the Herceptin containing (ACT versus AC→TH) group were: diarrhea, infection, maculopapular rash, dyspepsia, rhinitis, and epistaxis.

The most common cardiac adverse events of any grade reported in  $\geq 5\%$  of subjects with higher incidence  $\geq 2\%$  in the Herceptin containing (ACT versus AC→TH) group were: hypertension and left heart failure.

The most common non-cardiac adverse events reported in  $\geq 5\%$  of subjects with a higher between group difference of  $\geq 5\%$  in the Herceptin containing (ACT versus TCH) group were: diarrhea, rash, dyspepsia, abdominal pain, epistaxis, and allergic reaction.

The most common cardiac adverse events of any grade reported in  $\geq 5\%$  of subjects with higher incidence  $\geq 2\%$  in the Herceptin containing (ACT versus TCH) group were: hypertension and palpitations.

**Less Common Adverse Events**

Rare but serious adverse events with a higher incidence (ACT vs. ACTH) in the Herceptin group include: chest pain, anemia, "reaction unevaluable", and cerebral vascular accident. Clinically the most significant difference was in the incidence of chest pain, anemia, and cerebral vascular accident in the ACTH arm in comparison to the control arm. Refer to Table 45, Adverse Events Grades 3-4 Across all Groups Rare but Serious.

Rare but serious adverse events with a higher incidence (ACT vs. TCH in the Herceptin) group include: anemia, chest pain, vertigo, hypokalemia, "reaction unevaluable". Cerebral vascular accident, colitis, hematuria, gastrointestinal hemorrhage, stomach atony, cirrhosis of the liver, liver necrosis, stomach ulcer, thrombocytopenia, and kidney failure. Clinically the most significant difference reported was anemia, vertigo, cerebral vascular accident, and thrombocytopenia, and kidney failure. Refer to Table 45, Adverse Events Grades 3-4 Across all Groups Rare but Serious.

**Table 45 Adverse Events Grades 3-4 Across all Groups Rare but Serious**

<b>COSTART Adverse Event</b>	<b>ACT (n=1050) %</b>	<b>AC→TH (n=1068) %</b>	<b>TCH (n=1056) %</b>
CHEST PAIN	0.2	0.6	0.5
ANEMIA	0.0	0.4	0.6
VERTIGO	0.1	0.3	0.6
HYPOKALEMIA	0.2	0.3	0.6
REACTION UNEVALUABLE	0.0	0.3	0.1
CEREBROVASCULAR ACCIDENT	0.0	0.1	0.3
COLITIS	0.0	0.0	0.4
HEMATURIA	0.0	0.0	0.3
GASTROINTESTINAL HEMORRHAGE	0.0	0.0	0.1
STOMACH ATONY	0.0	0.0	0.1
CIRRHOSIS OF LIVER	0.0	0.0	0.1
LIVER NECROSIS	0.0	0.0	0.1
STOMACH ULCER	0.0	0.0	0.1
THROMBOCYTOPENIA	0.1	0.0	0.7
KIDNEY FAILURE	0.0	0.0	0.1

## Laboratory Findings

### 7.1.1.9 Overview of laboratory testing in the development program

The schedule of assessment for laboratory parameters included hematology and chemistry labs. Prestudy hematology labs consisted of ; whit blood count with neutrophil count, hemoglobin, and platelet count. Chemistry labs included liver function testing (alkaline phosphatase, AST (SGOT), ALAT (SGPT) and bilirubin. Renal function labs included serum creatinine and creatinine clearance (if indicated). During chemotherapy, hematology and chemistry labs were obtained every three weeks. All laboratory toxicities were graded according to NCI-CTC version 2.0.

The applicant notified the Agency by written communication dated November 2, 2007, of errors in lab data for BCIRG 006. The applicant was notified by the CIRG that errors were discovered in the institution's upper limit of normal values and in the conversion of lab values to standard units for the BCIRG006 hematology and chemistries datasets submitted in sBLA 103792/5187 and 103792/5189. These errors were corrected by CIRG, and the lab datasets of hematology and chemistries were re-transferred to the applicant. The updated datasets (HEMC.xpt, CHMC.xpt) as well as the derived dataset for the laboratory assessments (PATLAB.xpt) were provided to the Agency.

After re-analysis of the lab data based on the corrected data, a comparison of the lab results with those in the original sBLA was performed. There were minor differences that affected the results presented in Section 12.4 of the CSR, Clinical Laboratory Evaluations, Tables 71 and 72.

**Table 46 Original CSR Table 71 Hematologic Laboratory Toxicity**

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)	All Patients (n=3174)
Number of patients with anemia <sup>a</sup>	957 (91.1%)	1036 (97.0%)	1017 (96.3%)	3010 (94.8%)
Grade 3/4	<b>26 (2.5%)</b>	34 (3.2%)	61 (5.8%)	<b>121 (3.8%)</b>
Number of patients with neutropenia <sup>b</sup>	<b>858 (81.7%)</b>	922 (86.3%)	<b>858 (81.3%)</b>	2638 (83.1%)
Grade 3/4	<b>663 (63.1%)</b>	761 (71.3%)	696 (65.9%)	<b>2120 (66.8%)</b>
Number of patients with thrombocytopenia	296 (28.2%)	349 (32.7%)	667 (63.2%)	<b>1312 (41.3%)</b>
Grade 3/4	10 (1.0%)	13 (1.2%)	57 (5.4%)	80 (2.5%)
Number of patients with leukopenia	878 (83.6%)	929 (87.0%)	877 (83.0%)	2684 (84.6%)
Grade 3/4	540 (51.4%)	<b>642 (60.1%)</b>	507 (48.0%)	<b>1689 (53.2%)</b>

Note: Values affected by the data corrections are in **bold**.

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; G-CSF=granulocyte colony-stimulating factors; TCH=docetaxel, carboplatin, and Herceptin.

<sup>a</sup> Anemia is defined as hemoglobin level < 12 g/dL.

<sup>b</sup> Neutropenia is defined as absolute neutrophil count < 1.0 × 10<sup>9</sup>/L.

Source: Tables 14.3/100, 14.3/101, 14.3/102, and 14.3/103.

**Table 47 Updated CSR table 71, after data Corrections Hematologic toxicity**

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)	All Patients (n=3174)
Number of patients with anemia <sup>a</sup>	957 (91.1%)	1036 (97.0%)	1017 (96.3%)	3010 (94.8%)
Grade 3/4	<b>25 (2.4%)</b>	34 (3.2%)	61 (5.8%)	<b>120 (3.8%)</b>
Number of patients with neutropenia <sup>b</sup>	<b>859 (81.7%)</b>	922 (86.3%)	<b>859 (81.3%)</b>	<b>2640 (83.2%)</b>
Grade 3/4	<b>664 (63.1%)</b>	761 (71.3%)	696 (65.9%)	<b>2121 (66.8%)</b>
Number of patients with thrombocytopenia	296 (28.2%)	<b>350 (32.8%)</b>	667 (63.2%)	<b>1313 (41.4%)</b>
Grade 3/4	10 (1.0%)	13 (1.2%)	57 (5.4%)	80 (2.5%)
Number of patients with leukopenia	878 (83.6%)	929 (87.0%)	877 (83.0%)	2684 (84.6%)
Grade 3/4	540 (51.4%)	<b>643 (60.2%)</b>	507 (48.0%)	<b>1690 (53.2%)</b>

Note: Corrected data are shown in **bold**.

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; G-CSF=granulocyte colony-stimulating factors; TCH=docetaxel, carboplatin, and Herceptin.

<sup>a</sup> Anemia is defined as hemoglobin level < 12 g/dL.

<sup>b</sup> Neutropenia is defined as absolute neutrophil count < 1.0 × 10<sup>9</sup>/L.

**Table 48 Original CSR Table 72 Chemistry Laboratory Toxicities**

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)	All Patients (n=3174)
Number of patients with creatinine toxicity	39 (3.7%)	<b>73 (6.8%)</b>	102 (9.7%)	<b>214 (6.7%)</b>
Grade 3/4	7 (0.7%)	<b>6 (0.6%)</b>	6 (0.6%)	<b>19 (0.6%)</b>
Number of patients with phosphatase toxicity	<b>204 (19.4%)</b>	<b>209 (19.6%)</b>	<b>217 (20.5%)</b>	<b>630 (19.8%)</b>
Grade 3/4	<b>7 (0.7%)</b>	<b>7 (0.7%)</b>	<b>6 (0.6%)</b>	<b>20 (0.6%)</b>
Number of patients with AST (SGOT) toxicity	426 (40.6%)	454 (42.5%)	<b>403 (38.2%)</b>	<b>1283 (40.4%)</b>
Grade 3/4	2 (0.2%)	<b>11 (1.0%)</b>	<b>13 (1.2%)</b>	<b>26 (0.8%)</b>
Number of patients with ALT (SGPT) toxicity	<b>508 (48.4%)</b>	<b>581 (54.4%)</b>	<b>562 (53.2%)</b>	<b>1651 (52.0%)</b>
Grade 3/4	<b>10 (1.0%)</b>	<b>21 (2.0%)</b>	<b>28 (2.7%)</b>	<b>59 (1.9%)</b>
Number of patients with bilirubin toxicity	52 (5.0%)	<b>55 (5.1%)</b>	<b>65 (6.2%)</b>	<b>172 (5.4%)</b>
Grade 3/4	<b>7 (0.7%)</b>	<b>5 (0.5%)</b>	<b>10 (0.9%)</b>	<b>22 (0.7%)</b>

Note: Values affected by the data corrections are in bold.

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; TCH=docetaxel, carboplatin, and Herceptin.

**Table 49 Updated CSR Table 7, after Data Corrections Chemistry Laboratory Toxicities**

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)	All Patients (n=3174)
Number of patients with creatinine toxicity	39 (3.7%)	<b>72 (6.7%)</b>	102 (9.7%)	<b>213 (6.7%)</b>
Grade 3/4	7 (0.7%)	<b>5 (0.5%)</b>	6 (0.6%)	<b>18 (0.6%)</b>
Number of patients with phosphatase toxicity	<b>202 (19.2%)</b>	<b>206 (19.3%)</b>	<b>215 (20.4%)</b>	<b>623 (19.6%)</b>
Grade 3/4	<b>3 (0.3%)</b>	<b>3 (0.3%)</b>	<b>3 (0.3%)</b>	<b>9 (0.3%)</b>
Number of patients with AST (SGOT) toxicity	426 (40.6%)	454 (42.5%)	<b>401 (38.0%)</b>	<b>1281 (40.4%)</b>
Grade 3/4	2 (0.2%)	<b>9 (0.8%)</b>	<b>11 (1.0%)</b>	<b>22 (0.7%)</b>
Number of patients with ALT (SGPT) toxicity	<b>506 (48.2%)</b>	<b>579 (54.2%)</b>	<b>561 (53.1%)</b>	<b>1646 (51.9%)</b>
Grade 3/4	<b>7 (0.7%)</b>	<b>19 (1.8%)</b>	<b>25 (2.4%)</b>	<b>51 (1.6%)</b>
Number of patients with bilirubin toxicity	52 (5.0%)	<b>54 (5.1%)</b>	<b>61 (5.8%)</b>	<b>167 (5.3%)</b>
Grade 3/4	<b>6 (0.6%)</b>	<b>4 (0.4%)</b>	<b>4 (0.4%)</b>	<b>14 (0.4%)</b>

Note: Corrected data are shown in bold.

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; TCH=docetaxel, carboplatin, and Herceptin.

In comparing hematologic lab toxicities between ACT and ACTH, overall the ACTH group had a higher incidence of anemia, neutropenia, and leukopenia. For comparison between ACT and TCH groups, overall the TCH group had a higher incidence of anemia, neutropenia, and leukopenia with the most clinically significant difference in thrombocytopenia ACT (28.2%) vs. TCH (41.4%).

In comparing chemistry lab toxicities between ACT and ACTH, overall, the Herceptin containing regimen had higher incidence of toxicity in creatinine, phosphatase, SGOT, SGPT, and bilirubin with the most clinically significant difference in creatinine toxicity [ACT (3.7%) vs. ACTH (6.7%)] and in grade 3-4 SGPT toxicity [ACT (0.7%) vs. ACTH (1.8%)]. For comparison between ACT and TCH group, the TCH arm had lower incidence of chemistry lab toxicity compared to ACTH overall with the exception of SGOT toxicity [ACT (38%) vs. TCH (40.4%)].

#### 7.1.1.10 Special assessments

No other special assessments were conducted.

## Vital Signs

Vital signs were not recorded for Study BCIRG 006.

## Electrocardiograms (ECGs)

A normal ECG was required within three months prior to registration onto study BCIRG 006. During therapy ECG's were obtained as clinically indicated.

As part of the cardiac secondary endpoint of BCIRG 006, cardiac arrhythmias of grade 3 and 4 were specifically monitored for and reviewed by the ICRP. The NCI-CTC version 2 grading was used and defines a grade 3 arrhythmia as symptomatic and requiring treatment, or grade 4 which is an arrhythmia considered to be life threatening. Subjects who developed grade 3 or 4 arrhythmia were required to have an ECG repeated during follow-up every three months for the first year, and every year until the end of follow-up or otherwise as clinically indicated.

The ACTH group had a higher incidence of grade 3-4 arrhythmia compared to the control group ACT (.08% vs. 0.5%). The TCH group and the control arm were equal in incidence of these events. Refer to Table 50 Reviewer's Incidence of Arrhythmias Events.

**Table 50 Reviewer's Incidence of Arrhythmias Events**

	<b>ACT (n=1050)</b>	<b>ACTH (n=1068)</b>	<b>TCH (n=1056)</b>
<b>Arrhythmia</b>	5 (0.5%)	8 (0.8%)	5 (0.5%)
ICRP Grade 3	3 (0.3%)	0 (0%)	1 (0.1%)
ICRP Grade 4	0 (0%)	0 (0%)	0 (0%)

\* ICRP= Independent Cardiac Review Panel

\*\* GNECARD dataset

## Immunogenicity

The BCIRG 006 study was not designed to collect serum samples in order to determine the incidence of human anti-human antibody (HAHA) to Trastuzumab. Data to immunogenicity is limited to legacy data in the metastatic setting. The incidence of immune response (HAHA) to trastuzumab in the setting of metastatic disease is low. The impact on HAHA, if any, is of minimal risk and does not offset the benefits of the effects on DFS.

### **Human Carcinogenicity**

Human carcinogenicity studies were not required and therefore not conducted or included in the application in support of this proposed labeling extension.

### **Special Safety Studies**

No special safety studies were conducted in support of this application.

### **Withdrawal Phenomena and/or Abuse Potential**

No withdrawal phenomenon is known. Trastuzumab has no expected abuse potential.

### **Human Reproduction and Pregnancy Data**

No new reproductive and/or pregnancy data with study BCIRG 006.

### **Assessment of Effect on Growth**

There is no information on the use of this drug in children.

### **Overdose Experience**

There was no report of overdose in the sBLA application.

### **Postmarketing Experience**

There were no additional spontaneous post-marketing reports provided within the application or reviewed independently by this reviewer from this application. Review of post-marketing reports was not conducted because it was extensively reviewed with recent supplement BL STN 103792/5175 with approval date January 18, 2008.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

#### 7.2.1.1 Study type and design/patient enumeration

Refer to section 6.1.3 Study Design

#### 7.2.1.2 Demographics

There were no significant differences in demographic characteristics between the treatment groups. All patients underwent primary surgery for breast cancer prior to study enrollment. A total of 59.5% of patients in the AC→T arm, 62.8% in the AC→TH arm, and 59.7% in the TCH arm had a mastectomy.

Positive HER2 status by FISH performed at the central laboratory was mandatory at the time of enrollment. A total of 99.6% of patients (3209 of 3222) were HER2-positive, as assessed by the central laboratory. There were 12 patients who were HER2 negative per central FISH assessment. Nodal involvement was very similar across the three treatment arms, with 28.8%, 28.5%, and 28.6% of patients having node-negative disease and 13.4%, 11.4%, and 11.3% of patients having ten or more nodes involved in the AC→T, AC→TH, and TCH arms, respectively. Approximately half of the patients were ER-positive and/or PR-positive: Infiltrating ductal carcinoma was the most common histopathologic type in all treatment arms. Most tumors were poorly differentiated and were excised with clear margins.

#### 7.2.1.3 Extent of exposure (dose/duration)

In the original protocol, following chemotherapy, patients in both the AC→TH and TCH arms were to receive 2 mg/kg doses of Herceptin weekly for a year from the first Herceptin administration. However, in Amendment 2 (dated 7/30/2001), the frequency of Herceptin administration during the mono therapy was changed from once every week to once every 3 weeks. There were 43 patients who had started Herceptin monotherapy prior to the amendment (19 and 24 for AC-- TH and TCH arms, respectively). Of these 43 patients, 32 continued to receive Herceptin monotherapy on a weekly basis, while the remaining 11 patients switched from a once weekly to a once-every-3-week schedule. A summary of Herceptin exposure is shown in the following Table 51. The median duration (378 days) and the median total dose (107.4 and 109.5 for AC--TH and TCH arms, respectively) of Herceptin appear to be similar between AC--TH and TCH arms.

**Table 51 Herceptin Exposure**

	AC→T (n= 1050)	AC→TH (n= 1068)	TCH (n= 1056)
<b>Duration (days)</b>			
n	NA	1045	1056
Mean (SD)	NA	336.0 (102.6)	360.1 (73.7)
Median	NA	378	378
Range	NA	21-1046	21-685
<b>Total dose (mg/kg)</b>			
n	NA	1045	1056
Mean (SD)	NA	95.3 (30.1)	103.0 (24.1)
Median	NA	107.4	109.5
Range	NA	3.9-157.3	4.0-272.0
<b>Relative dose intensity</b>			
n	NA	1045	1056
Mean (SD)	NA	1.000 (0.086)	1.005 (0.096)
Median	NA	1.004	1.004
Range	NA	0.44-1.36	0.29-2.47

**Description of Secondary Clinical Data Sources Used to Evaluate Safety**

There were no secondary clinical data sources for this application.

**7.2.1.4 Other studies**

There are no other studies.

**7.2.1.5 Postmarketing experience**

There were no additional spontaneous post-marketing reports provided within the application or reviewed independently by this reviewer from this application. Review of post-marketing reports was not conducted because it was extensively reviewed with recent supplement 103792/5175 with approval date January 18, 2008.

**7.2.1.6 Literature**

There was no additional new data in the literature to support the safety of this application.

### **Adequacy of Overall Clinical Experience**

An adequate number of subjects had exposure to drug to provide safety information.

### **Adequacy of Special Animal and/or In Vitro Testing**

Not applicable to this efficacy supplement.

### **Adequacy of Routine Clinical Testing**

Routine clinical testing was adequate. Refer to section 6.1.3 Schedule of Assessments.

### **Adequacy of Metabolic, Clearance, and Interaction Workup**

No drug-drug interactions were conducted or necessary during study BCIRG 006.

### **Assessment of Quality and Completeness of Data**

The following statements regarding data quality and completeness with regard to adverse event evaluation and toxicity grading are pertinent to the review of this application:

- The study was open labeled, which could lead to over and/or under reporting of toxicities in both treatment arms. The extent to which observed toxicities concurred with the investigator's pre-study bias, whether seen on the treatment or control arm could have influenced reporting. It is not possible to estimate the magnitude of this potential bias.
- Although the schedule of assessments was identical to all three arms, subjects in the Herceptin arm had the opportunity to report symptoms more often in conjunction with the infusion appointment (every three weeks).

### **Additional Submissions, Including Safety Update**

The applicant submitted a 120 day safety update at the FDA's request.

### **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

#### Cardiac

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

#### Infection

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

(b) (4)

#### Diarrhea

The incidence of Grade 3-4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1-4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin.

### **7.4 General Methodology**

#### **Pooling Data Across Studies to Estimate and Compare Incidence**

Data from were reviewed to assess the overall frequency of adverse events for subjects treated with Herceptin as contrasted with those in the comparator arm. In addition, these results were compared to summaries of data from the legacy studies and the current product label. There was no pooling of data from these sources.

## **8 ADDITIONAL CLINICAL ISSUES**

### **8.1 Dosing Regimen and Administration**

The following are the recommended doses and schedules of Herceptin for a total of 52 weeks, for the treatment of adjuvant breast cancer:

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

- Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30-60 minutes every three weeks.

## **8.2 Drug-Drug Interactions**

There has been no formal drug interaction studies performed with Herceptin in humans during BCIRG 006.

## **8.3 Special Populations**

This efficacy supplement contained no specific studies to evaluate dosing based on race, gender, age or major organ impairment. No data from study BCIRG 006 suggested dosing should be modified based on demographic characteristics.

## **8.4 Pediatrics**

A waiver for pediatric studies under PREA is granted in this application because the indication sought is for a condition which does not occur in children.

## **8.5 Advisory Committee Meeting**

The review team, including this reviewer, decided not to present the findings in the application to the Oncologic Drugs Advisory Committee for the following reasons: 1) the effects of Herceptin on the primary endpoint, DFS, and related secondary endpoints were both clinically relevant, highly significant, and internally consistent across relevant subgroups. In addition, this study replicates the findings of an early supplemental application (BL STN 103792.5175) for essentially the same indication; 2) the primary endpoint, prolongation of disease-free survival, is considered an appropriate and feasible measure of clinical benefit for adjuvant treatment of solid tumors, including breast cancer; and 3) there were no safety signals that were considered to outweigh the clinical benefit demonstrated.

## **8.6 Literature Review**

In study BCIRG 006, the comparison between the control arm (AC followed by docetaxel) and the experimental arm (docetaxel-carboplatin- Herceptin) does not isolate the effect of Herceptin.

FDA reviewers asked the sponsor to provide data which support that the effects seen on DFS can be attributed primarily to Herceptin rather than other components of the treatment arm.

Data directly addressing the use of a taxane/platinum (TC) combination given alone in the adjuvant treatment of HER2-positive breast cancer are not currently available. This may be due in part to data suggesting a need for anthracyclines in the management of HER2-positive breast cancer. Therefore, the sponsor provided data in the neoadjuvant setting and metastatic breast cancer setting.

*Neoadjuvant breast cancer:*

Platinum compounds in combination with other anti-tumoral agents have been employed as neoadjuvant breast cancer. Although these combinations are active, the contribution of platinum to the overall activity is unknown. A review of ten single-arm studies by Martín (2001) noted clinical complete response (CR) rates of 77%–100% and rates of pathologic CR in the range of 20%–27%. However, HER2 status was not specified.

Efficacy and safety of weekly docetaxel/carboplatin as primary therapy for 44 patients with HER2-negative locally advanced breast cancer were studied in a single-arm Phase II study at the University of Miami (Hurley et al.2005). Post-operatively, patients received four cycles of adjuvant AC, standard radiation therapy, and tamoxifen, if indicated. The clinical CR rate was 25% (n = 11), and clinical partial responses were seen in 66% of patients (n = 29), resulting in a 91% objective responses rate. The pathologic CR rate was 14% (n = 6). DFS data are not available. The contribution of carboplatin to the regimen remains to be defined in randomized, comparative studies.

The sponsor states that recent data demonstrate pharmacologic synergy between Herceptin and both platinum in HER2-positive human breast cancer cell lines. Because of this potential synergy with Herceptin, combinations of platinum compounds with docetaxel and trastuzumab have been tested in patients with metastatic breast cancer, which overexpresses HER2.

*Metastatic breast cancer:*

Results of a Study BCIRG007, a Phase III study evaluating Herceptin plus docetaxel with or without carboplatin for the first-line treatment of HER2-positive MBC were presented at the American Society of Clinical Oncology in 2007 (Pegram et al. 2007). The primary endpoint of the BCIRG 007 study was time to progression (TTP); secondary endpoints included OS, response rate, duration of response, clinical benefit, and safety. Efficacy results at a median follow-up of 39 + mon

	TH	TCH	p-value
Median TTP (months)	11.07	10.35	0.57
Median OS (months)	39.1	39.2	0.65
Overall response rate	72.5%	72.7%	-

Study M77001 (Marty et al. 2005), in 188 HER2-positive patients (3+ by immunohistochemistry and/or FISH-positive disease) were randomized to receive 100 mg/m<sup>2</sup> docetaxel for six cycles with or without Herceptin given weekly until disease progression in the first-line metastatic setting. The primary endpoint was overall response rate (ORR); secondary endpoints were safety, TTP, time to treatment failure, and survival. Overall response rate was 61% in the TH combination arm (7% with CR, 54% partial response) versus 36% (2% CR, 34% partial response) in the docetaxel-alone arm (p = 0.001). TTP was 10.6 months in the combination arm compared with 6.1 months (p = 0.0001) in the docetaxel arm. Overall survival was 27.7 months in the combination arm versus 18.3 months (p = 0.0002). These results demonstrate that the addition of Herceptin to docetaxel in the first-line metastatic setting significantly improves both PFS and OS in patients with HER2-positive breast cancer.

The addition of carboplatin to paclitaxel and Herceptin has also been studied. Robert et al. (2004) in a Phase III randomized, multicenter trial in 196 women with HER2-overexpressing metastatic breast cancer. The addition of carboplatin to paclitaxel and Herceptin in this study significantly improved response rate (52% vs. 36%; p = 0.04) and TTP (11.9 months vs. 6.8 months; p = 0.02).

In summary, there is limited data regarding the use of platinum compounds in the adjuvant treatment of HER2-positive breast cancer. Anthracycline-containing regimens have been shown to be particularly beneficial in patients with HER2-positive breast cancer and are the standard of care against which investigational agents should be measured. Because of the cardiac risk associated with anthracyclines, and the increased risk of cardiotoxicity seen when anthracyclines are used in combination with Herceptin, investigation of a non-anthracycline-containing adjuvant regimen for HER2-positive early breast cancer was felt to be appropriate. Through synergistic activity with both Taxotere and carboplatin, Herceptin given as part of the TCH regimen has been shown to be an active combination in the metastatic setting and provide a PFS as well as an OS benefit relative to taxanes alone in this setting. This regimen was chosen to compare with standard AC→T, offering the possibility of a less cardiotoxic regimen with improved efficacy for the adjuvant treatment of early stage HER2-positive breast cancer. TCH is the first non-anthracycline-based regimen to

show greater efficacy than AC followed by T in HER2-positive breast cancer.

### 8.7 Postmarketing Risk Management Plan

Pregnancy registry was part of a post marketing commitment with BLA STN 103792/5175 with January 18, 2008 approval.

### 8.8 Other Relevant Materials

There were no additional studies, including actual use, labeling comprehension studies and marketing studies, were considered in this review.

Consultation on product labeling was requested from the Division of Division of Drug Marketing, Advertising, and Communication (DDMAC).

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

This review addresses an efficacy supplement to BLA 103792.5189 for use of Herceptin® (trastuzumab) in combination with docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer. The current supplement presents the results of a single, randomized trial comparing Herceptin® (trastuzumab) in combination with docetaxel and carboplatin with Herceptin® (trastuzumab) following the combination with doxorubicin and cyclophosphamide and the combination of doxorubicin and cyclophosphamide followed by docetaxel, as adjuvant treatment in women with HER2-overexpressing, node-positive (b) (4) breast cancer.

Results of the protocol-specified **second efficacy interim analysis** demonstrated that Herceptin as part of either an anthracycline-based (AC→TH) or non-anthracycline-based (TCH) adjuvant treatment regimen results in a clinically meaningful and statistically significant improvement in DFS relative to AC→T irrespective of nodal status. For the primary efficacy endpoint, DFS, the risk of a first event was reduced by 39% (95% confidence interval [CI]: 23, 51; p <0.0001) in the AC→TH arm relative to the AC→T arm. For the primary efficacy endpoint, DFS, the risk of a first event was reduced by 33% (95% CI: 17, 46; p =0.0003) in the TCH arm relative to the AC→T arm.

- The DFS benefit in all clinically important subgroups, including those defined by age, menopausal status, hormone receptor status, nodal status, tumor size, nuclear grade, and surgery or radiation therapy, was consistent with the treatment effect in the overall population.

• Follow-up was too short for an adequate comparison of survival. In addition, the protocol did not have a pre-specified alpha spending for overall survival, no preplanned interim analyses and no pre-specified significance levels. (b) (4)

Overall, the submitted trial demonstrated efficacy and clinical benefit for TCH as adjuvant therapy in women with HER2-overexpressing, node-positive (b) (4) breast cancer. While there is increased toxicity with the TCH therapy compared to the control arm, the benefit conveyed is greater than the incidence of serious adverse events. The data from Study BCIRG006 support approval for this indication.

BCIRG006 was also submitted to support the Herceptin approval for a second indication. "As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer" This indication is also going to be approved. Please see a separate review by Katherine Fedenco, MS, CRNP.

## 9.2 Recommendation on Regulatory Action

The Division of Drug Biology Oncology Products recommends full approval, of Herceptin® for the proposed indication:

"As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer".

The efficacy claims in support of this application are based on the results of a single large randomized well controlled trial (BCIRG006) entitled, "A multicenter phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) and with docetaxel, platinum salt and trastuzumab (TCH) in the treatment of node positive and high risk node negative adjuvant patients with operable breast cancer containing the HER2neu alteration."

The protocol primary endpoint was disease free survival. Secondary endpoints included overall survival and to compare cardiac and non-cardiac toxicity between the 3 arms, in order to determine the safety of Herceptin with these chemotherapy regimens. At the second interim analysis and 36 months of median follow-up, the protocol primary endpoint was disease free survival. Secondary endpoints included overall survival and to compare cardiac and non-cardiac toxicity between the 3 arms, in order to determine the safety of Herceptin with these chemotherapy regimens. At the second interim analysis and 36 months of median follow-up, AC→TH, the anthracycline containing arm (Herceptin concurrently with docetaxel) demonstrated a significantly longer disease-free survival as compared to the AC→T (doxorubicin and cyclophosphamide followed by docetaxel) treatment arm. Follow-up was too short for an adequate comparison of survival. In addition, the protocol did not have a pre-specified alpha spending for overall survival, no preplanned interim analyses and no pre-

specified significance levels. (b) (4)

The safety profile of docetaxel in combination with carboplatin and Herceptin are consistent with the known toxicities of the three agents and typical antineoplastic therapy. The TCH arm appears to have similar incidence rates of the LVEF related events (e.g. post-baseline LVEF: 50% and significant LVEF drop) as compare the rates in the AC→T arm.

### 9.3 Recommendation on Postmarketing Actions

#### Risk Management Activity

There are no additional risk evaluation and mitigation strategies associated with this review.

#### Required Phase 4 Commitments

1. Updated efficacy data at 10 years of follow-up from all 3 treatment arms in BCIRG006, with an interim update at 5 years of follow-up

To provide an efficacy update from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled (March 2004) in the trial reaches approximately 10 years of follow-up, with an interim report on the updated efficacy at 5-years of follow-up. It is estimated that the completion of 5-year follow-up will occur in Q2 2009. The DFS and OS update based on 5-year follow-up date will be submitted to the FDA in Q1 2010. It is estimated that the completion of 10-year follow-up will occur in Q2 2014. The updated DFS and OS data will be submitted to the FDA in Q1 2015.

2. Cardiac safety update at 5 years of follow-up from all 3 treatment arms in BCIRG006

To provide an update on cardiac safety from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 5 years of follow-up. The update will include analysis of per-protocol defined cardiac events, changes in LVEF measurements, and narratives for any patients who developed a new per-protocol defined cardiac event. The completion of 5-year follow-up will occur in Q2 2009 and the 5-year cardiac update will be submitted to FDA in Q1 2010.

### 9.4 Labeling Review

The following sections from the label were changed compared to the January 18, 2008:

- Indications and Usage, Adjuvant Treatment of Breast Cancer

- Dosage and Administration, Recommended Doses and Schedules
- Dosage and Administration, Dose Modifications
- Warnings and Precautions, Cardiomyopathy

From:

#### 1.1 Adjuvant Breast Cancer

Herceptin is indicated:

- As part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of HER2-overexpressing, breast cancer.
- As a single agent, for the adjuvant treatment of HER2-overexpressing node-negative (ER/PR negative or with one high-risk feature) or nodepositive breast cancer, following multi-modality anthracycline based therapy. [see Clinical Studies (14.1)]

To:

#### 1.1 Adjuvant Breast Cancer

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

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

From:

#### 1.2 Metastatic Breast Cancer

Herceptin is indicated:

- In combination with paclitaxel for treatment of HER2 overexpressing metastatic breast cancer

To:

#### 1.2 Metastatic Breast Cancer

Herceptin is indicated:

- In combination with paclitaxel for first- line treatment of HER2-overexpressing metastatic breast cancer

From:

#### 2.1 Recommended Doses and Schedules

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

Adjuvant Treatment, Breast Cancer:

Administer according to one of the following doses and schedules:

- Initiate Herceptin following completion of anthracycline and concurrently with paclitaxel for the first 12 weeks. Administer Herceptin at an initial

dose of 4 mg/kg as a 90 minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30 minute intravenous infusions, as tolerated, for a total of 52 doses. [see Dose Modifications (2.2)]

- Initiate Herceptin following completion of all chemotherapy. Administer Herceptin at an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg every three weeks for a total of 17 doses (52 weeks of therapy). Administer all doses >4 mg/kg as 90 minute intravenous infusions.

To:

#### 2.1 Recommended Doses and Schedules

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

Adjuvant Treatment, Breast Cancer:

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

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

- Initial dose of 4mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30-60 minutes every three weeks.

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

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

From:

#### 5.1 Cardiomyopathy

Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [see Boxed Warning: Cardiomyopathy]. Herceptin can also cause a symptomatic decline in left ventricular ejection fraction (LVEF).

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

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

Cardiac Monitoring

Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan, prior to the first dose of Herceptin. The following schedule was used to monitor cardiac function in clinical studies:

- Baseline LVEF measurement immediately prior to initiation of Herceptin
- LVEF measurements every 3 months during and upon completion of Herceptin
- LVEF measurements every 6 months for at least 2 years following completion of Herceptin
- Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction [see Dosage and Administration (2.2)]

In Study 1, 16% (136/844) of patients discontinued Herceptin due to clinical evidence of myocardial dysfunction or significant decline in LVEF.

In Study 3, the number of patients who discontinued Herceptin due to cardiac toxicity was 2.6% (44/1678).

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

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

Study	Event	Incidence	
		Herceptin	Control
1 & 2	Congestive heart failure*	2% (32/1677)	0.4% (7/1600)
3	Congestive heart failure	2% (30/1678)	0.3% (5/1708)

\*Includes 1 patient with fatal cardiomyopathy.

To:

#### 5.1 Cardiomyopathy

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

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

There is a 46 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an anthracycline.

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

#### Cardiac Monitoring

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

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

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

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

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

<sup>a</sup> Includes 1 patient with fatal cardiomyopathy.

<sup>b</sup> Anthracycline (doxorubicin) and cyclophosphamide

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

**New Data:**

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

**Table 5\***  
 Per-patient Incidence of New Onset  
 Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

	LVEF <50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF <50%	≥10% decrease	≥16% decrease	<20% and ≥10%	
				≥10%	≥20%
<b>Studies 1 &amp; 2<sup>b</sup></b>					
AC→TH (n=1606)	22.8% (366)	18.3% (294)	11.7% (188)	33.4% (536)	9.2% (148)
AC→T (n=1488)	9.1% (136)	5.4% (81)	2.2% (33)	18.3% (272)	2.4% (36)
<b>Study 3</b>					
Herceptin (n=1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n=1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
<b>Study 4<sup>c</sup></b>					
TCH (n=1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n=1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n=1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

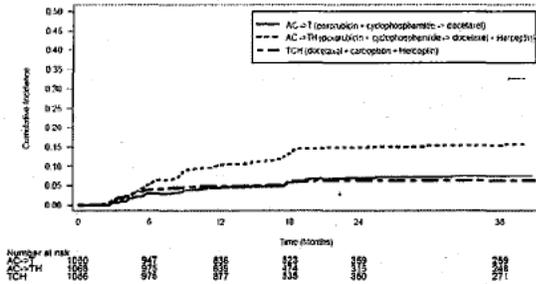
\* For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization.

<sup>b</sup> Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)

<sup>c</sup> Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH)

Figure 3

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



### Infection

In study 4, the overall incidence of infection was higher with the addition of Herceptin to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC grade 3-4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms. In a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of febrile neutropenia was higher (23% vs. 17%) in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

### Thrombosis/Embolism

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

### Diarrhea

In Study 4, the incidence of Grade 3-4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1-4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer.

## 14CLINICAL STUDIES

### 14.1 Adjuvant Breast Cancer

#### Study 4

In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory. Patients were required to have either node-positive

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disease, or node-negative disease with at least one of the following high-risk features: ER/PR-negative, tumor size > 2 cm, age < 35 years, or histologic and/or nuclear Grade 2 or 3. Patients with a history of CHF, myocardial infarction, Grade 3 or 4 cardiac arrhythmia, angina requiring medication, clinically significant valvular heart disease, poorly controlled hypertension (diastolic > 100 mmHg), any T4 or N2 or known N3 or M1 breast cancer were not eligible.

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

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

**Table 6**  
 Efficacy Results from Adjuvant Treatment of  
 Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	Hazard ratio (95% CI) p value	Deaths	Hazard ratio p value
<b>Studies 1 + 2<sup>e</sup></b>				
AC→TH (n = 1872)	133	0.48 <sup>a</sup> (0.39, 0.59) p < 0.0001 <sup>b</sup>	62	0.67 p = NS <sup>d</sup>
AC→T (n = 1880)	261		92	
<b>Study 3</b>				
Chemo→ Herceptin (n = 1693)	127	0.54 (0.44, 0.67) p < 0.0001 <sup>c</sup>	31	0.75 p = NS <sup>d</sup>
Chemo→ Observation (n = 1693)	219		40	
<b>Study 4<sup>f</sup></b>				
TCH (n = 1075)	134	0.67 (0.54 - 0.84) p = 0.0006 <sup>b</sup>	56	
AC→TH (n = 1074)	121	0.60 (0.48 - 0.76) p < 0.0001 <sup>b</sup>	49	
AC→T (n = 1073)	180		80	

CI = confidence interval.

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

<sup>b</sup> stratified log-rank test.

<sup>c</sup> log-rank test.

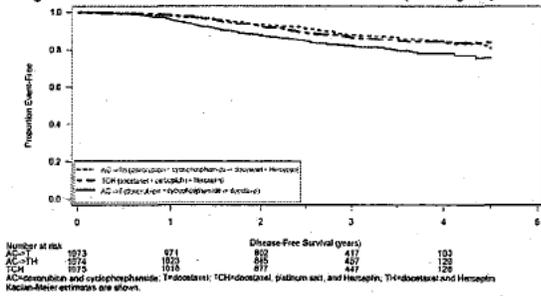
<sup>d</sup> NS = non-significant.

<sup>e</sup> Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)

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

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

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



### 9.5 Comments to Applicant

No additional comments to the applicant were provided.

## **10 APPENDICES**

### **10.1 Review of Individual Study Reports**

Study BCIRG 006 was the only study with supporting datasets reviewed for this application. The review discusses the data from this study in depth. FDA review of legacy study reports were also reviewed (STN 103792.0, STN 103792/5150, and STN 103792/5175).

### **10.2 Line-by-Line Labeling Review**

Refer to section 9.4

Appears this way on the original

## CLINICAL REVIEW

Application Type: Prior approval supplement  
Submission Number: BL STN 103792.5189  
Letter Date: July 5, 2007  
PDUFA Goal Date: May 4, 2008

Reviewers Names: Patricia Cortazar, M.D.  
Katherine Fedenko, MS, CRNP

Review Completion Date:

Established Name: Herceptin® (trastuzumab)  
Therapeutic Class: HER2/neu receptor antagonist  
Applicant: Genentech, Inc.  
Priority Designation: Standard

### Indications:

“As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer”

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## 1 EXECUTIVE SUMMARY

This multidisciplinary medical-statistical review addresses an efficacy supplement to BLA 103792 for use of Herceptin® (trastuzumab) for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer. The original BLA for Herceptin® was approved in 1998 as a single agent for patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Herceptin® was also approved in 1998 in combination with paclitaxel for treatment of patients with metastatic breast cancer whose tumors overexpress HER2 protein and who have not received chemotherapy for their metastatic disease. On November 2006, FDA approved Herceptin® for the adjuvant treatment of patients with HER2 overexpressing, node-positive breast cancer as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel. In this regimen, Herceptin is given concurrently with paclitaxel and then as monotherapy, for a total duration of Herceptin therapy of 52 weeks. On January 2008, Herceptin® was also approved for the adjuvant treatment of patients with HER2 overexpressing, node-positive and high risk node-negative breast cancer, as a single agent for 52 weeks, after completion of surgery, chemotherapy, and radiotherapy (if applicable).

The current supplement presents the results of a randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC-T) with doxorubicin and cyclophosphamide followed by docetaxel plus Herceptin (AC-TH) and docetaxel plus carboplatin plus Herceptin (TCH), as adjuvant treatment in women with HER2 overexpressing, node-positive and high risk node-negative breast cancer.

The applicant submitted data to support two new indications. The sBLA 103792 was reviewed by two medical reviewers. This review, 103792\5189, addresses the following proposed indication, "As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer". sBLA 103792\5187, supports the following proposed indication, "As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer" and was reviewed by Clinical Reviewer, Katherine Fedenko.

### 1.1 Recommendation on Regulatory Action

The Division of Biologic Oncology Products recommends full approval of Herceptin® for the proposed indication:

"As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer".

The efficacy claims in support of this application are based on the results of a single large randomized well controlled trial (BCIRG006) entitled, "A multicenter phase III randomized trial

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comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) and with docetaxel, platinum salt and trastuzumab (TCH) in the treatment of node positive and high risk node negative adjuvant patients with operable breast cancer containing the HER2neu alteration.”

The protocol primary endpoint was disease free survival. Secondary endpoints included overall survival and to compare cardiac and non-cardiac toxicity between the 3 arms, in order to determine the safety of Herceptin with these chemotherapy regimens. At the second interim analysis and 36 months of median follow-up, TCH, the non-anthracycline containing arm (Herceptin concurrently with docetaxel and carboplatin) demonstrated a significantly longer disease-free survival as compared to the AC→T (doxorubicin and cyclophosphamide followed by docetaxel) treatment arm.

(b)

(4)

The safety profile of docetaxel in combination with carboplatin and Herceptin are consistent with the known toxicities of the three agents and typical antineoplastic therapy. The TCH arm appears to have similar incidence rates of the LVEF related events (e.g. post-baseline LVEF: 50% and significant LVEF drop) as compared to the rates in the AC→T arm.

## 1.2 Recommendation on Postmarketing Actions

### Risk Management Activity

#### Required Phase 4 Commitments

1. Updated efficacy data at 10 years of follow-up from all 3 treatment arms in BCIRG006, with an interim update at 5 years of follow-up

To provide an efficacy update from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled (March 2004) in the trial reaches approximately 10 years of follow-up, with an interim report on the updated efficacy at 5-years of follow-up. It is estimated that the completion of 5-year follow-up will occur in Q2 2009. The DFS and OS update based on 5-year follow-up date will be submitted to the FDA in Q1 2010. It is estimated that the completion of 10-year follow-up will occur in Q2 2014. The updated DFS and OS data will be submitted to the FDA in Q1 2015.

2. Cardiac safety update at 5 years of follow-up from all 3 treatment arms in BCIRG006

To provide an update on cardiac safety from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 5 years of follow-up. The update will include analysis of per-protocol defined cardiac events, changes in LVEF measurements, and narratives for any patients who developed a new per-protocol defined cardiac event. The completion of 5-year follow-up will occur in Q2 2009 and the 5-year cardiac update will be submitted to FDA in Q1 2010.

## **Other Phase 4 Requests**

### **1.3 Summary of Clinical Findings**

#### **Brief Overview of Clinical Program**

Genentech submitted Study BCIRG006, an multinational randomized, open-label, active-controlled clinical trial, to evaluate Herceptin given either concurrently with a non-anthracycline chemotherapy regimen of docetaxel and carboplatin (TCH) or with docetaxel after completion of doxorubicin and cyclophosphamide (AC→TH) compared with the control arm: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) as adjuvant treatment of HER-2 over-expressing, node-positive and high-risk node-negative patients with operable breast cancer.

Study BCIRG006 was conducted by BCIRG and sponsored by sanofi-aventis (under IND 35,555) and Genentech. About 30% of the patients were from the US. The rest of the patients were from Europe, Asia, New Zealand, Australia, Canada and other countries. Patient assignment to treatment was based on a stochastic minimization scheme with center, status of axillary lymph nodes involved and hormonal receptor status as factors. The primary endpoint of this study was disease-free survival and the secondary efficacy endpoints included overall survival and quality of life. The primary comparison of this study was between each of the arms containing Herceptin versus the AC→T arm using the stratified log-rank test.

#### **Efficacy**

A total of 3222 patients were randomized into the three treatment arms. The primary efficacy analysis population consisted of all the randomized patients (ITT) according to the randomized treatment. The median follow-up of the study was 36 months. The treatment arms were well balanced for important baseline characteristics. (b) (4)



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At the second interim analysis and 36 months of median follow-up, TCH, the non-anthracycline containing arm which consisted of Herceptin given concurrently with docetaxel and carboplatin, demonstrated a significantly longer disease-free survival as compared to the AC→T (doxorubicin and cyclophosphamide followed by docetaxel) treatment arm (p-value=0.0006; hazard ratio=0.67, 95% C.I.=(0.54, 0.84). The beneficial treatment effect of the TCH arm is consistently demonstrated in various subgroups and is robust based on several sensitivity analyses.

There were no pre-specified alpha spending, no pre-planned interim analyses and no pre-specified significance levels for overall survival in the protocol. (b) (4)

The conclusion that adding Herceptin to TC (docetaxel + carboplatin) is beneficial involves extrapolation of data (e.g. assuming TC is worse than AC→T). The sponsor provided information on 2/29/08 in response to the Agency's requests of justification on how the TCH effect is attributed to Herceptin rather than other components in the treatment arm. Most of the sponsor's justification is based on the metastatic setting. For details on the sponsor's response see section 8.8 Additional clinical Issues-Other relevant materials.

## Safety

The safety profile of Herceptin given as monotherapy and in combination therapy is contained in the current label based on clinical trial data in patients with adjuvant and metastatic breast cancer as well as post-marketing reports. Therefore, the safety profile of Herceptin given as a combination therapy is consistent with the toxicities described in the label for the individual study drugs.

Toxicity in Study BCIRG006 was greater in the Herceptin containing treatment arms, ACTH and TCH. Most common Herceptin related adverse events were congestive heart failure and decreased left ventricular ejection fraction. The incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was 0.3% (3/1068) in the AC→TH arm and 0.2% (2/1056) in the TCH arm with no cases in the control arm. Incidence of CHF was also higher in both Herceptin-containing regimens as compared to the control, ACTH (2%), TCH (0.4%) compared to 0.3% in the control arm.

The toxicity consisted predominantly of diarrhea (TCH: 62%, ACTH: 51% compared to ACT:43%), infection (TCH: 37%, ACTH: 44% compared to ACT:38%) and rash (TCH: 9%, ACTH: 34% compared to ACT:28%). The incidence of grade 3/4 neutropenia was higher in the ACTH arm (TCH: 66%, ACTH: 71% compared to ACT:63%). The incidence of grade 3/4 thrombocytopenia was higher in the TCH arm (TCH: 5%, ACTH: 1% compared to ACT: 1%). The incidence of thrombotic adverse events was higher in patients receiving Herceptin and

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chemotherapy compared to chemotherapy alone (TCH: 3.7%, ACTH: 2.5% compared to ACT: 2.2%). The most common cardiac adverse events were: hypertension and palpitations.

Long-term serious toxicity cardiac and non-cardiac toxicity is unknown. For this reason FDA requested a PMC to fulfill this important information.

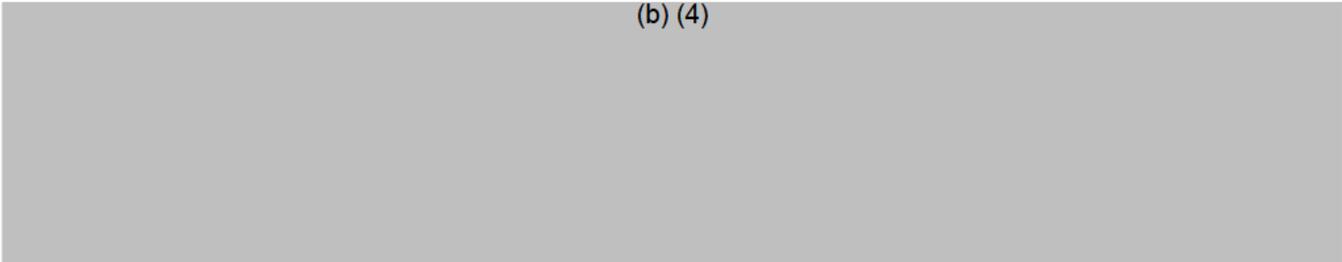
### **Dosing Regimen and Administration**

The following are the recommended doses and schedules of Herceptin for a total of 52 weeks, for the treatment of adjuvant breast cancer:

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

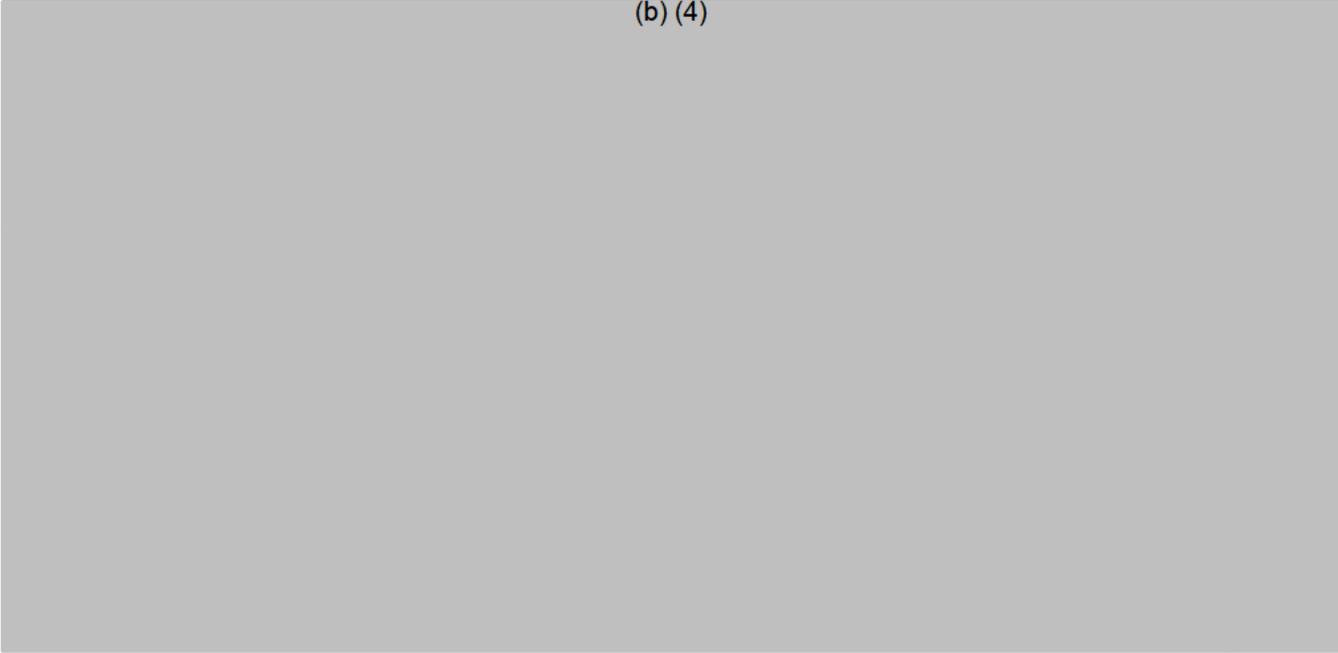
- Initial dose of 4mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30-60 minutes every three weeks.

(b) (4)



### **Special Populations**

(b) (4)



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(b) (4)

(b) (4)

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

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

**Renal Impairment**

The sponsor has not performed any renal impairment studies with Herceptin.

**Hepatic Impairment**

The sponsor has not performed any hepatic impairment studies with Herceptin.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Herceptin (Trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG<sub>1</sub> kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2. The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary [CHO]) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Herceptin is supplied in a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. The content of each Herceptin vial is 440 mg Trastuzumab, 400 mg  $\alpha,\alpha$ -trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection (BWI), USP, containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing 21 mg/mL Trastuzumab, at a pH of approximately 6

### 2.2 Currently Available Treatment for Indications

Approximately 25% of patients with invasive breast cancer have tumors that are HER2-positive, determined by either HER2 protein overexpression or HER2 gene amplification (Slamon et al. 1987, 1989). This characteristic is strongly associated with an unfavorable prognosis regardless of other prognostic factors (Slamon et al. 1987, 1989). Patients with HER2-positive breast cancer have a more aggressive disease course, evidenced by a shortened disease-free interval following adjuvant therapy and inferior overall survival (OS) compared with patients without HER2-amplified cancers (Slamon et al. 1987; Winstanley et al. 1991; Press et al. 1997; Pauletti et al. 2000).

Herceptin was initially studied in the metastatic breast cancer setting. Initial studies were designed to establish the benefits and risks of Herceptin administered either in combination with chemotherapy (Study H0648g) or as a single agent (Study H0649g) to women with HER2 overexpressing metastatic breast cancer. Efficacy and safety data supporting the current licensed indication for Herceptin in HER2 overexpressing MBC were based on two pivotal studies, H0648g and H0649g. In Study H0648g, the addition of Herceptin to chemotherapy for patients with HER2 overexpressing MBC was associated with a longer time to disease progression (median, 7.2 months for the Herceptin + chemotherapy arm vs. 4.5 months for the chemotherapy-alone arm;  $p < 0.0001$ ), a higher objective response rate (45% vs. 29%;  $p < 0.001$ ), a longer duration of objective response (median, 8.3 vs. 5.8 months), and a longer median survival (25.1 vs. 20.3 months;  $p = 0.05$ ).

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In view of the survival advantage conferred in the metastatic setting by Herceptin (trastuzumab), four large randomized studies (BCIRG 006, B-31, N9831, and HERA) were designed to evaluate the addition of Herceptin to commonly used adjuvant chemotherapy regimens.

The joint analysis of Studies **NSABP B-31** and **NCCTG N9831** formed the basis of a previous supplemental Biologics License Application (sBLA) for Herceptin, which was approved on November 2006. The studies were conducted by two major U.S. cooperative groups, the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the North Central Cancer Treatment Group (NCCTG). The **NSABP B-31** trial compared doxorubicin and cyclophosphamide followed by paclitaxel every 3 weeks (Arm 1) with the same regimen plus 52 weeks of Herceptin beginning with the first dose of paclitaxel (Arm 2). The **NCCTG N9831** study compared three regimens: doxorubicin and cyclophosphamide followed by weekly paclitaxel (Arm A), the same regimen plus 52 weeks of Herceptin initiated concurrently with paclitaxel (Arm C), or the same regimen followed by 52 weeks of Herceptin after paclitaxel (Arm B). Initially, enrollment in both studies was restricted to patients with node-positive disease; however, because of accumulating data on the risk of recurrence in women with node-negative, HER2-positive EBC, the NCCTG protocol was amended to allow the inclusion of high-risk node-negative patients. The addition of Herceptin to standard adjuvant chemotherapy led to a clinically meaningful and statistically significant improvement in DFS. The risk of recurrence among patients who received Herceptin plus chemotherapy was reduced by 52% compared with chemotherapy alone, [HR]:0.48; 95% [CI]: 0.39, 0.59;  $p < 0.0001$ ).

At the HERA study first planned interim analysis (median follow-up of 2 years), results of treatment with Herceptin for 1 year ( $n = 1693$ ) versus observation ( $n = 1694$ ) were reviewed by the Agency. Results of the 1-year analysis of Herceptin versus 2-year analysis were not released by the Independent Data Monitoring Committee (IDMC). Patients in the 1-year Herceptin arm had a 46% reduction in risk of recurrence compared with the observation arm (HR = 0.54; 95% CI: 0.44, 0.67 and a  $p < 0.0001$ ). Similar benefits were observed across important patient subgroups, including patients with node-negative disease. An unplanned survival analysis at the time of the DFS interim did not suggest a worse survival in the Herceptin arm.

The administration of adjuvant chemotherapy to women with early-stage breast cancer is a critical component of optimal treatment, especially for those women with the highest risk for recurrence. Prognostic factors of clinical outcome following systemic therapy for early-stage breast cancer include nodal status, tumor size, tumor histologic type or nuclear grade, and HER2 status (Goldhirsch et al. 2005). However, patients without lymph node involvement (node-negative patients) are also at high risk for recurrence, if at least one of the following conditions is present: tumor size  $> 2$  cm, histologic and/or nuclear Grade 2 or 3, evidence of peri-tumoral vascular invasion, HER2-positive status, or age  $< 35$  years (Goldhirsch et al. 2005). Therefore, women with node-negative, HER2-positive tumors are considered to have a similar risk for recurrence as those with node-positive, HER2-negative tumors (Goldhirsch et al. 2005). HER2-positive status has been shown in two independent analyses to be an independent and unfavorable prognostic factor for DFS in both node-negative and node-positive patients (Andrulis et al. 1998; Sun et al. 2004).

## **2.3 Availability of Proposed Active Ingredient in the United States**

Herceptin was approved by the FDA in 1998 as a single agent for patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Herceptin was also approved in 1998 in combination with paclitaxel for treatment of patients with metastatic breast cancer whose tumors overexpress HER2 protein and who have not received chemotherapy for their metastatic disease.

On November 2006, FDA approved Herceptin for the adjuvant treatment of patients with HER2 overexpressing, node-positive breast cancer as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel. In this regimen, Herceptin is given concurrently with paclitaxel and then as monotherapy, for a total duration of Herceptin therapy of 52 weeks.

On January 2008, Herceptin was approved based on efficacy and safety data from the HERA study, which demonstrated that the administration of Herceptin as a single agent for 52 weeks, after completion of surgery, chemotherapy, and radiotherapy (if applicable).

## **2.4 Important Issues With Pharmacologically Related Products**

There are no commercially available pharmacologically related products. Herceptin is the only US-FDA approved antibody product directed against the HER2 receptor.

There is one approved drug, lapatinib (Tykerb), a tyrosine kinase inhibitor that is approved for treatment of HER2-overexpressing metastatic breast cancer that has progressed following Herceptin therapy. However, lapatinib is not pharmacologically related to Herceptin.

## **2.5 Presubmission Regulatory Activity**

The study design of BCIRG006 was not discussed with FDA.

## **2.6 Other Relevant Background Information**

# **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

## **3.1 CMC (and Product Microbiology, if Applicable)**

The submission contained no new Chemistry, Manufacturing and Controls information. See Wendy Weinberg CMC Review for additional information.

### **3.2 Animal Pharmacology/Toxicology**

No new animal pharmacology/toxicology data were submitted with this BLA submission. Given the available extensive clinical experience with Herceptin, animal pharmacology toxicology data is not very useful.

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

The sBLA consisted of an electronic submission of the BCIRG006 trial, a clinical study report, CRFs and datasets.

### **4.2 Tables of Clinical Studies**

BCIRG006 was the only clinical trial submitted to support the Herceptin approval for the two indications. Two supplements were submitted with a single study with two indications under consideration:

“As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer”

“As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer”

### **4.3 Review Strategy**

The applicant submitted data to support two new proposed indications. The data were reviewed by two medical reviewers. The data supporting the proposed indication, “As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer” were reviewed by Medical Reviewer, Patricia Cortazar. The data supporting the proposed indication, “As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer” were reviewed by Medical Reviewer, Katherine Fedenko.

### **4.4 Data Quality and Integrity**

Because this is the fourth study in the of adjuvant treatment of breast cancer and the BCIRG006 data were consistent with the study results of the previous trials, FDA did not request source data verification and auditing of study sites through FDA’s Division of Scientific Integrity.

#### **4.5 Compliance with Good Clinical Practices**

The trials were conducted in compliance with good clinical practices:

Informed consents were obtained as a routine

The trials conformed to acceptable ethical standards

#### **4.6 Financial Disclosures**

Financial disclosure information submitted by the applicant was reviewed.

The submitted information seems to be adequate and the reviewer believes it to be in compliance with financial disclosure requirements.

### **5 CLINICAL PHARMACOLOGY**

#### **5.1 Pharmacokinetics**

The pharmacokinetics of Herceptin were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively. Herceptin's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377 µg/mL.

In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range = 1 to 32 days) was observed. Between Weeks 16 and 32, Herceptin serum concentrations reached a steady state with mean trough and peak concentrations of approximately 79 µg/mL and 123 µg/mL, respectively.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the sera of some patients with HER2 overexpressing tumors.

Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients with metastatic breast cancer had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations. However, with weekly dosing, most patients with elevated shed antigen levels achieved target serum Herceptin concentrations of 20 µg/mL (based on pre-clinical tumor efficacy models) by Week 8.

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

Mean serum trough concentrations of Herceptin, when administered in combination with paclitaxel, were consistently elevated approximately 1.5-fold as compared with serum concentrations of Herceptin used in combination with anthracycline plus cyclophosphamide. In primate studies, administration of Herceptin with paclitaxel resulted in a reduction in Herceptin clearance. Serum levels of Herceptin in combination with cisplatin, doxorubicin, or epirubicin

plus cyclophosphamide did not suggest any interactions; no formal drug interaction studies were performed.

## 5.2 Pharmacodynamics

There were no studies provided in the application which justified the dose and schedule based on pharmacodynamic findings. The mechanism(s) of action of trastuzumab are not well-understood. In previous submissions, a rough correlation between pharmacodynamic effects, specifically the blockade of HER-2 receptor signaling and anti-tumor activity has been identified in preclinical but not in clinical models. No additional data were provided in the application that investigated the pharmacodynamic effects of trastuzumab at the new dose and schedule.

## 5.3 Exposure-Response Relationships

The application did not contain data which addressed exposure-response relationships. The primary efficacy study was conducted at a fixed dose and dose-ranging studies were not provided which could have provided insight into the relationship between dose and efficacy or safety outcomes.

# 6 INTEGRATED REVIEW OF EFFICACY

## 6.1 Indication

BCIRG006 was submitted to support two supplements and two indications:

**“As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer”**

**“As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer”**

This medical review will address only the first indication.

## Detailed Review of Study BCIRG 006

**“A multicenter phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) and with docetaxel, platinum salt and trastuzumab (TCH) in the treatment of node positive and high risk node negative adjuvant patients with operable breast cancer containing the HER2neu alteration. BCIRG 006”**

*Principal Investigators*

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The study was sponsored by Aventis. The following were the study co-chairs:

Jean-Marc Nabholz, MD  
UCLA School of Medicine  
USA

Dennis Slamon, MD, PhD  
UCLA School of Medicine  
USA

John Crown, MD  
St. Vincent's University Hospital  
Ireland

**6.1.1.1 Protocol Milestones:**

**Table 1 BCIRG006 Protocol Milestones**

<b>Milestone</b>	<b>Dates</b>
Open for accrual	March 2001
Protocol Original Version	December, 2000
First Patient recruited	March 2001
Last Patient recruited	September 2003
1 <sup>st</sup> Planned interim analysis	June, 2005
2 <sup>nd</sup> Planned interim analysis	November, 2006
Study close to accrual	
Data Cutoff	November, 2006
Study Completion	Ongoing
sBLA submission	June, 2007
clinical study report and datasets submission	June, 2007

**6.1.1.2 Objectives:**

**Primary:**

To compare disease-free survival after treatment with doxorubicin and cyclophosphamide followed by docetaxel (Taxotere®) (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (Herceptin™) (AC→TH) and with docetaxel in combination with platinum salt and Herceptin (TCH) in the treatment of node positive and high risk node negative adjuvant patients with operable breast cancer containing the HER2neu alteration.

**Secondary:**

The secondary objectives of the study are:

- To compare overall survival between the 3 above mentioned arms.
- To compare cardiac toxicity between the 3 above mentioned arms.
- To compare toxicity and quality of life between the 3 above mentioned arms.
- To evaluate pathologic and molecular markers for predicting efficacy in these patient groups.
- To compare peripheral levels of shed HER2 ECD with FISH determination in predicting outcome to treatment with Herceptin.
- In addition, an independent socioeconomic study was to be conducted in parallel with the clinical study.

**Study Design**

The protocol design is a Phase III, multicenter, multinational, randomized, non-blinded study comparing the efficacy and safety of doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) and with docetaxel, platinum salt and trastuzumab (TCH) in the treatment of node positive and high risk node negative adjuvant patients with operable breast cancer containing the her2neu alteration. A total of 3,150 patients, 1,050 patients per treatment arm, were to be randomized to either (AC→T), (AC→TH) or (TCH). The randomization was to be centralized and stratified for node status: node negative, node positive 1-3 nodes and node positive  $\geq 4$  nodes, and for hormonal receptor status (estrogen and/or progesterone receptor positive versus negative).

All included patients in each arm will receive a fixed number of cycles of treatment.

The study primary endpoint was disease free survival. A secondary endpoint of the trial was to compare the cardiac toxicity between the 3 arms, in order to determine the safety of Herceptin with these chemotherapy regimens.

**6.1.1.3 Protocol Amendments:**

Subsequent to study initiation, there were four protocol amendments, as summarized below.

*First amendment* was dated 8 May 2001, after 4 patients had been randomized. This amendment contained the following changes:

- Echocardiography was allowed at study entry (in addition to MUGA scans) for confirmation of a patient's LVEF status.
- Echocardiography guidelines and availability of videotapes of echocardiograms were added upon request.

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- An LVEF evaluation was added at 36 months to allow for long-term assessment of cardiac function.
- Clarifications regarding the dosing of carboplatin and Herceptin, were added according to a patient's weight modification.

*Second Amendment* was dated 30 July 2001, after 34 patients had been randomized. This amendment contained the following changes:

- The dosing schedule for Herceptin monotherapy after completion of chemotherapy was modified from once a week to every 3 weeks based on the safety results and pharmacokinetics of Herceptin in two studies in patients with HER2-positive (by IHC or FISH) MBC.
- Guidelines for Herceptin initiation were modified for the AC→TH arm.
- The Herceptin post-infusion observation periods were revised.
- The optional HER2 extracellular domain (ECD) and cardiac biochemical marker sub studies were extended.

*Third amendment* was dated 10 April 2002, after 468 patients had been randomized. This amendment contained the following changes:

- The TCH regimen was modified so that the platinum salt was limited to carboplatin (i.e., cisplatin was no longer allowed), based on updated results from the BCIRG 101 and 102 studies.
- The instructions describing the administration of Herceptin and the dose calculation for carboplatin was clarified.
- Measurement of the follicle-stimulating hormone to luteinizing hormone ratio to assess menopausal status in patients < 55 years old with a history of hysterectomy without bilateral ovariectomy was no longer required.

*Fourth amendment* was dated 17 March 2005, after 3222 patients had been randomized. This amendment contained the following changes:

- Statistical considerations were revised based on the results of BCIRG 001 study: The assumed DFS rate at 5 years in the AC→T arm was changed from 55% to 70%. The IDMC requested interim efficacy analyses when 300, 450, and 650 DFS events had been observed and a main analysis when 900 DFS events had been observed (the initial protocol called for one interim analysis at 654 events and a final analysis at 1308 events).
- Following a request from the IDMC, one additional cardiac safety analysis was to be conducted when all patients had been observed for at least 9 months.
- The indication for adjuvant hormonal therapy was modified to allow the use of aromatase inhibitors for postmenopausal patients who were ER- or PR-positive, as well as for patients for whom tamoxifen was contraindicated. In addition, the use of letrozole was allowed for patients having completed 5 years of tamoxifen therapy.
- Based on American Society of Clinical Oncology 2002 follow-up guidelines, hematologic and blood chemistry evaluations and chest X-rays were no longer required during the follow-up period.

#### 6.1.1.4 Eligibility Criteria

##### Inclusion Criteria:

The protocol states:

1. Histologically proven breast cancer with an interval between definitive surgery that includes axillary lymph node involvement assessment and registration of less than or equal to 60 days. A central pathology review may be performed post randomization for confirmation of diagnosis and molecular studies. The same block used for HER2neu determination prior to randomization may be used for the central pathology review.
2. Definitive surgical treatment must be either mastectomy with axillary lymph node involvement assessment, or breast conserving surgery with axillary lymph node involvement assessment for operable breast cancer (T1-3, Clinical N0-1, M0). Margins of resected specimen from definitive surgery must be histologically free of invasive adenocarcinoma and/or ductal carcinoma in situ (DCIS). The finding of lobular carcinoma in-situ will not be scored as a positive margin.
3. Patients must be either lymph node positive or high risk node negative. Lymph node positive patients will be defined as patients having invasive adenocarcinoma with at least one axillary lymph node (pN1) showing evidence of tumor among a minimum of six resected lymph nodes. High risk lymph node negative patients will be defined as patients having invasive adenocarcinoma with either 0 (pNo) among a minimum of 6 resected lymph nodes or negative sentinel node biopsy (pNo) AND at least one of the following factors: tumor size > 2 cm, ER and/or PR status is negative, histologic and/or nuclear grade 2-3, or age < 35 years.
4. Tumor must show the presence of the HER2neu gene amplification by Fluorescence In-Situ Hybridization (FISH analysis) in a designated central laboratory.
5. Estrogen and/or progesterone receptor analysis performed on the primary tumor prior to randomization. Results must be known at the time of randomization.
6. Age  $\geq$  18 years and age  $\leq$  70 years. The upper age limit is not meant to be exclusionary but rather is based on the lack of safety data for the TCH regimen in women >70 years of age.
7. Karnofsky Performance status index  $\geq$  80%.
8. Normal cardiac function must be confirmed by LVEF (MUGA scan) and ECG within 3 months prior to registration. The result of the MUGA must be equal to or above the lower limit of normal for the institution.
9. Laboratory requirements: (within 14 days prior to registration)
  - a) Hematology:
    - i Neutrophils  $\geq$  2.0 10<sup>9</sup>/L
    - ii Platelets  $\geq$  100 10<sup>9</sup>/L
    - iii Hemoglobin  $\geq$  10 g/Dl
  - b) Hepatic function:
    - i Total bilirubin < 1 UNL
    - ii ASAT (SGOT) and ALAT (SGPT)  $\leq$  2.5 UNL
    - iii Alkaline phosphatase  $\leq$  5 UNL
    - iv Patients with ASAT and/or ALAT > 1.5 x UNL associated with alkaline phosphatase > 2.5 x UNL are not eligible for the study.

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- c) Renal function:
- i Creatinine  $\leq$  175  $\mu$ mol/L (2 mg/dL)
  - ii If limit reached, the calculated creatinine clearance should be  $\geq$  60 mL/min.
10. Complete staging work-up within 3 months prior to registration. All patients will have bilateral mammography, chest Xray (PA and lateral) and/or CT and/or MRI, abdominal ultrasound and/or CT scan and/or MRI, and bone scan. In cases of positive bone scans, bone X-ray evaluation is mandatory to rule out the possibility of metastatic bone scan positivity. Other tests may be performed as clinically indicated.
11. . Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential.
12. . An audiology assessment with normal results will be performed within 3 months of registration. This is only for those centers who have selected cisplatin as their platinum salt of choice for the BCIRG 006 study.
- \* A sample of serum/blood is requested prior to study start, and is to be sent to the central laboratory for detection of shed HER2 ECD.

Exclusion Criteria:

1. Prior systemic anticancer therapy for breast cancer (immunotherapy, hormone therapy, chemotherapy).
2. . Prior anthracycline therapy, taxoids (paclitaxel, docetaxel) or platinum salts for any malignancy.
3. . Prior radiation therapy for breast cancer.
4. Bilateral invasive breast cancer.
5. Pregnant, or lactating patients. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures during study treatment (chemotherapy, Herceptin and tamoxifen therapy) and must have negative urine or serum pregnancy test within 7 days prior to registration.
6. Any T4 or N2 or known N3 or M1 breast cancer.
7. Pre-existing motor or sensory neurotoxicity of a severity  $\geq$  grade 2 by NCI criteria.
8. Cardiac disease that would preclude the use of doxorubicin, docetaxel and Herceptin.
  - a) any documented myocardial infarction
  - b) angina pectoris that requires the use of antianginal medication
  - c) any history of documented congestive heart failure
  - d) Grade 3 or Grade 4 cardiac arrhythmia (NCI CTC, version 2.0)
  - e) clinically significant valvular heart disease
  - f) f) patients with cardiomegaly on chest x-ray or ventricular hypertrophy on ECG, unless they demonstrate by MUGA scan within the past 3 months that the LVEF is  $\geq$  the lower limit of normal for the radiology facility;
  - g) g) patients with poorly controlled hypertension i.e. diastolic greater than 100 mm/Hg. (Patients who are well controlled on medication are eligible for entry
  - h) h) patients who currently receive medications (digitalis, beta-blockers, calcium channel-blockers, etc) that alter cardiac conduction, if these medications are administered for cardiac arrhythmia, angina or congestive heart failure. If these medications are administered for other reasons (ie hypertension), the patient will be eligible.

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9. Other serious illness or medical condition:
  - a) a) history of significant neurologic or psychiatric disorders including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent
  - b) b) active uncontrolled infection
  - c) c) active peptic ulcer, unstable diabetes mellitus
  - d) d) impaired hearing (only for those patients treated at centers who have selected cisplatin as their platinum salt of choice)
10. Past or current history of neoplasm other than breast carcinoma, except for:
  - a) curatively treated non-melanoma skin cancer
  - b) in situ carcinoma of the cervix
  - c) other cancer curatively treated and with no evidence of disease for at least 10 years
  - d) ipsilateral ductal carcinoma in-situ (DCIS) of the breast
  - e) lobular carcinoma in-situ (LCIS) of the breast
11. Current therapy with any hormonal agent such as raloxifene, tamoxifen, or other selective estrogen receptor modulators (SERMs), either for osteoporosis or prevention. Patients must have discontinued these agents prior to randomization.
12. Chronic treatment with corticosteroids unless initiated > 6 months prior to study entry and at low dose ( $\leq 20$  mg methylprednisolone or equivalent).
13. Concurrent treatment with ovarian hormonal replacement therapy. Prior treatment must be stopped prior to randomization.
14. Definite contraindications for the use of corticosteroids.
15. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry.
16. Concurrent treatment with any other anti-cancer therapy.
17. Male patients.

## Study Therapy

### Dosage schedule

Patients were to be post surgically assigned to receive adjuvant treatment with either:

- AC→T: Doxorubicin  $60 \text{ mg/m}^2$  as an IV bolus in combination with cyclophosphamide  $600 \text{ mg/m}^2$  IV for four cycles. Three weeks after the last course of AC, docetaxel will be given  $100 \text{ mg/m}^2$  as 1 hour IV infusion on day 1 every 3 weeks for 4 cycles.
- AC→TH: Doxorubicin  $60 \text{ mg/m}^2$  IV in combination with cyclophosphamide  $600 \text{ mg/m}^2$  IV on an every 3 week basis for 4 cycles. Three weeks after the last cycle of AC, Herceptin  $4 \text{ mg/kg}$  initial dose by IV infusion over 90 minutes on Day 1 of Cycle 5 will be administered, followed by Herceptin  $2 \text{ mg/kg}$  by IV infusion over 30 minutes weekly starting Day 8; and docetaxel  $100 \text{ mg/m}^2$  administered by IV infusion over 1 hour on Day 2 of Cycle 5, then on day 1 on an every 3 week basis for all subsequent cycles (total 4 cycles of docetaxel). Herceptin to continue weekly for 1 year from date of first administration.

- TCH: Herceptin 4 mg/kg initial dose by IV infusion over 90 minutes on Day 1 of Cycle 1 only, followed by Herceptin 2 mg/kg by IV infusion over 30 minutes weekly starting on Day 8; and docetaxel 75 mg/m<sup>2</sup> administered on Day 2 of Cycle 1, then on day 1 of all subsequent cycles by IV infusion over 1 hour followed by carboplatin at target AUC=6 mg/mL administered by IV infusion over 30-60 minutes or minutes or cisplatin at 75 mg/m<sup>2</sup> by IV infusion over at least one hour (duration of cisplatin infusion as per center's guidelines) repeated every 3 weeks. A total of six cycles of docetaxel and platinum salt will be administered on an every 3 week basis. Herceptin will continue weekly for 1 year from date of first administration.

#### Selection of Platinum Salt for the TCH Arm:

Selection of either carboplatin or cisplatin for use in the TCH arm was at the investigator's discretion. However, a center could select only one platinum salt for all patients randomized to the BCIRG 006 study at their institution, and BCIRG was to be informed of the choice at the time of study initiation. In the case where a patient on cisplatin experiences serious toxicity (s), the investigator may change to carboplatin for remaining cycles.

- Tamoxifen Indication - Each Arm: Tamoxifen 20 mg p.o. daily for 5 years, starting 3 to 4 weeks after the last course of chemotherapy for patients with positive estrogen and/or progesterone receptor status unless there is a contraindication for the use of tamoxifen therapy.
- Radiation Indication - Each Arm: Patients treated with lumpectomy were to undergo postoperative radiation therapy after completion of chemotherapy and resolution of any side effect. Postmastectomy radiation therapy, and ipsilateral nodal radiation therapy, could be used at the discretion of the treating radiation oncologist. This was to be done in a consistent manner according to the guidelines at each institution. Radiation guidelines were to be requested from each institution prior to study start at the institution.
- Each Arm: No more than 8 days should elapse between the date of randomization and the start date of the first cycle of adjuvant chemotherapy.

#### Prophylactic premedication:

- Dexamethasone was to be given as prophylaxis for docetaxel-related hypersensitivity reactions and fluid retention.
- Primary prophylactic use of antibiotics was not allowed in either arm. Prophylactic use of antibiotics was allowed in subsequent chemotherapy cycles for those patients who experienced a serious or life-threatening infection only.
- Primary prophylactic use of G-CSF was not allowed in either arm. Prophylactic G-CSF was to be used in subsequent cycles for those patients who experienced an episode of febrile neutropenia or infection during chemotherapy.
- Antiemetic prophylaxis was mandatory for all patients.
- Hydration TCH – Cisplatin: a minimum of 1 liter intravenous fluid pre-cisplatin and 1 litre intravenous fluid post-cisplatin was required.

Prophylactic premedication regimen for Docetaxel-related hypersensitivity reactions and fluid

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retention was to be administered for all patients treated with docetaxel. The following premedication regimen included Dexamethasone 8 mg p.o. for total of 6 doses.

1. night before chemotherapy
2. immediately upon waking the morning of chemotherapy
3. one hour before infusion of docetaxel (may be given oral or intravenous)
4. night of chemotherapy
5. morning the day after chemotherapy
6. evening the day after chemotherapy

Dexamethasone 8 mg equivalent could be used

Dexamethasone 8 mg = Methylprednisolone 40 mg = Prednisone 50 mg = Prednisolone 50 mg

Treatment Duration:

AC → T arm: 4 cycles of AC every 3 weeks followed by 4 cycles of single agent docetaxel every 3 weeks was to be administered.

AC → TH arm: 4 cycles of AC every 3 weeks followed by 4 cycles of single agent docetaxel every 3 weeks with weekly Herceptin for 1 year from the time of 1st dose of Herceptin.

TCH arm: 6 cycles of TC every 3 weeks administered with weekly Herceptin for 1 year from the time of 1st dose of Herceptin.

Formulation:

Multidose vial nominally containing 440 mg Herceptin as a lyophilized, sterile powder and one vial of 20 mL Bacteriostatic Water for Injection, USP, 1.1% benzyl alcohol.

**Dose Modifications**

**Cardiac Toxicity**

The table below shows the protocol guidelines for Initiation of Herceptin in AC→ TH at the time of MUGA #2.

**Table 2 Parameters for LVEF changes at MUGA # 2**

Absolute change in LVEF between baseline and 3 weeks after last AC cycle (MUGA 2)	Decision regarding initiation of Herceptin treatment
Increase or no change	Initiate Herceptin
Decrease of ≤ 15 percentage points but at or above the radiology facility's lower limit of normal	Initiate Herceptin
Decrease of ≤ 15 percentage points and below the radiology facility's lower limit of normal	Administration of Herceptin is prohibited
Decrease of 16 or more percentage points (regardless of the radiology's facility's lower limit of normal)	Administration of Herceptin is prohibited

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The following are the protocol guidelines for performing MUGA scan and management of Herceptin in patients who have an asymptomatic decrease in LVEF from baseline (for AC→TH and TCH).

**Asymptomatic Decrease LVEF Percentage Points From Baseline**

RELATIONSHIP OF LVEF TO THE LOWER LIMIT OF NORMAL (LLN)	ABSOLUTE DECREASE OF < 10 PERCENTAGE POINTS	ABSOLUTE DECREASE OF 10 TO 15 PERCENTAGE POINTS	ABSOLUTE DECREASE OF ≥ 16 PERCENTAGE POINTS
Within radiology facility's normal limits	Continue Herceptin	Continue Herceptin	Hold Herceptin and repeat MUGA after 4 weeks
1 to 5 percentage points below the LLN	Continue Herceptin	Hold Herceptin and repeat MUGA after 4 weeks	Hold Herceptin and repeat MUGA after 4 weeks
≥ 6 percentage points below the LLN	Hold Herceptin and repeat MUGA after 4 weeks	Hold Herceptin and repeat MUGA after 4 weeks	Hold Herceptin and repeat MUGA after 4 weeks

Herceptin was to be permanently discontinued following two consecutive "hold" categories. Patients who do develop a symptomatic cardiac toxicity while on active treatment (receiving chemotherapy and/or Herceptin) were to have their treatment discontinued.

*Management of Treatment Arms in case of Cardiac Arrhythmia*

**Table 3 Dose modifications for arrhythmias**

Treatment Arm	Grade 1	Grade 2	Grade 3 / Grade 4
AC→ T During AC	Not necessary to permanently stop doxorubicin if acute dysrhythmias occurring during and shortly after	Hold AC and conduct cardiac evaluation. Based on results, continue AC at Investigator discretion. Docetaxel at discretion of	Discontinue AC. Docetaxel at discretion of investigator if recovery.
During Docetaxel	Stop or slow docetaxel infusion. Subsequent cycles to be done under continuous cardiac monitoring	Hold docetaxel and conduct cardiac evaluation. Based on results, continuation of docetaxel at investigator's discretion.	Discontinue Docetaxel .
AC→ TH During AC	Not necessary to permanently stop doxorubicin if acute dysrhythmias occurring during and shortly after doxorubicin infusion. Monitor often Docetaxel +/-Herceptin may be given.	Hold AC and conduct cardiac evaluation. Based on results, continue of AC at investigator discretion. Docetaxel +/- Herceptin at discretion of investigator.	Discontinue AC. Herceptin not permitted. Docetaxel at discretion of investigator if recovery.
During Docetaxel and Herceptin	If during either docetaxel or Herceptin, slow or stop infusion. Subsequent cycles to be done under continuous cardiac monitoring.	Hold Docetaxel and Herceptin. Conduct cardiac evaluation. Continuation of Docetaxel +/- Herceptin at investigator's discretion.	Discontinue docetaxel and Herceptin
TCH	If during either docetaxel or Herceptin, slow or stop infusion. Subsequent cycles to be done under continuous cardiac monitoring.	Hold TCH and conduct cardiac evaluation. Based on results, continuation of docetaxel/platinum +/- Herceptin at discretion of investigator.	Discontinue TCH

*Symptomatic Cardiac Left Ventricular Function*

Clinical signs and symptoms suggesting congestive heart failure (dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea,

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peripheral edema, etc) was to be confirmed by a decrease in MUGA and a chest X-ray. All CHF events and associated reports were to be reviewed by an independent team of cardiologists. LVEF assessment were to be repeated 4 to 7 days afterwards to confirm a diagnosis of congestive heart failure before considering the patient to come off treatment as per the guidelines in the table below.

**Table 4 Dose modifications for symptomatic CHF.**

Treatment Arm	Grade 3 or 4
AC→ T During AC  During Docetaxel	Discontinue AC when symptoms of heart failure present and diagnosis of CHF confirmed. Docetaxel at discretion of investigator if heart failure adequately controlled.  Docetaxel to continue at discretion of investigator.
AC→ TH During AC  During Docetaxel and Herceptin	Discontinue AC when symptoms of heart failure present and diagnosis of CHF confirmed.  Herceptin not permitted. Docetaxel at discretion of investigator if heart failure adequately controlled.
TCH	Discontinue Herceptin. Docetaxel / platinum at discretion of investigator.

*Cardiac Ischemia / Infarction*

Management of treatment arms in case of cardiac ischemia is shown in the table below.

**Table 5 Dose modifications for cardiac ischemia or infarction.**

Treatment Arm	Grade 1 or 2	Grade 3 or 4
AC→ T During AC	Continue AC with frequent monitoring. Docetaxel may be given with frequent monitoring.	Discontinue AC. Docetaxel at discretion of investigator.
During Docetaxel	Continue docetaxel with frequent monitoring.	Docetaxel to continue at investigator discretion.
AC→ TH During AC	Continue AC with frequent monitoring. Docetaxel +/- Herceptin may be given with frequent monitoring.	Discontinue AC. Herceptin not permitted. Docetaxel at discretion of investigator.
During Docetaxel and Herceptin	If during either Docetaxel or Herceptin, slow or stop infusion. Docetaxel +/- Herceptin to continue with frequent monitoring.	Discontinue Herceptin. Docetaxel to continue at investigator discretion.
TCH	If during either docetaxel or Herceptin, slow or stop infusion. TCH to continue with frequent monitoring.	Discontinue Herceptin. Docetaxel / platinum to continue at investigator discretion.

### Hematological Toxicities

*Febrile neutropenia* was defined as fever of  $\geq 38.5^{\circ}\text{C}$  or  $101.3^{\circ}\text{F}$  in the presence of neutropenia (where neutropenia is defined as  $\text{ANC} < 1.0 \times 10^9/\text{L}$ ). In case of febrile neutropenia, blood counts must be done every 2 days until recovery of  $\text{ANC} \geq 1.0$  or temperature  $< 38.5^{\circ}\text{C}$ . For all subsequent chemotherapy cycles, prophylactic G-CSF was to be added. Prophylactic antibiotics were not allowed as prophylaxis for febrile neutropenia. In the case of a second febrile neutropenia event, patient were to continue with the prophylactic G-CSF for all subsequent cycles. In addition, all chemotherapeutic drug doses were to be reduced by 20% for all remaining cycles except Herceptin dose. Chemotherapy dose reductions by 20% are as follows:

- Docetaxel Single Agent: from  $100 \text{ mg}/\text{m}^2$  to  $80 \text{ mg}/\text{m}^2$
- Docetaxel in Combination: from  $75 \text{ mg}/\text{m}^2$  to  $60 \text{ mg}/\text{m}^2$
- Doxorubicin: from  $60 \text{ mg}/\text{m}^2$  to  $48 \text{ mg}/\text{m}^2$
- Cyclophosphamide: from  $600 \text{ mg}/\text{m}^2$  to  $480 \text{ mg}/\text{m}^2$
- Carboplatin: from AUC  $6 \text{ mg}/\text{mL}$  to AUC of  $5 \text{ mg}/\text{mL}$
- Cisplatin: from  $75 \text{ mg}/\text{m}^2$  to  $60 \text{ mg}/\text{m}^2$

In the case of a 3rd event, there will be no further dose reduction. Patient were to go off study (into regular follow-up).

*Infection with (or without) neutropenia:*