17 March 2011
EMA/234266/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Herceptin

(trastuzumab)

Procedure No.: EMEA/H/C/000278/II/0053

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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CHMP variation assessment report

Type II variation EMEA/H/C/000278/II/0053

Invented name/name:	Herceptin
International non-proprietary name/common name:	trastuzumab
Indication summary (as last approved):	treatment of metastatic and early breast cancer and metastatic gastric cancer (MGC)
Marketing authorisation holder:	Roche Registration Ltd.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Extension of indication to include concurrent use of Herceptin with chemotherapy in the adjuvant treatment of patients with HER2-positive early breast cancer as part of a treatment regimen consisting of doxorubicin and cyclophosphamide followed by combination with paclitaxel or docetaxel, or as part of a treatment regimen in combination with docetaxel and carboplatin. In addition, the package leaflet has been updated to reflect the results of the user testing further to the assessment of FUM 078.
Rapporteur: Co-Rapporteur:	Christian Schneider Ian Hudson
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	1, 2 and 5
Product Information affected:	Summary of Product Characteristics, Annex II and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	17 June 2010
Start of procedure:	27 June 2010

Step	Step date
Rapporteur's assessment report circulated on:	24 August 2010
Co-Rapporteur's assessment report circulated on:	16 August 2010
Rapporteur & Co-Rapporteur's joint assessment report circulated on:	15 September 2010
Request for supplementary information and extension of timetable adopted by the CHMP on :	23 September 2010
MAH's responses submitted to the CHMP on :	25 October 2010
Rapporteur's and Co-Rapporteur's joint assessment report on the MAH's responses circulated on:	5 January 2011
2nd Request for supplementary information and extension of timetable adopted by the CHMP on :	20 January 2011
MAH's responses submitted to the CHMP on :	7 February 2011
Rapporteur's and Co-Rapporteur's joint assessment report on the MAH's responses circulated on:	3 March 2011
CHMP opinion:	17 March 2011

3. Scientific discussion

3.1. Introduction

Herceptin (trastuzumab) is a recombinant deoxyribonucleic acid (DNA)-derived humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER-2). Trastuzumab is indicated for the treatment of patients with breast cancer (early and metastatic) and in patients with metastatic gastric cancer. Herceptin can only be used when the cancer has shown to 'overexpress' HER2: this means that the cancer produces a protein called HER2 in large quantities on the surface of the tumour cells. Herceptin was authorised in the EU on 28th August 2000. The presentation granted in Europe was the 150 mg trastuzumab vial.

The currently approved indication for Herceptin is shown below:

Breast Cancer

Metastatic Breast Cancer (MBC)

Herceptin is indicated for the treatment of patients with HER2 positive metastatic breast cancer:
- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.
- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.

Early Breast Cancer (EBC)
Herceptin is indicated for the treatment of patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).

Herceptin should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

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

Herceptin should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see Sections 4.4 and 5.1).

In the current variation application, the MAH proposed an extension of indication to include concurrent use of Herceptin with chemotherapy in the adjuvant treatment of patients with HER2-positive early breast cancer as part of a treatment regimen consisting of doxorubicin and cyclophosphamide followed by combination with paclitaxel or docetaxel, or as part of a treatment regimen in combination with docetaxel and carboplatin.

3.2. Clinical aspects

3.2.1. Introduction

Adjuvant treatment of early breast cancer with Herceptin as single agent for one year was approved in 2006 based on the results from the HERA trial. The MAH now intends to extend the indication to include concurrent use of Herceptin with chemotherapy in the adjuvant setting based on the results from three studies. These studies NSABP B-31, NCCTG N9831 and BCIRG006 performed independently by different academic study groups are described in Table 1. The MAH has provided the study report of the joint analysis of studies NSABP B-31 and NCCTG N9831 (these studies were submitted as supportive data during the assessment of the HERA trial data), an 18-month update addendum to the joint analysis, the study report of study BCIRG006 and a 5-year cardiac safety update report from BCIRG006.

Table 1 Overview of the three pivotal phase III trials

	NSABP B-31 (H1971s)	NCCTG N9831 (H2061s)	BCIRG 006 (H2296s)
Design	Open-label, phase III randomized	Open-label, phase III randomized	Open-label, phase III randomized
Planned enrollment	2700	3300	3182
Date first patient in	22 March 2000	25 May 2000	5 April 2001
Date last patient in	May 2006	May 2006	March 2004
Final enrollment	2130 [a]	3505 [de]	3222
Cut-off date	February 15, 2005 (1st interim analysis)	March 15, 2005 (1st interim analysis)	November 1, 2006 (2nd interim analysis)
Nodal status	Node-positive (100%)	Node-positive (88%) & high risk node-negative	Node-positive (71%) & high risk node-negative
Control treatment	**AC→P** AC q3w x 4 → paclitaxel q3w x 4 [b]	**AC→P** AC q3w x 4 → paclitaxel q1w x 12	**AC→D** AC q3w x 4 → docetaxel q3w x 4
Experimental treatment (1)	**AC→PH** AC q3w x 4 → paclitaxel q3w x 4 [b] + trastuzumab q1w x 12 → trastuzumab q1w x 40	**AC→P→H** AC q3w x 4→ paclitaxel q1w x 12 → trastuzumab q1w x 52	**AC→DH** AC q3w x 4 → docetaxel q3w x 4 + trastuzumab for 1 year (q1w during chemo, then q3w)
Experimental treatment (2)	-	**AC→PH** AC q3w x 4 → paclitaxel q1w x 12 + trastuzumab q1w x 12 → trastuzumab q1w x 40	**DCarbH** docetaxel + carboplatin q3w x 6 + trastuzumab for 1 year (q1w during chemo, then q3w)
Primary Efficacy endpoints	OS	DFS	DFS
	DFS (joint analysis)		
Data in public domain [c]	2005 Tan-Chiu E, 2005	2004 Perez EA, 2004 2005 Perez EA, 2005 2008 Perez EA, 2008 2009 Perez EA, 2009	2005 Slamon D, 2005 2006 Slamon D, 2006 2007 Slamon D, 2007, Robert NJ, 2007 2009 Slamon D, 2009
	Joint analysis, 2005 Romond EH, 2005 Joint analysis, 2007 Perez EA, 2007		

AC = anthracycline plus cyclophosphamide; H = trastuzumab; D: docetaxel; Carb: carboplatin; P: paclitaxel; q1w: weekly: q3w: 3-weekly; chemo: chemotherapy

[a] 11 patients who were enrolled shortly after the interim analysis of efficacy were not randomized; all received treatment in the AC→PH arm

[b] Weekly paclitaxel became an option during the study

[c] Key publications and presentations (other than prescribing information for trastuzumab/trastuzumab)

[d] Patients (N=1216) randomized to receive sequential treatment with trastuzumab (AC→P→H) in study NCCTG N9831 were not included in the joint analysis

[e] 152 patients enrolled to AC→P between February 1, 2002 and September 3, 2002 (while arm AC→PH was temporarily closed to enrollment) were excluded from the joint analysis.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

3.3. Clinical efficacy

3.3.1. Study BCIRG006

This study was a randomized multicenter Phase III Randomized Trial conducted by the Breast Cancer International Research Group (CIRG), comparing Doxorubicin and Cyclophosphamide followed by Docetaxel (AC→T) with Doxorubicin and Cyclophosphamide and Trastuzumab (Herceptin) (AC→TH) and with Docetaxel, Carboplatin, and Trastuzumab (DCarbH) in the Adjuvant Treatment of Node-Positive and High-Risk Node-Negative Patients with Operable Breast Cancer.

High-risk node-negative status was defined as node-negative status with at least one of the following: tumour size > 2 cm, hormonal receptor status negative (estrogen receptor–negative and progesterone receptor–negative), histologic and/or nuclear grade 2 or 3, or age < 35 years.

3.3.1.1. Methods

Study Participants

The study was a multinational trial conducted in 43 countries.

Inclusion criteria:
- Histologically proven breast cancer with an interval between definitive surgery that included axillary lymph node involvement assessment and registration of ≤60 days
- Definitive surgical treatment that consisted of either mastectomy with axillary lymph node involvement assessment, or breast-conserving surgery with axillary lymph node involvement
- Presence of lymph node–positive or high-risk lymph node–negative disease. Lymph node–positive patients had invasive adenocarcinoma with at least one axillary lymph node showing evidence of tumor (pN1) of a minimum of six resected lymph nodes. High-risk lymph node–negative patients had invasive adenocarcinoma with either 1) no axillary lymph nodes showing evidence of tumor (pN0) of a minimum of six resected lymph nodes or 2) a negative sentinel node biopsy (pN0); and at least one of the following factors: tumor size >2 cm, negative ER and PR status, histologic and/or nuclear grade of 2 or 3, or age <35 years.
- Tumor showing the presence of the HER2 gene amplification based on FISH analysis by a designated central laboratory.
- Performance of ER and/or PR analysis on the primary tumor prior to randomization, with results known at the time of randomization
- Age 18–70 years
- Karnofsky performance status ≥80%
- Normal cardiac function confirmed by LVEF (based on echocardiography or multiple-gated acquisition [MUGA] scan) and electrocardiogram (ECG) within 3 months prior to registration. The result of the echocardiogram or MUGA scan had to be greater than or equal to the lower limit of normal (LLN) for the radiology facility.
- Adequate hematologic, hepatic, renal function

Exclusion criteria:
- Prior systemic anti-cancer therapy for breast cancer (immunotherapy, hormone therapy, or chemotherapy)
- Prior treatment with anthracycline therapy, taxanes (paclitaxel or docetaxel), or platinum salts for any malignancy
- Prior radiation therapy for breast cancer
- Bilateral invasive breast cancer
- Pregnant or lactating
- Patients of childbearing potential were required to employ adequate non-hormonal contraceptive measures during study treatment and had to have a negative urine or serum pregnancy test within 7 days prior to registration.
- Any T4 or N2, or known N3 or M1 breast cancer
- Preexisting motor or sensory neurotoxicity of Grade ≥2 severity based on NCI-CTC, v2.0
- Cardiac disease that would preclude the use of doxorubicin, docetaxel, or Herceptin

Treatments

There were three treatment arms:

AC→T Arm: Every 3 weeks for four cycles, patients in the AC→T arm received 60 mg/m2 doxorubicin as a 5- to 15-minute intravenous (IV) bolus injection followed by 600 mg/m2 IV cyclophosphamide as a 5- to 60-minute IV bolus injection. Beginning 3 weeks after the last cycle of AC, patients received 100 mg/m2 docetaxel as a 1-hour IV infusion every 3 weeks for four cycles.

AC→TH Arm: Every 3 weeks for four cycles, patients in the AC→TH arm received 60 mg/m2 doxorubicin as a 5- to 15-minute IV bolus injection followed by 600 mg/m2 IV cyclophosphamide as a 5- to 60-minute IV bolus injection. Three weeks after the last treatment with AC (i.e., on Day 1 of Cycle 5), a 4-mg/kg Herceptin loading dose was administered as a 90-minute IV infusion. Beginning on Day 8 of Cycle 5, 2 mg/kg Herceptin was administered as a 30-minute IV infusion every week. Docetaxel 100 mg/m2 was administered as a 1-hour IV infusion every 3 weeks for four cycles, beginning on Day 2 of Cycle 5 and then on Day 1 of all subsequent cycles. Beginning 3 weeks after the last treatment with docetaxel, 6 mg/kg Herceptin was administered as a 30-minute IV infusion every 3 weeks. Herceptin treatment was to continue for 1 year from the date of first administration, regardless of the number of doses received or missed. For days on which docetaxel and Herceptin were both due to be administered, docetaxel was administered first.

DCarbH **Arm:** The doses of docetaxel and carboplatin in the DCarbH arm are based on those used in this previous study, BCIRG 102. Herceptin was given intravenously at a dose of 4 mg/kg load followed by 2 mg/kg weekly during chemotherapy. After completion of chemotherapy, Herceptin was administered at a dose of 6 mg/kg every 3 weeks. This 3 weekly dosing regimen was also used in the adjuvant setting in the HERA study.

The DCarbH regimen was modified so that the platinum salt was limited to carboplatin (i.e., cisplatin was no longer allowed), based on updated results from the BCIRG 101 and 102 studies. At that time (April 2002) 28 patients were already treated with cisplatinum.

Dose modifications:

In case of severe toxicity, chemotherapy discontinuation, dose reductions, or dosing delays were planned for each of the treatment arms. No dose reductions were planned for Herceptin. For patients who experienced Herceptin-related Grade 3 or 4 non-hematologic toxicities other than those related to cardiac dysfunction, Herceptin was to be held until recovery to Grade 1 or 2. If recovery to Grade 1 or 2 did not occur, continuation of Herceptin was left to the discretion of the investigator. If the same Grade 3 or 4 non-hematologic toxicity recurred, Herceptin was permanently discontinued. Herceptin was not to be held for hematologic toxicity. Dose modification for cardiac toxicity was not allowed.

Objectives

Primary Objective: To compare disease-free survival after treatment with doxorubicin and cyclophosphamide followed by docetaxel (Taxotere) (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (Herceptin) (AC→TH) and with docetaxel in combination with carboplatin and Herceptin (DCarbH) in the adjuvant treatment of node positive and high risk node negative patients with operable breast cancer containing the HER2 alteration.

Secondary Objectives:
- To compare overall survival between the 3 above mentioned arms.
- To compare cardiac toxicity between the 3 above mentioned arms.
- To compare toxicity and quality of life between the 3 above mentioned arms.
- To evaluate pathologic and molecular markers for predicting efficacy in these patient groups.
- In addition, an independent socio-economic study will be conducted in parallel with the clinical study.

Outcomes/endpoints

The primary efficacy outcome measure was DFS, defined as the time from the date of randomization to the date of local, regional or distant relapse, date of second primary cancer and death from any cause, whichever occurred first. Relapse was defined as any clinical or radiologic evidence of tumor recurrence.

The secondary efficacy outcome measure was OS, defined as the time from the date of randomization to the date of death from any cause or last contact. Other secondary outcome measures were related to quality of life and evaluation of pathologic and molecular markers for predicting efficacy (data not shown).

Sample size

The initial sample size calculation was based on a 5 year DFS rate of 55% in patients receiving AC→T, a clinically relevant improvement of 5 years DFS to be detected of 7%, α = 0.017 (2-sided) for each of the planned 3 pair wise comparisons and 80% power. Based on these assumptions it was calculated that a total of 1308 DFS events had to be observed, translating to 1050 subjects per treatment arm (i.e. a total of 3150 subjects). It was planned to perform one interim analysis when 654 DFS events would have been observed (applying a Haybittle-Peto error spending function).

When the results of the BCIRG001 study became available the IDCM and the steering committee of the study proposed a modification of the assumptions for sample size consideration (taking into account the BCIRG001 data indicating a presumed 5-year DFS of 70% in the AC→T arm) as well as additional interim analyses when 300, 450, and 650 DFS events had been observed (error spending function of O'Brien and Fleming type was to be used with overall significance levels of 0.0002, 0.0030, and 0.0111, respectively, for the interim analyses). The overall significance level for the main analysis was 0.0461. Furthermore, the testing strategy was modified in order to gain more power. It was calculated that 900 DFS events were to be observed at the final analysis in order to achieve 80% power.

In addition, instead of the initially planned Bonferroni adjustment a "step-down" testing procedure was used to account for the 3 pair wise intergroup comparisons. Each of the 2 Herceptin arms was to be compared to the AC→T arm at the $\alpha/2$ level. If both comparisons were statistically significant, the comparison between the two Herceptin-containing regimens could be conducted at the α level.

Randomisation

Subjects were randomised to one of the three treatment arms. A minimisation algorithm balancing for center, number of axillary lymph nodes involved (0, 1–3, or ≥ 4) and hormonal receptor status (ER and/or PR positive vs. negative) was used for treatment allocation.

Blinding (masking)

This was an open-label study.

Statistical methods

The primary analysis was conducted on the ITT population according to the randomised treatment assignment. Time to event endpoints were compared by means for a log-rank test, the impact of pre-specified covariates was assessed by means of COX regression. For DFS and OS respectively the results of log-rank tests stratified for nodal status and hormone receptor status was applied. Observed treatment effects were described by means of 95% confidence intervals. Specific measures (see sample size section) were planned to account for the multiplicity issues arising from the interim analyses and multiple group comparisons.

To assess the homogeneity of treatment effects, subgroup analyses were planned for important subgroups (e.g. nodal status, age, number of positive lymph nodes). Furthermore, additional sensitivity analyses (e.g. applying an alternative definition of DFS endpoint or assessing time to first distant disease recurrence) were planned to assess the robustness of study results.

3.3.1.2 Results

The primary efficacy analysis is based upon data from the second interim analysis, which included 474 DFS events: 195 in the AC→T arm, 134 in the AC→TH arm, and 145 in the DCarbH arm and corresponding to a median duration of follow-up of 36 months (Kaplan-Meier estimates). The results of this 2nd interim analysis (data cut-off 01 November 2006) are reported below.

Participant Flow

A summary of the patient populations is shown in Table 2.

Table 2. Patient Populations

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

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

[a] The efficacy population consists of all randomized patients, and all analyses were conducted according to the ITT principle.

[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.

Per protocol, crossover was not allowed; however, a total of 18 patients from the control arm crossed over and received Herceptin.

Recruitment

Enrollment started in March 2001 and stopped in March 2004. A total of 3222 patients were entered into the study. At the time of study report, the study was still ongoing.

In the all randomized patient population, median duration of follow-up was 2.9 years in the **AC→T** (range: 0.0–5.2 years) arm, 3.0 years in both the AC→TH (range: 0.1–5.3 years) and DCarbH (range: 0.0–5.1 years) arms.

Conduct of the study

The study was conducted by oncologist investigators in 43 countries. A total of 433 sites recruited the 3222 enrolled patients. The number of centres by country ranged from one centre (Bosnia, Cyprus, Greece, Sweden, and Switzerland) to 177 centres (United States). The number of patients by country ranged from two to 990. The largest enrolling countries were the United States (= 990; 30.7%), Germany (n = 313; 9.7%), Australia (n = 293; 9.1%) and Poland (n = 260; 8.1%).

Subsequent to study initiation, the protocol was amended to clarify study conduct, amend the statistical considerations, and report changes to the administrative structure. In total, there were four protocol amendments.

Baseline data

Baseline characteristics for the stratification factors used (center, number of positive lymph nodes, hormonal receptor status) are shown in Table 3:

Table 3. Tumor and surgery history (All randomised subjects)

	AC→T (n=1073)	AC→TH (n=1074)	TCH (n=1075)
HER2 status per central laboratory			
n	1072 [a]	1074	1075
Positive	1066 (99.4%)	1070 (99.6%)	1073 (99.8%)
Negative	6 (0.6%)	4 (0.4%)	2 (0.2%)
Primary surgery type			
n	1073	1074	1075
Mastectomy	638 (59.5%)	674 (62.8%)	642 (59.7%)
Quadrantectomy	270 (25.2%)	255 (23.7%)	268 (24.9%)
Lumpectomy	165 (15.4%)	145 (13.5%)	165 (15.3%)
Detection type			
n	869	864	871
Sentinel node	113 (13.0%)	112 (13.0%)	115 (13.2%)
Axillary dissection	757 (87.1%)	753 (87.2%)	757 (86.9%)
Both	1 (0.1%)	1 (0.1%)	1 (0.1%)
Number of positive nodes			
n	1073	1074	1075
0	309 (28.8%)	306 (28.5%)	307 (28.6%)
1–3	413 (38.5%)	410 (38.2%)	415 (38.6%)
4–9	207 (19.3%)	236 (22.0%)	232 (21.6%)
10+	144 (13.4%)	122 (11.4%)	121 (11.3%)
Hormone receptor	1073	1074	1075
ER-positive and/or PR-positive	577 (53.8%)	578 (53.8%)	579 (53.9%)
ER-negative and PR-negative	496 (46.2%)	496 (46.2%)	496 (46.1%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; ER=estrogen receptor; PR=progesterone receptor; TCH=docetaxel plus carboplatin plus Herceptin.

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

Positive HER2 status by FISH performed at the central laboratory was mandatory at the time of enrolment. A total of 99.6% of patients (3209 of 3222) were HER2-positive.

All patients underwent primary surgery for breast cancer prior to study enrolment and treatment randomization. Infiltrating ductal carcinoma was the most common histopathologic type in all treatment arms (≥ 90 % of patients). Most tumours were poorly differentiated and were excised with clear margins. The treatment arms were well balanced with respect to the type of primary breast cancer surgery and other tumour characteristics.

Furthermore, the mean age of patients was 48.8 years for the AC→T arm (range, 23–74 years), 48.7 years for the AC→TH arm (range, 22–74 years), and 48.6 years for the DCarbH arm (range, 23–73 years). The median weight was 66.0 kg for the AC->T arm, 68.0 kg for the AC→TH arm, and 66.4 kg for the DCarbH arm. Karnofsky performance status was 100% for 79.8% of patients in the AC→T arm, for 79.4% of patients in the AC→TH arm, and for 80.2% of patients in the DCarbH arm.

No notable differences in non-cardiac medical history were observed across the three treatment arms. Of note, ongoing hypertension at baseline was observed for 16.2% of patients in the AC→T arm, 16.7% of patients in the AC→TH arm, and 17.7% of patients in the DCarbH arm. Similarly, 12.9% of patients in the AC→T arm, 14.1% of patients in the AC→TH arm, and 14.8% of patients in the DCarbH arm reported prior use of a cardiovascular medication.

Likewise, no notable differences are observed with regard to hormonal therapies, also broken down by menopausal status.

Numbers analysed

The primary efficacy analysis was based on the intent-to-treat (ITT) population (i.e., all inclusion of all randomized patients, analyzed according to their randomized treatment assignment). For a summary of the patient populations see Table 2.

All safety analyses included patients who received any amount of study treatment according to actual treatment regimen received. With a few exceptions, patients followed their allocated treatment assignment.

Outcomes and estimation

Primary endpoint (DFS)

The primary efficacy analysis is based upon data from the second interim analysis, which included 474 DFS events: 195 in the AC→T arm, 134 in the AC→TH arm, and 145 in the DCarbH arm and corresponding to a median duration of follow-up of 36 months (Kaplan-Meier estimates).

A summary of DFS events is presented in Table 43.

Table 4. Disease-Free Survival (All Randomised Subjects)

	AC→T (n=1073)	AC→TH (n=1074)	TCH (n=1075)
Patients with an event [a]	195 (18.2%)	134 (12.5%)	145 (13.5%)
Distant recurrence	142	89	97
Local/regional recurrence	40	28	37
Second primary cancer	23	21	15
Death NED	5	5	7
Patients without an event	878 (81.8%)	940 (87.5%)	930 (86.5%)
Stratified analysis			
Hazard ratio [b]	NA	0.61	0.67
95% CI	NA	(0.49, 0.77)	(0.54, 0.83)
p-value [c]	NA	<0.0001	0.0003
Percent event free at: (95% CI); **absolute benefit** [d]			
Year 1	95.2% (93.9%, 96.5%)	97.8%; **2.6%** (96.9%, 98.7%)	98.0%; **2.8%** (97.1%, 98.8%)
Year 2	86.6% (84.5%, 88.7%)	92.6%; **6.0%** (91.0%, 94.2%)	91.8%; **5.2%** (90.1%, 93.5%)
Year 3	80.9% (78.3%, 83.5%)	86.7%; **5.8%** (84.4%, 89.0%)	85.5%; **4.6%** (83.2%, 87.9%)
Year 4	77.3% (74.1%, 80.5%)	82.9%; **5.6%** (79.6%, 86.1%)	82.0%; **4.7%** (78.8%, 85.1%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; CI=confidence interval; NA=not applicable; NED=no evidence of disease; TCH=docetaxel plus carboplatin plus Herceptin.

[a] Earliest contributing event. A patient could be included in more than one event category; thus, the sum across rows may not equal the value in the "Major" row.

[b] Relative to AC→T. Estimated using Cox regression stratified by number of positive nodes and hormonal receptor status.

[c] Stratified log-rank p-value.

[d] Absolute benefit in percent event free compared with AC→T.

The HR for a first event for the AC→TH arm relative to the AC→T arm was 0.61 (95% CI: 0.49, 0.77; p<0.0001). The HR for a first event for the DCarbH arm relative to the AC→T arm was 0.67 (95% CI: 0.54, 0.83; p<0.0003).

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 with the exception of distant metastases to the central nervous system.

Very few deaths (AC→T: 5; AC→TH: 5; and DCarbH: 7) occurred without a prior relapse or second primary cancer.

A Kaplan-Meier plot for DFS is shown in Figure 1.

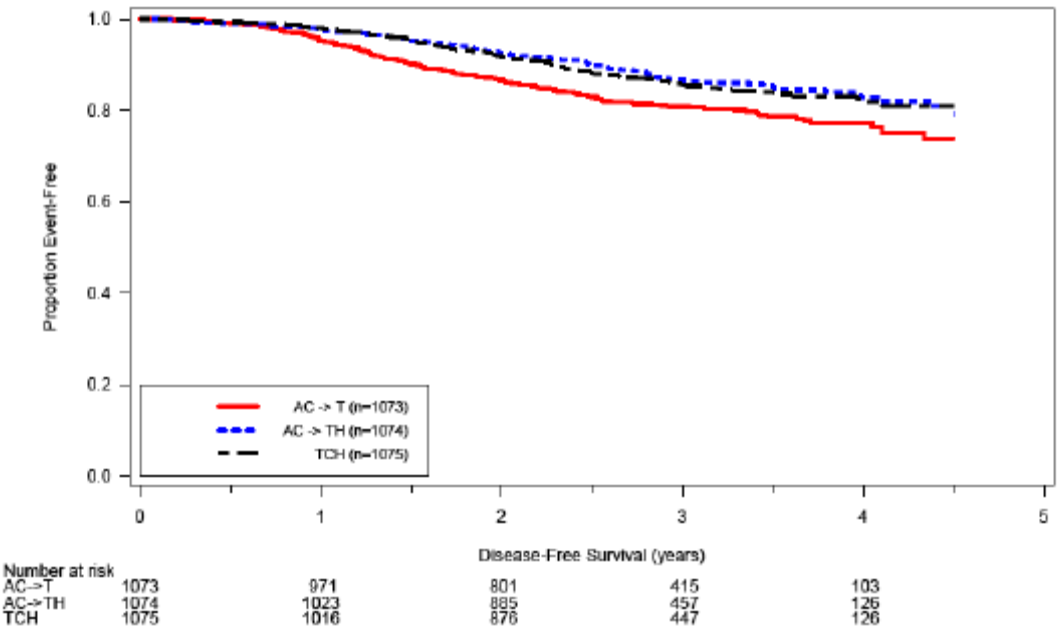


Figure 1: Disease-Free Survival (All Randomised Patients)

Secondary Endpoint: Overall Survival (OS)

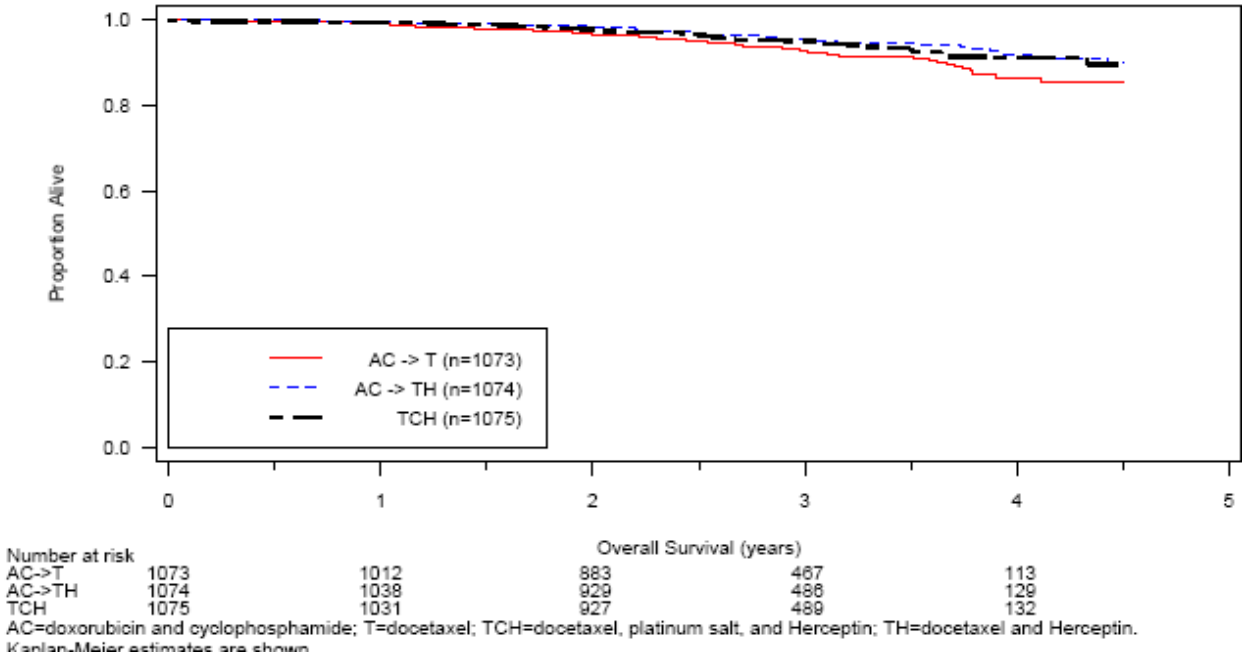
At the time of the second interim analysis, deaths had been reported for 185 patients. Of these patients, 80 were in the AC→T arm, 49 were in the AC→TH arm, and 56 were in the DCarbH arm.

There was an increase in duration of OS among patients in each of the Herceptin-containing arms compared with the AC→T arm (see Table 5 and Figure 2). The hazard ratio of 0.58 (95%-CI: [0.40, 0.83), p = 0.0024) indicates a 42% risk reduction in the AC→TH arm.

Table 5. Overall Survival (All Randomised Subjects)

	AC→T (n=1073)	AC→TH (n=1074)	TCH (n=1075)
Patients who died	80 (7.5%)	49 (4.6%)	56 (5.2%)
Patients alive	993 (92.5%)	1025 (95.4%)	1019 (94.8%)
Stratified analysis			
Hazard ratio [a]	NA	0.58	0.66
95% CI	NA	(0.40, 0.83)	(0.47, 0.93)
p-value [b]	NA	0.0024	0.0182
Percent event free at: (95% CI); **absolute benefit** [c]			
Year 1	99.3% (98.8%, 99.8%)	99.6%; **0.3%** (99.2%, 100%)	99.5%; **0.2%** (99.1%, 99.9%)
Year 2	96.8% (95.7%, 97.9%)	98.5%; **1.8%** (97.8%, 99.3%)	97.8%; **1.1%** (96.9%, 98.7%)
Year 3	93.0% (91.2%, 94.8%)	95.5%; **2.5%** (94.0%, 96.9%)	95.2%; **2.2%** (93.7%, 96.6%)
Year 4	86.6% (83.2%, 90.1%)	92.2%; **5.5%** (89.5%, 94.8%)	91.1%; **4.4%** (88.4%, 93.8%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; NA=not applicable; TCH=docetaxel plus carboplatin plus Herceptin; TCH=docetaxel, carboplatin, and Herceptin.



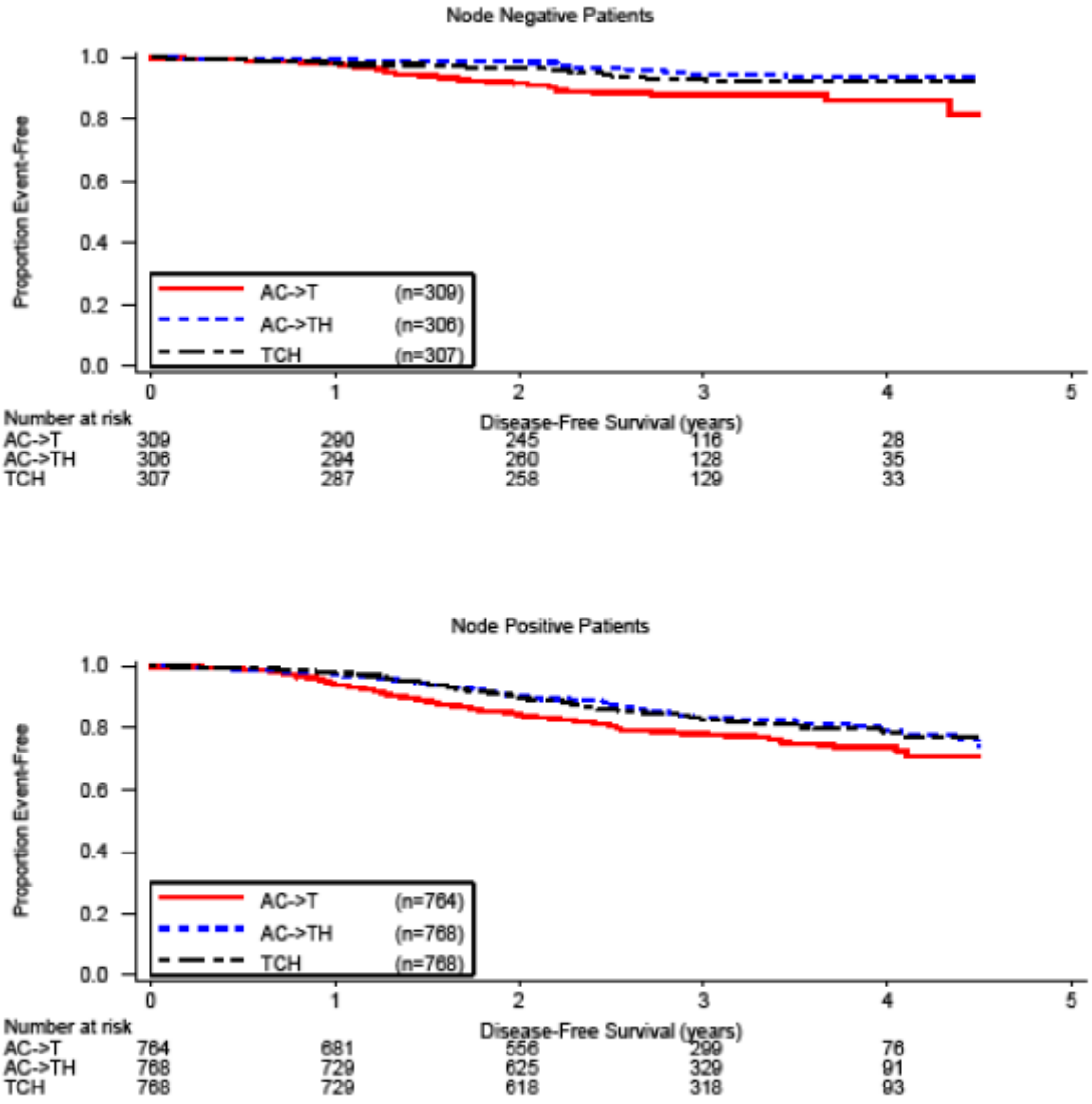
AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and Herceptin; TH=docetaxel and Herceptin.
Kaplan-Meier estimates are shown.

Figure 2: Duration of Overall Survival (All Randomised Patients)

Ancillary analyses

Disease free survival by nodal status and other clinically important baseline characteristics
Of the 3222 randomized patients, 922 (28.6%) were classified as being high-risk node-negative. Among all randomized node-negative patients, there was a 64% risk reduction (HR= 0.36 ;95% CI: 0.19, 0.68; p <0.0010) for a first event for the AC->TH arm relative to the AC->T arm compared to a 33% risk reduction (HR=0.67; 95% CI: 0.53, 0.85; p <0.0008), among all randomized node-positive patients. Similarly, among all randomized node-negative patients, there was a 48% (HR=0.52; 95%

CI: 0.30, 0.92; p <0.0209) risk reduction for a first event for the AC->TH arm relative to the AC->T arm compared to a 30% (HR= 0.70; 95% CI: 0.56, 0.89; p <0.0029) risk reduction, among all randomized node-positive patients. The Kaplan-Meier plots for node negative and positive patients are shown in Figure 3.



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

Figure 3: Disease Free Survival by nodal status (All Randomised Patients)

Additional analyses for the primary efficacy endpoint benefit (DFS) in all clinically important subgroups, including those defined by age, menopausal status, hormone receptor status, nodal status, tumor size, tumor histopathology, nuclear grade, and surgery or radiation therapy, were consistent with the treatment effect in the overall population (see Table 6). There was no indication that trastuzumab is not effective in one of the specified subgroups. Furthermore analyses looking at the different events contributing to DFS are shown in Table 6.

Table 6. Additional DFS analyses

Endpoint	**AC->D (n=1073)**	**AC->DH (n=1074)**	**Hazard Ratio (95% CI)[a]**	**p-value[b] (log-rank)**
Number of Events				
DFS	195	134	0.61 (0.49, 0.77)	<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
Distant recurrence	144	95	0.59 (0.46, 0.77)	<0.0001
Endpoint	**AC->D (n=1073)**	**DcarbH (n=1075)**	**Hazard Ratio (95% CI)[a]**	**p-value[b] (log-rank)**
Number of Events				
DFS	195	145	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
Distant recurrence	144	103	0.65 (0.50, 0.84)	0.0008

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

In study BCIRG 006, 213/1075 patients in the DCarbH (TCH) arm , 221/1074 patients in the AC→DH (AC→TH) arm, and 217/1073 in the AC→D (AC→T) arm had a Karnofsky performance status ≤90 (either 80 or 90). No disease-free survival (DFS) benefit was noticed in this subgroup of patients (hazard ratio = 1.16, 95% CI [0.73, 1.83] for DCarbH (TCH) vs AC→D (AC→T); hazard ratio 0.97, 95% CI [0.60, 1.55] for AC→DH (AC→TH) vs AC→D).

In addition, data comparing the efficacy of concurrent trastuzumab treatment (AC→PH) to sequential trastuzumab treatment (AC→P→H) from the NCCTG N9831 study (alone) were presented. The data cut-off for this analysis was November 3, 2009. At this time, 50% of the planned number of DFS events required for the final analysis of the NCCTG N9831 study itself had occurred (312 actual events). A total of 1903 patients were included (patients who had been randomized to AC→T→H when arm AC→T+H was temporarily closed were excluded). The median follow-up duration was 5.3 years and 75% of patients had been followed for 5 years.

After 5 years, 84.2% of patients in the concurrent arm (AC→T+H) had not experienced a DFS event compared to 79.8% of patients in the sequential arm (AC→T→H). There was a 25% reduction in the risk of a DFS event when trastuzumab was administered concurrently with paclitaxel as opposed to sequential administration after paclitaxel (unadjusted HR = 0.77 [0.61; 0.96]; log-rank p = 0.019). However, the boundary for statistical significance had been preset at p = 0.00116 and so this result was not statistically significant but was considered a strong trend (see Figure 4). After adjusting for tumour size, number of positive nodes, and ER, the HR was 0.75 [0.60-0.94)].

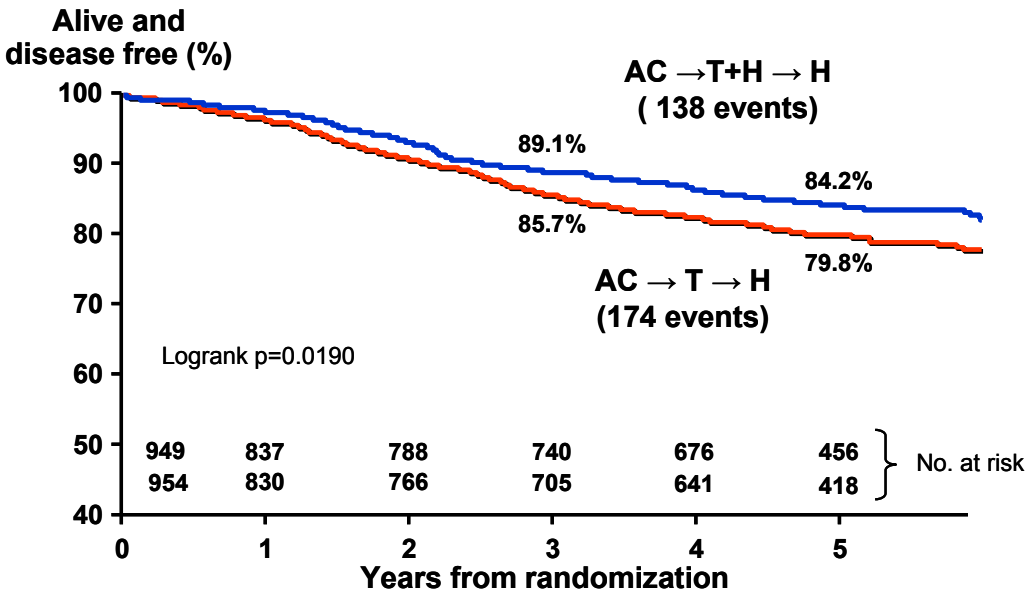


Figure 4. Kaplan-Meier curves for DFS

Overall survival did not differ significantly between patients in the AC→T→H arm compared to the AC→T+H arm (unadjusted HR: 0.79 [95% CI: 0.59, 1.08] log rank p = 0.135) at that time.

3.3.2. Studies B-31 and N9831

The results from two studies were analysed jointly.

NSABP B-31: A Randomized Trial Comparing The Safety And Efficacy Of Adriamycin And Cyclophosphamide Followed By Taxol (Ac->T) To That Of Adriamycin And Cyclophosphamide Followed By Taxol Plus Herceptin (Ac->T + H) In Node-Positive Breast Cancer Patients Who Have Tumors That Overexpress Her2

NCCTG N9831: Phase III Trial Of Doxorubicin And Cyclophosphamide (Ac) Followed By Weekly Paclitaxel With Or Without Trastuzumab As Adjuvant Treatment For Women With Her-2 Over-Expressing Or Amplified Node Positive Or High-Risk Node Negative Breast Cancer

3.3.2.1. METHODS

Study Participants

Study B-31 enrolled women with HER2-positive, early-stage, node-positive breast cancer. Study N9831 enrolled women with early-stage breast cancer who were at high risk of recurrence.

Key inclusion criteria for both trials were:

- Pathologic diagnosis of adenocarcinoma of the breast with strongly positive (3 +) HER2 protein overexpression by immunohistochemistry or HER2 gene amplification by fluorescence in situ hybridization

- Histologically confirmed node-positive disease **or** (Study N9831 only following the May 2003 amendment) high-risk node-negative disease (defined as tumor size > 1 cm and estrogen receptor [ER] and progesterone receptor [PR] negative, or tumor size > 2 cm regardless of hormone receptor status)

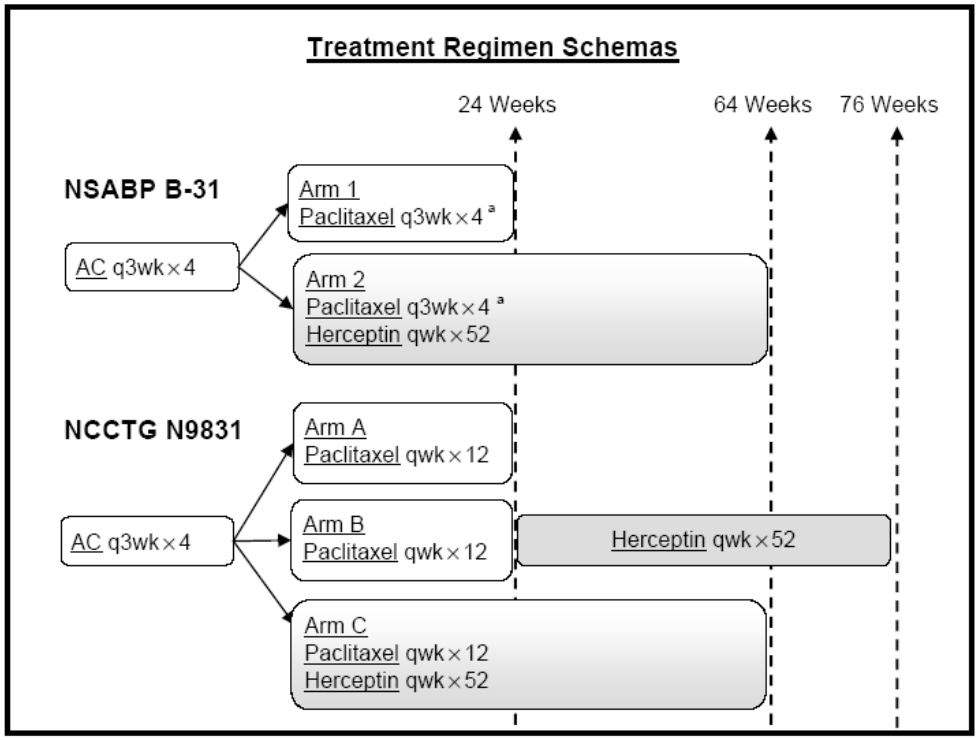
- Left ventricular ejection fraction (LVEF) greater than or equal to the lower limit of normal for the local radiologic facility

- Complete resection of the primary breast tumor and axillary nodal dissection (sentinel node biopsy alone, if negative, was allowed on Study N9831)

- ≤ 84 days (12 weeks) between surgery and randomization

Treatments

The treatment regimens in both studies were as follows:



A=doxorubicin; C=cyclophosphamide; qwk=every week; q3wk=every 3 weeks.
[a] Study B-31 was amended to allow weekly paclitaxel in May 2003.

All patients received four 3-week cycles of AC chemotherapy followed by paclitaxel for 12 weeks. Patients randomized to Arm 2 of Study B-31 or Arm C of Study N9831 began Herceptin therapy concurrently with paclitaxel. The total duration of Herceptin therapy was 52 weeks.

Patients in Study B-31, received four cycles (3 weeks per cycle) of doxorubicin, at 60 mg/m2 IV push, concurrently with IV cyclophosphamide, at 600 mg/m2 over 30 minutes. After completion of these four cycles, patients received paclitaxel IV for four cycles (3 weeks per cycle) at 175 mg/m2 over 3 hours, or weekly for 12 weeks at 80 mg/m2 over 1 hour (weekly administration of paclitaxel was allowed following a protocol amendment in May 2003; investigators chose the paclitaxel regimen at randomization).

Patients in Study N9831 received four cycles (3 weeks per cycle) of doxorubicin, at 60 mg/m2 IV push, concurrently with IV cyclophosphamide at 600 mg/m2 over 20–30 minutes (the latter was administered with 250 mL of normal saline). After completion of these four cycles, patients received paclitaxel IV weekly for 12 weeks at 80 mg/m2 (with 250 mL or D5W or normal saline) over 1 hour.

Herceptin was administered weekly as an intravenous (IV) infusion. The initial (loading) dose was 4 mg/kg; subsequent weekly doses were 2 mg/kg.

Objectives

Primary Objective:

- To evaluate the efficacy of weekly Herceptin plus chemotherapy versus chemotherapy alone as adjuvant therapy for women with early-stage, HER2-positive breast cancer, as measured by disease-free survival (DFS).

- To evaluate the safety of Herceptin plus chemotherapy versus chemotherapy alone, as evidenced by the incidence and severity of cardiac and non-cardiac events

Secondary objective:

- To determine the efficacy of weekly Herceptin plus chemotherapy versus chemotherapy alone as adjuvant therapy for women with early-stage, HER2-positive breast cancer, as measured by overall survival

Outcomes/endpoints

The primary efficacy endpoint for the analysis was disease-free survival defined as the time from randomization until the first occurrence of any of the following events: local, regional, or distant recurrence of breast cancer; development of a contralateral breast cancer or other second primary cancer (other than squamous or basal cell carcinoma of the skin or melanoma in situ, carcinoma in situ of the cervix, or lobular carcinoma in situ of the breast); or death from any cause. DFS for patients who were not known to have experienced any of these events was censored at the date of the last available follow-up assessment.

An annual history and physical examination (including pelvic examinations and annual mammography) were required in each protocol. Other evaluations, such as a bone scan, were done if clinically indicated to rule out disease progression. Patients who were felt to have signs or symptoms of disease progression at any time during treatment were evaluated with appropriate radiographic tests (chest X-ray, computed tomography [CT] scan, etc). All patients who had evidence of disease progression were contacted at least annually for survival status.

Other efficacy endpoints included time to first distant recurrence, time to central nervous system metastases, and additional exploratory analysis.

For study BCIRG 006, subgroup and sensitivity analyses were performed to assess the robustness of the primary efficacy results. These included sensitivity analyses in which the definition of DFS was changed by excluding certain sub-categories from the endpoint eg excluding second primary cancers, non-breast cancer second primary cancers, or distant recurrences. For each of these endpoints, time to event was the time from randomization to the occurrence of the event, irrespective of all intervening events.

Sample size

The sample size of the joint analysis including patients from Arms 1 and 2 of Study B-31 and patients from Arms A and C of Study N9831 was calculated in order to detect a 21.6% reduction in DFS events with about 90% power in a log-rank test applying a significance level of 0.025 (one-sided). These assumptions resulted in 710 events to be observed.

The first interim analysis of the combined data set was planned when (overall) a total of 355 DFS events had been observed; subsequent interim analyses were to be presented semi-annually. The trial could be stopped at any interim analysis in case the null-hypothesis of no treatment difference was rejected at a nominal one-sided 0.0005 level. In case the trial stopped not at one of the interim analyses, the final significance level had to be calculated using a method of α-spending to ensure a global α of 0.025 (one-sided).

Randomisation

Treatment allocation in both trials was done by means of dynamic randomisation. Stratification factors for study B-31 where: number of positive nodes, planned hormonal therapy, surgery/radiation therapy, institution and intended frequency of paclitaxel application. Balancing was based on the variance method as described by White and Freedman (1978). In study N9831 a dynamic randomization scheme according Pocock and Simon (1975) stratifying for cooperative group, nodal status, and receptor status was applied.

Blinding (masking)

Both studies were open label trials.

Statistical methods

The primary analysis was conducted on the ITT population according to the randomised treatment assignment. All patients from study B-31 were included. From study N9831 patients from arms A and C were included. To account for a temporary suspension of enrolment in Arm C of Study N9831, only patients in arm A who were enrolled concurrently with arm C were included.

Time to event endpoints were compared by means of a log-rank test, the impact of pre-specified covariates was assessed by means of COX regression. For DFS and OS respectively the analyses were stratified for study (B-31, N9831), intended paclitaxel schedule (weekly, every 3 weeks), pathological nodal status (0, 1-3, 4-9, 10+ positive nodes) and hormone receptor status (ER-positive and/or PR-positive, ER-negative and PR-negative). In addition the results of an unstratified log-rank test were also provided. In case a statistical significant difference was observed for DFS a supportive OS analysis had to be performed. To control the Type I error at α = 0.025 (one-sided) an O'Brien-Fleming error spending function (with 710 deaths=100% information) was be applied. Observed treatment effects were described by means of 95% confidence intervals. Specific measures (outlined below) were planned to account for the multiplicity issues arising from the interim analyses and multiple group comparisons.

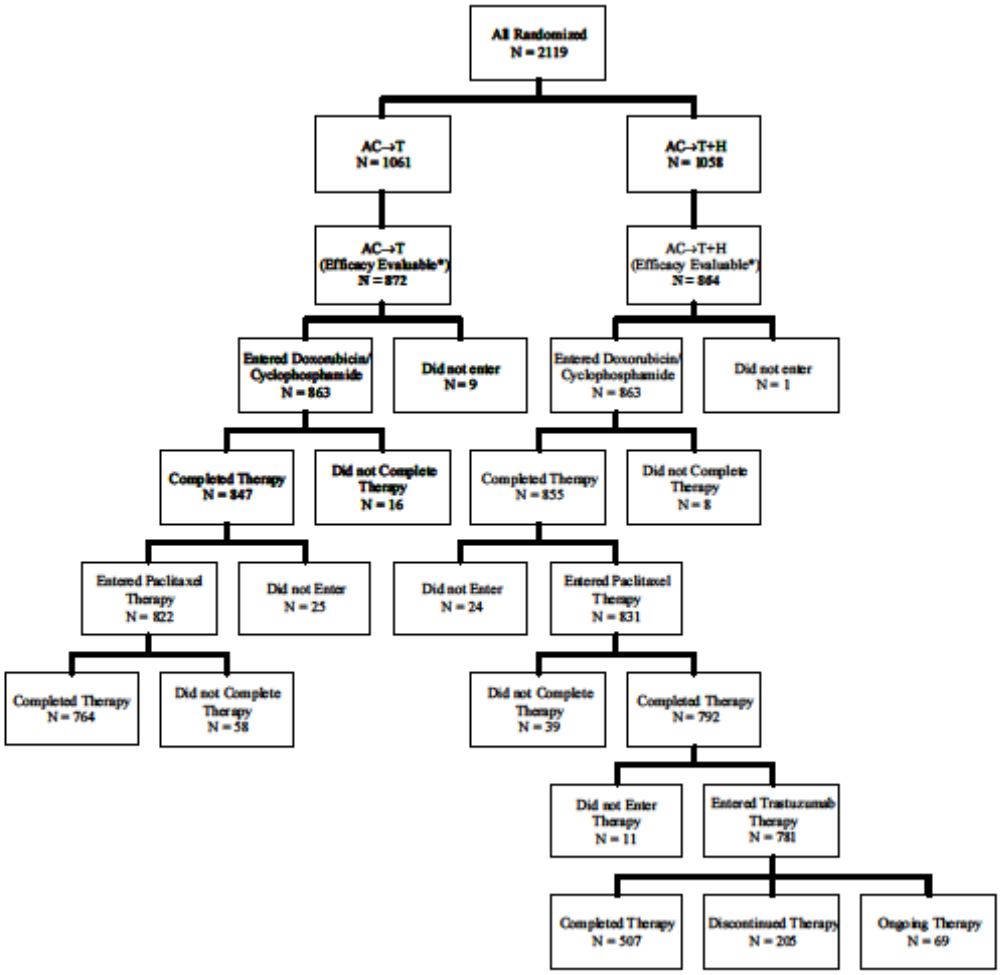
To assess the homogeneity of treatment effects, several subgroup analyses were pre-planned (e.g. age, race, performance status, pathologic node positive, pathologic tumor size etc). Various analyses were planned to assess the poolability of patients from both trial with regard to DFS and OS respectively.
The first interim analysis of the combined data set was planned when (overall) a total of 355 DFS events had been observed; subsequent interim analyses were to be presented semi-annually. The trial could be stopped at any interim analysis in case the null-hypothesis of no treatment difference was rejected at a nominal one-sided 0.0005 level. In case the trial stopped not at one of the interim analyses, the final significance level had to be calculated using a method of α-spending to ensure a global α of 0.025 (one-sided).

3.3.2.2. Results

Participant flow

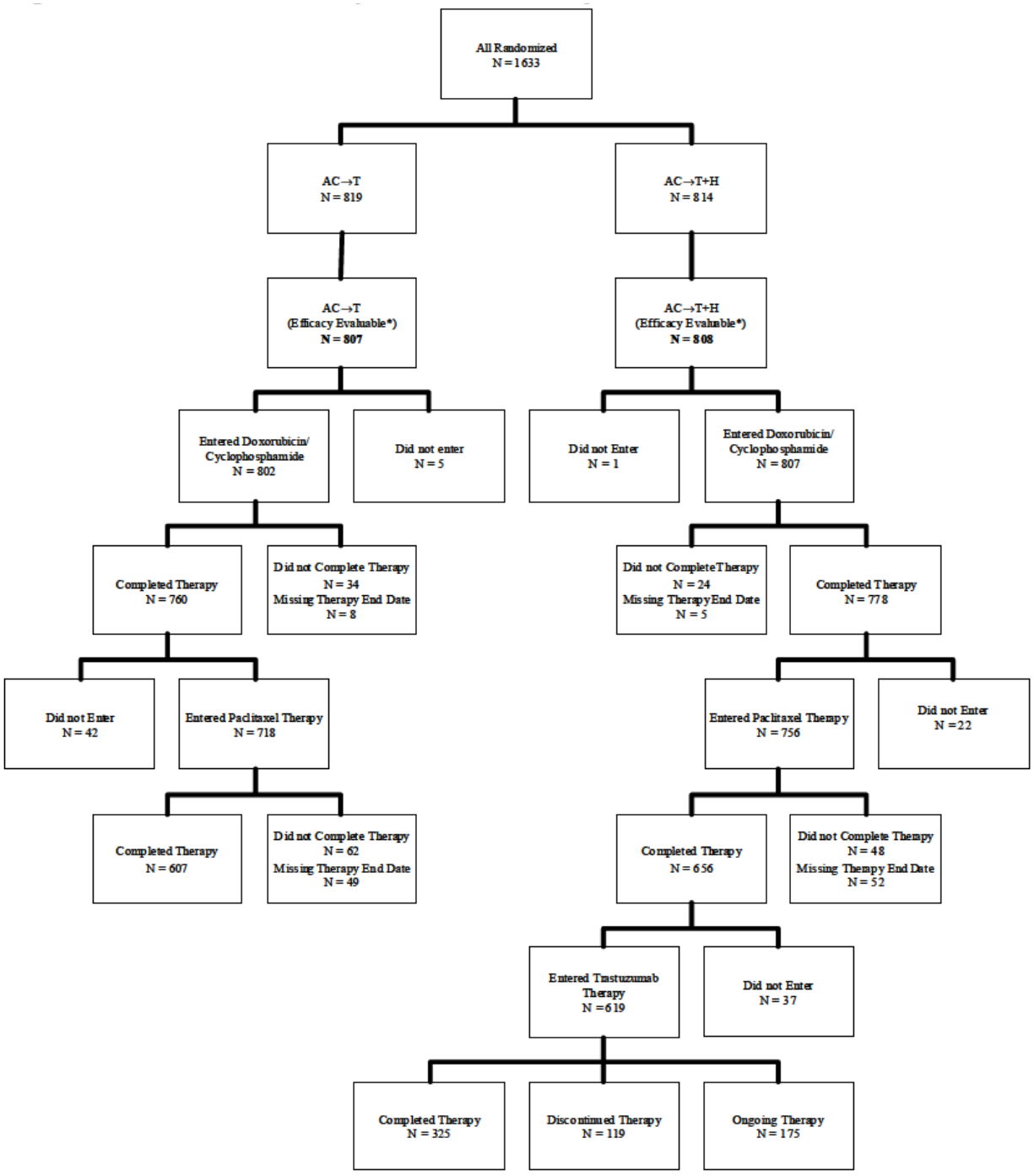
The disposition of patients was as follows:

Patient Disposition for Study NSABP B-31



* Study NSABP B-31 efficacy evaluable refers to patients randomized as of February 15, 2005 and with at least one follow-up assessment for disease recurrence.

Patient Disposition for Study NCCTG N9831



* Study NCCTG N9831 efficacy evaluable refers to patients randomized as of November 1, 2004 and with at least one follow-up for analysis.

Recruitment

Both trials recruited independently. The joint analysis includes patients randomised up to November 2004 in study N9831 and enrolled up to April 2005 in study B-31.

Conduct of the study

As of March 2005, clinical cut off date for the CSR, there were 10 amendments for study B-31 and 15 for N9831. The amendments were largely refinements of the original protocol and improved the definition of the patient population (e.g. HER2 central confirmation) and the safety of patients (e.g. exclusion criteria for cardiac disease). The most substantial amendment was the decision to close the study at interim analysis and offer all patients Herceptin treatment.

Baseline data

Patients were mainly enrolled in the United States. There were no notable imbalances between treatment arms for any of the demographic characteristics. The mean age of women in the Joint Efficacy Population was 49.3 years for the chemotherapy alone arm and 49.6 years for the Herceptin + chemotherapy arm. The two most frequently occurring racial groups for the chemotherapy alone arm and the Herceptin + chemotherapy arm were Black (7.3% in the chemotherapy alone arm; 7.2% in the Herceptin + chemotherapy arm) and White (83.7% in the chemotherapy alone arm; 83.4% in the Herceptin + chemotherapy arm). The median weight was 72.0 kg for the chemotherapy alone arm and 70.8 kg for the Herceptin + chemotherapy arm. ECOG status in Study B-31 was 0 for 92% of patients in the chemotherapy alone arm and 94% of the patients in the Herceptin + chemotherapy arm; ECOG status was not collected in Study N9831.

A total of 61.7% of patients in the chemotherapy alone arm and 62.4% in the Herceptin + chemotherapy arm had a mastectomy. Nodal involvement was similar in the two treatment arms, with 6.1% and 5.3% of patients having 0 nodes involved and 14.2% and 13.7% of patients having 10 + nodes involved in the chemotherapy alone and Herceptin + chemotherapy arms, respectively. Only Study N9831 allowed enrolment of node-negative patients. The majority of women were ER-positive and/or PR-positive: 55.9% for the chemotherapy alone arm and 55.3% for the Herceptin + chemotherapy arm.

Populations were generally well balanced. A slight overrepresentation of tumors > 2 cm is noted in the Herceptin group (58.9% vs. 62%). Compared to the HERA trial this patient population is more homogenous as a defined chemotherapy protocol including doxorubicin and paclitaxel was mandatory. Compared to HERA there are more patients with node positive disease which is generally regarded as being associated with worse prognosis.

11 patients assigned to AC->T and 4 patients assigned to AC->T+H were recorded as HER2 negative in the joint efficacy population.

Numbers analysed

The analysis populations are shown in Table 6.

Table 6. Populations analysed.

	B-31				N9831				Total		
	Arm 1 AC→T	Arm 2 AC→T+H	Not Rand.	Total	Arm A AC→T	Arm B	Arm C AC→T+H	Total	AC→T	AC→T+H	All Patients
Enrolled [a]	1061	1069	11	2130	1232	1216	1057	3505	2293	2115	5635
Concurrent randomization with control [b]	1061	1058	11	2130	1080	—	1057	2137	2141	2115	4267
Datasets supporting this submission [c]	1061	1058	11	2130	819	—	814	1633	1880	1872	3763
Datasets supporting the NEJM efficacy paper [d]	1024	1019	—	2043	819	—	814	1633	1843	1833	3676
Analysis populations in this CSR											
Efficacy-evaluable [e]	872	864	—	1736	807	—	808	1615	1679	1672	3351
Safety-evaluable [f]	972	992	—	1964	803	—	807	1610	1775	1799	3574
AC	971	988	—	1959	803	—	807	1610	1774	1795	3569
T/T+Herceptin	876	920	—	1796	724	—	757	1481	1600	1677	3277
Herceptin monotherapy [g]	0	796	—	796	1	—	633	634	1	1429	1430

A=doxorubicin; C=cyclophosphamide; CSR=clinical study report; H=Herceptin; NEJM=New England Journal of Medicine; T=paclitaxel.

[a] In Study B-31, 11 patients were enrolled shortly after the interim analysis of efficacy and were not randomized; all received treatment in the Herceptin arm; in Study N9831, 283 patients were removed from the randomization database because the central pathology review did not confirm HER2-positive status.

[b] A total of 152 patients in Study N9831 assigned to Arm A from 1 February to 3 September 2002 while Arm C was closed to enrollment were excluded from analysis. Patients already in Arm C had the option of starting Herceptin following paclitaxel while Arm C was closed to enrollment.

[c] Randomized as of 1 November 2004 in Study N9831 and enrolled as of 29 April 2005 in Study B-31.

[d] Randomized as of 15 February 2005 in Study B-31. The analysis set used for the efficacy analysis in the NEJM article (Romond et al. 2005) was derived from this population.

[e] B-31 patients with at least one follow-up assessment for disease recurrence; excludes 1 patient (710693022) who was found to have had a distant recurrence at randomization and therefore was not at risk for a DFS event. N9831 patients with at least one follow-up of any type.

[f] Safety-evaluable refers to patients who received at least one dose of the indicated treatment.

[g] Patient 2316 (Arm A) received seven cycles of Herceptin.

Outcomes and estimation

Primary endpoint

The primary efficacy endpoint DFS of the joint analysis at the time of the interim analysis is shown in Table 7 and Figure 2. The p-value for the hazard ratio crossed the pre-specified early-reporting boundary of 0.001 (nominal 0.0005 one-sided) for DFS. As a result, the DMCs of both cooperative groups independently recommended closing the studies to accrual and offering Herceptin to eligible patients in the chemotherapy alone arms.

This first interim analysis, which was planned to take place after 355 DFS events had been reported (i.e. 50% of the total), was conducted in April 2005 (median follow-up: 1.8-2.0 years; data cut-off March 15, 2005). At this time, 394 events had been actually reported.

Table 7. Disease-Free Survival (Patients from the Joint Efficacy Population)

	AC→T (n=1679)	AC→T+H (n=1672)
Patients with an event [a]	261 (15.5%)	133 (8.0%)
Distant recurrence	174	90
Local/regional recurrence	57	27
Contralateral breast cancer	6	3
Other second primary cancer	18	5
Death NED	6	8
Patients without an event	1418 (84.5%)	1539 (92.0%)
Stratified analysis		
Hazard ratio [b]	NA	0.48
95% CI	NA	(0.39, 0.59)
p-value (log-rank)	NA	<0.0001
Events per 1000 woman years (95% CI)		
Entire study	83 (73, 94)	40 (33, 47)
Year 1	45 (35, 57)	30 (22, 40)
Year 2	120 (99,145)	55 (42, 72)
Year 3	118 (91, 151)	49 (33, 71)
Year 4	107 (67, 163)	17 (5, 43)

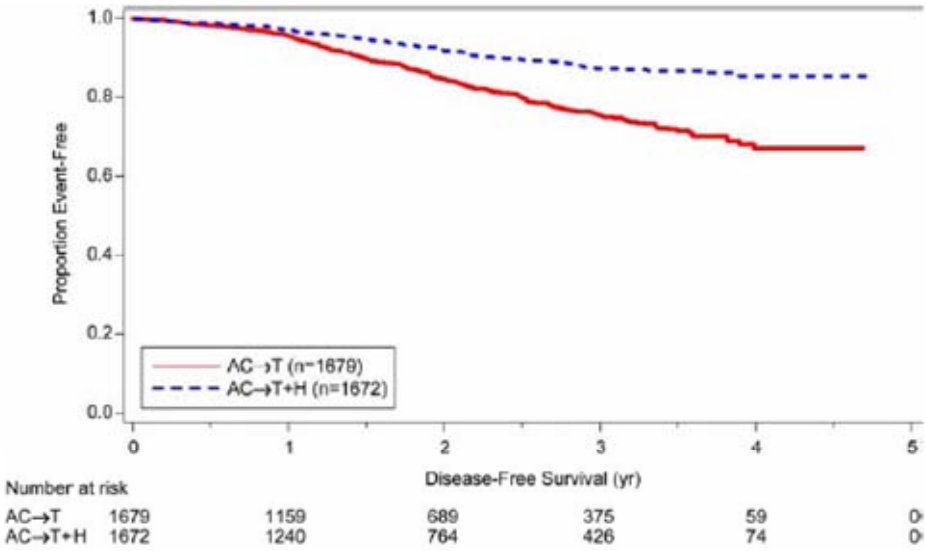


Figure 2: Disease-Free Survival (Patients from the Joint Efficacy Population)

Updated results from the addendum confirm the results observed at interim analysis.

An updated joint efficacy analysis was performed when all patients had had at least 18 months of follow-up from the initiation of adjuvant chemotherapy (median follow-up > 3 years for the joint efficacy population and > 3.5 years for the joint safety population). At this time, 747 patients had experienced a DFS event: 475 in the AC→P arm and 272 in the AC→PH arm. Results in DFS confirmed the results observed at the interim analysis.

Secondary endpoint

Overall survival was the secondary endpoint for the joint analysis (see Table 8 and Figure 3). The O'Brien-Fleming α-spending function was used to control the type I error. With approximately 22% information (154 deaths, and 100% information occurring at 710 deaths for the final analysis), the formal boundary for statistical significance for overall survival at this interim analysis was 1.5×10^{-6}.

Table 8. Overall Survival (Patients from the Joint Efficacy Population)

	AC→T (n=1679)	AC→T+H (n=1672)
Patients who died	92 (5.5%)	62 (3.7%)
Patients alive	1587 (94.5%)	1610 (96.3%)
Stratified analysis		
Hazard ratio [a]	NA	0.67
95% CI	NA	(0.48,0.92)
p-value (log-rank)	NA	0.014
Deaths per 1000 woman years (95% CI)		
Entire study	27 (22, 34)	18 (14, 23)
Year 1	7 (4,13)	11 (7, 18)
Year 2	40 (28, 54)	16 (10, 26)
Year 3	39 (25, 58)	29 (17, 45)
Year 4	59 (33, 97)	35 (16, 66)

A=doxorubicin; C=cyclophosphamide; CI=confidence interval; H=Herceptin; NA=not applicable; T=paclitaxel.

[a] Relative to the chemotherapy alone arm. Estimated by Cox regression stratified by study, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

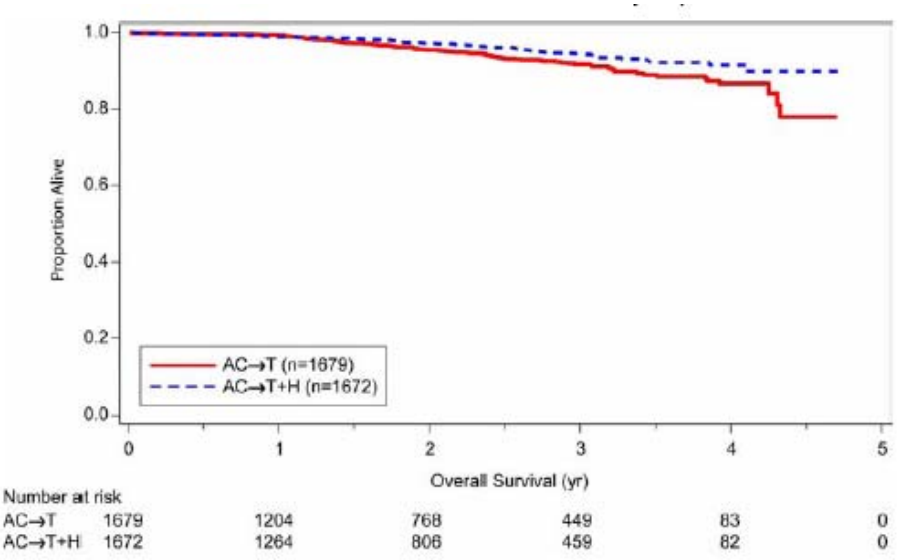


Figure 3: Overall Survival (Patients from the Joint Efficacy Population)

Results of the updated joint analysis of OS were consistent with the first joint analysis results. At this time, 350 deaths had occurred (211 in the AC→P arm, 139 in the AC→PH arm) and the median duration of follow-up for efficacy was 3.5 years in the AC→P arm and 3.8 years in the AC→PH arm.

Other secondary endpoints

Other secondary endpoints are shown in Table 9.

Table 9. Secondary Endpoints (Patients from the Joint Efficacy Population)

Endpoint	AC→T (n=1679)	AC→T+H (n=1672)	Hazard Ratio (95% CI)[a]	p-Value
DFS event	261	133	0.48 (0.39, 0.59)	<0.0001
Death (OS event)	92	62	0.67 (0.48, 0.92)	0.014
Recurrence	235	117	0.47 (0.37, 0.58)	<0.0001
Distant recurrence	193	96	0.47 (0.37, 0.60)	<0.0001
Breast cancer-specific death	79	53	0.66 (0.46, 0.94)	0.019
Contralateral breast cancer	6	4	0.61 (0.17, 2.16)	0.44
Other second primary cancer	20	5	0.24 (0.09, 0.64)	0.002

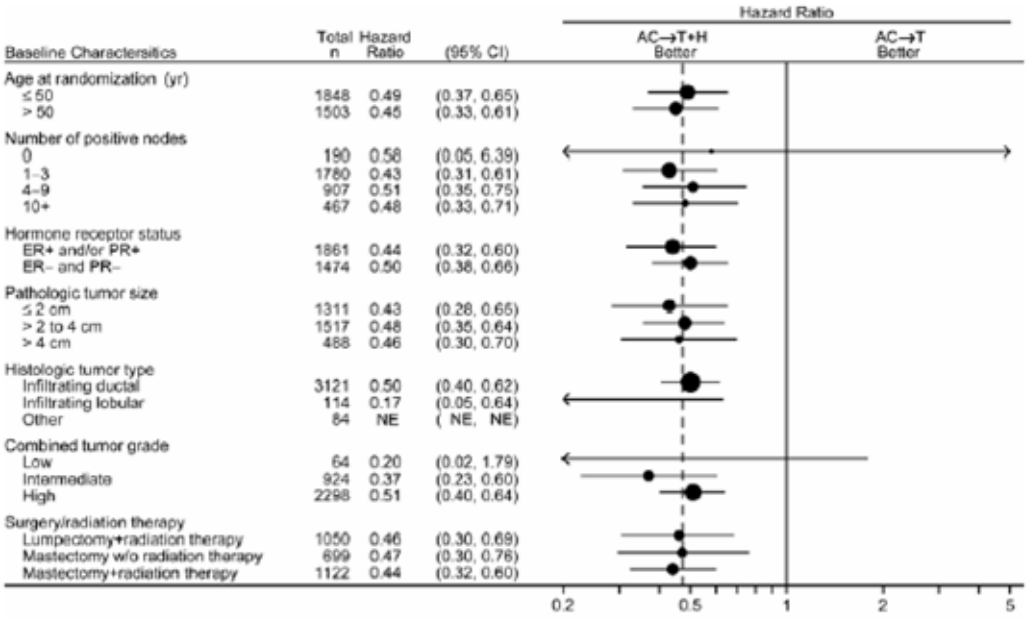
A=doxorubicin; C=cyclophosphamide; CI=confidence interval; DFS=disease-free survival; H=Herceptin; OS=overall survival; T=paclitaxel.

[a] Relative to the chemotherapy alone arm. Estimated by Cox regression stratified by study, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

Ancillary analyses

Pre-specified subgroup analyses were performed to assess the homogeneity of the primary analysis in clinically important patient groups (see Table 10).

Table 10. Disease-Free Survival in Key Subgroups (Patients from the Joint Efficacy Population)



A=doxorubicin; C=cyclophosphamide; CI=confidence interval; ER=estrogen receptor; H=Herceptin; NE=not estimable; PR=progesterone receptor; T=paclitaxel.

Note: Dashed vertical line represents the overall hazard ratio (0.48) for DFS stratified by study, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

The hazard ratio of Herceptin+chemotherapy:chemotherapy alone was estimated by Cox regression stratified by study and intended paclitaxel schedule.

An updated joint analysis of studies NSABP B-31 and NCCTG N9831 (submitted as an addendum) in which all patients had at least 18 months of follow-up from the initiation of adjuvant chemotherapy (median duration of follow-up > 3 years) confirmed the efficacy results of the first interim joint analysis.

3.3 Discussion on clinical efficacy

The joint analysis of B-31 and N9831 has demonstrated the efficacy of adjuvant Herceptin following the adjuvant chemotherapy combination of doxorubicin, cyclophosphamide and paclitaxel. Efficacy has also been demonstrated for the combination of Herceptin, carboplatin and docetaxel as administered in the third arm of the BIRG006 trial as well as the in combination with docetaxel following administration of doxorubicin and cyclophosphamide. A statistically significant and substantial increase in DFS and OS was achieved with the concurrent addition of 52 weeks of trastuzumab to taxanes (either weekly or 3-weekly paclitaxel or 3-weekly docetaxel) following doxorubicin + cyclophosphamide. .

In the joint analysis of the NCCTG 9831 and NSABP B-31 trials, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence (primary endpoint, DFS). The hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 11.8 percentage points (87.2 % vs 75.4 %) in favour of the AC→PH (Herceptin) arm. At the time of a safety update after a median of 3.5-3.8 years follow up, an analysis of DFS reconfirms the magnitude of the benefit shown in the definitive analysis of DFS. Despite the cross-over to Herceptin in the control arm, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence. The addition of Herceptin to paclitaxel chemotherapy also resulted in a 37% decrease in the risk of death.

In the BCIRG 006 study for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 5.8 percentage points (86.7 % vs 80.9 %) in favour of the AC→DH (Herceptin) arm and 4.6 percentage points (85.5 % vs 80.9 %) in favour of the DCarbH (Herceptin) arm compared to AC→D.

The median follow-up duration of more than 5-years in study BCIRG 006 has shown that the combination of trastuzumab with chemotherapy is more effective than delaying trastuzumab therapy by 3 months after the completion of the whole chemotherapy. 5-year DFS was increased from 80% with AC→T→H to 84% for AC→T+H. In addition, in study BCIRG 006, the clinical outcomes (DFS and OS) of the combination of trastuzumab with an anthracycline-containing regimen were numerically (but not statistically) superior to those of the combination of trastuzumab with carboplatin + docetaxel.

The benefit of trastuzumab appeared greater in node-negative than in node-positive patients, with an HR estimate as low as 0.36 for the AC→T+H regimen although confidence intervals were large. The results were essentially the same for both adjuvant regimens (AC→T+H and DCarbH) in node-positive patients. Interestingly, in this group of node-positive patients, trastuzumab did not show any evidence of effect at local/regional sites, only at distant sites. Importantly, there was no difference in CNS metastases between the three treatment arms.

Adjuvant trastuzumab is part of a treatment strategy that also involves surgery, chemotherapy and radiotherapy. At present it is not clear which of the employed chemotherapy protocols is best in combination with trastuzumab. Although not statistically significant, there was a consistent numerical benefit of the anthracycline-containing regimen and concurrent trastuzumab administration over the anthracycline-free regimen. The clinical relevance of this difference is unknown.

Using HR for the primary endpoint generated from the trials gives the following order:

AC-PH (B-31 subgroup, mostly 3-weekly P)	0.44
AC-PH (B-31 and N9831 joint)	0.48
AC-PH (N9831 subgroup, weekly P)	0.54
Any approved chemotherapy (HERA)	0.54
AC-TH (BCIRG006)	0.61
DCarbH or TCH(BCIRG)	0.67

A doxorubicin, **C** cyclophosphamide, **P** paclitaxel, **H** Herceptin, **D** or **T** docetaxel, **Carbo** Carboplatin

Study populations were not easily comparable, for example HERA allowed the inclusion of node negative patients if considered at high risk by tumor size of > 1cm; in B-31 and N9831 (until amendment) had as inclusion criterion only node positive disease. On the other hand HERA may have employed chemotherapy protocols that are not regarded as optimal today.

In order to further study the benefits of trastuzumab in this setting the MAH has committed to provide the data on the follow up efficacy analyses of all three trials as a follow up measure.

3.4. Clinical safety

The joint safety database from B-31 and N9831 was based on data from all patients who had at least 18 months of follow-up from the initiation of their adjuvant chemotherapy (both arms from NSABP B-31 and two of the three arms from NCCTG N9831). The safety data for BCIRG006 were based on the second planned interim efficacy analysis. This analysis was conducted after a median follow-up of 36 months using a database cut-off date of November 01, 2006.
In addition, a cardiac safety update to the BCIRG006 CSR was provided based on the data available when the last patient enrolled had been followed for at least 5 years. The clinical data cut-off date for this update was October 16, 2009 when the median follow-up duration was approximately 66 months (5.5 years).

Safety in the joint analysis was analysed in two subsets

- Safety-evaluable patients included all patients who received at least one dose of protocol treatment. Treatment exposure and deaths were evaluated in this population. All safety-evaluable patients were also considered to be evaluable for cardiac safety.
- AE-evaluable patients included safety-evaluable patients for whom an Adverse Event CRF had been submitted and entered into the database prior to the data cut-off date. Routinely reported AEs were evaluated in this subset.

In the BCIRG006 study, the safety population included all patients who received at least one dose of study treatment.

Patient exposure

The median duration of trastuzumab treatment was close to one year in all trastuzumab-containing arms; 356 days in the NSABP B-31 study and 322 days in the NCCTG N9831 study and 378 days for both the AC→DH and DCarbH regimens in the BCIRG006 study. The majority of patients received the planned dose at each cycle and the median dose intensity was close to 1.0 in all groups.
At the time of the joint analysis, 51.3% and 40.3% of the patients in the AC→PH arms of the NSABP B-31 and NCCTG N9831 studies, respectively, had completed the planned duration of trastuzumab monotherapy per protocol, and similarly 75.3% in the AC→DH arm of the BCIRG006 study. More patients completed trastuzumab therapy (86.5%) in the DCarbH arm of the BCIRG006 study.

Exposure to trastuzumab in the safety population is shown in Table 11.

Table 11. Exposure to trastuzumab in the safety population

	NSABP B-31	NCCTG N9831	Joint Analysis	BCIRG006	
	AC→PH N = 992	AC→PH N = 807	AC→PH N = 1799	AC→DH N = 1068	DCarbH N = 1056
Duration (days)					
n	844	720	1564	1045	1056
mean (SD)	279.6 (110.5)	255.5 (119.4)	268.5 (115.3)	336.0 (102.6)	360.1 (73.7)
median	356.0	322.0	354.0	378.0	378.0
range	0-431	7-454	0-454	21.0-1046.0	21.0-685.0
Total Dose (mg/m^2)					
n	844	721	1565	1045	1055
mean (SD)	3255.6 (1293.9)	3060.8 (1464.3)	3165.9 (1378.0)	3798.5 (1278.4)	4076.1 (1020.6)
median	3677.7	3452.9	3601.4	4106.7	4203.8
range	145-6492	0-8521	0-8521	141.2-7260.0	125.0-9724.0
Relative Dose Intensity					
n	844	720	1564	1045	1056
mean (SD)	0.956 (0.068)	0.970 (0.111)	0.963 (0.090)	1.000 (0.086)	1.005 (0.096)
median	0.980	0.980	0.980	1.004	1.004
range	0.48-1.05	0.34-2.02	0.34-2.02	0.44-1.36	0.29-2.47

A: doxorubicin; C: cyclophosphamide; Carb: carboplatin; D: docetaxel; H: trastuzumab; P: paclitaxel.

Adverse events

Grade 3 or higher adverse events (AE) from B-31 and N9831 are shown in Table 12:

Table 12. Adverse events Grade 3 or higher from studies B-31 and N9831

	NSABP B-31		NCCTG N9831	
	AC→P N = 962	AC→PH N = 967	AC→P N = 797	AC→PH N = 803
Any adverse event	**564 (58.6%)**	**577 (59.7%)**	**350 (43.9%)**	**422 (52.6%)**
Infection*^	128 (13.3%)	128 (13.2%)	37 (4.6%)	60 (7.5%)
Neutrophils^	105 (10.9%)	104 (10.8%)	204 (25.6%)	258 (32.1%)
Leukocytes^	104 (10.8%)	101 (10.4%)	61 (7.7%)	66 (8.2%)
Nausea*^	66 (6.9%)	75 (7.8%)	44 (5.5%)	49 (6.1%)
Vomiting*^	65 (6.8%)	69 (7.1%)	39 (4.9%)	37 (4.6%)
Arthralgia*^	56 (5.8%)	62 (6.4%)	10 (1.3%)	14 (1.7%)
Myalgia*^	84 (8.7%)	60 (6.2%)	8 (1.0%)	9 (1.1%)
Fatigue*^	54 (5.6%)	57 (5.9%)	32 (4.0%)	35 (4.4%)
Hyperglycemia	46 (4.8%)	47 (4.9%)	17 (2.1%)	9 (1.1%)
Febrile neutropenia*^	53 (5.5%)	43 (4.4%)	29 (3.6%)	58 (7.2%)
Neuropathy – sensory*^	53 (5.5%)	43 (4.4%)	30 (3.8%)	34 (4.2%)
Irregular menses	29 (3.0%)	35 (3.6%)	5 (0.6%)	3 (0.4%)
Thrombosis/embolism*^	20 (2.1%)	33 (3.4%)	16 (2.0%)	10 (1.2%)
Cardiac left ventricular function*^	5 (0.5%)	32 (3.3%)	1 (0.1%)	18 (2.2%)
Lymphopenia	24 (2.5%)	30 (3.1%)	-	-
Hemoglobin^	29 (3.0%)	29 (3.0%)	0	2 (0.2%)
Diarrhea without prior colotomy*^	25 (2.6%)	25 (2.6%)	8 (1.0%)	18 (2.2%)
Headache*	20 (2.1%)	25 (2.6%)	7 (0.9%)	5 (0.6%)
Dyspnea	19 (2.0%)	24 (2.5%)	3 (0.4%)	19 (2.4%)
Hypertension	3 (0.3%)	16 (1.7%)	3 (0.4%)	4 (0.5%)
Anorexia*	11 (1.1%)	12 (1.2%)	2 (0.3%)	3 (0.4%)
Neuropathy – motor*^	16 (1.7%)	12 (1.2%)	6 (0.8%)	9 (1.1%)
Platelets^	11 (1.1%)	12 (1.2%)	3 (0.4%)	0
Mood alteration/depression	11 (1.1%)	10 (1.0%)	7 (0.9%)	3 (0.4%)

* AE term itemized on the CRF for NSABP B-31 study
^ AE term itemized on the CRF for the NCCTG N9831 study.
Events are presented in descending order of frequency in the trastuzumab arm of the NSABP B-31 study.
NSABP B-31: Only Grade 3–5 events, treatment-related Grade 2 events, Grade 2–5 cardiac left ventricular dysfunction, and Grade 2–5 dyspnea were collected during and 3 months following protocol treatment.
NCCTG N8931: Only treatment-related Grade 4 and 5 hematological toxicities, Grade 3–5 non-hematological toxicities, Grade 1–5 cardiac toxicities, as well as Grade 2–5 arthralgia, myalgia, nail changes, neuropathy–motor, and neuropathy–sensory adverse events were collected during the treatment period. During the post-treatment follow-up period, only Grade 3–5 cardiac ischemia/infarction, thrombosis/embolism, pneumonitis/pulmonary infiltrates, and lymphatic events were collected.

Grade 3 or higher AE from BCIRG006 are shown in Table 13:

Table 13. Adverse events Grade 3 or higher from studies BCIRG006

Adverse Event	AC→D N = 1050	AC→DH N = 1068	DCarbH N = 1056
Any Grade 3 or 4 non-cardiac adverse event	694 (66.1%)	696 (65.2%)	655 (62.0%)
Any Grade 3 or 4 cardiac adverse event	37 (3.5%)	67 (6.3%)	67 (6.3%)
Neutropenia	663 (63.1%)	761 (71.3%)	696 (65.9%)
Leucopenia	540 (51.4%)	642 (60.1%)	507 (48.0%)
Irregular menses	286 (27.2%)	258 (24.2%)	282 (26.7%)
Infection with neutropenia	119 (11.3%)	128 (12.0%)	116 (11.0%)
Febrile neutropenia	96 (9.1%)	119 (11.0%)	104 (9.8%)
Infection with unknown ANC	120 (11.4%)	118 (11.0%)	87 (8.2%)
Fatigue	73 (7.0%)	78 (7.3%)	76 (7.2%)
Vomiting	64 (6.1%)	73 (6.8%)	36 (3.4%)
Nausea	63 (6.0%)	61 (5.7%)	51 (4.8%)
Diarrhea	32 (3.0%)	61 (5.7%)	58 (5.5%)
Myalgia	55 (5.2%)	56 (5.2%)	19 (1.8%)
Infection without neutropenia	32 (3.0%)	47 (4.4%)	31 (2.9%)
Arthralgia	34 (3.2%)	35 (3.3%)	15 (1.4%)
Anemia	26 (2.5%)	34 (3.2%)	61 (5.8%)
Stomatitis/pharyngitis	38 (3.6%)	33 (3.1%)	15 (1.4%)
Dyspnea	12 (1.1%)	29 (2.7%)	23 (2.2%)
Neutrophils/granulocytes	24 (2.3%)	25 (2.3%)	21 (2.0%)
Neuropathy-sensory	26 (2.5%)	24 (2.2%)	8 (0.8%)
Cardiac left ventricular function	3 (0.3%)	21 (2.0%)	1 (0.1%)
Hypertension	9 (0.9%)	21 (2.0%)	32 (3.0%)
Syncope	18 (1.7%)	20 (1.9%)	18 (1.7%)
Allergic reaction	12 (1.1%)	19 (1.8%)	27 (2.6%)
Thrombosis/embolism	15 (1.4%)	18 (1.7%)	25 (2.4%)
Headache	11 (1.0%)	16 (1.5%)	7 (0.7%)
Hand-foot skin reaction	20 (1.9%)	15 (1.4%)	0
Constipation	8 (0.8%)	15 (1.4%)	6 (0.6%)
Rash/desquamation	18 (1.7%)	14 (1.3%)	9 (0.9%)
Thrombocytopenia	10 (1.0%)	13 (1.3%)	57 (5.4%)
Mood alteration – depression	4 (0.4%)	13 (1.2%)	6 (0.6%)
Hyperglycemia	18 (1.7%)	12 (1.1%)	20 (1.9%)
Catheter-related infection	8 (0.8%)	11 (1.0%)	9 (0.9%)
Bone pain	18 (1.7%)	9 (0.8%)	3 (0.3%)

Events are presented in descending order of frequency in the AC→DH arm.

Serious adverse event

Serious adverse events were not reported in the NSABP B-31 and NCCTG N9831 studies. Instead, certain adverse events were reported via the NCI's Adverse Event Expedited Reporting System (AdEERS), as specified in each protocol. Expedited reporting of adverse events via AdEERS was required for patients in the experimental (trastuzumab-containing) arms of each study who had received at least one dose of trastuzumab, but not in the control arms. The most commonly reported events in the NSABP B-31 and NCCTG N9831 studies, respectively, were left ventricular failure (0.8%, 1.9%), infection (1.3%, 2%), dyspnoea (1.1%, 1.2%), pneumonitis (0.7% in both studies), and thrombosis (0.6%, 1.1%).

Serious AEs were collected and analyzed in the BCIRG006 study according to standard ICH criteria.

Serious non-cardiac AE occurring in ≥1% of patients and serious cardiac AE occurring at any time in BCIRG006 are shown in Tables 14 and 15, respectively.

Table 14. Serious non-cardiac AE occurring in ≥1% of patients in BCIRG006.

Adverse Event	AC→D N = 1050	AC→DH N = 1068	DCarbH N = 1056
Non-cardiac SAE	**202 (19.2%)**	**240 (22.5%)**	**228 (21.6%)**
Febrile neutropenia	72 (6.9%)	90 (8.4%)	79 (7.5%)
Infection with Grade 3/4 neutropenia	47 (4.5%)	51 (4.8%)	47 (4.5%)
Infection without neutropenia	20 (1.9%)	24 (2.2%)	19 (1.8%)
Neutrophils/granulocytes	16 (1.5%)	21 (2.0%)	14 (1.3%)
Vomiting	13 (1.2%)	17 (1.6%)	17 (1.6%)
Fever	9 (0.9%)	19 (1.8%)	5 (0.5%)
Diarrhea	2 (0.2%)	13 (1.2%)	15 (1.4%)

Table 15. Serious cardiac AE occurring at any time in patients in BCIRG006.

NCI-CTC Term	AC→D N = 1050	AC→DH N = 1068	DCarbH N = 1056
Any Cardiac SAE	**14 (1.3%)**	**43 (4.0%)**	**25 (2.4%)**
Thrombosis/embolism	7 (0.7%)	11 (1.0%)	14 (1.3%)
Cardiac left ventricular function	3 (0.3%)	23 (2.2%)	1 (0.1%)
Cardiac ischemia infarction	0	4 (0.4%)	3 (0.3%)
Supraventricular arrhythmias	2 (0.2%)	1 (0.1%)	2 (0.2%)
Palpitations	0	3 (0.3%)	1 (0.1%)
Sinus tachycardia	2 (0.2%)	0	2 (0.2%)
Conduction abnormality/atrioventricular block	0	1 (0.1%)	1 (0.1%)
Edema	0	0	1 (0.1%)
Hypertension	0	0	1 (0.1%)
Hypotension	0	1 (0.1%)	0
Pericardial effusion / pericarditis	1 (0.1%)	0	0
Ventricular arrhythmia	0	1 (0.1%)	0
Phlebitis (superficial)	0	1 (0.1%)	0

Deaths

Deaths from the B-31 and N9831 joint safety population are shown in Table 16.

Table 16. Deaths from the B-31 and N9831 joint safety population

	NSABP B-31		NCCTG N9831		Joint Analysis	
	AC→P N = 972	AC→PH N = 992	AC→P N = 803	AC→PH N = 807	AC→P N = 1775	AC→PH N = 1799
Death	62 (6.4%)	38 (3.8%)	37 (4.6%)	27 (3.3%)	99 (5.6%)	65 (3.6%)
Death during treatment[a]	6 (0.6%)	7 (0.7%)	1 (0.1%)	5 (0.6%)	7 (0.4%)	12 (0.7%)
Deaths during post-treatment period[b]	56 (5.8%)	31 (3.1%)	36 (4.5%)	22 (2.7%)	92 (5.2%)	53 (2.9%)
Cause of death, n (%)						
n	62	38	37	27	99	65
MBC	48 (77.4%)	34 (89.5%)	31 (83.8%)	22 (81.5%)	79 (79.8%)	56 (86.2%)
Unknown	3 (4.8%)	0	1 (2.7%)	0	4 (4.0%)	0
New second primary malignancy	3 (4.8%)	0	2 (5.4%)	1 (3.7%)	5 (5.1%)	1 (1.5%)
Pneumonia	1 (1.6%)	2 (5.3%)	0	0	1 (1.0%)	2 (3.1%)
Sudden death	1 (1.6%)	1 (2.6%)	0	0	1 (1.0%)	1 (1.5%)
Cardiac death	0	0	0	2 (7.4%)	0	2 (3.1%)
Embolism	0	0	1 (2.7%)	1 (3.7%)	1 (1.0%)	1 (1.5%)
GI Bleed	0	0	1 (2.7%)	0	1 (1.0%)	0
Other	2 (3.2%)	1 (2.6%)	0	0	2 (2.0%)	1 (1.5%)
Septicemia	3 (4.8%)	0	0	0	3 (3.0%)	0
Febrile neutropenia with pneumonia	0	0	1 (2.7%)	0	1 (1.0%)	0
Emphysema	1 (1.6%)	0	0	0	1 (1.0%)	0
Respiratory failure with neutropenia	0	0	0	1 (3.7%)	0	1 (1.5%)

Deaths from the BCIRG006 safety population are shown in Table 17:

Table 17. Deaths from the BCIRG006 safety population.

Adverse Event	AC→D N = 1050	AC→DH N = 1068	DCarbH N = 1056
Deaths	78 (7.4%)	48 (4.5%)	55 (5.2%)
On chemotherapy	1 (0.1%)	0	2 (0.2%)
During trastuzumab monotherapy (within 30 days)	0	1 (0.1%)	1 (0.1%)
> 30 days after last infusion of study treatment	77 (7.3%)	47 (4.4%)	52 (4.9%)
Cause of death			
n	78	48	55
Breast cancer	68 (6.5%)	43 (4.0%)	47 (4.5%)
Other cancer	5 (0.5%)	1 (0.1%)	2 (0.2%)
Septic toxicity due to study chemotherapy	1 (0.1%)	0	2 (0.2%)
Other	4 (0.4%)	4 (0.4%)	4 (0.4%)
Cerebral stroke	0	0	1 (0.1%)
Complication of hypercalcemia	1 (0.1%)	0	0
Cranial trauma with acute subdural hematoma	0	0	1 (0.1%)
Pneumonia	1 (0.1%)	0	0
Pulmonary consolidation	0	0	1 (0.1%)
Septic shock	0	1 (0.1%)	0
Sudden death	1 (0.1%)	0	0
Truck rollover accident	1 (0.1%)	0	0
Unknown	0	3 (0.3%)	1 (0.1%)

Significant adverse events: Cardiac safety

Cardiac safety was assessed in the three studies using the following parameters:
- Cardiac events
- Cardiac deaths
- Asymptomatic LVEF events

The numbers and percentage of patients with evidence of cardiac dysfunction (defined as cardiac events, cardiac deaths and asymptomatic LVEF events) were summarized by treatment group and by individual study periods.

The following definitions of cardiac events were used:

Cardiac Events	
NSABP B-31 and NCCTG N9831	**BCIRG006**
– Symptomatic CHF: symptoms (shortness of breath, orthopnea, pedal edema), objective findings on examination (such as elevated jugular venous pressure, sinus tachycardia, tachypnea, S3, crackles) and significant decrease in LVEF (≥ 10% points) from baseline by MUGA or echocardiogram, or chest X-ray findings of pulmonary edema and increased vascular markings	– Congestive heart failure (CHF; Grade 3 or 4 cardiac left ventricular function [CLVF], per the National Cancer Institute Common Toxicity Criteria [NCI-CTC], Version 2.0)
– Definite cardiac death	– Grade 3 or 4 cardiac arrhythmia
– Probable cardiac death: some data were available indicating that the cause of death might be related to a cardiac event, such as myocardial infarction, arrhythmia, CHF, or shock, but there were no clear documentation to determine specific etiology	– Grade 3 or 4 cardiac ischemia/infarction
– Not evaluable: no data available to determine the proximate cause of death	– Cardiac death. – SAEs with cardiac etiology not pre-defined as a cardiac event in the protocol but assessed as being a significant cardiac event by the IRCP.

The following definitions of cardiac death were used:

In studies NSABP B-31 and NCCTG N9831 cardiac deaths were defined as deaths due to CHF, myocardial infarction, or primary arrhythmia as well as sudden death without documented etiology. These were reported on a Cardiac Report Form in the NSABP B-31 study and on a Cardiac Death Report Form in the NCCTG N9831 study. These deaths were reviewed and confirmed by each respective cardiac study committee. Cardiac deaths were summarized by treatment as received for each study and for the joint safety population.

In study BCIRG006 cardiac deaths were reviewed and confirmed by the Independent Cardiac Review Panel (IRCP); they were defined as death due to one of the following:
• confirmed congestive heart failure
• myocardial infarction
• documented primary arrhythmia
• probable cardiac death ie, sudden death without documented etiology.
An autopsy was preferred in cases where cause of death had a cardiac etiology.

The following definitions of asymptomatic LVEF events were used:

In studies NSABP B-31 and NCCTG N9831 an asymptomatic LVEF event was defined as an absolute drop in LVEF of 10% to < 55% (eg, from 64% to 54%) or an absolute drop in LVEF of 5% to below the institution's LLN. Scheduled LVEF assessments were to be performed at baseline and at 3, 6, 9, and 18 months following randomization.

In study BCIRG006 an asymptomatic absolute decline of > 15% in LVEF from baseline and to a value below the LLN was considered a clinically significant asymptomatic LVEF event. Scheduled LVEF assessments were to be performed at baseline and at 3, 6, 9, and 18 months following randomization.

Cardiac Events

Cardiac events reported in the safety population of studies B-31, N9831 and BCIRG006 are summarised in Tables 18 and 19.

Table 18. B-31 and N9831: Cardiac AE (collected on cardiac AE form at any time during study)

AEs	NSABP B-31		NCCTG N9831	
	AC→P N = 962	AC→PH N = 967	AC→P N = 797	AC→PH N = 803
Any cardiac-related AEs				
Any grade	112 (11.6%)	258 (26.7%)	63 (7.9%)	182 (22.7%)
Grade 3-5	29 (3.0%)	51 (5.3%)	5 (0.6%)	35 (4.4%)
Cardiac left ventricular function[a]				
Any grade	28 (2.9%)	132 (13.7%)	48 (6.0%)	157 (19.6%)
Grade 3-5	5 (0.5%)	32 (3.3%)	1 (0.1%)	18 (2.2%)
Cardiac ischemia/infarction[a]				
Any grade	2 (0.2%)	5 (0.5%)	3 (0.4%)	5 (0.6%)
Grade 3-5	0	2 (0.2%)	1 (0.1%)	2 (0.2%)
Sinus tachycardia				
Any grade	7 (0.7%)	9 (0.9%)	4 (0.5%)	5 (0.6%)
Grade 3-5	3 (0.3%)	3 (0.3%)	1 (0.1%)	0
Edema				
Any grade	27 (2.8%)	43 (4.4%)	7 (0.9%)	9 (1.1%)
Grade 3-5	1 (0.1%)	0	0	0
Dyspnea (shortness of breath)				
Any grade	62 (6.4%)	126 (13.0%)	3 (0.4%)	24 (3.0%)
Grade 3-5	19 (2.0%)	24 (2.5%)	3 (0.4%)	19 (2.4%)
Cardiac troponin I				
Any grade	1 (0.1%)	1 (0.1%)	-	-
Grade 3-5	1 (0.1%)	1 (0.1%)	-	-
Cough				
Any grade	9 (0.9%)	26 (2.7%)	-	-
Grade 3-5	1 (0.1%)	1 (0.1%)	-	-

Table 19. BCIRG006: Cardiac AE occurring in >1% of patients at any time during the study

AEs	AC→D N = 1050	AC→DH N = 1068	DCarbH N = 1056
Any cardiac AEs			
Any grade	366 (34.9%)	486 (45.5%)	448 (42.4%)
Grade 3/4	41 (3.9%)	70 (6.6%)	76 (7.2%)
Cardiac left ventricular function			
Any grade	23 (2.2%)	81 (7.6%)	23 (2.2%)
Grade 3/4	3 (0.3%)	21 (2.0%)	1 (0.1%)
Cardiac ischemia/infarction			
Any grade	7 (0.7%)	13 (1.2%)	11 (1.0%)
Grade 3/4	0	4 (0.4%)	2 (0.2%)
Cardiovascular disorder[a]			
Any grade	35 (3.3%)	45 (4.2%)	29 (2.7%)
Grade 3/4	1 (0.1%)	0	1 (0.1%)
Sinus tachycardia			
Any grade	47 (4.5%)	44 (4.1%)	57 (5.4%)
Grade 3/4	4 (0.4%)	1 (0.1%)	0
Tachycardia[a]			
Any grade	5 (0.5%)	17 (1.6%)	15 (1.4%)
Grade 3/4	0	0	2 (0.2%)
Chest pain[a]			
Any grade	6 (0.6%)	16 (1.5%)	15 (1.4%)
Grade 3/4	0	0	0
Hypertension			
Any grade	172 (16.4%)	205 (19.2%)	212 (20.1%)
Grade 3/4	9 (0.9%)	21 (2.0%)	32 (3.0%)
Hypotension			
Any grade	22 (2.1%)	31 (2.9%)	21 (2.0%)
Grade 3/4	1 (0.1%)	0	2 (0.2%)
Palpitations			
Any grade	78 (7.4%)	92 (8.6%)	95 (9.0%)
Grade 3/4	0	0	0
Pericardial effusion/pericarditis			
Any grade	17 (1.6%)	19 (1.8%)	15 (1.4%)
Grade 3/4	0	0	0
Phlebitis (superficial)			
Any grade	14 (1.3%)	22 (2.1%)	8 (0.8%)
Grade 3/4	0	0	0
Thrombosis/embolism			
Any grade	17 (1.6%)	22 (2.1%)	29 (2.7%)
Grade 3/4	15 (1.4%)	18 (1.7%)	25 (2.4%)

A = doxorubicin; C: cyclophosphamide; D: docetaxel; H: trastuzumab
[a]COSTART term

In addition symptomatic cardiac events in studies B-31, N9831 and BCIRG006 are summarised in Tables 20 and 21.

Table 20. B-31 and N9831: Symptomatic cardiac event occurring at any time of the study (per study committee)

Type of Event	NSABP B-31		NCCTG N9831		Joint Analysis	
	AC→P N = 972	AC→PH N = 992	AC→P N = 803	AC→PH N = 807	AC→P N = 1775	AC→PH N = 1799
Any symptomatic cardiac event	10 (1.0%)	32 (3.2%)	1 (0.1%)	21 (2.6%)	11 (0.6%)	53 (2.9%)
Symptomatic CHF (non-fatal)	9 (0.9%)	31 (3.1%)	1 (0.1%)	19 (2.4%)	10 (0.6%)	50 (2.8%)
Cardiac death	1 (0.1%)	1 (0.1%)	0	2 (0.2%)	1 (0.1%)	3 (0.2%)
Death due to CHF, MI, or primary arrhythmia	0	0	0	1 (0.1%)	0	1 (0.1%)
Sudden death without documented etiology	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	2 (0.1%)

A = doxorubicin; C: cyclophosphamide; CHF: congestive heart failure; MI: myocardial infarction;

Table 21. BCIRG006: Symptomatic cardiac AE occurring at any time during the study

Type of Event	AC→D N = 1050	AC→DH N = 1068	DCarbH N = 1056
Any symptomatic cardiac event[a]	6 (0.6%)	23 (2.2%)	12 (1.1%)
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

A = doxorubicin; C: cyclophosphamide; CHF: congestive heart failure; CLVF: cardiac left ventricular function; D: docetaxel; H: trastuzumab

[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.

Exploratory analyses of risk factors for cardiac events (NSABP B-31 and NCCTG N9831 studies) demonstrated that trastuzumab therapy, older age, prior or current use of antihypertensive medications at baseline, low LVEF prior to or following initiation of paclitaxel and LVEF value < 55% at least 28 days prior to the event were significant predictors of a cardiac event. In the AC→PH arm, the risk of a cardiac event increased with the number of these risk factors present, from an incidence of 0.8% when no risk factors were present to 13.0% when all three risk factors were present. When all three risk factors were present in the AC→P arm, the incidence of cardiac events was 4.8%.

For study BCIRG006, treatment with AC→DH, decreased on-study LVEF and older age (> 50 years) were identified as key risk factors for development of a symptomatic cardiac event. Patients in the AC→DH arm had an estimated 3.75-fold higher risk of a cardiac event compared with patients in the AC→D arm.

Findings were similar in the 18-month update to the joint analysis NSABP B-31/NCCTG N9831 and the 5-year cardiac update to the BCIRG006 study.

Cardiac Deaths

In studies B-31 and N9831, there were 12 cardiac deaths: 2 patients treated with AC→T + H and 10 treated with AC→T (6 randomised to AC→T→H and 4 randomised to AC→T). In study BCIRG006 one patient who developed atrial fibrillation and heart failure with cardiomyopathy eventually died in the AC→T group.

Asymptomatic drop in LVEF

The incidence of asymptomatic LVEF declines was higher in the trastuzumab groups than in the chemotherapy only group (see Figures 4 and 5)

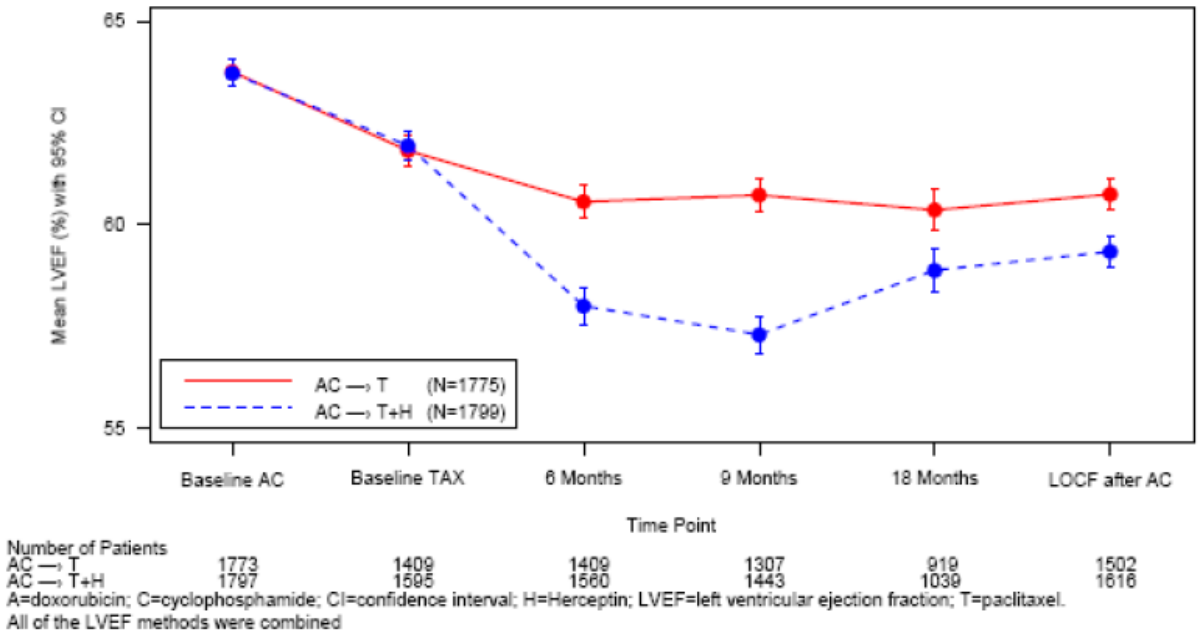


Figure 4. LVEF drop during therapy (studies B-31 and N9831)

BCIRG006: LVEF during the course of treatment

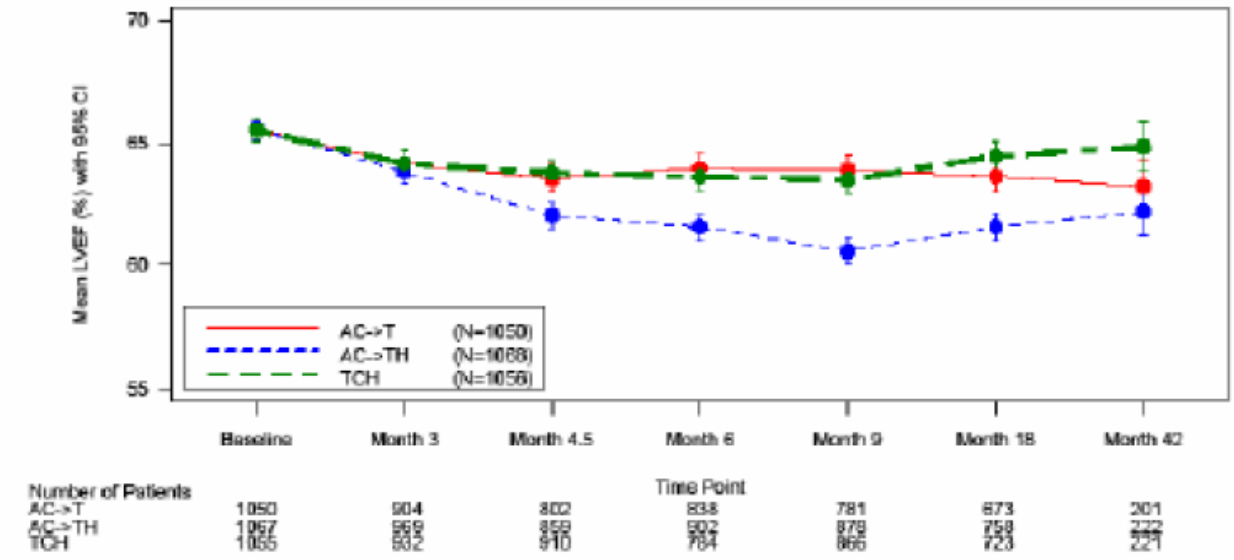


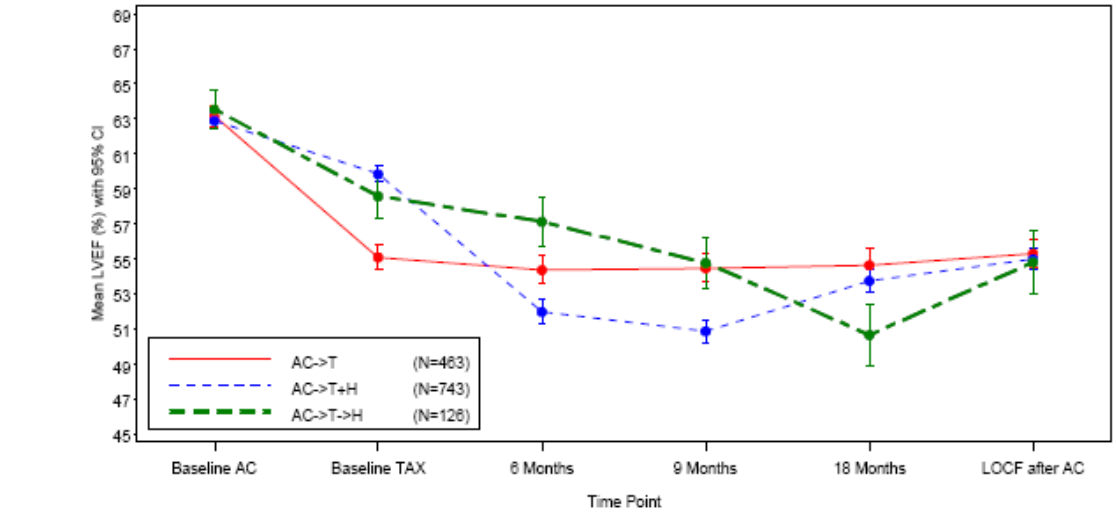
Figure 5. LVEF during the course of treatment (study BCIRG006)

Longer term data on cardiac events

For the joint analysis (NSABP B-31 and NCCTG N9831), patients who developed cardiac dysfunction are patients who had any cardiac event, defined as symptomatic CHF (non-death) or cardiac death; or patients with an asymptomatic LVEF event defined as an absolute drop of LVEF of 10% compared with baseline to below 55% or an absolute drop in LVEF of 5% compared with baseline to below the LLN.

There were 463, 743 and 126 patients who developed cardiac dysfunction in the AC→P, AC→PH and AC→P→H arms.

Figure 6 presents mean LVEF over time for this subgroup of patients based on the database supported 18-month safety update, in the Joint Analysis study, starting from the doxorubicin plus cyclophosphamide (AC) baseline. The mean AC baseline was similar between the trastuzumab groups and the AC→P (AC→T) group in this subgroup of patients. In the AC→PH (AC→TH) patients, the largest mean absolute percentage point decrease from baseline was seen at 9 months, similarly to the mean LVEF over time for all patients. In the AC→P→H (AC→T→H) group, the largest mean absolute percentage point decrease from baseline was seen at 18 months, similarly to the whole population.



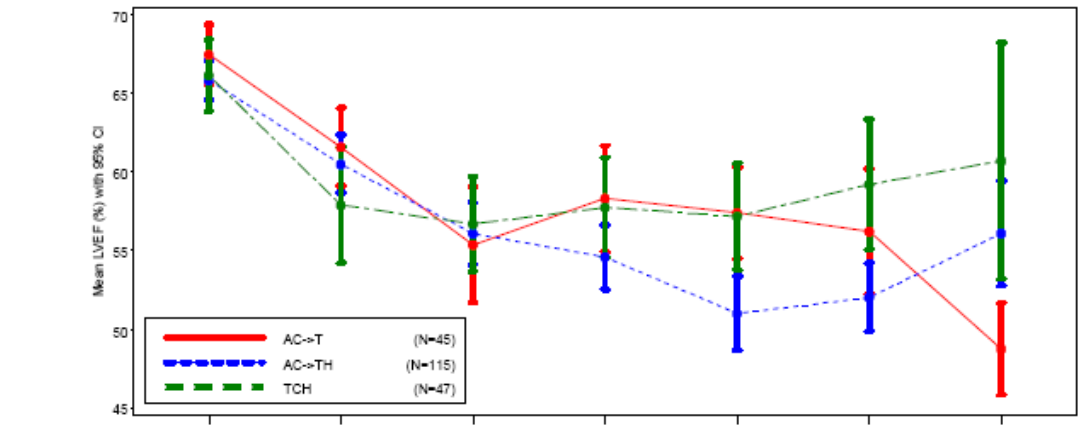
Number of Patients						
AC->T	463	393	411	405	366	435
AC->T+H	743	715	718	722	643	743
AC->T->H	126	121	117	123	117	126

Patients who developed Cardiac Dysfunction are patients with any cardiac event where cardiac event is defined as symptomatic CHF (non-death) or cardiac death or patients with an asymptomatic LVEF event defined as an absolute drop of LVEF of 10% compared with baseline to below 55% or an absolute drop in LVEF of 5% compared with baseline to below the LLN. All of the LVEF methods were combined.
A=doxorubicin; C=cyclophosphamide; CI=confidence interval; H=Herceptin; LVEF=left ventricular ejection fraction; T=paclitaxel.
Source: Biostatistics(clum) pgm(/immuno/her2/abcjoint/eu_bl/programs/g_lvefsum_cardiac) output (g_lvefsum_cardiac)
Database (From ABC Joint 18 Months Safety Update) Datasets (patcard, patsaf)
: Generated 16SEP10 11:40 Page 1 of 1

Figure 6. Joint analysis (NSABP B-31 and NCCTG N9831) study: Mean LVEF for patients who developed cardiac dysfunction

For the BCIRG006 study, patients who developed cardiac dysfunction were defined as patients with any cardiac event where cardiac event, defined as Grade 3 or 4 symptomatic congestive heart failure (CHF), Grade 3 or 4 myocardial infarction, or cardiac death; or patients with an asymptomatic left ventricular ejection fraction (LVEF) event, defined as an absolute decline of > 15% in LVEF from baseline and to a value below the lower limit of normal (LLN). There were 45, 115 and 47 patients who developed cardiac dysfunction in the AC→D (AC→T), AC→DH (AC→TH) and DCarbH (TCH) arms, respectively.

Figure 7 presents the mean LVEF over time for those patients in the BCIRG006 study. There was a general decrease in LVEF values across treatment arms from baseline to the 3-month evaluation for this subgroup of patients. The mean of the largest absolute decline in LVEF values in trastuzumab arms was at the 9-month evaluation.



Number of Patients							
AC->T	45	43	37	37	39	36	8
AC->TH	115	110	94	101	95	79	23
TCH	47	41	42	35	37	32	14

Patients who developed Cardiac Dysfunction are patients with any cardiac event where cardiac event is defined as symptomatic CHF, Grade 3 or 4, myocardial infarction, Grade 3 or 4 or cardiac death or patients with an asymptomatic LVEF event defined as an absolute decline of > 15% in LVEF from baseline and to a value below the LLN.
AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and Herceptin; TH=docetaxel and Herceptin.
CI=confidence interval; LVEF=left ventricular ejection fraction.
Source: Biostatistics(cium) pgm(/immuno/her2/bcirg006/eu_bi/programs/g_lvefsum) output (g_lvefsum_same)
Database (From Interim2: Cutoff 01 NOVEMBER 2006) Datasets (lvef, patcard)
BCIRG 006 Broad Label : Generated 15SEP10 10:10 Page 1 of 1

Figure 7. Study BCIRG006: Mean LVEF for Patients who Developed Cardiac Dysfunction

The data showed that in patients who develop cardiac dysfunction the drop in LVEF associated with combined trastuzumab therapy returned to a level that was consistent across the treatment arms of all three studies, however it did not return to a normal level after completion of study treatment. In conclusion, the data did not show a recovery of the cardiac function after treatment with Herceptin.

Disease progression and cardiac dysfunction (post-hoc, exploratory analysis)

The MAH performed an exploratory, post-hoc combined analysis of disease progression (disease-free survival events) and symptomatic cardiac events) on the datasets that were the basis for the joint analysis (JA) NSABP B-31/NCCTG N9831 and BCIRG006 clinical study reports (CSRs), respectively.

The following definitions of asymptomatic cardiac events were used in the individual study protocols:

- NSABP B-31 and NCCTG N9831: absolute drop in left ventricular ejection fraction (LVEF) of 10% to < 55% or absolute drop in LVEF of 5% to below the institution's lowest limit of normal (LLN).
- BCIRG006: absolute decline in LVEF of > 15% from baseline and to a value below the LLN.

As the LLN of each participating institution was used as baseline not a single one threshold for "baseline" can be defined for the requested analysis, rendering it not possible to apply a common definition of asymptomatic events across all studies.

In the joint analysis NSABP B-31/NCCTG N9831, the primary analysis comprised 394 DFS events; of these, 261 events were in the chemotherapy alone arm and 133 events in the trastuzumab plus chemotherapy arm. When cardiac dysfunction (symptomatic and asymptomatic events) was also included, the combined analysis comprised 1173 events; of these, 532 events were in the chemotherapy alone arm and 641 events in the trastuzumab plus chemotherapy arm. The earliest contributing events by treatment arm, hazard ratio (HR) and its 95% confidence interval (CI) are also summarized in Table 22. It is noted that the large majority of contributing events for the combined analysis were asymptomatic cardiac events.

Table 22. Joint Analysis of NSABP B-31 and NCCTG N9831: Time to First Disease-Free Events and Cardiac Dysfunction Events (Symptomatic and Asymptomatic Events)

	Joint Analysis of NSABP B-31 and NCCTG N9831	
	AC→P	**AC→PH**
No of patients	1679	1672
No patients with an event (%)	532 (31.7%)	641 (38.3%)
Earliest Contributing Event:		
Distant recurrence	171	89
Local/regional recurrence	54	27
Contralateral breast cancer	5	3
Second primary cancer	18	5
Death NED	6	8
Cardiac dysfunction (symptomatic and asymptomatic events)	278	509
Stratified Analysis		
Hazard Ratio (relative to AC→P)		1.31
(95% CI)		(1.17, 1.47)

AC→P = AC→T; AC→PH = AC→TH

When symptomatic cardiac events were included, the combined analysis comprised 440 events; of these, 265 events were in the chemotherapy alone arm and 175 events in the trastuzumab plus chemotherapy arm. The earliest contributing events by treatment arm, HR and its 95% CI are also summarized in Table 23. This analysis of the new combined endpoint resulted in a hazard ratio of 0.64 for the trastuzumab plus chemotherapy arm relative to the chemotherapy alone arm and a p-value for the log-rank test of < 0.0001 (based on stratified analysis).

Table 23. Joint Analysis of NSABP B-31 and NCCTG N9831: Time to First Disease-Free Events and Symptomatic Cardiac Events

	Joint Analysis of NSABP B-31 and NCCTG N9831	
	AC→PH	**AC→PH**
No of patients	1679	1672
No. patients with an event (%)	265 (15.8%)	175 (10.5%)
Earliest Contributing Event:		
Distant recurrence	174	90
Local/regional recurrence	57	27
Contralateral breast cancer	6	3
Second primary cancer	18	5
Death NED	6	8
Cardiac dysfunction (symptomatic events)	4	42
Stratified Analysis		
Hazard Ratio (relative to AC→P)		0.64
(95% CI)		(0.53, 0.77)

AC→P = AC→T; AC→PH = AC→TH

In the BCIRG006 study, the primary analysis comprised 474 DFS events; of these, 195 in the AC→D (AC→T) arm, 134 in the AC→DH (AC→TH) arm, and 145 in the DCarbH (TCH) arm. When cardiac dysfunction (symptomatic and asymptomatic events) was included, the combined analysis comprised 649 events; of these, 230 in the AC→D arm, 232 in the AC→DH arm, and 187 in the DCarbH arm. The earliest contributing events by treatment arm, HR and its 95% CI are also summarized in Table 24.

Table 24. BCIRG006: Time to First Disease-Free Events and Cardiac Dysfunction Events (Symptomatic and Asymptomatic Events)

	BCIRG006		
	AC→D (AC→T)	**AC→D (AC→TH)**	**DCarbH (TCH)**
No. of patients	1073	1074	1075
No. patients with an event (%)	230 (21.4%)	232 (21.6%)	187 (17.4%)
Earliest Contributing Event:			
Local relapse	23	22	22
Regional relapse	16	6	15
Distant relapse	137	88	97
Second primary cancer	22	21	15
Death NED	5	5	7
Cardiac dysfunction (symptomatic and asymptomatic events)	41	99	42
Stratified Analysis			
Hazard Ratio (relative to AC→T) (95% CI)		0.98 (0.82, 1.18)	0.75 (0.62, 0.91)

When the symptomatic cardiac events were included, the combined analysis comprised 509 events; of these, 200 in the AC→D arm, 153 in the AC→DH arm, and 156 in the DCarbH arm. The earliest contributing events by treatment arm, HR and its 95% CI are also summarized in Table 25. This analysis of the new combined endpoint resulted in a hazard ratio of 0.70 for the AC→DH arm relative to the AC→D arm and a p-value for the log-rank test of 0.0009 (based on stratified analysis); a hazard ratio of 0.71 for the DCarbH arm relative to the AC→D arm and a p-value for the log-rank test of 0.0012 (based on stratified analysis).

Table 25. BCIRG006: Time to First Disease-Free Events and Symptomatic Events

	BCIRG006		
	AC→D (AC→T)	**AC→DH (AC→TH)**	**DCarbH (TCH)**
No. of patients	1073	1074	1075
No. patients with an event (%)	200 (18.6%0	153 (14.2%)	156 (14.5%)
Earliest Contributing Event:			
Local relapse	24	22	22
Regional relapse	16	6	15
Distant relapse	142	89	97
Second primary cancer	23	21	15
Death NED	5	5	7
Cardiac dysfunction (symptomatic events)	5	19	11
Stratified Analysis			
Hazard Ratio (relative to AC→T) (95% CI)		0.70 (0.57, 0.87)	0.71 (0.57, 0.87)

Laboratory findings

Haematology

In the B-31 and N9831 trials the incidence of haematological toxicities was higher in the AC→PH arm compared with the AC→P arm (38.6% vs 34.6% for any grade AEs in NSABP B-31; 33.1% vs 27.1% Grade 3-5 AEs in NCCTG N9831). The most frequent events were decreased haemoglobin (in NSABP B-31 only), decreased leukocytes and decreased neutrophils. These occurred with a higher incidence in the AC→PH arm compared with the AC→P arm. However, for Grade 3-5 toxicities, the differences between the trastuzumab-containing and control arms were small in the NSABP B-31 (< 1%). In the NCCTG N9831 study, a higher incidence of neutropenia was observed in the AC→PH arm (32.1%) compared with the AC→P arm (25.8%); this correlated with the increased incidence of febrile neutropenia in the AC→PH arm (7.2% vs 3.5%).

In BCIRG006 study the incidence of Grade 3/4 neutropenia and leucopenia was higher in the AC→DH arm (71.3% and 60.1%, respectively) compared with the AC→D arm (63.1% and 51.4%, respectively) (see Table 26). However, the incidence of neutropenic infection and febrile neutropenia was only slightly higher in the AC→DH arm compared to the AC→D arm. The incidence of Grade 3/4 anemia, neutropenia and thrombocytopenia was higher in the DCarbH arm (5.8%, 65.9% and 5.4%, respectively) compared with the AC→D arm (2.5%, 63.1% and 1.0%, respectively). However, the incidence of neutropenic infection and febrile neutropenia was very similar in the DCarbH and AC→D arms. More patients in the DCarbH arm received prophylactic treatment with granulocyte-colony stimulating factor (G-CSF) during the first 5 cycles of treatment but by Cycle 6, the frequency of G-CSF use was similar in the three arms (32.6% in AC→D, 34.6% in AC→DH and 30.6% in DCarbH) and overall, fewer patients in the DCarb H arm (40.5%) used G-CSF during the study than in the AC→D (45.8%) and AC→DH arms (46.7%).

Table 26. Haematological toxicity from BCIRG006

No. of Patients	AC→D N = 1050	AC→DH N = 1068	DCarbH N = 1056
Anemia[a]	957 (91.1%)	1036 (97.0%)	1017 (96.3%)
Grade 3/4	26 (2.5%)	34 (3.2%)	61 (5.8%)
Neutropenia[b]	858 (81.7%)	922 (86.3%)	858 (81.3%)
Grade 3/4	663 (63.1%)	761 (71.3%)	696 (65.9%)
Thrombocytopenia	296 (28.2%)	349 (32.7%)	667 (63.2%)
Grade 3/4	10 (1.0%)	13 (1.2%)	57 (5.4%)
Leukopenia	878 (83.6%)	929 (87.0%)	877 (83.0%)
Grade 3/4	540 (51.4%)	642 (60.1%)	507 (48.0%)

[a]Anemia defined as hemoglobin level < 12 g/dL.
[b]Neutropenia defined as absolute neutrophil count < 1.0 x 10^9/L

Clinical chemistry toxicity from BCIRG006 is shown in Table 27.

Table 27. Clinical chemistry toxicity from BCIRG006

	AC→D N = 1050	AC→DH N = 1068	DCarbH N = 1056
Creatinine	39 (3.7%)	73 (6.8%)	102 (9.7%)
Grade 3/4	7 (0.7%)	6 (0.6%)	6 (0.6%)
Phosphatase	204 (19.4%)	209 (19.6%)	217 (20.5%)
Grade 3/4	7 (0.7%)	7 (0.7%)	6 (0.6%)
AST (SGOT)	426 (40.6%)	454 (42.5%)	403 (38.2%)
Grade 3/4	2 (0.2%)	11 (1.0%)	13 (1.2%)
ALT (SGPT)	508 (48.4%)	581 (54.4%)	562 (53.2%)
Grade 3/4	10 (1.0%)	21 (2.0%)	28 (2.7%)
Bilirubin	52 (5.0%)	55 (5.1%)	65 (6.2%)
Grade 3/4	7 (0.7%)	5 (0.5%)	10 (0.9%)

Discontinuation due to adverse events

Adverse events leading to withdrawal of study chemotherapy or trastuzumab monotherapy were collected in the BCIRG 006 study. Non-cardiac AEs led to discontinuation of chemotherapy in a similar proportion of patients in each of the anthracycline treatment groups (AC→T 4.2% and AC→T+H 3.6%) and in fewer patients in the DCarbH group (2.1%). The most common non-cardiac AEs leading to discontinuation were neuropathy-sensory, fatigue, rash, and allergic reaction. Non-cardiac AEs led to withdrawal of trastuzumab monotherapy treatment in a small proportion (1.1%-1.2% of patients) in each trastuzumab group, the most common reasons being dyspnoea and fatigue

Discontinuation due to cardiac adverse events
In Study NSABP B-31, 16% (136/844) of patients discontinued trastuzumab at any time due to clinical evidence of myocardial dysfunction or significant decline in left ventricular ejection fraction (LVEF). In Study BCIRG006, a total of 2.9% (31/1056) patients in the DCarbH (TCH) arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) patients in the AC→DH (AC→TH) arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued trastuzumab at any time due to cardiac toxicity.

Post marketing experience

The estimated cumulative exposure to trastuzumab since September 25, 1998 via commercially obtained drug and through clinical trials until March 24, 2010 is 815,060 patients.

Cumulatively to January 31, 2010, 15,920 adverse events reported to the MAH met the criteria required for inclusion in PSURs. There were 8941 (56% of the total) serious adverse events and 6979 (44%) non-serious adverse events in a treated population.

The most frequently reported AEs were categorized under the following System Organ Classes (SOCs):
- general disorders and administration site conditions (2787 events [18% of the sum total of all AEs]),
- investigations (1654 [10%]),
- cardiac disorders (1630 events [10%]),
- and respiratory, thoracic and mediastinal disorders (1529 [9.6%]).

This cumulative analysis replicates to a large extent the findings of the PSUR covering the period from March 25, 2009 to September 24, 2009 inclusive, in which the SOCs into which adverse events were most frequently categorized were:
- investigations: (138 SAEs [15.6% of total SAEs]),
- cardiac disorders (127 SAEs [14.4% of total SAEs]),
- general disorders and administration site conditions (106 SAEs [12.0% of total SAEs]).

Overall, the safety profile of trastuzumab appears to have remained essentially unchanged over time.

3.4.1. Discussion on clinical safety

The data provided by the MAH in the proposed extension of indication confirmed the known safety profile of Herceptin with respect to cardiac-related AE, haematological toxicity and pulmonary reactions. Nevertheless updated information with regard to adverse events in the early breast cancer indication has been included in sections 4.4 and 4.8 of the SmPC and in the package leaflet.

The main findings from studies BCIRG 006, N9831 and NSABP B31 have shown that in patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when Herceptin was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months

and the cumulative incidence did not increase after 3 years. In addition, the incidence of grade 3/4 cardiac dysfunction (symptomatic Congestive Heart Failure) was similar in patients who were administered chemotherapy alone (i.e. did not receive Herceptin) and in patients who were administered Herceptin sequentially to a taxane (0.3-0.4%). The rate was highest in patients who were administered Herceptin concurrently with a taxane (2.0%).

In addition it has been shown that in patients who develop cardiac dysfunction the drop in LVEF associated with combined trastuzumab therapy returned to a level that was consistent across the treatment arms of all three studies; however it did not return to a normal level after completion of study treatment. In one of the 3 pivotal studies conducted (BCIRG006; median follow-up of 5.5 years) a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed in patients who were administered Herceptin concurrently with a taxane following anthracycline therapy up to 2.37% compared to approximately 1% in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and Herceptin). To address the recovery of the cardiac function after treatment with trastuzumab the MAH has committed to provide further follow-up data on LVEF from studies BCIRG 006 and N9831. In addition, details of evolution of symptomatic events and asymptomatic declines in ejection fraction with the need and changes in the treatment of these events will be provided by the MAH from an ongoing observational study (OHERA/BO20652) as a post-authorisation commitment.

When symptomatic cardiac events are counted in a combined analysis with disease progression events, the benefit of trastuzumab is reduced; however it remains both clinically meaningful and statistically significant in favour of the trastuzumab plus chemotherapy arms. From the data presented, it is still unclear whether some patients with asymptomatic LV dysfunction may show improvements while others may progress to symptomatic LV dysfunction. Thus, long-term monitoring of cardiac safety was considered necessary and the MAH is currently addressing this through the extended follow-up of four large adjuvant trastuzumab studies and a large prospective observational study (OHERA/BO20652) to further investigate cardiac safety in 3,800 patients enrolled in a community hospital setting in Europe. A clear analysis of all asymptomatic events and their evolution over time including need for treatment is considered necessary and will be provided by the MAH as a post-authorisation commitment. The MAH has been also requested to perform a study to address long-term cardiac safety using cardiovascular magnetic resonance imaging (CMR) as a post-authorisation commitment.

In addition, the MAH has committed to provide results of sub-studies investigating markers of cardiac toxicity when available.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

3.5. Changes to the product information

The main changes agreed in the product information are summarised below (deletions in strikethrough; additions underlined).

- Section 4.1 of the SmPC

[…]
Early Breast Cancer (EBC)

Herceptin is indicated for the treatment of patients with HER2 positive early breast cancer:

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).

- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.

- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.

[…]

- Section 4.4 of the SmPC

[…]

Cardiotoxicity

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when Herceptin was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. In one of the 3 pivotal studies conducted in which a median follow up of 5.5 years was available (BCIRG006) a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed in patients who were administered Herceptin concurrently with a taxane following anthracycline therapy up to 2.37% compared to approximately 1% in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and Herceptin).

[…]

For early breast cancer patients, cardiac assessment, as performed at baseline, should be repeated every 3 months during treatment and ~~and~~every 6 months following discontinuation of treatment until 24 months from the last administration. In patients who receive anthracycline containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration, or longer if a continuous decrease of LVEF is observed~~at 6, 12 and 24 months following cessation of treatment~~.

[…]

- Section 4.8 of the SmPC

The frequency of the adverse reaction "Ejection fraction decreased" has been revised as "very common" (instead of common) to reflect the increased frequency observed with combination therapy following anthracyclines and combined with taxanes.

In addition the following changes were agreed in the text:

[…]

Cardiotoxicity

[…]

In 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (symptomatic Congestive Heart Failure) was similar in patients who were administered chemotherapy alone (ie did not receive Herceptin) and in patients who were administered Herceptin sequentially to a taxane (0.3-0.4%). The rate was highest in patients who were administered Herceptin concurrently with a taxane (2.0%).

[…]

Haematology

[…]
The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.
[…]

- Section 5.1 of the SmPC

Updated data on the efficacy in the adjuvant setting (results from studies BCIRG 006, N9831 and NSABP B31) has been included. In addition, the data on the post-hoc exploratory analysis combining DFS events and symptomatic cardiac events has been presented.

- Package Leaflet

The package leaflet has been updated accordingly to include the new data on the extension of indication. In addition changes have been introduced following the latest user testing submitted by the MAH.

3.6. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table Summary of the risk management plan

Safety issues	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Important Identified Risk		

Safety issues	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Cardiotoxicity	▪ **Additional** Cardiac AE specific safety study BO20652 (OHERA) **Primary objective**: • To observe the incidence of symptomatic congestive heart failure (CHF) (NYHA class II, III and IV) and cardiac death in patients treated with Herceptin® in routine clinical practice setting. **Secondary objectives**: • To explore potential risk factors for symptomatic congestive heart failure. • To observe the time to onset and the time to recovery of symptomatic congestive heart failure. • To observe the incidence of asymptomatic cardiac failure and other significant cardiac conditions. • To observe the incidence of asymptomatic cardiac failure. Baseline information will be collected from all enrolled patients who signed the informed consent form. All patients receiving Herceptin® will be treated and monitored according to the local clinical practice. Data will be collected from centre's medical records for up to 5 years or death, unless they are lost to follow-up or withdraw the informed consent. Patients will be monitored irrespective of actual treatment regimen they receive for the early as well as recurrent or metastatic disease. Once a year the data will be analyzed and presented to Competent Authorities for review. Study H4613g AKA Her-Q-Les A Phase Ib, Single-Arm, Open-Label Clinical Trial To Evaluate Corrected Qt Interval And Drug–Drug Interaction Of Trastuzumab On Carboplatin In The Presence Of Docetaxel In Patients With HER2-Positive Metastatic Or Locally Advanced Inoperable Cancer. This study will be run entirely in the United States of America.	**Section 4.4 Warnings and Precautions for Use** *Cardiotoxicity* Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving Trastuzumab therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. This may be moderate to severe and has been associated with death (see 4.8). All candidates for treatment with Trastuzumab, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, ECG, echocardiogram, or MUGA scan or magnetic resonance imaging. A careful risk-benefit assessment should be made before deciding to treat with Trastuzumab. In EBC, the following patients were excluded from the HERA trial, there are no data about the benefit/risk balance, and therefore treatment can not be recommended in such patients: • History of documented CHF • High-risk uncontrolled arrhythmias • Angina pectoris requiring medication • Clinically significant valvular disease • Evidence of transmural infarction on ECG • Poorly controlled hypertension Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop

Safety issues	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	Her-Q-Les was designed to meet two post-marketing commitments required by the FDA, namely: 1) To conduct a QT interval protocol according to the principles of ICH E14 (The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs), Section IID, in a minimum of 50 patients receiving trastuzumab (ICH E14 2005). 2) To perform a drug–drug interaction trial in patients with metastatic or locally advanced inoperable cancer who are positive for human epidermal growth factor receptor 2 (HER2), to evaluate the impact of trastuzumab on carboplatin pharmacokinetics, and carboplatin on trastuzumab Pharmacokinetics. The study is scheduled to report in 2013. Cardiac Safety Study ML20529 A Prospective, randomized, pharmacological intervention study evaluating the effect of the angiotensin II-receptor (AT1) blocker candesartan versus placebo in prevention of trastuzumab-associated cardiotoxicity in patients with primary breast cancer treated with trastuzumab The primary endpoint of the study is the occurrence of cardiotoxicity during the one-year trastuzumab therapy and during the 26 weeks after discontinuation of trastuzumab treatment, defined as a decline in LVEF (MUGA) of more than 15% or a decrease to an absolute value below 45%. This study is sponsored by the Netherlands Cancer Institute in collaboration with Astra Zeneca. Analyses will be made available to Roche as these become available.	cardiac dysfunction. For early breast cancer patients, cardiac assessment, as performed at baseline, should be repeated every 3 months during treatment and at 6, 12 and 24 months following cessation of treatment. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6-8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Trastuzumab therapy has been seen. Caution should be exercised in treating patients with symptomatic heart failure, a history of hypertension or documented coronary artery disease, and in early breast cancer, in those patients with an LVEF of 55 % or less. The safety of continuation or resumption of Trastuzumab in patients who experience cardiotoxicity has not been prospectively studied. However, most patients who developed heart failure in the pivotal trials improved with standard medical treatment. This included diuretics, cardiac glycosides, beta-blockers and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Trastuzumab treatment continued on weekly therapy with Trastuzumab without additional clinical cardiac events. **Trastuzumab Treatment Algorithm** If LVEF drops 10 ejection points from baseline AND to below 50 %, Trastuzumab should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of Trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be

Safety issues	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	Additional (Proposed) ▪ **Guided Questionnaire** Guided Questionnaire to better characterise cardiac adverse event reports. ▪ **Routine** Signal Detection –automated, validated signal detection system. The signal detection system QScan, is an interface with the MAHs safety database, Advent, that creates alerts based on single MedDRA preferred terms that meet or exceed any of the following three criteria: PRR ≥ 2, Observed Count ≥ 3 or Chi-squared ≥ 4 Periodic Safety Update Report (PSUR) (EU) – Safety information for trastuzumab will be submitted periodically in scheduled PSURs, taking into account the identified/potential risks, use in patients < 18 years old, and long-term treatment. In the PSUR, all spontaneous and clinical cases reported during the review period are discussed in detail under the relevant System Organ Class (SOC).	referred for assessment by a cardiologist and followed up. If symptomatic cardiac failure develops during Trastuzumab therapy, it should be treated with the standard medications for this purpose. Discontinuation of Trastuzumab therapy should be strongly considered in patients who develop clinically significant heart failure unless the benefits for an individual patient are deemed to outweigh the risks.
Infusion-Related Reactions	▪ **Additional (Proposed)** Guided Questionnaire to better characterise reports of IRR including a request for details of evidence of HAHA. ▪ **Routine** Signal Detection –automated, validated signal detection system. The signal detection system QScan, is an interface with the MAHs safety database, Advent, that creates alerts based on single MedDRA preferred terms that meet or exceed any of the following three criteria: PRR ≥ 2, Observed Count ≥ 3 or Chi-squared ≥ 4 Periodic Safety Update Report (PSUR) (EU) – Safety information for trastuzumab will be submitted periodically in scheduled PSURs, taking into	**Section 4.2 Method of Administration** Trastuzumab is administered as a 90-minute intravenous infusion. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms (see 4.4 and 4.8). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion. Emergency equipment must be available. **Section 4.4 Warnings and Precautions for Use** Serious adverse reactions to Trastuzumab infusion that have

Safety issues	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	account the identified/potential risks, use in patients < 18 years old, and long-term treatment. In the PSUR, all spontaneous and clinical cases reported during the review period are discussed in detail under the relevant System Organ Class (SOC).	been reported infrequently include dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the Trastuzumab infusion should be discontinued and the patient monitored until resolution of any observed symptoms. The majority of patients experienced resolution of symptoms and subsequently received further infusions of Trastuzumab. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Trastuzumab.
Haematotoxicity	▪ **Routine** Signal Detection –automated, validated signal detection system. The signal detection system QScan, is an interface with the MAHs safety database, Advent, that creates alerts based on single MedDRA preferred terms that meet or exceed any of the following three criteria: PRR ≥ 2, Observed Count ≥ 3 or Chi-squared ≥ 4 Periodic Safety Update Report (PSUR) (EU) – Safety information for trastuzumab will be submitted periodically in scheduled PSURs, taking into account the identified/potential risks, use in patients < 18 years old, and long-term treatment. In	**Section 4.8 Undesirable Effects** Haematological toxicity was infrequent following the administration of Trastuzumab as a single agent in the metastatic setting, WHO Grade 3 leucopenia, thrombocytopenia and anaemia occurring in < 1 % of patients. No WHO Grade 4 toxicities were observed. There was an increase in WHO Grade 3 or 4 haematological toxicity in patients treated with the combination of Trastuzumab and paclitaxel compared with patients receiving paclitaxel alone (34 % versus 21 %). Haematological toxicity was also increased in patients receiving Trastuzumab and docetaxel, compared with docetaxel alone

Safety issues	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	the PSUR, all spontaneous and clinical cases reported during the review period are discussed in detail under the relevant System Organ Class (SOC).	(32 % grade 3/4 neutropenia versus 22 %, using NCI-CTC criteria). Note that this is likely to be an underestimate since docetaxel alone at a dose of 100 mg/m^2 is known to result in neutropenia in 97 % of patients, 76% grade 4, based on nadir blood counts. The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Trastuzumab plus docetaxel (23 % versus 17 % for patients treated with docetaxel alone). Using NCI-CTC criteria, in the HERA trial, 0.4% of Trastuzumab-treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.
Oligohydramnios	▪ **Additional** Study H4621g AKA MotHER Pregnancy Registry An Observational Study Of Pregnancy And Pregnancy Outcomes In Women With Breast Cancer Treated With Trastuzumab During Pregnancy Or Within 6 Months Prior To Conception • This registry will be run entirely in the United States of America • MotHER was designed to meet a post-marketing commitment required by the FDA, namely: 1) To submit a protocol for review for a prospectively and actively enrolled pregnancy registry that will collect information assessing pregnancy complications and birth outcomes in women with breast cancer exposed to Trastuzumab-containing regimen prior to conception or during pregnancy. Annual updates from this Registry will be compiled and submitted to regulatory authorities for review annually with a Data-lock point of 31 January and appended to the PSUR. **Routine**	**Section 4.6 Pregnancy and Lactation** Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin and have revealed no evidence of impaired fertility or harm to the foetus. Placental transfer of trastuzumab during the early (days 20–50 of gestation) and late (days 120–150 of gestation) foetal development period was observed. It is not known whether Herceptin can affect reproductive capacity. As animal reproduction studies are not always predictive of human response, Herceptin should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin. Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for at least 6 months after treatment has concluded.

Safety issues	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	Signal Detection –automated, validated signal detection system. The signal detection system QScan, is an interface with the MAHs safety database, Advent, that creates alerts based on single MedDRA preferred terms that meet or exceed any of the following three criteria: PRR ≥ 2, Observed Count ≥ 3 or Chi-squared ≥ 4 Periodic Safety Update Report (PSUR) (EU) – Safety information for trastuzumab will be submitted periodically in scheduled PSURs, taking into account the identified/potential risks, use in patients < 18 years old, and long-term treatment. In the PSUR, all spontaneous and clinical cases reported during the review period are discussed in detail under the relevant System Organ Class (SOC).	Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Herceptin, close monitoring by a multidisciplinary team is desirable.
Pulmonary Disorders	▪ **Additional (Proposed)** Guided Questionnaire to better characterise reports of ILD and such-like. ▪ **Routine** Signal Detection –automated, validated signal detection system. The signal detection system QScan, is an interface with the MAHs safety database, Advent, that creates alerts based on single MedDRA preferred terms that meet or exceed any of the following three criteria: PRR ≥ 2, Observed Count ≥ 3 or Chi-squared ≥ 4 Periodic Safety Update Report (PSUR) (EU) – Safety information for trastuzumab will be submitted periodically in scheduled PSURs, taking into account the identified/potential risks, use in patients < 18 years old, and long-term treatment. In the PSUR, all spontaneous and clinical cases reported during the review period are discussed in detail under the relevant System Organ Class (SOC).	**Section 4.3 Contraindications** Patients with severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy. **Section 4.4 Warnings and Precautions for Use** Severe pulmonary events have been reported rarely with the use of Trastuzumab in the post-marketing setting (see 4.8). These rare events have occasionally been fatal. In addition, rare cases of pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Trastuzumab (see 4.3). Caution should be exercised for

Safety issues	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		pneumonitis, especially in patients being treated concomitantly with taxanes.
Important Potential Risk		
Infections	**Routine** Signal Detection –automated, validated signal detection system. The signal detection system QScan, is an interface with the MAHs safety database, Advent, that creates alerts based on single MedDRA preferred terms that meet or exceed any of the following three criteria: PRR ≥ 2, Observed Count ≥ 3 or Chi-squared ≥ 4 Periodic Safety Update Report (PSUR) (EU) – Safety information for trastuzumab will be submitted periodically in scheduled PSURs, taking into account the identified/potential risks, use in patients < 18 years old, and long-term treatment. In the PSUR, all spontaneous and clinical cases reported during the review period are discussed in detail under the relevant System Organ Class (SOC).	**Section 4.8 Undesirable Effects** Adverse reactions attributed to Trastuzumab in pivotal clinical trials included the following: Infection, pharyngitis, rhinitis, sinusitis, urinary tract infection, nasopharyngitis, upper respiratory tract infection, sinusitis, cystitis, bronchitis. *Infection* An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, has been observed primarily in patients treated with Trastuzumab plus paclitaxel or docetaxel compared with patients receiving paclitaxel or docetaxel alone.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

3.7. Benefit-Risk Balance

Benefits

- Beneficial effects

Adjuvant trastuzumab was associated with a statistically significant and clinically relevant effect on disease free survival. In the joint analysis of the NCCTG 9831 and NSABP B-31 trials, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence (primary endpoint, DFS). The difference in terms of DFS in favour of the Herceptin arm was 6% or 9% at 3 years, depending on the studies. With the longest follow-up available (median of 65 months), it was estimated to be 9% at 5 years.

The effect was observed in both node-negative and node-positive tumours, and was independent of age or menopausal status, type of surgery/radiation therapy, and main tumour characteristics such as hormonal receptor status, size, or histological grade.

In addition a clinically relevant effect on overall survival has been observed. The difference in terms of OS was above 2% at 3 years in all studies and with the longest follow-up available, it was estimated to be 5% at 5 years.

The superiority of TCH or DCarbH treatments was also observed in one trial when compared to the control regimen (AC→T) with a difference in terms of DFS estimated to be 5% at 3 years (6% at 5 years). The difference in terms of OS was above 2% at 3 years and with the longest follow-up available, it was estimated to be 4% at 5 years.

Adjuvant treatment of trastuzumab given concurrently compared to trastuzumab given sequentially after completion of chemotherapy shortened the therapy by around 3 months (from 18 months to 15 months). With the DCarbH regimen the duration of intravenous adjuvant therapy is also shortened by around 3 months compared with the AC→T+H regimens and by around 6 months compared with sequential trastuzumab.

- Uncertainty in the knowledge about the beneficial effects.

No uncertainties have been identified about the benefit of the concurrent use of trastuzumab with chemotherapy (doxorubicin and cyclophosphamide followed by combination with paclitaxel or docetaxel, or as part of a treatment regimen in combination with docetaxel and carboplatin) in the adjuvant treatment of patients with HER2-positive early breast cancer. All tested chemotherapy protocols in the provided randomised trials in combination with trastuzumab increased progression free survival and decreased the risk for relapse.

A direct comparison of the different chemotherapy protocols was not available. It is therefore possible that there are differences in efficacy for the different protocols, but the clinical relevance of these differences are unknown. Patient risk factors may determine the choice of the regimen and should be assessed in a case by case base according to the current recommendations available in the SmPC.

Risks

- Unfavourable effects

Important risks that have been identified in the adjuvant treatment with trastuzumab are cardiac events including death from cardiac compromise, infection, neutropenia, infusion reactions and pulmonary reactions.

Concurrent administration of trastuzumab with a taxane increased a certain number of taxane-related toxicities, including haematological toxicities. Most importantly, cardiac toxicity appeared worse than with sequential administration. When taking into account both symptomatic CHF events and asymptomatic declines in LVEF, the cumulative incidence of cardiac dysfunction events - depending on the definition of LVEF decline - reached at 3 years 36% (AC→T+H) vs. 24% (for AC→T) in the B-31 and N9831 studies and 11% vs. 5%, respectively, in the BCIRG 006 study. Results were intermediate with sequential administration.

All adverse reactions and risks associated with the treatment have been addressed adequately in the SmPC.

- Uncertainty in the knowledge about the unfavourable effects.

It is not clear whether a true difference exists in the occurrence of cardiac events between different chemotherapy protocols in combination with trastuzumab. AE collection was not standardised and is not comparable across trials. Only one chemotherapy regimen (DCarbH or TCH) tested in BCIRG006 appears to have a considerably lower risk of cardiac events than the other protocols. It is at present unknown whether the rate of patients with cardiac compromise will continue to rise in the future. To address the recovery of the cardiac function after treatment with trastuzumab the MAH has committed to provide further follow-up data on LVEF from studies BCIRG 006 and N9831. In addition, details of evolution of symptomatic events and asymptomatic declines in ejection fraction with the need and changes in the treatment of these events will be provided by the MAH from an ongoing observational study (OHERA/BO20652) as a post-authorisation commitment.

Moreover, long-term monitoring of cardiac safety was considered necessary and the MAH is currently addressing this through the extended follow-up of four large adjuvant trastuzumab studies and the

large prospective observational study (OHERA/BO20652) to further investigate cardiac safety in 3,800 patients enrolled in a community hospital setting in Europe. The MAH has been also requested to perform a study to address long-term cardiac safety using cardiovascular magnetic resonance imaging (CMR) as a post-authorisation commitment.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

Survival without recurrence of disease is of utmost importance to the patient in the adjuvant setting. The predominant short term risk, i.e. non-fatal cardiac AE, infusion reactions, infections appear less important in this context. Long term or later occurring consequences of cardiac compromise could be of major importance to the patient later in life. Given that the majority of patients will not have a relapse (at least according to current data) the issue of cardiac damage in later life could become increasingly important. The long-term consequences of the declines in LVEF observed after trastuzumab therapy are still not well understood while several large scale studies have proven beyond doubt that asymptomatic LV dysfunction irrespective of original injury has poor prognosis.

In order to better characterise the benefit-risk balance of trastuzumab, a combined analysis of DFS and cardiac dysfunction events was assessed. With beneficial effects in terms of DFS and long-lasting cardiac dysfunction, this analysis becomes even more valuable in order to better define and quantify the margin of benefit allowed by trastuzumab treatment.

In addition, the new anthracycline-free regimen proposed may decrease the long-term and life-altering toxicities (CHF or acute leukemia) of anthracycline-containing regimens.

- Benefit-risk balance

The benefit-risk balance of addition of trastuzumab to adjuvant chemotherapy protocols is favourable and the beneficial effects as reflected in increased PFS and OS outweigh the unfavourable effects.

Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns,

no additional risk minimisation activities were required beyond those included in the product information.

4. Conclusion

On 17 March 2011 the CHMP considered this Type II variation to be acceptable and recommended the agreed amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.