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

Delayed ANC Recovery on Day 21
Blood counts on day 21
Neutrophils $\geq$1.5(x 10^9/L): treat on time
Neutrophils <1.5(x 10^9/L):CBC should be repeated every other day till day 35. Proceed with full dose chemotherapy as soon as ANC $\geq$1.5. Add G-CSF remaining cycles if recovery occurred after day 28.
If there is no recovery on day 35, (ANC < 1.5 x 10^9/L), the patient will go off chemotherapy. In arms with Herceptin, Herceptin may continue at the discretion of the investigator

Thrombocytopenia:
The following dose adjustments were recommended based on the hematologic counts on the day of or day prior to chemotherapy treatment.
> 100,000 (cells/μL): No change
50,000 to 99,000 (cells/μL):If during AC, reduce doxorubicin from 60 to 50 mg/m^2
If during docetaxel, reduce docetaxel from 100 to 75 mg/m^2
If during TCH with carboplatin, decrease carboplatin to AUC of 5 mg/mL and docetaxel from 75 to 60 mg/m^2.
If during TCH, with cisplatin, decrease docetaxel from 75 mg/m^2 to 60 mg/m^2
< 50,000 (cells/μL):Hold for 2 weeks. If after 2 weeks, and no recovery above 50,000, all chemotherapy is permanently discontinued.
If after 2 weeks, recovery > 50,000, treat with dose reduction above for all subsequent doses. Herceptin may continue in all cases above.

Anemia:
In case of $\geq$grade 2 decrease in hemoglobin, treatment with blood transfusion or erythropoietin were to be given. If the next cycle of chemotherapy was due, chemotherapy to be administered if hemoglobin is < 10 g/dL. In case of $\geq$grade 3 or 4 decrease in hemoglobin, doses were to be reduced as follows:
With docetaxel as single agent in AC→T and AC→TH, docetaxel dose to be decreased from 100 mg/m^2 to 80 mg/m^2.
If during TCH with carboplatin, docetaxel to be reduced from 75 mg/m^2 to 60 mg/m^2 and carboplatin reduced from an AUC of 6 mg/mL to an AUC of 5 mg/mL.
If during TCH with cisplatin, docetaxel to be reduced from 75 mg/m^2 to 60 mg/m^2 and cisplatin reduced from 75 mg/m^2 to 60 mg/m^2.

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

patient still experienced grade 3 or more diarrhea, the following dose reductions were recommended.
In case of diarrhea ≥ grade 3 in the AC segment of AC→T or AC →TH, reduce the dose of doxorubicin from 60 to 50 mg/m^2 in the subsequent cycles. If despite dose reduction, diarrhea still occurs at grade ≥3, the patient was to go off chemotherapy as per investigator discretion.
Docetaxel (T) Segment in AC→T, AC→TH, TCH
In case of diarrhea ≥grade 3 during treatment with docetaxel , reduce the dose of docetaxel from 75 to 60 mg/m^2 (TCH) or from 100 to 75 mg/m^2
If despite dose reduction diarrhea still occurs at grade ≥3, investigator to consider taking patient off study.

Stomatitis:
In case of grade 3 stomatitis (and/or esophagitis):
AC→T or AC→TH During AC Segment
Doxorubicin was to be reduced from 60 to 50 mg/m^2. If despite dose reduction, stomatitis still occurred at grade ≥3, doxorubicin was to be reduced from 50 to 40 mg/m^2. No further dose reduction was planned.
During Docetaxel (+/- Herceptin) Segment
Docetaxel was to be reduced from 100 to 75 mg/m^2. If despite dose reduction, stomatitis still occurred at grade ≥3, docetaxel was to be further reduced from 75 to 60 mg/m^2. No further dose reduction was planned.
TCH Docetaxel was to be reduced from 75 to 60 mg/m^2. If despite dose reduction, stomatitis still occurred at grade ≥3, docetaxel was to be further reduced from 75 to 60 mg/m^2. No further dose reduction was planned.

Hepatic Toxicity
Bilirubin and impaired liver function tests:
Docetaxel and doxorubicin doses were to be modified for hepatic toxicity. If docetaxel was delayed due to hepatic toxicity, other drugs being used in combination at that time were also to be delayed and administered when docetaxel was resumed. The same applied for delays with doxorubicin i.e. other drugs being used in combination with doxorubicin were also to be delayed until doxorubicin was resumed.
In the event that bilirubin levels are abnormal during the study, the next cycle was to be delayed by a maximum of two weeks. If no recovery, the patient was to be taken off chemotherapy.

In the event that ASAT and/or ALAT and/or alkaline phosphatase levels were abnormal in the absence of relapse, the following dose modifications were to be applied:
ASAT / ALAT/ Alkaline PhosphataseValues
≤1.5 x UNL / ≤5 x UNL: no dose modification
> 1.5 x UNL to ≤2.5 x UNL / ≤2.5 x UNL:no dose modification
> 2.5 x UNL to ≤5 x UNL / ≤2.5 x UNL:TCH: Reduce dose of docetaxel from 75 to 60 mg/m^2
AC→T: AC→TH Reduce dose of doxorubicin
from 60 to 50 mg/m^2. Reduce dose of docetaxel from 100 to 75 mg/m^2
> 1.5 x UNL to ≤5 x UNL / > 2.5 x UNL

to ≤5 x UNL:TCH: Reduce dose of docetaxel from 75 to 60 mg/m²
AC→T: AC→TH Reduce dose of doxorubicin
from 60 to 50 mg/m². Reduce dose of docetaxel from 100 to 75 mg/m²
> 5 x UNL / > 5 x UNL:All Arms: Dose delay by a maximum of 2 weeks. If
no recovery to the above figures, patient was to go off chemotherapy.
In case of recovery of liver function tests on the following cycle, the dose should be re-escalated to the previous dose-level.

Peripheral neuropathy:
In case of symptoms or signs experienced by the patient, dose modifications of docetaxel should be performed as follows:
Grade 0,1:Each Arm: no change
Grade 2: TCH (carboplatin): Delay carboplatin and docetaxel treatment by maximum of two weeks. As soon as patient recovers, treatment was to be continued with the following dose recommendations:
If patient recovered to Grade 1 toxicity, dose of docetaxel was to be decreased from 75 to 60 mg/m^2.
If grade ≥2 persisted for > 2 weeks, patient will either go off study or continue with carboplatin and Herceptin only.
In case of 2nd episode, the docetaxel dose was to be reduced from 60 to 50 mg/m^2 .
TCH (cisplatin): Delay cisplatin and docetaxel treatment by maximum of two weeks. As soon as patient recovers, treatment was to be continued with the following dose recommendations:
If patient recovers to Grade 1 toxicity, dose of docetaxel was to be decreased from 75 to 60 mg/m^2 and cisplatin from 75 to 60 mg/m^2.
If patient not recovered to Grade 1 in two weeks, patient was to either go off study or be switched to carboplatin.
If grade ≥2 persists for > 2 weeks, patient will either go off study or be switched to carboplatin.

AC→T and AC→TH:
Delay docetaxel treatment by maximum of two weeks. As soon as patient recovers, treatment should continue with the following dose recommendations:
If patient recovers to Grade 1 toxicity, dose of docetaxel will be decreased from 75 to 60 mg/m^2.
If patient not recovered to Grade 1 in two weeks, patient will go off study.
If grade ≥2 persists for > 2 weeks, patient will go off study. In case of 2nd episode, reduce dose from 75 to 60 mg/m². No further dose reduction was planned.
Grade 3: patient was to go off chemotherapy.
The same guideline also applies for patients with grade 1 neuropathy at baseline.

Cutaneous reactions:
Grade 0, 1, 2 Each Arm: no change
Grade 3: maximum two weeks delay until ≤grade 1 then for subsequent cycles of TCH:
Dose reduction of docetaxel from 75 to 60 mg/m²; Second reduction allowed of docetaxel from 60 to 50 mg/m^2
AC→T and AC→TH: Dose reduction of docetaxel 100 to 75 mg/m². Second reduction allowed of docetaxel from 75 to 60 mg/m².

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

Docetaxel anaphylactoid-type and hypersensitivity reactions:
The protocol states that in the event that a hypersensitivity reaction occurs despite premedication, it is then very likely to occur within few minutes of start of the first or of the second infusion of docetaxel. Therefore, during the 1st and the 2nd infusions, the infusion was to be given drop by drop for the first 5 minutes, and a careful evaluation of general sense of well being and whenever possible blood pressure and heart rate monitoring was to be performed so that immediate intervention would occur in response to symptoms of an untoward reaction. Facilities and equipment for resuscitation were to be immediately available: antihistamine, corticosteroids, aminophylline, epinephrine.
If a reaction occurred, the specific treatment that could be medically indicated for a given symptom was epinephrine in case of anaphylactic shock and aminophylline in case of bronchospasm. In addition, it was recommended to take the measures listed below:

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

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

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

Docetaxel related fluid retention:
No dose reduction was planned for fluid retention occurred during treatment with docetaxel. Fluid retention treatment was to start when signs and/or symptoms of fluid retention were observed, including weight gain from baseline ≥ grade 1 not otherwise explained.
The following treatment was recommended:
Furosemide 20 mg p.o. o.d. If the symptoms could not be controlled adequately, i.e. worsening of the fluid retention or spread to another area, the dose of furosemide was to be increased to 40 mg. It was recommended, that patients with fluid retention of grade 3 severity should be withdrawn from chemotherapy. In case of difficulty to make a judgment whether an effusion would be disease related or study drug related, the treatment should be continued until progressive disease in other organs is documented.

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

Table 6 Cisplatin and carboplatin modifications for renal toxicity

Creatinine Clearance mL/min	Carboplatin Dose to be Administered	Cisplatin Dose to be Administered
≥ 50 mL/min	AUC 6 mg/mL (regular dose as in protocol)	75 mg/m2
49 – 31 mL/min	AUC 5 mg/mL	60 mg/m2
≤ 30 mL/min	Delay	Delay

Auditory Toxicity:
Cisplatin is known to cause high-frequency hearing loss. If Grade 1 hearing loss occurs cisplatin was to be discontinued. Cisplatin was to be replaced with carboplatin.
Treatment Delays
Treatment with chemotherapy could be delayed no more than 2 weeks (up to Day 35) to allow recovery from acute toxicity.

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

Events which require discontinuing protocol therapy:

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

Patient Evaluations

Pre-therapy evaluations:
Women selected for entry into the study will also have the following required of them:
Concomitant medications, and their indication, used within one month prior to study entry.

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

Participants' follow-up:
All patients during the study were to be evaluated according to the following schedule until they come off chemotherapy.

Medical history and laboratory studies:

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

Table 7 Protocol Evaluations

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

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

*Physical exam will be performed at day 1 or –1 of the cycle.
** signs and symptoms will be recorded for baseline in the appropriate CRFs and for ALL other visits in the Clinical Adverse Experience CRF.
***Concomitant medication will be recorded for baseline on the appropriate CRFs, and will include all medication used within one month prior to registration. For ALL other visits concomitant medication will be captured ONLY if related to adverse events.
**** The End of Chemotherapy evaluation will be performed at 21 to 28 days after the last dose of chemotherapy (including patients that did not complete all cycles)
***** see Table 5 for follow up schedule

Follow-up After End of Chemotherapy (EOC):
Because of the difference in duration of chemotherapy treatments between the three arms, the sponsor tried to balance the timing of the follow-up assessments in order to assess efficacy at equivalent intervals.
Follow-up Visit # 1 for
AC→ T was planned 3 months after EOC
AC→ TH was planned 3 months after EOC
TCH was planned 4 ½ months after EOC.
An extra follow-up visit (FUp1a) was planned 6 weeks after EOC for the TCH arm. The timing of this extra Follow-Up occurs at the timing of the EOC for the AC→T and AC→TH arms. Physical exam, quality of life, assessment of adverse effects, and MUGA 4 was to be performed at this visit. Timing of follow-up visits were based on EOC and were to be performed according to the following schedule (see Table 5). Clinical follow-up could be more frequent according to the standard of practice at the participating center and at the discretion of the investigator.

Table 8 Follow-up visit flow chart

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

**follow up visits will occur every 6 months
***follow up visits will occur every 12 months

First 2 years: (all patients)

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

1. For patients in the TCH arm:
   A follow-up visit #1 was planned 6 weeks after EOC. The timing of this extra Follow-Up occurred at the timing of the EOC for the AC→T and AC→TH arms. Physical exam, quality of life, assessment of adverse effects, and MUGA 4 were to be performed at this visit.
2. At Follow-Up #1 (corresponds to 9 months from randomization) all arms were to have LVEF assessment (MUGA 5).
3. At Follow-Up #4 (corresponds to 18 months from randomization) all arms were to have LVEF assessment (MUGA 6).
4. Follow-up information on cardiac status were to be collected in the case report form on all patients in the cardiac safety analysis, at baseline, every 6 months for 5 years, and then annually for years 6 to 10.
   - Patients who develop congestive heart failure at any time during the study (either during active treatment or in follow-up), were required to have a repeated LVEF

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

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

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

Years 3 to 5: (all patients)

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

Years 6 to 10: (all patients)

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

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

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

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

Symptoms and toxicity:

Breast examinations

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

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

- Biostatistical Center for medical review.

Gynecologic examinations

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

Ophthalmic monitoring

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

Cardiovascular monitoring

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

Fracture monitoring

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

Mortality

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

Follow-up

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

- Disease-free survival
- Survival
- Further therapy

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

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

- Survival
- Congestive Heart Failure

Criteria for Efficacy Assessment

Disease-Free Survival (DFS):

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

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

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

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

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

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

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

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

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

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

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

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

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

Definitions of Cardiac Toxicity
Symptomatic Cardiac Event
A cardiac event occurred if a patient had a cardiac death, congestive heart failure, grade 3 or grade 4 arrhythmias, or grade 3 or grade 4 ischemia/infarction.

Cardiac Death:
Cardiac death was defined as death due to one of the following
confirmed congestive heart failure
myocardial infarction
documented primary arrhythmia
probable cardiac death i.e. sudden death without documented etiology
An autopsy was preferred in cases where cause of death has a cardiac etiology.

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

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

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

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

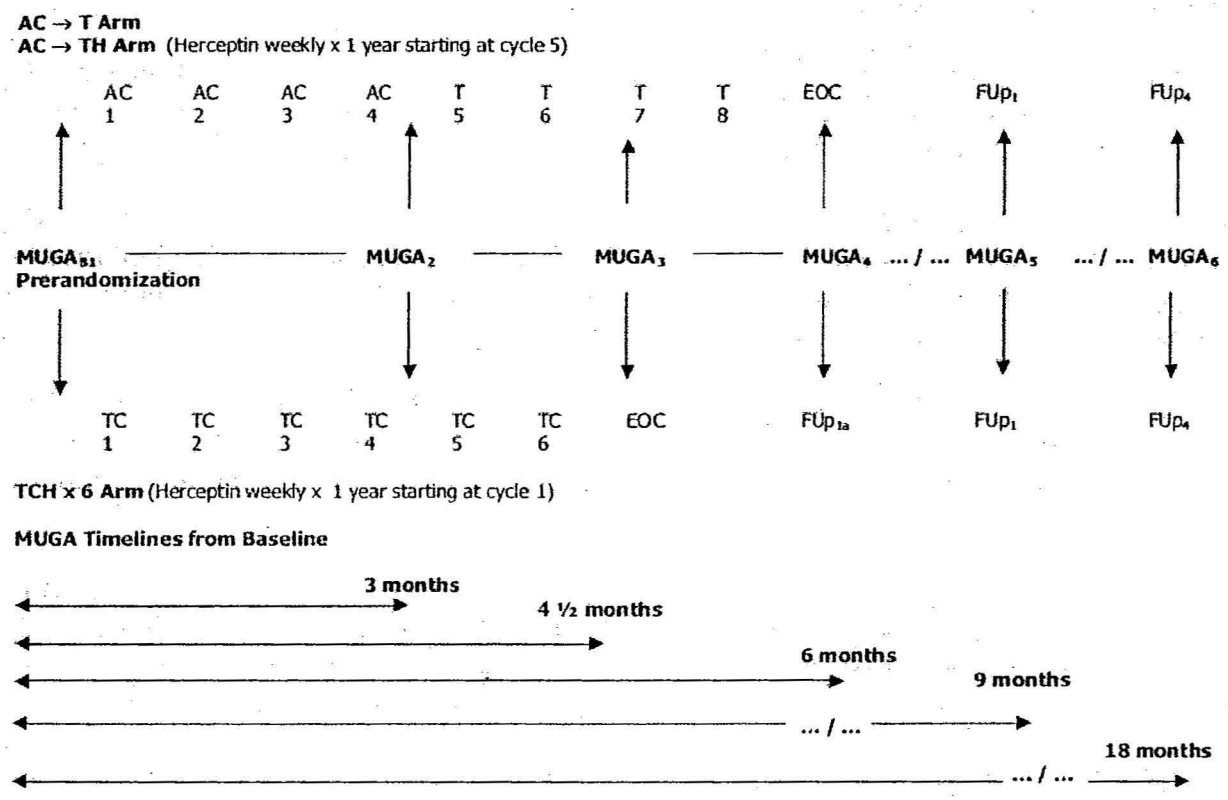
Data on the incidence and degree of LVEF decrease in the first 1,500 patients randomized were to be collected at scheduled time points and reviewed as defined below. All randomized patients will continue with the scheduled MUGAs until results on the first 1,500 patients in the cardiac safety analysis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

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

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

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

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



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

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

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

Criteria for Safety Assessment

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

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

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

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

Endpoints and Statistical Considerations

Endpoints:

Primary Endpoint:

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

Secondary Endpoints:

- Overall Survival
- Cardiac Safety
- Non- Cardiac Safety

- Quality of Life

Statistical Considerations:

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

1) Expected rate of disease free survival:
It is assumed that the proportions of patients who have no axillary lymph node involved (No), 1 to 3 axillary lymph nodes involved (N1-3) and 4 or more axillary lymph nodes involved (N4+) will be approximately 20% , 50% and 30%, respectively.
It is expected that DFS at 5 years of patients receiving AC→T in these three strata, are, respectively equal to about 67%, 57% and 42%. The overall DFS of all patients receiving AC→T will therefore be equal to about 55%. It is of clinical interest to detect a 7% improvement in 5-year DFS (ie an increase from 55% to 62%).

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

If the 5-year **DFS** were different from 55%, the trial would have a power of about 80% or higher to detect a difference of 7% between the treatment arms regardless of the 5-year DFS.
The absolute 5-year DFS difference of 7% corresponds to a hazard ratio of 0.807, i.e., a 20% relative reduction in the risk of an event (recurrence or death). The trial will have a power of 96% to detect a 25% relative reduction in the risk of an event, which corresponds to an absolute 5-year DFS difference of about 9%.

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

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

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

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

Statistical Methods

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

Cox's proportional hazards regression analysis will be performed for DFS and OS in order to adjust the treatment comparison for the major prognostic factors. These factors include age, menopausal status, type of surgery, histopathological findings, tumor size, pathological markers and molecular markers.
A statistical analysis does not plan to include any center effect in the analyses.

Primary analysis plan:

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

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

Interim Analysis and Follow-up Analyses

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

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

Cardiac Safety Analysis

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

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

The following assumptions were made:

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

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

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

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

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

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

Populations to be analyzed

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

Statistical Methods

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

permanently stopped.

Independent Data Monitoring Committee (IDMC)

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

Quality of life evaluation

A quality of life assessment for each arm was a secondary endpoint of the study. Centers participating in the analysis needed to be predefined. Some countries may be unable to participate due to the unavailability of the tools in the patient's first language.
The EORTC cancer-specific and EUROQUOL (ED-5D) general health indexes were chosen in this comparative study. The QLQ-30 (v.3.0) profile questionnaire and the BR-23 module specific to breast cancer were, respectively, 30 and 23 items in a questionnaire format. The EUROQUOL ED-5D is a five question format in addition to a visual analog scale. They were to be self-administered by the patient and completed in accordance with the following schedules.

Table 9 QOL questionnaire schedule

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

Reviewer's Comments:

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

Study Results

6.1.1.5 Patient Demographics/ Disposition

Patient Demographics

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

Enrollment:

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

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

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

Table 10 Analysis Population

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

[a] The efficacy population consists of all randomized patients.
[b] The safety population consists of all treated patients and all analyses were conducted on an "as-treated" basis.

[c] Patients 30857, 31363, 31579, 32022, 32376, and 33197 were randomized to receive AC→TH but did not receive Herceptin.
[d] Patient 31682 was randomized to AC→T but received her first dose of Herceptin during the monotherapy phase of the study. One patient (30344) was randomized to receive TCH but received AC→TH.
[e] Patients 32533 and 32816 received Herceptin but no chemotherapy.

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

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

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

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

Table 11 Patient Disposition

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

[a] Other includes "other deviation from protocol" and "other."
[b] Patients whose total duration from initial to final Herceptin infusion was > 11 months were classified as having "completed" Herceptin monotherapy.
[c] 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."
[d] other than anti-tumor therapy

6.1.1.6 Protocol Violations and Deviations:

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

Table 12 BCIRG006 Protocol Violations

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

Patient Crossover

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

Patient Characteristics

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

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

Table 13 BCIRG006 Patient Tumor Characteristics

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

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

* Patient # 30839 was HER2-positive based on local test results not assessed by the central laboratory.
** Patients # 30091, 30104, 30149, 30483, 30948, 31051, 31236, 31253, 31281, 31931, 31980, 32162
GX: not assessable, G1: well differentiated, G2: moderately differentiated, G3: poorly differentiated , G4: undifferentiated

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

Table 14 High Risk Patient Population

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

DFS

Sponsor's Analysis of time to disease recurrence:

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

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

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event	147 (13.7%)	77 (7.2%)	98 (9.1%)
Stratified analysis			
Hazard ratio [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.

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

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

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
First event [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].

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

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

	AC→T	AC→TH	Hazard Ratio (95% CI) [a]	P-value [b]
	(n = 1073)	(n =1074)		
	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	182	122	0.60 (0.48, 0.76)	< 0.0001
DFS, excluding metastatic disease or who were HER2-negative	194	134	0.61 (0.49, 0.76)	< 0.0001
Distant recurrence	144	95	0.59 (0.46, 0.77)	< 0.0001

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

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

	AC→T	TCH	Hazard Ratio (95% CI) [a]	P-value[b]
	(n = 1073)	(n =1075)		
	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	182	135	0.67 (0.54, 0.84)	0.0005
DFS, excluding metastatic disease or who were HER2-negative	194	144	0.67 (0.54, 0.83)	0.0002
Distant recurrence	144	103	0.65 (0.50, 0.84)	0.0008

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

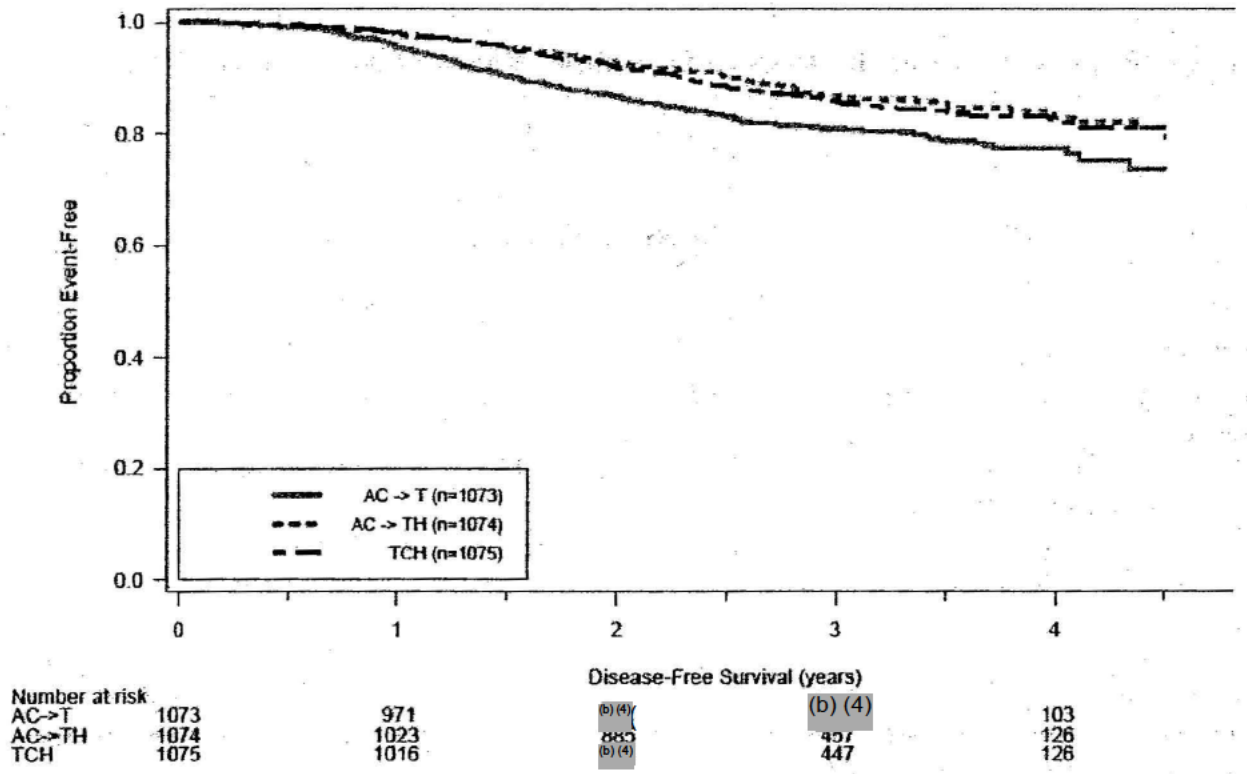


Figure 2 Disease Free Survival All Patients (Sponsor's figure)

FDA's Analysis of time to disease recurrence:

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

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

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

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

Table 19 FDA's Analysis of DFS events

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

a First event modify by the reviewer.
b First event modify by the reviewer. The value is the first event for each patient, either local or regional recurrence.
c Relative to AC→T. Estimated using Cox model stratified by number of positive nodes and hormonal receptor status.
d Stratified log-rank p-value.
e The 95% C.I. for the comparison between AC→TH vs. AC→T was revised by the reviewer. The sponsor's original 95% C.I. is [0.49, 0.77].

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

Table 20 Secondary Malignancies:

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

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

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

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

The following patients had non invasive cancers:
ACT30293 DCIS Right breast,
32861 Right DCIS
ACTHPatient 31548 had basal cell
30643 DCIS Right
TCH31185, 32148 Carcinoma in situ
30479 had DCIS left breast
31510 superficial cancer on a sigmoid polyp

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

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

The fifth patient was not counted as a DFS event:

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

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

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

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

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

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

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

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.

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

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

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

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

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

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

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

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

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

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

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

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

Table 24 Reviewer Table: Deaths (ITT population)

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

For 13 patients death cause was listed as" other:
Patient 30341, 30365, 31218, and 31549 had an unknown cause of death.
Patient 32172 died from cranial trauma, acute subdural hematoma.
Patient 30993 committed suicide.
Patient 30947 had complications of hypercalcemia.
Patient 30685 died from sudden death.
Patient 30422 septic shock.
Patient 30390 stroke.
Patient 30345 pneumonia.
Patient 30248 car accident.
Patient 30073 pulmonary consolidation, autopsy did not show evidence of relapse.

Three patients died from toxicity:
Patients 30437 and 30611treated in the TCH arm died from sepsis.
Patient 32353 treated in the AC T arm died from sepsis

Nine patients died from malignant disease other than breast cancer:
AC T:30533 (Rectal ca),
30649 (leukemia),
31212 (leukemia),
32782 (leukemia),
32336 (pancreatic)
TCH:32938 (glioblastoma),
33039 (pancreatic),
32265 (gastric)
AC TH :31395 (ovarian)

Efficacy Conclusions

• Results of the protocol-specified **second efficacy interim analysis** demonstrated that Herceptin as part of either an anthracycline-based (AC→TH) or non–anthracycline-based (TCH) adjuvant treatment regimen results in a clinically meaningful and statistically significant improvement in

DFS relative to AC→T irrespective of nodal status. For the primary efficacy endpoint, DFS, the risk of a first event was reduced by 39% (95% confidence interval [CI]: 23, 51; p <0.0001) in the AC→TH arm relative to the AC→T arm. For the primary efficacy endpoint, DFS, the risk of a first event was reduced by 33% (95% CI: 17, 46; p =0.0003) in the TCH arm relative to the AC→T arm.

• The DFS benefit in all clinically important subgroups, including those defined by age, menopausal status, hormone receptor status, nodal status, tumor size, nuclear grade, and surgery or radiation therapy, was consistent with the treatment effect in the overall population.

• There was a clinically meaningful and statistically significant improvement in duration of OS. The risk of death was reduced by 42% (95% CI: 17, 60; p =0.0024) in the AC→TH arm relative to the AC→T arm. Similarly, the risk of death was reduced by 34% (95% CI: 7, 53; p =0.0182) in the TCH arm relative to the AC→T arm.

7 INTEGRATED REVIEW OF SAFETY

• The incidence of adverse events in Study BCIRG 006 was consistent with the known toxicityprofiles of doxorubicin, cyclophosphamide, docetaxel, platinum salts, and Herceptin.
• The 3-year cumulative incidence of all symptomatic cardiac events was 0.5%, 2.36%, and 1.16% in the AC→T, AC→TH, and TCH arms, respectively.

• The 3-year cumulative incidence of symptomatic CHF (Grade 3 or 4 CLVF) events was 0.3%, 2.06%, and 0.4% in the AC→T, AC→TH, and TCH arms, respectively.

• The TCH regimen is a safe and efficacious treatment option with a reduced (relative to AC→TH) incidence of symptomatic cardiac events overall and CHF specifically.

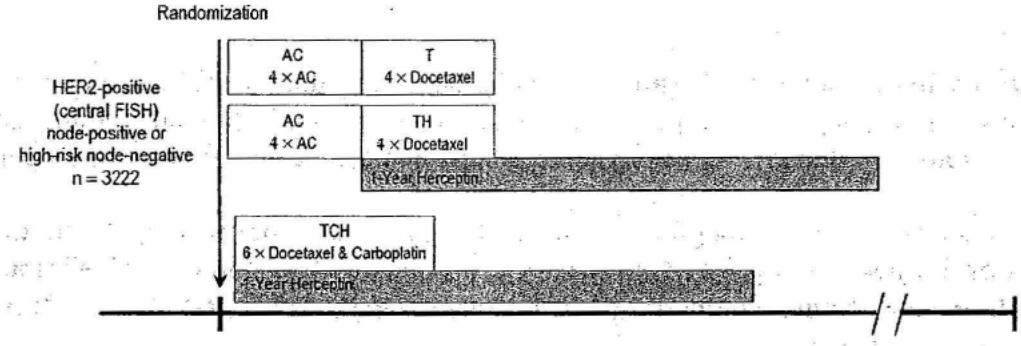
• Decreased on-study LVEF and increased age (>50 years) were identified as key risk factors for development of a symptomatic cardiac event.

• The magnitude of the clinical benefit observed in this trial favors the use of Herceptin in this population of women, who have a high risk for disease recurrence and subsequent death from metastatic breast cancer, including women with high-risk, node-negative HER2-positive early breast cancer.

7.1 Methods and Findings

In this application data from 3222 subjects were randomized (1:1:1) either: adriamycin and cyclophosphamide followed by taxotere (AC→T) [control], or adriamycin and cyclophosphamide followed by Herceptin containing regimens of concurrent taxotere and Herceptin (AC→TH), or concurrent taxotere, carboplatin, and Herceptin (TCH). Herceptin containing regimens continued Herceptin post completion of adjuvant chemotherapy for a total

of 52 weeks. The safety population consisted of subjects who received at least one dose of study treatment (AC→T: n = 1050; AC→TH: n = 1068; and TCH: n = 1056).



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

Safety was assessed by evaluating summaries of treatment exposure, adverse events, deaths, symptomatic cardiac events, and asymptomatic declines in LVEF by MUGA scan or echocardiogram, according to treatment received. The safety database was analyzed using COSTART terms and adverse event intensity was coded using NCI CTCAE v. 2.0. The relevant data sources in the application are the clinical study report; pertinent case report forms (CRF's), periodic update safety report (PSUR), case narratives, and data listings were reviewed in order to address specific safety issues. **Error! Reference source not found.** 25, displays the raw and derived datasets reviewed for study BCIRG 006.
The adverse events datasets for BCIRG 006 were structured from four CRF's that captured the following: Clinical adverse events (non-laboratory); febrile neutropenia and infection; Cardiac toxicity monitoring from which included left ventricular ejection fraction (LVEF) and Cardiac Adverse events; and hematology and blood chemistry labs.

Reviewer's Comment: The case report forms for the capturing of clinical adverse events and cardiac adverse events for BCIRG 006 was structured as a pre-specified check-list.

Table 25 Raw and Derived Datasets Reviewed for Study BCIRG 006

Safety Review	Efficacy Review
AE (Adverse Event)	BCELAP (Breast Cancer Relapse Information)
CARDAE (Cardiac History and Adverse Event Experience)	BCSURG (Breast Cancer Surgery and Diagnosis)
CARDFU (Cardiac Event Report and Follow-up)	CANCERHX (Past or Current History of neoplasm)
CARDIAC (Cardiac Outcome)	CANCERRX (Anti-Tumor Therapy)
CHMC (Chemistry Lab Test)	DEMOG (Demographics)
CONMED (Concomitant Therapy)	FEVAL (Final Efficacy Evaluation)
DEATH (Death Report)	HORMREC (Hormone Receptor Status)
DXSCAN (Patient Imaging Scan Information)	PATHO (Tumor Pathology Report)
ECHO (Echocardiography Report)	SPMALIG (Second Primary Mailgnancy)
EKGRAW (Electrocardiogram Report)	SURV (Patient Status Follow-up)
ELIG (Eligibility and Cardiac Disease Criteria)	*ABCFU (Recurrence Analysis File)
HEMC (Hematology lab Test)	*PATEFF (Patient Efficacy Analysis File)
HER2 (Her2neu Screening Information)	
HORMTX (Concomitant Hormonal Treatment)	
HOSP (Inpatient Hospitalization)	
LVEFRAW (Left Ventricular Ejection Fraction)	
TXCHEMO (Chemotherapy Administration)	
TXHER (Herceptin Administration)	
Vital (Vital Signs)	
*CAE (Cardiac Adverse Event Analysis File)	
*EKG (EKG Analysis File)	
*LVEF (LVEF Analysis File)	
*PATEXPO (Study Drug Exposure)	
*PATSAF (Patient Safety Analysis File)	

* Derived Data

All adverse events reported during the clinical study occurred from the time the subject starts treatment with the study medication (chemotherapy or Herceptin) until 30 days after the last infusion of study treatment. Subjects were evaluated for safety the same whether they received Herceptin containing regimen or not. Safety assessments were divided into during chemotherapy and end of chemotherapy. The schedule of assessments during chemotherapy to end of chemotherapy (EOC) included: physical examinations, labs (hematology and chemistry) every three weeks, and LVEF (MUGA or Echo) all arms after cycle 4, before cycle 5, and Herceptin arms after cycle 6. End of chemotherapy follow-up assessments were also the same across groups. Physical exam every three months for 2.5 years, then every six months up to year five, and then yearly up to year ten. Routine hematology and chemistry exams every six months. Mammography and chest x-ray annually.
Left ventricular ejection fraction measurements occurred at: 3 months after EOC in the AC→T and AC→TH group, and 4.5 months after EOC in the TCH group (corresponds to

follow-up visit 1); Follow-up visit #4 measurements occurred at 12 months EOC for AC→T and AC→TH group, and 13.5 months EOC for the TCH group; and finally at follow-up visit # 10 measurements occurred at 36 months EOC for AC→T and AC→TH group, and 37.5 months EOC for the TCH group. For subjects in the Herceptin groups who developed a decrease in LVEF as a result of Herceptin that required a dose to be held or discontinued and did not have recovery of the LVEF by month 36, were to receive LVEF measurements annually until recovery or until end of follow-up, whichever comes first. Cardiac adverse events reporting occurred; Every 3 months during the first two years of the follow-up period, every 6 months years 3-5, and annually years 6-10.

Adverse events per-event were reproducible by the reviewer using the raw datasets and was comparable to the applicant's table, refer to Table 26. Summary of Per-Event Incidence of non-Laboratory Adverse Events Across Treatment Arms.

Table 26 Summary of Per-Event Incidence of Non-laboratory Adverse Events Across Treatment Arms

AE Grade	ACT (n=1050)	ACTH (n=1068)	TCH (n=1056)
1	8594 (17%)	9447 (18%)	8763 (17%)
2	5865 (11%)	6350 (12%)	5294 (10%)
3	1294 (3%)	1385 (3%)	1188 (2%)
4	68 (0.1%)	103 (0.2%)	80 (0.2%)

*Total # of events across three arms =51666

Early in the review the term "unmapped" was found within the variable "Preferred Term" of the AE dataset refer to Table 27, "Per-Patient Incidence of Non-Laboratory Adverse Events Unmapped".
Greater than 10% of all non-laboratory adverse event across all three study groups was coded as "unmapped". The FDA asked the applicant to explain this term. The following response was provided.

"If an investigator verbatim was not classified according to the NCI-CTC version 2.0, then the value of AENCIPT (AE NCI preferred term) was set equal to "unmapped". Similarly, if an investigator verbatim term was not mapped using the COSTART dictionary, then the value of AEPT (AE COSTART preferred term) was set equal to "unmapped." In both of the above cases, the value of variable AEBODY (AE COSTART body system) was also set equal to "unmapped."

The reason for terms being unmapped was two-fold: In most instances, it was because terms were not specific enough to allow for mapping. In other instances, it was because at the time of data cut-off date for the second interim analysis, not all terms had been mapped by the coding group at BCIRG.

In total, 99.4% and 99.8% of all reported non-cardiac and cardiac adverse events, respectively, were coded at the time of the data cut-off date for the second interim analysis. Thus, we believe the submitted data and associated tables provide an adequate characterization of the safety profile for patients in Study BCIRG006".

Table 27 Per-Patient Incidence of Non-Laboratory Adverse Events Unmapped

COSTART	AC→T (n=1050)		AC→TH (n=1068)		TCH (n=1056)	
Preferred Term	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Unmapped	11.9%	1.5%	12.1%	1.7%	12.4%	2.3%

With regard to serious adverse events (SAE), the incidence of non-cardiac events was similar across treatment groups with slightly higher incidence in the Herceptin containing groups. The incidence of SAEs for cardiac events was higher in the Herceptin containing regimens (AC→TH, TCH) compared to the control (ACT). Between Herceptin containing regimens the AC→TH group had a higher incidence of cardiac SAEs compared to the TCH group 5.0% versus 3.5%. Adverse events resulting in discontinuation of chemotherapy was highest in the control group ACT (4.2%) and lowest in the TCH group (2.1%). The incidence of adverse events resulting in discontinuation of Herceptin was similar between ACTH and TCH. Refer to Table 28 , Per-Patient Incidence of Serious Adverse Events.

Table 28 Per-Patient Incidence of Serious Adverse Events

	ACT (n=1050)	**ACTH (n=1068)**	**TCH (n=1056)**
Any SAE Non-Cardiac	219 (21%)	265 (25%)	256 (24%)
SAE Cardiac	20 (2%)	53 (5%)	37 (3.5%)
AE's Resulting in Death	2 (0.2%)	1 (0.1%)	4 (0.4%)
AE's Resulting in Discontinuation of Chemotherapy	44 (4.2%)	38 (3.6%)	22 (2.1%)
AE's Resulting in Discontinuation of Herceptin	———	14 (1.3%)	12 (1.1%)

The most common non-cardiac adverse events reported in the ACT versus AC→TH group occurring in ≥ 5 % of subjects with a difference between groups of ≥ 5% were: diarrhea, infection, maculopapular rash, dyspepsia, rhinitis, and epistaxis.

The most common cardiac adverse events reported of any grade with ≥ 5% in the ACT versus AC→TH group with higher incidence ≥ 2% in the Herceptin containing arm were: hypertension and left heart failure.

The most common non-cardiac adverse events reported in the ACT versus TCH group occurring in ≥ 5 % of subjects with a difference between groups of ≥ 5% were: diarrhea, rash, dyspepsia, abdominal pain, epistaxis, and allergic reaction.

The most common cardiac adverse events reported of any grade with ≥ 5% in the ACT versus TCH group with higher incidence ≥ 2% in the Herceptin containing arm were: hypertension and palpitations.

The most commonly reported non-cardiac SAEs for the ACT group were: vomiting, stomatits, nausea, maculopapular rash, cellulitis and neuropathy. For the ACTH group the most commonly reported non-cardiac SAEs were fever, infection, leukopenia, vomiting, diarrhea, nausea and anemia. The TCH group reported the following most common SAEs: fever, infection, vomiting, diarrhea, and leukopenia.

The most commonly reported cardiac SAEs for the ACT group were deep thrombophlebitis, left heart failure, arrhythmia, and tachycardia. For the ACTH group, these were left heart failure, deep thrombophlebitis, myocardial ischemia, and palpitation. The TCH group reported the following most common SAEs: deep thrombophlebitis, myocardial ischemia, arrhythmia, and tachycardia.

The following adverse events resulting in death were reported:

ACT: 30572 Dyspnea, 32354 Infection

ACTH: 32173 "Unmapped"

TCH: 30437 Coma, dehydration, diarrhea, infection, kidney failure, and vomiting.

30611 Infection

30997 Leukopenia, thrombocytopenia

32172 Accidental Injury

Deaths

The incidence of all deaths (related and unrelated) was higher in the control arm (78 deaths or 7.4%) in the ACTH arm (48 deaths or 4.5%) and in the TCH arm (55 deaths or 5.2%). The table below shows the different death categories. Most of the patients died from breast cancer. Four patients died from treatment related toxicity: two patients in the TCH arm, 1 patient in the ACTH arm and 1 patient in the ACT arm. There were no cardiac deaths reported in the study treatment arm. Only 1 patient (30685) died from a heart attack but this patient did not receive Herceptin since she was treated in the control arm. The causality of the event is probably unrelated to study drug.

Table 29 Overall Causes of Death: Safety population

	ACT (n=1050)	ACTH (n=1068)	TCH (n=1056)
Overall Deaths	78	48	55
Causes			
Breast Cancer	68	43	47
Malignant Disease Other than Breast	5	1	2
Septic Toxicity Due to Chemotherapy	1	1	2
Other	4	4	4

The following table shows the causes of death reported in the "other" category.

Table 30 Summary of Deaths in Other Category

	PT #	Death Cause Reported
ACT	30248	Truck Roll Over accident
	30345	Pneumonia
	30685	Sudden Death
	30947	Complications of Hypercalcemia
ACTH	30365	Unknown
	30422	Septic Shock
	31218	Unknown
	31549	Unknown
TCH	30073	Pulmonary Consolidation
	30341	Unknown
	30390	Cerebral Stroke
	32172	Cranial Trauma with Acute Subdural Hematoma

Other Serious Adverse Events

Accuracy of coding using NCI-CTC term and COSTART preferred term was verified by a review of AE line listings. Events were then grouped and analyzed by treatment group and other

relevant subgroups. Data listings, CRF's, and narratives were reviewed for cases of particular interest. Finally these data were compared to legacy study data.

In BCIRG006 a serious adverse event was defined as one of the following occurring at any dose that results in: death, life threatening (the subject was at immediate risk of death at the time of the SAE), inpatient hospitalization or prolongation of exiting hospitalization, is a congential anomaly /birth defect, or an important medical event. The definition of SAE used is consistent with 21 CFR 312.32 (a). Serious adverse events were graded according to NCI CTC version 2.0.

The most commonly reported non-cardiac SAEs for the ACT group were: vomiting , stomatits, nausea, maculopapular rash, cellulitis and neuropathy. For the ACTH group the most common SAEs were: fever, infection, leukopenia, vomiting, diarrhea, nausea and anemia. The TCH group reported the following most common SAEs: fever, infection, vomiting, diarrhea, and leukopenia.

The most commonly reported cardiac SAEs for the ACT group were deep thrombophlebitis, left heart failure, arrhythmia, and tachycardia. For the ACTH group these were left heart failure, deep thrombophlebitis, myocardial ischemia, and palpitation. The TCH group reported the following most common SAEs: deep thrombophlebitis, myocardial ischemia, arrhythmia, and tachycardia.

120-day Safety Update

The 120-day safety update for the HERCEPTIN® (trastuzumab) sBLA, originally submitted on 28 June 2007 (STN BL 103792/5187) and 29 June 2007 (STN BL 103892/5189), includes data on patients from Study BCIRG006. Narratives for 8 patients who experienced specified types of adverse events occurring between 1 November 2006 and 31 March 2007 are included in this amendment. The specified adverse events for this update were agreed to by Genentech and the FDA during a teleconference on 18 April 2007 and consist of deaths from causes other than breast cancer; serious adverse events leading to discontinuation of chemotherapy or Herceptin; new symptomatic cardiac events per protocol definition; and updated information (independent cardiac review panel (ICRP)–confirmed or awaiting confirmation) for existing cardiac events submitted in the original sBLA.

ACT
4 Deaths;

- patient 31585pulmonary embolism,
- patient 31377 unspecified second primary malignancy,
- patient 31797 acute myelogenous leukemia
- patient 33090 *update* (death from grade 4 heart failure)

ACTH
CHF

- (Grade 3) patient 30471and 32515
- (Grade 4) patient 33090 lead to Death
- Patient 31758 *update* (CHF grade 3-4)

Death

- 30137, automobile accident (b) (6)

Dropouts and Other Significant Adverse Events

7.1.1.1 Overall profile of dropouts

Per BCIRG 006 clinical study protocol, patients in the Herceptin containing arms who drop out because of chemotherapy related toxicities may continue Herceptin until completion of 1 year or relapse or Herceptin related toxicity (including cardiac safety analysis), whichever comes first. These patients are to be followed in regular follow-up.

The criteria followed in the BCIRG 006 protocol for discontinuation and withdrawal from chemotherapy of Herceptin was: unacceptable toxicity, withdrawal of consent, relapse, second primary malignancy, death, or administration of other systemic cancer treatment other than study drug or Tamoxifen.

The majority of subjects participating in BCIRG 006 completed the chemotherapy and Herceptin portion of treatment. For chemotherapy ACT (91.2%), ACTH (92.4%), and TCH (95.6%) completed, and for the Herceptin containing arms ACTH (90.9%) and TCH (95.4%).

Table 31 Reasons for Discontinuation of Chemotherapy Treatment for BCIRG 006

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Began chemotherapy treatment	1050 (100.0%)	1068 (100.0%)	1054 (99.8%)
Completed chemotherapy	958 (91.2%)	987 (92.4%)	1010 (95.6%)
Discontinued chemotherapy	92 (8.8%)	81 (7.6%)	44 (4.2%)
Reason for discontinuation			
Breast cancer relapse	5 (0.5%)	4 (0.4%)	1 (0.1%)
Second primary malignancy	0 (0.0%)	1 (0.1%)	0 (0.0%)
Cardiac adverse event	4 (0.4%)	2 (0.2%)	7 (0.7%)
Non-cardiac adverse event	41 (3.9%)	40 (3.7%)	22 (2.1%)
Withdrawal of consent/refusal	40 (3.8%)	30 (2.8%)	10 (0.9%)
Death	1 (0.1%)	0 (0.0%)	2 (0.2%)
Other [a]	0 (0.0%)	3 (0.3%)	1 (0.1%)

Table 32 Reasons for Discontinuation of Herceptin Treatment for BCIRG 006

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Started Herceptin	0 (0.0%)	1043 (97.7%)	1056 (100.0%)
Herceptin therapy completed	NA	971 (90.9%)	1007 (95.4%)
Herceptin therapy discontinued	NA	72 (6.7%)	49 (4.6%)
Reason for discontinuation			
Breast cancer relapse	NA	1 (0.1%)	1 (0.1%)
Second primary malignancy	NA	1 (0.1%)	0 (0.0%)
Adverse experience	NA	6 (0.6%)	13 (1.2%)
Cardiac-related event	NA	1 (0.1%)	5 (0.5%)
Non–cardiac-related event	NA	5 (0.5%)	8 (0.8%)
Consent withdrawn	NA	12 (1.1%)	9 (0.9%)
Death	NA	0 (0.0%)	2 (0.2%)
Required not permitted therapy	NA	0 (0.0%)	0 (0.0%)
Other deviation from protocol	NA	0 (0.0%)	0 (0.0%)
Lost to follow-up	NA	0 (0.0%)	0 (0.0%)
Herceptin toxicity	NA	35 (3.3%)	13 (1.2%)
Patient refusal to continue Herceptin	NA	11 (1.0%)	8 (0.8%)
Other	NA	3 (0.3%)	3 (0.3%)
Missing	NA	3 (0.3%)	0 (0.0%)

During the chemotherapy portion of BCIRG 006, the most common reason for discontinuation of chemotherapy across treatment arms was due to non-cardiac adverse events: ACT (3.9%), ACTH (3.7%), and TCH (2.1%). The second most common reason for discontinuation of chemotherapy was "withdrawal of consent/refusal": ACT (3.8%), ACTH 2.8%), and TCH (0.9%), Table 31 , Reasons for Discontinuation of Chemotherapy Treatment for BCIRG 006.

During the Herceptin portion of BCIRG 006, the most common reason for discontinuation of Herceptin for the Herceptin containing treatment arms was "Herceptin toxicity": ACTH (3.3%) , TCH (1.2%). %). The second most common reason for discontinuation of Herceptin was "consent withdrawn", Table 32 , Reasons for Discontinuation of Herceptin Treatment for BCIRG 006.

7.1.1.2 Adverse events associated with dropouts

The datasets containing reasons for discontinuation of chemotherapy or Herceptin were located in the TXCHEMO.xpt and TXHER.xpt files. The variables listing reasons for discontinuation categorized adverse events under "adverse experience and "Herceptin toxicity". Individual adverse experiences and toxicity from Herceptin were not listed. During chemotherapy non-cardiac adverse events was the most common reason for discontinuation with the TCH arm having the least reported. Herceptin toxicity was higher in the ACTH arm (3.3%) versus TCH (1.2%).

7.1.1.3 Other significant adverse events

Symptomatic Cardiac Adverse Event

All adverse experiences related to cardiac toxicities were graded based on NCI-CTC version 2.0. A clinically significant cardiac event was defined in BCIRG 006 as the occurrence of one or more of the following: .

•cardiac death (all non-septic deaths due to study treatment will be reviewed)
• grade 3 or 4 cardiac left ventricular ejection fraction (congestive heart failure)
• grade 3 or 4 arrythmias
• grade 3 or 4 cardiac ischemia / infarction.

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

Table 33 The Applicant's Symptomatic Cardiac Events per ICRP Occurring at Any Time during BCIRG 006. (Safety Population)

Event Type	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
CHF (Grade 3/4 CLVF)	3 (0.3%)	20 (1.9%)	4 (0.4%)
Grade 3/4 cardiac ischemia/infarction	0 (0.0%)	2 (0.2%)	2 (0.2%)
Grade 3/4 arrhythmia	3 (0.3%)	2 (0.2%)	6 (0.6%)
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any symptomatic cardiac event [a]	6 (0.6%)	23 (2.2%)	12 (1.1%)

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

[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.

Table 34 Reviewer's Incidence of Cardiac Events

	ACT (n=1050)	ACTH (n=1068)	TCH (n=1056)
CHF	4 (0.4%)	20 (2%)	4 (0.4%)
ICRP	2 (0.2%)	8 (0.8%)	4 (0.4%)
Arrythmia	5 (0.5%)	8 (0.8%)	5 (0.5%)
ICRP Grade 3	3 (0.3%)	0 (0%)	1 (0.1%)
ICRP Grade 4	0 (0%)	0 (0%)	0 (0%)
Cardiac Ischemia/Infarction Grade ¾	0 (0%)	3 (0.3%)	2 (0.2%)
ICRP	----	0	1
Cardiac Death	0 (0%)	0 (0%)	0 (0%)

The following narratives support the data for NCI CTC grades 3-5 cardiac ischemia/infarction presented in Table 34, Reviewer's Incidence of Cardiac Events.

Patient No.: 30529
Demographics: 61-year-old female
Treatment Arm: AC→TH
Event: Cardiac ischemia
The patient's concurrent medical conditions included diabetes mellitus treated with glipazide. On 29 April 2002, a baseline echocardiogram revealed an LVEF of 64%, a baseline ECG was within normal limits.

Chemotherapy was completed per the protocol. The last cycle of docetaxel was administered on 16 October 2002. An echocardiogram performed on 5 November 2002 (Cycle 8) revealed an LVEF of 46%. Monotherapy with Herceptin was delayed. An echocardiogram performed on 3 December 2002 (FU1), revealed an LVEF of 57%. On 4 December 2002 (FU1), the patient started Herceptin monotherapy (6 mg/kg) every 3 weeks. The last dose of Herceptin was administered on 23 July 2003 (FU3). An echocardiogram performed on 6 November 2003 (FU4) revealed an LVEF of 68%.

The patient was hospitalized on (b) (6) with a serious event of Grade 4 myocardial ischemia. An ECG performed on (b) (6) revealed significant abnormalities. An echocardiogram performed on (b) (6) revealed an LVEF of 53%. Further information on the presenting symptoms, course of hospitalization, and treatment was not reported. The investigator assessed chemotherapy and Herceptin as the most likely cause of the patient's myocardial ischemia. The patient's case was reviewed on an unreported date by an independent cardiac review panel, whose review was inconclusive.

Patient No.: 31978

Demographics: 54-year-old female
Treatment Arm: AC→TH
Event: Cardiac ischemia
A baseline ECG performed on 23 April 2003 was within normal limits. On 21 May 2003, a baseline echocardiogram revealed an LVEF of 80%. The patient received Cycles 1–4 of AC between 23 May 2003 and 28 July 2003. She then received Cycles 5–8 of Herceptin between 18 August 2003 and 3 November 2003 and Cycles 5–8 of docetaxel between 19 August 2003 and 21 October 2003. On 12 November (FU1) 2003, the patient started Herceptin monotherapy (6 mg/kg) every 3 weeks.

On 27 January 2004 (FU1), the patient reported for radiation treatment; an ECG revealed a singular ventricular extrasystole. On 28 January 2004, the patient had an irregular heartbeat during radiation. The patient's vital signs were normal the next day, and she was started on metoprolol in addition to her enalapril. She was hospitalized (b) (6) with chest pain and hypertension (160/90 mmHg). An ECG revealed a singular ventricular and supraventricular extrasystole with lateral wall ischemia and tachycardia (100 bpm). She was hospitalized on (b) (6) with chest pain and hypertension (160/90 mmHg). An ECG revealed a singular ventricular and supraventricular extrasystole with lateral wall ischemia and tachycardia (100 bpm). The investigator assessed this episode as unrelated to Herceptin; treatment was continued, and the last dose of Herceptin was administered on 9 August 2004 (FU3).The patient's case was reviewed on an unreported date by an independent cardiac review panel, who confirmed the diagnosis of myocardial ischemia.

Treatment Arm: AC→TH
Event: Cardiac ischemia
A baseline ECG performed on 6 August 2003 was within normal limits. On 27 August 2003, a baseline echocardiogram revealed an LVEF of 61%. The patient received Cycles 1–4 of AC between 22 September 2003 and 24 November 2003. She then received Cycles 5–8 of Herceptin between 15 December 2003 and 2 March 2004 and Cycles 5–8 of docetaxel between 16 December 2003 and 18 February 2004. Docetaxel was reduced during Cycle 6 because of non-hematologic toxicity.

During Cycle 5, the patient also experienced palpitations and angina pectoris. An echocardiogram obtained on 5 January 2004 (Cycle 5) showed an LVEF of 59%. An echocardiogram performed on 8 March 2004 (Cycle 8) revealed an LVEF of 79%. Chemotherapy was completed per the protocol. The last cycle of docetaxel was administered on 18 February 2004. On 10 March 2004 (FU1), the patient started Herceptin monotherapy (6 mg/kg) every 3 weeks.

On (b) (6), the patient was admitted to the hospital with retrosternal chest heaviness radiating to the left arm and jaw, with associated diaphoresis and dyspnea. A MUGA scan revealed an LVEF of 55% with no evidence of left ventricular dysfunction. The first ECG showed normal sinus rhythm with some early repolarization; another ECG about 6 hours later revealed ST elevation consistent with an acute infarction. Cardiac catheterization showed 70%–75% occlusion in the left anterior descending coronary artery with flow limitation. Angioplasty

was successfully performed, with stent insertion into the proximal LAD; intracoronary nitroglycerin and intravenous bivalirudin were also administered. She was reported to have experienced a serious event of Grade 4 myocardial ischemia, which improved to Grade 3 in intensity. The myocardia ischemia was reported resolved on (b) (6) The last dose of Herceptin was administered on 30 March 2004, and therapy was discontinued because of concerns over Herceptin cardiotoxicity.

The patient's case was reviewed on an unreported date by an independent cardiac review panel, who diagnosed the patient with Grade 3 myocardial ischemia/infarction.

Patient No.: 30185
Demographics: 43-year-old female
Treatment Arm: TCH
Event: Cardiac ischemia
On 14 November 2001, a baseline MUGA scan revealed an LVEF of 69%. During Cycle 2, the patient experienced chest pain radiating to the left arm that developed into ventricular fibrillation cardiac arrest requiring resuscitation. The patient suffered a 2-minute seizure, anoxic brain injury, and epistaxis. An ECG confirmed an acute anterior myocardial infarction. chest pain radiating tothe left arm that developed into ventricular fibrillation cardiac arrest requiring resuscitation. The patient suffered a 2-minute seizure, anoxic brain injury, and epistaxis. An ECG confirmed an acute anterior myocardial infarction. An echocardiogram performed on (b) (6) revealed an LVEF of 40% with regional wall motion abnormalities and mild mitral and tricuspid regurgitation.
The last cycles of docetaxel cisplatin were administered on 9 January 2002, and the last dose of Herceptin was administered on (b) (6) (Cycle 2). Chemotherapy and Herceptin were discontinued because of the patient's myocardial ischemia.

The patient's case was reviewed on an unreported date by an independent cardiac review panel, which agreed with the diagnosis of acute myocardial infarction but disagreed with the grade of the adverse event. The panel assessed the event as a Grade 4 acute myocardial infarction.

Patient No.: 31944
Demographics: 55-year-old female
Treatment Arm: TCH
Event: Cardiac ischemia
The patient's medical history included surgical carpal tunnel release (2001), and her concurrent medical conditions included Grade 3 hypertension treated with fosinopril, Type 2 diabetes treated with insulin, a Grade 3 cellulitis, and left hip osteoarthritis and sciatica. On 30 April 2003, a baseline MUGA scan revealed an LVEF of 59% and a baseline ECG revealed non-significant abnormalities. MUGA scans performed on 8 August 2003 (Cycle 4) and 6 September 2003 (Cycle 6) revealed LVEFs of 69% and 49%, respectively. On 19 September 2003 (FU1A), the patient started Herceptin (6 mg/kg) every 3 weeks. The patient discontinued tamoxifen because of an unspecified adverse event.

On (b) (6) (FU2), the patient was hospitalized with chest heaviness, bilateral arm discomfort, and a general feeling of malaise. A chest X-ray performed on (b) (6) showed no cardiomegaly or pulmonary consolidation, and an ECG revealed a regular rate (91 bpm), a premature complex of uncertain mechanism, and abnormal T waves in the inferior leads suggestive of ischemia. A coronary angiogram revealed an occlusion in the mid–left circumflex coronary artery, long diffuse disease proximal and severe disease in the mid–right coronary artery, moderate disease in the left anterior diagonal, a larger posteroinferior scar, left ventricular impairment, and inferior and posterior akinesis. These findings were suggestive of an acute myocardial infarction.

The investigator assessed this episode as unrelated to Herceptin. However, further Herceptin therapy was discontinued because of the patient's significant cardiac disease. The last dose of Herceptin was administered on 5 March 2004 (FU2). The patient's case was reviewed on an unreported date by an independent cardiac review panel, who confirmed the diagnosis of inferior myocardial infarction.

The clinical reviewer found an additional case with grade 3 myocardial ischemia/infarction, in the AC→TH group, although reported cause of death was septic shock.

Patient No.: 30422
Demographics: 68-year-old female
Treatment Arm: AC→TH
Events: Cardiac failure left and death resulting from septic shock This patient was diagnosed with a 1.70-cm, ER-negative/PR-negative, poorly differentiated, infiltrating ductal carcinoma of the left breast and underwent a mastectomy and axillary node dissection (eight of 12 axillary nodes were positive) on (b) (6) The central laboratory confirmed HER2-positive status by FISH assay. On 15 March 2002, a baseline echocardiogram revealed an LVEF of 67%, and a baseline ECG was within normal limits. A baseline physical examination performed 26 March 2002 was normal.

The patient received Cycles 1–4 of AC between 26 March 2002 and 29 May 2002. She then received Cycles 5–8 with Herceptin between 19 June 2002 and 11 September 2002 and Cycles 5–8 of docetaxel between 20 June 2002 and 21 August 2002. During Cycles 1–4, the patient experienced non-serious events of alopecia, stomatitis/pharyngitis, fatigue, dysgeusia, nausea, and dry skin. An echocardiogram performed 26 June 2002 revealed an LVEF of 68%. During Cycles 5–8, the patient experienced non-serious events of alopecia, diarrhea, stomatitis/pharyngitis, fatigue, constipation, rash/desquamation, rhinorrhea, dizziness, nausea, dry skin, vomiting, nail changes, pruritus, conjunctivitis, and tearing. Echocardiograms performed 31 July 2002 and 11 September 2002 revealed LVEF values of 50% and 61%, respectively. Chemotherapy was completed per the protocol. The patient's last cycle of docetaxel (Cycle 8) was administered on 21 August 2002. At the end of Cycle 8, on 11 September 2002, the patient started Herceptin monotherapy (6 mg/kg) every 3 weeks.

During FU1, on 3 December 2002, an echocardiogram revealed an LVEF of 51%. On (b) (6) the patient presented with dyspnea, tachycardia, and left arm pain. A chest X-

ray revealed cardiomegaly and pulmonary edema; LVEF by echocardiogram was 20%. Serum troponin was elevated at 1.34 ng/mL (normal, 0.03 ng/mL), and the patient was hypoxemic (pO_2, 70 mmHg). The patient was treated with furosemide, spironolactone, captopril, enoxaparin, and digoxin. Coronary arteriography performed on (b) (6) revealed no coronary artery deficits. The patient's clinical symptoms had resolved as of (b) (6) (FU2); she had a normal ECG and serum troponin level of 0.8 ng/mL. An echocardiogram revealed an LVEF of 50%. She was discharged on spironolactone.

The patient's last dose of Herceptin was administered on 13 November 2002; additional therapy with Herceptin was discontinued because of the patient's decline in cardiac status. Her case was reviewed on an unreported date by an independent cardiac review panel that agreed with the diagnosis of congestive heart failure and also noted a diagnosis of Grade 3 myocardial ischemia/infarction.

As of January 2003, the patient had ongoing asthenia, dyspnea, and chest pressure. An echocardiogram obtained on 8 January 2003 (FU2) revealed an LVEF of 48% with moderate systolic and diastolic dysfunction. Echocardiograms from 30 January 2003, 4 February 2003, and 12 March 2003 (FU2) revealed LVEF values of 30% (with noted severe diastolic and systolic dysfunction), 38%, and 28%, respectively. An echocardiogram performed 30 June 2003 (FU3) revealed an LVEF of 31%; on 16 October 2003 (FU4), LVEF was 44% by echocardiogram. During FU5, the patient was reported to have experienced serious Grade 3 NCI CTC left ventricular dysfunction (mapped to COSTART as "cardiac failure left"), for which she was hospitalized on unreported dates. The event had resolved to Grade 1 left-sided heart failure as of 17 December 2003; an echocardiogram obtained on that date revealed an LVEF of 59%.

Echocardiograms from 8 March 2004 (FU6) and 10 June 2004 (FU7) revealed LVEF values of 58% and 39%, respectively. The patient died of septic shock on (b) (6) no additional details were reported. No autopsy was performed.

Reviewer Comment's: The information presented in Table 34 , Reviewer's Incidence of Cardiac Events, cardiac ischemia/infarction grade ¾ will be added to the current Herceptin label..

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

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

Asymptomatic LVEF decline according to the BCIRG 006 protocol, left ventricular ejection fraction was measured at baseline and 3, 4.5, 6, 9, 18 and 42 months after randomization. This schedule was adjusted for each patient according to the actual number of cycles of chemotherapy received. A clinically significant asymptomatic decline in LVEF was defined as an absolute

reduction in LVEF of 15% or more from baseline and a LVEF value of less than the lower limit of normal.

For the primary analysis of the asymptomatic LVEF decline, any LVEF measured with a technique different than the one used at baseline was excluded. An additional analysis was performed based on an absolute decline of 10% or more from baseline in LVEF that is also below 50%.

According to the protocol, a new observed asymptomatic cardiac abnormality would be confirmed by repeat LVEF within 1 month. The confirmation was calculated using a 28 day window for the second evaluation.

Time to the first LVEF decline (defined as the date of randomization to the date of the first LVEF that meets the definition of asymptomatic LVEF decline -- 10% and 15% decline definitions) analyses would be performed. Patients who have not experienced such a decline would be censored at their last LVEF examination.

For time to first clinically significant asymptomatic cardiac event, data from patients not experiencing an event were censored at the earliest date of either the last LVEF assessment or the data cut-off date (1 November 2006). Data from patients with no post-randomization follow-up were censored on Day 1.

Table 35 Reviewer's Summary of Asymptomatic LVEF Change or Post Baseline Values during BCIRG 006 (Safety Population)

	AC→T (n = 1050)	AC→TH (n = 1068)	TCH (n = 1056)
Post-baseline LVEF <50%	96(9.14%)	181(16.95%)	90(8.52%)
LVEF< LLN* and ≥15% decrease from baseline	43(4.10%)	109(10.21%)	36(3.41%)
LVEF<50% and ≥10% decrease from baseline	67(6.38%)	141(13.20%)	62(5.87%)
LVEF<50% and ≥16% decrease from baseline	34(3.24%)	104(9.74%)	35(3.31%)
LVEF absolute decrease of ≥10%, <20%	352(33.52%)	470(44.01%)	360(34.09%)
LVEF absolute decrease ≥20%	56(5.33%)	141(13.20%)	66(6.25%)

*LLN = lower limit of normal.

The summary on all LVEF events are based on events after time of randomization. Based on table 59 of the sponsor's clinical study report, AC→ TH arm shows consistently higher median LVEF drop from 4.5 months up to 42 months (at months 42, the median LVEF changes from baseline are -2.5%, 0% and -1 % for AC→TH, TCH and ACT, respectively). The longer term

effect (longer than 42 months) of the Herceptin + chemotherapy on the change in LVEF can not be determined from the current data.

In the adverse reaction section of the labeling, the sponsor provided a cumulative incidence plots of time to first LVEF decline of ≥ 10% from baseline and to below 50% with death as the competing events for 2-year periods (based on EL Korn, FJ Dorey. Applications of crude incidence curves. Statistics in Medicine 1992, 11, 813-829).

(b) (4)

The plots show that the cumulative incidence of the significant LVEF drop in AC → TH arm continues to be higher than the other two arms through 42 months., refer to Figure 3.

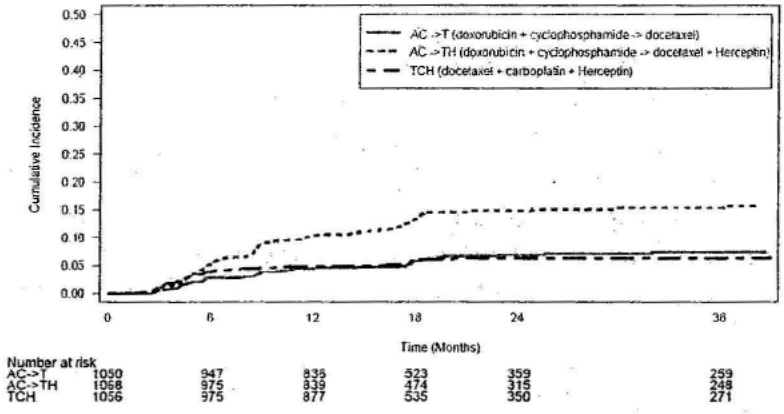


Figure 3 Cumulative Incidence of Time to First LVEF

(b) (4)

Reviewer Comment's: The above figure will be included in the Herceptin label for BCIRG 006.

Deep thrombophlebitis events were reported across all treatment groups in BCIRG 006. The Herceptin containing regimens had a higher incidence of events with particularly highest incidence in the TCH arm (3.7%) versus ACTH (2.5%) and lowest incidence in the control arm ACT (2.2%). Refer to Table 36, Reviewer's Incidence of Deep Thromophlebitis Events.

Table 36 Reviewer's Incidence of Deep Thromophlebitis Events

Safety Population	AC→T (n-1050)	AC→TH (n=1068)	TCH (n=1056)
Deep Thrombophlebitis			
All	23 (2.2%)	27 (2.5%)	39 (3.7%)
Grade 3/4	19 (1.8%)	25 (2.3%)	31 (2.9%)
SAE	7 (0.7%)	11 (1.0%)	14 (1.3%)

Reviewer Comment's: The current Herceptin label will contain additional information regarding thrombosis/embolism from BCIRG 006 study (b) (4)

Common Adverse Events

7.1.1.4 Eliciting adverse events data in the development program

According to the BCIRG 006 protocol, the term adverse event refers to any sign, symptom, illness that appears or worsens in a patient during the period of observation in the clinical study and that may impair the well-being of the patient. The term covers laboratory findings or results of other diagnostic procedures that are considered relevant (e.g., that required unscheduled diagnostic procedures or treatment measures, or resulted in patient withdrawal from the study). All adverse events, including those potentially related to chemotherapy, Herceptin, radiotherapy, and hormonal therapy, were classified and graded according to the NCI-CTC, v2.0. For adverse events that could not be classified according to the NCI-CTC, the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) coding dictionary was used (FDA 1989) (1 = mild, 2 = moderate, 3 = severe, and 4 = life-threatening).

During chemotherapy, evaluation of cardiac and non-cardiac adverse events was to be conducted at each cycle. A final evaluation of cardiac and non-cardiac adverse events was conducted at the end of chemotherapy (EOC) visit, defined as 21 days following the last infusion of chemotherapy. The first follow-up visit was scheduled 3 months following the EOC visit in the AC.T and AC.TH arms and 4.5 months following the EOC visit in the TCH arm. Patients in the TCH arm underwent an additional follow-up visit 6 weeks after the EOC visit to coincide with the EOC visit for the ACT and AC→TH arms. During the first two years of the follow-up period, cardiac adverse event reporting was to be conducted every 3 months. During Years 3–5 of the follow-up period, cardiac adverse event reporting was to be conducted every 6 months. During Years 6–10 of the follow-up period, cardiac adverse event reporting was to be conducted annually. Further evaluation of non-cardiac adverse events was limited to ongoing events deemed possibly or probably related to study treatment at the EOC assessment. The assessment schedule was identical for all three treatment arms throughout the follow-up period. For additional details, see Section 6.1.3.

The adverse events datasets for BCIRG 006 were structured from four CRF's that captured the following: Clinical adverse events (non-laboratory); febrile neutropenia and infection; Cardiac toxicity monitoring from which included left ventricular ejection fraction (LVEF) and Cardiac adverse events; and hematology and blood chemistry labs. All adverse events reported during the clinical study occurred from the time the subject starts treatment with the study medication (chemotherapy or Herceptin) until 30 days after the last infusion of study treatment arm and maximum AE grade. This resulted in a dataset containing one subject per row per AE by maximum grade. The remaining dataset contained only those subjects who experienced at least one AE. These data were then tabulated for the total number of subjects, AE events by grade, and incidence rates per arm. Refer to section 7.1, for overview of AE by intensity and overall incidence of adverse events.

7.1.1.5 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using COSTART terms and NIC-CTC terms. The variables within the datasets had paralleled terms to one another. The safety database of study BCIRG 006, had a total of 3222 subjects broken down into the following; ACT (n=1050), AC→TH (n=1068), and TCH (n=1056). To determine the number of subjects who had an adverse event (AE) at any time during the study , the AE.xpt dataset was grouped patient identifier, COSTART preferred term.

7.1.1.6 Incidence of common adverse events

The most common non-cardiac adverse events reported in ≥ 5 % of subjects with a higher between group difference of ≥ 5% in the Herceptin-containing (ACT versus AC→TH) group were: diarrhea, infection, maculopapular rash, dyspepsia, rhinitis, and epistaxis.

The most common cardiac adverse events reported in ≥ 5% of subjects, with a difference of ≥ 2% in adverse events between ACT and AC→TH were hypertension and left heart failure.

The most common non-cardiac adverse events reported in ≥ 5 % of subjects with a higher between group difference of ≥ 5% in the Herceptin-containing (ACT versus TCH) group were: diarrhea, rash, dyspepsia, abdominal pain, epistaxis, and allergic reaction.

The most common cardiac adverse events reported of any grade in ≥ 5% of subjects with a difference of ≥ 2% in adverse events between ACT and AC→TH were; hypertension and palpitations.

7.1.1.7 Common adverse event tables

<u>ACT versus AC→TH</u>

Table 37 Per Patient Incidence of ACT vs. AC→TH Adverse Events occurring in ≥ 5% of Patients with a Between Group difference in Herceptin Arm ≥ 5%

	ACT (n=1050)				ACTH (n=1068)			
COSTART Adverse Event	**All Grades**	**%**	**Grade 3-4**	**%**	**All Grades**	**%**	**Grade 3-4**	**%**
DIARRHEA	453	43.1	32	3.0	547	51.2	61	5.7
INFECTION	399	38.0	243	23.1	469	43.9	266	24.9
MACULOPAPULAR RASH	298	28.4	18	1.7	365	34.2	14	1.3
DYSPEPSIA	209	19.9	5	0.5	269	25.2	3	0.3
RHINITIS	193	18.4	2	0.2	266	24.9	1	0.1
EPISTAXIS	64	6.1	0	0.0	139	13.0	0	0.0

Table 38 Table Per Patients Incidence of ACT vs. ACTH Non-Cardiac Adverse Events Occurring in ≥ 5% of Patients with Between Group difference in Herceptin Arm ≥ 2%

	ACT (n=1050)				ACTH (N=1068)			
COSTART Adverse Event	**All Grades**	**%**	**Grades 3-4**	**%**	**All Grades**	**%**	**Grades 3-4**	**%**
MYALGIA	557	53.0	55	5.2	597	55.9	56	5.2
DIARRHEA	453	43.1	32	3.0	547	51.2	61	5.7
ARTHRALGIA	454	43.2	35	3.3	500	46.8	35	3.3
INFECTION	399	38.0	243	23.1	469	43.9	266	24.9
PERIPHERAL EDEMA	362	34.5	4	0.4	397	37.2	4	0.4
MACULOPAPULAR RASH	298	28.4	18	1.7	365	34.2	14	1.3
INSOMNIA	248	23.6	3	0.3	283	26.5	4	0.4
FEVER	235	22.4	103	9.8	270	25.3	122	11.4
DYSPEPSIA	209	19.9	5	0.5	269	25.2	3	0.3
DYSPNEA	235	22.4	12	1.1	267	25.0	30	2.8
RHINITIS	193	18.4	2	0.2	266	24.9	1	0.1
LACRIMATION DISORDER	217	20.7	0	0.0	256	24.0	3	0.3
WEIGHT GAIN	210	20.0	9	0.9	249	23.3	6	0.6
BONE PAIN	197	18.8	18	1.7	229	21.4	9	0.8
ABDOMINAL PAIN	187	17.8	8	0.8	215	20.1	9	0.8
DIZZINESS	113	10.8	6	0.6	151	14.1	7	0.7
ALLERGIC REACTION	106	10.1	12	1.1	139	13.0	19	1.8
EPISTAXIS	64	6.1	0	0.0	139	13.0	0	0.0
BACK PAIN	86	8.2	4	0.4	137	12.8	12	1.1
CHILLS	58	5.5	0	0.0	87	8.1	1	0.1

Table 39 Per Patient Incidence of ACT vs. ACTH of Cardiac Adverse Events with a Difference of ≥ 5% in the Herceptin Arm

	ACT (n=1050)				ACTH (n=1068)			
COSTART Adverse Event	**All Grades**	**%**	**Grades 3-4**	**%**	**All Grades**	**%**	**Grades 3-4**	**%**
HYPERTENSION	194	18.5	162	15.4	221	20.7	174	16.3
LEFT HEART FAILURE	45	4.3	6	0.6	106	9.9	22	2.1

Table 40 Per Patient Incidence of All Cardiac Events for ACT Vs. ACTH

	ACT (n=1050)				ACTH (n=1068)			
COSTART Adverse Event	**All Grades**	**%**	**Grades 3-4**	**%**	**All Grades**	**%**	**Grades 3-4**	**%**
HYPERTENSION	194	18.5	162	15.4	221	20.7	174	16.3
LEFT HEART FAILURE	45	4.3	6	0.6	106	9.9	22	2.1
PALPITATION	79	7.5	0	0.0	100	9.4	0	0.0
TACHYCARDIA	56	5.3	5	0.5	63	5.9	1	0.1
CARDIOVASCULAR DISORDER	34	3.2	1	0.1	55	5.1	0	0.0
UNMAPPED	23	2.2	3	0.3	38	3.6	2	0.2
HYPOTENSION	23	2.2	1	0.1	36	3.4	2	0.2
DEEP THROMBOPHLEBITIS	23	2.2	19	1.8	27	2.5	25	2.3
PHLEBITIS	15	1.4	0	0.0	25	2.3	0	0.0
CARDIOMEGALY	7	0.7	0	0.0	22	2.1	0	0.0
PERICARDIAL EFFUSION	17	1.6	0	0.0	21	2.0	0	0.0
CHEST PAIN	9	0.9	0	0.0	18	1.7	1	0.1
ARRHYTHMIA	18	1.7	5	0.5	17	1.6	4	0.4
SINUS BRADYCARDIA	8	0.8	0	0.0	15	1.4	0	0.0
MYOCARDIAL ISCHEMIA	7	0.7	1	0.1	13	1.2	4	0.4
DYSPNEA	4	0.4	1	0.1	11	1.0	0	0.0
HEART FAILURE	6	0.6	2	0.2	8	0.7	0	0.0
VENTRICULAR ARRHYTHMIA	4	0.4	0	0.0	6	0.6	1	0.1
CARDIOMYOPATHY	0	0.0	0	0.0	5	0.5	1	0.1
SYNCOPE	1	0.1	0	0.0	4	0.4	2	0.2
BUNDLE BRANCH BLOCK	5	0.5	0	0.0	3	0.3	0	0.0
EDEMA	0	0.0	0	0.0	3	0.3	0	0.0
PERIPHERAL EDEMA	0	0.0	0	0.0	3	0.3	0	0.0
SUPRAVENTRICULAR TACHYCARDIA	3	0.3	0	0.0	3	0.3	1	0.1
CORONARY ARTERY DISORDER	1	0.1	1	0.1	2	0.2	0	0.0
ELECTROCARDIOGRAM ABNORMAL	2	0.2	0	0.0	2	0.2	0	0.0
EXTRASYSTOLES	3	0.3	0	0.0	2	0.2	0	0.0
SUPRAVENTRICULAR EXTRASYSTOLES	2	0.2	0	0.0	2	0.2	0	0.0
VASCULAR ANOMALY	0	0.0	0	0.0	2	0.2	0	0.0
VASCULAR DISORDER	0	0.0	0	0.0	2	0.2	0	0.0
VENTRICULAR EXTRASYSTOLES	3	0.3	1	0.1	2	0.2	0	0.0
ANGINA PECTORIS	2	0.2	0	0.0	1	0.1	0	0.0
ATRIAL FIBRILLATION	1	0.1	0	0.0	1	0.1	1	0.1
AV BLOCK	0	0.0	0	0.0	1	0.1	0	0.0
CAROTID OCCLUSION	0	0.0	0	0.0	1	0.1	1	0.1

	ACT (n=1050)				ACTH (n=1068)			
COSTART Adverse Event	**All Grades**	**%**	**Grades 3-4**	**%**	**All Grades**	**%**	**Grades 3-4**	**%**
ENDOCARDITIS	0	0.0	0	0.0	1	0.1	1	0.1
EPISTAXIS	0	0.0	0	0.0	1	0.1	0	0.0
HEART MALFORMATION	1	0.1	1	0.1	1	0.1	0	0.0
HYPERKINESIA	1	0.1	0	0.0	1	0.1	0	0.0
HYPERTONIA	0	0.0	0	0.0	1	0.1	0	0.0
HYPOKINESIA	0	0.0	0	0.0	1	0.1	0	0.0
PAIN	0	0.0	0	0.0	1	0.1	0	0.0
PERICARDITIS	0	0.0	0	0.0	1	0.1	0	0.0
T INVERTED	0	0.0	0	0.0	1	0.1	0	0.0
	1	0.1	1	0.1	0	0.0	0	0.0
AORTIC STENOSIS	1	0.1	0	0.0	0	0.0	0	0.0
ARTERIOSCLEROSIS	1	0.1	0	0.0	0	0.0	0	0.0
BIGEMINY	1	0.1	0	0.0	0	0.0	0	0.0
BRADYCARDIA	0	0.0	0	0.0	0	0.0	0	0.0
CEREBRAL ISCHEMIA	0	0.0	0	0.0	0	0.0	0	0.0
CHEST PAIN SUBSTERNAL	1	0.1	0	0.0	0	0.0	0	0.0
CONGESTIVE HEART FAILURE	1	0.1	0	0.0	0	0.0	0	0.0
DYSPEPSIA	0	0.0	0	0.0	0	0.0	0	0.0
DYSTONIA	0	0.0	0	0.0	0	0.0	0	0.0
FACE EDEMA	0	0.0	0	0.0	0	0.0	0	0.0
GLAUCOMA	0	0.0	0	0.0	0	0.0	0	0.0
HEART ARREST	0	0.0	0	0.0	0	0.0	0	0.0
HEART BLOCK	0	0.0	0	0.0	0	0.0	0	0.0
HYPERCHOLESTEREMIA	0	0.0	0	0.0	0	0.0	0	0.0
HYPERLIPEMIA	1	0.1	0	0.0	0	0.0	0	0.0
HYPOTONIA	0	0.0	0	0.0	0	0.0	0	0.0
LEUKOPENIA	1	0.1	0	0.0	0	0.0	0	0.0
MYOCARDIAL INFARCT	0	0.0	0	0.0	0	0.0	0	0.0
MYOCARDITIS	1	0.1	1	0.1	0	0.0	0	0.0
PERIPHERAL VASCULAR DISORDER	0	0.0	0	0.0	0	0.0	0	0.0

ACT versus TCH

Table 41 Per Patient Incidence of ACT vs. TCH Non-Cardiac Adverse Events occurring in ≥ 5% of Patients with a Between Group difference in Herceptin Arm ≥ 5%

	ACT (n=1050)				TCH (n=1056)			
Preferred Term	**All Grades**	**%**	**Grades 3-4**	**%**	**All Grades**	**%**	**Grades 3-4**	**%**
DIARRHEA	453	43.1	32	3.0	662	62.7	58	5.5
RASH	219	20.9	4	0.4	282	26.7	9	0.9
DYSPEPSIA	209	19.9	5	0.5	264	25.0	5	0.5
ABDOMINAL PAIN	187	17.8	8	0.8	245	23.2	8	0.8
EPISTAXIS	64	6.1	0	0.0	170	16.1	4	0.4
ALLERGIC REACTION	106	10.1	12	1.1	160	15.2	28	2.7

Table 42 Per Patients Incidence of ACT vs. TCH Non-Cardiac Adverse Events Occurring in ≥ 5% of Patients with Between Group Difference in Herceptin Arm ≥ 2%

	ACT (n=1050)				TCH (n=1056)			
COSTART Adverse Event	**All Grades**	**%**	**Grades 3-4**	**%**	**All Grades**	**%**	**Grades 3-4**	**%**
DIARRHEA	453	43.1	32	3.0	662	62.7	58	5.5
MACULOPAPULAR RASH	298	28.4	18	1.7	347	32.9	9	0.9
RASH	219	20.9	4	0.4	282	26.7	9	0.9
DYSPEPSIA	209	19.9	5	0.5	264	25.0	5	0.5
WEIGHT GAIN	210	20.0	9	0.9	252	23.9	9	0.9
ABDOMINAL PAIN	187	17.8	8	0.8	245	23.2	8	0.8
EPISTAXIS	64	6.1	0	0.0	170	16.1	4	0.4
ALLERGIC REACTION	106	10.1	12	1.1	160	15.2	28	2.7
LYMPHEDEMA	85	8.1	0	0.0	109	10.3	2	0.2
PRURITUS	39	3.7	0	0.0	66	6.3	1	0.1
DYSURIA	26	2.5	0	0.0	57	5.4	1	0.1
ACNE	11	1.0	0	0.0	33	3.1	0	0.0

Table 43 Table Per Patient Incidence of ACT vs. TCH of Cardiac Adverse Events with a Between Group Difference in Herceptin ≥ 2%

	ACT (n=1050)				TCH (n=1068)			
COSTART Adverse Event	**All Grades**	**%**	**Grades 3-4**	**%**	**All Grades**	**%**	**Grades 3-4**	**%**
HYPERTENSION	194	18.5	162	15.4	222	21.0	187	17.7
PALPITATION	79	7.5	0	0.0	102	9.7	0	0.0
UNMAPPED	23	2.2	3	0.3	45	4.3	5	0.5

Table 44 Table Per Patient Incidence of All Cardiac Events for ACT Vs. TCH

	ACT				TCH			
COSTART Adverse Event	**All Grades**	**%**	**Grades 3-4**	**%**	**All Grades**	**%**	**Grades 3-4**	**%**
HYPERTENSION	194	18.5	162	15.4	222	21.0	187	17.7
PALPITATION	79	7.5	0	0.0	102	9.7	0	0.0
TACHYCARDIA	56	5.3	5	0.5	71	6.7	2	0.2
UNMAPPED	23	2.2	3	0.3	45	4.3	5	0.5
CARDIOVASCULAR DISORDER	34	3.2	1	0.1	40	3.8	1	0.1
DEEP THROMBOPHLEBITIS	23	2.2	19	1.8	39	3.7	31	2.9
LEFT HEART FAILURE	45	4.3	6	0.6	39	3.7	1	0.1
HYPOTENSION	23	2.2	1	0.1	25	2.4	2	0.2
ARRHYTHMIA	18	1.7	5	0.5	18	1.7	7	0.7
CHEST PAIN	9	0.9	0	0.0	17	1.6	1	0.1
PERICARDIAL EFFUSION	17	1.6	0	0.0	17	1.6	0	0.0
CARDIOMEGALY	7	0.7	0	0.0	12	1.1	0	0.0
MYOCARDIAL ISCHEMIA	7	0.7	1	0.1	11	1.0	3	0.3
PHLEBITIS	15	1.4	0	0.0	10	0.9	0	0.0
SINUS BRADYCARDIA	8	0.8	0	0.0	9	0.9	0	0.0
SYNCOPE	1	0.1	0	0.0	8	0.8	1	0.1
DYSPNEA	4	0.4	1	0.1	7	0.7	2	0.2
HEART FAILURE	6	0.6	2	0.2	7	0.7	0	0.0
VENTRICULAR ARRHYTHMIA	4	0.4	0	0.0	7	0.7	1	0.1
BUNDLE BRANCH BLOCK	5	0.5	0	0.0	5	0.5	1	0.1

	ACT				TCH			
COSTART Adverse Event	**All Grades**	**%**	**Grades 3-4**	**%**	**All Grades**	**%**	**Grades 3-4**	**%**
VENTRICULAR EXTRASYSTOLES	3	0.3	1	0.1	4	0.4	0	0.0
ARTERIOSCLEROSIS	1	0.1	0	0.0	3	0.3	0	0.0
AV BLOCK	0	0.0	0	0.0	3	0.3	1	0.1
BIGEMINY	1	0.1	0	0.0	3	0.3	0	0.0
BRADYCARDIA	0	0.0	0	0.0	3	0.3	0	0.0
ELECTROCARDIOGRAM ABNORMAL	2	0.2	0	0.0	3	0.3	0	0.0
	1	0.1	1	0.1	2	0.2	1	0.1
ANGINA PECTORIS	2	0.2	0	0.0	2	0.2	0	0.0
CARDIOMYOPATHY	0	0.0	0	0.0	2	0.2	0	0.0
CORONARY ARTERY DISORDER	1	0.1	1	0.1	2	0.2	1	0.1
EDEMA	0	0.0	0	0.0	2	0.2	0	0.0
EXTRASYSTOLES	3	0.3	0	0.0	2	0.2	0	0.0
SUPRAVENTRICULAR EXTRASYSTOLES	2	0.2	0	0.0	2	0.2	0	0.0
SUPRAVENTRICULAR TACHYCARDIA	3	0.3	0	0.0	2	0.2	0	0.0
AORTIC STENOSIS	1	0.1	0	0.0	1	0.1	1	0.1
CEREBRAL ISCHEMIA	0	0.0	0	0.0	1	0.1	1	0.1
ENDOCARDITIS	0	0.0	0	0.0	1	0.1	0	0.0
GLAUCOMA	0	0.0	0	0.0	1	0.1	1	0.1
HEART ARREST	0	0.0	0	0.0	1	0.1	1	0.1
HYPERCHOLESTEREMIA	0	0.0	0	0.0	1	0.1	0	0.0
HYPERKINESIA	1	0.1	0	0.0	1	0.1	0	0.0
HYPOTONIA	0	0.0	0	0.0	1	0.1	0	0.0
MYOCARDIAL INFARCT	0	0.0	0	0.0	1	0.1	0	0.0
PAIN	0	0.0	0	0.0	1	0.1	0	0.0
VASCULAR ANOMALY	0	0.0	0	0.0	1	0.1	0	0.0
ATRIAL FIBRILLATION	1	0.1	0	0.0	0	0.0	0	0.0
CAROTID OCCLUSION	0	0.0	0	0.0	0	0.0	0	0.0
CHEST PAIN SUBSTERNAL	1	0.1	0	0.0	0	0.0	0	0.0
CONGESTIVE HEART FAILURE	1	0.1	0	0.0	0	0.0	0	0.0

DYSPEPSIA	0	0.0	0	0.0	0	0.0	0	0.0
DYSTONIA	0	0.0	0	0.0	0	0.0	0	0.0
EPISTAXIS	0	0.0	0	0.0	0	0.0	0	0.0
FACE EDEMA	0	0.0	0	0.0	0	0.0	0	0.0
HEART BLOCK	0	0.0	0	0.0	0	0.0	0	0.0
HEART MALFORMATION	1	0.1	1	0.1	0	0.0	0	0.0
HYPERLIPEMIA	1	0.1	0	0.0	0	0.0	0	0.0
HYPERTONIA	0	0.0	0	0.0	0	0.0	0	0.0
HYPOKINESIA	0	0.0	0	0.0	0	0.0	0	0.0
LEUKOPENIA	1	0.1	0	0.0	0	0.0	0	0.0
MYOCARDITIS	1	0.1	1	0.1	0	0.0	0	0.0
PERICARDITIS	0	0.0	0	0.0	0	0.0	0	0.0
PERIPHERAL EDEMA	0	0.0	0	0.0	0	0.0	0	0.0
PERIPHERAL VASCULAR DISORDER	0	0.0	0	0.0	0	0.0	0	0.0
PERIPHERAL VASCULAR DISORDER	0	0.0	0	0.0	0	0.0	0	0.0
T INVERTED	0	0.0	0	0.0	0	0.0	0	0.0
VASCULAR DISORDER	0	0.0	0	0.0	0	0.0	0	0.0

7.1.1.8 Identifying common and drug-related adverse events

Serious adverse events which are probable or definitely due to Herceptin, based on comparison between treatment groups of BCIRG 006 include; congestive heart failure, decreased LVEF, cardiac ischemia/infarction, and deep thrombophlebitis.

The most common non-cardiac adverse events occurring in ≥ 5 % of subjects with a higher between group difference of ≥ 5% in the in the Herceptin containing (ACT versus AC→TH) group were: diarrhea, infection, maculopapular rash, dyspepsia, rhinitis, and epistaxis.

The most common cardiac adverse events of any grade reported in ≥ 5% of subjects with higher incidence ≥ 2% in the Herceptin containing (ACT versus AC→TH) group were: hypertension and left heart failure.

The most common non-cardiac adverse events reported in ≥ 5 % of subjects with a higher between group difference of ≥ 5% in the Herceptin containing (ACT versus TCH) group were: diarrhea, rash, dyspepsia, abdominal pain, epistaxis, and allergic reaction.

The most common cardiac adverse events of any grade reported in ≥ 5% of subjects with higher incidence ≥ 2% in the Herceptin containing (ACT versus TCH) group were: hypertension and palpitations.

Less Common Adverse Events

Rare but serious adverse events with a higher incidence (ACT vs. ACTH) in the Herceptin group include: chest pain, anemia, "reaction unevaluable", and cerebral vascular accident. Clinically the most significant difference was in the incidence of chest pain, anemia, and cerebral vascular accident in the ACTH arm in comparison to the control arm. Refer to Table 45, Adverse Events Grades 3-4 Across all Groups Rare but Serious.

Rare but serious adverse events with a higher incidence (ACT vs. TCH in the Herceptin) group include: anemia, chest pain, vertigo, hypokalemia, "reaction unevaluable". Cerebral vascular accident, colitis, hematuria, gastrointestinal hemorrhage, stomach atony, cirrhosis of the liver, liver necrosis, stomach ulcer, thrombocytopenia, and kidney failure. Clinically the most significant difference reported was anemia, vertigo, cerebral vascular accident, and thrombocytopenia, and kidney failure. Refer to Table 45, Adverse Events Grades 3-4 Across all Groups Rare but Serious.

Table 45 Adverse Events Grades 3-4 Across all Groups Rare but Serious

COSTART Adverse Event	ACT (n=1050) %	AC→TH (n=1068) %	TCH (n=1056) %
CHEST PAIN	0.2	0.6	0.5
ANEMIA	0.0	0.4	0.6
VERTIGO	0.1	0.3	0.6
HYPOKALEMIA	0.2	0.3	0.6
REACTION UNEVALUABLE	0.0	0.3	0.1
CEREBROVASCULAR ACCIDENT	0.0	0.1	0.3
COLITIS	0.0	0.0	0.4
HEMATURIA	0.0	0.0	0.3
GASTROINTESTINAL HEMORRHAGE	0.0	0.0	0.1
STOMACH ATONY	0.0	0.0	0.1
CIRRHOSIS OF LIVER	0.0	0.0	0.1
LIVER NECROSIS	0.0	0.0	0.1
STOMACH ULCER	0.0	0.0	0.1
THROMBOCYTOPENIA	0.1	0.0	0.7
KIDNEY FAILURE	0.0	0.0	0.1

Laboratory Findings

7.1.1.9 Overview of laboratory testing in the development program

The schedule of assessment for laboratory parameters included hematology and chemistry labs. Prestudy hematology labs consisted of ; whit blood count with neutrophil count, hemoglobin, and platelet count. Chemistry labs included liver function testing (alkaline phosphatase, AST (SGOT), ALAT (SGPT) and bilirubin. Renal function labs included serum creatinine and creatinine clearance (if indicated). During chemotherapy, hematology and chemistry labs were obtained every three weeks. All laboratory toxicities were graded according to NCI-CTC version 2.0.

The applicant notified the Agency by written communication dated November 2, 2007, of errors in lab data for BCIRG 006. The applicant was notified by the CIRG that errors were discovered in the institution's upper limit of normal values and in the conversion of lab values to standard units for the BCIRG006 hematology and chemistries datasets submitted in sBLA 103792/5187 and 103792/5189. These errors were corrected by CIRG, and the lab datasets of hematology and chemistries were re-transferred to the applicant. The updated datasets (HEMC.xpt, CHMC.xpt) as well as the derived dataset for the laboratory assessments (PATLAB.xpt) were provided to the Agency.

After re-analysis of the lab data based on the corrected data, a comparison of the lab results with those in the original sBLA was performed. There were minor differences that affected the results presented in Section 12.4 of the CSR, Clinical Laboratory Evaluations, Tables 71 and 72.

Table 46 Original CSR Table 71 Hematologic Laboratory Toxicity

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)	All Patients (n=3174)
Number of patients with anemia [a]	957 (91.1%)	1036 (97.0%)	1017 (96.3%)	3010 (94.8%)
Grade 3/4	**26 (2.5%)**	34 (3.2%)	61 (5.8%)	**121 (3.8%)**
Number of patients with neutropenia [b]	**858 (81.7%)**	922 (86.3%)	**858 (81.3%)**	2638 (83.1%)
Grade 3/4	**663 (63.1%)**	761 (71.3%)	696 (65.9%)	**2120 (66.8%)**
Number of patients with thrombocytopenia	296 (28.2%)	349 (32.7%)	667 (63.2%)	**1312 (41.3%)**
Grade 3/4	10 (1.0%)	13 (1.2%)	57 (5.4%)	80 (2.5%)
Number of patients with leukopenia	878 (83.6%)	929 (87.0%)	877 (83.0%)	2684 (84.6%)
Grade 3/4	540 (51.4%)	**642 (60.1%)**	507 (48.0%)	**1689 (53.2%)**

Note: Values affected by the data corrections are in **bold.**

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; G-CSF=granulocyte colony-stimulating factors; TCH=docetaxel, carboplatin, and Herceptin.

[a] Anemia is defined as hemoglobin level <12 g/dL.

[b] Neutropenia is defined as absolute neutrophil count $<1.0\times10^9$/L.

Source: Tables 14.3/100, 14.3/101, 14.3/102, and 14.3/103.

Table 47 Updated CSR table 71, after data Corrections Hematologic toxicity

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)	All Patients (n=3174)
Number of patients with anemia [a]	957 (91.1%)	1036 (97.0%)	1017 (96.3%)	3010 (94.8%)
Grade 3/4	**25 (2.4%)**	34 (3.2%)	61 (5.8%)	**120 (3.8%)**
Number of patients with neutropenia [b]	**859 (81.7%)**	922 (86.3%)	**859 (81.3%)**	**2640 (83.2%)**
Grade 3/4	**664 (63.1%)**	761 (71.3%)	696 (65.9%)	**2121 (66.8%)**
Number of patients with thrombocytopenia	296 (28.2%)	**350 (32.8%)**	667 (63.2%)	**1313 (41.4%)**
Grade 3/4	10 (1.0%)	13 (1.2%)	57 (5.4%)	80 (2.5%)
Number of patients with leukopenia	878 (83.6%)	929 (87.0%)	877 (83.0%)	2684 (84.6%)
Grade 3/4	540 (51.4%)	**643 (60.2%)**	507 (48.0%)	**1690 (53.2%)**

Note: Corrected data are shown in **bold.**

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; G-CSF=granulocyte colony-stimulating factors; TCH=docetaxel, carboplatin, and Herceptin.

[a] Anemia is defined as hemoglobin level <12 g/dL.

[b] Neutropenia is defined as absolute neutrophil count $<1.0\times10^9$/L.

Table 48 Original CSR Table 72 Chemistry Laboratory Toxicities

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)	All Patients (n=3174)
Number of patients with creatinine toxicity	39 (3.7%)	**73 (6.8%)**	102 (9.7%)	**214 (6.7%)**
Grade 3/4	7 (0.7%)	**6 (0.6%)**	6 (0.6%)	**19 (0.6%)**
Number of patients with phosphatase toxicity	**204 (19.4%)**	**209 (19.6%)**	**217 (20.5%)**	**630 (19.8%)**
Grade 3/4	**7 (0.7%)**	**7 (0.7%)**	**6 (0.6%)**	**20 (0.6%)**
Number of patients with AST (SGOT) toxicity	426 (40.6%)	454 (42.5%)	**403 (38.2%)**	**1283 (40.4%)**
Grade 3/4	2 (0.2%)	**11 (1.0%)**	**13 (1.2%)**	**26 (0.8%)**
Number of patients with ALT (SGPT) toxicity	**508 (48.4%)**	**581 (54.4%)**	**562 (53.2%)**	**1651 (52.0%)**
Grade 3/4	**10 (1.0%)**	**21 (2.0%)**	**28 (2.7%)**	**59 (1.9%)**
Number of patients with bilirubin toxicity	52 (5.0%)	**55 (5.1%)**	**65 (6.2%)**	**172 (5.4%)**
Grade 3/4	**7 (0.7%)**	**5 (0.5%)**	**10 (0.9%)**	**22 (0.7%)**

Note: Values affected by the data corrections are in **bold.**

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; TCH=docetaxel, carboplatin, and Herceptin.

Table 49 Updated CSR Table 7, after Data Corrections Chemistry Laboratory Toxicities

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)	All Patients (n=3174)
Number of patients with creatinine toxicity	39 (3.7%)	**72 (6.7%)**	102 (9.7%)	**213 (6.7%)**
Grade 3/4	7 (0.7%)	**5 (0.5%)**	6 (0.6%)	**18 (0.6%)**
Number of patients with phosphatase toxicity	**202 (19.2%)**	**206 (19.3%)**	**215 (20.4%)**	**623 (19.6%)**
Grade 3/4	**3 (0.3%)**	**3 (0.3%)**	**3 (0.3%)**	**9 (0.3%)**
Number of patients with AST (SGOT) toxicity	426 (40.6%)	454 (42.5%)	**401 (38.0%)**	**1281 (40.4%)**
Grade 3/4	2 (0.2%)	**9 (0.8%)**	**11 (1.0%)**	**22 (0.7%)**
Number of patients with ALT (SGPT) toxicity	**506 (48.2%)**	**579 (54.2%)**	**561 (53.1%)**	**1646 (51.9%)**
Grade 3/4	**7 (0.7%)**	**19 (1.8%)**	**25 (2.4%)**	**51 (1.6%)**
Number of patients with bilirubin toxicity	52 (5.0%)	**54 (5.1%)**	**61 (5.8%)**	**167 (5.3%)**
Grade 3/4	**6 (0.6%)**	**4 (0.4%)**	**4 (0.4%)**	**14 (0.4%)**

Note: Corrected data are shown in **bold.**

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; TCH=docetaxel, carboplatin, and Herceptin.

In comparing hematologic lab toxicities between ACT and ACTH, overall the ACTH group had a higher incidence of anemia, neutropenia , and leukopenia. For comparison between ACT and TCH groups, overall the TCH group had a higher incidence of anemia, neutropenia, and leukopenia with the most clinically significant difference in thrombocytopenia ACT (28.2%) vs. TCH (41.4%).

In comparing chemistry lab toxicities between ACT and ACTH, overall, the Herceptin containing regimen had higher incidence of toxicity in creatinine, phosphatase, SGOT, SGPT, and bilirubin with the most clinically significant difference in creatinine toxicity [ACT (3.7%) vs. ACTH (6.7%)] and in grade 3-4 SGPT toxicity [ACT (0.7%) vs. ACTH (1.8%)]. For comparison between ACT and TCH group, the TCH arm had lower incidence of chemistry lab toxicity compared to ACTH overall with the exception of SGOT toxicity [ACT (38%) vs. TCH (40.4%)].

7.1.1.10 Special assessments

No other special assessments were conducted.

Vital Signs

Vital signs were not recorded for Study BCIRG 006.

Electrocardiograms (ECGs)

A normal ECG was required within three months prior to registration onto study BCIRG 006. During therapy ECG's were obtained as clinically indicated.

As part of the cardiac secondary endpoint of BCIRG 006, cardiac arrhythmias of grade 3 and 4 were specifically monitored for and reviewed by the ICRP. The NCI-CTC version 2 grading was used and defines a grade 3 arrythmia as symptomatic and requiring treatment, or grade 4 which is an arrhythmia considered to be life threatening. Subjects who developed grade 3 or 4 arrythmia were required to have an ECG repeated during follow-up every three months for the first year, and every year until the end of follow-up or otherwise as clinically indicated.

The ACTH group had a higher incidence of grade 3-4 arrythmia compared to the control group ACT (.08% vs. 0.5%). The TCH group and the control arm were equal in incidence of these events. Refer to Table 50 Reviewer's Incidence of Arrhythmias Events.

Table 50 Reviewer's Incidence of Arrhythmias Events

	ACT (n=1050)	ACTH (n=1068)	TCH (n=1056)
Arrythmia	5 (0.5%)	8 (0.8%)	5 (0.5%)
ICRP Grade 3	3 (0.3%)	0 (0%)	1 (0.1%)
ICRP Grade 4	0 (0%)	0 (0%)	0 (0%)

* ICRP= Independent Cardiac Review Panel
** GNECARD dataset

Immunogenicity

The BCIRG 006 study was not designed to collect serum samples in order to determine the incidence of human anti-human antibody (HAHA) to Trastuzumab. Data to immunogenecity is limited to legacy data in the metastatic setting. The incidence of immune response (HAHA) to trastuzumab in the setting of metastatic disease is low. The impact on HAHA, if any, is of minimal risk and does not offset the benefits of the effects on DFS.

Human Carcinogenicity

Human carcinogenicity studies were not required and therefore not conducted or included in the application in support of this proposed labeling extension.

Special Safety Studies

No special safety studies were conducted in support of this application.

Withdrawal Phenomena and/or Abuse Potential

No withdrawal phenomenon is known. Trastuzumab has no expected abuse potential.

Human Reproduction and Pregnancy Data

No new reproductive and/or pregnancy data with study BCIRG 006.

Assessment of Effect on Growth

There is no information on the use of this drug in children.

Overdose Experience

There was no report of overdose in the sBLA application.

Postmarketing Experience

There were no additional spontaneous post-marketing reports provided within the application or reviewed independently by this reviewer from this application. Review of post-marketing reports was not conducted because it was extensively reviewed with recent supplement BL STN 103792/5175 with approval date January 18, 2008.

7.2 Adequacy of Patient Exposure and Safety Assessments

Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Refer to section 6.1.3 Study Design

7.2.1.2 Demographics

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

7.2.1.3 Extent of exposure (dose/duration)

In the original protocol, following chemotherapy, patients in both the AC→TH and TCH arms were to receive 2 mg/kg doses of Herceptin weekly for a year from the first Herceptin administration. However, in Amendment 2 (dated 7/30/2001), the frequency of Herceptin administration during the mono therapy was changed from once every week to once every 3 weeks. There were 43 patients who had started Herceptin monotherapy prior to the amendment (19 and 24 for AC-- TH and TCH arms, respectively). Of these 43 patients, 32 continued to receive Herceptin monotherapy on a weekly basis, while the remaining 11 patients switched from a once weekly to a once-every-3-week schedule.
A summary of Herceptin exposure is shown in the following Table 51. The median duration (378 days) and the median total dose (107.4 and 109.5 for AC--TH and TCH arms, respectively) of Herceptin appear to be similar between AC--TH and TCH arms.

Table 51 Herceptin Exposure

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
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
Relative dose intensity			
n	NA	1045	1056
Mean (SD)	NA	1.000 (0.086)	1.005 (0.096)
Median	NA	1.004	1.004
Range	NA	0.44–1.36	0.29–2.47

Description of Secondary Clinical Data Sources Used to Evaluate Safety

There were no secondary clinical data sources for this application.

7.2.1.4 Other studies

There are no other studies.

7.2.1.5 Postmarketing experience

There were no additional spontaneous post-marketing reports provided within the application or reviewed independently by this reviewer from this application. Review of post-marketing reports was not conducted because it was extensively reviewed with recent supplement 103792/5175 with approval date January 18, 2008.

7.2.1.6 Literature

There was no additional new data in the literature to support the safety of this application.

Adequacy of Overall Clinical Experience

An adequate number of subjects had exposure to drug to provide safety information.

Adequacy of Special Animal and/or In Vitro Testing

Not applicable to this efficacy supplement.

Adequacy of Routine Clinical Testing

Routine clinical testing was adequate. Refer to section 6.1.3 Schedule of Assessments.

Adequacy of Metabolic, Clearance, and Interaction Workup

No drug-drug interactions were conducted or necessary during study BCIRG 006.

Assessment of Quality and Completeness of Data

The following statements regarding data quality and completeness with regard to adverse event evaluation and toxicity grading are pertinent to the review of this application:

- The study was open labeled, which could lead to over and/or under reporting of toxicities in both treatment arms. The extent to which observed toxicities concurred with the investigator's pre-study bias, whether seen on the treatment or control arm could have influenced reporting. It is not possible to estimate the magnitude of this potential bias.
- Although the schedule of assessments was identical to all three arms, subjects in the Herceptin arm had the opportunity to report symptoms more often in conjunction with the infusion appointment (every three weeks).

Additional Submissions, Including Safety Update

The applicant submitted a 120 day safety update at the FDA's request.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Cardiac

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

Infection

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

(b) (4)

Diarrhea

The incidence of Grade 3-4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1-4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin.

7.4 General Methodology

Pooling Data Across Studies to Estimate and Compare Incidence

Data from were reviewed to assess the overall frequency of adverse events for subjects treated with Herceptin as contrasted with those in the comparator arm. In addition, these results were compared to summaries of data from the legacy studies and the current product label. There was no pooling of data from these sources.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The following are the recommended doses and schedules of Herceptin for a total of 52 weeks, for the treatment of adjuvant breast cancer:
During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

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

8.2 Drug-Drug Interactions

There has been no formal drug interaction studies performed with Herceptin in humans during BCIRG 006.

8.3 Special Populations

This efficacy supplement contained no specific studies to evaluate dosing based on race, gender, age or major organ impairment. No data from study BCIRG 006 suggested dosing should be modified based on demographic characteristics.

8.4 Pediatrics

A waiver for pediatric studies under PREA is granted in this application because the indication sought is for a condition which does not occur in children.

8.5 Advisory Committee Meeting

The review team, including this reviewer, decided not to present the findings in the application to the Oncologic Drugs Advisory Committee for the following reasons: 1) the effects of Herceptin on the primary endpoint, DFS, and related secondary endpoints were both clinically relevant, highly significant, and internally consistent across relevant subgroups. In addition, this study replicates the findings of an early supplemental application (BL STN 103792.5175) for essentially the same indication; 2) the primary endpoint, prolongation of disease-free survival, is considered an appropriate and feasible measure of clinical benefit for adjuvant treatment of solid tumors, including breast cancer; and 3) there were no safety signals that were considered to outweigh the clinical benefit demonstrated.

8.6 Literature Review

In study BCIRG 006, the comparison between the control arm (AC followed by docetaxel) and the experimental arm (docetaxel–carboplatin– Herceptin) does not isolate the effect of Herceptin.

FDA reviewers asked the sponsor to provide data which support that the effects seen on DFS can be attributed primarily to Herceptin rather than other components of the treatment arm.

Data directly addressing the use of a taxane/platinum (TC) combination given alone in the adjuvant treatment of HER2-positive breast cancer are not currently available. This may be due in part to data suggesting a need for anthracyclines in the management of HER2-positive breast cancer. Therefore, the sponsor provided data in the neoadjuvant setting and metastatic breast cancer setting.

Neoadjuvant breast cancer:
Platinum compounds in combination with other anti-tumoral agents have been employed as neoadjuvant breast cancer. Although these combinations are active, the contribution of platinums to the overall activity is unknown. A review of ten single-arm studies by Martín (2001) noted clinical complete response (CR) rates of 77%–100% and rates of pathologic CR in the range of 20%–27%. However, HER2 status was not specified.

Efficacy and safety of weekly docetaxel/carboplatin as primary therapy for 44 patients with HER2-negative locally advanced breast cancer were studied in a single-arm Phase II study at the University of Miami (Hurley et al.2005). Post-operatively, patients received four cycles of adjuvant AC, standard radiation therapy, and tamoxifen, if indicated. The clinical CR rate was 25% (n = 11), and clinical partial responses were seen in 66% of patients (n = 29), resulting in a 91% objective responses rate. The pathologic CR rate was 14% (n = 6). DFS data are not available. The contribution of carboplatin to the regimen remains to be defined in randomized, comparative studies.

The sponsor states that recent data demonstrate pharmacologic synergy between Herceptin and both platinum in HER2-positive human breast cancer cell lines. Because of this potential synergy with Herceptin, combinations of platinum compounds with docetaxel and trastuzumab have been tested in patients with metastatic breast cancer, which overexpresses HER2.

Metastatic breast cancer:
Results of a Study BCIRG007, a Phase III study evaluating Herceptin plus docetaxel with or without carboplatin for the first-line treatment of HER2-positive MBC were presented at the American Society of Clinical Oncology in 2007 (Pegram et al. 2007). The primary endpoint of the BCIRG 007 study was time to progression (TTP); secondary endpoints included OS, response rate, duration of response, clinical benefit, and safety. Efficacy results at a median follow-up of 39 + months showed that the addition of carboplatin to TH did not meet the pre-specified study endpoint of a 50% improvement in TTP (see table below).

	TH	TCH	p-value
Median TTP (months)	11.07	10.35	0.57
Median OS (months)	39.1	39.2	0.65
Overall response rate	72.5%	72.7%	–

Study M77001 (Marty et al. 2005), in 188 HER2-positive patients (3+ by immunohistochemistry and/or FISH-positive disease) were randomized to receive100 mg/m^2 docetaxel for six cycles with or without Herceptin given weekly until disease progression in the first-line metastatic setting. The primary endpoint was overall response rate (ORR); secondary endpoints were safety, TTP, time to treatment failure, and survival. Overall response rate was 61% in the TH combination arm (7% with CR, 54% partial response) versus 36% (2% CR, 34% partial response) in the docetaxel-alone arm ($p = 0.001$). TTP was 10.6 months in the combination arm compared with 6.1 months ($p = 0.0001$) in the docetaxel arm. Overall survival was 27.7 months in the combination arm versus 18.3 months ($p = 0.0002$). These results demonstrate that the addition of Herceptin to docetaxel in the first-line metastatic setting significantly improves both PFS and OS in patients with HER2-positive breast cancer.

The addition of carboplatin to paclitaxel and Herceptin has also been studied. Robert et al. (2004) in a Phase III randomized, multicenter trial in 196 women with HER2-overexpressing metastatic breast cancer. The addition of carboplatin to paclitaxel and Herceptin in this study significantly improved response rate (52% vs. 36%; $p = 0.04$) and TTP (11.9 months vs. 6.8 months; $p = 0.02$).

In summary, there is limited data regarding the use of platinum compounds in the adjuvant treatment of HER2-positive breast cancer. Anthracycline-containing regimens have been shown to be particularly beneficial in patients with HER2-positive breast cancer and are the standard of care against which investigational agents should be measured. Because of the cardiac risk associated with anthracyclines, and the increased risk of cardiotoxicity seen when anthracyclines are used in combination with Herceptin, investigation of a non–anthracycline-containing adjuvant regimen for HER2-positive early breast cancer was felt to be appropriate. Through synergistic activity with both Taxotere□ and carboplatin, Herceptin given as part of the TCH regimen has been shown to be an active combination in the metastatic setting and provide a PFS as well as an OS benefit relative to taxanes alone in this setting. This regimen was chosen to compare with standard AC→T, offering the possibility of a less cardiotoxic regimen with improved efficacy for the adjuvant treatment of early stage HER2-positive breast cancer. TCH is the first non–anthracycline-based regimen to

show greater efficacy than AC followed by T in HER2-positive breast cancer.

8.7 Postmarketing Risk Management Plan

Pregnancy registry was part of a post marketing commitment with BLA STN 103792/5175 with January 18, 2008 approval.

8.8 Other Relevant Materials

There were no additional studies, including actual use, labeling comprehension studies and marketing studies, were considered in this review.

Consultation on product labeling was requested from the Division of Division of Drug Marketing, Advertising, and Communication (DDMAC).

9 OVERALL ASSESSMENT

9.1 Conclusions

This review addresses an efficacy supplement to BLA 103792.5189 for use of Herceptin® (trastuzumab) in combination with docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer. The current supplement presents the results of a single, randomized trial comparing Herceptin® (trastuzumab) in combination with docetaxel and carboplatin with Herceptin® (trastuzumab) following the combination with doxorubicin and cyclophosphamide and the combination of doxorubicin and cyclophosphamide followed by docetaxel, as adjuvant treatment in women with HER2-overexpressing, node-positive (b) (4) breast cancer.

Results of the protocol-specified **second efficacy interim analysis** demonstrated that Herceptin as part of either an anthracycline-based (AC→TH) or non–anthracycline-based (TCH) adjuvant treatment regimen results in a clinically meaningful and statistically significant improvement in DFS relative to AC→T irrespective of nodal status. For the primary efficacy endpoint, DFS, the risk of a first event was reduced by 39% (95% confidence interval [CI]: 23, 51; $p < 0.0001$) in the AC→TH arm relative to the AC→T arm. For the primary efficacy endpoint, DFS, the risk of a first event was reduced by 33% (95% CI: 17, 46; $p = 0.0003$) in the TCH arm relative to the AC→T arm.

• The DFS benefit in all clinically important subgroups, including those defined by age, menopausal status, hormone receptor status, nodal status, tumor size, nuclear grade, and surgery or radiation therapy, was consistent with the treatment effect in the overall population.

• Follow-up was too short for an adequate comparison of survival. In addition, the protocol did not have a pre-specified alpha spending for overall survival, no preplanned interim analyses and no pre-specified significance levels. (b) (4)

Overall, the submitted trial demonstrated efficacy and clinical benefit for TCH as adjuvant therapy in women with HER2-overexpressing, node-positive (b) (4) breast cancer. While there is increased toxicity with the TCH therapy compared to the control arm, the benefit conveyed is greater than the incidence of serious adverse events. The data from Study BCIRG006 support approval for this indication.

BCIRG006 was also submitted to support the Herceptin approval for a second indication. "As part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer" This indication is also going to be approved. Please see a separate review by Katherine Fedenco, MS, CRNP.

9.2 Recommendation on Regulatory Action

The Division of Drug Biology Oncology Products recommends full approval, of Herceptin® for the proposed indication:
"As part of a treatment regimen containing docetaxel and carboplatin for the adjuvant treatment of HER2-overexpressing, node-positive (b) (4) breast cancer".

The efficacy claims in support of this application are based on the results of a single large randomized well controlled trial (BCIRG006) entitled, "A multicenter phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) and with docetaxel, platinum salt and trastuzumab (TCH) in the treatment of node positive and high risk node negative adjuvant patients with operable breast cancer containing the HER2neu alteration."

The protocol primary endpoint was disease free survival. Secondary endpoints included overall survival and to compare cardiac and non-cardiac toxicity between the 3 arms, in order to determine the safety of Herceptin with these chemotherapy regimens. At the second interim analysis and 36 months of median follow-up, TCH, the non-anthracycline containing arm (Herceptin concurrently with docetaxel and carboplatin, demonstrated a significantly longer disease-free survival as compared to the AC→T (doxorubicin and cyclophosphamide followed by docetaxel) treatment arm. Follow-up was too short for an adequate comparison of survival. In addition, the protocol did not have a pre-specified alpha spending for overall survival, no preplanned interim analyses and no pre-specified significance levels. (b) (4)

The safety profile of docetaxel in combination with carboplatin and Herceptin are consistent with the known toxicities of the three agents and typical antineoplastic therapy. The TCH arm appears to have similar incidence rates of the LVEF related events (e.g. post-baseline LVEF: 50% and significant LVEF drop) as compare the rates in the AC→T arm.

9.3 Recommendation on Postmarketing Actions

Risk Management Activity

There are no additional risk evaluation and mitigation strategies associated with this review.

Required Phase 4 Commitments

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

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

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

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

9.4 Labeling Review

The following sections from the label were changed compared to the January 18, 2008:

- Indications and Usage, Adjuvant Treatment of Breast Cancer
- Dosage and Administration, Recommended Doses and Schedules
- Dosage and Administration, Dose Modifications
- Warnings and Precautions, Cardiomyopathy

From:
1.1 Adjuvant Breast Cancer
Herceptin is indicated:
• As part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of HER2-overexpressing, breast cancer.
• As a single agent, for the adjuvant treatment of HER2-overexpressing node-negative (ER/PR negative or with one high-risk feature) or nodepositive breast cancer, following multi-modality anthracycline based therapy. [see Clinical Studies (14.1)]

To:
1.1Adjuvant Breast Cancer
Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature [see Clinical Studies (14.1)]) breast cancer
•as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
•with docetaxel and carboplatin
• as a single agent following multi-modality anthracycline based therapy.

From:
1.2Metastatic Breast Cancer
Herceptin is indicated:
•In combination with paclitaxel for treatment of HER2 overexpressing metastatic breast cancer

To:

1.2 Metastatic Breast Cancer
Herceptin is indicated:
- In combination with paclitaxel for first- line treatment of HER2-overexpressing metastatic breast cancer

From:
2.1 Recommended Doses and Schedules
Do not administer as an intravenous push or bolus. Do not mix Herceptin with other drugs.
Adjuvant Treatment, Breast Cancer:
Administer according to one of the following doses and schedules:
• Initiate Herceptin following completion of anthracycline and concurrently with paclitaxel for the first 12 weeks. Administer Herceptin at an initial dose of 4 mg/kg as a 90 minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30 minute intravenous infusions, as tolerated, for a total of 52 doses. [see Dose Modifications

(2.2)]
• Initiate Herceptin following completion of all chemotherapy. Administer Herceptin at an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg every three weeks for a total of 17 doses (52 weeks of therapy). Administer all doses >4 mg/kg as 90 minute intravenous infusions.

To:
2.1Recommended Doses and Schedules
Do not administer as an intravenous push or bolus. Do not mix Herceptin with other drugs.
Adjuvant Treatment, Breast Cancer:
Administer according to one of the following doses and schedules for a total of 52 weeks of Herceptin therapy:
During and following paclitaxel, docetaxel, or docetaxel/carboplatin:
•Initial dose of 4mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
•One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30-60 minutes every three weeks.

As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens.
•Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
•Subsequent doses at 6 mg/kg as an intravenous infusion over 30-minutes every three weeks.

From:
5.1 Cardiomyopathy
Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [see Boxed Warning: Cardiomyopathy]. Herceptin can also cause a symptomatic decline in left ventricular ejection fraction (LVEF).
There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an anthracycline.
Withhold Herceptin for ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values. [see Dosage and Administration (2.2)] The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.
Cardiac Monitoring
Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan, prior to the first dose of Herceptin. The following schedule was used to

monitor cardiac function in clinical studies:
• Baseline LVEF measurement immediately prior to initiation of Herceptin
• LVEF measurements every 3 months during and upon completion of Herceptin
• LVEF measurements every 6 months for at least 2 years following completion of Herceptin
• Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction [see Dosage and Administration (2.2)]
In Study 1, 16% (136/844) of patients discontinued Herceptin due to clinical evidence of myocardial dysfunction or significant decline in LVEF. In Study 3, the number of patients who discontinued Herceptin due to cardiac toxicity was 2.6% (44/1678).
Among 32 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive heart failure, one patient died of cardiomyopathy and all other patients were receiving cardiac medication at last follow-up. Approximately half of the surviving patients had recovery to a normal LVEF (defined as ≥ 50%) on continuing medical management at the time of last follow-up. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

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

		Incidence	
Study	Event	Herceptin	Control
1 & 2	Congestive heart failure*	2% (32/1677)	0.4% (7/1600)
3	Congestive heart failure	2% (30/1678)	0.3% (5/1708)

*Includes 1 patient with fatal cardiomyopathy.

To:
5.1Cardiomyopathy
Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [see Boxed Warning: Cardiomyopathy]. Herceptin can also cause a symptomatic decline in left ventricular ejection fraction (LVEF). There is a 46 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not

receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an anthracycline.
Withhold Herceptin for □ 16% absolute decrease in LVEF from pre treatment values or an LVEF value below institutional limits of normal and □ 10% absolute decrease in LVEF from pretreatment values. [see Dosage and Administration (2.2)] The safety of continuation or resumption of Herceptin in patients with Herceptin induced left ventricular cardiac dysfunction has not been studied.
Cardiac Monitoring
Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:
•Baseline LVEF measurement immediately prior to initiation of Herceptin
•LVEF measurements every 3 months during and upon completion of Herceptin
•Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction [see Dosage and Administration (2.2)]
•LVEF measurements every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy.

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

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

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

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

[a] Includes 1 patient with fatal cardiomyopathy.
[b] Anthracycline (doxorubicin) and cyclophosphamide

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

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

Table 5[a]
Per-patient Incidence of New Onset
Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

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

[a] For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization.
[b] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)
[c] Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH)