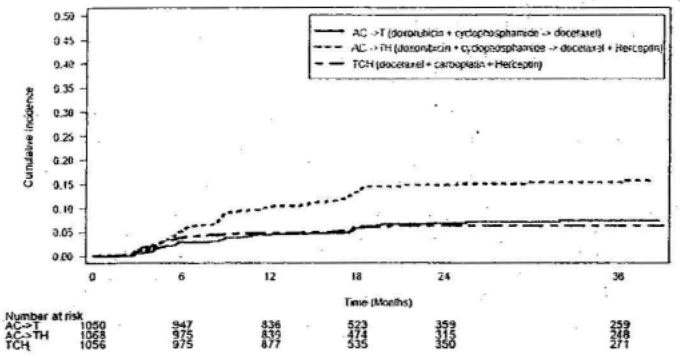
Figure 3
Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event




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 34 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
14.1Adjuvant 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

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$^2$ and cyclophosphamide 600 mg/m$^2$ were administered every 3 weeks for four cycles; docetaxel 100 mg/m2 was administered every 3 weeks for four cycles. In the TCH arm, docetaxel 75 mg/m2 and carboplatin (at a target AUC of 6 mg/mL/min as a 30 to 60 minute infusion) were administered every 3 weeks for six cycles. 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.

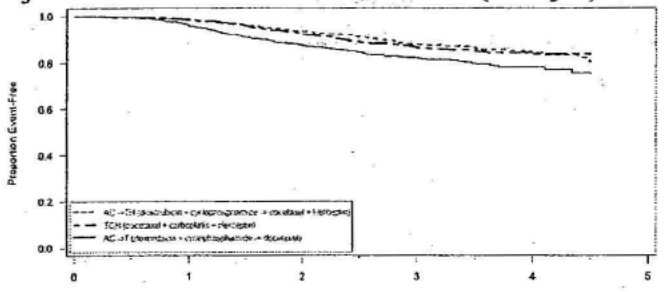
**Table 6**
Efficacy Results from Adjuvant Treatment of
Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

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

CI=confidence interval.
[a] Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.
[b] stratified log-rank test.
[c] log-rank test.
[d] NS= non-significant.
[e] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)
[f] 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)




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

## 9.5 Comments to Applicant

None

# 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

# REFERENCES

P Cortazar

Patricia Cortazar, MD
Medical Officer

5-2-08

Date

K. Fedenko

Katherine Fedenko, MS CRNP
Medical Officer

5/2/2008

Date

Patricia Keegan

Patricia Keegan, MD
Deputy Director / Acting MO Team Leader

5-2-08

Date

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# BLA 103792/5187/5189

# STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

04/21/08

**Medical Division:** Biologic Oncology Drug Products (HFD-107)
**Biometrics Division:** Division V, Office of Biostatistics (HFD-711)

| | |
|---|---|
| STATISTICAL KEY WORDS: | **Log-rank statistic; Cox's regression model** |
| BLA NUMBER: | **sBLA 103792/5187** |
| DRUG NAME: | **Herceptin ® (Trastuzumab)** |
| INDICATION: | **HER2-positive Breast Cancer** |
| SPONSOR: | **Genentech, Inc.** |
| STATISTICAL REVIEWER: | **Yuan-Li Shen, Dr. P.H. (HFD-711)** |
| STATISTICAL TEAM LEADER: | **Mark Rothmann, Ph.D. (HFD-711)** |

| | |
|---|---|
| DIVISION OF BIOMETRICS V: | |
| DIRECTOR: | **Aloka Chakravarty, Ph.D. (HFD-711)** |
| CLINICAL REVIEWERS: | **Katherine Fedenko, M.S. (HFD-107)** |
| CLINICAL TEAM LEADER: | **Patricia Keegan (HFD-107)** |
| PROJECT MANAGER: | **Erik Laughner (HFD-107)** |

**Distribution:** sBLA 103792/5187
HFD-107/ Gootenberg, Keegan, Laughner, Fedenko
HFD-150/Cortazar
HFD-711/Chakravarty, Rothmann, Shen
HFD-700/Nevius

**File directory:**
C:/BLA_2007/Herceptin/Herceptin_adj breast CA_BCIRG_statreview_AC-TH v AC-T_2007.doc

## Table of Contents

**List of Tables** ..... **iv**
**List of Figures** ..... **v**
**1 Executive Summary of Statistical Findings** ..... **1**
1.1 Recommendations and Conclusions ..... 1
1.2 Brief Overview of Clinical Studies ..... 2
1.3 Statistical Issues and Findings ..... 3
**2 Introduction** ..... **3**
2.1 Overview ..... 3
2.2 Data Sources ..... 4
**3 Statistical Evaluation** ..... **4**
3.1 Evaluation of Efficacy ..... 5
3.1.1 Introduction ..... 5
3.1.2 Efficacy Endpoints ..... 9
3.1.3 Sample Size Consideration ..... 10
3.1.4 Efficacy Analysis Method ..... 11
3.1.5 Sponsor's Efficacy and Baseline Characteristics Results and Statistical Reviewer's Findings/Comments ..... 11
3.1.6 Sponsor's Conclusions and Reviewer's Conclusions/Comments ..... 31
3.2 Evaluation of Safety ..... 33
3.2.1 Introduction ..... 33
3.2.2 Safety Endpoints ..... 33
3.2.3 Safety Analysis Method ..... 34
3.2.4 Sponsor's Safety Results and Statistical Reviewer's Findings/Comments ..... 35
3.2.5 Sponsor's Conclusions and Reviewer's Conclusions/Comments ..... 40
**4 Findings in Special/Subgroup Populations** ..... **41**
4.1 Gender ..... 41
4.2 Race ..... 41
4.3 Age ..... 41
4.4 Other Special/Subgroup Populations ..... 43
**5 Summary and Conclusions** ..... **44**
5.1 Summary of Collective Evidence ..... 45
5.2 Summary of Statistical Issues ..... 46

5.3 Conclusions and Recommendations ..... 47
**6 Appendix ..... 48**
6.1 Additional Subgroup Analysis for Disease-Free Survival ..... 48
**7 SIGNATURES/DISTRIBUTION LIST PAGE ..... 50**

## List of Tables


Table 1 Sponsor's Summary of Patient Populations ..... 12
Table 2 Sponsor's Summary of Patient Disposition While Receiving Chemotherapy ..... 13
Table 3 Sponsor's Summary of Patient Disposition While Receiving Herceptin Concurrently with Chemotherapy ..... 13
Table 4 Sponsor's Summary of Patient Disposition While Receiving Herceptin Monotherapy ..... 14
Table 5 Sponsor's Summary of Number of Physical Examination, Breast Imaging, and LVEF Assessments ..... 15
Table 6 Sponsor's Summary of Demographic and Baseline Characteristics 16
Table 7 Sponsor's Summary of Tumor and Surgery History (1) ..... 17
Table 8 Sponsor's Summary of Tumor and Surgery History (2) ..... 18
Table 9 Sponsor's Summary of High Risk Patient Population ..... 19
Table 10 Sponsor's Summary of Duration of follow-up ..... 19
Table 11 Sponsor's Summary of Disease Free Survival (using FEVAL data) – First Interim analysis ..... 20
Table 12 Reviewer's Summary of Disease Free Survival (using ITT data) – First Interim analysis ..... 21
Table 13 Sponsor's Summary of Disease Free Survival – Second Interim Analysis ..... 22
Table 14 Sponsor's Sensitivity Analyses for Efficacy Endpoint: ..... 24
Table 15 Sponsor's Sensitivity analyses for Efficacy Endpoint: ..... 25
Table 16 Sponsor's Summary of Overall Survival (using FEVAL data) – First Interim Analysis ..... 28
Table 17 Reviewer's Summary of Overall Survival (using ITT data) – First Interim analysis ..... 28
Table 18 Sponsor's Summary of Overall Survival (using ITT data) – Second Interim analysis ..... 29
Table 19 Sponsor's Summary of Sites of Distant Recurrence ..... 31
Table 20 Sponsor's Summary of Herceptin Exposure – Safety Population ... 36
Table 21 Sponsor's Summary of Symptomatic Cardiac Events per the ICRP Occurring at Any Time during the Study (Safety Population) ..... 37
Table 22 Sponsor's Summary of Asymptomatic and Symptomatic LVEF

Declines by Baseline Events (Safety Population) ..... 38
Table 23 Reviewer's Summary of the Asymptomatic LVEF Change or Post-baseline Values during the Study (Safety Population) ..... 39
Table 24 Reviewer's Summary of Disease Free Survival by Age Subgroup : *AC→TH vs. AC→T* ..... 41
Table 25 Reviewer's Summary of Disease Free Survival by Age Subgroup : *TCH vs. AC→T* ..... 42
Table 26 Reviewer's Summary of LVEF changes or post LVEF value by Age ..... 42
Table 27 Reviewer's Summary of Disease-free Survival by Baseline Prognostic Factors : *AC→TH versus AC→T* ..... 43
Table 28 Reviewer's Summary of Disease-free Survival by Baseline Prognostic Factors : *TCH versus AC→T* ..... 44
Table 30 Reviewer's Summary of Disease-free Survival by Baseline Prognostic Factors : *AC→TH versus AC→T* ..... 48

## List of Figures

Figure 1 Kaplan-Meier Estimates for Disease Free Survival (Second Interim Analysis) ..... 26
Figure 2 Kaplan-Meier estimates for Overall Survival (Second Interim Analysis) ..... 30

# 1 Executive Summary of Statistical Findings

The sponsor, Genentech, Inc., is seeking supplemental labeling claims of Herceptin® as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel, for adjuvant treatment in patients with HER-2 over-expressing, node-positive and high-risk node-negative breast cancer. This review provides a summary of the clinical efficacy and safety results, statistical issues and an overview of the studies submitted in this application. The review for the application (sBLA 103792/5189) that is seeking supplemental labeling claims of Herceptin® as part of a treatment regimen containing docetaxel and carboplatin is provided in a separated statistical review. This sponsor has requested labeling changes based on the results of the second interim analysis.

## 1.1 Recommendations and Conclusions

Based on study BCIRG006, the analysis results show that patients received Herceptin with docetaxel after completion of doxorubicin and cyclophosphamide (AC→TH) had a significantly longer disease-free survival (excluding non-breast cancer secondary malignancy) as compared with the patients who received docetaxel after completion of doxorubicin and cyclophosphamide (AC→T) (p-value<0.0001; hazard ratio=0.60, 95% C.I.=[0.48, 0.76]).

(b) (4)

The AC→TH arm appears to have higher incidences of the LVEF related events (e.g. post-baseline LVEF<50% and significant LVEF drop) as compared to AC→T arm. Further long term studies of the impact of Herceptin on cardiac adverse event are warranted.

## 1.2 Brief Overview of Clinical Studies

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

For the purpose of this statistical review, only the results for the following claim will be summarized:

1) Herceptin, as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel, is indicated for the adjuvant treatment of patients with HER2-overexpressin, node-positive (b) (4) breast cancer.

For the review of a second claim - Herceptin, as part of a treatment regimen containing docetaxel and carboplatin, is indicated for the adjuvant treatment of patients with HER2-overexpressin, node-positive (b) (4) breast cancer will be summarized in a separated statistical review (sBLA 103792/5189).

Study BCIRG006 was conducted by BCIRG and sponsored by Sanofi-Adventis (under IND 35,555) and Genentech, Inc.. About 30% of the patients were from the US. The rest of the patients were from Europe, Asia, New Zealand, Australia, Canada and others.

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 include 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.

## 1.3 Statistical Issues and Findings

The primary efficacy result based on disease-free survival (excluding non-breast cancer secondary malignancy) from study BCIRG006 shows statistical significance in favor of the AC→TH arm. The hazard ratio of the AC→TH arm versus AC→T arm is 0.60 (95% C.I. = [0.48, 0.76]) with p-value <0.0001 based on a stratified log-rank statistic.

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

The results show that higher incidences of the LVEF related events were observed, such as post-baseline LVEF<50% (17.0%and 9.1% for AC→TH, AC→T, respectively) and significant LVEF drop (13.2% and 6.4% for AC→TH and AC→T, respectively).

There are some statistical issues related to the analyses:

(b) (4)

- The by-age subgroup analyses show that the estimated hazards ratios (AC→TH vs. AC→T) are quite different between age subgroups (0.60, 95% C.I. = [0.47, 0.75] for age <65 and 1.42, 95% C.I. = [0.62, 3.24] for age ≥65). However, only 6% of patients were > 65 years old, therefore the estimated HR may not be reliable.

# 2 Introduction

This section provides an overview of the submitted trials.

## 2.1 Overview

This subsection provides a background of the design of the submitted trial, the data analyzed and the source, and any major statistical issues.

Genentech submitted the results from a multinational, randomized, open-label, active controlled clinical trial for Herceptin as an adjuvant treatment for patients with HER2-positive, early stage, node-positive or high-risk node-negative breast cancer trial. Patients who had any systemic anticancer therapy for breast cancer (immunotherapy, hormonotherapy, chemotherapy), prior anthracycline therapy, taxoids (paclitaxel, docetaxel), or platinum therapy and prior radiation therapy were excluded from the study. 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 efficacy endpoint of this trial is disease-free survival and the secondary efficacy endpoints include overall survival and quality of life.

This trial was sponsored by Sanofi-Aventis and Genentech, Inc., but the data management and ongoing validation were conducted by Breast Cancer International Research Group (BCIRG).

## 2.2 Data Sources

Data used for review is from the electronic submission received on 6/28/07. The network path is in:

\\cbsap58\M\EDRSubmissions\2007BLA\DCC60005034\blamain\crt\datasets\bcirg006

# 3 Statistical Evaluation

The efficacy and safety analysis results will be presented in this section for protocols BCIRG006.

## 3.1 Evaluation of Efficacy

### 3.1.1 Introduction

This was a phase III, open-label, randomized, active-controlled, multinational trial. Upon completion of definitive surgery and systemic adjuvant chemotherapy, patients were randomized on a 1:1:1 basis to

- AC → T (60 mg/m$^2$ doxorubicin and 600 mg/m$^2$ cyclophosphamide given every 3 weeks for four cycles followed by 100 mg/ m$^2$ docetaxel given every 3 weeks for four cycles)
- AC → TH (same chemotherapy regimen with the addition of 52 weeks of Herceptin. 2 mg/kg Herceptin was administered weekly along with 100 mg/m$^2$ docetaxel every 3 weeks for 4 cycles, and then every 3 weeks as monotherapy at 6 mg/kg for a total of 52 weeks)
- TCH (75 mg/m$^2$ docetaxel and carboplatin at an AUC of 6 mg/mL/min were administered every 3 weeks for 6 cycles, plus weekly infusions of 2 mg/kg Herceptin during chemotherapy, and then every 3 weeks at 6 mg/kg for a total duration of 52 weeks for the Herceptin).

Note: 7 days prior to starting the weekly 2 mg/kg Herceptin, the AC → TH and TCH arms receive a 4 mg/kg Herceptin loading doses.

A dynamic randomization method (Freedman and White: On the use of Pocock and Simon s method for balancing treatment numbers over prognostic factors in the controlled clinical trial. ***Biometrics* 32**: 691-694, 1976) was used for treatment allocation. The following factors were used to achieve a balance between the treatment arms:

1) Center (a total of 433 centers in 43 countries in this study);
2) Status of axillary lymph nodes involved: N0 vs. N1-3 vs. N4+;
3) Hormonal receptor status: estrogen and/or progesterone receptor positive vs. negative.

Treatment allocation was performed by an automated Interactive Voice Response System (IVRS).

Eligible patients must be between 18-70 years old, had Karnofsky Performance status index ≥ 80%, had histologically proven breast cancer with an interval between definitive surgery and registration of less than or equal to 60 days, had definitive surgical treatment that was either mastectomy or breast conserving surgery, had histologically free of invasive adenocarcinoma and/or ductal carcinoma in situ (DCIS) on the margin of resected specimen, had either lymph node positive or high risk node negative, had the presence of the HER2 gene amplification, had known estrogen and/or progesterone receptor status and had normal cardiac function confirmed by LVEF (echocardiography or MUGA scan) and ECG within 3 months prior to registration and the laboratory test results were within the protocol specified ranges.

The high risk lymph nodal negative patients was defined as patients having invasive adenocarcinoma with either 0 (pN0) among a minimum of 6 resected lymph nodes, or negative sentinel node biopsy (pN0) AND at least one of the following factors: tumor size > 2 cm, negative ER and PR status, histologic and/or nuclear grade 2-3, or age <35.

Patients who had prior systemic anticancer therapy for breast cancer (immunotherapy, hormonotherapy, chemotherapy), prior anthracycline therapy, taxoids (paclitaxel, docetaxel), or platinum therapy, prior radiation therapy, bilateral invasive breast cancer, had any T4 or N2 or known N3 or M1 breast cancer, had pre-existing motor or sensory neurotoxicity of a severity ≥ 2 by NCI criteria, had cardiac disease that would preclude the use of doxorubicin, docetaxel and Herceptin, other serious illness or medical condition, or past or current history of neoplasm other than breast carcinoma were excluded.

This trial was conducted by 433 investigators across 43 countries. Majority of patients were from Europe and North America.

The primary objective was to compare DFS after treatment with doxorubicin (Adriamycin®) and cyclophosphamide followed by docetaxel (Taxotere®) (AC→T), and doxorubicin and cyclophosphamide followed by docetaxel and Herceptin (trastuzumab) (AC→TH), or docetaxel in combination with carboplatin and Herceptin (TCH) in the adjuvant treatment of node-positive and high-risk node-negative patients with operable breast cancer containing the HER2

alteration.

The secondary objectives of this study were

- To compare OS among the three above-mentioned arms;
- To compare cardiac and non-cardiac toxicity among the three above-mentioned arms;
- Quality of life and evaluation of pathologic and molecular markers.

Efficacy assessments schedule

Patients were assessed every 3 weeks during chemotherapy, at the end of chemotherapy, and for 10 years of follow-up (after the end of chemotherapy). During follow-up, patients were assessed every 3 months for the first 2 years, every 6 months for the next 3 years, and then every year for the final 5 years. Patients in the TCH arm underwent an additional follow-up visit 6 weeks after the end of chemotherapy (EOC) visit to coincide with the EOC visit for the AC→T and AC→TH arms. The timing of the follow-up visit for TCH arm was 1.5 months behind the visit for AC→T and AC→TH arm according to the schedule.

Protocol amendments that may have impact on the statistical analysis are summarized below:

Second amendment (dated 7/30/01; after 34 patients randomized)

- Herceptin dose administration during monotherapy was change from once a week to every 3 weeks.

*Reviewer's note:*

- *Only 43 patients were randomized at this time and the number of events is very limited, so no further evaluation was performed for Herceptin dosing regimen.*

Fourth amendment (dated 3/17/05; after 3222 patients randomized)

- Change the required number of events for final analyses due to the change of the presumed 5 year survival rate in the AC-T arm (from 55% to 73%).
- Increase the number of interim analyses from one time to three times.

- O'Brien-Fleming spending function was used instead of the Haybittle-Peto's method.
- Adjustment for pair-wise comparisons was made (from based on $\alpha/3$ to a "step down" procedure).

One efficacy interim analysis was originally planned to compare Disease Free Survival (DFS) between treatments. The original efficacy interim analysis was based on Peto's method in which a significance level of 0.001 (654 out of 1308 DFS events) would be used for the interim analysis and 0.05 (a total of 1308 events) for the final analysis. In the fourth protocol amendment (dated 3/17/05), three interim analyses were planned instead. These three interim analyses were planned to be conducted after 300, 450 and 650 events observed. The main analysis would be conducted when 900 DFS events had been observed (sponsor used "main" analysis instead of "final" analysis to reflect the fact that two follow-up confirmatory analyses would be performed, 3 and 5 years after the main analysis). Based on the O'Brien-Fleming method, the overall significance levels of 0.0002, 0.0030 0.0111, for the three interim analyses, respectively, and an overall significance level of 0.0461 for the final analysis were planned for the study.

The interim analyses were performed by an independent statistician and the results were presented to IDMC (Independent Data Monitoring Committee).

In addition to the formal interim analyses, 4 safety evaluations were planned based on the accrual of 100 patients/arm, 300 patients/arm, 500 patients/arm and on all patients randomized. Each analysis took place after the last patient to be included in it was followed up to and including the date of follow-up visit 1 (approximately 9 months after treatment allocation). At the time of evaluation, under the planned visit schedule, at least 5 LVEF measurements should be available for each patient.

The final BCIRG statistical analysis plan (SAP) was dated 8/17/05 (note: later than the date of the first interim analysis 6/30/05). This SAP was submitted to FDA under the Sanofi-Aventis IND (IND 35,555, (b) (4) submitted on 5/1/06). Genentech also had the abbreviated statistical analysis plan (dated 1/24/07) submitted on 2/27/07. Since both documents were dated later than the first interim analysis, the statistical evaluation in this review will be primarily based on the information stated in the protocol.

### 3.1.2 Efficacy Endpoints

Primary Efficacy Variable

The primary efficacy endpoint of this study is the disease-free survival (DFS). DFS is defined as the interval from the date of randomization to the date of local, regional or metastatic breast cancer relapse or the date of second primary cancer or death from any cause, whichever occurs first.

A second invasive breast cancer diagnosis in either the ipsilateral or contralateral breast is considered a second primary malignancy. Non-melanoma skin cancer, in-situ carcinoma of the cervix, and in-situ carcinoma of the breast (lobular or ductal) are not considered as events in the assessment of DFS.

Patients who have not had an event at the time of the analysis were censored at the date of the last follow-up visit or the last contact if the last follow-up visit was missing (stated in the BCIRG's statistical analysis plan).

In the primary analysis, any data present beyond that cut-off date was censored at the cut-off date.

*Reviewer's comments:*

- *Based on the sponsor's SAS code, the last follow-up date is the latest date of LVEF, ECG, PE, AE, laboratory, scan and vital sign assessment dates and dosing dates. If the date is later than the cutoff date (11/1/06), the cutoff date will be used for the censoring date.*

- *FDA indicated that "second primary non-breast cancers are separated events from an already-diagnosed breast cancer, have different prognosis and should not be counted as a DFS event" in the April 17, 2007 pre-BLA meeting. The sponsor acknowledged the agency's comment and stated that based on their understanding the definition of DFS includes a) death; b) Relapses and c) Invasive breast cancer second primary malignancies (exclude DCIS and LCIS). The sponsor proposed a*

*sensitivity analysis to include an alternative definition of DFS in which all second primary malignancies have been removed as DFS events.*

Secondary Efficacy Variables

The secondary efficacy endpoint is overall survival (OS), defined as the time from randomization to death from any cause. Surviving patients will be censored at the date of last follow-up visit or the date of last contact if there is a missing last follow-up visit. Any data occurred after a pre-determined cutoff date will be censored at the cutoff date.

### 3.1.3 Sample Size Consideration

The sample size calculation was modified in the 4th amendment (dated 3/17/2005) after 3222 patients were randomized. The original sample size calculation was based on the following assumption:

- Assume the 5 years DFS in the AC→T arm of 55%.
- The improvement in DFS in AC-TH or TCH treated patients over AC-T is 7% (Hazard ratio=0.807).
- A level of $\alpha / 3$ to account for multiple testing of all three pairwise comparisons between these arms (i.e. AC-T vs. AC-TH, AC-T vs. TCH and AC-TH vs. TCH).

Due to the available results from study BCIRG001 in node positive early breast cancer patients, the IDMC and the steering committee of BCIRG 006 study proposed to modify the above mentioned assumptions. In the BCIRG 001 trial, 73% of patients (node positive and HER-2 positive) were disease free at a median follow-up of 55 months which translates into an estimated 5 year Disease Free Survival of 70% . Assuming the same absolute advantage of 7% in the 5 years disease free survival with power=80% and $\alpha$=0.05, the new sample size calculation was based on a presumed 5 year DFS of 70% in the AC-T. A total of 3,150 patients (1050 per arm) were necessary to have sufficient power to compare AC→T with AC→TH with TCH for all randomized patients, assuming an anticipated ineligible rate of 3%. Based on the new assumption, a total of 900 events instead of 1308 events were required for the final analysis.

*Reviewer's comments:*
*It is noted by the sponsor that no unblinded analyses of efficacy data had been performed at the time the statistical considerations were revised.*

### 3.1.4 Efficacy Analysis Method

The sponsor indicates that all analyses will be based on the intent-to-treat population unless otherwise specified. The intent to treat population consists of all patients randomized to the study. Patients are grouped according to the stratification factors and the treatment arm they were assigned to by the treatment allocation algorithm.

The stratified log-rank test (stratified by nodal status and hormonal receptor status) will be used to test for differences between treatment arms for DFS and OS data. The Kaplan-Meier method will be used to estimate and plot the probability of DFS and OS. A stratified Cox's proportional hazards model will be used to obtain hazard ratio estimates and the 95 % confidence intervals.

In the amendment 4 of the protocol (dated 3/17/05), a "step down" procedure was proposed to compare the control arm (AC-T) to each of the arm containing Herceptin (AC→TH and TCH) at a level of $\alpha/2$ to account for multiple testing. If both of these comparisons reach statistical significance then compare the two arms containing Herceptin at level $\alpha$, otherwise stop. This method was stated in the Genentech's clinical study report (CSR) and SAP.

The Genentech's SAP included subgroup analyses for the primary and secondary efficacy endpoints based on the age at randomization ($\leq$50 vs. >50; $\leq$60 vs. >60; <65 vs. $\geq$65, 40-49, 50-59), geographic region, performance status, menopausal status, ER/PR status, type of surgery and radiotherapy, number of positive lymph nodes, nodal status, pathological tumor size, nuclear grade, type of hormonal therapy received, and tumor histopathology.

### 3.1.5 Sponsor's Efficacy and Baseline Characteristics Results and Statistical Reviewer's Findings/Comments

The study was initiated on 3/19/2001. The first patient was enrolled occurred on 4/5/2001 and the last patient was enrolled occurred on 3/31/2004. This statistical review is based on sponsor's submitted data with the database cut-off date on 11/1/06 for the second interim analysis.

Twenty eight patients out of 1073 AC→T treated arm and 18 out of 1075 TCH treated patients did not receive any treatment, while only 2 patients in AC→TH treated arm did not receive any treatment. One patient in AC→T arm received Herceptin during monotherapy phase of the study. One patient was randomized to receive TCH but receive AC→TH. Six patients in AC→TH treated arm never received Herceptin. A summary of efficacy, safety and treated patient populations are shown in the following table:

**Table 1 Sponsor's Summary of Patient Populations**

| | Number of Patients | | | |
|---|---|---|---|---|
| | AC→T | AC→TH | TCH | All |
| Efficacy population [a] | 1073 | 1074 | 1075 | 3222 |
| Safety population [b] | 1050 | 1068 | 1056 | 3174 |
| Treatment received | | | | |
| AC→T | 1044 | 6 | 0 | 1050 |
| AC→TH | 1 | 1066 | 1 | 1068 |
| TCH | 0 | 0 | 1056 | 1056 |
| Untreated | 28 | 2 | 18 | 48 |

a. The efficacy population consists of all randomized patients.
b. The safety population consists of all treated patients.

The sponsor provides summaries of patient disposition based on three periods of time: during receiving chemotherapy, during receiving Herceptin concurrently with chemotherapy and during receiving Herceptin monotherapy. During receiving chemotherapy, the most frequent reason for not completing the study was adverse events (4.3%, 4.0% and 2.8% for AC→T, AC→TH and TCH, respectively). While receiving Herceptin concurrently with chemotherapy, the most frequent reason for not completing the study was due to Herceptin toxicity, which occurred higher in AC→TH (3.3%) as compared with TCH arm (1.2%) or AC→T arm (0%). While receiving Herceptin monotherapy, significant cardiac disease was the most frequent reason for patients not completing the study. The AC→TH arm had the highest incidence of significant cardiac disease during the Herceptin monotherapy (3.8%) as compared with TCH arm (1.2%) or in AC→T arm (0%).

**Table 2 Sponsor's Summary of Patient Disposition While Receiving Chemotherapy**

| | AC→T | AC→TH | TCH |
|---|---|---|---|
| Status | (n = 1073) | (n = 1074) | (n = 1075) |
| Entered chemotherapy | 1045 (97.4%) | 1072 (99.8%) | 1055 (98.1%) |
| Completed | 953 (88.8%) | 991 (92.3%) | 1011 (94.0%) |
| Did not complete because of | 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 | 0 (0.0%) | 3 (0.3%) | 1 (0.1%) |

**Table 3 Sponsor's Summary of Patient Disposition While Receiving Herceptin Concurrently with Chemotherapy**

| | AC→T | AC→TH | TCH |
|---|---|---|---|
| Status | (n = 1073) | (n = 1074) | (n = 1075) |
| Entered Herceptin during chemotherapy | 1 (0.1%) | 1041 (96.9%) | 1057 (98.3%) |
| Completed [a] | 1 (0.1%) | 969 (90.2%) | 1008 (93.8%) |
| Did not complete because of | 0 (0.0%) | 72 (6.7%) | 49 (4.6%) |
| Death | 0 (0.0%) | 0 (0.0%) | 2 (0.2%) |
| Breast cancer relapse | 0 (0.0%) | 1 (0.1%) | 1 (0.1%) |
| Second primary malignancy | 0 (0.0%) | 1 (0.1%) | 0 (0.0%) |
| Adverse experience | 0 (0.0%) | 6 (0.6%) | 13 (1.2%) |
| Herceptin toxicity | 0 (0.0%) | 35 (3.3%) | 13 (1.2%) |
| Patient refusal/consent withdrawn | 0 (0.0%) | 23 (2.1%) | 17 (1.6%) |
| Other | 0 (0.0%) | 3 (0.3%) | 3 (0.3%) |
| Missing | 0 (0.0%) | 3 (0.3%) | 0 (0.0%) |

[a] Patients whose total duration from initial to final Herceptin infusion was > 11 months were classified as having "completed" Herceptin monotherapy.

**Table 4 Sponsor's Summary of Patient Disposition While Receiving Herceptin Monotherapy**

| Status | AC→T (n = 1073) | AC→TH (n = 1074) | TCH (n = 1075) |
|---|---|---|---|
| Entered Herceptin monotherapy | 1 (0.1%) | 973 (90.6%) | 1009 (93.9%) |
| Completed [a] | 0 (0.0%) | 804 (74.9%) | 913 (84.9%) |
| Did not complete but no evidence of discontinuation [b] | 1 (0.1%) | 63 (5.9%) | 38 (3.5%) |
| Did not complete because of | 0 (0.0%) | 106 (9.9%) | 58 (5.4%) |
| Death | 0 (0.0%) | 0 (0.0%) | 1 (0.1%) |
| Breast cancer relapse | 0 (0.0%) | 8 (0.7%) | 7 (0.7%) |
| Second primary malignancy | 0 (0.0%) | 1 (0.1%) | 2 (0.2%) |
| Significant cardiac disease | 0 (0.0%) | 41 (3.8%) | 13 (1.2%) |
| Patient refusal/consent withdrawn | 0 (0.0%) | 24 (2.2%) | 12 (1.1%) |
| Lost to follow-up | 0 (0.0%) | 0 (0.0%) | 1 (0.1%) |
| Significant concomitant therapy other than anti-tumor therapy | 0 (0.0%) | 1 (0.1%) | 0 (0.0%) |
| Other | 0 (0.0%) | 30 (2.8%) | 21 (2.0%) |
| Missing | 0 (0.0%) | 1 (0.1%) | 1 (0.1%) |

[a] Patients whose total duration from initial to final Herceptin infusion was > 11 months were classified as having "completed" Herceptin monotherapy.
[b] 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."

Protocol deviation

A total of 77 patients had at least one major protocol deviation (2.3%, 2.2% and 2.6% in the AC→T, AC→TH, and TCH arms, respectively). The most frequent reasons for ineligibility were no definitive surgery performed (0.6%, 0.5% and 1.3% for AC→T, AC→TH, and TCH arms, respectively) and TNM staging not classified as T1-T3, N0-N1, M0 or margin involvement (0.4%, 0.4% and 0.9% for AC→T, AC→TH, and TCH arms, respectively).

Ten patients in the all randomized population had deviation in study treatment administration: one patient in AC→T received AC→TH; 6 patients in AC→TH arm did not receive Herceptin and one patient in TCH arm received AC→TH; two patients in the TCH arm received Herceptin, but did not receive chemotherapy;

Consistency of study assessments

The sponsor provides a summary of the numbers of breast imaging, physical examination (PE) and LVEF to evaluate the comparability of these numbers. AC→TH arm seems to have more LVEF assessments and physical examination as compared to the other two arms. The sponsor indicated that the higher number of LVEF assessments may reflect the close monitoring of the LVEF values in patients receiving AC→TH. Also, the higher number of PE may correspond to close monitoring of patients who experience significant asymptomatic LVEF declines.

**Table 5 Sponsor's Summary of Number of Physical Examination, Breast Imaging, and LVEF Assessments**

| Type of Assessment | AC→T (n = 1073) | AC→TH (n = 1074) | TCH (n = 1075) |
|---|---|---|---|
| LVEF | 6274 | 7140 | 6706 |
| Physical examination | 16845 | 17570 | 16448 |
| Breast imaging | 5454 | 5432 | 5594 |

### 3.1.5.1 Baseline Characteristics

A total of 433 centers in 43 countries accrued patients in this study. The number of patients enrolled by country ranged from 2 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%).

A summary of demographic and baseline characteristics provided by the sponsor are shown in the following table. The distribution of age, weight, body surface area and Karnofsky performance status (PS) appears to be compatible between treatment arms. The mean age in the patient population is 49. Approximately 80% of the patients had 100% Karnofsky PS.

**Table 6 Sponsor's Summary of Demographic and Baseline Characteristics**

| Status | AC→T (n = 1073) | AC→TH (n = 1074) | TCH (n = 1075) |
|---|---|---|---|
| Age (yr) | | | |
| n | 1073 | 1074 | 1075 |
| Mean (SD) | 48.8 (9.7) | 48.7 (9.7) | 48.6 (9.9) |
| Median | 49.0 | 49.0 | 49.0 |
| Range | 23–74 | 22–74 | 23–73 |
| < 65 | 1009 (94%) | 1015 (94.5%) | 1004 (93.4%) |
| ≥ 65 | 64 (6.0%) | 59 (5.5%) | 71 (6.6%) |
| Weight (kg) | | | |
| n | 1072 | 1074 | 1075 |
| Mean (SD) | 69.5 (15.2) | 70.5 (16) | 69.6 (15.1) |
| Median | 66.0 | 68.0 | 66.4 |
| BSA ($m^2$) | | | |
| n | 1072 | 1074 | 1074 |
| Mean (SD) | 1.7 (0.2) | 1.7 (0.2) | 1.7 (0.2) |
| Median | 1.7 | 1.7 | 1.7 |
| Karnofsky PS | | | |
| n | 1073 | 1074 | 1075 |
| 100% | 856 (79.8%) | 853 (79.4%) | 862 (80.2%) |
| < 100% | 217 (20.2%) | 221 (20.6%) | 213 (19.8%) |
| Geographic Region | | | |
| Asia | 55 (5.1%) | 53 (4.9%) | 49 (4.6%) |
| Europe | 455 ( 42.4%) | 450 ( 41.9%) | 456 ( 42.4%) |
| Middle East | 46 (4.3%) | 42 (3.9%) | 39 (3.6%) |
| North America | 379 ( 35.3%) | 383 ( 35.7%) | 376 ( 35.0%) |
| Oceania | 102 (9.5%) | 108 ( 10.1%) | 115 ( 10.7%) |
| South Africa | 13 (1.2%) | 18 (1.7%) | 18 (1.7%) |
| South America | 23 (2.1%) | 20 (1.9%) | 22 (2.0%) |

BSA=body surface area;
PR=progesterone receptor; PS=performance status;

A summary of tumor and surgery history is shown in the following table. In general, the distribution of tumor and surgery type was quite compatible between treatment arms. Ninety nine percent of the patients had HER-2 positive status. Majority of the patients had mastectomy (approximately 60% for AC→T and TCH arm and 62% for AC→TH arm) or axillary dissection (approximately 87% in all three arms). Most patients (>71%) also had more than one positive nodes. Approximately 54% of the patients were ER-positive and/or PR-positive.

**Table 7 Sponsor's Summary of Tumor and Surgery History (1)**

| Status | AC→T (n = 1073) | AC→TH (n = 1074) | TCH (n = 1075) |
|---|---|---|---|
| HER2 status per central laboratory | | | |
| n | 1072 [a] | 1074 | 1075 |
| Positive | 1066 (99.4%) | 1070 (99.6%) | 1073 (99.8%) |
| Negative | 6 (0.6%) | 4 (0.4%) | 2 (0.2%) |
| Primary surgery type | | | |
| n | 1073 | 1074 | 1075 |
| 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 | | | |
| n | 869 | 864 | 871 |
| Sentinel node | 113 (13.0%) | 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 | | | |
| n | 1073 | 1074 | 1075 |
| 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 | 1073 | 1074 | 1075 |
| ER-positive and/or PR-positive | 577 (53.8%) | 578 (53.8%) | 579 (53.9%) |
| ER-negative and PR-negative | 496 (46.2%) | 496 (46.2%) | 496 (46.1%) |

[a] Patient 30839 was found to be HER2-positive based on local test results but could not be assessed by the central laboratory.

Additional tumor and surgery history are summarized in the following table. Approximately 60% of the patients had greater than 2 cm tumor size. More than ninety nine percent of the patients had no margin involvement. Approximately 65%, 64% and 66% (for AC→T, AC→TH and ACT arm, respectively) had poorly differentiated nuclear grade. Approximately 90% of the patients had Infiltrating ductal carcinoma.

**Table 8 Sponsor's Summary of Tumor and Surgery History (2)**

| Status | AC→T (n = 1073) | AC→TH (n = 1074) | TCH (n = 1075) |
|---|---|---|---|
| Tumor size (cm) | | | |
| n | 1073 | 1074 | 1075 |
| ≤2 | 439 (40.9%) | 411 (38.3%) | 429 (39.9%) |
| >2 | 636 (59.3%) | 663 (61.5%) | 641 (59.7%) |
| Margin involvement | | | |
| n | 1073 | 1074 | 1074 |
| Yes | 2 (0.2%) | 3 (0.3%) | 3 (0.3%) |
| No | 1071 (99.8%) | 1071 (99.7%) | 1071 (99.7%) |
| Nuclear grade | | | |
| n | 1073 | 1074 | 1075 |
| GX: grade not assessable | 44 (4.1%) | 52 (4.8%) | 45 (4.2%) |
| G1: well differentiated | 24 (2.2%) | 12 (1.1%) | 18 (1.7%) |
| G2: moderately differentiated | 301 (28.1%) | 321 (29.9%) | 300 (27.9%) |
| G3: poorly differentiated | 701 (65.3%) | 688 (64.1%) | 709 (66.0%) |
| G4: undifferentiated | 3 (0.3%) | 1 (0.1%) | 3 (0.3%) |
| Histologic type | | | |
| n | 1073 | 1074 | 1075 |
| Infiltrating ductal carcinoma | 966 (90.0%) | 981 (91.3%) | 986 (91.7%) |
| Infiltrating lobular carcinoma | 38 (3.5%) | 31 (2.9%) | 30 (2.8%) |
| Other | 69 (6.4%) | 62 (5.8%) | 59 (5.5%) |

The following table summarized the high risk criteria among node-negative patients. Among node-negative patients, the majority of the patients met the "nuclear grade 2 or 3" high-risk criterion. The distribution based on the high risk criteria appears similar to those of the randomized population, except that the percentage of patients with tumor size >2 was approximately 10% lower than those of the randomized population.

**Table 9 Sponsor's Summary of High Risk Patient Population**

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

In the all randomized patient population, the median duration of follow-up appears to be comparable between treatment arms (median duration of follow-up was 2.9 years in the AC→T arm, 3.0 years in both the AC→TH and TCH arms). The duration of follow-up was based on time-to-the-last-contact analysis. Patients with DFS event was censored at the time of the DFS event.

**Table 10 Sponsor's Summary of Duration of follow-up**

| | AC→T (n = 1073) | AC→TH (n = 1074) | TCH (n = 1075) |
|---|---|---|---|
| Median (yr) | 2.9 | 3.0 | 3.0 |
| Range (yr) | 0.0–5.2 | 0.1–5.3 | 0.0–5.1 |
| < 1 year | 61 (5.7%) | 36 (3.4%) | 44 (4.1%) |
| 1 year | 129 (12.0%) | 109 (10.1%) | 104(9.7%) |
| 2 years | 416 (38.8%) | 443 (41.2%) | 438 (40.7%) |
| 3 years | 351 (32.7%) | 356 (33.1%) | 354 (32.9%) |
| 4 years | 114 (10.6%) | 125 (11.6%) | 127 (11.8%) |
| 5 years | 2 (0.2%) | 5 (0.5%) | 8 (0.7%) |

Note: Follow-up was the time from randomization to the last follow-up date regardless of whether a disease-free survival event occurred.

### 3.1.5.2 Primary Efficacy Endpoint Analyses

The first interim analysis was conducted by BCIRG after 322 DFS event (data cut-off date: June 30, 2005). Based on the sponsor's summary of DFS using the FEVAL dataset, the results shows that the comparison of each Herceptin treated arm (AC→TH or TCH versus AC→T) appears to have 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 11 Sponsor's Summary of Disease Free Survival (using FEVAL data) – 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 [a] | NA | 0.49 | 0.61 |
| 95% CI | NA | (0.37, 0.65) | (0.47, 0.79) |
| p-value [b] | NA | 0.0000005 | 0.000153 |

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

*Reviewer's comments:*

- *It was noted that the boundary was not calculated based on the protocol specified method (1-sided $\alpha/2$ = 0.0125 for each Herceptin-containing arm vs.* AC→T *arm). If the boundary was calculated based on the protocol specified level, the O'Brien-Fleming boundary would be 0.00002, then the comparison between TCH arm versus* AC→T *arm may not cross the boundary at the first interim analysis.*

To confirm the sponsor's results, the reviewer replicated the BCIRG's analysis (using the June 30, 2005 cutoff date) based on the ITT population. It is noted that the BCIRG's first interim analysis was based on FEVAL population. The re-analysis results are close to those from the sponsor's analyses (shown in the following table).

**Table 12 Reviewer's Summary of Disease Free Survival (using ITT data) – First Interim analysis**

| Status | AC→T (n = 1073) | AC→TH (n = 1074) | TCH (n = 1075) |
|---|---|---|---|
| Patients with an event | 156 (14.5%) | 89 (8.3%) | 106 (9.9%) |
| Stratified analysis | | | |
| Hazard ratio [a] | NA | 0.52 | 0.62 |
| 95% CI | NA | (0.40, 0.67) | (0.49, 0.80) |
| p-value [b] | NA | < 0.0001 | 0.0001 |

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

Although the BCIRG indicated that the boundary for the comparison between each Herceptin containing arm versus AC→T arm was crossed, BCIRG continued to follow-up the patients and performed the second interim analyses based on 474 DFS events (using November 1, 2006 as the cutoff date). Both Herceptin treated arms continued to show beneficial effect as compared with the AC→T arm. The hazard ratios based on the Cox's proportional hazards model was 0.61 (with 95% C.I. = [0.49, 0.76] and the nominal p-value <0.0001) and 0.67 (with 95% C.I. = [0.54, 0.83] and the nominal p-value=0.0003) for AC→TH versus AC→T and TCH versus AC→T, respectively.

The summary of DFS shows that the most dominant DFS events were the distant relapses and very few deaths contributed to the first event of the disease-free survival (AC→T: 5; AC→TH:5; and TCH:7).

**Table 13 Sponsor's Summary of Disease Free Survival – Second Interim Analysis**

| Status | AC→T (n = 1073) | AC→TH (n = 1074) | TCH (n = 1075) |
|---|---|---|---|
| First event [a] | 195 (18.2%) | 134 (12.5%) | 145 (13.5%) |
| Distant recurrence | 141 [a] | 89 | 97 |
| Local/regional recurrence [b] | 25 | 19 | 26 |
| Second primary cancer | 24 [a] | 21 | 15 |
| Death | 5 | 5 | 7 |
| Stratified analysis | | | |
| Hazard ratio [c] | NA | 0.61 | 0.67 |
| 95% CI | NA | (0.49, 0.76[e]) | (0.54, 0.83) |
| p-value [d] | 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].

*Reviewer's comments:*

- *In the second interim analysis, the comparison between TCH and* AC→T *arms crossed the O'Brien-Fleming boundary even if the boundary would have been calculated based on the 1-sided $\alpha/2 = 0.0125$ level (nominal $\alpha=0.0008$).*
- *Sponsor censored patients who did not have a DFS event at the last contact date or the cutoff date, whichever occurs earlier. The sponsor's last contact date was defined as the last follow-up date and randomization date. In order to define the last follow-up date, the sponsor select the last date from the following dates: last LVEF assessment date, last ECG date, physical examination date, cardiac AE or regular assessment dates, hematology and chemistry assessment dates, vital sign assessment date and last scan date.*

  *To evaluate the robustness of the treatment effect based on different censoring time calculation, the reviewer performed the time to DFS analysis by censoring the patients who did not have DFS event at the last scan date. If the last scan date is missing, the patients were censored at the last survival follow-up date. If the censoring date is still missing, the last contact date based on the definition similar to that used by the sponsor was used. Based on the revised censoring*

*scheme, this reviewer obtained very similar results to those shown on the sponsor provided table for the second interim analysis for DFS (i.e. Hazard ratios [95% CI] are 0.61 [0.49, 0.76]) and 0.66[0.53, 0.82] for AC→TH vs. AC→T and TCH vs. AC→T, respectively).*

- *Based on the protocol, the TCH arm started the follow-up visit about 1.5 months earlier than the follow-up visit for the AC→TH and AC→T arms. This earlier scheduled visit occurred 6 weeks after the EOC visit in the TCH arm and coincided with the end of the chemotherapy visit for the AC→TH and AC→T arms. During the follow-up visits, the clinical visit time for TCH arm was scheduled consistently 1.5 months earlier than the schedules timing planned for the AC→TH and AC→T arms to ensure equal duration between visits among all three arms. Due to such time staggering, all the subsequent visits after visit 1 during follow-up in TCH arm was 1.5 months later than the previous schedule visit time for the other two arms. To evaluate whether such timing difference may affect the DFS results, a sensitivity analysis was performed by assuming that DFS events (for patients with a DFS event) and the last contact date (for patients without a DFS event) occurred 1.5 months earlier than their actual event time or last contact time for the TCH arm. The results still indicate a significant beneficial effect in favor of the TCH arm (nominal p-value=0.0009, HR=0.70, 95% C.I. = [0.56, 0.87]).*
- *The patient allocation to treatment arms was not a stratified randomization, but an allocation that adjusts on the margin (not for combination of factors) for center, lymph nodal status and hormonal receptor status. A stratified randomization performs for each strata (which is a combination of levels) a random allocation of patients to treatment arms. A stratified analysis first performs individual comparisons within each strata (within each strata patients were randomized to treatment arms) and then integrates these comparisons into a single result. Since patients were not randomized within each strata, a stratified analysis may not be appropriate for the primary analysis. Since an adjusted analysis was sought based on lymph nodal status and hormonal receptor status, a Cox proportional hazards model with treatment indicators as factors and nodal status indicators and an ER/PR status indicator as the covariates was additionally performed. The results of that analysis are a HR = 0.61 (95 % C.I. = [0.49, 0.76]) and HR = 0.67 (95 % C.I. = [0.54, 0.83]) for*