

AC→TH vs. AC→T and TCH vs. AC→T, respectively (very close to the sponsor's results for a stratified Cox's model).

In addition an unstratified log rank test was performed. The results indicate a nominal p-value of <0.0001 and 0.0006 for AC→TH vs. AC→T and TCH vs. AC→T, respectively. The corresponding estimates from a Cox model with treatment as a factor (no covariates) are HR =0.63 (95 % C.I. = [0.51, 0.78]) and HR=0.69 (95 % C.I. = [0.56, 0.85]) for AC→TH vs. AC→T and TCH vs. AC→T, respectively.

Sponsor performed several sensitivity analyses for DFS based on a) FEVAL dataset, b) excluding second primary cancer; c) excluding metastasis disease and HER-2 negative or d) non-breast cancer second primary cancer for comparison 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 14 Sponsor's Sensitivity Analyses for Efficacy Endpoint:
AC→T versus AC→TH**

	AC→T (n = 1073)	AC→TH (n = 1074)	Hazard Ratio (95% CI) ^a	P-value ^b
	Number of events			
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 ^c	180	121	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

^c Revised by the reviewer (see comments below)

**Table 15 Sponsor's Sensitivity analyses for Efficacy Endpoint:
TCH versus AC→TH**

	AC→T (n = 1073)	TCH (n = 1075)	Hazard Ratio (95% CI) ^a	P-value ^b
	Number of events			
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 ^c	180	134	0.67 (0.54, 0.84)	0.0006
DFS, excluding metastatic disease or who were HER2-negative	194	144	0.67 (0.54, 0.84)	0.0003
Distant recurrence	144	103	0.65 (0.50, 0.84)	0.0008

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

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

c Revised by the reviewer (see comments below)

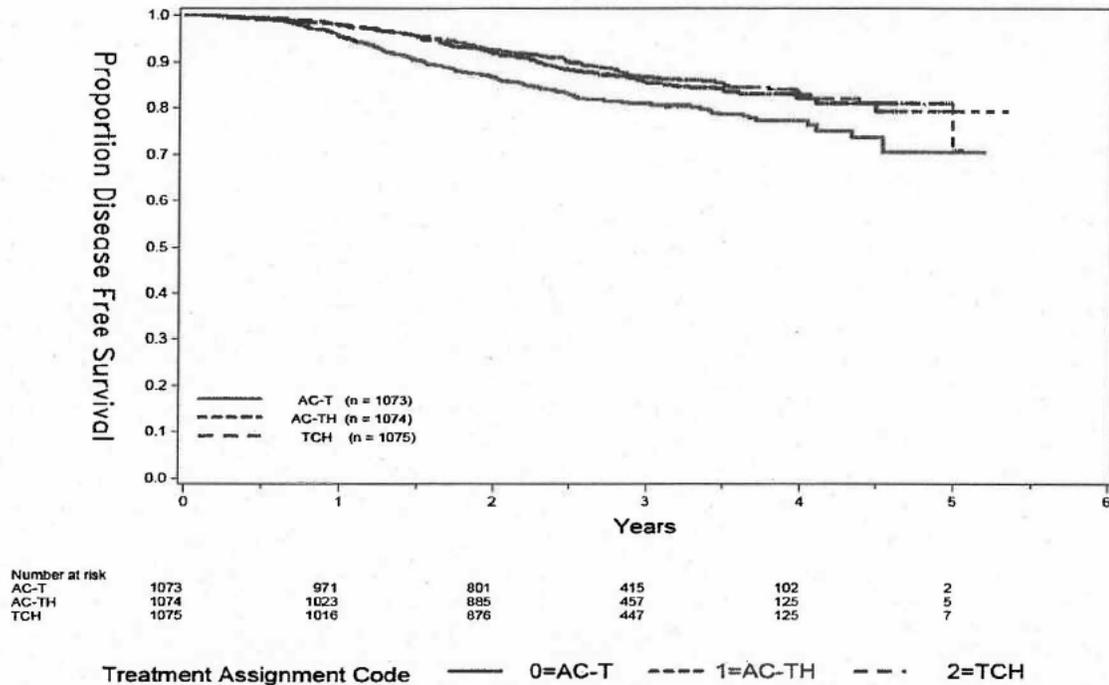
Reviewer's comments:

Per medical officer's request, a re-analysis was performed by removing 2 disease recurrence events (patients 30138, 30364, because their locoregional recurrence was not confirmed) and remove all DFS events due to the secondary primary except 8 patients (patients 32624, 31961, 30852, 31520, 33184, 31815, 31998, 31420 who had another breast primary tumor). 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).

Note : Based on the discussion in the office of Oncology meeting (4/7/08), the office decided that the definition of DFS events should exclude non-breast cancer related secondary primary tumor. The results shown in this analysis are close to the sponsor's proposed results including all secondary primary tumor and will be used for the primary efficacy analysis result.

The following figure shows this reviewer's calculated Kaplan-Meier estimate plot for disease free survival based on the November 1, 2006 cutoff date.

Figure 1 Kaplan-Meier Estimates for Disease Free Survival (Second Interim Analysis)



Reviewer's comments:

- A conclusion that adding Herceptin to TC (docetaxel + carboplatin) is beneficial would additionally involve extrapolation (e.g. assuming TC is worse than AC→T). To respond to the agency's request, the sponsor stated in the 2/29/08 submission that anthracycline-based regimens are superior to non-anthracycline-based regimens with respect to DFS and OS (quoted study EBCTCG 2005 from the Early Breast Cancer Trialists' Collaborative Group) in early stage breast cancer with HER2 overexpression. At this time, anthracycline-based chemotherapy regimens are the standard of care in the treatment of HER2-positive early stage breast cancer. The sponsor also quoted a few breast cancer study results based on metastatic setting:*

 - The results of two pilot phase II trials indicate that TCH were active based on objective tumor response rate (ORR) in HER-2 positive breast cancer in metastatic settings (ORR=79% in BCIRG101; ORR=58% in BCIRG102).*
 - A phase III trial demonstrated that Herceptin+docetaxel arm was more efficacious based on overall response rate, TTP (Time to Progression) and OS as compared with docetaxel alone arm in first line metastatic setting (In*

study M77001: ORR=61% vs. 36%; TTP=10.6 months vs. 6.1 months; OS=27.7 months vs. 18.3 months).

- (3) *The addition of carboplatin to paclitaxel and Herceptin also shows significant improved response rate and TTP as compared with Herceptin+paclitaxel in HER2-overexpressed metastatic breast cancer setting (ORR=52% vs. 36%; TTP=11.9 months vs. 6.8 months; by Robert et al., 2004).*

The sponsor indicates that TCH was chosen to offer the possibility of a less cardiotoxic regimen with improved efficacy for the adjuvant treatment of early stage HER2-positive breast cancer. Since most of the sponsor's justification is based on metastatic setting, whether AC→T is an adequate comparator arm will be subject to further justification.

3.1.5.3 Secondary Efficacy Endpoint Analyses

There was no proposal about the alpha allocation for the secondary endpoints in the protocol. Also, there was no pre-planned interim analysis for the overall survival and the significance level for the evaluation of the overall survival was not pre-specified, so the OS results can not be confirmed.

For the first interim analysis, the sponsor stated in the clinical study report that at the time of the first interim analysis (cut off date: June 30, 2005), the number of deaths was not sufficient for statistical evaluation (AC→T: 36 [3.4%]; AC→TH: 20 [1.9%]; and TCH: 28 [2.6%]). Based on this number of deaths (n=84, i.e. from data based on the Final Evaluation-FEVAL process), the sponsor indicates that the OS results did not show nominal significance at the first interim analysis (see the following table).

Table 16 Sponsor's Summary of Overall Survival (using FEVAL data) – First Interim Analysis

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event	36 (3.4%)	20 (1.0%)	28 (2.6%)
Stratified analysis			
Hazard ratio ^a	NA	0.52	0.71
95% CI	NA	(0.30, 0.90)	(0.43,1.17)
p-value ^b	NA	0.0172	0.1784

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.

To confirm the results, the reviewer performed analysis of OS based on the ITT population. Based on the submitted data and June 30, 2005 cutoff date, the reviewer obtained n=48 (4.5%) for AC→T, 26 (2.4%) for AC→TH and 31 (2.9%) for TCH arm (a total of 105 deaths). Based on this results from the ITT population, the results of OS still did not seem to cross the boundary if the O'Brien Fleming nominal significance level for evaluation of DFS were used for evaluation of OS ($\alpha=0.0002$). This reviewer's summaries of the first interim analysis results for the overall survival are shown in the following table below:

Table 17 Reviewer's Summary of Overall Survival (using ITT data) – First Interim analysis

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event	48 (4.5%)	26 (2.4%)	31 (2.9%)
Stratified analysis			
Hazard ratio ^a	NA	0.51	0.61
95% CI	NA	(0.32, 0.82)	(0.39, 0.96)
p-value ^b	NA	0.0043	0.0320

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.

At the time of the second interim analysis, a total of 185 deaths were observed (AC→T: 80; AC→TH: 49; and TCH: 56). The results indicate a favorable results of each Herceptin treated arms versus the AC→T arm. The hazard ratios based on the Cox's

proportional hazards model was 0.58 (with 95% C.I. = [0.40, 0.83], the nominal p-value =0.0024) and 0.66 (with 95% C.I. = [0.47, 0.93], the nominal p-value=0.0182) for AC→TH versus AC→T and TCH versus AC→T, respectively.

Table 18 Sponsor's Summary of Overall Survival (using ITT data) – Second Interim analysis

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event	80 (7.5%)	49 (4.6%)	56 (5.2%)
Stratified analysis			
Hazard ratio ^a	NA	0.58	0.66
95% CI	NA	(0.40, 0.83)	(0.47, 0.93)
p-value ^b	NA	0.0024	0.0182

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:

- *The sponsor censored the patients who were still alive at the cutoff date at the last contact date defined similarly to those used for the DFS analysis.*

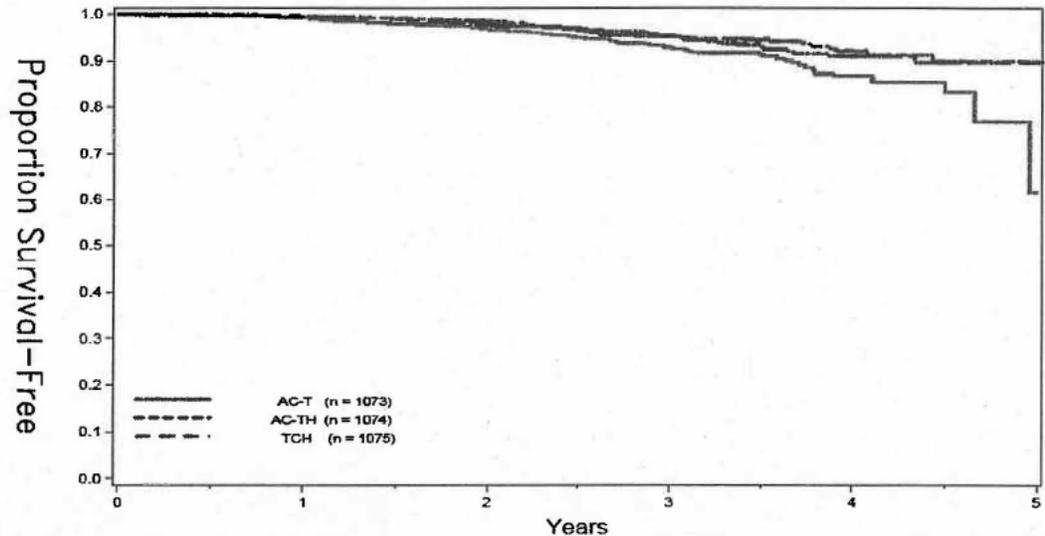
To evaluate the robustness of the treatment effect based on different censoring mechanism, this reviewer performed an OS analysis by censoring the patients who did not have a DFS event at the last follow up date. If the last follow-up date is missing, the last contact date based on the definition similar to that used for the DFS analysis was used. Based on the revised censoring scheme, the reviewer obtained similar results to those shown on the sponsor provided table for the second interim analysis for OS (i.e. nominal p-values are 0.0026 and 0.0179 for AC→TH vs. AC→T and TCH vs. AC→T, respectively).

- *According to amendment 4 of the protocol, it indicates that if both of the comparisons between each Herceptin containing arm versus AC→T reach statistical significance, then compare the two Herceptin-containing arms at α -level, otherwise stop. Beside these descriptions, the protocol did not allocate alpha for the secondary endpoints and did not plan interim analyses for overall survival. Therefore, the significance level for the comparison of each Herceptin*

containing arm versus AC→T arm for overall survival can not be determined.

The Kaplan-Meier estimates for overall survival calculated by this reviewer are presented in the following figure (based on the November 1, 2006 cutoff date):

Figure 2 Kaplan-Meier estimates for Overall Survival (Second Interim Analysis)



Number at risk	0	1	2	3	4	5
AC-T	1073	1012	883	467	112	2
AC-TH	1074	1038	929	488	128	5
TCH	1075	1031	927	469	131	8

Treatment Assignment Code 0=AC-T 1=AC-TH 2=TCH

Sponsor summarized the sites of first distant disease recurrence (shown in the following table). The most common sites of distant disease recurrence were the liver for AC→TH and AC→T arms and central nervous system (CNS) for TCH arm.

Table 19 Sponsor's Summary of Sites of Distant Recurrence

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Any distant disease recurrence	144 (13.4%)	95 (8.8%)	103 (9.6%)
Multiple liver lesions	50 (4.7%)	26 (2.4%)	18 (1.7%)
Multiple bone lesions	43 (4.0%)	21 (2.0%)	21 (2.0%)
Multiple lung lesions	35 (3.3%)	24 (2.2%)	24 (2.2%)
Central nervous system	26 (2.4%)	23 (2.1%)	26 (2.4%)
Other	15 (1.4%)	11 (1.0%)	19 (1.8%)
Ipsilateral supraclavicular lymph node	13 (1.2%)	6 (0.6%)	9 (0.8%)
Other distant nodes	13 (1.2%)	14 (1.3%)	12 (1.1%)
Solitary bone lesion	9 (0.8%)	9 (0.8%)	11 (1.0%)
Solitary lung lesion	7 (0.7%)	4 (0.4%)	7 (0.7%)
Solitary liver lesion	4 (0.4%)	8 (0.7%)	5 (0.5%)
Contralateral breast cancer	3 (0.3%)	0 (0.0%)	0 (0.0%)
Skin ^a	1 (0.1%)	1 (0.1%)	1 (0.1%)

^a Other than specific in local or regional relapse.

3.1.6 Sponsor's Conclusions and Reviewer's Conclusions/Comments

The sponsor's conclusion for efficacy include

- Results of the protocol-specified second efficacy interim analysis demonstrated that Herceptin given 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 was reduced by 39% (95% CI : 23%, 51%, p<0.0001) in the AC→TH arm relative to AC→T arm; and the risk was reduced by 33% (95% CI: 17%, 46%, =0.0003) in the TCH arm relative to AC→T arm.
- The DFS benefit in all clinically important subgroups, including subgroup based on 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 the duration of OS. The risk of death was reduced by 42% (95% CI: 17%, 60%,

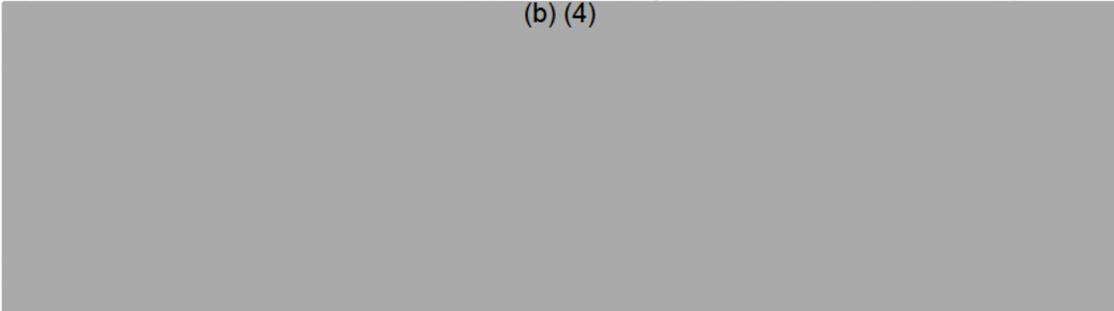
p=0.0024) in the AC→TH arm relative to AC→T arm; and the risk of death was reduced by 34% (95% CI: 7%, 53%, =0.0182) in the TCH arm relative to AC→T arm.

In summary, the sponsor concluded that 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 HER-2 positive early breast cancer.

This reviewer concluded that

- The comparisons of AC→TH vs. AC→T and TCH vs. AC→T crossed the O'Brien-Fleming boundary (nominal significance level of 0.0002) at the first interim analysis based on a total of 351 DFS events.
- Based on the second interim analysis results (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 0.60 (with 95% C.I. = [0.48, 0.76] and the nominal p-value <0.0001) and 0.67 (with 95% C.I. = [0.54, 0.84] and the nominal p-value=0.0006) for AC→TH versus AC→T and TCH versus AC→T, respectively.
- The beneficial results based on DFS in each Herceptin arm relative to the AC→T arm are consistent in many subgroups, such as Hormonal receptor status, age <65, node + or -, menopause status, KPS=100. However, the beneficial effect was less clear in some subgroups, such as patients age ≥65, KPS<100 and tumor size <2 cm. The beneficial effect of Herceptin treated arms based on DFS also appears to be robust based on various sensitivity analyses.

(b) (4)



3.2 Evaluation of Safety

3.2.1 Introduction

In this section, cardiac endpoints and analyses of cardiac adverse events for study BCIRG 006 will be discussed and the evaluation results for symptomatic and asymptomatic cardiac events will be presented.

3.2.2 Safety Endpoints

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 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.

These symptomatic grade 3 or 4 cardiac events were confirmed by the Independent Cardiac Review Panel (ICRP).

Congestive heart failure (CHF) was summarized according to three criteria:

- CHF with signs/symptoms in association with an absolute decrease of LVEF > 15% from baseline and below LNL (lower limit of normal)
- CHF with signs/symptoms in association with an absolute decrease of LVEF > 10% from baseline and below LNL
- CHF with signs/symptoms from a clinical standpoint, regardless of LVEF decline.

Asymptomatic LVEF decline

According to the 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 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 the last LVEF assessment or data cut-off date (1 November 2006). Data from patients with no post-randomization follow-up were censored on Day 1 (stated in section 9.7.3 Missing data).

3.2.3 Safety Analysis Method

Any patient who started at least one cycle of study chemotherapy or Herceptin® will be included in analysis of safety parameters. Patients are grouped according to the treatment received during the chemotherapy phase of the study.

In the Genentech's SAP, censoring time for time to safety event analyses was specified. For analysis of time to first symptomatic cardiac event, patients not experiencing an event will be censored at the earliest of the following data cutoff date (11/1/06), date of last follow-up assessment, or date of last contact. For time to first clinically significant asymptomatic cardiac event, patients not experiencing an event will be censored at the earliest of the following: the date of last LVEF assessment, data cutoff date (11/1/06), date of last follow-up assessment or date of last contact.

3.2.4 Sponsor's Safety Results and Statistical Reviewer's Findings/Comments

In this section, the chemotherapy and Herceptin exposure, sponsor's results in cardiac events and the reviewer's evaluation of the LVEF assessment will be presented.

3.2.4.1 Chemotherapy, Herceptin Exposure and Results of Cardiac Event and LVEF Assessment

Safety analyses were based on safety population (defined as the group of patients who received at least one dose of study medication).

Chemotherapy Exposure and discontinuation

The sponsor provides summaries of the exposure for doxorubicin, cyclophosphamide and docetaxel as well as platinum salts. There was no noticeable difference between the treatment arms.

A summary of discontinuation of chemotherapy was provided by the sponsor. TCH arm had slightly higher percentage (95.6%) of patients completed protocol specified number of cycles as compared with the percentages in AC→T and AC→TH arms (91.2% and 92.4% for AC→T and AC→TH arms, respectively). The most frequent reason for premature discontinuation of chemotherapy was non-cardiac adverse event (3.9%, 3.7% 2.1% for AC→T, AC→TH and TCH arm, respectively)... Early discontinuation of chemotherapy due to a cardiac adverse event was rare (0.4%, 0.2% and 0.7% for AC→T, AC→TH and TCH arm, respectively).

Herceptin Exposure and discontinuation

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 monotherapy 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. 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 compatible between AC→TH and TCH arms.

Table 20 Sponsor's Summary of Herceptin Exposure – Safety Population

	AC→T (n = 1050)	AC→TH (n = 1068)	TCH (n = 1056)
Duration (days)			
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
Total dose (mg/kg)			
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

Summaries of Herceptin discontinuation were provided by the sponsor. In general, TCH arms appear to have higher percentage of patients completing the Herceptin treatment prior to the end of chemotherapy and during the monotherapy.

Prior to the end of chemotherapy, more patients in TCH arm had completed Herceptin therapy (91% and 95% of patients in AC→TH and TCH arms, respectively). The most

frequent reason for Herceptin discontinuation is Herceptin toxicity (3.3% and 1.2% for AC→TH and TCH arms, respectively).

There are more patients discontinued Herceptin during monotherapy than that prior to the end of chemotherapy. During the monotherapy, more patients in TCH arm had completed Herceptin therapy than those in the AC→TH arm (75% and 87% of patients in AC→TH and TCH arms, respectively). During the monotherapy, the most often reason for Herceptin discontinuation was significant cardiac disease (3.9% and 1.1% for the AC→TH and TCH arms, respectively).

3.2.4.2 Symptomatic Cardiac Events

The sponsor summarized the protocol defined symptomatic cardiac events confirmed by the ICRP in the following table. The most frequent occurred symptomatic cardiac events was grade 3/4 CLVF (0.3%, 1.9% and 0.4% for AC→T, AC→TH and TCH, respectively).

Table 21 Sponsor's Summary of Symptomatic Cardiac Events per the ICRP Occurring at Any Time during the Study (Safety Population)

	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 ^a	6 (0.6%)	23 (2.2%)	12 (1.1%)

CHF = congestive heart failure; CLVF = cardiac left ventricular function

^a 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.

- *The sponsor also presented the 3-year cumulative incidence for the symptomatic cardiac events (0.5%, 2.36% and 1.16% in the AC→T, AC→TH and TCH, respectively) and the 3-year cumulative incidence of Grade 3 or 4 CLVF events (CHF) (0.3%, 2.06% and 0.4% in the AC→T, AC→TH and TCH, respectively). In these two presentations, AC→TH arm had the highest 3-year cumulative incidence rate for the symptomatic cardiac events.*

3.2.4.3 Asymptomatic Cardiac Events

According to the protocol, left ventricular ejection fraction was measured at baseline and 3, 4.5, 6, 9, 18, and 42 months after randomization. The sponsor provided a summary of compliance of LVEF assessment. The overall results indicate that all three arms appear to have compatible compliance rates (percentage of actual LVEF evaluations over expected LVEF evaluations: 81%, 85% and 84% for AC→T, AC→TH and TCH arm, respectively).

Sponsor's summary of asymptomatic cardiac events is presented in the following table based on the data which were obtained using the same methods (MUGA scan or echocardiograms) for the baseline and post-baseline LVEF assessments.

Table 22 Sponsor's Summary of Asymptomatic and Symptomatic LVEF Declines by Baseline Events (Safety Population)

	AC→T (n = 1050)	AC→TH (n = 1068)	TCH (n = 1056)
Absolute decline of > 15% from baseline and to a value below the LLN*	43 (4.1%)	109 (10.2%)	36 (3.4%)
Absolute decline of > 10% from baseline and to a value below 50%	60 (5.7%)	130 (12.2%)	48 (4.5%)
Symptomatic and/or asymptomatic decline of > 15%, below the LLN*	45 (4.3%)	115 (10.8%)	47 (4.5%)

*LLN = lower limit of normal.

Since LVEF provides more objective measurement of cardiac adverse events, this reviewer performed several analyses based on LVEF changes and post baseline LVEF values to confirm the summary results which appear on the proposed labeling (shown in the following table). These analyses indicate that AC→TH arm had higher incidence rates based on all criteria as compared with rates in the AC→T and TCH arm.

Table 23 Reviewer's Summary of the Asymptomatic LVEF Change or Post-baseline Values during the Study (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.

Reviewer's comments:

- *These summaries are based on all LVEF events after time of randomization.*
- *Based on table 59 of the sponsor's clinical study report, AC→TH arm shows consistently higher median LVEF level drop from 4.5 months up to 42 months (at months 42, the median LVEF change from baseline are -2.5%, 0% and -1% for AC→TH, TCH and AC→T, 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). In this time-to-event type of analysis, time 0 is the initiation of docetaxel or Herceptin + docetaxel for the AC \rightarrow T and AC \rightarrow TH arms and the date of randomization for the TCH arm. Since the time 0 for AC \rightarrow T and TCH arms was not comparable and the sponsor's original plots only included data up to 2 years, the sponsor was asked to provide the cumulative incidence plots based on all available data using the randomization date as the time 0 for all arms. The sponsor provided the revised cumulative incidence plots on 4/10/08. The plots show that the cumulative incidence of the significant LVEF drop in AC \rightarrow TH arm continues to be higher than the other two arms through 42 months.*

3.2.5 Sponsor's Conclusions and Reviewer's Comment

For the cardiac safety analysis, the sponsor concluded that

- The 3-year cumulative incidence of all symptomatic cardiac events and symptomatic CHF (Grade 3 or 4 CLVF) are the highest in the AC \rightarrow TH arm (see the reviewer's comment on the symptomatic cardiac events section).
- The TCH regimen is a safe and efficacious treatment option with lower incidence (relative to AC \rightarrow T) of symptomatic cardiac events overall and CHF specifically.

In cardiac safety analysis based on the change and post-baseline LVEF, the reviewer concluded that

- The result shows that AC \rightarrow TH arm had the highest incidences of post-baseline LVEF <50% (9.1%, 17.0% and 8.5% for AC \rightarrow T, AC \rightarrow TH and TCH arms, respectively) and significant LVEF drop (post-baseline LVEF <50% and change of LVEF from baseline $\geq 10\%$; 6.4%, 13.2% and 5.9% for AC \rightarrow T, AC \rightarrow TH and TCH arms, respectively) among three treatment arms. There was not much difference in the incidences of post-baseline LVEF<50% and significant LVEF drop between AC \rightarrow T and TCH arms.

4 Findings in Special/Subgroup Populations

This section provides summary statistics (hazard ratio, median survival time, count of patients) based on selected subgroups for DFS and the incidence rates of post-baseline LVEF<50%, LVEF \geq 10% reduction from baseline and significant LVEF drop.

4.1 Gender

Only female patients were included in the study.

4.2 Race

The racial information was not collected for this study, so no summary is provided. However, a subgroup analysis for DFS based on geographic region is provided in the Appendix.

4.3 Age

Sub-group analyses based on age subgroup (<65, \geq 65 years old) for DFS were performed by this reviewer. The *AC*→*TH* and *TCH* arm showed a lower risk in disease free survival as compared with the *AC*→*T* arm in patients younger than 65 years old. However, the risk reduction was not observed in patients 65 years or older. Due to the small sample size, such results should be interpreted with caution.

**Table 24 Reviewer's Summary of Disease Free Survival by Age Subgroup :
AC→*TH* vs. *AC*→*T***

Endpoint	Level	# of Patients	P-value ^a	Hazard Ratio <i>AC</i> → <i>TH</i> vs. <i>AC</i> → <i>T</i>
Age	<65	2024	0.00000	0.60(0.47,0.75)
	\geq 65	123	0.41000	1.42(0.62,3.24)

^aP-value based on Wald statistic from unstratified Cox's proportional hazards model.

**Table 25 Reviewer's Summary of Disease Free Survival by Age Subgroup :
TCH vs. AC→T**

Endpoint	Level	# of Patients	P-value ^a	Hazard Ratio TCH vs. AC→T
Age	<65	2013	0.00100	0.68(0.54,0.85)
	≥65	135	0.79500	0.89(0.37,2.15)

^aP-value based on Wald statistic from unstratified Cox's proportional hazards model.

AC→TH arm appears to have the highest incidences of the post-baseline LVEF<50%, LVEF ≥10% reduction from baseline and significant LVEF drop as compared with the AC→T arm. The higher incidence rates of these LVEF events are consistently shown in both age <65 years old and ≥65 years old.

Table 26 Reviewer's Summary of LVEF changes or post LVEF value by Age Subgroup

LVEF endpoint	Age group	AC→T # events/ # total(%)	AC→TH # events/ # total(%)	TCH # events/ # total(%)
LVEF<50% and ≥10% decrease from baseline		67/1050(6.38%)	141/1068(13.20%)	62/1056(5.87%)
	<65	62/986(6.29%)	127/1010(12.57%)	57/985(5.79%)
	≥65	5/64(7.81%)	14/58(24.14%)	5/71(7.04%)
LVEF<50%		96/1050(9.14%)	181/1068(16.95%)	90/1056(8.52%)
	<65	91/986(9.23%)	166/1010(16.44%)	84/985(8.53%)
	≥65	5/64(7.81%)	15/58(25.86%)	6/71(8.45%)
LVEF ≥10% reduction from baseline		365/1050(34.76%)	485/1068(45.41%)	374/1056(35.42%)
	<65	343/986(34.79%)	457/1010(45.25%)	347/985(35.23%)
	≥65	22/64(34.38%)	28/58(48.28%)	27/71(38.03%)

4.4 Other Special/Subgroup Populations

Additional subgroup analyses based on several baseline prognostic factors were performed by this reviewer (see Appendix) for disease-free survival event. The AC→TH and TCH arm had consistently lower risk of a disease free survival event, except in several cases where the numbers of patients are small and the trend is less clear. In this section, the subgroup analysis is based on high risk nodal status, performance status and tumor size.

The AC→TH and TCH arms show lower risk of DFS as compared with the AC→T arm in both high risk node negative and positive subgroups as well as in the performance ≥100 subgroup. However, the benefit of AC→TH or TCH treatment is less clear in the performance <100 subgroup

Table 27 Reviewer's Summary of Disease-free Survival by Baseline Prognostic Factors : AC→TH versus AC→T

Endpoint	Level	# of patients	P-value ^a	Hazard Ratio	
				AC→TH	vs. AC→T
High Risk Node	NEGATIVE	615	0.00100	0.35(0.19,0.67)	
	POSITIVE	1532	0.00200	0.68(0.54,0.87)	
Performance status	KARNOFSKY PS<100	438	0.88800	0.97(0.60,1.55)	
	KARNOFSKY PS=100	1709	<0.0001	0.56(0.44,0.72)	
Pathological tumor size	<=2	850	0.14200	0.73(0.48,1.11)	
	>2	1297	<0.0001	0.58(0.45,0.75)	

^aP-value based on Wald statistic from unstratified Cox's proportional hazards model.

Table 28 Reviewer's Summary of Disease-free Survival by Baseline Prognostic Factors : TCH versus AC→T

Endpoint	Level	# of patients	P-value ^{a*}	Hazard Ratio TCH vs. AC→T
High Risk Node	NEGATIVE	616	0.02500	0.53(0.30,0.92)
	POSITIVE	1532	0.00500	0.72(0.57,0.90)
Performance status	KARNOFSKY PS<100	430	0.53300	1.16(0.73,1.83)
	KARNOFSKY PS=100	1718	<0.0001	0.59(0.46,0.76)
Pathological tumor size	<=2	870	0.29000	0.80(0.53,1.21)
	>2	1277	0.00100	0.64(0.50,0.82)

^{a*}P-value based on Wald statistic from unstratified Cox's proportional hazards model.

5 Summary and Conclusions

Genentech submitted study BCIRG006, 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.

In study BCIRG006, a total of 3222 patients were randomized to AC → T, AC → TH and TCH arms, respectively. 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 protocol specified that three interim analyses would be conducted at the number of DFS events of 300, 450 and 650, respectively. The first interim analysis was conducted by BCIRG after 322 DFS event (data cut-off date: June 30, 2005) using FEVAL data and the second interim analysis (data cut-off date : Nov. 1, 2006) was conducted based on 474 events. This data submission is based on the data from the second interim analysis.

In this study, the primary efficacy endpoint of this trial is disease-free survival and the secondary efficacy endpoints include overall survival and quality of life.

5.1 Summary of Collective Evidence

The efficacy results demonstrated that the AC→TH had a statistically significant treatment effect based on the disease free survival (excluding non-breast cancer secondary malignancy) for adjuvant breast cancer ($p < 0.0001$; hazard ratio=0.60, 95% C.I. = [0.48, 0.76] for AC→TH vs. AC→T) (see section 3.1.5.2 Primary Efficacy Endpoint Analyses). The beneficial treatment effect of arms containing Herceptin is consistently demonstrated in various subgroups (see Section 4 Findings in Special/Subgroup Populations).

The results for AC→TH arm from study BCIRG 006 confirm the beneficial treatment effect of the 1-year Herceptin on disease free survival for adjuvant breast cancer ($p < 0.0001$ based on log-rank test; hazard ratio=0.54, 95% C.I. = [0.44, 0.67]) from HERA study. The results also further confirm the beneficial treatment effect of Herceptin in combination of chemotherapy in adjuvant breast cancer based on the joint analysis of two previous trials (NSABP B31 and NCCTG 9831; Hazard ratio of 0.48, 95% C.I. = [0.39, 0.59], comparing patients who received doxorubicin and cyclophosphamide followed by paclitaxel alone: AC→T or paclitaxel plus Herceptin: AC→T+H; see the Herceptin label for further details). The AC→TH and AC→T arms in study BCIRG 006 are similar to the treatment arms in the latter two trials for the joint analysis, except that paclitaxel (note docetaxel was used for BCIRG 006) was used in the trials for the joint analysis and was administered only weekly in one of the trial.

In cardiac event assessment of study BCIRG 006, the AC→TH arm shows higher incidences in post-baseline LVEF<50% (17.0%, 9.1% for AC→TH and AC→T, respectively) and significant LVEF drop (13.2% and 6.4% for AC→TH and AC→T, respectively). These higher incidence rates of LVEF related events in AC→TH arm observed in study BCIRG 006 confirm the higher incidence rates of LVEF related events in the Herceptin-containing arm found in HERA and the joint analysis results.

The incidence rates of the LVEF related events in AC→TH and AC→T arms of study

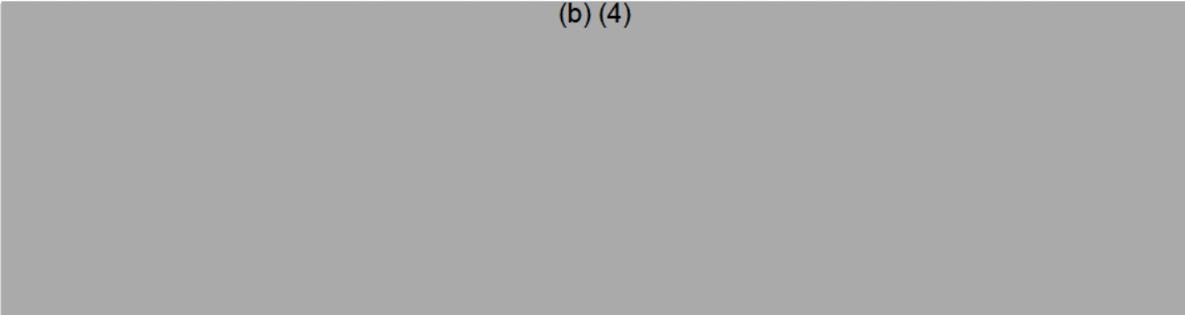
BCIRG 006 appear to be higher than those incidence rates found in the 1-year Herceptin and observation arm, respectively, of the HERA study. The incidence rates of the worst post-baseline LVEF <50% was 8.6% vs. 2.7% for 1-year Herceptin and the observation arm, respectively, in HERA; while the incidence rates of significant drop in LVEF value was 7.0% vs. 2.0% for 1-year Herceptin and the observation arm, respectively, of HERA.

The incidence rates of the LVEF related events in AC→T arm in study BCIRG 006 is similar to the incidence rates observed in the AC→T arm of the joint analysis results. However, the incidences of the LVEF related events in AC→TH arm in joined analysis results appears to be about 7% higher than the rates observed in the BCIRG 006. The incidence rates of the worst post-baseline LVEF <50% was 22.8% vs. 9.1% for AC→TH and AC→T arms, respectively, in the joined analysis; while the incidence rates of the significant drop in LVEF value was 18.3% vs. 5.4% for AC→TH and AC→T arms, respectively, in the joined analysis.

5.2 Summary of Statistical Issues

The major statistical/data issues are summarized as follows:

(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.

5.3 Conclusions and Recommendations

Based on the BCIRG006 study, the results demonstrated a beneficial treatment effect of Herceptin-containing arm (AC→TH) on disease free survival (excluding non-breast cancer secondary malignancy) for adjuvant breast cancer ($p < 0.0001$ based on stratified log-rank test; hazard ratio=0.60, 95% C.I. = [0.48, 0.76]). This beneficial treatment effect of Herceptin containing arm on disease free survival appears to be consistent across various subgroups and is robust based on several sensitivity analyses.

(b) (4)

The AC→TH arm appears to have higher incidence rates of the events defined by the change or post baseline LVEF level (e.g. post-baseline LVEF<50% and significant LVEF drop) as compared with the AC→T arm. Further long term studies of the impact of Herceptin on cardiac adverse event is warranted.

6 Appendix

6.1 Additional Subgroup Analysis for Disease-Free Survival

Table 29 Reviewer's Summary of Disease-free Survival by Baseline Prognostic Factors : *AC*→*TH* versus *AC*→*T*

Endpoint	Level	# of patients	P-value ^a	Hazard Ratio	
				<i>AC</i> → <i>TH</i>	vs. <i>AC</i> → <i>T</i>
ER and PR status	ER+ and/or PR+	1155	0.00100	0.57(0.41,0.79)	
	ER- and PR-	992	0.01000	0.68(0.51,0.91)	
Estrogen receptor status	NEGATIVE	1085	0.00600	0.68(0.51,0.90)	
	POSITIVE	1062	0.00200	0.56(0.39,0.81)	
Progesterone receptor status	NEGATIVE	1268	0.00900	0.70(0.54,0.92)	
	POSITIVE	848	0.00000	0.49(0.32,0.73)	
	UNKNOWN	31	NE	NE	
Geographic Region	ASIA	108	0.66300	1.34(0.36,4.99)	
	EUROPE	905	0.00000	0.54(0.39,0.76)	
	MIDDLE EAST	88	0.99200	1.00(0.36,2.78)	
	NORTH AMERICA	762	0.00700	0.59(0.40,0.87)	
	OCEANIA	210	0.94200	1.02(0.55,1.89)	
	SOUTH AFRICA	31	0.37500	0.51(0.11,2.28)	
	SOUTH AMERICA	43	0.23200	0.26(0.03,2.35)	
Tumor Histopathology	INFILTRATING DUCTAL	1947	0.00000	0.63(0.50,0.79)	
	INFILTRATING LOBULAR	69	0.70000	0.78(0.22,2.72)	
	OTHER	131	0.27900	0.57(0.21,1.57)	

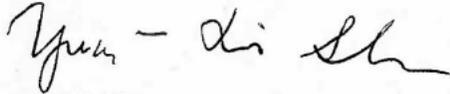
Hormonal therapy		1071	0.01700	0.71(0.54,0.94)
	AROMATASE INHIBITOR	124	0.20400	0.50(0.17,1.46)
	OTHER HORMONAL THERA	45	NE	NE
	TAMOXIFEN AND AROMAT	263	0.29200	0.64(0.28,1.47)
	TAMOXIFEN ONLY	644	0.00100	0.48(0.32,0.74)
Menopause Status	POST-MENOPAUSAL	740	0.00100	0.52(0.35,0.78)
	PRE-MENOPAUSAL	1084	0.02300	0.70(0.52,0.95)
	UNKNOWN, AGE <= 50 Y	124	0.37200	0.69(0.30,1.57)
	UNKNOWN, AGE > 50 YR	199	0.15800	0.60(0.30,1.22)
Nuclear Grade	GRADE CANNOT BE ASSE	96	0.22000	0.55(0.21,1.44)
	MODERATELY DIFFERENT	622	0.11700	0.71(0.46,1.09)
	POORLY DIFFERENTIATE	1389	0.00000	0.60(0.46,0.79)
	UNDIFFERENTIATED	4	NE	NE
	WELL DIFFERENTIATED	36	NE	NE
Pathological tumor size	<=2	850	0.14200	0.73(0.48,1.11)
	>2	1297	0.00000	0.58(0.45,0.75)
Radiation status	NO	826	0.01700	0.63(0.43,0.92)
	YES	1321	0.00100	0.63(0.48,0.83)
Radiation/lumpectomy/mastectomy	Lumpectomy only	151	0.05600	0.33(0.10,1.03)
	Lumpectomy+radiation	398	0.36300	0.77(0.44,1.35)
	Mastectomy only	591	0.06800	0.68(0.44,1.03)
	Mastectomy+radiation	552	0.00200	0.56(0.39,0.81)

^aP-value based on Wald statistic from unstratified Cox's proportional hazards model.

7 SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewer:

Date: April 21, 2008



4-21-08

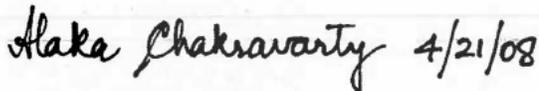
Dr. Yuan-Li Shen
Mathematical Statistician

Concurrence:



4-21-08

Dr. Mark Rothmann
Statistical Team Leader



Dr. Aloka Chakravarty
Director, Division of Biometrics V

CC:

HFD-107/ Gootenberg, Keegan, Fedenko, Laughner,
HFD-150/Cortazar
HFD-711/Chakravarty, Rothmann, Shen
HFD-700/Nevius

This review consists of 50 pages

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

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**

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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)**

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1 Executive Summary of Statistical Findings

The sponsor, Genentech, Inc., is seeking supplemental labeling claims of Herceptin[®] as part of a treatment regimen containing docetaxel and carboplatin 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 103792/5187) that is seeking supplemental labeling claims of Herceptin[®] as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel, 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 concurrently with a non-anthracycline chemotherapy regimen of docetaxel and carboplatin (TCH) 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=0.0006; hazard ratio=0.67, 95% C.I.=[0.54, 0.84]).

(b) (4)

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.

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 docetaxel and carboplatin, 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 doxorubicin, cyclophosphamide, and docetaxel, is indicated for the adjuvant treatment of patients with HER2-overexpressin, node-positive (b) (4) breast cancer will be presented in a separated statistical review (sBLA 103792/5187).

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 0.67 (p-value=0.0006 based on a stratified log-rank statistic; 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.

The results show that the incidence rates of the LVEF related events, such as post-baseline LVEF<50% (8.5% and 9.1% for TCH, AC→T, respectively) and significant LVEF drop (5.9% and 6.4% for TCH and AC→T, respectively) are similar between TCH and AC→T arms.

There are some statistical issues related to the analyses:

(b) (4)

- During the follow-up visits, the scheduled clinical visit time for TCH arm occurred consistently earlier by 1.5 months as compared with the scheduled timing for the AC→TH and AC→T arms. However, an exploratory analysis performed to assess the effect of the timing difference shows that the difference in timing of study visits does not appear to affect the efficacy results.
- A conclusion that adding Herceptin to TC (docetaxel + carboplatin) is beneficial would additionally involve extrapolation (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. Since most of the sponsor's justification is based on the metastatic setting, whether AC→T is an adequate comparator arm will be subject to further justification. For details on the sponsor's response see section 3.1.5.2 Primary Efficacy Endpoint Analyses.

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, hormone therapy, 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\bci
rg006

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/m² doxorubicin and 600 mg/m² cyclophosphamide given every 3 weeks for four cycles followed by 100 mg/m² 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/m² 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/m² 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 $\geq 80\%$, 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 α , 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 (≤ 50 vs. >50 ; ≤ 60 vs. >60 ; <65 vs. ≥ 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 (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Status			
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 (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Status			
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

	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 (m²)			
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)

	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			
n	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)

	AC→T	AC→TH	TCH
Status	(n = 1073)	(n = 1074)	(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.