17 November 2011
EMA/36190/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for Herceptin (trastuzumab) Procedure No.: EMEA/H/C/000278/II/57

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

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1. Scientific discussion

1.1. Introduction

Trastuzumab is currently approved in the EU for the treatment of:

Metastatic Breast Cancer (MBC)

- 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)
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.

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.

The MAH applied for an additional indication in early breast cancer in combination with neoadjuvant chemotherapy – as follows:

> *Herceptin is indicated for the treatment of patients with HER2-positive EBC in combination with neoadjuvant chemotherapy, followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) breast cancer or tumours > 2 cm in diameter.*

To support this claim, the MAH has submitted data from one pivotal study MO16432/NOAH.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006, the application included an EMA decision P/17/2008 on the granting of a class waiver.

1.2. Clinical Pharmacology aspects

No new information on clinical pharmacology is submitted with this application

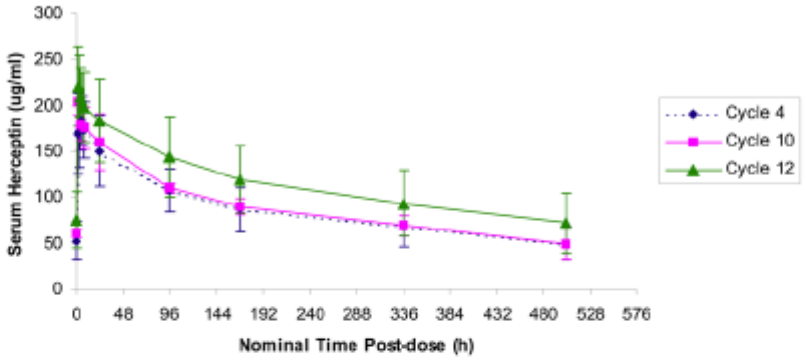
Pharmacokinetic/pharmacodynamic (PK/PD) data specific for trastuzumab in the neoadjuvant setting or data on the influence of shed-HER2 in this patient population is currently not available.

At the request of the CHMP the MAH provided an overview on available PK data of trastuzumab in EBC adjuvant patient populations (previously submitted in the context of variation applications and follow up measures).

The mean serum concentration-time profiles for trastuzumab administered every three weeks in EBC (study BO16348/HERA), and in MBC as monotherapy (study WO16229) or in combination with paclitaxel (study BO15935), are shown in Figure 1.

Figure 1 Mean (SD) Trastuzumab Serum Concentration-Time Profiles When Administered in Combination with Paclitaxel (a), as Monotherapy (b), and in the HERA Study in EBC (c)

a) Study BO15935 (cycle 4, n = 25; cycle 10, n = 3; cycle 12, n = 15)



b) Study WO16229 (cycle 6, n = 22)

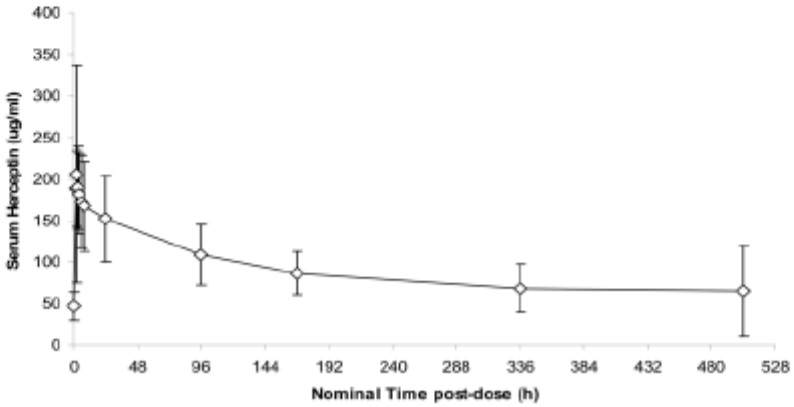
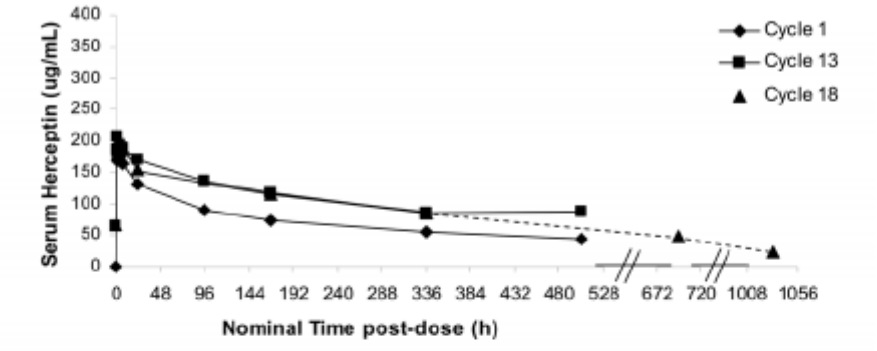


Figure 1 Mean (SD) Trastuzumab Serum Concentration-Time Profiles When Administered in Combination with Paclitaxel (a), as Monotherapy (b), and in the HERA Study in EBC (c) (cont.)

c) HERA Study (cycle 1, n = 37; cycle 13, n = 12; cycle 18, n = 8)



To compare the trough (C_{min}; pre-dose) serum concentrations of the EBC BO16348/HERA study to those in MBC, data from studies BO15935 and WO16229 in the MBC setting were combined. These data are presented in Table 1.

Table 1 Summary of Dose-Normalized* Trastuzumab Trough Serum Concentrations (µg/mL) by Cycle of Treatment in EBC and MBC Patients

Statistic	Cycle 2		Cycle 3		Cycle 13		Cycle 14	Cycle 18
	MBC	EBC	MBC	EBC	MBC	EBC	EBC	EBC
N	128	32	109	31	26	12	12	8
Mean	21.8	27.7	36.5	48.2	63.0	68.2	88.3	86.5
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
Median	20.8	25.7	35.3	44.4	61.3	60.3	67.4	83.4
Max	129	61	203	110	122	86.9	217	111
CV%	67	29	66	30	42	22	64	33
Geom Mean	16.9	26.9	25.4	46.6	55.7	61.9	77.4	83.6

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

* Trough data at Cycle 2 was normalized to take into account that the dose administered at Cycle 1 was 8 mg/kg versus the 6 mg/kg dose administered at every other cycle. Dose-normalized values were calculated by multiplying the mean concentration achieved at Cycle 2 by 0.75 (6/8).

In the EBC patient population, the geometric mean values for trastuzumab Cmin concentrations were higher than that for MBC; 59% higher in Cycle 2 and 84% in Cycle 3. In the EBC group, there were approximately 30 patients with concentration data, which showed less variability as noted by a CV% value of approximately 30%, in contrast to approximately 67% for the MBC patient population. Consistent with these findings, the values for the range of concentrations were also higher for the EBC patients as compared to the MBC patients, with the observed ranges in Cycle 3 of 28-110 and 0.18-203 µg/mL, for the EBC and MBC groups, respectively.

In addition to the Cmin evaluations described above, trastuzumab pharmacokinetic parameters have been derived using non-compartmental methods at selected cycles of treatment where rich PK sampling was obtained in patients administered trastuzumab on an every three weeks schedule in early breast cancer (study BO16348/HERA), and in metastatic breast cancer as monotherapy (study WO16229) or in combination with paclitaxel (study BO15935); these data are shown in Table 2.

Table 2 Mean (CV%) Pharmacokinetic Parameters Obtained by Non-compartmental Analysis for Trastuzumab Administered on a 3-Weekly Schedule

Study	N	C_{min} (µg/mL)	C_{max} (µg/mL)	T_{max} (h)	AUC_{last}[a] (mg.day/L)	$t_{½}$[b] (days)	Cl[c] (mL/h)
BO19535							
Cycle 4	25	50.1 (46)	196 (14)	4.4 (56)	1681 (25)	16.9 (41)	0.233 (23)
Cycle 10	3	66.0 (39)	203 (7)	1.7 (22)	1801 (10)	27.0 (22)	0.210 (24)
Cycle 12	15	72.3 (46)	237 (12)	2.7 (45)	2221 (35)	18.3 (44)	0.195 (57)
WO16229							
Cycle 6	22	46.3 (36)	221 (48)	3.5 (50)	1741 (32)	16.4 (42)	0.252 (30)
HERA							
Cycle 1	34-37[g]	27.7 (29)[d]	198 (19)	16.5 (500)[e]	1494 (21)	-	0.232 (23)
Cycle 3	31	48.2 (30)	-	-	-	-	-
Cycle 13	10-12[g]	63.2 (42)	216 (10)	45.1 (320)[f]	2255 (16)	-	0.169 (24)
Cycle 14	12	88.3 (64)	-	-	-	-	-
Cycle 18	8	66.5 (33)	210 (6)	3.0 (72)	2206 (18)	16.4 (25)	0.181 (21)

[a] AUC_{last} at cycle 1; AUC_{τ} at cycles 13 and 18 in the HERA study
[b] The half-life values quoted are considered an underestimate and should be interpreted with caution
[c] Cl_{ss} in cycles 13 and 18 in the HERA study
[d] Predose Cycle 2, dose-normalized to 8 mg/kg for comparison with later cycles
[e] Mean (%CV) of 2.9 (66) h with patient 6438 excluded
[f] Mean (%CV) of 3.5 (44) h with patient 5974 excluded
[g] Not all PK parameters were calculable in every patient

Since the full PK profiles in the three studies were measured at different cycles, to allow a comparison across studies, the steady-state clearance and AUCτ values obtained by non-compartmental analysis of Cycle 13 data in EBC (HERA study) were compared to simulated values using a population PK model derived from data which included three studies in metastatic breast cancer (BO15935, WO16229 and M77004) and one study in non-small cell lung cancer (BO15899)**.** In this comparison, the mean AUCτ and clearance at steady-state for every three weeks dosing of trastuzumab in patients with MBC, were 1793 mg.day/L and 0.226 L/day, compared to those obtained in EBC of 2255 mg.day/L and 0.181 L/day, an approximate 25% difference between the two patient populations. The predicted median Cmin steady-state estimates in MBC were estimated to be 47.3 µg/mL compared to 63.2 µg/mL at Cycle 13 in the EBC HERA study. In the population PK analysis in MBC, serum shed-HER2 has been shown to influence trastuzumab clearance; in the HERA study, the effect shed-HER2 on the PK was not available for assessment.

Altogether, with respect to predicted or measured exposure levels of trastuzumab during steady state the following order can be stated:

Table 1. PK parameters in EBC, MBC, Gastric cancer				
	MBC (+Paclitaxel)	EBC adjuvant	MBC (Mono)	AGC
Ctrough (µg/mL)	72.3	63.2	47.3	27.6
Cmax (µg/mL)	237	216	189	132
AUCtau,ss	2221	2255	1793	1213
(Shed antigen levels have not been measured in the HERA study)				

1.2.1. Discussion

The MAH has not provided pharmacokinetic/pharmacodynamic data of trastuzumab in the neoadjuvant treatment setting. In particular data on shed Ag levels and usual PK parameters (such as dose Cmin, Cmax, AUC, T1/2,..) would be of interest, however such data are currently not available.

Instead the MAH provided an overview on available PK data of trastuzumab in EBC and MBC adjuvant patient populations including full PK data of the HERA study. Interestingly, the comparison of all full

profile PK data in MBC and EBC confirms that exposure in EBC is 25% higher than in MBC patients in terms of steady state AUC and Ctrough, whereas steady state Cmax is merely affected. Data on Cmin values suggest a more consistent exposure in the EBC patient population above a target concentration of 20 µg/mL, in contrast to the MBC patient population. The higher Cmin values in the EBC patients are likely explained by the lack of known factors in the EBC patients which are present in the MBC patient, such as a higher number of metastatic sites or other factors which have been identified in population pharmacokinetic analyses to be associated with a higher drug clearance. It would be expected that in the neoadjuvant setting, trastuzumab would have similar pharmacokinetic behavior to that observed in the EBC/adjuvant setting, given that the tumor load of neoadjuvant patients is only small.

The difference between the populations is lower than might be expected from the difference in tumor load. On the other hand, the difference in tumor load is suggested to be a reason for the lower (30-50%) trastuzumab exposure in AGC versus MBC patients. This is not plausible.

Data indicate that when the EBC patient population in the study BO16348/HERA study is compared to the MBC patient population, the geometric mean ratios for the Cmin concentrations in the EBC patients are higher, less variable, and show a more consistent exposure above a minimum target serum concentration of 20 µg/mL. There is likely no difference in the PK of trastuzumab between the adjuvant and neo-adjuvant treatment setting since key factors known to influence clearance in the MBC patient population are absent.

The PK profile of trastuzumab in the neoadjuvant-adjuvant setting is being investigated in the ongoing HannaH study (BO22227). This data will be submitted in the context of the upcoming line extension (tentative filing date 2nd March 2012). The HannaH study will provide intra-patient trastuzumab PK data in the neoadjuvant as well as adjuvant setting. Data available will include rich sampling during cycles 8 (neoadjuvant) and adjuvant (cycle 13) of treatment, where Cmin, Cmax, AUC, T 1/2 and CL will be determined by non-compartmental analysis. In addition, Cmin and Cmax will be available at each cycle through to cycle 13.

1.2.2. Conclusions on clinical pharmacology

The MAH has not submitted new data on clinical pharmacology and this is acceptable given the extensive study of the pharmacology of trastuzumab over the years through a number of variation submissions and relevant follow-up measures.

An overview of PK data in EBC and MBC data indicate that when the EBC patient population in the study BO16348/HERA study is compared to the MBC patient population, the geometric mean ratios for the Cmin concentrations in the EBC patients are higher, less variable, and show a more consistent exposure above a minimum target serum concentration of 20 µg/mL. There is likely no difference in the PK of trastuzumab between the adjuvant and neo-adjuvant treatment setting since key factors known to influence clearance in the MBC patient population are absent.

Additional PK data aiming to complement the understanding of trastuzumab PK.in the EBC population will be generated in an ongoing study and will be filled in the context of a line extension for a subcutaneous formulation in March 2012.

1.3. Clinical Efficacy aspects

Neoadjuvant therapy has become a standard treatment option for many patients with newly diagnosed breast cancer and is given prior to surgery. Although originally developed for patients with large and/or inoperable tumours to enable definitive surgery to be performed, neoadjuvant therapy is also now used in patients with operable EBC to try to avoid a mastectomy and enable breast-conserving surgery (BCS) to take place. Neoadjuvant therapy is also indicated for patients with inflammatory breast cancer (IBC), a sub-type characterised by erythema and oedema (peau d'orange) of a third or more of the skin of the breast with a palpable border, and an aggressive clinical course. IBC is always considered stage T4 disease (T4d). Whether in patients with early, operable breast cancer, locally advanced breast cancer (LABC) or IBC, administration of systemic therapy before definitive surgery also has the potential advantages of treating systemic micrometastatic disease with minimal delay

after diagnosis and of enabling clinicians to detect and stop or change ineffective systemic therapy by directly observing the effects of treatment on the breast tumour.

The adverse prognostic significance of HER2-positivity is recognized by both European (St. Gallen Consensus Guidelines – 2007 & 2009) and US (National Comprehensive Cancer Network [NCCN] - 2010) guidelines. Both sets of guidelines justify neoadjuvant systemic chemotherapy in invasive breast cancer, primarily to enhance the possibility of breast-conservative surgery, and this includes trastuzumab in HER-2 positive disease. For example, the regimen recommended in NCCN guidelines is trastuzumab in combination first with paclitaxel then with CEF (cyclophosphamide, epirubicin, fluorouracil).

This assessment primarily focuses on the data provided in the Clinical Study Report (CSR) of the single pivotal trial MO16432/NOAH. The MAH has also submitted additional data from supportive trials as advised by the rapporteurs during pre-submission meetings.

GCP

The MAH confirms that the trials meet the ethical requirements of Directive 2001/20/EC. Local Institutional Review Boards reviewed and approved the protocol and the Informed Consent Forms. Study sites were audited according to a published NCI guideline.

1.3.1. Clinical trial MO16432/NOAH

The MO16432/NOAH study was conducted in 25 centres from 6 countries: Italy, Spain/Portugal, Germany/Austria, and Russia.

This study was conducted by the Michelangelo (Milan, Italy) and SOLTI (Madrid, Spain) collaborative groups and independent centres.

Patients were recruited between 2002 and 2005. In 2005, Roche Clinical Quality Assurance group conducted audits at 5 centres. Major finding(s) involving non-compliance with GCP were observed.

Between November 26, 2009 and September 2010, Roche performed a re-monitoring of the study with complete source data verification. Importantly, source data were no longer available for 6% of the patients. Three patients had to be excluded from the analysis due to major GCP violation (late protocol approval by the Ethics Committee and missing informed consent). A relatively high number of patients (59) required a change of the disease stage category as recorded at randomisation; 44 of these patients were from the largest Russian site (47296). During the Roche re-monitoring, it was discovered that, for these patients, the source data did not correspond to the disease stage used for stratification. In most of these patients, the disease stage was changed from IBC to either T4 non-inflammatory or any TN2. Additionally, hormone receptor status as recorded at randomisation was later changed for a total of 5 patients.

Clinical Study MO16432 was an international, open-label, phase III trial in women with newly diagnosed locally advanced breast cancer (LABC) or inflammatory breast cancer (IBC) defined as TNM stage T3N1 or T4 (skin or nipple invasion, peau d'orange, extension into chest wall or inflammatory carcinoma); any T plus N2 or N3; or any T plus involvement of ipsilateral supraclavicular nodes.

Patients with HER2-positive disease (immunohistochemistry [IHC] 3+ and/or HER2 amplification) were randomized to receive neoadjuvant trastuzumab plus neoadjuvant chemotherapy followed by adjuvant trastuzumab (HER2+TC group), or neoadjuvant chemotherapy alone (HER2+C group).

A parallel observational cohort of patients with HER2-negative disease was included in the study. Patients with HER2-negative disease (IHC 0 or 1+) were randomly allocated to a parallel observation group (HER2–C) in a ratio of 1:3 (on-study/offstudy). These patients received the same chemotherapy regimen as patients with HER2-positive disease, but without trastuzumab.

Objectives
The primary objective of study MO16432 was:

• To compare event-free survival (EFS) in patients with HER2-positive disease who received chemotherapy alone or chemotherapy plus trastuzumab.

The secondary objectives of study MO16432 were:

1. To compare the following in patients with HER2-positive disease who received chemotherapy alone or chemotherapy plus trastuzumab:
• Pathological complete response (pCR) rate
• Overall clinical response rate (ORR) including:
  – Complete response (CR) rate
  – Partial response (PR) rate
• Overall Survival (OS)
• Safety and tolerability
• Changes in left ventricular ejection fraction (LVEF)

2. To document the same efficacy (EFS, ORR, OS) and safety parameters (safety, tolerability and LVEF) in patients with HER2-negative disease who received the same chemotherapy regimen without trastuzumab.

3. To describe the biological characteristics of tumors that might predict tumor response.

Primary efficacy parameter

The primary efficacy variable was event-free survival (EFS). This was defined as the time between randomization and date of documented occurrence of an event, defined as disease recurrence or progression (local, regional, distant or contralateral), or death due to any cause. For patients with HER2-negative disease, 'randomization' was defined as the date of study registration.

If there was any tumor assessment prior to surgery satisfying the criteria for progressive disease, the patient was evaluated as having an event even if the investigator did not judge the patient as having progressed. For these cases, the date of progression was set to the date of the examination.

For patients who did not undergo surgery and thus were not free of breast cancer at any time in the study, only disease progression or death was considered as an event during follow-up.

All events up to and including the cut-off date of March 30, 2009 were included in the analysis irrespective of whether there was missing follow-up information for the patient prior to the event. Patients without event up to the cut-off date and with follow-up information after the cut-off date were censored at the cut-off date.

Secondary Efficacy Parameters

Secondary efficacy variables were as follows:

• Pathological Complete Response Rate
– Pathological complete response of the primary tumor (breast pathological complete response [bpCR]) was defined as the absence of any invasive cancer cell of the primary tumor at major surgery after neoadjuvant chemotherapy ± trastuzumab.

– Pathological complete response of the primary tumor and axillary lymph nodes (total pathological complete response [tpCR]): bpCR was associated with the presence or absence of positive axillary nodes at pathology.

• **Overall Clinical Response Rate**
During the study, response was assessed clinically, by mammogram and ultrasound after each of the chemotherapy phases of the treatment period (doxorubicin + paclitaxel, paclitaxel alone, CMF). For the overall clinical response assessment, only the findings from the clinical evaluation were used.

The response categories (complete response [CR], partial response [PR], stable disease [SD] and progressive disease [PD]) were calculated according to modified RECIST Criteria.

For assessing response in inflammatory carcinoma (T4d; ie, extent of breast edema or erythema), the NOAH Protocol Steering Committee defined the following criteria

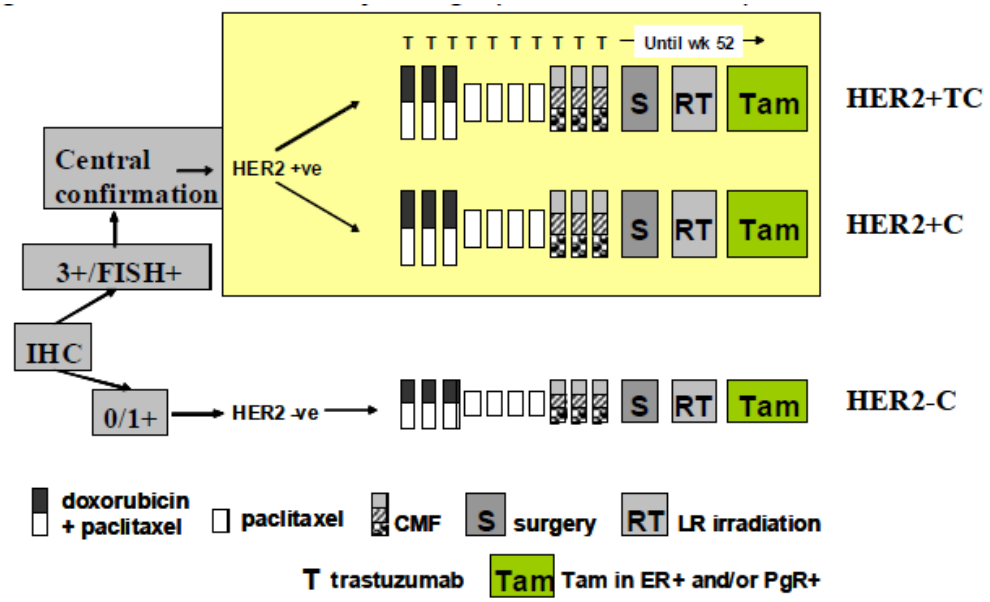
Parameter	CR	PR	SD	PD*
Edema	Complete resolution	Decrease or stable	Decrease or stable	Progression
Erythema	Complete resolution	Clear decrease	Stable	Progression

*PD was defined by the progression of any of the two signs

Overall response rate was defined as CR plus PR.

• Overall Survival
Overall survival (OS) was defined as the time from the date of randomization to the date of death due to any cause. If patients had not been reported as having died at the time of the cut-off date of March 30, 2009, they were censored at the last date of `last tumor measurement`, 'last follow-up' or 'last drug intake'.

MO16432 (NOAH) Study Design



For brevity, the three treatment arms in the study have been abbreviated in subsequent parts of this document, as follows:

- **HER2+TC:** Patients with HER2-positive disease randomized to treatment with trastuzumab plus chemotherapy
- **HER2+C:** Patients with HER2-positive disease randomized to treatment with chemotherapy alone
- **HER2-C:** Parallel control group of patients with HER2-negative disease treated with chemotherapy alone

Study participants

Inclusion Criteria
1. Female patients, presenting for the first time with locally advanced breast cancer, who had not received any previous treatment for an invasive malignancy.
2. Age ≥ 18 years.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1.
4. Histologically proven diagnosis of breast cancer.
5. Patients might have HER2-negative or -positive disease.
6. The primary tumor had to be T3N1, or T4 (skin or nipple invasion, peau d'orange, extension into chest wall or inflammatory carcinoma); any T plus N2 or N3; or any T plus involvement of ipsilateral supraclavicular nodes.

7. At least one measurable lesion according to RECIST criteria (Note: the minimum indicator lesion size is defined ≥ 20 mm, measured by palpation), except for inflammatory carcinoma (T4d). Patients who had either a primary or secondary lesion (eg, axillary lymph nodes) ≥ than 20 mm were allowed to enter the study.
8. Had hormonal receptors (ER and PgR) assessed.
9. Signed written informed consent (approved by the Institutional Review Board [IRB]/Independent Ethics Committee [IEC]) obtained prior to any study specific screening procedures.
10. Able to comply with the protocol.

Exclusion Criteria
1. Pregnant or lactating women. Documentation of a negative pregnancy test had to be available for pre-menopausal women with intact reproductive organs and for women less than one year after the menopause.
2. Women of childbearing potential unless (1) surgically sterile or (2) using adequate measures of contraception. For example: intra-uterine device or barrier method of contraception in conjunction with spermicidal jelly.
3. Evidence of metastases, with the exception of ipsilateral supraclavicular nodes.
4. Bilateral breast cancer.
5. Previous treatment with chemotherapy or hormonal therapy or any prior therapy with an anti-HER2 therapy for any malignancy.
6. Previous extensive radiotherapy or major surgery for any malignancy.
7. Previous or concomitant malignancy of any type, except adequately treated basal cell carcinoma of the skin or in situ cervix cancer.
8. Treatment with any investigational drug within 30 days before beginning of treatment with study drugs.
9. Patients with New York Heart Association (NYHA) class ≥ II heart disease.
10. Patients with a LVEF of < 55% by MUGA scan or echocardiography.
11. Other serious illness or medical condition s (defined in protocol).
12. Any of the following abnormal baseline hematological values:
neutrophils < 1.5×10^9/L, platelets < 100×10^9/L.
13. Any of the following abnormal laboratory tests:
serum total bilirubin > 1.25 × upper limit of normal (ULN) (except for patients with clearly documented Gilbert's syndrome), alanine transaminase (ALT) or aspartate transaminase (AST) > 1.25 × ULN, alkaline phosphatase > 1.25 × ULN, serum creatinine > 1.5 × ULN. Hepatic metastases were excluded as a cause of abnormal liver function tests.

Cross over

After positive results from adjuvant trastuzumab trials became available, HER2-positive patients randomized to receive neoadjuvant chemotherapy alone were offered one year of postoperative adjuvant trastuzumab and 20 patients crossed over to adjuvant therapy.

Sample size

Sample size calculation was based on a 50% EFS rate at 3 years in HER2 positive subjects receiving chemotherapy alone compared to a 68,5% EFS rate in HER2 positive subjects receiving chemotherapy and trastuzumab (HR = 0.545). Based on these assumptions it was calculated that a Log- Rank test on EFS required 86 EFS events in the two HER2-positive arms to achieve 80% power to detect a hazard ratio of 0.545 at a 2-sided significance level of 5%. It was estimated that about 116 patients per HER2-positive treatment were needed to observe 86 within a reasonable time frame.

In addition, 100 patients with HER2-negative disease were planned as a control arm.

Randomisation

Subjects were centrally randomized applying a minimization technique according to Taves (Taves, DR et al; Minimization: a new method of assigning patients to treatment and control group. Clin Pharmacol Ther. 1974; 15: 443-453) to assign HER2-positive patients to the two treatment groups. Randomization was stratified for geographical area (Germany/Austria; Italy; Russia; Spain/Portugal; other), disease stage (T3N1M0 or T4 non inflammatory, N0-1, M0; inflammatory disease, M0; any T,

N2 or ipsilateral supraclavicular nodes) and hormone receptor status (ER and/or PgR positive; both negative).
Patients with HER2-negative tumours were stratified according to the same pre-specified variables and randomly allocated to the parallel study cohort or not, using the same minimization technique and a ratio of 1 (study):3 (off-study).

Blinding (masking)

This was an open-label trial. Pathological response assessment was performed by the local pathologist because this has been standard practice in neoadjuvant trials to date. Central pathology review has not yet become a standard procedure in this setting. Also, the local pathologist was not formally blinded as to the study treatment. However, treatment information was usually not included in the pathology request form, so it can be assumed that most pathologists were unaware of the study treatment.

Statistical methods

The confirmatory statistical analysis was done for both HER2+ groups, descriptive analyses were used to compare the HER2+ and HER2- groups of patients receiving only chemotherapy.

Baseline demographic and disease characteristics were tabulated and presented by treatment group.

Kaplan-Meier estimates were applied to estimate the distribution of time-to-event variables. An unstratified log-rank test was used to compare both HER2+ groups with respect to the primary and secondary time-to-event efficacy endpoints. COX regression was applied to estimate hazard ratios including the pertinent 95% confidence intervals. Response rates where compared by means of the chi-squared test. All statistical tests were conducted at the 2-sided 5% level of significance.

The primary efficacy analysis was done for the Full Analysis Set (FAS) population (excluding patients with significant GCP problems or missing informed consent). In order to assess the robustness of the study results, sensitivity analyses were performed: censoring EFS for patients from the HER2+C arm who crossed over to trastzumab and COX regression analyses (in case of event data) as well as logistic regression analyses (in case of response data) using the stratification factors as covariates.

1.3.2. Results

The first patient was randomized in the study on June 2002 and the last patient on December 12, 2005. The clinical cut-off date for the analysis presented in this report was March 30, 2009. After data transfer and further data cleaning conducted, the database was locked on July 27, 2010.

At this time the median duration of follow-up was 45.9 months (range 2.1-76.8 months) in the HER2+TC arm, 42.1 months (range 0.0-77.5 months) in the HER2+C and 48.1 months (range 0.9-75.5 months) in the HER2–C arm.

Study conduct and Protocol amendments

Three committees were involved in the MO16432 study:
- An International Advisory Committee
- A Protocol Steering Committee
- A NOAH Biomarker (BM) Steering Committee reporting to NOAH Protocol Steering Committee

Details of the duties, meeting frequencies etc of these committees are documented. Essentially, the International Advisory Committee was responsible for providing general advice related to emerging data from other trials, reviewing safety data, including LVEF data, on an ongoing basis. The Protocol Steering Committee was responsible for running the MO16432 trial and implementing recommendations from International Advisory Committee, as appropriate.

The study protocol was amended six times (version B to version G).

Protocol Amendment Version B, dated March 13, 2002
Cardiac data from the NCCTG N9831 study were reviewed by the NOAH Protocol Steering Committee and the protocol was modified to improve the cardiac safety of patients in the trial

Protocol Amendment Version C, dated June 1, 2004
Revision of the entry criteria in order to increase recruitment; e.g. also inclusion of patients with T3N1 disease (previously only patients with T4 disease or patients with N2 or N3 disease or ipsilateral supraclavicular lymph nodes were allowed in the study).

Protocol Amendment Version D, dated November 9, 2005
Announcement of positive interim results from several adjuvant trastuzumab studies (study BO16348 [HERA], the BCIRG006 study, and a joint analysis of the NSABP B-31 and NCCTG N9831 trials) necessitated that patients with HER2-positive disease randomized to the comparator arm of the MO16432 trial were to be offered adjuvant trastuzumab.

Protocol Amendment Version E, dated June 30, 2006
Change in the number of events required for the primary analysis. Instead of 106 events, 86 events were required. This change was based on the observation that a higher percentage of patients than expected crossed over to receive trastuzumab as part of their treatment regimen.

Protocol Amendment Version F, dated July 21, 2008
Clarification on when the full clinical study report would be written (at the time of the primary analysis).

Protocol Amendment Version G, dated August 20, 2009
At the time of the primary analysis, median EFS had not been reached in either arm, and the number of deaths was low. It was therefore decided to extend follow-up for another three years. Based on data simulations, approximately 60% of patients would be expected to have experienced an EFS event and 32% of patients to have died after an additional 3 years of follow-up.

- **Treatments**

The following chemotherapy regimen was used for all patients:

o Doxorubicin 60 mg/m2 and paclitaxel 150 mg/m2, every three weeks for 3 cycles, followed by
o Paclitaxel 175 mg/m2, every three weeks for 4 cycles, followed by
o CMF (cyclophosphamide, methotrexate, fluoracil) every 4 weeks for 3 cycles.

Surgery and radiotherapy were scheduled after completion of CMF chemotherapy. Adjuvant tamoxifen (Tam) was also to be started in patients with tumors that were estrogen receptor (ER) and/or progesterone receptor (PgR) positive.

In patients randomized to receive trastuzumab, treatment was to start at the beginning of chemotherapy (with doxorubicin plus paclitaxel), and to be given throughout chemotherapy and up until surgery. Trastuzumab was to be given at a dose of 6 mg/kg every 3 weeks, 3 weeks after an initial 8 mg/kg loading dose. After surgery, trastuzumab was to recommence before or during radiotherapy treatment, and to continue until 1 year after starting. Depending on when trastuzumab was re-started after surgery, up to 17 cycles of trastuzumab would be received in total.

Patient disposition

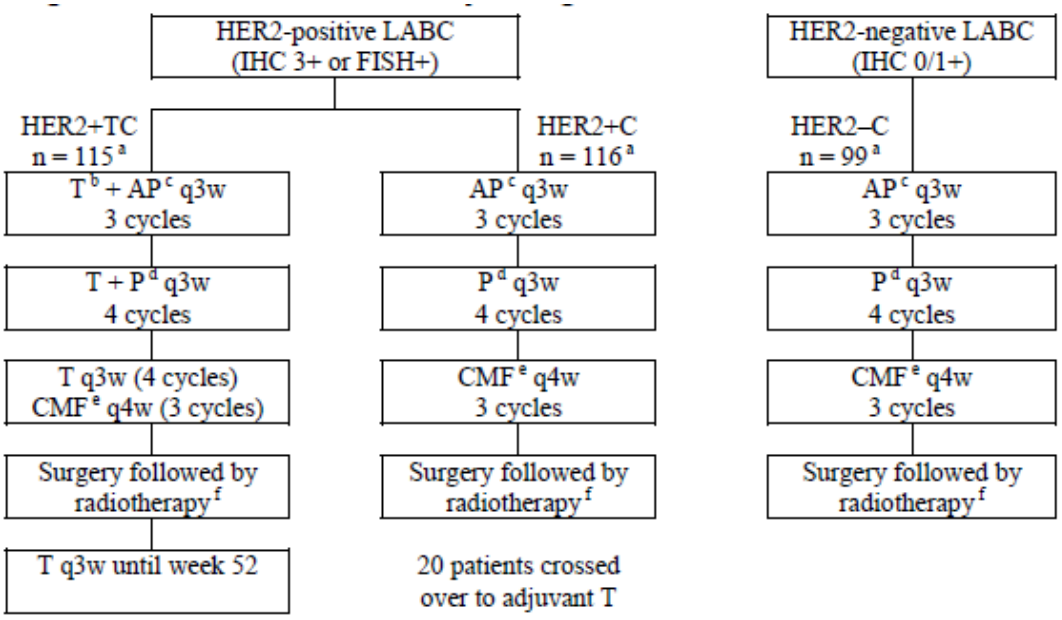
A total of 333 patients were enrolled in the study: 234 with HER2-positive disease (116 randomized to the HER2+TC arm, 118 to the HER2+C arm) and 99 with HER2-negative disease (HER2-C arm). The number of patients screened but not enrolled was not collected.

Patients were recruited from 25 centers in 6 countries: Russia, Spain, Italy, Germany, Austria and Portugal. The majority of the patients were enrolled in Russia (178 patients, 53.5% of the total). Spain and Portugal enrolled 71 patients (21.3%), Italy enrolled 57 (17.1%) and the rest were enrolled in Germany and Austria (27 patients, 8.1%).

Full Analysis Set (FAS)
A total of 3 patients were excluded from all statistical analyses. Thus, the primary efficacy population (FAS) consisted of 330 patients (115 in HER2+TC, 116 in HER2+C, 99 in HER2-C).

Safety Analysis Population (SAP)
Overall, six patients did not receive any study treatment (1 in HER2+TC, 5 in HER2+C).

Patient Disposition across study periods (FAS)



T: trastuzumab; A: doxorubicin; P: paclitaxel; CMF: cyclophosphamide, methotrexate, 5-fluorouracil.
[a] number of patients in the full analysis set used for the primary analysis.
[b] trastuzumab dose: 8 mg/kg intravenous (iv) loading dose followed by 6 mg/kg iv every 3 weeks (q3w) for up to one year.
[c] doxorubicin 60 mg/m^2 iv and paclitaxel 150 mg/m^2 iv.
[d] paclitaxel 175 mg/m^2 iv.
[e] day 1 and day 8 of each cycle: C 600 mg/m^2 by iv bolus, M 40 mg/m^2 iv bolus, F 600 mg/m^2 iv bolus.
[f] hormone receptor-positive patients received adjuvant tamoxifen.

A total of 84.5% [279/330] of patients (112 pts in HER2+TC, 20 pts in HER2+C→T, 68 pts in HER2+C, 79 pts in HER2-C) was considered to enter the post-operative phase ie, they received at least one dose of study medication and had at least one safety assessment after surgery.

Demographic Data and Baseline Characteristics

Parameter	Statistic/Category	HER2+TC (N=115) N	%	HER2+C (N=116) N	%	HER2-C (N= 99) N	%
Age (years)	N	114		116		99	
	Mean	50.2		51.9		50.6	
	SD	9.78		11.13		10.46	
	Min	25		29		30	
	Median	50.0		51.5		49.0	
	Max	75		80		80	
Age group	<40 years	16	(13.9)	15	(12.9)	14	(14.1)
	40 - < 50 years	40	(34.8)	36	(31.0)	39	(39.4)
	50 - 65 years	50	(43.5)	49	(42.2)	35	(35.4)
	>65 years	8	(7.0)	16	(13.8)	11	(11.1)
	Missing	1	(0.9)	0		0	
Race	Caucasian/White	115	(100)	116	(100)	99	(100)
	Black	0		0		0	
	Oriental	0		0		0	
	Other	0		0		0	
Weight (kg)	N	115		116		99	
	Mean	69.8		69.4		71.5	
	SD	14.55		13.08		12.50	
	Min	38		48		44	
	Median	68.0		68.5		70.0	
	Max	118		118		113	
Height (cm)	N	115		116		99	
	Mean	162.0		161.2		161.6	
	SD	6.36		6.33		6.70	
	Min	148		148		135	
	Median	162.0		161.5		162.0	
	Max	181		176		181	
Body Mass Index (kg/m**2)	N	115		116		99	
	Mean	26.65		26.75		27.43	
	SD	5.655		5.187		4.807	
	Min	16.9		17.9		16.4	
	Median	25.28		25.79		27.29	
	Max	43.0		46.7		42.0	
Body Surface Area (m**2)	N	115		116		99	
	Mean	1.74		1.73		1.75	
	SD	0.168		0.152		0.151	
	Min	1.3		1.4		1.4	
	Median	1.73		1.74		1.74	
	Max	2.2		2.2		2.2	
Physical examination	Normal	102	(88.7)	106	(91.4)	94	(94.9)
	Abnormal	13	(11.3)	10	(8.6)	5	(5.1)
Female reproductive status	Childbearing potential with contraceptive protection	54	(47.0)	52	(44.8)	55	(55.6)
	Surgically sterilized	10	(8.7)	7	(6.0)	1	(1.0)
	Postmenopausal	50	(43.5)	57	(49.1)	43	(43.4)
	Missing	1	(0.9)	0		0	

Percentages are calculated with respect to the total number of patients in each treatment group.

Program : $PROD/cdp10326/mo16432/btdemo.sas / Output : $PROD/cdp10326/mo16432/reports/btdemofa.r18
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Data source: page 226.

Primary Tumor Assessment at Baseline: Clinical Findings (FAS)

Parameter	Statistic/Category	HER2+TC (N=115) N	%	HER2+C (N=116) N	%	HER2-C (N= 99) N	%
Site of breast tumor	Left	65	(56.5)	58	(50.0)	56	(56.6)
	Right	50	(43.5)	58	(50.0)	43	(43.4)
Tumor size							
Tumor measurable	Yes	102	(88.7)	108	(93.1)	92	(92.9)
	No	13	(11.3)	8	(6.9)	7	(7.1)
Edema	No	43	(37.4)	43	(37.1)	43	(43.4)
	<= 1/3	15	(13.0)	21	(18.1)	14	(14.1)
	> 1/3	56	(48.7)	52	(44.8)	39	(39.4)
	Not evaluable	1	(0.9)	0		3	(3.0)
Erythema	No	75	(65.2)	75	(64.7)	76	(76.8)
	<= 1/3	11	(9.6)	9	(7.8)	3	(3.0)
	> 1/3	29	(25.2)	31	(26.7)	20	(20.2)
	Not evaluable	0		1	(0.9)	0	
Ulceration	Yes	7	(6.1)	7	(6.0)	7	(7.1)
	No	108	(93.9)	109	(94.0)	92	(92.9)
Chest wall fixation	Yes	5	(4.3)	8	(6.9)	3	(3.0)
	No	110	(95.7)	108	(93.1)	96	(97.0)
Axillary nodes							
Stage	N0	15	(13.0)	19	(16.4)	16	(16.2)
	N1	50	(43.5)	52	(44.8)	38	(38.4)
	N2	50	(43.5)	45	(38.8)	45	(45.5)
Ipsilateral supraventricular nodes							
Present	Yes	6	(5.2)	4	(3.4)	3	(3.0)
	No	109	(94.8)	112	(96.6)	96	(97.0)

Percentages are calculated with respect to the total number of patients in each treatment group.

Program : $PROD/cdp10326/mol6432/bttumor.sas / Output : $PROD/cdp10326/mol6432/reports/bttumorfa.rl8
10NOV2010 12:24

Data source: page 237.

Primary Tumor Assessment at Baseline: Radiological and Other Examinations (FAS)

Parameter	Statistic/Category	HER2+TC (N=115) N	%	HER2+C (N=116) N	%	HER2-C (N= 99) N	%
Mammography							
Performed	Yes	111	(96.5)	109	(94.0)	92	(92.9)
	No	4	(3.5)	7	(6.0)	7	(7.1)
Echography							
Performed	Yes	55	(47.8)	54	(46.6)	54	(54.5)
	No	60	(52.2)	62	(53.4)	45	(45.5)
Assessment of metastases							
Chest X-Ray	Performed	111	(96.5)	109	(94.0)	93	(93.9)
	Not performed	4	(3.5)	7	(6.0)	6	(6.1)
Bone scan	Performed	115	(100)	116	(100)	98	(99.0)
	Not performed	0		0		1	(1.0)
Liver ultrasound	Performed	106	(92.2)	109	(94.0)	93	(93.9)
	Not performed	9	(7.8)	7	(6.0)	6	(6.1)
Other	Performed	11	(9.6)	30	(25.9)	19	(19.2)
	Not performed	104	(90.4)	86	(74.1)	80	(80.8)
Presence of metastases	No	115	(100)	116	(100)	99	(100)
	Yes	0		0		0	

Percentages are calculated with respect to the total number of patients in each treatment group.
Note: Tumor size is not given for all patients for whom mammography or radiography was performed, because for several patients the tumor was classified as non-measurable.

Program : $PROD/cdp10326/mol6432/bttmrad.sas / Output : $PROD/cdp10326/mol6432/reports/bttmradfa.rl8
10NOV2010 12:25

Data source: page 235.

Distribution of patients by stratification variables as corrected in the CRF (FAS)

Characteristic	HER2+TC (N=115) N	%	HER2+C (N=116) N	%	HER2-C (N= 99) N	%
Geographical area						
Germany/Austria	9	(7.8)	11	(9.5)	7	(7.1)
Italy	22	(19.1)	22	(19.0)	13	(13.1)
Russia	62	(53.9)	61	(52.6)	53	(53.5)
Spain/Portugal	22	(19.1)	22	(19.0)	26	(26.3)
Other	0		0		0	
Disease stage						
T3N1M0 or T4 non-inflammatory, N0-1, M0	49	(42.6)	51	(44.0)	41	(41.4)
Inflammatory disease, M0	19	(16.5)	24	(20.7)	16	(16.2)
Any T, N2 or ipsilateral supraclavicular node	47	(40.9)	41	(35.3)	42	(42.4)
Receptors						
ER and/or PgR positive	41	(35.7)	41	(35.3)	64	(64.6)
Both negative	74	(64.3)	75	(64.7)	35	(35.4)

Percentages are calculated with respect to the total number of patients in each treatment group.

Program : $PROD/cdp10326/mo16432/btstrat.sas / Output :
$PROD/cdp10326/mo16432/reports/btstratcrffa.rl8
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As a consequence of the re-monitoring, a relatively high number of patients (59 patients in FAS, 28 in the HER2+C arm and 31 in the HER2+TC arm) required a change of the disease stage category as recorded at randomization.

This imbalance arose due to a change to the initial disease stage category for 59/231 HER2-positive patients during the Roche re-monitoring (44 of these patients were from centre 47296). It was discovered that, for these patients, the source data did not correspond to the disease stage used for stratification. In most of these patients, the disease stage was changed from IBC to either T4 non-inflammatory or any TN2

Reclassification of Initial Disease Stage in HER2-positive Patients following Source Data Verification (FAS)

Change of Disease Stage used for Randomization		**Number of Patients Affected**	
From	**To**	**HER2+TC**	**HER2+C**
IBC	either T4 non-inflammatory or any TN2	26	23
T4 non-inflammatory	any TN2	4	2
T4 non-inflammatory	IBC	-	1
any TN2	T4	1	1
any TN2	IBC	-	1
Total		**31**	**28**

Source: page 212

Results: Primary Efficacy Parameter:

Event free survival

Fewer patients in the HER2+TC arm than in the HER2+C arm experienced an EFS event (disease progression, recurrence or death): 46 patients (40%) vs 59 patients (51%). The risk of having an EFS event was reduced by 35% for HER2-positive patients who received trastuzumab plus chemotherapy compared with those who received chemotherapy alone, and this difference was statistically significant (hazard ratio [HR] = 0.65; 95% CI [0.44,0.96]; p = 0.0275).

Summary of event free survival

etsvefsfa Summary of event-free survival (EFS) from randomization (months) - Full analysis set

Characteristic / Statistic	HER2+TC (N=115) N %	HER2+C (N=116) N %	HER2-C (N=99) N %
Kaplan-Meier Estimate of EFS (months) from randomization			
Number (%) of patients with events	46 (40.0)	59 (50.9)	42 (42.4)
Number (%) of patients censored	69 (60.0)	57 (49.1)	57 (57.6)
Third Quartile [95%-CI]	22.7 [17.9, 34.3]	14.1 [11.7, 18.9]	15.3 [8.4, 34.6]
Median [95%-CI]	- [47.7, -]	43.6 [24.1, -]	64.5 [57.7, -]
Treatment effect - comparison vs. the HER2+C group			
Log-Rank p-value (two-sided)	0.0275		
Hazard ratio [95%-CI]	0.65 [0.44, 0.96]		
EFS rate [95%-CI] at			
12 months	0.89 [0.84, 0.95]	0.82 [0.74, 0.89]	0.80 [0.73, 0.88]
Patients at risk	101	89	78
24 months	0.73 [0.64, 0.81]	0.61 [0.51, 0.70]	0.69 [0.60, 0.78]
Patients at risk	81	66	67
36 months	0.65 [0.56, 0.74]	0.52 [0.43, 0.62]	0.63 [0.53, 0.72]
Patients at risk	66	52	57

Percentages are calculated with respect to the total number of patients in each treatment group.

Summary of composition of events

Type of EFS event	HER2+TC (N=115) N %	HER2+C (N=116) N %	HER2-C (N=99) N %
Total number of patients with EFS event	46 (40.0)	59 (50.9)	42 (42.4)
Number of patients with EFS event after crossing over to adjuvant trastuzumab		5 (4.3)	
Progression	11 (9.6)	12 (10.3)	17 (17.2)
New lesion	1 (0.9)	4 (3.4)	4 (4.0)
Progression of existing lesion	1 (0.9)	2 (1.7)	3 (3.0)
Other	1 (0.9)	1 (0.9)	3 (3.0)
Missing [1]	8 (7.0)	5 (4.3)	7 (7.1)
Recurrence	31 (27.0)	43 (37.1)	23 (23.2)
Opposite breast	1 (0.9)	3 (2.6)	1 (1.0)
Local	4 (3.5)	6 (5.2)	1 (1.0)
Regional	1 (0.9)	2 (1.7)	1 (1.0)
Distant	25 (21.7)	32 (27.6)	20 (20.2)
Death	4 (3.5)	4 (3.4)	2 (2.0)

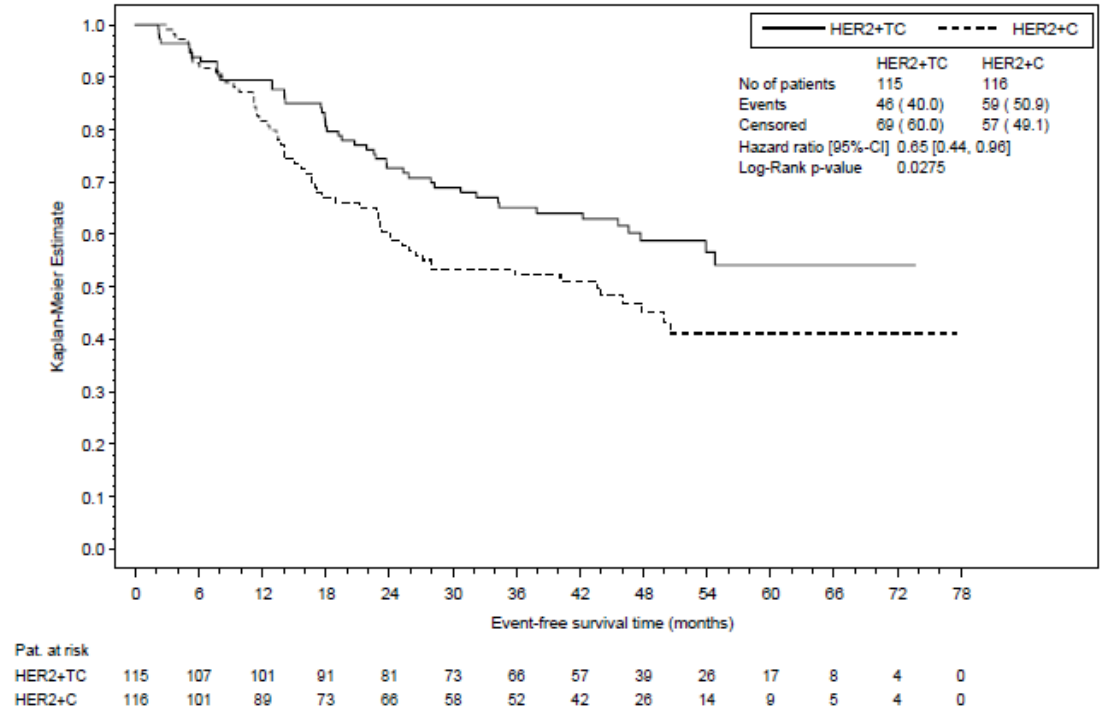
Percentages are calculated with respect to the total number of patients in each treatment group.
[1] Details on progression are missing because progression was not reported by the investigator but there was objective progression
according to the modified RECIST criteria, see SAP.

Most of the events reported were disease recurrence (31 pts in HER2+TC, 43 pts in HER2+C) and disease progression (11 pts in HER2+TC, 12 pts in HER2+C).

Of these 74 patients who had disease recurrence, 57 of them had distant disease recurrence (25 pts in HER2+TC, 32 pts in HER2+C).

In the disease progression category, five patients were classified as "other":
in the HER2+TC arm, a patient had an edema,in the HER2+C arm, a patient had a cerebral progressive disease and in the HER2-C arm, a patient had metastases to the liver and new axillary lymph node, and two patients had both new lesion and progression of the existing lesion.

Kaplan-Meier distribution of EFS in HER2-positive patients randomized to chemotherapy plus trastuzumab or to chemotherapy only - FAS



Pat. at risk

HER2+TC	115	107	101	91	81	73	66	57	39	26	17	8	4	0
HER2+C	116	101	89	73	66	58	52	42	26	14	9	5	4	0

Program : $PROD/cdp10326/mo16432/efkm.sas / Output : $PROD/cdp10326/mo16432/reports/efkmefs1fa.cgm
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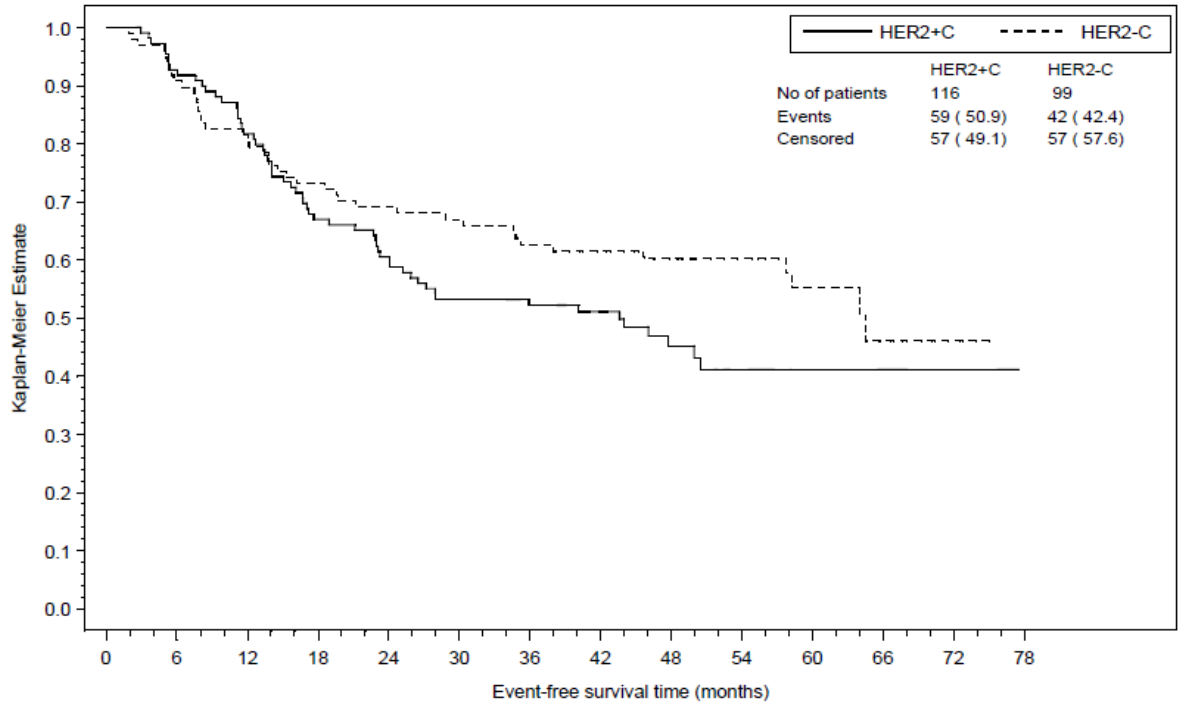
Kaplan-Meier distribution of EFS in HER2-positive patients randomized to chemotherapy only and HER2-negative patients - FAS

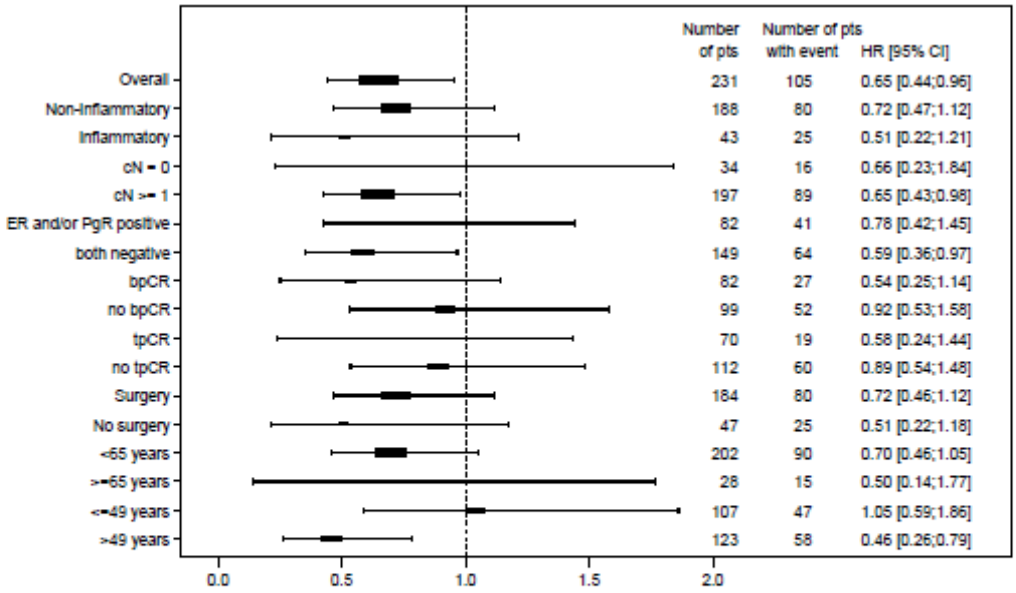


Pat. at risk

HER2+C	116	101	89	73	66	58	52	42	26	14	9	5	4	0
HER2-C	99	88	78	71	67	62	57	51	41	29	17	8	2	0

Event-Free Survival Subgroup Analyses
Subgroup analyses of patients were performed based on age (≤ 49 yrs vs > 49 yrs; < 65 yrs vs ≥ 65 yrs), type of breast cancer (non-inflammatory/inflammatory), nodal status (cN = 0 vs cN ≥ 1), pathological response and surgery

Forest Plot of Hazard Ratios for Event-Free Survival by Subgroup in HER2-Positive Patients (FAS)



Hazard ratios and confidence intervals are obtained from an unadjusted Cox-model comparing patients randomized to chemotherapy plus trastuzumab (HER2+TC) to patients randomized to chemotherapy only (HER2+C). The size of the squares is proportional to the number of events and the length of the horizontal lines shows the 95% confidence interval. cN = clinical nodal status, bpCR = breast pathological complete response, tpCR = total pathological complete response
Program : $PROD/cdp10326/mo16432/efforest.sas / Output : $PROD/cdp10326/mo16432/reports/efforestf.cgm
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Sensitivity analysis EFS: Censoring of data from patients who crossed over

Of the 20 patients who were originally randomized to the HER2+C arm and subsequently crossed over to receive adjuvant trastuzumab, 5 patients experienced an EFS event after cross-over.

When data from these 19 patients (1 patient of 20 had an EFS event prior to cross-over) were censored at the time of their first trastuzumab infusion, the reduction in risk of an EFS event was 41% (unadjusted HR 0.59; 95% CI [0.40, 0.88]; p = 0.0084, Log-Rank test). At 3 years, 65% of the patients in the HER2+TC arm and 48% of those in the HER2+C arm survived event-free

Sensitivity analysis EFS: Exclusion of patient data from Site CRTN 47296

An exploratory analysis of EFS was performed excluding the patients from the site CRTN 47296.
A high number of patients from this site did not undergo surgery and the complete clinical response rate was unusually high for that site. In this analysis, the hazard ratio was the same as for the FAS population (HR 0.65; 95% CI [0.42, 1.00]; 0.0467, Log-Rank test) with the confidence interval including 1.

Summary of EFS FAS without center 47296

Characteristic / Statistic	HER2+TC (N=90) N %	HER2+C (N=91) N %	HER2-C (N=99) N %
Kaplan-Meier Estimate of EFS (months) from randomization			
Number (%) of patients with events	38 (42.2)	48 (52.7)	42 (42.4)
Number (%) of patients censored	52 (57.8)	43 (47.3)	57 (57.6)
Third Quartile [95%-CI]	22.7 [14.2, 34.3]	14.1 [11.2, 17.6]	15.3 [8.4, 34.6]
Median [95%-CI]	- [46.6, -]	35.9 [23.3, -]	64.5 [57.7, -]
Treatment effect - comparison vs. the HER2+C group			
Log-Rank p-value (two-sided)	0.0467		
Hazard ratio [95%-CI]	0.65 [0.42, 1.00]		
EFS rate [95%-CI] at			
12 months	0.88 [0.81, 0.94]	0.82 [0.74, 0.90]	0.80 [0.73, 0.88]
Patients at risk	77	70	78
24 months	0.72 [0.62, 0.81]	0.60 [0.50, 0.70]	0.69 [0.60, 0.78]
Patients at risk	63	51	67
36 months	0.64 [0.54, 0.74]	0.49 [0.39, 0.60]	0.63 [0.53, 0.72]
Patients at risk	54	38	57

Results: Secondary Efficacy Parameters

Surgery

A total of 266 patients (80.6% [266/330]) underwent surgery (85.2% [98/115] in HER2+TC, 74.1% [86/112] in HER2+C, 82.8% [82/99] in HER2-C). Therefore, 64 patients did not undergo surgery, the majority of these patients being from a Russian centre: CRTN 47296; 13 patients in HER2+TC, 15 patients in HER2+C

Summary of Surgeries (FAS)

Characteristic	HER2+TC (N=115) N %	HER2+C (N=116) N %	HER2-C (N= 99) N %
Total number of patients	115 (100)	116 (100)	99 (100)
Patients undergoing surgery	98 (85.2)	86 (74.1)	82 (82.8)
Patients not undergoing surgery	17 (14.8)	30 (25.9)	17 (17.2)
Details on surgery			
Patients undergoing surgery	98 (100)	86 (100)	82 (100)
Type of surgery			
Wide excision	5 (5.1)	3 (3.5)	6 (7.3)
Lumpectomy	5 (5.1)	1 (1.2)	2 (2.4)
Quadrantectomy	11 (11.2)	5 (5.8)	9 (11.0)
Modified radical mastectomy	42 (42.9)	40 (46.5)	53 (64.6)
Radical mastectomy	31 (31.6)	34 (39.5)	10 (12.2)
Other	3 (3.1)	3 (3.5)	2 (2.4)
Missing	1 (1.0)	0	0
Axillary dissection			
First level only	2 (2.0)	1 (1.2)	0
First and second level	11 (11.2)	12 (14.0)	9 (11.0)
All three levels	82 (83.7)	69 (80.2)	67 (81.7)
Sampling	0	2 (2.3)	3 (3.7)
Not done	1 (1.0)	0	2 (2.4)
Missing	2 (2.0)	2 (2.3)	1 (1.2)

Program : $PROD/cdp10326/mo16432/stsurg.sas / Output : $PROD/cdp10326/mo16432/reports/stsurgfa.rl8
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More patients in the HER2+TC arm underwent surgery than in the HER2+C arm (85.2% vs 74.1%, respectively), and more patients in the HER2+TC arm (21.4% [21/98]) had a quadrantectomy, lumpectomy or wide excision (less radical procedures than a mastectomy) than patients in the HER2+C arm (10.5% [9/86]).

Fewer patients in the HER2-C arm had a radical mastectomy (12.2%) compared with the two HER2-positive arms of patients (31.6% HER2+TC and 39.5% HER2+C).

A high number of patients did not undergo surgery (14.8% [17/115]) in HER2+TC, 25.9% [30/116] in HER2+C, 17.2% [17/99] in HER2-C); the majority of patients in the HER2+TC and HER2+C arms not undergoing surgery were from one site CRTN 47296 (13 patients in HER2+TC, 15 patients in HER2+C)

As expected, patients who did not undergo surgery had a worse outcome for EFS than patients who underwent surgery, irrespective of the treatment arm (Table 34). For the HER2-positive patients, a

consistent reduction of the risk of having an EFS event was found for trastuzumab-treated patients (estimated HR < 1) who underwent surgery or not.

In contrast to the EFS result according to surgery or not with all HER2-positive patients, the EFS hazard ratio among trastuzumab-treated patients was lower in the subgroup of patients not undergoing surgery compared to the subgroup of patients undergoing surgery (HR 0.51 vs 0.72).

Summary of event-free survival: surgery versus no surgery

Surgery/no surgery	Characteristic / Statistic	HER2+TC (N=115) N %	HER2+C (N=116) N %	HER2-C (N=99) N %
Surgery	Total number of patients in subgroup	98 (85.2)	86 (74.1)	82 (82.8)
	Kaplan-Meier Estimate of EFS (months) from randomization			
	Number (%) of patients with events	38 (33.0)	42 (36.2)	28 (28.3)
	Number (%) of patients censored	60 (52.2)	44 (37.9)	54 (54.5)
	Third Quartile [95%-CI]	25.3 [19.2, 45.6]	17.6 [14.1, 26.5]	34.6 [16.2, 64.0]
	Median [95%-CI]	- [53.9, -]	49.9 [35.9, -]	- [64.0, -]
	Treatment effect - comparison vs. the HER2+C group			
	Log-Rank p-value (two-sided)	0.1408		
	Hazard ratio [95%-CI]	0.72 [0.46, 1.12]		
	EFS rate [95%-CI] at			
	12 months	0.91 [0.85, 0.97]	0.92 [0.86, 0.98]	0.89 [0.82, 0.96]
	Patients at risk	89	79	73
	24 months	0.76 [0.67, 0.84]	0.70 [0.60, 0.79]	0.78 [0.69, 0.87]
	Patients at risk	74	60	64
	36 months	0.67 [0.58, 0.76]	0.59 [0.49, 0.70]	0.72 [0.62, 0.82]
	Patients at risk	61	46	55
No surgery	Total number of patients in subgroup	17 (14.8)	30 (25.9)	17 (17.2)
	Kaplan-Meier Estimate of EFS (months) from randomization			
	Number (%) of patients with events	8 (7.0)	17 (14.7)	14 (14.1)
	Number (%) of patients censored	9 (7.8)	13 (11.2)	3 (3.0)
	Third Quartile [95%-CI]	17.9 [7.7, 37.9]	6.0 [3.8, 11.4]	5.1 [2.2, 7.5]
	Median [95%-CI]	37.9 [18.0, -]	11.5 [8.5, 22.7]	7.5 [5.4, 12.1]
	Treatment effect - comparison vs. the HER2+C group			
	Log-Rank p-value (two-sided)	0.1075		
	Hazard ratio [95%-CI]	0.51 [0.22, 1.18]		
	EFS rate [95%-CI] at			
	12 months	0.81 [0.62, 1.00]	0.44 [0.23, 0.64]	0.34 [0.10, 0.58]
	Patients at risk	12	10	5
	24 months	0.54 [0.29, 0.79]	0.26 [0.08, 0.44]	0.20 [0.00, 0.41]
	Patients at risk	7	6	3
	36 months	0.54 [0.29, 0.79]	0.26 [0.08, 0.44]	0.13 [0.00, 0.31]
	Patients at risk	5	6	2

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Pathological Complete Response

Pathological complete response rates were higher in patients with HER2-positive disease receiving trastuzumab compared to those treated with chemotherapy alone.

The pathological complete response rate of the primary tumour (bpCR) was 44.3% vs 26.7%; the pathological complete response of the primary tumour and lymph nodes (total pathological response [tpCR]) was 40.0% vs 20.7%. The differences in the bpCR and tpCR rates were associated with a p-value of 0.0051 and 0.0014, respectively. Subgroup analyses of patients were performed based on age (≤ 49 yrs vs > 49 yrs), type of breast cancer (non-inflammatory/inflammatory), nodal status (cN = 0 vs cN ≥ 1), and hormone receptor status and generally confirmed overall results.

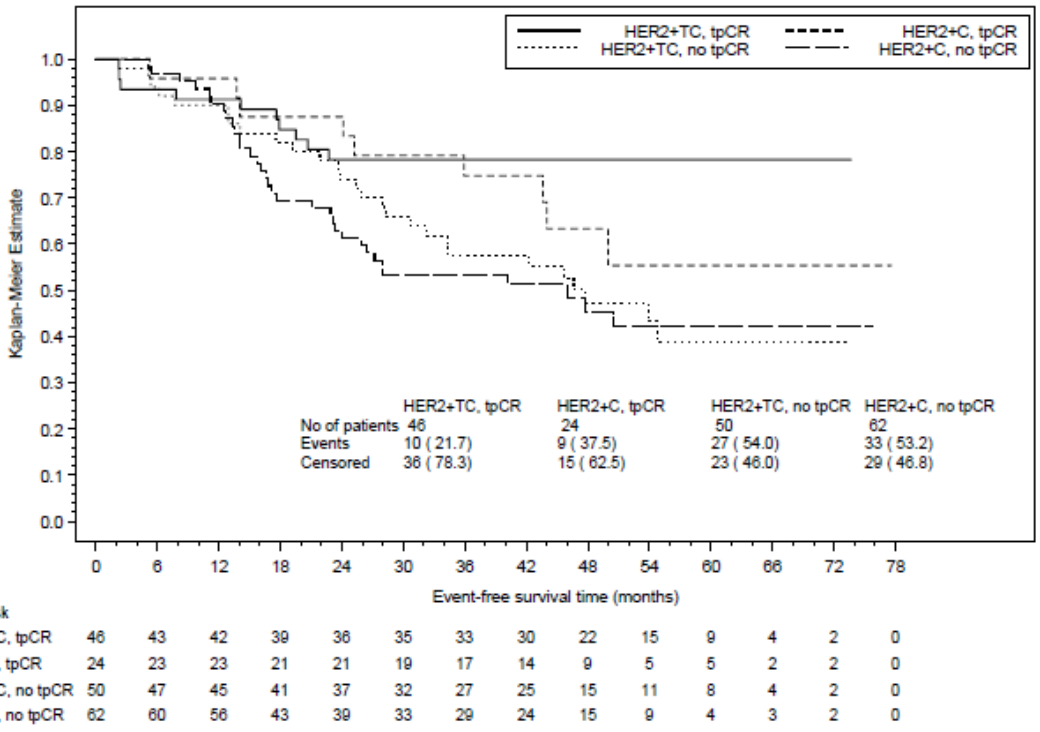
Summary of Pathological Complete Response (MO16432 FAS)

Parameter	Statistic	HER2+TC N = 115	HER2+C N = 116	HER2-C N = 99
Breast pathological complete response (bpCR)	N (%)	51 (44.3)	31 (26.7)	19 (19.2)
	95% CI	[35.1,53.9]	[18.9,35.7]	[12.0,28.3]
Difference in bpCR rates	%	17.6		
	95% CI	[5.0,30.2]		
	p-value	0.0051		
Not evaluable for bpCR	N (%)	19 (16.5)	31 (26.7)	17 (17.2)
No surgery performed	N (%)	17 (14.8)	30 (25.9)	17 (17.2)
Missing information on breast tumour remnants	N (%)	2 (1.7)	1 (0.9)	0
Total pathological complete response (tpCR)	N (%)	46 (40.0)	24 (20.7)	18 (18.2)
	95% CI	[31.0,49.6]	[13.7,29.2]	[11.1,27.2]
Difference in tpCR rates	%	19.3		
	95% CI	[7.2,31.4]		
	p-value	0.0014		
Not evaluable for tpCR	N (%)	19 (16.5)	30 (25.9)	18 (18.2)
No surgery performed	N (%)	17 (14.8)	30 (25.9)	17 (17.2)
Missing information on breast tumour remnants	N (%)	2 (1.7)	0	0
Missing information on axillary nodes	N (%)	0	0	1 (1.0)

Percentages were calculated with respect to the total number of patients in each treatment group.
Source: etpcrfa.

Pathological examination of surgical specimens revealed that almost twice as many patients in the HER2+TC arm achieved a pathological complete response in breast and axilla (tpCR) and in breast (bpCR) compared with the HER2+C arm (tpCR: 40.0% HER2+TC vs. 20.7% HER2+C, p = 0.0014, Chi-squared test; bpCR: 44.3% HER2+TC vs. 26.7% HER2+C, p = 0.0051, Chi-squared test).

Kaplan-Meier Plot of Event-free Survival by tpCR in HER2-positive Patients (MO16432 FAS)



Subgroup analyses of EFS by tpCR response achieved showed that the group of HER2-positive patients who had a tpCR on average also had a longer duration of EFS than HER2-positive patients without tpCR (HR = 0.43; 95% CI [0.26, 0.72]; p = 0.0010). The analyses of the EFS by bpCR subgroups showed similar results.

Secondary Endpoint – Overall Clinical Response

The overall clinical response to treatment was determined in all patients who had measurable disease at baseline. The proportion of patients with an overall clinical response (complete response and partial response) was slightly higher in the HER2+TC arm than in the HER2+C arm.

However, the 95% confidence interval for the difference in response rates included zero [-6.4%, 19.1%], p-value 0.3077, indicating no treatment effect.

Summary of Overall Clinical Response (MO16432 FAS)

Parameter	Statistic	HER2+TC N = 115	HER2+C N = 116	HER2–C N = 99
Number of patients with measurable disease at baseline	N (%)	110 (100)	107 (100)	96 (100)
Overall clinical response (complete or partial response)	N (%)	80 (72.7)	71 (66.4)	63 (65.6)
	95% CI	[63.4,80.8]	[56.6,75.2]	[55.2,75.0]
Difference in OR rates	%	6.4		
	95% CI	[-6.4, 19.1]		
	p-value	0.3077		
Number (%) of patients with				
Progressive disease	N (%)	12 (10.9)	11 (10.3)	16 (16.7)
Stable disease	N (%)	9 (8.2)	10 (9.3)	11 (11.5)
Partial response	N (%)	21 (19.1)	21 (19.6)	32 (33.3)
Complete response	N (%)	59 (53.6)	50 (46.7)	31 (32.3)
Not evaluable	N (%)	9 (8.2)	15 (14.0)	6 (6.3)

Percentages were calculated using the number of patients with measurable disease at baseline.
Source: etocrfa.

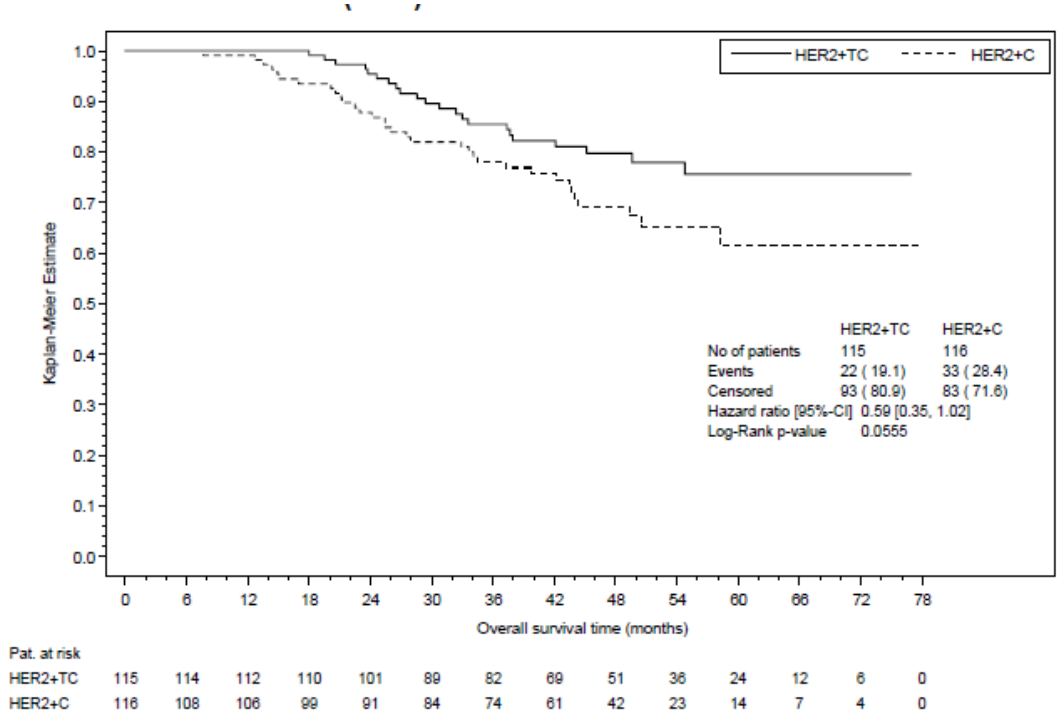
Overall survival

At the time of the analysis (clinical cut-off March 30, 2009), a total of 55 randomized patients had died in the HER2-positive arms: 22 patients (19.1%) in the HER2+TC arm and 33 patients (28.4%) in the HER2+C arm. Twenty-one patients (21.2%) had died in the parallel HER2-C arm.

Most of the deaths observed were cancer related, with 90.9% (20/22) of deaths in the HER2+TC arm, 100% (33/33) of deaths in the HER2+C arm and 90.5% (19/21) of deaths in the HER2-C arm due to breast cancer progression.

Three –year overall survival (based on Kaplan-Meier estimates) was 85.0% in the HER2+TC arm versus 78.0% in the HER2+C arm (85.0% in HER2-C). The hazard ratio indicates a 41% reduction in the risk of death (HR 0.59; 95% CI [0.35, 1.02]; p = 0.0555, Log-Rank test)

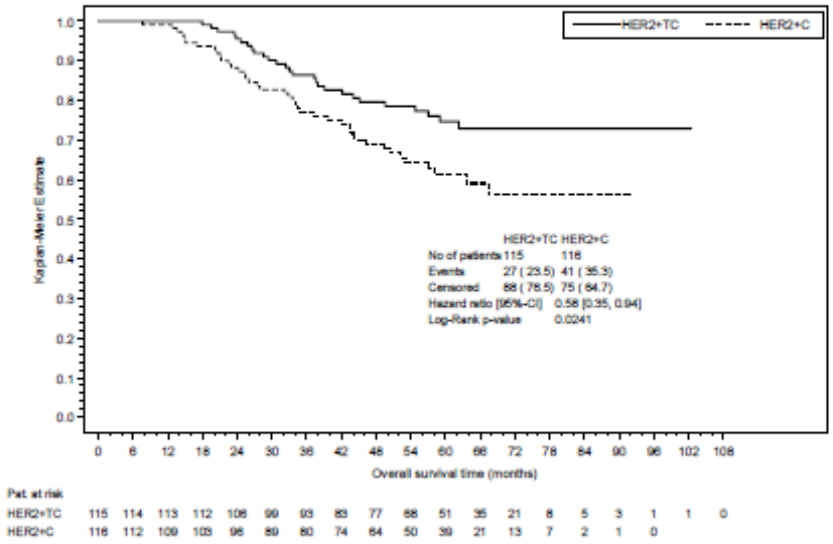
Kaplan Meier curve of overall survival in Her 2 positive patients



An exploratory analysis of OS was performed excluding the patients from the site CRTN 47296. In this analysis, the hazard ratio was slightly better (HR = 0.52, 95% CI [0.28, 0.96])

As part of the responses to the RSI the applicant provided an update on OS. There are 5 and 8 additional events in the HER2+TC arm and HER2+C arm, respectively. The hazard ratio for the updated overall survival data is 0.58 (95% CI: 0.35, 0.94; p-value of log-rank test: 0.0241),

Figure 1 Kaplan-Meier Distribution of Overall Survival from Randomization in HER2-positive Patients – Updated Analysis Using Data from Michelangelo Operation Office (FAS)



Summary of the Main Efficacy Results in HER2-Positive Patients

Parameter	CSR Results		Published Results*	
	HER2+TC N = 115	HER2+C N = 116	HER2+TC N = 117	HER2+C N = 118
Event-Free Survival				
Total number of patients with EFS event	46 (40.0%)	59 (50.9%)	36	51
HR (95%CI); p-value (Log-Rank test)	0.65 (0.44, 0.96) p = 0.0275		0.59 (0.38, 0.90) p = 0.013	
EFS rate at 36 months (95% CI)	0.65 (0.56, 0.74)	0.52 (0.43, 0.62)	0.71 (0.61, 0.78)	0.56 (0.46, 0.65)
Pathologival Complete Response				
bpCR				
% of patients (95% CI)	44.3 (35.1, 53.9)	26.7 (18.9, 35.7)	43	22
Difference in bpCR rate (95%CI); p-value (Chi-square test)	17.6 (5.0, 30.2) p = 0.0051			
tpCR				
% of patients (95% CI)	40.0 (31.0, 49.6)	20.7 (13.7, 29.2)	38	19
Difference in tpCR rate (95%CI); p-value (Chi-square test)	19.3 (7.2, 31.4) p = 0.0014			
Overall Clinical Response (CR + PR)				
% of patients (95% CI)	72.7 (63.4, 80.8)	66.4 (56.6, 75.2)	87	74
Difference in OR rates (95% CI); p-value (Chi-square test)	6.4 (-6.4, 19.1) p = 0.3077		p = 0.009	
Overall Survival				
HR (95%CI); p-value (Log-Rank test)	0.59 (0.35, 1.02) p = 0.0555		0.62 p = 0.114	
36 months OS rate (95% CI)	0.85 (0.79, 0.92)	0.78 (0.70, 0.86)	0.87 (0.79, 0.92)	0.79 (0.70, 0.86)

Michelangelo calculated the percentage for ORR with respect to all patients whereas Roche calculated them with respect to the number of patients with measurable disease at baseline.

In the published data, patients had been followed for a median follow-up of 3.2 years, whereas in the present CSR analysis, patients had been followed for a median follow-up of 3.8 years in the HER2+TC arm, 3.5 years in the HER2+C arm and 4.0 years in the HER2-C arm.

In order to be able to compare the two analyses, it is important to note that Roche made some significant changes to the Statistical Analysis Plan that was used for the publication. The number of patients included in the published analysis was slightly different from the number of patients included in the CSR analysis. Four patients were excluded from the Roche FAS analysis, two in each HER2-positive arm due to missing informed consent, one patient in the HER2+C arm for late protocol approval and a patient in the HER2+TC arm who was not included in Roche database because she withdrew informed consent prior to randomization but was randomized by mistake.

Key efficacy and safety results of the present analysis are very similar to the published data: in both analyses, the addition of trastuzumab to neoadjuvant chemotherapy resulted in a clinically relevant and statistically significant improvement in EFS. Improvements were also observed in OS, bpCR and tpCR rates.

1.3.3. Supportive Studies

Supportive studies

- **MDACC Study (Buzdar et al)**

This was a randomised phase III trial investigating the role of trastuzumab when given concurrently with neoadjuvant chemotherapy (paclitaxel followed by FEC) in patients with operable non-inflammatory early breast cancer

The treatment consisted of: four cycles of paclitaxel at 225 mg/m2 as a 24-h infusion at 3-week intervals. Patients were then treated with four cycles of FEC therapy, which consisted of 500 mg/m2 fluorouracil on days 1 and 4, 500 mg/m2 i.v. cyclophosphamide on day 1 only, and 75 mg/m2 epirubicin on day 1 only. The patients who had been randomized (in the original study) and assigned (additional study patients) to receive trastuzumab received 4 mg/kg trastuzumab i.v. over 90 min on day 1 of the first cycle of paclitaxel. These patients received 2 mg/kg trastuzumab weekly, administered i.v. over 30 min during the 24 weeks of chemotherapy.

One hundred and sixty-four patients were originally planned to be enrolled, but after only 42 patients were enrolled (23 randomised to chemotherapy plus trastuzumab and 19 to chemotherapy alone), the data monitoring committee requested an extraordinary interim analysis based on Bayesian principles because of the very high pCR rate observed in trastuzumab-treated patients at the time. Of the patients with efficacy data available then,26.3% in the chemotherapy alone arm achieved a pCR compared with 65.2% in the trastuzumab plus chemotherapy arm. The difference was highly clinically relevant. An update to the Bayesian analysis, incorporating results for all 42 patients, indicated a 96% probability that the trastuzumab plus chemotherapy arm would be found superior if accrual were continued to 164 patients. Accordingly, recruitment to the chemotherapy alone arm was discontinued, and an additional 22 patients were recruited to the chemotherapy plus trastuzumab arm.
At the end of the study, the pCR rate was 60% in the 45 patients who received trastuzumab plus chemotherapy. At a median follow-up of 36 months from study entry, the 3-year disease-free survival (DFS) rate in the trastuzumab arm was 100% compared to 85% in the control arm (p = 0.041). None of the 45 patients treated with trastuzumab plus chemotherapy experienced clinical cardiac dysfunction, and there were no cardiac deaths in the study.

- **GeparQuattro Study**

The GeparQuattro study enrolled 1509 patients with early breast cancer including inflammatory breast cancer, 445 of whom had HER2-positive disease. Patients with HER-2–positive tumors received trastuzumab 6 mg/kg intravenously (IV) every 3 weeks concomitantly to cytotoxic treatment, starting with a loading dose of 8 mg/kg IV on day 1 of the first EC cycle.

In this 3-arm trial, HER2-positive patients were randomised to receive neoadjuvant trastuzumab concurrently with either
a) 4 cycles of epirubicin plus cyclophosphamide followed by 4 cycles of docetaxel, or
b) 4 cycles of epirubicin plus cyclophosphamide followed by 4 cycles of docetaxel plus concomitant capecitabine, or
c) 4 cycles of epirubicin plus cyclophosphamide followed by 4 cycles of docetaxel followed by 4 cycles of q3w capecitabine.
d) HER2-negative patients received chemotherapy without trastuzumab and were used as a reference group.

Pathological complete response (defined as no invasive or in situ residual tumours in the breast) rate was 31.7%, compared to 15.7% in the reference group. HER2-positive patients without response to the first 4 cycles of EC showed an unexpectedly high pCR rate of 16.6% (3.3% in the reference group). Breast conservation rate was 63.1% and comparable to that of the reference group (64.7%). Chemotherapy plus trastuzumab was associated with more febrile neutropenia and conjunctivitis, but with a comparable short-term cardiac toxicity profile as the reference group.

- **Study WO20697 (NeoSphere)**

NeoSphere is a randomised phase II study in patients with operable (T2-3, N0-1,M0) or locally advanced/inflammatory (T4d, any N, M0) HER2-positive early or locally advanced breast cancer who have not received prior chemotherapy. A total of 417 patients were randomised to one of 4 neoadjuvant treatment arms:
Arm A: trastuzumab and docetaxel (n = 107)

Arm B: trastuzumab, pertuzumab and docetaxel (n = 107)
Arm C: trastuzumab and pertuzumab (n = 107)
Arm D: pertuzumab and docetaxel (n = 96)

All patients were treated every 3 weeks (q3w) for 4 cycles prior to breast surgery. The primary endpoint of the study was pCR. The pCR rate in arm B (45.8%) was significantly greater than that in arm A (29.0%; p = 0.0141), which in turn was significantly greater than the pCR rate in arm C (16.8%;p = 0.0198). The pCR rate in arm B was also significantly greater than that in arm D (24.0%; p = 0.003). An exploratory subset analysis showed that a higher proportion of patients with ER/PgR-negative tumours had a pCR compared with patients with ER/PgRpositive tumours. The treatments had an acceptable safety profile.

- **NeoALTTO Study**

This is an international, multicentre, randomised study comparing the efficacy of lapatinib (L), trastuzumab (T), and their combination (L+T), each in combination with paclitaxel, given as neoadjuvant treatment in women with HER2-positive operable invasive breast cancer (size of primary tumour > 2 cm) The primary endpoint was pCR defined as no invasive or only non-invasive in situ cancer in the breast specimen.

A total of 455 patients were randomised (L: n = 154; T: n = 149; L+T: n = 152). The primary objective of the trial was met with a significantly higher pCR rate in the L+T arm compared to the T arm (51.3% vs. 29.5%; p = 0.0001), while the pCR rate in the L arm (24.7%) was not statistically different from the T arm (29.5%). There were no new safety findings reported in patients receiving trastuzumab.

- **GeparQuinto Study**

GeparQuinto is a randomised phase III study comparing trastuzumab versus lapatinib, each in combination with epirubicin/cyclophosphamide (4 cycles) followed by docetaxel (4 cycles) as neoadjuvant therapy for patients with untreated, uni-/bilateral HER2-positive early or locally advanced breast cancer

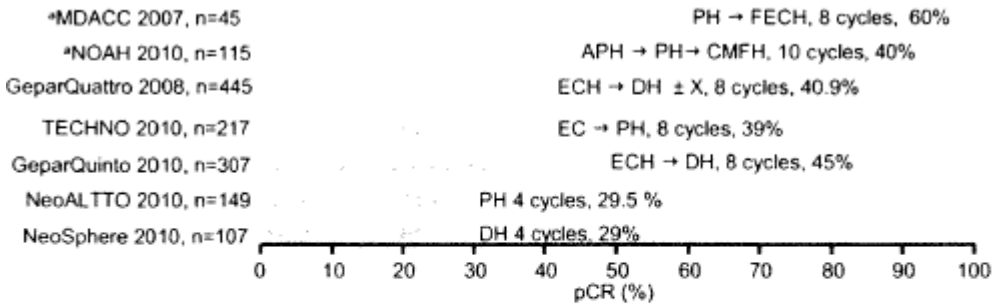
Trastuzumab was given concurrently with all 8 cycles of neoadjuvant chemotherapy (presurgery) and for an additional 6 months following after surgery. Lapatinib was given concurrently with chemotherapy, followed by trastuzumab for 12 months postsurgery.

The primary endpoint was pCR defined as no microscopic evidence of residual viable tumour cells (no invasive/non-invasive) in any resected specimens of the breast and axillary nodes. A total of 620 patients were randomised, and 615 were treated (EC-D+T: n = 307;EC-D+L: n = 308). In the EC-D+T arm 31.3% of patients achieved a pCR compared with 21.7% in the EC-D+L arm (p < 0.05). Additional analyses using less stringent definitionsfor pathological response showed a more pronounced difference between treatment arms in favour of trastuzumab: 45.0% vs 29.9% (p < 0.05; no invasive residual in breast andnodes) and 50.4% vs 35.2% (p < 0.05; no invasive residual in breast alone). A predefined subgroup analysis showed odds ratios below zero for all subtypes/strata (ER/PgR±, T1-3and N0-2, T4 or N3) favouring EC-D+T over EC-D+L. No new safety signals were reported, including cardiac safety.

- **TECHNO Study**

The Taxol Epirubicin Cyclophosphamide Herceptin NeOadjuvant (TECHNO) study investigated the efficacy and safety of 4 cycles of epirubicin/cyclophosphamide followed by 4 cycles of paclitaxel/trastuzumab as neoadjuvant treatment in patients with HER2-positive primary breast cancer . Eighty-four of 217 enrolled patients (39%) achieved a pCR (defined as no invasive tumour in the breast and in axillary nodes), and breast-conserving surgery was performed in 64% of patients. The OSrate in patients achieving a pCR was 96.3% (3 deaths in 84 patients) compared to 85.0% (20 deaths in 133 patients) in patients without pCR (log-rank test p-value = 0.0074). The DFS rate at 3 years was superior in patients with a pCR compared with patients without a pCR (88% vs 73%, respectively; p = 0.01). In addition, the rate of 3-year overall survival was greater in patients with a pCR than in patients without a pCR (96%vs 86%, respectively; p = 0.025). In a multivariate analysis, pCR was a significantprognostic factor for DFS (HR = 2.5; 95% CI [1.2,5.1]; p = 0.013) and OS (HR = 4.9;95% CI [1.4,17.4]; p = 0.012).
Six patients (2.8%) had an LVEF dec rease and two (0.9%) developed clinical congestiveheart failure.

Supporting Her2+ studies: Comparison of pCR rates



n is the number of patients in the chemotherapy plus Herceptin arm
[a] Randomized trial (i.e. non-Herceptin control arm)
F, 5-fluorouracil; E, epirubicin; C, cyclophosphamide; P, paclitaxel; D, docetaxel; H, Herceptin; M, methotrexate; X, Xeloda; A, doxorubicin
Number of cycles reflects q3w regimen.

1.3.4. Discussion on clinical efficacy

The efficacy data in this submission are mainly derived from one pivotal phase III study, MO16432 (NOAH), investigating the clinical benefit of neoadjuvant-adjuvant trastuzumab (T) in combination with neoadjuvant chemotherapy in patients with HER2+ locally advanced or inflammatory breast cancer.

The applicant has provided the requested sensitivity analyses to address methodological issues of the study as part of the responses. The results of these analyses do not raise any concerns of bias in favor of the treatment arm.

The chemotherapy regimen used in the NOAH trial is questionable as it was acceptable ten years ago but since then clinical practice has changed with taxane- and anthracycline-containing chemotherapies considered standard treatment in the adjuvant and neoadjuvant EBC setting . Cyclophosphamide and/or fluorouracil are now being combined with the anthracycline, reducing the number of cycles to only 8 instead of 10 as used in study MO16432 (St Gallen international expert consensus on the primary therapy of early breast cancer 2009.). Furthermore, additional CMF chemotherapy is no longer recommended.

However, several supportive studies which showed efficacy regarding pathological complete response, employed regimens which are in line with current guidelines, i.e. employing treatment regimens containing a taxane plus anthracycline combined with cyclophosphamide +/-fluorouracil for a total of 8 (and not 10) cycles.

In the pivotal trial, significant reduction in the risk of obtaining an event of 35% (unadjusted HR 0.65; 95% CI [0.44, 0.96]; p = 0.0275, Log-Rank test) was observed for the entire population (FAS), even though 20/116=17% of patients in the control arm crossed over to treatment with trastuzumab after positive results of treatment with Herceptin in the adjuvant setting were known.

In a sensitivity analysis, in which patients who crossed over to adjuvant trastuzumab were censored at the time of their first trastuzumab infusion, the resulting EFS hazard ratio was slightly better than in the primary analysis (unadjusted HR 0.59; 95% CI [0.40, 0.88]; p = 0.0084, Log-Rank test).

Results of subgroup analyses of EFS were generally consistent with those in the full analysis set. The only subgroup in which a benefit could not be shown was the group of patients ≤ 49 years of age, which may be due to the smaller patient numbers in the analysis or a chance event.

DFS is acceptable as a primary efficacy endpoint for registration trials, particularly in situations such as EBC where further lines of treatment following relapse may hamper the detection of a relevant treatment effect on OS. As an example, in the HERA trial, DFS was the primary endpoint. However, the primary endpoint of EFS should be supported by secondary efficacy endpoints of pCR, ORR and OS (Guideline on the Evaluation of Anticancer Med. Products in Man;CPMP/EWP/205/95/Rev3/Corr) to provide validity and clinical relevance to the primary endpoint.

Supportive evidence of clinical efficacy in this trial comes from pCR and OS data. Pathological examination of surgical specimens revealed that almost twice as many patients in the HER2+TC arm achieved a pathological complete response in breast and axilla (tpCR) and in breast (bpCR) compared with the HER2+C arm (tpCR: 40.0% HER2+TC vs. 20.7% HER2+C, p = 0.0014, Chi-squared test and bpCR: 44.3% HER2+TC vs. 26.7% HER2+C, p = 0.0051, Chi-squared test). Since pCR rate is widely regarded as a short term efficacy parameter which is highly correlated with EFS and OS, these data are reassuring.

The strongest evidence of benefit is provided by OS results. While the difference did not quite achieve statistical significance in the whole population, it did when the centre CRTN 47296 (for which issues were raised) was excluded with a hazard ratio of 0.52 (p = 0.034). Median survival time could not yet be estimated for patients in any of the arms due to the long survival duration of patients in the trial. This is not unexpected, since EBC is either curable or a disease with a long time course. An updated survival analysis provided as part of the responses confirmed the observed trend for OS 0.58 (95% CI: 0.35, 0.94; p-value of log-rank test: 0.0241)

Trials in the adjuvant setting have shown an overall survival benefit with the addition of one year of trastuzumab to chemotherapy (Smith I, et al 2007) which could not be shown in this trial.

Results obtained for ORR and also frequency/ type of surgery are somewhat peculiar with atypically high overall response rates and high numbers of patients not undergoing surgery which casts doubt on the validity of the data. However, reanalysis of the study data excluding the specific centre mostly responsible for these unexpected findings (ORR, surgery) with regard to the primary efficacy parameter, EFS, reconfirmed the study results and added robustness (HR 0.65; 95% CI [0.42, 1.00]; p= 0.0467, Log-Rank test).

Interestingly -though not a secondary endpoint-, twice as many patients had breast conserving surgery in the trastuzumab arm than in the chemo only arm (21.4% versus 10.5%).

Neoadjuvant plus adjuvant treatment was not compared with adjuvant treatment alone. Therefore, it cannot be concluded that the neoadjuvant component of trastuzumab treatment led to the improvement in event-free survival. In the product information it is reflected that the combination of one year of neoadjuvant-adjuvant therapy with trastuzumab led to the observed results.

The MAH provided additional supportive information to justify a broad therapeutic indication (ie, early as well as locally advanced breast cancer and inflammatory breast cancer) and the addition of trastuzumab to a broad range of neoadjuvant chemotherapy regimens (ie, current standard of care regimens, not just that employed in study MO16432). Thus, the relevance of supportive data from published trials was significant to the submission.

Supportive data are provided from six published randomized phase II or III studies of trastuzumab in the neoadjuvant setting. The additional supportive studies demonstrate that trastuzumab may be combined with different regimens in the neo-adjuvant/adjuvant setting and that combination therapy with trastuzumab leads to improved and consistent pCR rates. The supportive data provide also a positive correlation of the pathological response with DFS and OS and support the use of neoadjuvant trastuzumab in various disease stages with various chemotherapy regimens.

A consequence of the approval of the indicaton in the neoadjuvant indication would be the possibility of a continuum of treatment with Herceptin from beginning of diagnosis of early breast cancer until after progression of disease, with both indications being covered in the updated SmPC.

2. 3. 5. Conclusions on clinical efficacy

The pivotal trial met its primary endpoint of EFS (including both pre- and postoperative events), with a hazard ratio of 0.65 (p = 0.0275); this was essentially due to lower recurrence rates.

A compelling effect of trastuzumab was observed on pathological response which was reflected in a doubling of operations with more breast-conservative surgery (21% vs. 10%), but the strongest evidence of benefit was provided by OS results, which -after the exploratory analyses requested to resolve methodological issues,- achieved a statistical significance with a hazard ratio of 0.52 (p = 0.034).

In summary, the combined evidence of the supportive studies plus the NOAH trial support the general use of neoadjuvant-adjuvant trastuzumab in combination with clinically proven neoadjuvant chemotherapy regimens for HER2-positive breast cancer.

1.4. Clinical Safety aspects

In study MO16432, 115 patients with HER2-positive breast cancer were exposed to trastuzumab (6 mg/kg every three weeks, three weeks after an initial 8 mg/kg loading dose) in combination with neoadjuvant chemotherapy.

In the MDACC study, 45 patients with HER2-positive breast cancer received trastuzumab (2 mg/kg every week, after an initial 4 mg/kg loading dose) in combination with chemotherapy.

In the GeparQuattro study, 443 patients with HER2-positive breast cancer received trastuzumab (6 mg/kg every three weeks, three weeks after an initial 8 mg/kg loading Herceptin (trastuzumab) concomitantly to all chemotherapy cycles:

In the MO16432 and GeparQuattro studies, trastuzumab treatment was continued after surgery as adjuvant therapy for a total treatment duration of 1 year. Additionally, patients with HER2-positive disease randomized to receive neoadjuvant chemotherapy alone in study MO16432 were offered one year of post-operative adjuvant trastuzumab (protocol MO16432 amendment D).

The safety data presented here focuses primarily on study MO16432 and are supported by data from the two supportive publications where feasible and appropriate.

1.4.1. Clinical safety Results (NOAH trial)

All patients who received at least one dose of study medication and had documented informed consent and documented approval of protocol amendments were included in the safety analysis population (SAP) for the analysis of all assessments prior to and including surgery. Treatment arms were defined by the actual study medication received prior to surgery.

The **SAP** comprised **326 patients** (HER2+TC: 115 patients; HER2+C: 112 patients; HER2–C: 99 patients).

SAP-P: A second safety population was defined for the safety analyses of assessments/events after surgery: all patients in the SAP who had at least one safety assessment after surgery, or who did not undergo surgery but had at least one safety assessment starting more than 28 days after the last dose of neoadjuvant chemotherapy or after the first dose of adjuvant trastuzumab, were included in the post-surgery safety analysis population (SAP-P).

Forty-seven patients from the SAP were excluded from the SAP-P as they had no safety assessment after surgery (3 patients in the HER2+TC arm, 24 patients in the HER2+C arm, and 20 patients in the HER2–C arm). Twenty patients in the HER2+C arm crossed over to receive adjuvant trastuzumab and were analyzed separately as a fourth treatment group (HER2+C ->T). The SAP-P comprised **279 patients** (HER2+TC: 112 patients; HER2+C->T: 20 patients; HER2+C: 68 patients; HER2–C: 79 patients).

At the time of the clinical cut-off, the median duration of overall follow-up for the SAP was 45.9 months (range 2.1-76.8 months) in the HER2+TC arm, 42.55 months (range 2.1-77.5 months) in the HER2+C and 48.13 months (range 0.9-75.5 months) in the HER2-C arm

Extent of exposure

The number of patients in the full analysis set who received at least one dose of study medication was 115 in the HER2+TC arm, 112 in the HER2+C arm, and 99 in the HER2–C arm.

Exposure to Trastuzumab:
All patients treated with trastuzumab received at least two cycles. The median number of cycles administered to HER2+TC patients was 16 out of a planned number of 17. The median number of trastuzumab cycles administered during the pre-operative period was 11 (range 2-11), ie, the planned number of cycles.

The 20 patients who crossed over to receive adjuvant trastuzumab received a median of 17 trastuzumab infusions (range 11-18).

Overall Treatment Exposure of Trastuzumab (SAP)

Parameter	Statistic/Category	HER2+TC (N=115) N	%	HER2+C->T (N= 20) N	%
Total number of patients receiving at least one cycle	N (%)	115	(100)	20	(100)
Total number of cycles per treatment group	N	1812		337	
Number of cycles per patient	N	115		20	
	Mean	15.8		16.9	
	SD	2.47		1.53	
	Min	2		11	
	Median	16.0		17.0	
	Max	18		18	
	<= 8	3	(2.6)	0	
	> 8 and <= 16	58	(50.4)	2	(10.0)
	>= 17	54	(47.0)	18	(90.0)
Cumulative dose (mg)	N	114		20	
	Mean	6728.5		7404.0	
	SD	1632.02		1124.39	
	Min	812		5376	
	Median	6752.5		7254.0	
	Max	11805		9360	
Number of dose adjustments per patient [1]	None	96	(83.5)	18	(90.0)
	1	4	(3.5)	1	(5.0)
	2	13	(11.3)	1	(5.0)
	3	1	(0.9)	0	
	4	1	(0.9)	0	
Total number of dose adjustments per treatment group [1]	N	37		3	
Number of dose delays per patient	None	40	(34.8)	9	(45.0)
	1	28	(24.3)	3	(15.0)
	2	17	(14.8)	6	(30.0)
	3	11	(9.6)	1	(5.0)
	4	5	(4.3)	1	(5.0)
	5	8	(7.0)	0	
	6	1	(0.9)	0	
	7	2	(1.7)	0	
	8	1	(0.9)	0	
	9	2	(1.7)	0	
Total number of dose delays per treatment group	N	201		22	

[1] Only changes in dose from one cycle to the other of at least 10% in either direction were considered as dose adjustments.
Percentages are calculated with respect to the total number of patients receiving at least one cycle.

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Data source: page 360 .

Exposure to Chemotherapy:

A large proportion of patients across the 3 treatment arms received the planned number of 10 cycles of neoadjuvant chemotherapy; 3 cycles of doxorubicin and paclitaxel followed by 4 cycles of paclitaxel alone followed by 3 cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (110/115 HER2+TC patients [95.7%], 103/116 HER2+C patients [88.8%], 84/99 HER2−C patients [84.8%]). Although dose delays were relatively common (reported in up to 41% of patients per treatment), the majority of patients received the planned doses of neoadjuvant chemotherapy (dose adjustments of ≥ 10% were required in < 7% of patients per treatment across treatment arms).

The mean and median cumulative doses for each chemotherapy drug were the same or very similar across treatment arms, as was the frequency of dose delays. This indicates that chemotherapy dose intensity was similar with or without trastuzumab.

Exposure to Doxorubicin and Paclitaxel

More than 98% of patients across the treatment arms received the three cycles of doxorubicin and paclitaxel as planned. Exposure was similar in the three groups of patients, as indicated by the median cumulative dose of doxorubicin (306-312 mg), and paclitaxel (774-780 mg).

Exposure to Doxorubicin and Paclitaxel during the Pre-Operative Period (All Cycles, SAP)

Drug	Parameter	Statistic/Category	HER2+TC (N=115) N	%	HER2+C (N=112) N	%	HER2−C (N= 99) N	%
Doxorubicin	Total number of patients receiving at least one cycle	N (%)	115	(100)	112	(100)	99	(100)
	Number of cycles per patient	1	0		0		1	(1.0)
		2	1	(0.9)	0		1	(1.0)
		3	114	(99.1)	112	(100)	97	(98.0)
	Total number of cycles per treatment group	N	344		336		294	
	Cumulative dose (mg)	N	115		111		99	
		Mean	309.0		309.5		316.8	
		SD	34.68		28.18		58.98	
		Min	168		250		100	
		Median	306.0		308.0		312.0	
		Max	390		380		772	
Paclitaxel	Total number of patients receiving at least one cycle	N (%)	115	(100)	112	(100)	99	(100)
	Number of cycles per patient	1	0		0		1	(1.0)
		2	1	(0.9)	0		1	(1.0)
		3	114	(99.1)	112	(100)	97	(98.0)
	Total number of cycles per treatment group	N	344		336		294	
	Cumulative dose (mg)	N	115		111		99	
		Mean	778.7		775.0		777.0	
		SD	83.06		78.27		105.10	
		Min	480		627		248	
		Median	778.0		774.0		780.0	
		Max	990		1155		990	
Doxorubicin + Paclitaxel	Total number of patients receiving at least one cycle	N (%)	115	(100)	112	(100)	99	(100)
	Number of dose adjustments per patient [1]	None	111	(96.5)	105	(93.8)	96	(97.0)
		1	4	(3.5)	7	(6.3)	3	(3.0)
	Total number of dose adjustments per treatment group [1]	N	4		7		3	
	Number of dose delays per patient	None	83	(72.2)	85	(75.9)	80	(80.8)
		1	24	(20.9)	20	(17.9)	15	(15.2)
		2	8	(7.0)	5	(4.5)	3	(3.0)
		3	0		2	(1.8)	1	(1.0)
	Total number of dose delays per treatment group	N	40		36		24	

[1] Only changes in dose from one cycle to the other of at least 10% in either direction were considered as dose adjustments.
For each drug, percentages are calculated with respect to the total number of patients receiving at least one cycle.

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Exposure to Paclitaxel Alone

More than 96% of patients across the treatment arms received the four cycles of paclitaxel alone as planned. Exposure was similar in the three groups of patients, as indicated by similarities in the

median cumulative dose of paclitaxel (1200 mg). However, one patient in the HER2+TC arm, 2 patients, in the HER2+C arm and 4 patients in the HER2-C arm (based on the SAP) did not receive at least one cycle of paclitaxel alone.

Exposure to Paclitaxel Alone during the Pre-Operative Period (All Cycles, SAP)

Parameter	Statistic/Category	HER2+TC (N=115) N	%	HER2+C (N=112) N	%	HER2-C (N= 99) N	%
Total number of patients receiving at least one cycle	N (%)	114	(100)	110	(100)	95	(100)
Total number of cycles per treatment group	N	452		431		378	
Number of cycles per patient	1	1	(0.9)	2	(1.8)	0	
	2	0		1	(0.9)	0	
	3	1	(0.9)	1	(0.9)	2	(2.1)
	4	112	(98.2)	106	(96.4)	93	(97.9)
Cumulative dose (mg)	N	114		110		95	
	Mean	1190.6		1160.4		1207.9	
	SD	149.21		177.95		135.81	
	Min	345		285		647	
	Median	1200.0		1200.0		1200.0	
	Max	1504		1464		1556	
Number of dose adjustments per patient [1]	None	110	(96.5)	103	(93.6)	90	(94.7)
	1	4	(3.5)	7	(6.4)	4	(4.2)
	2	0		0		1	(1.1)
Total number of dose adjustments per treatment group [1]	N	4		7		6	
Number of dose delays per patient	None	77	(67.5)	66	(60.0)	64	(67.4)
	1	25	(21.9)	28	(25.5)	22	(23.2)
	2	8	(7.0)	13	(11.8)	8	(8.4)
	3	4	(3.5)	3	(2.7)	1	(1.1)
Total number of dose delays per treatment group	N	53		63		41	

[1] Only changes in dose from one cycle to the other of at least 10% in either direction were considered as dose adjustments.
Percentages are calculated with respect to the total number of patients receiving at least one cycle.

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Exposure to Cyclophosphamide, Methotrexate and Fluorouracil

Two patients in the HER2+TC arm, 8 patients in the HER2+C arm and 9 patients in the HER2-C arm (based on the SAP) did not receive at least one cycle of CMF. Of patients who received at least one cycle of CMF, more than 93% across the treatment arms received the 3 cycles of CMF as planned. Exposure was similar in the three groups of patients, as indicated by the median cumulative dose of cyclophosphamide (6120-6198 mg), methotrexate (414-420 mg) and fluorouracil (6102-6162 mg).

Exposure to Cyclophosphamide, Methotrexate and Fluorouracil during the Pre-Operative Period (All Cycles, SAP)

Drug	Parameter	Statistic/Category	HER2+TC (N=115) N	%	HER2+C (N=112) N	%	HER2-C (N= 99) N	%
Cyclophosphamide (C)	Total number of patients receiving at least one cycle	N (%)	113	(100)	104	(100)	90	(100)
	Number of cycles per patient	1	1	(0.9)	1	(1.0)	4	(4.4)
		2	1	(0.9)	0		1	(1.1)
		3	111	(98.2)	103	(99.0)	85	(94.4)
	Total number of cycles per treatment group	N	336		310		261	
	Cumulative dose (mg)	N	113		104		90	
		Mean	6086.9		6058.1		6032.2	
		SD	886.63		768.58		1207.26	
		Min	2160		1080		1104	
		Median	6120.0		6120.0		6198.0	
		Max	8600		7560		7980	
Methotrexate (M)	Total number of patients receiving at least one cycle	N (%)	113	(100)	104	(100)	90	(100)
	Number of cycles per patient	1	2	(1.8)	1	(1.0)	5	(5.6)
		2	1	(0.9)	0		1	(1.1)
		3	110	(97.3)	103	(99.0)	84	(93.3)
	Total number of cycles per treatment group	N	334		310		259	
	Cumulative dose (mg)	N	113		104		90	
		Mean	403.4		403.5		399.2	
		SD	63.93		52.39		84.85	
		Min	136		72		74	
		Median	420.0		420.0		414.0	
		Max	580		510		534	
Flourouracil (F)	Total number of patients receiving at least one cycle	N (%)	113	(100)	104	(100)	90	(100)
	Number of cycles per patient	1	1	(0.9)	1	(1.0)	5	(5.6)
		2	2	(1.8)	0		1	(1.1)
		3	110	(97.3)	103	(99.0)	84	(93.3)
	Total number of cycles per treatment group	N	335		310		259	
	Cumulative dose (mg)	N	113		104		90	
		Mean	6071.3		6010.1		5983.3	
		SD	915.44		850.06		1271.40	
		Min	2160		1080		1104	
		Median	6120.0		6102.0		6162.0	
		Max	8600		7560		7980	
CMF	Total number of patients receiving at least one cycle	N (%)	113	(100)	104	(100)	90	(100)
	Number of dose adjustments per patient [1]	None	108	(95.6)	98	(94.2)	89	(98.9)
		1	5	(4.4)	3	(2.9)	1	(1.1)
		2	0		3	(2.9)	0	
	Total number of dose adjustments per treatment group [1]	N	5		9		1	
	Number of dose delays per patient	None	68	(60.2)	61	(58.7)	58	(64.4)
		1	29	(25.7)	22	(21.2)	16	(17.8)
		2	10	(8.8)	14	(13.5)	12	(13.3)
		3	5	(4.4)	6	(5.8)	4	(4.4)
		4	1	(0.9)	1	(1.0)	0	
	Total number of dose delays per treatment group	N	68		72		52	

[1] Only changes in dose from one cycle to the other of at least 10% in either direction were considered as dose adjustments.
For each drug, percentages are calculated with respect to the total number of patients receiving at least one cycle.

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Overview of all grade adverse events by body system

Pre-operative period

During the pre-operative period, almost all patients experienced at least one treatment emergent adverse event (HER2+TC: 113 patients, 98.3%; HER2+C: 112 patients, 100%; HER2–C: 98 patients, 99.0%). However, the majority of events across all three treatment arms were Grade 1/2 in severity

Summary of the main characteristics of treatment-emergent adverse events in the pre-operative period - Safety analysis Population

Characteristic	HER2+TC		HER2+C		HER2-C	
	n %	N %	n %	N %	n %	N %
Total number of patients in treatment group		115 (100)		112 (100)		99 (100)
All adverse events	2210 (100)	113 (98.3)	2072 (100)	112 (100)	1230 (100)	98 (99.0)
Serious adverse events (SAEs)	18 (0.8)	12 (10.4)	14 (0.7)	8 (7.1)	8 (0.7)	6 (6.1)
Treatment related adverse events [1]	2037 (92.2)	113 (98.3)	1940 (93.6)	112 (100)	1130 (91.9)	98 (99.0)
Treatment related SAEs [1]	14 (0.6)	10 (8.7)	14 (0.7)	8 (7.1)	5 (0.4)	5 (5.1)
Fatal adverse events [2]	0	0	0	0	0	0
Treatment related fatal AEs [2]	0	0	0	0	0	0
Cardiac AEs	25 (1.1)	14 (12.2)	21 (1.0)	15 (13.4)	5 (0.4)	3 (3.0)
Cardiac AEs including abnormal investigations associated with left ventricular dysfunction	27 (1.2)	16 (13.9)	21 (1.0)	15 (13.4)	5 (0.4)	3 (3.0)
Grade						
1	1495 (67.6)	112 (97.4)	1347 (65.0)	109 (97.3)	808 (65.7)	93 (93.9)
2	624 (28.2)	110 (95.7)	645 (31.1)	108 (96.4)	352 (28.6)	92 (92.9)
3	65 (2.9)	43 (37.4)	70 (3.4)	44 (39.3)	50 (4.1)	32 (32.3)
4	2 (0.1)	2 (1.7)	7 (0.3)	6 (5.4)	5 (0.4)	5 (5.1)
Missing	24 (1.1)	5 (4.3)	3 (0.1)	3 (2.7)	15 (1.2)	6 (6.1)
Outcome						
Recovered, no sequelae	2082 (94.2)	113 (100)	1903 (91.8)	111 (99.1)	1071 (87.1)	96 (98.0)
Recovered with sequelae not required Rx	6 (0.3)	5 (4.4)	11 (0.5)	9 (8.0)	10 (0.8)	6 (6.1)
Recovered with sequelae required Rx	0	0	6 (0.3)	5 (4.5)	3 (0.2)	2 (2.0)
Ongoing	63 (2.9)	37 (32.7)	113 (5.5)	54 (48.2)	82 (6.7)	49 (50.0)
Missing	59 (2.7)	36 (31.9)	39 (1.9)	21 (18.8)	64 (5.2)	29 (29.6)

[1] Including events with unknown relationship to study medication
[2] Fatal adverse events are adverse events with outcome "died".
Note: n = number of events, N = number of patients. Due to the way that the data were recorded, information pertaining to one adverse event might have been found in several records in the database and thus needed to be combined to one record for analysis. For a detailed description, see the SAP. An adverse event is considered as treatment-emergent in the pre-operative period if it started or worsened on the day or after first administration of study drug up to the date of surgery (or up to the first dose of adjuvant trastuzumab / up to 28 days after the last dose of neo-adjuvant chemotherapy, whichever is first, for patients not undergoing surgery)

Characteristic	HER2+TC		HER2+C		HER2-C	
	n %	N %	n %	N %	n %	N %
Action taken						
None	2163 (97.9)	113 (100)	2042 (98.6)	112 (100)	1208 (98.2)	98 (100)
Discontinued	1 (<0.1)	1 (0.9)	0	0	4 (0.3)	3 (3.1)
Interrupted	18 (0.8)	9 (8.0)	8 (0.4)	7 (6.3)	5 (0.4)	5 (5.1)
Dose reduced	6 (0.3)	6 (5.3)	14 (0.7)	10 (8.9)	7 (0.6)	7 (7.1)
Dose frequency changed	10 (0.5)	8 (7.1)	2 (0.1)	1 (0.9)	1 (0.1)	1 (1.0)
Dose reduced and dose frequency changed	2 (0.1)	1 (0.9)	0	0	2 (0.2)	1 (1.0)
Missing	10 (0.5)	7 (6.2)	6 (0.3)	5 (4.5)	3 (0.2)	3 (3.1)

Treatment emergent AE´s with at least 5% incidence in any Her2+ treatment arm

Primary system organ class (SOC) Preferred term	HER2+TC (N=115) N %	HER2+C (N=112) N %	HER2-C (N= 99) N %
Total number of patients with TEAE(s)	113 (98.3)	112 (100)	98 (99.0)
GASTROINTESTINAL DISORDERS	106 (92.2)	99 (88.4)	80 (80.8)
NAUSEA	88 (76.5)	87 (77.7)	69 (69.7)
VOMITING	54 (47.0)	52 (46.4)	36 (36.4)
STOMATITIS	46 (40.0)	44 (39.3)	21 (21.2)
DIARRHOEA	34 (29.6)	32 (28.6)	18 (18.2)
ABDOMINAL PAIN UPPER	19 (16.5)	7 (6.3)	1 (1.0)
CONSTIPATION	15 (13.0)	20 (17.9)	11 (11.1)
ABDOMINAL PAIN	12 (10.4)	14 (12.5)	5 (5.1)
DYSPEPSIA	9 (7.8)	3 (2.7)	7 (7.1)
ABDOMINAL PAIN LOWER	3 (2.6)	7 (6.3)	1 (1.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	106 (92.2)	101 (90.2)	91 (91.9)
ALOPECIA	91 (79.1)	87 (77.7)	90 (90.9)
ALOPECIA TOTALIS	19 (16.5)	20 (17.9)	0
NAIL DISORDER	9 (7.8)	9 (8.0)	10 (10.1)
RASH	8 (7.0)	7 (6.3)	5 (5.1)
ERYTHEMA	6 (5.2)	8 (7.1)	1 (1.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	87 (75.7)	78 (69.6)	52 (52.5)
ASTHENIA	52 (45.2)	57 (50.9)	31 (31.3)
INFLUENZA LIKE ILLNESS	26 (22.6)	25 (22.3)	0
PYREXIA	23 (20.0)	13 (11.6)	8 (8.1)
FATIGUE	20 (17.4)	15 (13.4)	13 (13.1)
MUCOSAL INFLAMMATION	15 (13.0)	14 (12.5)	14 (14.1)
OEDEMA PERIPHERAL	7 (6.1)	10 (8.9)	6 (6.1)
CHEST PAIN	5 (4.3)	7 (6.3)	2 (2.0)
NERVOUS SYSTEM DISORDERS	84 (73.0)	85 (75.9)	68 (68.7)
NEUROPATHY PERIPHERAL	23 (20.0)	25 (22.3)	5 (5.1)
PARAESTHESIA	22 (19.1)	28 (25.0)	21 (21.2)
PERIPHERAL SENSORY NEUROPATHY	14 (12.2)	16 (14.3)	23 (23.2)
DYSGEUSIA	12 (10.4)	16 (14.3)	8 (8.1)
HEADACHE	11 (9.6)	15 (13.4)	8 (8.1)
SENSORY DISTURBANCE	10 (8.7)	10 (8.9)	11 (11.1)
DIZZINESS	7 (6.1)	7 (6.3)	2 (2.0)
NEUROTOXICITY	6 (5.2)	4 (3.6)	5 (5.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	77 (67.0)	56 (50.0)	58 (58.6)
MYALGIA	32 (27.8)	25 (22.3)	31 (31.3)
ARTHRALGIA	28 (24.3)	23 (20.5)	19 (19.2)
BONE PAIN	15 (13.0)	17 (15.2)	14 (14.1)
PAIN IN EXTREMITY	10 (8.7)	5 (4.5)	4 (4.0)
MUSCULOSKELETAL PAIN	9 (7.8)	4 (3.6)	4 (4.0)
MUSCULAR WEAKNESS	5 (4.3)	7 (6.3)	4 (4.0)
INFECTIONS AND INFESTATIONS	51 (44.3)	41 (36.6)	23 (23.2)
INFLUENZA	12 (10.4)	20 (17.9)	5 (5.1)
PHARYNGITIS	7 (6.1)	1 (0.9)	1 (1.0)
RHINITIS	7 (6.1)	1 (0.9)	0
CYSTITIS	6 (5.2)	4 (3.6)	0
EYE DISORDERS	49 (42.6)	34 (30.4)	12 (12.1)
CONJUNCTIVITIS	34 (29.6)	22 (19.6)	7 (7.1)
LACRIMATION INCREASED	15 (13.0)	5 (4.5)	1 (1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	46 (40.0)	25 (22.3)	10 (10.1)
RHINORRHOEA	21 (18.3)	9 (8.0)	0
EPISTAXIS	16 (13.9)	2 (1.8)	1 (1.0)
COUGH	12 (10.4)	3 (2.7)	2 (2.0)
DYSPNOEA EXERTIONAL	8 (7.0)	3 (2.7)	1 (1.0)
DYSPNOEA	7 (6.1)	8 (7.1)	4 (4.0)
VASCULAR DISORDERS	28 (24.3)	25 (22.3)	11 (11.1)
HOT FLUSH	15 (13.0)	6 (5.4)	7 (7.1)
HYPERAEMIA	6 (5.2)	4 (3.6)	0
HYPERTENSION	3 (2.6)	6 (5.4)	1 (1.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	25 (21.7)	32 (28.6)	26 (26.3)
AMENORRHOEA	14 (12.2)	13 (11.6)	14 (14.1)
MENSTRUATION IRREGULAR	12 (10.4)	8 (7.1)	11 (11.1)
BREAST PAIN	2 (1.7)	6 (5.4)	2 (2.0)
INVESTIGATIONS	19 (16.5)	9 (8.0)	8 (8.1)
WEIGHT INCREASED	6 (5.2)	3 (2.7)	1 (1.0)
METABOLISM AND NUTRITION DISORDERS	15 (13.0)	21 (18.8)	12 (12.1)
DECREASED APPETITE	15 (13.0)	20 (17.9)	9 (9.1)
PSYCHIATRIC DISORDERS	15 (13.0)	13 (11.6)	11 (11.1)
INSOMNIA	7 (6.1)	6 (5.4)	4 (4.0)
CARDIAC DISORDERS	14 (12.2)	15 (13.4)	3 (3.0)
ANGINA PECTORIS	5 (4.3)	5 (4.5)	0
TACHYCARDIA	5 (4.3)	5 (4.5)	1 (1.0)
PALPITATIONS	3 (2.6)	3 (2.7)	1 (1.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	13 (11.3)	9 (8.0)	7 (7.1)
FEBRILE NEUTROPENIA	8 (7.0)	4 (3.6)	3 (3.0)

Percentages are calculated with respect to the total number of patients in each treatment group.
Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.

Program : $PROD/cdp10326/mo16432/stteae.sas / Output : $PROD/cdp10326/mo16432/reports/stteaesa.r18
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Data source: page 437.

The most common AEs (in at least 50% of patients) by system organ class were as follows:

• **Gastrointestinal disorders** (HER2+TC: 92.2%; HER2+C: 88.4%; HER2–C: 80.8%): nausea, vomiting, stomatitis, diarrhea, abdominal pain, and constipation.
• **Skin and subcutaneous tissue disorders** (HER2+TC: 92.2%; HER2+C: 90.2%; HER2–C: 91.9%): alopecia, and nail disorder.

• **General disorders and administration site conditions** (HER2+TC: 75.7%; HER2+C: 69.6%; HER2–C: 52.5%): asthenia, influenza-like illness, pyrexia, fatigue, and mucosal inflammation.
• **Nervous system disorders** (HER2+TC: 73.0%; HER2+C: 75.9%; HER2–C: 68.7%): peripheral neuropathy, paresthesia, peripheral sensory neuropathy, dysgeusia, and headache.
• **Musculoskeletal and connective tissue disorders** (HER2+TC: 67.0%; HER2+C: 50.0%; HER2–C: 58.6%): myalgia, arthralgia, bone pain, and pain in extremity.

Adverse events which occurred with ≥ 5% higher incidence in the HER2+TC arm compared with the HER2+C arm included

conjunctivitis (29.6% vs 19.6%)
myalgia (27.8% vs 22.3%)
pyrexia (20.0% vs 11.6%)
hot flush (13.0% vs 5.4%)
rhinorrhea (18.3% vs 8.0%)
epistaxis (13.9% vs 1.8%)
lacrimation increase (13.0% vs 4.5%)
cough (10.4% vs 2.7%)
pharyngitis (6.1% vs 0.9%) and
rhinitis (6.1% vs 0.9%).

The higher incidence of events in the SOC investigations for patients in the HER2+TC arm compared with the HER2+C arm (16.5% vs 8.0%) was contributed to by higher incidences of increased weight (5.2% vs 2.7%), increased ALT (2.6% vs 1.8%), increased AST (2.6% vs 0.9%), and increased heart rate (2.6% vs 0.9%)

Among *blood and lymphatic system disorders*, the incidence of febrile neutropenia was slightly higher among patients in the HER2+TC arm (7.0%) compared with the HER2+C arm (3.6%). Importantly, the incidence of AEs in the SOC *cardiac disorders* was similar in the two groups of patients with HER2+ disease (12.2% vs 13.4%)

Post-operative period
More adverse events were reported for patients in the HER2+TC and HER2+C→T arms compared with the HER2+C and HER2–C arms during the post-operative period (HER2+TC: 76/112 patients, 67.9%; HER2+C→T: 17/20 patients, 85%; HER2+C: 34/68 patients, 50%; HER2–C: 40/79 patients, 50.6%)

The majority of adverse events reported during the post-operative period were Grade 1/2 in severity (HER2+TC: 259/286 events, 90.5%; HER2+C→T: 85/87 events, 97.7%; HER2+C: 70/78 events, 89.7%; HER2-C: 58/73 events, 79.5%)

There was one fatal adverse event in a patient in the HER2-negative parallel control arm and there were no fatal cardiac events.

Treatment-Emergent Adverse Events with Incidence Greater Than 5% in any HER2-Positive Treatment Arm in the Post-Operative Period (SAP-P)

Primary system organ class (SOC) Preferred term	HER2+TC (N=112) N %	HER2+C->T (N= 20) N %	HER2+C (N= 68) N %	HER2-C (N= 79) N %
Total number of patients with TEAE(s)	76 (67.9)	17 (85.0)	34 (50.0)	40 (50.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	27 (24.1)	8 (40.0)	4 (5.9)	5 (6.3)
ASTHENIA	16 (14.3)	3 (15.0)	3 (4.4)	1 (1.3)
FATIGUE	7 (6.3)	2 (10.0)	0	0
OEDEMA PERIPHERAL	6 (5.4)	2 (10.0)	1 (1.5)	0
PYREXIA	4 (3.6)	1 (5.0)	0	1 (1.3)
CHEST PAIN	2 (1.8)	2 (10.0)	0	0
CHILLS	1 (0.9)	2 (10.0)	0	0
INFLUENZA LIKE ILLNESS	0	1 (5.0)	0	0
MALAISE	0	1 (5.0)	0	0
INFECTIONS AND INFESTATIONS	26 (23.2)	7 (35.0)	6 (8.8)	6 (7.6)
INFLUENZA	4 (3.6)	4 (20.0)	0	0
NASOPHARYNGITIS	0	2 (10.0)	0	0
SUBCUTANEOUS ABSCESS	0	1 (5.0)	0	0
UPPER RESPIRATORY TRACT INFECTION	0	1 (5.0)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	22 (19.6)	6 (30.0)	9 (13.2)	5 (6.3)
ARTHRALGIA	9 (8.0)	3 (15.0)	3 (4.4)	1 (1.3)
BONE PAIN	6 (5.4)	4 (20.0)	2 (2.9)	0
BACK PAIN	5 (4.5)	1 (5.0)	2 (2.9)	1 (1.3)
PAIN IN EXTREMITY	2 (1.8)	2 (10.0)	1 (1.5)	1 (1.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	20 (17.9)	5 (25.0)	6 (8.8)	11 (13.9)
ERYTHEMA	10 (8.9)	1 (5.0)	3 (4.4)	4 (5.1)
DERMATITIS	2 (1.8)	1 (5.0)	1 (1.5)	3 (3.8)
RASH	2 (1.8)	3 (15.0)	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	15 (13.4)	2 (10.0)	4 (5.9)	10 (12.7)
RADIATION SKIN INJURY	7 (6.3)	1 (5.0)	2 (2.9)	7 (8.9)
SERUMA	2 (1.8)	1 (5.0)	0	1 (1.3)
NERVOUS SYSTEM DISORDERS	14 (12.5)	6 (30.0)	6 (8.8)	5 (6.3)
HEADACHE	6 (5.4)	0	2 (2.9)	0
DIZZINESS	3 (2.7)	1 (5.0)	2 (2.9)	0
NEUROPATHY PERIPHERAL	3 (2.7)	1 (5.0)	0	0
PERIPHERAL SENSORY NEUROPATHY	3 (2.7)	2 (10.0)	1 (1.5)	1 (1.3)
PARAESTHESIA	0	1 (5.0)	0	1 (1.3)
SYNCOPE	0	2 (10.0)	0	0
VASCULAR DISORDERS	12 (10.7)	1 (5.0)	4 (5.9)	5 (6.3)
LYMPHORRHOEA	1 (0.9)	1 (5.0)	0	0
GASTROINTESTINAL DISORDERS	11 (9.8)	4 (20.0)	6 (8.8)	1 (1.3)
VOMITING	4 (3.6)	2 (10.0)	1 (1.5)	0
NAUSEA	2 (1.8)	2 (10.0)	3 (4.4)	1 (1.3)
ABDOMINAL PAIN UPPER	1 (0.9)	2 (10.0)	0	0
DIARRHOEA	1 (0.9)	1 (5.0)	0	0
ODYNOPHAGIA	0	1 (5.0)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	11 (9.8)	4 (20.0)	8 (11.8)	2 (2.5)
COUGH	3 (2.7)	1 (5.0)	0	1 (1.3)
DYSPNOEA	0	1 (5.0)	4 (5.9)	0
OROPHARYNGEAL PAIN	0	3 (15.0)	0	0
RESPIRATORY DISTRESS	0	1 (5.0)	0	0
INVESTIGATIONS	9 (8.0)	2 (10.0)	1 (1.5)	0
ALANINE AMINOTRANSFERASE INCREASED	0	1 (5.0)	0	0
ELECTROCARDIOGRAM T WAVE ABNORMAL	0	1 (5.0)	0	0
CARDIAC DISORDERS	8 (7.1)	2 (10.0)	4 (5.9)	0
PALPITATIONS	0	1 (5.0)	0	0
SINUS TACHYCARDIA	0	1 (5.0)	0	0

Primary system organ class (SOC) Preferred term	HER2+TC (N=112) N %	HER2+C->T (N= 20) N %	HER2+C (N= 68) N %	HER2-C (N= 79) N %
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	6 (5.4)	1 (5.0)	4 (5.9)	1 (1.3)
BREAST PAIN	3 (2.7)	1 (5.0)	1 (1.5)	0
EAR AND LABYRINTH DISORDERS	3 (2.7)	1 (5.0)	0	1 (1.3)
VERTIGO	2 (1.8)	1 (5.0)	0	1 (1.3)
EAR PAIN	0	1 (5.0)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.9)	1 (5.0)	1 (1.5)	1 (1.3)
ANAEMIA	0	1 (5.0)	0	0
IMMUNE SYSTEM DISORDERS	0	1 (5.0)	0	1 (1.3)
HYPERSENSITIVITY	0	1 (5.0)	0	1 (1.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (5.0)	0	2 (2.5)
THYROID NEOPLASM	0	1 (5.0)	0	0
RENAL AND URINARY DISORDERS	0	1 (5.0)	0	0
DYSURIA	0	1 (5.0)	0	0

Percentages are calculated with respect to the total number of patients in each treatment group.
Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
Note: For patients receiving neoadjuvant chemotherapy only (groups HER2+C and HER2-C) fewer post-operative TEAEs were to be expected as adverse events were only to be reported until 28 days after last administration of study drug, with the exception of treatment related serious adverse events.

Program : $PROD/odp10326/mo16432/stteae.sas / Output : $PROD/odp10326/mo16432/reports/stteaeta.r18
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Data source: page 465 .

Grade 3 and 4 Adverse Events

During the pre-operative period, the proportion of patients reporting Grade 3 or 4 AEs was relatively similar across the treatment arms (HER2+TC: 39.1%; HER2+C: 41.1%; HER2–C: 34.3%).

The most common Grade 3 or 4 AEs reported (≥10% in at least one treatment arm) were in the system organ classes skin and subcutaneous tissue disorders (HER2+TC: 15.7%; HER2+C: 11.6%; HER2–C: 3.0%), reproductive system and breast disorders (HER2+TC: 9.6%; HER2+C: 8.9%; HER2–C: 16.2%), and gastrointestinal disorders (HER2+TC: 3.5%; HER2+C: 11.6%; HER2–C: 5.1%).

Treatment-emergent adverse events with a Grade 4 intensity were infrequent.
In the HER2+TC arm, Grade 4 febrile neutropenia was experienced by two patients (1.7%; pts 32078/003, 32086/020)

In the HER2+C arm, 5.4% of patients (6/112) had at least one Grade 4 event:
febrile neutropenia (pt 32057/008)
neutropenia (pts 32074/022, 33810/001)
nausea and vomiting (pt 32065/021)
pyrexia (pt 32059/004) and back pain(pt 32065/004).

In the HER2-C arm, 5.1% (5/99) of patients experienced a Grade 4 event:
febrile neutropenia (pts 33810/005, 32057/007),
neutropenia (pt 33809/001),
stomatitis(pt 32062/004) and pulmonary embolism (pt 32086/009).

Grade 3 AEs were reported in 43 patients (37.4%) in the HER2+TC arm, 44 patients (39.3%) in the HER2+C arm, and 32 patients (32.3%) in the HER2–C arm.

Grade 3 or 4 Treatment-Emergent Adverse Events occurring during the Pre-Operative Period (SAP)

Primary system organ class (SOC) Preferred term	HER2+TC (N=115) N %	HER2+C (N=112) N %	HER2-C (N= 99) N %
Total number of patients with TEAE(s) of grade 3 or 4	45 (39.1)	46 (41.1)	34 (34.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	18 (15.7)	13 (11.6)	3 (3.0)
ALOPECIA TOTALIS	14 (12.2)	11 (9.8)	0
ALOPECIA	5 (4.3)	4 (3.6)	2 (2.0)
PRURITUS	1 (0.9)	0	1 (1.0)
ONYCHOLYSIS	0	1 (0.9)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	11 (9.6)	10 (8.9)	16 (16.2)
AMENORRHOEA	7 (6.1)	5 (4.5)	7 (7.1)
MENSTRUATION IRREGULAR	5 (4.3)	4 (3.6)	8 (8.1)
BREAST PAIN	0	1 (0.9)	1 (1.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	9 (7.8)	6 (5.4)	5 (5.1)
FEBRILE NEUTROPENIA	7 (6.1)	3 (2.7)	3 (3.0)
NEUTROPENIA	2 (1.7)	2 (1.8)	1 (1.0)
PANCYTOPENIA	1 (0.9)	0	0
LEUKOPENIA	0	1 (0.9)	1 (1.0)
GASTROINTESTINAL DISORDERS	4 (3.5)	13 (11.6)	5 (5.1)
STOMATITIS	2 (1.7)	6 (5.4)	3 (3.0)
ABDOMINAL PAIN	1 (0.9)	1 (0.9)	0
CONSTIPATION	1 (0.9)	1 (0.9)	0
VOMITING	1 (0.9)	3 (2.7)	1 (1.0)
DIARRHOEA	0	2 (1.8)	1 (1.0)
NAUSEA	0	3 (2.7)	1 (1.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (3.5)	6 (5.4)	2 (2.0)
FATIGUE	2 (1.7)	2 (1.8)	0
ASTHENIA	1 (0.9)	2 (1.8)	1 (1.0)
PYREXIA	1 (0.9)	1 (0.9)	1 (1.0)
INJECTION SITE NECROSIS	0	1 (0.9)	0
MUCOSAL INFLAMMATION	0	1 (0.9)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4 (3.5)	6 (5.4)	5 (5.1)
MYALGIA	2 (1.7)	1 (0.9)	1 (1.0)
BACK PAIN	1 (0.9)	1 (0.9)	0
MUSCULAR WEAKNESS	1 (0.9)	0	0
PAIN IN EXTREMITY	1 (0.9)	2 (1.8)	1 (1.0)
ARTHRALGIA	0	2 (1.8)	3 (3.0)
MUSCULOSKELETAL PAIN	0	1 (0.9)	0
INFECTIONS AND INFESTATIONS	2 (1.7)	0	4 (4.0)
PHARYNGITIS	1 (0.9)	0	0
PNEUMONIA	1 (0.9)	0	0
INFECTION	0	0	1 (1.0)
NAIL INFECTION	0	0	1 (1.0)
RESPIRATORY TRACT INFECTION	0	0	1 (1.0)
SEPSIS	0	0	2 (2.0)
INVESTIGATIONS	2 (1.7)	0	1 (1.0)
EJECTION FRACTION DECREASED	1 (0.9)	0	0
WEIGHT INCREASED	1 (0.9)	0	0
BLOOD GLUCOSE INCREASED	0	0	1 (1.0)
NERVOUS SYSTEM DISORDERS	2 (1.7)	3 (2.7)	3 (3.0)
NEUROTOXICITY	1 (0.9)	0	0
PERIPHERAL SENSORY NEUROPATHY	1 (0.9)	1 (0.9)	1 (1.0)
HEADACHE	0	0	1 (1.0)
NEUROPATHY PERIPHERAL	0	0	1 (1.0)
PARAESTHESIA	0	2 (1.8)	0
VASCULAR DISORDERS	2 (1.7)	6 (5.4)	0
DEEP VEIN THROMBOSIS	1 (0.9)	3 (2.7)	0
HYPERTENSION	1 (0.9)	2 (1.8)	0
LYMPHORRHOEA	0	1 (0.9)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.9)	1 (0.9)	2 (2.0)
PLEURAL EFFUSION	1 (0.9)	0	0
DYSPNOEA	0	1 (0.9)	0
PNEUMONITIS	0	0	1 (1.0)
PULMONARY EMBOLISM	0	0	1 (1.0)
IMMUNE SYSTEM DISORDERS	0	0	1 (1.0)
HYPERSENSITIVITY	0	0	1 (1.0)
PSYCHIATRIC DISORDERS	0	1 (0.9)	0
ANXIETY	0	1 (0.9)	0

Percentages are calculated with respect to the total number of patients in each treatment group.
Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.

Program : $PROD/cdp10326/mol6432/stteae.sas / Output : $PROD/cdp10326/mol6432/reports/stteaegrsa.rtf
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Data source: page 416.

During the post-operative period, Grade 3 or 4 AEs were reported in 26 patients across he treatment arms (HER2+TC: 11 patients, 9.8%; HER2+C→T: 2 patients, 10.0%; HER2+C: 6 patients, 8.8%; HER2–C: 7 patients, 8.9%). Twenty-nine Grade 3 adverse events were reported for 22 patients across treatment arms (HER2+TC: 9 patients, 8.0%; HER2+C→T: 2 patients, 10.0%; HER2+C: 6 patients, 8.8%; HER2-C: 5 patients, 6.3%).

Grade 3 or 4 Treatment-Emergent Adverse Events occurring during the Post-Operative Period (SAP)

Primary system organ class (SOC) Preferred term	HER2+TC (N=112) N %	HER2+C->T (N= 20) N %	HER2+C (N= 68) N %	HER2-C (N= 79) N %
Total number of patients with TEAE(s) of grade 3 or 4	11 (9.8)	2 (10.0)	6 (8.8)	7 (8.9)
INFECTIONS AND INFESTATIONS	3 (2.7)	1 (5.0)	0	3 (3.8)
PNEUMONIA	1 (0.9)	0	0	1 (1.3)
POSTOPERATIVE WOUND INFECTION	1 (0.9)	0	0	0
WOUND ABSCESS	1 (0.9)	0	0	0
ABSCESS LIMB	0	0	0	1 (1.3)
HERPES ZOSTER	0	0	0	1 (1.3)
SUBCUTANEOUS ABSCESS	0	1 (5.0)	0	0
EAR AND LABYRINTH DISORDERS	2 (1.8)	0	0	0
DEAFNESS TRANSITORY	1 (0.9)	0	0	0
VERTIGO	1 (0.9)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (1.8)	0	0	1 (1.3)
PNEUMONITIS	1 (0.9)	0	0	0
PULMONARY EMBOLISM	1 (0.9)	0	0	1 (1.3)
VASCULAR DISORDERS	2 (1.8)	0	0	2 (2.5)
HYPERTENSION	2 (1.8)	0	0	0
DEEP VEIN THROMBOSIS	0	0	0	2 (2.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.9)	0	0	0
INFLAMMATION	1 (0.9)	0	0	0
INVESTIGATIONS	1 (0.9)	0	0	0
EJECTION FRACTION DECREASED	1 (0.9)	0	0	0
METABOLISM AND NUTRITION DISORDERS	1 (0.9)	0	0	0
HYPERCALCAEMIA	1 (0.9)	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.9)	0	1 (1.5)	1 (1.3)
MENSTRUATION IRREGULAR	1 (0.9)	0	1 (1.5)	0
AMENORRHOEA	0	0	0	1 (1.3)
NERVOUS SYSTEM DISORDERS	0	1 (5.0)	1 (1.5)	1 (1.3)
BALANCE DISORDER	0	0	1 (1.5)	0
CONVULSION	0	0	0	1 (1.3)
SYNCOPE	0	1 (5.0)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	1 (1.5)	0
IDIOPATHIC THROMBOCYTOPENIC PURPURA	0	0	1 (1.5)	0
CARDIAC DISORDERS	0	0	1 (1.5)	0
PERICARDIAL EFFUSION	0	0	1 (1.5)	0
IMMUNE SYSTEM DISORDERS	0	0	0	1 (1.3)
HYPERSENSITIVITY	0	0	0	1 (1.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1 (1.5)	1 (1.3)
POSTOPERATIVE WOUND COMPLICATION	0	0	1 (1.5)	0
RADIATION SKIN INJURY	0	0	0	1 (1.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	1 (1.3)
ENDOMETRIAL CANCER	0	0	0	1 (1.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	1 (1.5)	0
ERYTHEMA	0	0	1 (1.5)	0

Percentages are calculated with respect to the total number of patients in each treatment group.
Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
Note: For patients receiving neoadjuvant chemotherapy only (groups HER2+C and HER2-C) fewer post-operative TEAEs were to be expected as adverse events were only to be reported until 28 days after last administration of study drug, with the exception of treatment related serious adverse events.

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Data source: page 419 .

Adverse Events of Special Interest

Trastuzumab Infusion-Related Adverse Events

All adverse events that occurred during the first day of any cycle of trastuzumab treatment throughout the duration of the study (pre- and post-operative period) were reviewed for evidence suggestive of infusion-related reactions.

Summary of MedDRA Terms Suggestive of Infusion-Related Reactions

MedDRA PT	HER2+TC N = 115				HER2+C→T N = 20
	Doxorubicin + paclitaxel	Paclitaxel alone	Cyclophosphamide, methotrexate + 5-FU	Trastuzumab monotherapy	Trastuzumab monotherapy
Number of Patients receiving at least one cycle	115	114	113	115	20
Dyspnoea	-	-	1	-	1
Erythema	-	-	-	-	1
Flushing	2	-	-	-	-
Laryngospasm	-	1	-	-	-
[1] Oropharyngeal pain	-	-	-	-	2
Rash	2	-	-	-	1
Urticaria	-	-	-	1	-
[2] Infusion related reaction	1	-	-	-	-
[2] Hypersensitivity	-	-	-	-	1

N = number of patients
[1] Considered to be interchangeable with oropharyngeal spasm, [2] Not included in the SMQ but included here for reasons of completeness.
Data source: page 473, page 477, page 408, page 405, page 407, Table 37, Table 38, Table 39, Table 40.

Of these potential infusion-related reactions, all are considered to be listed adverse reactions for trastuzumab. There was no increase in frequency and there were no unexpected outcomes.

Cardiac Safety

Pre-operative period,
Thirty-four patients experienced 53 cardiac adverse events (13.9% [16/115] pts with 27 AEs in HER2+TC, 13.4% [15/112] pts with 21 AEs in HER2+C, 3.0% [3/99] pts with 5 AEs in HER2-C) . The incidence was similar in the two HER2-positive arms (13.9% of patients in HER2+TC vs 13.4% in HER2+).
Reported cardiac adverse events in at least 2 patients (cardiac disorders SOC) were as follows: angina pectoris (5 patients in each of the HER2-positive arms) tachycardia (5 patients in each of the HER2-positive arms and 1 patient in the HER2-negative arm) and palpitations (3 patients in each of the HER2-positive arms and 1 patient in the HER2-negative arm)

None of these cardiac events were reported as Grade 3 or 4 AEs or as an SAE.
The myocardial ischemia in the HER2+TC arm was of Grade 2 intensity at worst and recovered on the same day without sequelae.

In the SOC investigations, two HER2+TC patients, had a decrease of ejection fraction. One patient had a Grade 3 decrease of ejection fraction which was also reported as an SAE. Approximately 8 weeks after starting treatment this 64-year old patient's LVEF decreased to 42% (from 65% at baseline) and she was withdrawn from the study. Her cardiac decompensation then recovered with Captopril treatment.

Treatment-Emergent Cardiac Events in the Pre-Operative Period (SAP)

Primary system organ class (SOC) Preferred term	HER2+TC (N=115) N %	HER2+C (N=112) N %	HER2-C (N= 99) N %
Total number of patients with cardiac TEAE(s)	16 (13.9)	15 (13.4)	3 (3.0)
CARDIAC DISORDERS	14 (12.2)	15 (13.4)	3 (3.0)
ANGINA PECTORIS	5 (4.3)	5 (4.5)	0
TACHYCARDIA	5 (4.3)	5 (4.5)	1 (1.0)
PALPITATIONS	3 (2.6)	3 (2.7)	1 (1.0)
ARRHYTHMIA	1 (0.9)	0	0
CARDIOMYOPATHY	1 (0.9)	0	0
LEFT VENTRICULAR DYSFUNCTION	1 (0.9)	1 (0.9)	0
MYOCARDIAL ISCHAEMIA	1 (0.9)	1 (0.9)	0
BRADYCARDIA	0	1 (0.9)	0
BUNDLE BRANCH BLOCK RIGHT	0	0	1 (1.0)
SINUS TACHYCARDIA	0	1 (0.9)	0
INVESTIGATIONS	2 (1.7)	0	0
EJECTION FRACTION DECREASED	2 (1.7)	0	0

Percentages are calculated with respect to the total number of patients in each treatment group.
Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
This table displays all events in the system organ class 'cardiac disorders' and selected events associated with left ventricular dysfunction in the system organ class 'Investigations'.

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During the post-operative period

Sixteen patients experienced 22 cardiac adverse events (8.9% [10/112] pts with 15 AEs in HER2+TC, 10.0% [2/20] pts with 2 AEs in HER2+C→T, 5.9% [4/68] pts with 5 AEs in HER2+C).

In the HER2+C arm, patient 32065/013 experienced a Grade 3 pericardial effusion and in the HER2+TC arm, a patient had a Grade 3 decreased ejection fraction considered related to study medication and reported as an SAE . Two days after completing her 1-year course of trastuzumab, this 59-year old patient experienced pneumonia. This resolved after 13 days. Seven days after onset her LVEF decreased to 42% from 56% at baseline. With treatment her LVEF began to increase (following an initial decrease to 30% recorded 4 months later) and the last known measurement was 53% (recorded approximately 2 years after onset).

A Grade 1 restrictive cardiomyopathy was diagnosed in a patient from the HER2+TC arm. The LVEF value at the time of diagnosis was 45%. This patient received 17 cycles of trastuzumab with a cumulative dose of 3724 mg. The diagnosis was made 9 months after the last dose of trastuzumab had been administered. At subsequent visits, the patient was not reported to have any significant cardiac disease, but no LVEF values are available. Thirty-four months after the diagnosis of the Grade 1 restrictive cardiomyopathy, and 43 months after the last trastuzumab dose, the patient experienced a fatal myocardial infarction. The patient had several cardiovascular risk factors (smoker, hyperlipidemia, insulin-dependent diabetes).

Treatment-Emergent Cardiac Events in the Post-Operative Period (SAP)

Primary system organ class (SOC) Preferred term	HER2+TC (N=112) N %	HER2+C->T (N= 20) N %	HER2+C (N= 68) N %	HER2-C (N= 79) N %
Total number of patients with cardiac TEAE(s)	10 (8.9)	2 (10.0)	4 (5.9)	0
CARDIAC DISORDERS	8 (7.1)	2 (10.0)	4 (5.9)	0
ANGINA PECTORIS	2 (1.8)	0	0	0
TACHYCARDIA	2 (1.8)	0	1 (1.5)	0
ARRHYTHMIA	1 (0.9)	0	1 (1.5)	0
DIASTOLIC DYSFUNCTION	1 (0.9)	0	0	0
EXTRASYSTOLES	1 (0.9)	0	0	0
LEFT VENTRICULAR DYSFUNCTION	1 (0.9)	0	0	0
RESTRICTIVE CARDIOMYOPATHY	1 (0.9)	0	0	0
CARDIAC FAILURE	0	0	1 (1.5)	0
PALPITATIONS	0	1 (5.0)	0	0
PERICARDIAL EFFUSION	0	0	1 (1.5)	0
SINUS TACHYCARDIA	0	1 (5.0)	0	0
INVESTIGATIONS	3 (2.7)	0	0	0
EJECTION FRACTION DECREASED	2 (1.8)	0	0	0
CARDIAC FUNCTION TEST	1 (0.9)	0	0	0

Percentages are calculated with respect to the total number of patients in each treatment group.
Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
This table displays all events in the system organ class 'cardiac disorders' and selected events associated with left ventricular dysfunction in the system organ class 'Investigations'.
Note: For patients receiving neoadjuvant chemotherapy only (groups HER2+C and HER2-C) fewer post-operative TEAEs were to be expected as adverse events were only to be reported until 28 days after last administration of study drug, with the exception of treatment related serious adverse events.

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Left Ventricular Ejection Fraction

At study entry, a LVEF value of 55% or more (measured by ECHO or MUGA) was required after amendment B. At baseline, the median LVEF value was 63% (range 55-82) in the HER2+TC arm, 63% (range 55-89) in the HER2+C arm and 63% (range 56-78) in the HER2-C arm.

Left Ventricular Ejection Fraction During Pre- and Post-Operative Period

Time point Characteristic	HER2+TC (N = 115) N%	HER2+C (N = 112) N%		HER2-C (N = 99) N%
Worst value prior to surgery				
Evaluable patients [1]	113 (100)	109 (100)		96 (100)
Increase or no change from baseline	15 (13.3)	30 (27.5)		20 (20.8)
Decrease of < 10 points from baseline	78 (69.0)	65 (59.6)		67 (69.8)
Decrease of ≥ 10 points from baseline	20 (17.7)	14 (12.8)		9 (9.4)
45 ≤ LVEF < 50	4 (3.5)	1 (0.9)		0
LVEF < 50 and decrease of ≥ 10 points from baseline	4 (3.5)	1 (0.9)		0
LVEF < 45 and decrease of < 10 points from baseline	0	0		0
LVEF < 45 and decrease of ≥ 10 points from baseline	1 (0.9)	0		0
	HER2+TC (N = 112) N%	**HER2+C→T (N = 20) N%**	**HER2+C (N = 68) N%**	**HER2-C (N = 79) N%**
Worst value after surgery				
Evaluable patients [1]	90 (100)	16 (100)	59 (100)	70 (100)
Increase or no change from baseline	18 (20.0)	8 (50.0)	15 (25.4)	14 (20.0)
Decrease of < 10 points from baseline	50 (55.6)	7 (43.8)	34 (57.6)	47 (67.1)
Decrease of ≥ 10 points from baseline	22 (24.4)	1 (6.3)	10 (16.9)	9 (12.9)
45 ≤ LVEF < 50	4 (4.4)	0	0	0
LVEF < 50 and decrease of ≥ 10 points from baseline	4 (4.4)	0	0	0
LVEF < 45 and decrease of < 10 points from baseline	0	0	0	0
LVEF < 45 and decrease of ≥ 10 points from baseline	1 (1.1)	0	0	0

[1] Number of patients with a non-missing baseline LVEF value and a non-missing value at the respective point in time.

Note: Values are always summarized according to the time point recorded in the CRF but they are attributed to the pre-operative or post-operative period depending on their assessment date. If there was more than one value for LVEF recorded at the same time point, only the worst (i.e. lowest) value was used for analysis.

Data source: page 394 , page 396 .

As expected, more patients in the HER2+TC arm had a decline in LVEF during the chemotherapy period, compared with patients in the other two arms who did not receive trastuzumab.

Overall, only 13.3% of patients in the HER2+TC arm showed no change or an increase in LVEF during chemotherapy, compared with 27.5% of patients in the HER2+C arm and 20.8% in the HER2-C arm. Most of the declines in LVEF were < 10% points compared with baseline.

However, combination therapy with trastuzumab led to a significantly higher number of patients with significant LEVF decrease (defined as decline of $\geq$ 10 points from baseline and decrease to < 50%) in the HER2+TC arm (5/113=4,4%) preoperatively and also postoperatively (5/90=5,6%)

Pre-operative period
Four (4) patients in the HER2+TC arm had a decline in LVEF of ≥ 10% points to an LVEF of < 50% versus one in the HER2+C arm and none in the HER2-C arm and in one patient in the HER2+TC arm the LVEF declined to < 45%

Declines in LVEF were seen during each stage of chemotherapy (doxorubicin + paclitaxel, paclitaxel alone and CMF) with no marked difference in incidence (in any of the treatment arms) between these periods.

Post operative period
After surgery, 4 patients in the HER2+TC arm had a decline in LVEF of ≥ 10% points to an LVEF of < 50%, and in one of the patients did the LVEF decline to < 45%. No such declines were observed in the control groups.

One patient had the decline in LVEF during the pre- and post-operative period.

In the postoperative combination therapy arm, two patients had a Grade 3 decreased ejection fraction considered related to study medication and reported as an SAE, months later she developed pneumonia and also a decrease in LVEF which resolved upon therapy. One patient is already listed above as one of those with LVEF decreases, however another patient listed as having the grade 3 event needs to be added, bringing the total up to six.

The MAH states that LVEF values improved again over time in all three treatment arms and presents data at 24- months follow-up, the median LVEF values were similar across the three treatment arms: 60% (range 40–78) in the HER2+TC arm, 61% (range 50–71) in the HER2+C arm, and 59% (range 51–72) in the HER2–C arm.

Deaths
At the time of clinical data cut-off, 76 patients had died. The main cause of death was disease progression in all 3 treatment arms:
20 patients (17.2% [20/116]) in the HER2+TC arm,
33 patients (28.0% [33/118]) in the HER2+C arm, and
19 patients (19.2% [19/99]) in the HER2-C arm

In the HER2-C arm, patient 33810/007 died of a Grade 4 thromboembolism of the lung arteria (a surgical complication) that was reported as an SAE

In the HER2+TC arm, one patient died of 'other' cause: cardiac infarction. This patient had a fatal myocardial infarction 34 months after being diagnosed with a Grade 1 restrictive cardiomyopathy, and 43 months after the last trastuzumab dose. These deaths were not reported as AEs or SAEs because they all occurred after the mandatory AE/SAE reporting period (up to 4 weeks after the last dose of study medication for AEs/SAEs regardless of causality, thereafter only SAEs considered related to study medication were reported). No treatment-related deaths were reported in the study.

Summary of the Main Safety Results in HER2-Positive Patients During Pre-Operative Period

Characteristics	CSR Results		Published Results*	
	HER2+TC N = 115	HER2+C N = 112	HER2+TC N = 115	HER2+C N = 113
All adverse events	113 (98.3%)	112 (100%)	113 (98%)	113 (100%)
Grade 3/4 AEs				
Febrile neutropenia	7 (6.1%)	3 (2.7%)	2 (2%)	2 (2%)
Neutropenia	2 (1.7%)	2 (1.8%)	3 (3%)	5 (4%)
Diarrhea	0	2 (1.8%)	1 (1%)	4 (4%)
Stomatitis	2 (1.7%)	6 (5.4%)	1 (1%)	4 (4%)
Infection	0	0	0	0
Pneumonia	1 (0.9%)	0	1 (1%)	0
Arthralgia	0	2 (1.8%)	0	3 (3%)
Myalgia	2 (1.7%)	1 (0.9%)	1 (1%)	1 (1%)
Peripheral neuropathy	1 (0.9%)	1 (0.9%)	1 (1%)	2 (2%)
Left ventricular dysfunction	0	0	2 (2%)	0
Cardiac events				
Angina pectoris	5 (4.3%)	5 (4.5%)	5 (4.3%)	5 (4.4%)
Arrhythmia	1 (0.9%)	0	1 (0.9%)	0
Bradycardia	0	1 (0.9%)	0	1 (0.9%)
Left ventricular dysfunction	1 (0.9%)	1 (0.9%)	2 (1.7%)	0
Palpitations	3 (2.6%)	3 (2.7%)	3 (2.6%)	2 (1.8%)
Sinus tachycardia	0	1 (0.9%)	0	1 (0.9%)
Tachycardia	5 (4.3%)	5 (4.5%)	4 (3.5%)	4 (3.5%)

* Data source: [42, 43].

Overall, the safety results from the published and CSR data were similar.

It has to be noted that the published results were only based on the events occurring during the pre-operative phase. During the pre-operative period, 13 cases of Grade 3/4 febrile neutropenia were reported by Roche monitoring (7 in the HER2+TC arm, 3 in the HER2+C arm and 3 in the HER2-C arm) compared with 6 cases by Michelangelo (2 in each arm).

1.4.2. Clinical safety data from supportive trials

The MDACC study is of interest since trastuzumab was administered in the weekly trastuzumab posology.
In the MDACC study, there were no new safety concerns observed among patients treated concomitantly with chemotherapy plus trastuzumab. No clinical cardiac dysfunction was reported under neoadjuvant treatment.

In the GeparQuattro study, the combined use of chemotherapy and trastuzumab as neoadjuvant treatment did not lead to a clinically relevant increase in toxic events. The short-term cardiac toxicity profile was comparable across the two treatment groups.

1.4.3. Discussion on clinical safety

MO16432 is the only MAH-sponsored study investigating the safety of concurrent trastuzumab and an anthracycline in patients not pretreated with anthracyclines and allows comparison of the cardiac safety of concurrent administration of trastuzumab and chemotherapy to chemotherapy alone in HER2-positive and negative patients.

Overall, there were no new or unexpected safety findings when patients with LABC were treated with trastuzumab in combination with neoadjuvant chemotherapy. Almost all patients experienced at least one AE but the majority of patients experienced only Grade 1/2 AEs.

The addition of trastuzumab to neoadjuvant doxorubicin, paclitaxel and CMF was well-tolerated and the proportion of trastuzumab-treated patients who discontinued neoadjuvant therapy due to an AE was similar to that in the patients with HER2-positive disease treated with chemotherapy alone (0.9% discontinuations in each HER2-positive arm). The incidence of all grade AEs (98.3% HER2+TC vs 100.0% HER2+C), Grade 3 AEs (37.4% vs 39.3%) and Grade 4 AEs (1.7% vs 5.4%), and SAEs (10.4% vs 7.1%) was also similar in HER2-positive patients treated with and without trastuzumab, during the neoadjuvant (pre-surgery) part of the trial

The following specific AEs (preferred terms) were reported in at least 5% more patients in the HER2+TC arm than the HER2+C arm during the neoadjuvant part of the trial: increased lacrimation, conjunctivitis, epistaxis, rhinorrhea, upper abdominal pain, dyspepsia, pyrexia, myalgia, cough, pharyngitis, rhinitis and hot flush. Conjunctivitis and hot flush are now added to the SmPC.

The incidence and severity of trastuzumab infusion-related events were within the expected frequencies and severities during the neoadjuvant part of the trial. No serious infusion-reactions occurred.

There were no new or unexpected safety findings during post-operative monotherapy with trastuzumab.

Cardiac safety showed no unexpected results. Despite concurrent administration of trastuzumab with doxorubicin, the incidence of symptomatic cardiac dysfunction was low in the HER2+TC arm. The incidence of cardiac AEs was similar in the preoperative period for the two HER2-positive arms; 13.9% of patients in HER2+TC vs 13.4% in HER2+. None of these cardiac events were reported as Grade 3 or 4 AEs or as an SAE. The number of patients and AEs during the postoperative period were about the same (8.9% pts with 15 AEs in HER2+TC, 10.0% pts with 2 AEs in HER2+C→T)

Combination therapy with trastuzumab led to a significantly higher number of patients with significant LVEF decrease (defined as decline of $\geq$ 10 points from baseline and decrease to < 50% or grade 3 decreased ejection fraction) in the HER2+TC arm (5/113=4,4% versus 1/112= 1%) preoperatively and also postoperatively (5/90=5,5% versus none)

An increase in the absolute magnitude of significant drops in LVEF could be observed in the pre- and postoperative period of patients treated with trastuzumab and long term follow up data should be submitted for all affected patients.

An attempt to compare these results with those obtained in early breast cancer in the adjuvant setting, where trastuzumab was administered after completion of anthracycline therapy, indicates that less patients suffer from significant drops in LVEF when the anthracycline is administered at the reduced dose together with trastuzumab. However, in view of the narratives provided, it may be questioned whether regular LVEF measurements were indeed performed, and in any case, no long-term follow-up was planned in the protocol. Therefore, the data collected in this small trial and in the available literature are not considered sufficient to establish the safety profile of the concomitant administration of trastuzumab with an anthracycline. However, with the proposed restrictions based on the supporting trials, an opening to concomitant administration of trastuzumab and anthracyclines is acceptable,

The MAH has evaluated the possibility of extending the OHERA (BO20652) trial by re-opening the recruitment to include patients with neoadjuvant therapy and concludes that this would not be an appropriate approach for evaluating cardiac safety in the neoadjuvant setting as this would either not be feasible or would result in very low recruitment.

This assessment has been made based upon actual recruitment rates in neoadjuvant studies including the HannaH study (BO22227), which enrolled HER2+ patients with clinical stage I to III early breast cancer, including inflammatory disease. Even with wider eligibility as compared to the proposed label (i.e. including tumors > 1cm), the maximum recruitment rate was 500 patients per year. Recruitment into an observational study in the proposed label population would be considerably lower, and is estimated at a maximum of 300 patients per year.
Furthermore, an observational study (as opposed to a clinical trial) may have several disadvantages when addressing this type of specific cardiac monitoring question, as compliance with reporting of

cardiac events (treatment information, date of event resolution) may not been optimal. Most importantly, it is not possible to obtain complete information on LVEF measurements in an observational study as these assessments are not performed as rigorously in a clinical practice setting as in a clinical trial.

In conclusion, it was considered that an observational study, whether re-opening enrollment in the OHERA trial or a new study, would not be an adequate instrument to collect more data on the cardiac safety of Herceptin given concurrently with low-dose anthracyclines in the neoadjuvant setting Such data will be available from the HannaH study. In this study, a total of 595 patients have been treated with neoadjuvant-adjuvant Herceptin (either the IV or the new subcutaneous formulation for a total duration of 1 year) concurrently with epirubicin (4 cycles of 75mg/m^2). LVEF and cardiac event data have been collected. Three-year follow-up data is anticipated to be available in Q 3 2014 and analysis results will subsequently be provided to CHMP.

Conclusion on Clinical Safety

No unexpected new safety signals during treatment with neoadjuvant trastuzumab plus chemotherapy, or adjuvant treatment with trastuzumab alone were observed.

Cautionary wording regarding cardiac safety has been implemented in the Product Information. To highlight the need of cardiac assessments in patients with early breast cancer, at baseline, and every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin. In patients who receive anthracycline containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of Herceptin, or longer if a continuous decrease of LVEF is observed. Details on cardiological assessment and management of patients in whom there are cardiovascular concerns following baseline screening is included.

In the SPC section 4.4 it is also stated that the safety of continuation or resumption of Herceptin in patients who experience cardiotoxicity has not been prospectively studied. However, most patients who developed heart failure in the pivotal (H0648g, H0649g, M77001, BO16216, BO16348, BO18255, NSABP B31, NCCTG N9831, BCIRG 006, MO16432) 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 Herceptin treatment continued on therapy without additional clinical cardiac events.

Further cardiac safety follow-up data in the neoadjuvant/adjuvant setting especially with regard to concomitant use of Herceptin with low dose anthracyclines can be available from the HannaH study, a detailed proposal on this will be included in the next RMP to be submitted 2nd March 2012. In this study, a total of 595 patients have been treated with neoadjuvant-adjuvant Herceptin (either the IV or the new subcutaneous formulation for a total duration of 1 year) concurrently with epirubicin (4 cycles of 75mg/m^2). LVEF and cardiac event data have been collected. Three-year follow-up data is anticipated to be available in Q 3 2014 and analysis results will subsequently be provided to CHMP. The current product information contains a statement that Herceptin and anthracyclines should not be given concurrently in combination in the adjuvant treatment setting and in patients with early breast cancer eligible for neoadjuvant-adjuvant treatment, Herceptin should only be used concurrently with anthracyclines in chemotherapy-naive patients and only with low-dose anthracycline regimens (maximum cumulative doses: doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2).
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Additionally, in the SPC section 4.8 conjuctivitis and hot flush were added to the table of adverse reactions per System- organ- class, where as the frequencies of the adverse drug events of lacrimation, cough, epistaxis and rhinorrhoea were upgraded from "common" to "very common".

1.5. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure which included a risk minimisation plan.

Based on the safety conclusions, the CHMP requested the submission of an updated Risk Management Plan which included a risk minimisation plan within this procedure.

Table 1. Summary of the risk management plan (including the changes related to the application presented highlighted)- version 10

Table 1 Summary of the EU Risk Management Plan

Safety Issues	Agreed Pharmacovigilance Activities	Agreed Risk Minimisation Activities
Important Identified Risk		
Cardiotoxicity	▪ **Additional** Cardiac AE specific safety study BO20652 (OHERA) **<u>Primary objective</u>**: • 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. **<u>Secondary objectives</u>**: • 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. Her-Q-Les was designed to meet two	**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 cardiac dysfunction. For early breast cancer patients, cardiac assessment, as performed at baseline, should be

Safety Issues	Agreed Pharmacovigilance Activities	Agreed Risk Minimisation Activities
	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. **Additional (Proposed)** ▪ **Guided Questionnaire** Guided Questionnaire to better characterise cardiac adverse event reports.	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 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

Safety Issues	Agreed Pharmacovigilance Activities	Agreed Risk Minimisation Activities
	▪ **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 PSUR – 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 SOC.	individual patient are deemed to outweigh the risks.
Infusion-Related Reactions	▪ **Additional** 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 PSUR – 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 SOC.	**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 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

Safety Issues	Agreed Pharmacovigilance Activities	Agreed Risk Minimisation Activities
		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 $\geq$ 2, Observed Count $\geq$ 3 or Chi-squared $\geq$ 4 PSUR – 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 SOC.	**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 (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	**Section 4.6 Pregnancy and Lactation** Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the

Safety Issues	Agreed Pharmacovigilance Activities	Agreed Risk Minimisation Activities
	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** 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 $\geq$ 2, Observed Count $\geq$ 3 or Chi-squared $\geq$ 4 PSUR – 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 SOC.	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. 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.	**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

Safety Issues	Agreed Pharmacovigilance Activities	Agreed Risk Minimisation Activities
	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 PSUR– 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 SOC.	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 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 PSUR – 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 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 below pharmacovigilance activity(ies) in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Plans for Further follow-up of cardiac safety in the neo-adjuvant setting to be more detailed in the next revision of the RMP. MAH's proposal: Cardiac safety follow-up data in the neoadjuvant/adjuvant setting will be available from the HannaH study (595 patients treated with neoadjuvant-adjuvant Herceptin iv or sc for 1 year), a detailed proposal on this will be included	To be included in next revision of the RMP (March 2012)

Description	Due date
in the next RMP to be submitted 2nd March 2012.	

This pharmacovigilance activity is in addition to those already requested.

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted :

- The MAH has amended section 1.4.1 as requested. Section 1.4.2 includes actual post-authorisation usage data based on experience in the USA but no information has been provided on the actual post-authorisation usage in Europe. The MAH should provide a breakdown of usage by indication and country in the EU and include this in the next update to the RMP.
- The objective of study ML20529 in Table 83 should be updated to be consistent with the title of the protocol "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." This minor change should be implemented in the next update to the RMP.
- In the new version of the RMP, table 58 is not completely readable; the right part of the table is not printed on the page. This should be solved with the next update of the RMP.

The MAH is requested to submit an RMP by 2nd March 2012 in order to properly reflect the safety profile of the product and the following important safety concerns:

- Long term cardiac safety evaluation – detailed plan (see above)

1.6. Changes to the Product Information

The MAH proposed to update sections 4.1, 4.4, 4.8 and 5.1 of the SmPC to reflect the change in the indication. The PL has been updated accordingly. Finally, Annex II has been updated in order to include the new version number of the Risk Management Plan.

The CHMP agreed with the proposed changes.

2. Overall conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

Neoadjuvant-adjuvant trastuzumab in combination with neoadjuvant chemotherapy has a statistically significant and clinically relevant effect on event free survival, defined as recurrence, progression or death, in HER2-positive early breast cancer patients. In addition, pathological complete response in breast and axilla (tpCR) and in breast (bpCR) doubled under trastuzumab therapy compared with the HER2+C arm and a clinically relevant improvement in overall survival was observed, even though results were not statistically significant at 3 years median follow up time. The results were obtained with 17% of patients in the control arm having crossed over to trastuzumab therapy after results obtained with trastuzumab therapy in the adjuvant setting were known.

The observed effects have been supported by other randomized phase 2 and 3 trials with regard to the short term efficacy parameter pCR and in one study (MDACC) also the 3 year-event free survival rate was significantly reduced.

Uncertainty in the knowledge about the beneficial effects

All efficacy (methiodology) concerns have been resolved, there is no uncertainty in the evaluation of the benefit of trastuzumab in the claimed indication.

Risks

Unfavourable effects

Important risks that have been identified in the neoadjuvant-adjuvant therapy with trastuzumab are cardiac events including death due to cardiac injury, infusion reactions, febrile neutropenia, infection and pulmonary reactions. An increase in CHF and also in significant LVEF was observed under trastuzumab therapy. These risks were already known for trastuzumab therapy in early breast cancer.

Uncertainty in the knowledge about the unfavourable effects

Safety aspects are well known and there is no uncertainty in the safety of trastuzumab in the population reflected by this indication.

Balance

Importance of favourable and unfavourable effects
The demonstration of improved event-free and overall survival is of great importance to the patient and is therefore clinically meaningful. This must be weighed against cardiac safety risks, especially in long term use. Careful monitoring of cardiac safety is emphasized in the product information.

Benefit-risk balance
The pivotal data shows that neoadjuvant trastuzumab has a clinically relevant benefit in terms of complete pathological response and event-free survival. Importantly, these data are supported by pathological response rates from the literature in the neoadjuvant setting and by robust evidence of benefit for trastuzumab in adjuvant treatment of early breast cancer.

These significant benefits for the patient outweigh the safety risks which are well studied from past experience with trastuzumab and manageable in the clinical setting.

The proposed indication for neoadjuvant-adjuvant trastuzumab includes patients with HER2-positive early breast cancer (stage II, if the tumour is larger than 2 cm in diameter) as well as patients with HER2-positive locally advanced (stage III), and/or inflammatory breast cancer. This is supported by the pivotal trial supplemented by the literature and is considered acceptable.

Conclusion on the benefit-risk assessment

The overall benefit-risk balance of Herceptin in combination with neoadjuvant chemotherapy for the treatment of patients with locally advanced (including inflammatory) breast cancer or tumours > 2 cm in diameter is considered positive.

3. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The Extension of indication to include treatment of patients with HER2-positive EBC in combination with neoadjuvant chemotherapy, followed by adjuvant trastuzumab monotherapy, for locally advanced (including inflammatory) breast cancer or tumours > 2 cm in diameter

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

Risk management system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 10 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow a half yearly cycle until otherwise agreed by the CHMP.

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