London, 22 May 2006
Product Name: **Herceptin**
Procedure no.: **EMEA/H/C/278/II/0026**

SCIENTIFIC DISCUSSION

Introduction

Trastuzumab is currently approved for the treatment of Her2 over-expressing metastatic breast cancer, either as monotherapy if therapy with anthracycline and taxanes has failed or is contraindicated, or in combination with paclitaxel inpatients who have not received prior chemotherapy for metastatic disease and for whom an anthracycline is not suitable or in combination with docetaxel in patients who have not received prior chemotherapy for metastatic disease.

The MAH has submitted data from the BO16348 (HERA) trial to support an extension of the indication to include adjuvant treatment of patients with Her2 positive, early breast cancer after surgery and completion of chemotherapy.

Clinical aspects

Clinical pharmacology

Pharmacokinetics

Pharmacokinetics of trastuzumab has been evaluated in patients with metastatic breast cancer previously. Posology in metastatic breast cancer is a loading dose of 4 mg/kg followed by weekly infusion at a dose of 2 mg/kg. Initially pharmacokinetic analysis was performed using a one-compartmental model in phase I, II and III studies. This analysis gave a half-life estimate of 6-8 days which was included in the initial SPC. A reassessment using a two-compartmental model gave a half-life estimate of 28.5 days.
The BO16348 (HERA) trial contained a pharmacokinetic sub-study because of a different posology. Additional data using the same posology in the metastatic breast cancer setting have been submitted.

Methods

Serum samples were assayed for trastuzumab concentration by a validated enzyme-linked immunosorbent assay (ELISA). The lower limit of quantification of the assay was 0.15 ng/mL.
Pharmacokinetic parameters were derived by model-independent methods. The principal parameters of interest from cycles 1 and 13 were Cmin, Cmax, tmax, AUC and Cl. The principal parameter of interest from cycle 18 was the terminal half-life (t½). Trough (pre-dose) concentrations from cycles 2, 3 and 13 were compared with those obtained previously from patients with metastatic breast cancer at the same time points. Data from metastatic breast cancer studies WO16229 and BO15935 were combined and a graphical comparison with data from the HERA study was made.
Forty-four patients from the 1 year treatment group entered the PK substudy. Treatment consisted of a 8 mg/kg loading dose followed by 6 mg/kg every three weeks. Blood samples for pharmacokinetic analysis were collected pre-dose and at 1.5, 2, 3, 4, 6, 8, 24, 96, 168 and 336 h after the start of infusion at cycles 1 and 13. In addition, a pre-dose sample was taken prior to dosing on day 1 of cycles 2, 3 and 14. On the day of administration of the final dose of Trastuzumab (cycle 18 at the end of year 1) samples were collected pre-dose and at 1.5, 2, 3, 4, 6, 8 and 24 hours post-dose, with further samples taken on days 7, 14, 28 and 42 after the final Trastuzumab administration.

Fig 1: The mean Trastuzumab concentration profile at cycle 1, cycle 13 and cycle 18.

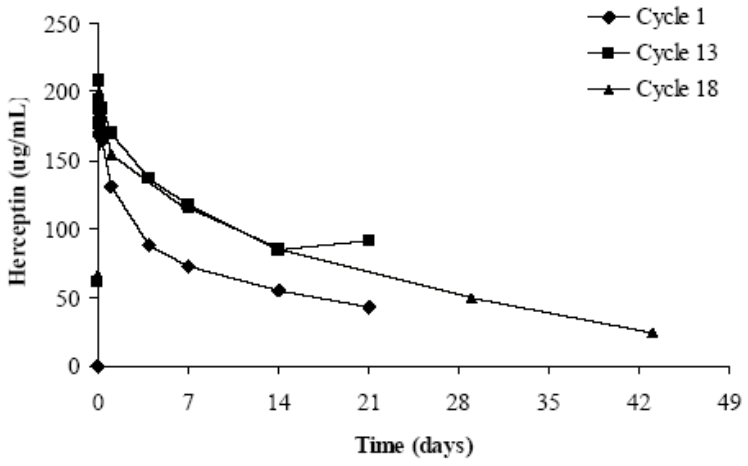


Table 1: Mean ± SD (n) pharmacokinetic Parameters estimated at cycles 1, 13 and 18

Parameter	Cycle 1	Cycle 13	Cycle 18
Tmax (h after the start of infusion)	16.5[c] ± 82.4 (37)	45.1[d] ±144.4 (12)	3.0 ±2.2 (8)
Tlast (h)	494.3 ±48.6 (37)	504.8 ±1.6 (12)	1047.5 ±73.7 (8)
Cmax (ug/mL)	198 ±38.2 (37)	216 ±21.7 (12)	210 ±12.3 (8)
AUC[a] (mg.day/L)	1494 ±317.1 (37)	2255 ±369.8 (10)	2206 ±387.8 (8)
Cl[b] (L/day)	0.232 ±0.054 (34)	0.169 ±0.040 (12)	0.181 ±0.038 (8)
T½ (day)	-	-	16.4 ±4.0 (8)

a AUClast at cycle 1; AUCτ at cycles 13 and 18
b Clss at cycles 13 and 18
c Mean (%CV) of 2.92 (66) with patient 6438 excluded
d Mean (%CV) of 3.46 (44) with patient 5974 excluded

Table 2: Summary of Dose Normalized Trough Concentrations by Cycle of Early Breast Cancer and Metastatic Breast Cancer

	Cycle 2		Cycle 3		Cycle 13		Cycle 14	Cycle 18
Statistic	MBC	EBC	MBC	EBC	MBC	EBC	EBC	EBC
N	128	32	108	31	26	12	12	8
Median	20.8	25.7	35.3	44.4	61.3	60.3	67.4	63.4
SD	14.6	7.9	24.1	14.5	27.5	13.7	56.7	22.0
Min	0.3	20.3	0.180	28.0	2.40	44.1	48.8	40.5
Max	129	61	203	110	122	86.0	217	111

EBC = Early Breast Cancer (HERA) and MBC = Metastatic Breast Cancer (combined data from BO15935 and WO16229)

In order to make comparisons of Cmin from cycles 2 versus cycles 3, 14 and 18 were made as an assessment of accumulation using the following equation:

accumulation ratio RA = Cmin at steady state/ Cmin after a single dose

Table 3: Accumulation ratios for early and metastatic breast Cancer

	Cycle 2-3		Cycle 2-13		Cycle 2-14	Cycle 2-18
Statistic	**MBC**	**EBC**	**MBC**	**EBC**	**EBC**	**EBC**
N	102	31	25	12	12	8
Mean	1.8	1.7	3.0	2.3	3.3	2.5
Median	1.6	1.7	2.6	2.3	2.5	2.2
GeomMean	1.5	1.7	2.5	2.3	2.9	2.4
SD	1.6	0.2	1.7	0.3	2.2	0.6
Min	0.0	1.3	0.2	1.9	1.9	2.0
Max	15.9	2.4	7.6	2.7	9.3	3.7
CV%	91	13	56	11	68	25

where EBC = Early Breast Cancer (current study) and MBC = Metastatic Breast Cancer (combined data from BO15935 and WO16229).

Discussion on pharmacokinetics

A different posology has been chosen for the treatment of patients with early breast cancer. Instead of a 4 mg/kg loading dose and 2 mg/kg weekly dose an 8 mg/kg loading dose and a 6 mg/kg dose is administered every 3 weeks. The results from the ongoing PK study are preliminary, in particular population PK analyses will be performed after completion of the HERA study.

Accumulation ratios, median trough concentrations and drug concentration profiles at week 13 and 18 indicate that steady state has been reached by week 13, the exact time-point prior to week 13 is not known. Accumulation ratios and median trough concentrations are similar to the results obtained in studies in patients with metastatic breast cancer using identical posology.
Half-life at cycle 18 was 16 days, calculated using a non-compartmental model. Although this is in disagreement to population PK analysis in the metastatic setting, these results should be regarded with caution because of low number of individuals (n=8). Final analysis is pending after completion of the HERA study.

No data comparing efficacy for the different posologies have been provided.

Clinical efficacy

The MAH submitted data from one pivotal trial (HERA, BO16438) investigating trastuzumab in an adjuvant setting after completed chemotherapy and data from two studies investigating trastuzumab concurrent to adjuvant chemotherapy (NSABP B-31, NCCTG N9831).

Main study HERA (BO16438)

HERA is a multi-centre, randomised, open label, parallel group study comparing observation to one or two years of treatment with trastuzumab. The study was conducted worldwide with the exception of the USA. Patients were enrolled at 462 centers in 39 countries.

- Inclusion criteria

-Female gender
-Age ≥ 18 years
-Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
-Non-metastatic operable primary invasive adenocarcinoma of the breast histologically confirmed, adequately excised, axillary node positive or negative, any tumour size for node positive disease or tumour size ≥ T1c for node negative disease
-Known hormone receptor status (ER/PgR or ER alone)
-Must have received at least four cycles of an approved (neo-) adjuvant chemotherapy regimen
-Baseline LVEF ≥ 55% after completion of all (neo-) adjuvant chemotherapy and radiotherapy.
-Completion of radiotherapy for any patients undergoing radiotherapy
-Overexpression of HER2 in the invasive component of the primary tumour (3+ overexpression by immunohistochemistry (IHC) or 2+ IHC and c-erbB2 gene amplification by fluorescence in situ hybridisation (FISH) or FISH-positive.

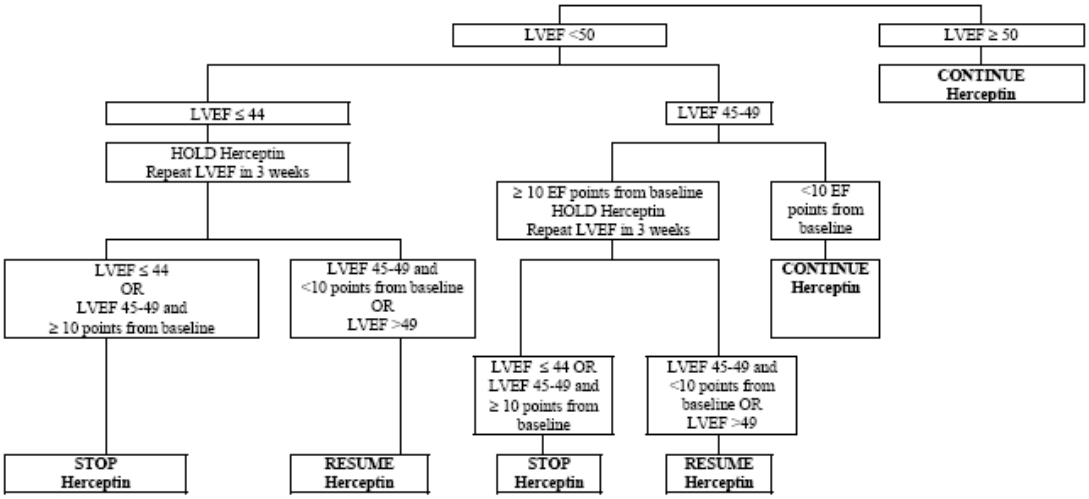
- Exclusion criteria

-History of any prior (ipsi- and/or contralateral) invasive breast carcinoma
-Past or current history of malignant neoplasms, except for curatively treated: Basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix
-Any “clinical” T4 tumor, including inflammatory breast cancer.
-Maximum cumulative dose of doxorubicin > 360 mg/m2 or maximum cumulative dose of epirubicin > 720 mg/m2 or any prior anthracyclines unrelated to the present breast cancer.
-(Neo-) or adjuvant chemotherapy using peripheral stem cell or bone marrow stem cell support.
-Any prior mediastinal irradiation except internal mammary node irradiation for the present breast cancer
-Patients with positive or suspicious internal mammary nodes identified by sentinel node technique which had not been irradiated or patients with supraclavicular lymph node involvement
-Prior use of anti-HER2 therapy for any reason or other prior biologic or immunotherapy for breast cancer.
-Concurrent anti-cancer treatment in another investigational trial
-Serious cardiac illness or medical conditions, including but not confined to history of documented congestive heart failure (CHF), high-risk uncontrolled arrhythmias, angina pectoris requiring

antianginal medication, clinically significant valvular heart disease, evidence of transmural infarction on ECG, poorly controlled hypertension
-abnormal laboratory tests immediately prior to randomization for bilirubin, ALAT, ASAT, ALP, serum creatinine, WBC, neutrophil count, platelet count.

Trastuzumab treatment consisted of an 8 mg/kg loading dose and a 6 mg/kg dose that was administered every 3 weeks. Patients were randomised to either observation or Trastuzumab for one or two years. Concomitant treatment with tamoxifen or anastrozole was allowed according to centre practice.
In the case of cardiac toxicity a detailed algorithm was used to define discontinuation/continuation/stopping rules for trastuzumab (Figure 2). Dose modification for cardiac toxicity was not allowed.

Fig 2: Discontinuation rules algorithm



Primary objectives were: To compare disease-free survival in patients with HER2 over-expressing breast cancer who have completed acceptable adjuvant chemotherapy and radiotherapy, if applicable, and who have been randomized to trastuzumab for one year versus no trastuzumab.

Secondary objectives were:
-To compare overall survival in patients randomized to no trastuzumab versus one year of trastuzumab, and in patients randomized to no trastuzumab versus two years of trastuzumab.
-To compare recurrence-free survival in patients randomized to no trastuzumab versus one year of trastuzumab, and in patients randomized to no trastuzumab versus two years of trastuzumab.
-To compare distant disease-free survival in patients randomized to no trastuzumab versus one year of trastuzumab, and in patients randomized to no trastuzumab versus two years of trastuzumab.
-To evaluate safety and tolerability of trastuzumab.
-To compare the incidence of cardiac dysfunction in patients treated and not treated with trastuzumab.

- Primary endpoint

The primary endpoint was disease-free survival (DFS) defined as the time from randomisation until the first event. An event was defined as any loco-regional or distant recurrence of breast cancer, the development of secondary primary cancer other than basal or squamous carcinoma of the skin and carcinoma in situ of the cervix, or death from any cause without documentation of one of these events. Lobular carcinoma in situ was not considered an event. The diagnosis of a first breast cancer recurrence could be made only when both clinical and laboratory findings met criteria for loco-regional or distant recurrence.

- Secondary endpoints

Secondary endpoints included overall survival, recurrence free survival and distant disease-free survival. Overall survival was defined from time of randomisation to death due to any cause. Recurrence free survival was defined as the time from randomisation to the first local, regional and/or distant tumour recurrence. Second primary cancers, contralateral breast cancer, and deaths without evidence of disease were treated as censoring events. Distant disease-free survival is defined as the time between randomisation and the date of the first distant tumour recurrence, second primary cancer, or contralateral breast cancer, whichever occured first. Local and regional recurrences were ignored for calculating distant disease free survival. Deaths without evidence of disease were treated as censoring events.

- Sample size

Sample size was calculated applying a (two-sided) Type I error of 0.025 and anticipating a 5 years disease free survival (DFS) rate of 65% in the observational arm, a 23% reduction in the risk of DFS following treatment with Trastuzumab and one interim analysis a total number of 951 events to be observed was calculated in order to achieve a power of 80% in a log-rank test. Assuming an annualized recruitment rate of 1992 patients per year over 2.25 years and a minimum follow-up period of 12 months this translates into a sample size of 1494 subjects per group (total: 4482).

- Randomisation

Subjects were centrally randomized on a 1:1:1 basis (no Trastuzumab, 1 year Trastuzumab, 2 years Trastuzumab) using an interactive voice response system (IVRS). Randomization was stratified for the following factors:

Nodal status

1. Any nodal status, neo-adjuvant chemotherapy (nodal status unknown prior to chemotherapy)
2. No positive nodes, no neoadjuvant chemotherapy
3. 1-3 nodes positive, no neoadjuvant chemotherapy
4. >4 nodes positive, no neoadjuvant chemotherapy

Adjuvant chemotherapy regimen

1. no anthracyclines or taxanes
2. anthracyclines but no taxanes
3. anthracyclines + taxanes

Receptor status and endocrine therapy

1. negative
2. positive and no endocrine therapy
3. positive and endocrine therapy

Age

1. < 35 years
2. 35 - 49 years
3. 50 - 59 years
4. ≥ 60 years

Region

European, Nordic countries, Canada, Republic of South Africa, Australia and New Zealand, Asian/Pacific region and Japan, Eastern Europe ('CEE' countries including Croatia, Hungary, Poland, Russia and Slovakia), Central and South America

Randomization was done using the minimization technique to balance assignments across stratification groups (xx1).

- Statistical methods

This study report deals with (partial) results of a pre-planned interim analysis.

The study protocol planned for one interim efficacy analysis after half (475) of the required 951 events had been observed. The aim of this interim analysis was to compare DFS for patients randomized to one year of Trastuzumab versus no Trastuzumab and two years of Trastuzumab versus no Trastuzumab. The interim analysis was performed by an independent statistician and the results presented to the IDMC.

To account for the interim analysis an error-spending function of O'Brien-Fleming type was applied. The Bonferroni-Holm approach was used to account for the two comparisons vs. the observational arm. The significance levels for the most significant pair-wise comparison were 0.0010 for the interim analysis and 0.0247 for the final analysis assuring an overall significance level of 0.025 for the more significant pair-wise comparison. If significance was reached, the significance levels for the second pair-wise comparison were to be 0.0020 for the interim analysis and 0.0494 for the final analysis. The overall study-wide significance level for this procedure was 0.05.

The pairwise comparisons were made using an unstratified log-rank test. The time course of events was described by Kaplan-Meier curves and two year DFS rates including their 95% confidence limits were given for each treatment group. Risk ratios and 95% confidence limits were given for each pair-wise comparison. As the IDMC disclosed data from the observation arm and the 1 year Trastuzumab arm (but not from the 2 years Trastuzumab arm), all data displays in this report are limited to two arms (observational arm and 1 year Trastuzumab).

Explorative subgroup analyses (e.g. for the stratification factors applied in treatment allocation) were performed to assess the consistency of results.

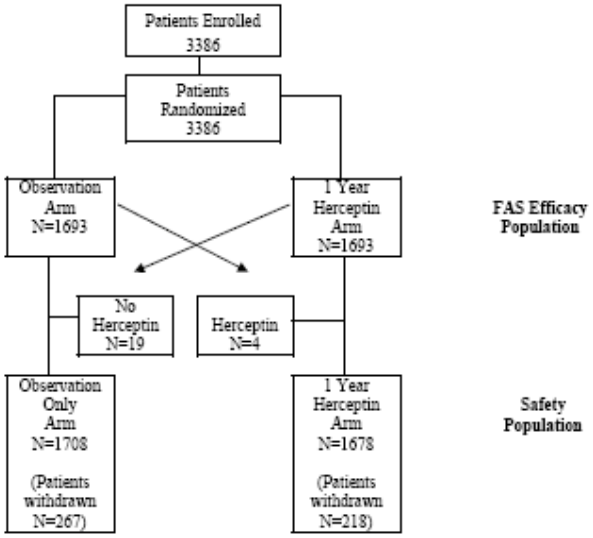
Similar methods as for DFS were used to analyse the secondary parameter overall survival (OS), recurrence free survival (RFS), distant disease free survival (DDFS), time to recurrence (TTR), and time to distant recurrence (TTDR).

All efficacy analyses in this report are based on the Full Analysis Set.

RESULTS

The trial was started on 30.11.2001 and is still ongoing. Recruitment was complete in March 2005 with 5090 patients enrolled. The planned interim analysis was performed after 3386 patients had been included in the trial, 1693 of these patients were randomised to the observation arm and 1693 were randomised to the 1 year trastuzumab arm. 475 events had been recorded at this point. Disposition of patients is shown in the following flow diagram.

Fig 3: Patients' disposition



The FAS population consists of all patients randomised, irrespective of treatment received (intention to treat principle). The safety population consists of all patients according to treatment received.

Nineteen patients randomised to trastuzumab did not receive trastuzumab and 4 patients randomised to observation received trastuzumab.

Table 4: Baseline characteristics for stratification factors are shown in the following table.

	Observation Only N=1693	Trastuzumab 1 Year N=1693
Nodal Status		
Any Nodal Status, neo-adj chemotherapy	176(10.4%)	190 (11.2%)
No Positive Nodes, no neo-adj chemotherapy	555 (32.8%)	543 (32.1%)
1-3 Nodes Positive, no neo-adj chemotherapy	490 (28.9%)	483 (28.5%)
>=4 Nodes Positive, no neo-adj chemotherapy	471 (27.8%)	477 (28.2%)
missing values	1 (0.1%)	0 (0.0%)
Adjuvant Chemotherapy Regimen[1]		
No Anthracyclines or Taxanes	99 (5.8%)	97 (5.7%)
Anthracyclines but no Taxanes	1154 (68.2%)	1150 (67.9%)
Anthracyclines + Taxanes	438 (25.9%)	443 (26.2%)
Receptor Status and Endocrine Therapy		
Negative	841 (49.7%)	838 (49.5%)
Positive and no Endocrine Therapy	34 (2.0%)	53 (3.1%)
Positive and Endocrine Therapy	818 (48.3%)	802 (47.4%)
Unknown	0 (0.0%)	0 (0.0%)
Age group		
< 35 years	126 (7.4%)	126 (7.4%)
35 - 49 years	749 (44.2%)	751 (44.4%)
50 - 59 years	546 (32.3%)	546 (32.3%)
>= 60 years	272 (16.1%)	270 (15.9%)
Missing and invalid values	0 (0.0%)	0 (0.0%)
Region		
Europe, Nordic Countries, Canada, South Africa, Australia, New Zealand	1222 (72.2%)	1208 (71.4%)
Asia Pacific and Japan	202 (11.9%)	202 (11.9%)
Eastern Europe	175 (10.3%)	189 (11.2%)
Central and South America	94 (5.6%)	94 (5.6%)

Table 5: The following table shows <u>demographic data</u> at baseline (FAS population)

	Observation Only N = 1693	Trastuzumab 1 Year N = 1693
Race		
Caucasian	1411 (83%)	1414 (84%)
Black	5 (<1%)	9 (<1%)
oriental	213 (13%)	213 (13%)
Other	64 (4%)	57 (3%)
n	1693	1693
Age in years		
Mean	49.2	49.0
SD	10.08	10.05
Min-Max	23 – 77	21 - 80
n	1693	1693
Weight in kg		
Mean	67.43	67.98
SD	13.009	13.142
Min-Max	40.0 – 137.5	36.0 - 149.0
n	1675	1686
Female reproductive status		
postmenopausal	745 (44%)	718 (42%)
Surgical steril..	215 (13%)	206 (12%)
with cont. protection.	723 (43%)	763 (45%)

Without cont. protection.	8 (<1%)	6 (<1%)
n	1691	1693
Does subject consume tobacco?		
No	1470 (87%)	1450 (86%)
yes	223 (13%)	243 (14%)
n	1693	1693

Table 6: Breast Cancer History (FAS Population)

	Observation Only N=1693	Trastuzumab 1 Year N=1693
Duration of Disease at Randomization (months)		
n	1693	1693
Median	8	8
Range	3 – 20	3 - 20
Pathologic Tumour Size (mm)		
n	1649	1657
Median	22	22
Range	0 - 220	0 - 260
Breast Cancer Subtype[3]		
n	1692	1693
Ductal	1598 (94.4%)	1600 (94.5%)
Lobular	89 (5.3%)	97 (5.7%)
Medullary	23 (1.4%)	22 (1.3%)
Tubular	12 (0.7%)	13 (0.8%)
Mucinous	16 (0.9%)	13 (0.8%)
Comedo	120 (7.1%)	134 (7.9%)
Inflammatory	2 (0.1%)	3 (0.2%)
Not known	0 (0.0%)	0 (0.0%)
Other	96 (5.7%)	88 (5.2%)
Histological Grade		
n	1685	1682
Gx: Can't be assessed	77 (4.5%)	72 (4.3%)
G1: Well differentiated	38 (2.2%)	37 (2.2%)
G2: Moderately differentiated	557 (32.9%)	550 (32.5%)
G3: Poorly/Undifferentiated	1013 (59.8%)	1023 (60.4%)

Table 7: HER2 status at baseline (FAS population)

	Observation Only N=1693	Trastuzumab 1 Year N=1693
Central Results		
HER2 3+ only	1160 (68.5%)	1098 (64.9%)
FISH Positive only	342 (20.2%)	382 (22.6%)
HER2 3+ and FISH Positive	38 (2.2%)	53 (3.1%)
Other	153 (9.0%)	160 (9.5%)

N.B. Other criteria includes IHC 2+ and FISH positive, IHC3+ and FISH negative

Prior and concomitant treatment

All patients had surgical treatment, approximately one half had breast conserving surgery and the other half had mastectomy. More than 95% in both groups had resection of axillary nodes and about half had adjuvant endocrine therapy (tamoxifen, aromatase inhibitors, LHRH-agonists, ovarian ablation and combinations thereof). 94% of patients in both groups had received anthracycline-containing chemotherapy regimen. A summary of adjuvant chemotherapy is table 8.

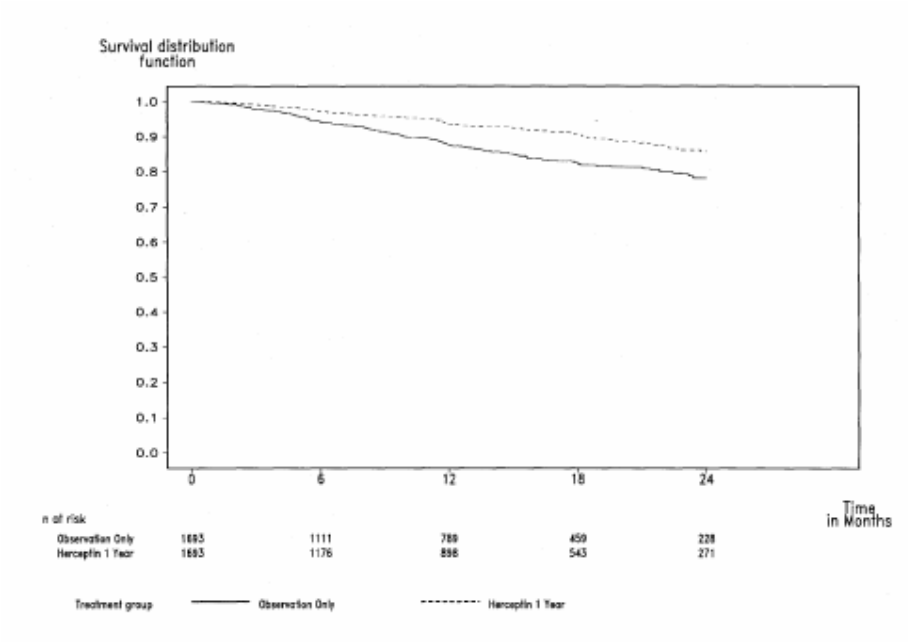
Table 8: Previous chemotherapy (adjuvant)

	Observation Only	Trastuzumab 1 Year
Anthracycline containing	94%	94%
Epirubicin containing (median 6 cycles)	55%	56%
Doxorubicin containing (median 4 cycles)	33%	31%
Paclitaxel containing (median 4 cycles)	13.7%	14.7%
Docetaxel containing	8.4%	8.9%
Cyclophosphamide containing (median 6 cycles)	90%	90%
5-Fluorouracil containing	57%	57%

Efficacy Results

The primary endpoint of the HERA study is DFS. At the time of interim analysis 219 patients in the observation arm and 127 patients in the trastuzumab arm had an event defined as any recurrence of breast cancer, contralateral breast cancer, second non-breast malignancy or death from any cause (log-rank test $p<0.0001$). The mean duration of follow-up was 12.4 months for the observation group and 12.7 months for the trastuzumab group. Analysis survival by Kaplan-Meier curve (FAS population) is shown in the following figure. The hazard ratio is 0.54 (95% confidence interval 0.44-0.67). The 2-year disease-free survival rate is 78.2% in the observation group and 85.8% in the trastuzumab group.

Fig 4:



Subgroup analysis that was performed for patients' nodal status, hormone receptor positivity, previous chemotherapy regimen, age and other prognostic important variables is shown in the following table.

Table 9:

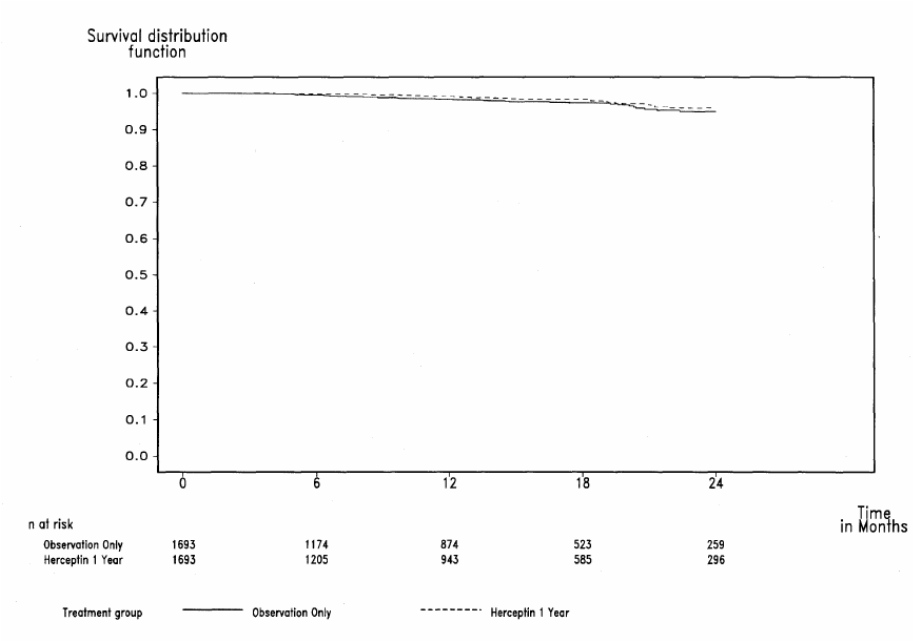
Baseline parameter	Category	N	Lower CL	Hazard Ratio	Upper CL
All		3386	0.44	0.54	0.67
Estrogen Receptor status	Positive	1534	0.43	0.62	0.89
	Negative	1851	0.38	0.49	0.65
Progesterone Receptor status	Positive	1152	0.39	0.61	0.94
	Negative	2077	0.43	0.55	0.71
	Unknown	157	0.07	0.23	0.84
Menopausal Status	Premenopausal	487	0.35	0.59	0.99
	Postmenopausal	1530	0.41	0.57	0.79
	uncertain	1367	0.34	0.49	0.70
ECOG score	0	3092	0.41	0.52	0.66
	1 or 2	292	0.37	0.73	1.46
Race	Caucasian	2825	0.44	0.56	0.71
	Non-caucasian	561	0.24	0.43	0.78
Nodal status	Any, neo adj chemo	366	0.33	0.54	0.90
	0 pos, no neo-adj chemo	1098	0.29	0.49	0.84
	1-3 pos, no neo-adj chemo	973	0.30	0.49	0.80
	>=4 pos, no neo-adj chemo	948	0.39	0.54	0.76
Adj chemor regimen	No Anthrac or taxane	196	0.29	0.68	1.62
	Anthrac, no taxane	2304	0.32	0.43	0.58
	Anthrac + taxane	881	0.53	0.76	1.11
Age	< 35 yrs	252	0.24	0.47	0.95
	35-49 yrs	1500	0.36	0.50	0.69
	50-59 yrs	1092	0.36	0.54	0.80
	>=60 yrs	542	0.45	0.79	1.39
Recep Status/Endocr Ther	Negative	1679	0.37	0.49	0.65
	Pos, no endocr therapy	87	0.15	0.54	1.88
	Pos, endocr therapy	1620	0.43	0.62	0.88
Histological Grade	Gx: unknown	1749	0.0.8	0.29	1.04
	G1	75	0.29	1.17	4.73
	G2	1107	0.22	0.35	0.55
	G3	2036	0.49	0.64	0.83

Secondary efficacy parameters

Overall survival

At the time of interim analysis 40 (2.4%) patients in the observation arm compared to 31 (1.8%) patients in the trastuzumab arm had died. A Kaplan-Meier plot for overall survival is shown in the following figure.

Fig 5:



Recurrence free survival

At the time of interim analysis 208 (12.3%) patients in the observation arm compared to 113 (6.7%) patients in the trastuzumab arm had a relapse of disease (local, regional or distant). This result is statistically significant (log-rank test $p<0.0001$). The hazard ratio was 0.51 (95% CI 0.40-0.64).

Distant disease-free survival

At the time of interim analysis 184 (10.9%) patients in the observation arm compared to 99 (5.8%) patients in the trastuzumab arm had a distant recurrence of disease. This result is statistically significant (log-rank test $p<0.0001$). The hazard ratio was 0.50 (95% CI 0.39-0.64).

SUPPORTIVE STUDIES

Two additional studies are provided to support the claim for treatment in early breast cancer. NSABP B-31 and NCCTG N9831 are two randomised phase III studies comparing adjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel with and without trastuzumab in patients with HER2 positive breast cancer. Both studies were independently planned but of similar design. Therefore a joint interim analysis was performed

Methods

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.

Important inclusion criteria for both studies were:
-Pathologic diagnosis of adenocarcinoma of the breast with strongly positive (3 +) HER2 protein overexpression or HER2 gene amplification
-Histologically confirmed node-positive disease or (Study N9831 only following the May 2003 amendment) high-risk node-negative disease (defined as tumour size > 1 cm and oestrogen receptor [ER] and progesterone receptor [PR] negative, or tumour 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 radiological facility
-Complete resection of the primary breast tumour and axillary nodal dissection (sentinel node biopsy alone, if negative, was allowed on Study N9831)
-84 days (12 weeks) between surgery and randomization

Both studies were conducted primarily in the USA, smaller numbers of patients were recruited in Canada, Guam, Lithuania, Peru, South Africa, United States, and Puerto Rico.

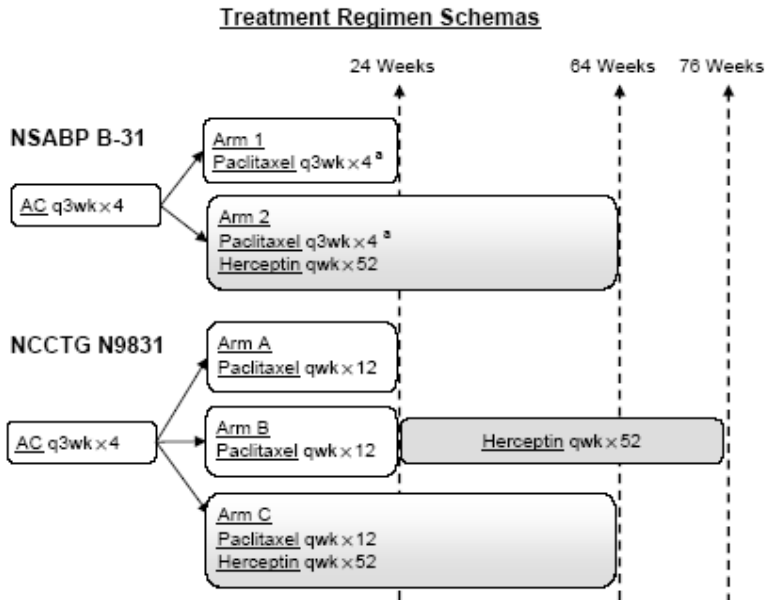
Treatments

Patients received four 3-week cycles of doxorubicin (60 mg/m²)/cyclophosphamide (600 mg/m²) followed by paclitaxel (weekly 80 mg/m²or three-weekly 175 mg/m²) for 12 weeks.

Patients randomized to Arm 2 of Study B-31 or Arm C of Study N9831 began trastuzumab therapy concurrently with paclitaxel. The total duration of trastuzumab therapy was 52 weeks.

The trastuzumab loading dose was 4 mg/kg and the weekly dose was 2 mg/kg.

Fig 6:



- Objectives

Primary objective for the planned joint interim analysis was to evaluate the efficacy of weekly trastuzumab plus chemotherapy (four cycles of doxorubicin/cyclophosphamide followed by 12 weeks of paclitaxel [weekly or every-3-week administration] plus weekly trastuzumab) versus chemotherapy alone as adjuvant therapy for women with early-stage, HER2-positive breast cancer as measured by disease-free survival.

Co-primary objective was to evaluate safety of combined therapy as evidence by incidence and severity of cardiac and non-cardiac events.

Secondary objective was to evaluate efficacy as measured by overall survival.

- Sample size

The joint analysis of Studies B-31 and N9831 included patients from Arms 1 and 2 of Study B-31 and patients from Arms A and C of Study N9831. The joint analysis was designed to detect a 25% decrease in the event rate for DFS (the primary endpoint) and overall survival (the secondary endpoint). To achieve 90% power against this alternative and have an overall one-sided 0.025 level of significance, 710 events, accumulated across both trials, were required. A formal plan for interim analyses of efficacy was incorporated into the description of the joint analysis of the two studies. This plan was documented before any efficacy evaluations were done in either study.

Results

- **Table 10 : Patient disposition in studyB31 efficacy population**

	AC->T (n = 872)	AC->T + H (n = 864)
Randomized	872	864
Entered AC chemotherapy	863 (99.0%)	863 (99.9%)
Completed	847 (97.1%)	855 (99.0%)
Did not complete	16 (1.8%)	8 (0.9%)
Death or relapse	3 (0.3%)	3 (0.3%)
Other	13 (1.5%)	5 (0.6%)
Entered paclitaxel chemotherapy	822 (94.3%)	831 (96.2%)
Completed	764 (87.6%)	792 (91.7%)
Did not complete	58 (6.7%)	39 (4.5%)
Death or relapse	5 (0.6%)	3 (0.3%)
Other	53 (6.1%)	36 (4.2%)
Entered trastuzumab therapy	NA	781 (90.4%)
Completed	NA	507 (58.7%)
Did not complete	NA	205 (23.7%)
Death or relapse	NA	16 (1.9%)
Other	NA	189 (21.9%)

- **Table 11 : Patient disposition in study N9831 efficacy population**

	AC->T (n = 807)	AC->T + H (n = 808)
Randomized	807	808
Entered AC chemotherapy	802 (99.4%)	807 (99.9%)
Completed	760 (94.2%)	778 (96.3%)
Did not complete	34 (4.2%)	24 (3.0%)
Death or relapse	2 (0.2%)	7 (0.9%)
Other	32 (4.0%)	17 (2.1%)
Entered paclitaxel or Trastuzumab + paclitaxel chemotherapy	718 (89.0%)	756 (93.6%)
Completed	607 (75.2%)	656 (81.2%)
Did not complete	62 (7.7%)	48 (5.9%)
Death or relapse	4 (0.5%)	1 (0.1%)
Other	58 (7.2%)	47 (5.8%)
Entered trastuzumab monotherapy	1 (0.1%) b	619 (76.6%)
Completed	0	325 (40.2%)
Did not complete	0	119 (14.7%)
Death or relapse	0	6 (0.7%)
Other	0	113 (14.0%)

- **Table 12: Baseline data**

	AC->T	AC->T+H
Age		
N	1679	1672
Median	49	49
Range	24-80	22-79
<=39	284	270
40-49	579	577
52-59	565	541
>59	251	284
Pathological nodal status		
N	1673	1671
0	102 (6.1%)	88 (5.3%)
1-3	881 (52.7%)	899 (53.8%)
4-9	452 (27.0%)	455 (27.2%)
10+	238 (14.2%)	229 (13.7%)
Pathologic hormone receptor status		
N	1676	1672
ER-positive, PR-positive	642 (38.3%)	589 (35.2%)
ER-positive, PR-negative	242 (14.4%)	269 (16.1%)
ER-negative, PR-positive	51 (3%)	64 (3.8%)
ER-positive, PR-other	2 (0.1%)	2 (0.1%)
ER-negative, PR-negative	732 (43.7%)	742 (44.4%)
Unknown	7 (0.4%)	6 (0.4%)
Histological Grade		
N	1661	1656
Low	31(1.9%)	33 (2.0%)
Intermediate	468 (28.2%)	456 (27.5%)
High	1146 (69.0%)	1152 (69.6%)
Unknown	16 (1.0%)	15 (0.9%)
Pathological tumor size		
N	1657	1659
<=2 cm	681 (41.1%)	630 (38.0%)
>2 cm	976 (58.9%)	1029 (62%)

- Efficacy

The primary efficacy endpoint of the joint analysis was DFS. At the time of the first scheduled interim analysis to evaluate efficacy, 394 patients had experienced a DFS event. Of these, 261 patients were in the chemotherapy alone arm and 133 patients were in the trastuzumab + chemotherapy arm. The p-value for the hazard ratio crossed the prespecified 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 trastuzumab to eligible patients in the chemotherapy alone arms. The following table gives a summary of results.

Table 13: Efficacy results following the joint interim analysis

	AC->T (n=1679)	AC->T+H (n =1672)
Patients with an event	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 without evidence of disease	6	8
Patients without an event	1418 (84.5%)	1539 (92.0%)
Stratified analysis		
Hazard ratio	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)

A =doxorubicin; C =cyclophosphamide; CI =confidence interval; H =Trastuzumab; NA =not applicable; NED =no evidence of disease; T =paclitaxel.

Fig 7: Kaplan Meier Analyis for the joint population is shown in the following figure

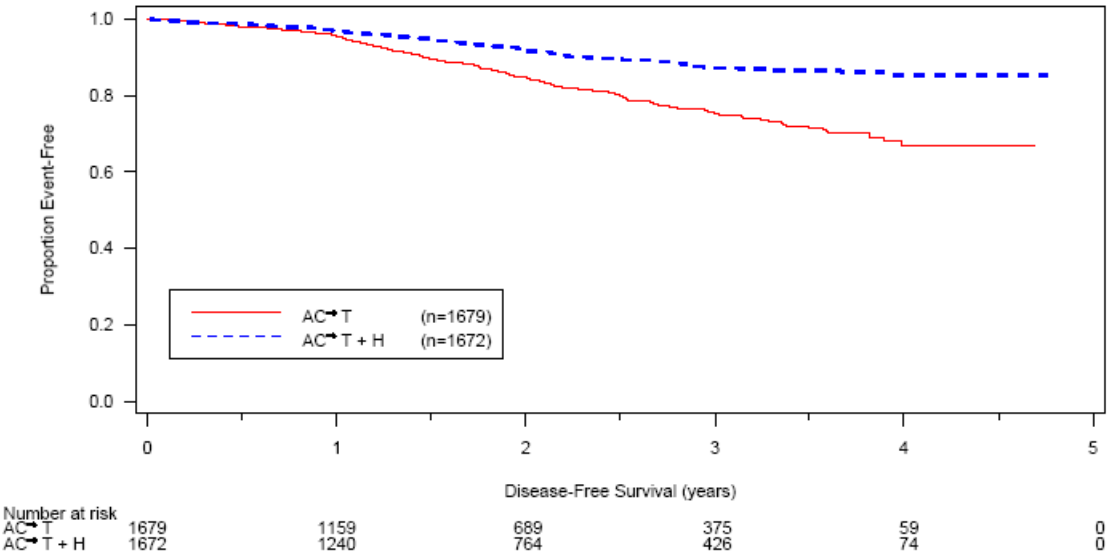


Table 14: DFS rate

	AC->T	AC->T+H
DFS rate at 3 years	75.4% (95% CI: 72.4%, 78.3%)	87.2% (95% CI: 85.0%, 89.4%)
DFS rate at 4 years	67.1% (95% CI: 62.5%, 71.7%)	85.3% (95% CI: 82.4%, 88.3%)

Interim analysis of combined data showed significantly decreased hazard ratio in favour of the trastuzumab group. There is an increase in disease free survival in the trastuzumab group. At 3 years this translates to an absolute benefit with respect to disease free survival rate of 11.8% (95% CI:8.7%, 15.0%), at 4 years of 18.2% (95% CI: 14.4%, 22.1%). Subgroup analysis is shown in the table.

Baseline characteristic	N	Hazard Ratio	95% CI
Age at randomisation			
<=50 yrs	1848	0.49	(0.37, 0.65)
>50 yrs	1503	0.45	(0.33, 0.61)
Number of positive nodes			
0	190	0.58	(0.0.5, 6.39)
1-3	1780	0.43	(0.31,0.61)
4-9	907	0.51	(0.35, 0.75)
>=10	467	0.48	(0.33, 0.77)
Hormone receptor status			
ER+ and/or PR+	1861	0.44	(0.32, 0.60)
ER- and PR-	1474	0.5	(0.38, 0.66)
Pathologic tumor size			
<=2 cm	1311	0.43	(0.28, 0.65)
2-4 cm	1517	0.48	(0.35, 0.64)
>4 cm	488	0.46	(0.30, 0.70)
Tumor Grade			
Low	64	0.20	(0.02, 1.79)
Intermediate	924	0.37	(0.23, 0.60)
High	22998	0.51	(0.40, 0.64)
Surgery/radiation			
Lumpectomy+radiation	1050	0.46	(0.30, 0.69)
Mastectomy, no radiation	699	0.47	(0.30, 0.76)
Mastectomy+radiation	1122	0.44	(0.32, 0.60)

Fig 8: Kaplan Meier Analysis of the B31 study population is shown in the following figure

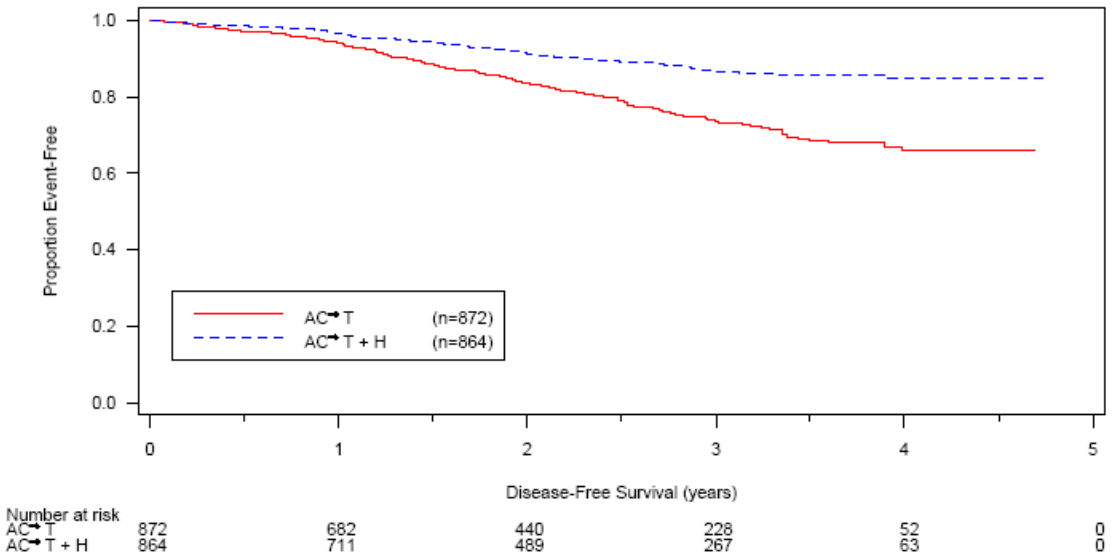


Fig 9: Kaplan Meier Analysis of the N9831 study population is shown in the following figure

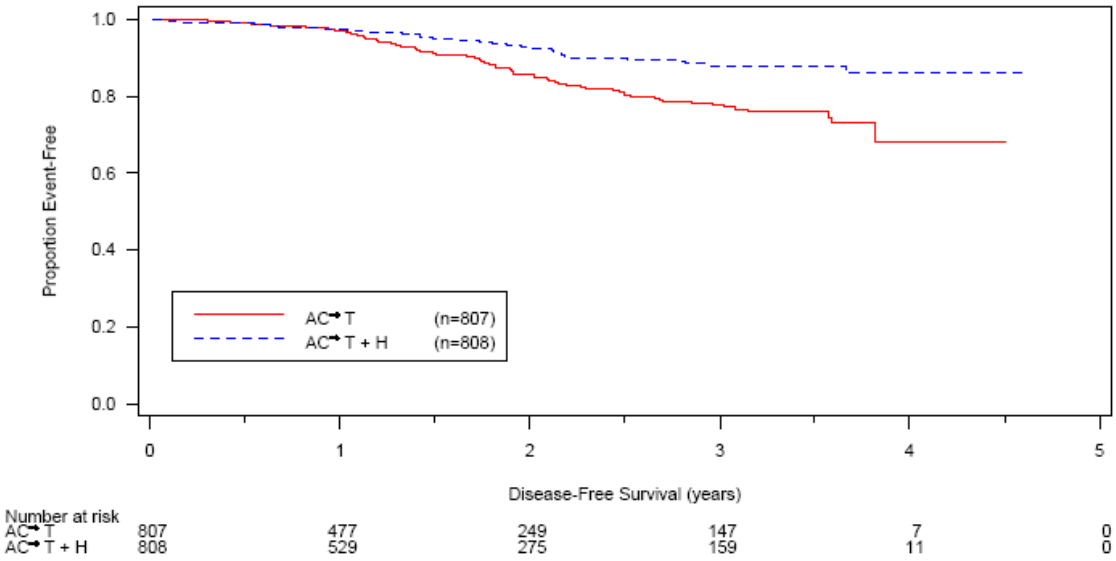


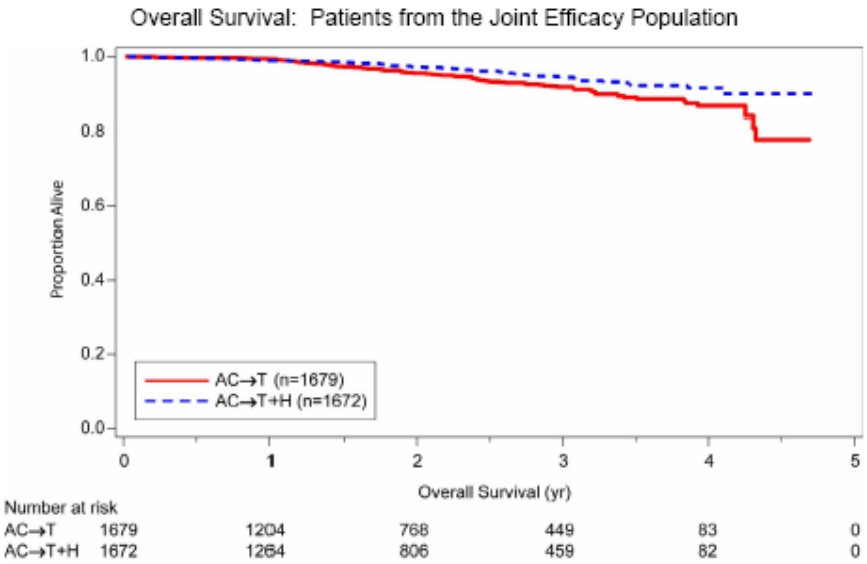
Table 15: **Summary of the secondary endpoint overall survival (Joint efficacy population) is shown in the following table**

	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 = Trastuzumab; 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.

Fig 10: Kaplan-Meier analysis of overall survival



Update of Efficacy results of the HERA trial

The MAH provided an update of DFS, OS for the 1-year Herceptin arm vs observation at 2years follow-up, while the procedure for this variation was ongoing.

Summary of Disease-Free Survival

	Observation N=1698	1-year Herceptin N=1703	
Number of patients with event	321 (18.9%)	218 (12.8%)	
2 year DFS Rate	78.0%	86.1%	
95% CI for 2 year DFS Rate[2]	(76%, 80%)	(84%, 88%)	
Range of DFS time (months)[3]	0.00, 48.13	0.00, 48.95	
Log-rank statistic (vs. observation)	35		
P-Value vs observation (log-rank test)			<.0001
Hazard Ratio vs observation	0.60		
95% CI for hazard ratio	(0.50, 0.71)		

[2] Kaplan-Meier estimates
[3] Including censored observations

Summary of Overall Survival

	Observation N=1698	1-year Herceptin N=1703
Number of patients with event	90 (5.3%)	59 (3.5%)
2 year OS Rate	93.6%	96.9%
95% CI for 2 year OR Rate[2]	(92%, 95%)	(96%, 98%)
Range of OS time (months)[3]	0.00, 48.13	0.00, 48.95
Log-rank statistic (vs. observation)	9.935	
P-Value vs observation (log-rank test)	0.0016	
Hazard Ratio vs observation	0.59	
95% CI for hazard ratio	(0.43, 0.82)	

[2] Kaplan-Meier estimates
[3] Including censored observations

Discussion on Clinical Efficacy

The MAH has provided the results from one pivotal study (HERA) and two supportive studies (B13 and N9831) for the evaluation of safety and efficacy of trastuzumab for the adjuvant treatment of HER2-positive, early breast cancer. The conduct of these studies is acceptable and no deviations from GCP are apparent.

In these trials the effect of chemotherapy followed by a one year treatment with trastuzumab on disease recurrence and overall survival was examined. While HERA allowed a spectrum of currently used adjuvant chemotherapy protocols, B31 and N9831 had a defined chemotherapy protocol consisting of cyclophosphamide, doxorubicin and paclitaxel. However, most patients in the HERA trial had received anthracyclines which is in line with current recommendations.

For the HERA trial the MAH has chosen a new posology, the loading dose has been increased from 4 mg/kg to 8 mg/kg and the maintenance dose from 2 mg/kg to 4 mg/kg, schedule has been changed from once weekly to once every three weeks. Both supportive studies have been performed using the approved posology. Efficacy data comparing both posologies directly are not available but the effect size in pivotal study and supportive studies is comparable.

Primary objective in the HERA trial and in the joint analysis of the supportive studies was demonstration of efficacy as determined by disease-free survival. Primary endpoint was met in both analyses and a significantly reduced hazard ratio in favour of trastuzumab treatment was demonstrated (log-rank $p<0.0001$). The hazard ratio of disease free survival in the HERA study was 0.54 (95% confidence interval 0.44-0.67). The 2-year disease-free survival rate was 78.2% in the observation group and 85.8% in the trastuzumab group. The hazard ratio of disease free survival in the joint analysis of B-31 and N9831 study was 0.48 (95% confidence interval 0.39-0.59). The 3-year disease-free survival rate was 75.4% (95% CI: 72.4%, 78.3%) in the observation group and 87.2% (95% CI: 85.0%, 89.4%) in the trastuzumab group.

There was no statistically significant effect on overall survival in the HERA trial yet, while the joint analysis of B-31 and N9831 showed a significantly reduced hazard ratio of 0.67 (95% CI 0.48-0.92) in favour of the trastuzumab treatment arm. Overall survival is significantly increased in the trastuzumab group although absolute benefit (difference in 4 year overall survival rate 4.8%, 95% CI 1.4-8.2) is considerably lower than for disease free survival.

Efficacy was demonstrated in all clinically relevant subgroups, there was no indication that certain subgroups do not have a benefit from treatment. External validity for efficacy is considered to be high, however, as discussed in the safety assessment in detail there is concern that inclusion and exclusion criteria define a population with a considerably lower cardiac risk compared to patients that will be treated outside of strictly controlled trials.

Current data allow evaluating efficacy of one-year treatment only; data from the two year treatment arm have not been submitted.

In conclusion trastuzumab is effective in the adjuvant treatment of HER2-positive breast cancer if given after adjuvant or neo-adjuvant chemotherapy and radiotherapy if appropriate. Efficacy has not been demonstrated in node-negative disease with a tumour-size of less than or equal to 1 cm, which is generally regarded as a low risk group for recurrence and thus was not included in the trial.

Clinical safety

Analyses presented in this report focus on the comparison of efficacy and safety of the 1 year trastuzumab arm versus observation only arm based on a protocol-specified interim analysis of the data performed after half of the required (951) events of disease free survival were recorded on the database (clinical cut-off March 29th 2005).

Secondary objectives of the trial with regard to the safety were

- To evaluate the safety and tolerability of trastuzumab.

- To compare the incidence of cardiac dysfunction.

Patients entering the HERA trial were required to have an LVEF of ≥ 55% at baseline. Cardiac monitoring was performed at weeks 13 and 25 and every 3 months thereafter and comprised ECG, echocardiogram or MUGA scan, clinical signs and symptoms of cardiac failure and completion of a cardiac questionnaire by the investigator. Trastuzumab treatment was discontinued in any patient who developed clinical signs and symptoms of congestive heart failure. In addition, an algorithm was provided for the discontinuation of trastuzumab in individual patients based on interval LVEF assessments, as described earlier (Figure 2).

Primary and secondary cardiac endpoints were defined and used in three pre-defined interim analyses of cardiac safety, after 300, 600 and 900 patients had completed 6 months from randomization. A significant LVEF drop was defined as an absolute decrease of at least 10 points below the baseline measurement and to below 50%.

Primary Cardiac Endpoint

The occurrence in any patient at any time after randomization, but prior to the start of any new therapy for recurrent disease of any of the following:

- Symptomatic congestive heart failure of NYHA class III or IV (confirmed by a cardiologist) and a drop in LVEF of at least 10 EF points from baseline and to below 50%.
- Cardiac death defined as either:
  - Definite cardiac death: due to CHF, myocardial infarction or documented primary arrhythmia
  - Probable cardiac death: sudden unexpected death within 24 hrs of a definite or probable cardiac event (syncope, cardiac arrest, chest pain, infarction, arrhythmia etc.) without documented aetiology.

All primary cardiac endpoints, as defined above, were to be reported as serious adverse events (SAEs) irrespective of treatment allocation.

Secondary Cardiac Endpoint

A secondary cardiac endpoint could occur any time after randomization, but prior to the start of any new therapy for recurrent disease, and was defined as:

- A significant asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) drop in LVEF identified by MUGA scan or echocardiogram, unless the following LVEF assessment indicated a return to levels which did not meet the definition of a significant LVEF drop. NYHA class II CHF had to be confirmed by a cardiologist. A repeat assessment had to be performed approximately 3 weeks after the first documented LVEF drop. If such a repeat assessment or confirmation of NYHA class II CHF by a cardiologist was not available, the Cardiac Advisory Board (CAB) was to review the case to determine acceptability as a secondary cardiac endpoint. A *significant* LVEF drop was defined as an absolute decrease of at least 10 EF points below baseline and to below 50%.

Events such as acute coronary syndrome, acute myocardial infarction or severe rhythm disturbances requiring treatment were not considered as primary or secondary cardiac endpoints unless fatal. These events were, however, reported as AEs or SAEs, as applicable.

The analyses were performed by an independent statistician and presented to the IDMC, who would have recommended stopping or modifying the trial if an absolute difference of more than 4% in the incidence of primary cardiac endpoints was observed between the trastuzumab and observation groups. The IDMC recommended that the study continued as planned after each interim analysis, implying that the difference remained below 4%.

Patient exposure

Overview of the 4 large studies of trastuzumab in early breast cancer:

Table 16:

Study ID	Location	Trial Treatments	N in Analyses
HERA (BIG01-01/ BO16348)	Global ex-US	Approved Chemotherapy → Observation only	1693
		Approved Chemotherapy → Herceptin q3w x for 1 year	1693
		Approved Chemotherapy → Herceptin q3w x for 2 years	N/A
NSABP B-31	US	1. AC q3w x 4 → Paclitaxel q3w x 4*	872
		2. AC q3w x 4 → Paclitaxel q3w x 4* + H qw x 52	864
NCCTG N9831	US	A. AC q3w x 4 → Paclitaxel qw x 12	807
		B. AC q3w x 4 → Paclitaxel qw x 12 → H qw x 52	N/A
		C. AC q3w x 4 → Paclitaxel qw x 12 + H qw x 12 → H qw x 40	808
BCIRG 006	Global	AC q3w x 4 → Docetaxel q3w x 4	1073
		AC q3w x 4 → Docetaxel q3w x 4 + H for 1 year (qw during chemo, then q3w)	1074
		Docetaxel + Carboplatin q3w x 6 + H for 1 year (qw during chemo, then q3w)	1075

N = number of patients
N/A = not available
AC = anthracycline plus cyclophosphamide
H = Herceptin,
* Beginning in May 2003, paclitaxel could alternatively be given weekly for 12 weeks at the discretion of the investigator.

Adverse events

A total of 46% (792/1708) of patients in the observation arm and 70% (1179/1678) of patients in the trastuzumab arm experienced at least one adverse event during the study. A higher percentage of patients in the trastuzumab treatment arm (8.6%; 145/1678) compared with the observation arm (4.6%; 79/1708) experienced at least one grade III adverse event. The most frequent of these were hypertension, hot flush, vomiting, headache, diarrhoea and congestive cardiac failure. Ten observation arm patients and 13 trastuzumab arm patients experienced a Grade IV adverse event. Two grade IV adverse events (cardiac failure, congestive cardiac failure) were considered related to trastuzumab treatment. In both cases, treatment with trastuzumab was discontinued and the events resolved without sequelae.

Arthralgia, headache, hot flush, nasopharyngitis and fatigue were each reported by > 10% of all patients. Not unexpectedly, adverse events occurring with a higher frequency in the trastuzumab arm than the observation arm included headache, nasopharyngitis, fatigue, diarrhoea, nausea, pyrexia and chills, all of which are commonly associated with trastuzumab infusions.

The vast majority of adverse events were classified as NCI-CTC grade 1 or 2 (2130/2251 events in the observation arm and 5046/5248 events in the trastuzumab arm). A total of 102 grade 3 adverse events

were reported by 79 patients (4.6%) in the observation arm, compared with 183 grade 3 adverse events in 145 patients (8.6%) recorded during treatment with trastuzumab. Higher frequencies of grade 3 infections (including influenza and acute bronchitis), general disorders and administration site conditions (most commonly fatigue and chills) and gastrointestinal disorders (mainly diarrhoea and vomiting) were reported by patients in the trastuzumab group than in the observation arm.

Grade 4 (life-threatening) adverse events were reported by 10 patients (12 events) in the observation arm and 13 patients (14 events) in the trastuzumab arm, with no event occurring in more than one patient within each group.

During the study, 10 observation arm patients and 13 trastuzumab arm patients reported at least one adverse event that was considered life-threatening (grade IV) in intensity. No single grade IV adverse event occurred in more than one patient in each treatment arm. The 12 grade IV events reported in 10 patients from the observation arm were pain, paresis, hypotension, pulmonary embolism, cardiac failure, breast cancer, uterine cancer, breast cancer in situ, cervix carcinoma, pancreatic carcinoma, papillary thyroid carcinoma and leukopenia. The 14 grade IV events reported in 13 patients from the trastuzumab arm were central line infection, appendicitis, catheter related complication, sudden death, cerebrovascular accident, cerebral ischemia, lymphoedema, deep vein thrombosis, pulmonary hypertension, depression, congestive cardiac failure, cardiac failure, breast cancer and malignant melanoma. Two grade IV adverse events were considered related to trastuzumab treatment: Patient 31412/5416, a 53-year-old patient reported grade IV cardiac failure on day 85 of trastuzumab treatment which was reported as a serious adverse event. The cardiac failure was assessed as related to trastuzumab treatment. Patient 31289/1650, a 40-year-old patient reported grade IV congestive cardiac failure on day 155 of trastuzumab treatment. The event was reported as a serious adverse event and assessed as related to trastuzumab treatment. In both cases, treatment with trastuzumab was discontinued and the events resolved without sequelae.

A total of 1276 adverse events reported by 600 patients in the trastuzumab arm were considered to be related to treatment. The most common treatment-related adverse events included known trastuzumab infusion reactions, such as chills, pyrexia and nausea, and known cardiac-related events, predominantly decreased ejection fraction and cardiac failure.

Cardiac Safety

Primary cardiac endpoints (symptomatic CHF of NYHA class III or IV **and** a drop in LVEF to below 50% **and** at least 10 points below baseline, or cardiac death) were recorded by 1 patient (0.1%) in the observation arm (cardiac failure leading to death) and 10 patients (0.6%) in the trastuzumab arm (CHF of NYHA class III [8 patients] or class IV [2 patients], no deaths). Secondary cardiac endpoints (asymptomatic-NYHA I or mildly symptomatic-NYHA II **and** decreases in LVEF of at least 10% of baseline value **and** below 50%) were recorded by 9 patients (0.5%) in the observation arm and 51 patients (3.0%) in the trastuzumab arm.

Summary of cardiac endpoints in the HERA study:

Table 17:

	Observation Only N=1708 n (%)	Herceptin 1 year N=1678 n (%)
Primary Cardiac Endpoint		
Incidence of Primary Cardiac Endpoint	1 (0.1)	10 (0.6)
Exact 95% CI for Incidence[1]	(0.00, 0.33)	(0.29, 1.09)
Difference in Incidence	0.537	
95% CI for the difference[2]	(0.12, 0.95)	
Secondary Cardiac Endpoint		
Incidence of Secondary Cardiac Endpoint[1]	9 (0.5)	51 (3.0)
Exact 95% CI for Incidence	(0.24, 1.00)	(2.27, 3.98)
Difference in Incidence	3	
95% CI for the difference[2]	(1.6, 3.4)	

[1] Exact 95% Confidence Interval for one sample binomial using Pearson-Clopper method
[2] Approximate 95% Confidence Interval for difference of two rates using Hauck-Anderson correction.
Source: stscardev1_3001, stscardev2a_3001 (HERA study report [7504])

Of the 10 trastuzumab patients with a primary cardiac endpoint, 8 were asymptomatic at the last scheduled assessment on the database (as per 15th December 2005). Six of the ten patients had a recovery of the LVEF to at least 55% at a median of 121 days (36-409 days) from the initial LVEF drop. Nine of the 10 trastuzumab patients received treatment for congestive heart failure.
Of the 51 trastuzumab patients with a secondary cardiac endpoint, 45 (88%) were asymptomatic at the last scheduled assessment on the database (as per 15th December 2005). Thirty-five of the 51 patients (69%) had a recovery of the LVEF to at least 55% at a median of 189 days (13-831 days) from the initial LVEF drop. Twelve of the 51 trastuzumab patients (24%) have been reported as having received treatment for congestive heart failure.

All observation patients were asymptomatic at the last scheduled assessment on the database (as per 15th December 2005). Six of the 9 observation patients exhibited a recovery of the LVEF to at least 55% at a median of 204 days (139-274 days) from the initial LVEF drop. One of the 9 observation patients have been reported as having received treatment for congestive heart failure.

As expected, patients treated with trastuzumab had a higher incidence of asymptomatic cardiac dysfunction, defined as at least one drop in LVEF of ≥ 10 EF points from baseline and to < 50% (7.4% of patients in the 1 year trastuzumab arm compared with 2.3% of patients in the observation arm). Approximately 50% of trastuzumab patients who had an initial significant LVEF drop were later confirmed by a subsequent assessment to have a primary or secondary cardiac endpoint. The clinical significance of single, unconfirmed LVEF drops is unclear.

The majority of patients in the study (94% in each treatment arm) had received a previous treatment regimen containing anthracyclines. All 11 patients experiencing a primary cardiac endpoint had received previous anthracycline therapy and all but 2 of the 60 patients experiencing a secondary cardiac endpoint (both of whom were receiving trastuzumab) had received previous anthracycline therapy.

The Applicant stated that the results regarding cardiac event compare favourably with rates of cardiac events from a pooled analysis of studies in patients with MBC, in which 2.7% of patients treated with trastuzumab experienced serious cardiac events and 10.2% of trastuzumab patients experienced a decrease in LVEF of ≥ 10% to below 50% .

In the majority of cases, LVEF values stabilized or returned towards baseline following cessation of trastuzumab treatment.

It is well known from the MBC setting that the risk of cardiotoxicity is higher in patients who receive anthracycline chemotherapy. In the HERA trial, 94% of all patients had previously been treated with

chemotherapy regimens which included epirubicine or doxorubicine. Each of the 10 trastuzumab patients experiencing primary cardiac endpoints (severe CHF, NYHA class III or IV), and all but two of the patients who recorded secondary cardiac endpoints (NYHA class I or II) had received anthracycline treatment before entering the study.

Slightly higher rates of cardiac disorders and LVEF drops were seen in the other large EBC trials. Assessment of cardiac dysfunction in trial B-31 showed that the cumulative incidence of cardiac events (CHF of NYHA class III or IV, or cardiac death) was 4.1% (31/850) for patients treated with trastuzumab compared with 0.8% (5/814) for patients in the control group. 14% of patients discontinued Trastuzumab therapy as a result of asymptomatic decreases in LVEF and 4% discontinued because of symptomatic cardiotoxicity. As seen in MBC patients, the trastuzumab-related cardiac dysfunction in this trial was generally reversible on cessation of treatment. The higher incidence in this study may be related to the concomitant treatment of trastuzumab with paclitaxel. Recent data from the N9831 trial suggests that lower rates of severe cardiac disorder are seen when trastuzumab treatment is administered after completion of taxane therapy. The Applicant stated that the temporal proximity of trastuzumab treatment to AC chemotherapy may play a bigger role, based on results from the BCIRG-006 trial where symptomatic cardiac events were recorded by 2.3% of patients receiving trastuzumab concomitantly with docetaxel following AC therapy compared to 1.2% of patients in both the control group (AC→T) and the group of patients who received Trastuzumab in combination with docetaxel and carboplatin. LVEF decreases (> 15% and below lower limit of normal) occurred in 2.4%, 0.6% and 0.4% of patients, respectively, in the AC→TH, AC→T and TCH groups.

The Applicant stated that the rates of severe CHF seen in early breast cancer are lower than those observed in the metastatic setting. At the point of data cut-off in the HERA trial, rates of CHF, LVEF decreases and other cardiac disorders were lower than predicted from historical data, however, the duration of follow-up is short (median 12 months) and the possibility that the rates may rise over time cannot be excluded. The current SmPC provides clear information on the risks of cardiac dysfunction associated with trastuzumab therapy, particularly following anthracycline-containing chemotherapy. The SmPC also outlines recommended cardiac assessments prior to prescribing trastuzumab, and provides discontinuation criteria. The same precautions should be followed when considering treatment in patients with early breast cancer.

LVEF changes from baseline

At baseline, the median LVEF value was 64% in both treatment arms. The percentage of patients with significant LVEF drops at each time point was greater in the 1 year trastuzumab arm than in the observation arm. Decreases in LVEF of ≥ 10% were recorded at some point during the study by 25% (394/1600) of patients in the trastuzumab arm compared with 14% (213/1545) of patients in the observation arm. Significant LVEF drops (i.e. LVEF value < 50% and a decrease of > 10%) were recorded on at least one occasion during the study by 7.4% (118/1600) of patients treated with trastuzumab compared with 2.3% (35/1545) of patients in the observation arm. Sixty-one of the 118 trastuzumab patients who had an initial significant LVEF drop were later confirmed by a subsequent assessment to have either a primary (10 patients) or secondary (51 patients) cardiac endpoint.

Summary of Change from Baseline to Worst LVEF Value (Safety Population)

Table 18:

	Observation Only N=1708	Herceptin 1 Year N=1678
Overall (worst value)		
n	1545	1600
Increase or no change	516 (33.4%)	323 (20.2%)
Decrease < 10%	816 (52.8%)	883 (55.2%)
Decrease ≥ 10%	213 (13.8%)	394 (24.6%)
LVEF < 50%	49 (3.2%)	144 (9.0%)
LVEF < 50% and decrease ≥ 10% (significant LVEF drop)	35 (2.3%)	118 (7.4%)

derived from output 'stslvef_3001'

61 of the 118 trastuzumab patients who had an initial significant LVEF drop were later confirmed by a subsequent assessment to have a primary or secondary cardiac endpoint.

Infusion Reactions

Common adverse events in patients treated with trastuzumab included those usually associated with infusions, namely pyrexia, chills, headache and nausea. The majority of these events were of mild or moderate intensity (NCI-CTC grade 1 or 2), short-lasting (app. 2 days) and resolved without sequelae. There was no evidence of an increase in the incidence or severity of infusion-associated adverse events associated with the higher doses (6 mg/kg) used in the three-weekly regimen compared with the approved weekly dose of 2 mg/kg. Serious infusion-associated adverse events were reported by only eight patients in the study and resulted in the discontinuation of trastuzumab treatment in three of these patients.

Serious adverse events and deaths

At the time of data cut-off, serious adverse events had been reported for 5% (92/1708) of patients in the observation arm compared with 8% (134/1678) of patients in the 1 year trastuzumab arm. Serious infections and infestations were reported by 36 (2%) patients in the trastuzumab arm compared with 16 (< 1%) control patients, cardiac disorders were reported by 22 trastuzumab patients (1%) and 4 (< 1%) observation arm patients and general disorders and administration site conditions were reported by 13 (< 1%) trastuzumab arm patients compared with 2 (< 1%) observation arm patients.

The most common, treatment-related serious adverse event was cardiac failure, reported by 11 trastuzumab patients (preferred terms 'congestive cardiac failure' [7 patients] and 'cardiac failure'[4 patients]) vs. no observation patients. In total, 30 patients in the Trastuzumab group recorded 38 serious adverse events that were considered to be related to treatment, most commonly congestive cardiac failure/cardiac failure (11 patients), chills (4 patients), pyrexia (3 patients) and hypotension (2 patients).

After congestive cardiac failure, the next most frequently reported serious adverse events were erysipelas (reported by 7 trastuzumab patients and 1 observation patient), central line infection (6 trastuzumab patients and 1 observation patient), breast fibrosis (5 trastuzumab patients and 1 observation patient), cellulitis and deep vein thrombosis (each reported by 4 trastuzumab patients).

Ninety-seven patients were withdrawn from the study as a result of an adverse event. In 88 of these patients, the adverse event which led to withdrawal was considered to be related to trastuzumab treatment. "Cardiac disorders" (SOC) accounted for discontinuation in 44 patients (3%), of whom 30 experienced congestive cardiac failure/cardiac failure. A further 23 patients had trastuzumab discontinued due to ejection fraction decrease (recorded within the SOC "Investigations"). Cardiac disorder and chills were each recorded as the reason for discontinuation by three patients.

At the time of the interim efficacy analysis, two patients in the observation arm and 4 patients in the trastuzumab arm had died as a result of an adverse event. In the observation arm, patient 31307/6503 committed suicide on study day 146 and patient 31508/2771 died on day 205 due to cardiac failure which the investigator considered to be probably a result of pulmonary embolism. Deaths in the trastuzumab arm resulted from cerebral haemorrhage (study day 115, patient 31216/7913), cerebrovascular accident (study day 289, patient 31218/3621), sudden death (study day 290, patient 31351/7392) and appendicitis (study day 366, patient 31562/4095). A further patient in the trastuzumab arm died as a result of a road accident, which was not reported as an AE.

In addition, disease progression of the underlying breast cancer accounted for 38 deaths in the observation arm and 26 deaths in the Trastuzumab arm.

In the B-31 and N9831 trials, some rare cases of interstitial pneumonitis were reported that appeared to be related to trastuzumab therapy. Four patients treated with trastuzumab in trial B-31 had interstitial pneumonitis, one of whom died. In N9831, five patients in the trastuzumab arm had grade 3+ pneumonitis or pulmonary infiltrates, one of whom died. These occurred during or shortly after the paclitaxel phase of treatment, however, the relationship to paclitaxel treatment is unclear. In the HERA trial, one patient in the trastuzumab group recorded pneumonitis during the study. The event was considered unrelated to treatment by the investigator, was of NCI-CTC grade 2 and resolved without sequelae following appropriate treatment.

Laboratory findings

During the study the majority of patients in either study arm did not exhibit a shift from their baseline laboratory test parameter values or exhibited a shift of 2 grades or less between baseline and their worst test value. Fewer patients in the trastuzumab 1 year arm experienced a shift of 3 or 4 grades from baseline than in the observation arm.

A total of 31 observation arm patients and 21 patients in the 1 year trastuzumab arm experienced a 3-grade worsening) from baseline in one or more laboratory test parameter values (40 events and 24 events, respectively). Twenty-four observation arm patients and 16 trastuzumab arm patients experienced a 4-grade worsening in one or more laboratory test parameters (30 events and 17 events, respectively). There was no difference between the treatment arms with respect to the type of 3grade or 4-grade shifts from baseline.

Risk Management Plan

The applicant has submitted a risk management plan in accordance with the EC directive EC/27/2004. The plan details the steps to be taken post marketing authorisation in order to minimise the risks associated with the use of this agent.

The submitted EU-RMP will be revised in accordance with CHMP comments and will be resubmitted by June 2006.

In view of the likelihood that cardiac failure will occur at higher rates in ordinary practice than in the HERA study, proposals for an observational study should be included. The RMP should incorporate a set of guidelines to " initiate and monitor cardiac function/dysfunction associated with Herceptin use" in early breast cancer.

Risk Minimisation

On the basis of the safety profile detailed above, it is considered that the major identified risk for trastuzumab is of cardiotoxicity. In keeping with current regulatory guidelines, and in order to maximise the benefit/ risk ratio in the adjuvant setting this section, Roche proposes a risk minimisation plan.

The MAH amended the trastuzumab label, as per the HERA data, to emphasise the current warning regarding cardio toxicity. In addition to good pharmacovigilance practice, the following measures will be implemented

- A guided questionnaire will be sent as part of good follow-up practice for all serious adverse events of cardiotoxicity received by the MAH.
- A workshop is organised to design guidance for physicians.
- A manuscript of the workshop proceedings will be published and distributed via the sales force.
- In addition, the MAH is sponsoring a scientific project and clinical trials investigating mechanism of cardiac toxicity in relation to trastuzumab as well as further clinical trials in which cardiotoxicity is actively addressed.

Discussion on clinical safety

Cardiotoxicity is a known risk of treatment with trastuzumab and described in the SmPC in the metastatic setting. The current SPC states that all MBC candidates for treatment should undergo baseline cardiac assessment including history and physical examination, ECG, echocardiogram and/or MUGA scan, and a careful risk-benefit assessment conducted prior to starting treatment with trastuzumab. It is also recommended that cardiac function be monitored regularly (e.g. every three months) during treatment, and patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6-8 weeks). Discontinuation of treatment should be considered in patients who develop cardiac failure or who have a continued decrease in LVEF.

The major adverse event that could be a limiting factor for the use of Herceptin in breast cancer is the cardiac safety. Herceptin use in the metastatic breast cancer setting is associated with heart failure that varied in incidence depending up on the concomitant chemotherapy used. In the metastatic setting the incidence of cardiac dysfunction was ~7% when used as monotherapy, 28% combined with anthracyclines, and 11% when combined with paclitaxel. Use of broader criteria has led to newer events and redefinition of percentages.

In the "early breast cancer" setting, the HERA trial provides the first clues towards the incidence of cardiac dysfunction. The findings of other studies (B-31, N9831 and BCIRG-006), support the findings but in a slightly different context. In the B-31 and N9831 studies, Herceptin was used in conjuction with a taxane and are therefore not identical to the HERA trial. However, overall, the incidence of heart failure or cardiac dysfunction is lower in this setting than that seen earlier with the metastatic setting.

The incidence of cardiac dysfunction in the HERA trial should taken as a composite of the primary and secondary end points. The long-term effects of drop in LV ejection fraction in this subset of other wise healthy patients will need to be addressed carefully. The 'investigators' cardiac questionnaire' showed a higher incidence of cardiac symptoms and clinical findings, suggesting that the 0.6% heart failure incidence projected by the applicant is an underestimate. In this context, it is considered appropriate to raise questions to the applicant.

Safety data have been reported from patients who have been treated with trastuzumab in the three other large studies of trastuzumab in early breast cancer (B-31, N9831 and BCRIG-006). The joint efficacy analysis of trials B-31 and N9831 included 1672 women in the trastuzumab arm (weekly Trastuzumab treatment given concurrently with paclitaxel following 4 cycles of doxorubicin and cyclophosphamide). In study BCIRG 006, a total of 2147 patients were randomized to receive trastuzumab, either in combination with docetaxel following 4 cycles of doxorubicin and cyclophosphamide (N=1074), or with docetaxel and carboplatin (N=1075). In these trials trastuzumab had been administered in combination with taxane in the adjuvant setting after administration of an anthracycline containing chemotherapy regimen. The definition of cardiac events for confirmation by a committee for evaluation of cardiac events were very strict, so that only 16 of 40 adverse events in the chemotherapy alone arm had been confirmed and only 43 of 133 events in the trastuzumab plus chemotherapy arm. The joint analyses demonstrated 2.0% of confirmed symptomatic cardiac events in the trastuzumab plus chemotherapy arm and 0.5% in the chemotherapy alone group. The rate of cardiac events determined by the cardiac review committee pooling the data of both studies was lower than that determined by the individual study committees of both studies. The worst case rate of symptomatic cardiac events was 0.7% in the chemotherapy alone arm and 3.2% in the Trastuzumab plus chemotherapy arm and this rate was nearly similar in the study where trastuzumab had been co-administered with taxanes of 0.7% in the arm without trastuzumab and 3.5% for the trastuzumab

containing regimen. In the trastuzumab plus chemotherapy arm, 3 patients died because of cardiac events and in the chemotherapy alone arm 2 patients died because of cardiac event

The primary and secondary cardiac endpoint defined by the MAH are very selected which may lead to an underestimation of cardiac toxicity of trastuzumab in EBC. In the US studies the definition of cardiac dysfunction differed from those in the HERA study (less exclusive). The cardiac dysfunction was described in two ways:; cardiac events and asymptomatic LVEF events.

It is stated that the majority of primary and secondary cardiac endpoints were recorded during the first 6 months post-randomization, which may suggest there is no increase in the risk of cardiac dysfunction with long term (1 year) treatment with trastuzumab. It remains to be seen whether a higher incidence of CHF will be observed with longer follow-up and following 2 years treatment with trastuzumab.

In the EBC setting all patients with risk factors for cardiotoxicity were excluded from study participation. In addition, the cumulative dose of AC was limited to certain thresholds. This precautionary measure might explain the difference between the results of cardiac toxicity in the MBC and EBC setting. The different definitions of cardiac toxicity should also be taken into account.

Infusion reactions associated with trastuzumab treatment are well characterized, generally mild in intensity and are manageable by interruption of the dose and/or appropriate medical care. As demonstrated in the HERA trial, patients who experience mild infusion reactions in the early treatment cycles usually go on to receive subsequent infusions without problem. There are no additional concerns relating to infusion-associated adverse events in early breast cancer patients.

Overall Conclusion and Benefit-risk assessment

The HERA trial has demonstrated an impressive level of efficacy for both primary and secondary end points that include disease free survival, recurrence free survival, and distant disease free survival within the limited median follow up of 1 year. The reduction in relative risk is of the order of ~45-50%, while the absolute risk reduction is ~5.4% for the primary end point. The hazard ratio of disease free survival in the HERA study was 0.54 (95% confidence interval 0.44-0.67, log-rank $p<0.0001$). No benefit in overall survival was seen yet but this may require further follow up as the number of events were few and the overall survival in early breast cancer with the current modalities of treatment exceeds 85%. The results are based on interim analysis only and the 2 year arm results are still awaited. The 2-year disease-free survival rate was 78.2% in the observation group and 85.8% in the trastuzumab group. The hazard ratio of disease free survival in the joint analysis of B-31 and N9831 study was 0.48 (95% confidence interval 0.39-0.59, log-rank $p<0.0001$). The 3-year disease-free survival rate was 75.4% in the observation group and 87.2% in the trastuzumab group. Efficacy results were consistent in clinically relevant subgroups.

There was no statistically significant effect on overall survival in the HERA trial, while the joint analysis of B-31 and N9831 showed a significantly reduced hazard ratio of 0.67 (95% CI 0.48-0.92) in favour of the trastuzumab treatment arm. Since all patients in the observation arms were offered active treatment evaluation of overall treatment benefit in terms of overall survival may become difficult.

Herceptin is a rather well-known medicinal product, currently licensed in the metastatic disease. The safety profile is characterised in this setting, and a major known safety issue is cardiotoxicity. Therefore, already at this stage the consequences as regards risk management and other measures are clear-cut and can be defined at this stage.

Herceptin infusion was associated with a number of adverse events greater than the observation arm, especially cardiac dysfunction. The combined incidence of primary and secondary end points should be taken as the level of cardiac dysfunction induced by herceptin and at 3.6% this is considerable in this relatively healthy female population. The added degree of asymptomatic LV dysfunction that may or may not be truly reversible should be considered together with the cardiac safety end points. Only further follow up will address this. Other adverse events with Herceptin are well known and manageable.

As the used inclusion/exclusion criteria and the strict case definition of cardiac toxicity might lead to an underestimation of cardiac risk of the target population, the SPC wording reflects the real risk of cardiac toxicity in EBC.

Finally, there is no information available on the long-term effects of treatment with trastuzumab. The patients treated in an adjuvant setting have a considerably longer live expectancy than patients treated in the metastatic setting. In the case of recurrence they will be faced with the additional, possibly cardiotoxic treatment. In addition other factors, e.g. relating to age and life-style may increase the cardiac risk unproportionally. Further, patients might in case of a recurrence again be candidates for Herceptin treatment (which would resemble the setting of the currently licensed indication). The re-exposure of Herceptin both as regards safety and efficacy is unknown, but could bear potential risks (immunogenicity, infusion reactions, reduced efficacy etc.). The long-term outcome of patients treated with trastuzumab should therefore examined in a postmarketing study.

The long-term impact of the new adjuvant treatment with Herceptin should be systematically studied. While there might be immediate benefit in terms of PFS, the long-term impact of treatment both in terms of safety and efficacy should be understood. While only hypothetically at the current stage of knowledge, it could turn out that patients relapsing following adjuvant treatment with Herceptin might not anymore be candidates for re-treatment with Herceptin (e.g. due to immunogenicity), negatively influencing prognosis. Further, cardiotoxicity could negatively impact on prognosis and long-term outcome. This needs to be studied adequately to better define the value of (neo-) adjuvant treatment with Herceptin.

In view of the outstanding efficacy seen in the interim analysis of the 1-year Herceptin arm of the HERA trial and the supportive studies and with cardiac safety considerations in mind the overall benefit-risk of Herceptin in the adjurant treatment of Breast Cancer patients overexpressing HER-2 is considered positive. Data from the interim analysis of the 2-year trastuzumab arm will be submitted when available.