Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Trastuzumab

Proprietary Product Name: Herceptin

Sponsor: Roche Products Pty Ltd

December 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	Extension of indications
Decision:	Approved
Date of Decision:	29 June 2012
Active ingredient(s):	Trastuzumab
Product Name(s):	Herceptin
Sponsor's Name	Roche Products Pty Ltd
	PO Box 255
	Dee Why 2099 NSW
Dose form(s):	Powder for injection
Strength(s):	60 mg and 150 mg
Container(s):	Glass vial
Pack size(s):	1's
Approved Therapeutic use:	For the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin. [1]
Route(s) of administration:	Intraveneous (IV)
Dosage:	8 mg/kg initially then 6 mg/kg every 3 weeks (3 weekly regimen).
ARTG Number (s)	171014 and 73229

Product background

This AusPAR describes the application by the sponsor to extend the indications of Herceptin (trastuzumab) to include neoadjuvant plus adjuvant use in localised breast

[1] The full indications are now:

Localised Breast Cancer. Herceptin is indicated for the treatment of patients with HER2 positive localised breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.

Locally Advanced Breast Cancer. Herceptin is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin.

Metastatic Breast Cancer. Herceptin is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2: a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease, b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.

Advanced Gastric Cancer. Herceptin is indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

cancer, add the details of another adjuvant trial (BCIRG 006) to the *Clinical Trials* section of the Product Information (PI) and make other changes to the PI (changes to the PI are beyond the scope of this AusPAR).

The proposed new indication:

> *Herceptin is indicated for the treatment of patients with HER2-positive localised breast cancer in association with (neo)adjuvant chemotherapy and, if applicable, radiotherapy.*

The current indication:

> *Herceptin is indicated for the treatment of patients with HER2-positive localised breast cancer following surgery and in association with chemotherapy and, if applicable, radiotherapy.*

Trastuzumab is a recombinant deoxyribonucleic acid (DNA)-derived humanised monoclonal antibody that selectively targets human epidermal growth factor receptor 2 protein (HER2). HER2 is overexpressed in 25-30% of breast cancers. Trastuzumab inhibits proliferation of tumour cells that overexpress HER2. Serious adverse effects include hypersensitivity, interstitial lung disease and cardiotoxicity.

A related product is the small molecule lapatinib (Tykerb). This product does not have an adjuvant or neoadjuvant indication in breast cancer.

The TGA has adopted the European Medicines Agency (EMA) *Guideline on the Evaluation of Anticancer Medicinal Products in Man* (CPMP/EWG/205/95)[2] which is relevant to this application.

Regulatory status

A summary of the current international regulatory status is provided in the table below (Table 1).

Table 1. International regulatory status

Country	Submission Date	Approval
EU	5 Apr 2011	December 2011
US	TBD	-
Canada	TBD	-
Switzerland	6 May 2011	March 2012
New Zealand	Following Aus approval	-

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

[2] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017748.pdf

List of abbreviations

AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
BCIRG	Breast cancer international research group
bpCR	Breast pathological (pathologic) complete response
BSA	Body surface area
BSV	Between Subjects Variability
CBC	Complete blood count
CER	Clinical Evaluation Report
CI	Confidence Interval
CL	Clearance
CMF	Cyclophosphamide, methotrexate, and 5-fluorouracil
CR	Complete response
CRF	Case Report Form
CV (%)	Coefficient of Variation
CWRES	Conditional Weighted Residual
DFS	Disease-free survival
EBC	Early Breast Cancer
ECD	Extracellular domain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EGF	Epidermal growth factor
ELISA	Enzyme-linked immunosorbent assay
ER	Estrogen receptor
EU	European Union
FAS	Full analysis set
FISH	Fluorescent in situ hybridization
FO	First Order estimation
FOCE	First Order Conditional Estimation
GCP	Good clinical practice
GemCis	Gemcitabine and cisplatin
GOF	Goodness of Fit
Hb	Haemoglobin
HER2	Human Epidermal growth factor Receptor 2
IBC	Inflammatory breast cancer

ICH International conference on harmonisation
IEC Independent ethics committee
IHC Immunohistochemistry
IIV Inter-Individual Variability
IOV Inter-Occasion Variability
IPRED Individual PREDiction
IRB Institutional review board
IRES Individual RESidual
IV Intravenous
IWRES Individual Weighted RESidual
LABC Locally advanced breast cancer
LLOQ Lower Limit of Quantification
LVEF Left ventricular ejection fraction
MBC Metastatic Breast Cancer
MedDRA Medical dictionary for drug regulatory activities
MRI Magnetic resonance imaging
MUGA Multiple-gated radionuclide angiography
NCCTG North Central Cancer Treatment Group
NCI-CTC National Cancer Institute Common Toxicity Criteria
NE Non-evaluable
NONMEM NONlinear Mixed Effects Model
NSABP National surgical adjuvant breast and bowel project
NYHA New York Heart Association
OFV Objective Function Value
OS Overall survival
pCR Pathological (pathologic) complete response
PD Pharmacodynamic(s)
PD Progressive disease
PFS Progression-free survival
PgR Progesterone receptor
PK Pharmacokinetic(s)
PK-PD Pharmacokinetic-Pharmacodynamic
PP Pharmacovigilance Plan
PPS Per protocol set
PR Partial response
RECIST Response evaluation criteria in solid tumours
RES Population RESidual
RSE Relative Standard Error

SAE	Serious adverse event
SAP	Safety analysis population
SAP-P	Post-surgery safety analysis population
SD	Stable disease
SHED	HER2 ECD
SOLTI	Solid tumor intensification
SS	Safety Specification
T4d	Stage T4 disease
tpCR	Total pathological complete response
ULN	Upper limit of normal
V	Volume Distribution
Vc	Central Volume Distribution
Vp	Peripheral Volume Distribution
WRES	Population Weighted RESidual

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Introduction

Clinical rationale

Extension of indication to include neoadjuvant treatment

In the covering letter provided with the submission, the sponsor states that neoadjuvant therapy has "become a standard treatment option for many patients with localised breast cancer", and is now used in "patients with operable disease to increase the likelihood of breast conserving surgery". The sponsor claimed that in "the Australian clinical setting ~30% of patients with operable disease are being treated with neoadjuvant chemotherapy". However, the sponsor did not provide the source for this statement. In addition, the sponsor stated that "although an additional survival benefit has not yet been shown for neoadjuvant chemotherapy over adjuvant chemotherapy, it does provide an important clinical benefit by decreasing the rate of distant metastases and increasing the likelihood of achieving a pathological complete response (pCR)".

Furthermore, the sponsor stated that "the use of trastuzumab in the pre-operative setting has strong clinician support", and commented that the Medical Oncology Group of Australia (MOGA) approached Roche in August 2009, with a position paper supporting the (neo)adjuvant (pre-operative) use of trastuzumab for the treatment of patients with locally advanced disease. In addition, the sponsor stated that the "adverse prognostic significance of HER2-positivity in breast cancer is strongly recognised in the Australian

clinical setting, with clinicians particularly concerned about tailoring the breast cancer therapy in these women", and requested the TGA to consider "the important clinical significance of the proposed therapy when assessing the nature of the [provided] supportive clinical data".

Comment: The sponsor's clinical rationale for the submission is considered acceptable. It has recently been stated that neoadjuvant (pre-operative) chemotherapy is becoming a commonly used treatment option for women with early stage breast cancer allowing a greater proportion of patients to undergo conservative breast surgery.[3] In a Cochrane Review of pre-operative chemotherapy for women with operable breast cancer, the authors suggested that pre-operative chemotherapy can be safely used "in the treatment of women with early stage breast cancer in order to down-stage surgical requirements, to evaluate chemosensitivity and to facilitate translational research".[4] This review identified 14 eligible studies including 5,500 randomised patients with a median follow-up of from 18 to 124 months. Overall survival (OS) and disease free survival (DFS) rates were equivalent in women treated with pre-operative (neoadjuvant) chemotherapy and women treated with post-operative (adjuvant) chemotherapy. Pre-operative (neoadjuvant) chemotherapy increased breast conservation rates, but at the cost of increased loco-regional recurrence rates. However, loco-regional recurrence rates were not increased provided that surgery remained part of treatment even after complete tumour regression.

Furthermore, there appears to be a move in clinical practice to the use of neoadjuvant trastuzumab in combination with chemotherapy to treat early breast cancer in patients with HER2-positive disease, despite this treatment not being currently approved by any major drug regulatory authority. The current US National Comprehensive Cancer Network (NCCN) Guidelines (v 2.2011)[5] relating to "invasive breast cancer" recommends the use of neoadjuvant chemotherapy in patients with invasive breast cancer, and includes a neoadjuvant regimen in HER2-positive patients containing trastuzumab in combination with specified sequential chemotherapy (the regimen used in the MDACC study[6, 7], with an additional alternative paclitaxel dosing schedule). The majority of the panel at the St Gallen 2011 Consensus Conference on early breast cancer supported the use of neoadjuvant chemotherapy containing anthracyclines and taxanes.[8] In addition, the majority of the panel considered that standard adjuvant chemotherapy can be used

[3] Moreno-Aspitia A. Neoadjuvant therapy in early-stage breast cancer. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.04.013

[4]van der Hage JA Mieog JS, van de Vijver MJ, van de Velde CJ; European Organization for Research and Treatment of Cancer. Efficacy of adjuvant chemotherapy according to hormone receptor status in young patients with breast cancer: a pooled analysis. Breast Cancer Res. 2007;9(5):R70.

[5] http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

[6] Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomised trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005;23:3676-3685,

[7] Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2–positive operable breast cancer: an update of the initial randomised study population and data of additional patients treated with the same regimen. Clin Cancer Res. 2007; 13:228-233.

[8]Gnant M, Harbeck N, Thomssen C. St Gallen 2011: Summary of consensus discussion. Breast Care 2011;6:136-141.

in the neoadjuvant indication (82% of the panel), and in HER2-overexpressing tumours neoadjuvant regimens should also contain anti-HER2 medication (87% of the panel).

Contents of the Clinical Dossier

The submission contained the following clinical data (presented in 3 separate dossiers):

Clinical data

- Dossier 1: Hybrid submission: one study (sponsor's Company Study Report (CSR)) considered to be the pivotal study [MO16432/NOAH]; two published studies MDACC and GeparQuattro formally nominated by the sponsor as supportive [MDACC and GeparQuattro]; and published reports from more than 30 studies considered by the sponsor to be supportive.
- Dossier 2: One Clinical Study Report BCIRG 006; one Addendum BCIRG 006 addendum (5 year follow-up cardiac safety); and literature references.
- Dossier 3: Two population-PK reports : Report 1034069 and Report 1039626; one drug-drug PK interaction study JP199959 (Japanese patients); one post-marketing drug safety report (number 1040470) on the effects of trastuzumab in pregnant women; one in vitro Method Comparison Study (D008548) FISH versus SISH in gastric tumours; and one published population-PK study identified as reference 59 Bruno PK paper.

Paediatric data

The proposed indication is not applicable to the paediatric population.

Good clinical practice

All studies sponsored by Roche in this submission have been conducted in accordance with Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data (Dossier 3)

Dossier 3 of the submission included three clinical pharmacology studies submitted to support changes to the PI. These three studies were:

- Report 1034069: Population-PK analysis of combined Phase II/III studies BO15899, BO15935, WO16229, M77004 and MO16982. This report was submitted to support the changes to the *Pharmacokinetics* section of the PI relating to *Breast Cancer.*
- Report 1039626: Population-PK analysis of trastuzumab in patients with HER2 positive advanced gastric cancer (Phase III study BO18255). This report was submitted to support the changes to the *Pharmacokinetics* section of the PI relating to *Gastric Cancer.*
- CSR JP19959): Drug-drug PK interaction study of capecitabine and cisplatin used alone or in combination with trastuzumab in patients with HER2-positive advanced gastric cancer; a PK substudy of Study BO18255 in Japanese patients. This study was submitted to support the addition of PK information to the *Interactions With Other Medicines* section of the PI relating to the combined administration of capecitabine, cisplatin, and trastuzumab.

Report 1034069. Population-PK analysis

Objectives

The *primary objectives* of this population-PK analysis (dated 5 June 2009) were:

(1) to establish a comprehensive population PK model for trastuzumab, taking data from the three dosing regimens into account, which can then be used as a reference for future PK analyses in other cancer types;

(2) to explore and quantify the effect of covariates on the PKs of trastuzumab; and

(3) to assess the potential influence of the characteristics of the treatment regimen on the PKs of trastuzumab (that is, novel loading regimen, once weekly maintenance and three weekly maintenance regimens).

The *secondary objectives* of the population-PK analysis were to generate the following PK data for Study MO16982:

(1) primary PK parameters (e.g., clearance and volumes of distribution); and

(2) secondary PK parameters peak plasma concentration (C_{max}), trogh plasma concentration (C_{min}) and area under the plasma concentration time curve over a dosing interval (AUC_{τ}) during the 1st, 2nd and 4th cycles of treatment.

Description

The analysis included pooled PK data from 5 Phase I/II/III clinical studies. PK data from 4 of these studies [BO15899, BO15935, WO16229, M77004] had been previously pooled in a population-PK analysis.[9] The submitted population PK analysis was initiated to update the previous population-PK analysis with data from 1 new study [MO16982].

The new study [MO16982] was a Phase I/II study investigating a more aggressive loading regimen to enable higher serum levels of trastuzumab to be reached earlier in the treatment of women with HER2+ MBC. Loading doses of trastuzumab 6 mg/kg (n=72) were administered on Days 1, 8 and 15, followed by maintenance doses of 6 mg/kg every 3 weeks. Intensive blood sampling was planned for all patients in order to characterise the PKs of the novel loading regimen. Blood samples were drawn pre-dose and immediately after and at 1.5 h after the end of the infusion in Cycles 1, 2, 3 and 4. Additionally, several samples were taken after infusion following Cycle 2 and 4. However, for practical reasons the majority of patients could not fully comply with this intensive schedule of PK sampling and the pre planned non-compartmental PK analysis (NCA) was unable to be undertaken. Therefore a population-PK analysis was performed in order to utilise the collected PK data and characterise the PKs of the patient population.

Methods

Analytical methods

Trastuzumab: Serum concentrations of trastuzumab were determined by enzyme-linked immunosorbent assay (ELISA) (Genentech, Inc., CA, USA). The standard curve range was 1.56 to100 ng/mL. For studies BO15935, WO16229, BO15899 and M77004, the inter-assay and intra-assay variability (CV%) were reported as 3% and 1% respectively. For Study MO16982, it was reported that the inter-assay precision for low, mid and high matrix controls was in the range of 8-16% and the intra-assay precision was 7-8%.

Trastuzumab Shed Antigen Assay: Shed antigen concentrations were assessed by ELISA (Bayer Heath Care), a colorimetric assay utilising two monoclonal antibodies directed to the extra cellular domain (ECD) of HER-2/neu. No assay interference was shown in the presence of trastuzumab. The lower limit of quantification (LLOQ) was 40 pg/mL and inter- and intra-assay variability was less than 10%.

[9]Bruno R, Washington CB, Lu J-F. Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. 2005:361-369.

Pharmacokinetic analysis

The population-PK analysis was performed using the non-linear mixed effects modelling (NONMEM) program (versions 5.1 and 6). The population-PK analysis was based on standard analytical assumptions (actual sampling times, dosing times and dose amounts are recorded accurately), and standard modelling assumptions (weighted residuals are normally distributed; eta (η) variables [between-subjects random variables] and epsilon (ε) variables [random variables related to the error model] are both independent, identically and symmetrically distributed with mean zero).

The basic population-PK model developed for the previous analysis was a two-compartment model with first-order elimination.[10] The basic parameters were clearance (CL, L/day), volume of distribution of the central compartment (Vc, L), and inter-compartmental rate constants (K_{12}, K_{21}, day^{-1}). This model was used as the reference model for the updated population-PK analysis. The final Bayesian estimates of individual PK parameters from the updated population-PK analysis were graphically analysed in order to detect any discrepancies between the updated and reference models. Model refinement was carried out after the validity of the reference model structure was confirmed.

The first-order conditional estimation with interaction (FOCE INTER) method was used to estimate the population-PK parameters. Modelling of baseline covariate effects was carried out with the same set of covariates and significance levels (a nominal p-value of 0.001) as used in the previous population-PK analysis. The effect of each baseline covariate on CL, Vc and Vp was assessed by using automated stepwise covariate model building. The baseline continuous covariates tested were age, weight, creatinine clearance, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, and HER2 shed antigen (HER2 ECD). The baseline categorical covariates tested were number of metastatic sites ≥ 4, and HER2 overexpression ≥ 3+. In addition, the effect of regimen (novel loading regimen, once weekly maintenance and 3 weekly maintenance) and cancer types (MBC or NSCL) were evaluated after covariate analysis was completed. The final model was evaluated using goodness-of-fit plots and final model stability was assessed by bootstrap re sampling, visual and numerical predictive checks, and shrinkage.

> *Comment*: The report included a comprehensive description of the methods used to create and analyse the population-PK data. The reporting of the results of the population-PK analysis is consistent with the relevant TGA adopted EU guideline.[11]

Results

Descriptive summary of the database

The population-PK analysis included 3967 evaluable PK data points from 265 patients from 5 studies. The characteristics of the database are outlined below in Table 2. In addition, the continuous baseline covariates (all studies), continuous covariates at baseline (individual studies) and the categorical covariates at baseline (all and individual studies) were summarised in the study report.

[10] Bruno R, Washington CB, Lu J-F. Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. 2005:361-369.

[11] CHMP/EWP/185990/06Guideline on Reporting the results of Population Pharmacokinetic Analysis. http://www.tga.gov.au/pdf/euguide/ewp18599006en.pdf

Table 2: Population-PK report [1034069]. Descriptive summary of database.

	MO16982 Phase I/II	BO15935 Phase I/II	WO16229 Phase II	BO15899 Phase II	M77004 Phase IIIb
Regimen loading Regimen maintenance	6 mg/kg 1qwk x 3 6 mg/kg 3qw	8 mg/kg 6 mg/kg 3qw	8 mg/kg 6 mg/kg/3qw	4 mg/kg 2 mg/kg 1qw	4 mg/kg 2 mg/kg 1qw
Patient population	MBC HER2 2+/3+	MBC HER 2+/3+	MBC HER 2+/3+	NSLC HER2 2+/3+	MBC HER 2+/3+
Subjects treated with Herceptin (n)	72	32	105	51	32
Subjects for assessment (n)	71	30	98	51	15
Evaluable PK data points	1469	824	800	529	355
Sampling design	T & P, some full	T & P, some full	Full and T	T & P	T & P, some full
Samples/patient median [range]	30 [3-1]	35.5 [1-40]	4.0 [1-33]	12.0 [2-17]	25 [8-31]
Observation (days) median [90th]	84.0 [84.2]	243.2 [258.4]	95.5 [316.6]	116.95 [181.9]	230 [328.6]

Basic model

The reference model previously developed was a two-compartment model with proportional residual errors and between subject variabilities (BSVs) on CL, V, k_{12} and k_{21}. Bayesian feedbacks for the patients in MO16982 were obtained using the reference model without covariates. The results for the two populations are summarised below in Table 3.

Table 3: Population-PK report [1034069]. MO16892 and 4 pooled studies.

	CL (L/day)	K_{12} (/day)	K_{21} (/day)	Vc (L)	Vp (L)	Vss (L)	k* (/day)	t1/2α (day)	t1/2β (day)
M016892 (n=71)	0.21 (0.08-0.67)	0.09 (0.05-0.23)	0.11 (0.02-0.30)	2.82 (1.62-4.71)	2.53 (0.62-11.7)	5.42 (3.19-15.2)	0.07 (0.03-0.24)	2.74 (1.61-4.52)	22.7 (1.61-4.52)
4 Studies (n=194)	0.23 (0.08-0.44)	0.08 (0.03-0.18)	0.05 (0.10-0.26)	3.11 (1.97-6.89)	5.31 (0.75-27.4)	8.51 (3.34)	0.07 (0.03-0.16)	3.57 (1.97-7.73)	37.7 (11.9-167.5)

* derived from k = CL/Vc

Comment: Overall, goodness-of-fitness plots showed that the PKs of the MO16982 population were generally similar to the reference population, apart from smaller volumes of distribution (Vc, Vp, and Vss) in the MO16982 population compared with the reference population. The results indicate that the reference model fitted well to the PK data obtained from the novel loading regimen from MO16982. Therefore the reference model structure was employed for further basic model building.

Final model

Bases on the covariate assessments, the final model retained HER2 extracellular domain (SHED), weight (WT), alkaline phosphatase (ALP) on clearance (CL), weight (WT) on central volume of distribution (Vc), and HER2 overexpression on peripheral volume of distribution (Vp). The precision of parameter estimates (RSE%) were in the range 2.6% to

33.4% which was considered acceptable. The model adequately predicted the PKs and no obvious trend in model mis-specification was detected. The population parameter estimates for the final model are summarised below in Table 4.

The covariates in the final population PK model were added as followed:

$CL = 0.241\ (SHED/17.9)^{0.102}\ x\ (WT/68)^{0.557}\ x\ (ALKP/107)^{0.141}$

$Vc = 3.02\ x\ (WT/68)^{0.484}$

HER2 overexpression (+): Vp = 2.68

HER2 overexpression (-): Vp = 2.68 x (1+0.518)

Table 4: Population-PK report [1034069]. Estimates for the final PK model.

Parameters	Unit	Estimates	RSE (%)	95% CI
Fixed effect parameters				
θ1 Clearance (CL)	(L/day)	0.241	2.55	0.229 – 0.253
θ2 Central volume of distribution (Vc)	(L)	3.02	1.82	2.91 – 3.13
θ3 Inter-compartmental clearance (Q)	(L/day)	0.460	7.37	0.394 – 0.526
θ4 Peripheral volume of distribution (Vp)	(L)	2.68	6.19	2.35 – 3.01
θ5 CL-ALKP	-	0.141	31.2	0.0548 – 0.227
θ6 CL-SHED	-	0.102	28.1	0.0457-0.158
θ7 CL-WT	-	0.557	22.4	0.312 – 0.802
θ8 Vc-WT	-	0.484	16.3	0.329 – 0.639
Random effect parameters				
ω1 BSV on CL	%CV	38.6	12.2	33.7 – 43.0
ω2 BSV on Vc	%CV	21.4	27.2	14.6 – 26.4
ω3 BSV on Vp	%CV	72.6	16.3	59.9 – 83.4
ε1 proportional residual error	%CV	20.9	7.16	19.4 – 22.3

Comment: The study found that alkaline phosphatase levels, shed antigen and body weight were statistically significant covariates for trastuzumab clearance, body weight was a statistically significant covariate for trastuzumab central volume of distribution and HER2 expression was a statistically significant covariate for trastuzumab peripheral volume of distribution.

Report 1039626. Population-PK analysis

Population-PK report 1039626 (dated 14 June 2010) is based on data from Study BO18255, a Phase III, randomised, open label, multicentre study that evaluated the efficacy, safety and PKs of trastuzumab in combination with a fluoropyrimidine and cisplatin compared with chemotherapy alone as first-line therapy in patients with HER2 positive advanced gastric cancer. Both Study BO18255 and the population-PK analysis based on this study have been previously evaluated by the TGA. Consequently, this current CER centres on verification of the data from the submitted population-PK report used to update the *Pharmacokinetics* section of the PI relating to *Gastric Cancer*. The NONMEM PK dataset for the population-PK analysis included 1419 serum concentrations collected from 266 gastric cancer patients. The analytical methods have been described in a previous CER.

The data from the population PK report provided in the current submission supporting the amendments to the PI are:

- At high trastuzumab concentrations, where only the linear part of trastuzumab determines the total clearance, a terminal half-life of approximately 26 days was derived from the population parameter estimates. At concentrations above 75 μg/mL, the total clearance of trastuzumab is dominated by linear clearance.
- With a loading dose of 8 mg/kg (on Day 1) followed by 6 mg/kg every 3 weeks, 95% of steady state was reached after the 5th cycle (84 days) for Cmax, after the 7th cycle (126 days) for AUC, and after the 9th cycle (168 days) for Cmin.
- The median steady state AUC value is approximately 1213 mg.day/L and the median steady state Cmax and Cmin values are 132 mg/mL and 27.6 mg/mL, respectively.
- The statement that "it is expected that serum trastuzumab levels will fall to less than 5% of the trough levels at steady state approximately 19 weeks after dose discontinuation" is supported by knowledge that the half-life is approximately 28 days (elimination is almost complete at five half-lives following discontinuation).
- There are no data in the population PK report on the ECD level of circulating HER2 receptor (shed antigen) in the serum of gastric cancer patients.

The PI includes the following statement which is not supported by the data in the population-PK report: "Short duration IV infusions of 8 mg/kg followed by 6 mg/kg HERCEPTIN every 3 weeks in patients with advanced gastric cancer demonstrated concentration-dependent clearance comprised of predominantly linear and non-linear components at high (> 75 mg/L and low (< 25 mg/L) serum concentrations, respectively". The relevant data from the population PK report are:

- Short duration IV infusions of 8 mg/kg followed by 6 mg/kg Herceptin every 3 weeks in patients with advanced gastric cancer demonstrated concentration-dependent clearance comprised of predominantly linear and non-linear components. The two components of the total clearance contribute equally to the elimination of trastuzumab for concentrations around 25 μg/mL. At very low concentrations (below 10 μg/mL), the nonlinear clearance represents almost the entire total clearance and is approximately 7 fold higher than the linear clearance. For concentrations above 75 μg/mL, the nonlinear clearance represents less than 30% of the total clearance and the total clearance is dominated by the linear clearance.

Study JP19959. PK interaction capecitabine + cisplatin ± trastuzumab

Overview

Study JP19959, a PK substudy of BO18255 in patients with advanced gastric cancer, was conducted at 9 Japanese sites in 22 patients from 19 June 2006 until 8 January 2008. This substudy was submitted to support the addition of a new paragraph to the *Interactions with Other Medicines* of the PI. The proposed paragraph is:

> A substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer, to study the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab, suggested the PK of capecitabine (and its metabolites) were not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab. The pharmacokinetics of trastuzumab were not evaluated in this study.

Objective and treatment

The objective of the substudy was to investigate the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab in patients with HER2-positive advanced gastric cancer. The treatments were those for the previously evaluated Study BO18255 in which patients were assigned to the XP group (capecitabine and cisplatin) or the HXP group (trastuzumab in combination with capecitabine and cisplatin).

In JP19959, the PK analysis was based on samples collected on the first day of Cycle 1 (see Table 5, below). The relevant doses for the PK analysis were: (1) Trastuzumab administered by IV infusion at a dose of 8 mg/kg over 90 minutes; (2) Capecitabine administered orally at a dose of 1000 mg/m^2 in the morning. In the HXP group, capecitabine was administered when starting the infusion of trastuzumab; (3) Cisplatin administered at a dose of 80 mg/m^2 by IV infusion over a period of 2 h, together with hydration and premedication (corticosteroids and an antiemetic). In the XP group the infusion of cisplatin was started 2 to 2½ h after administration of capecitabine wherever possible and in the HXP group the infusion of cisplatin was started 30 to 60 minutes after finishing the trastuzumab infusion wherever possible.

Table 5: Study JP199959. Study schedule.

Procedure		Scheduled Time (hr)[a)]												
Day		1												
Time after administration of trastuzumab and capecitabine (hr)[b)]		0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	8.0	12
Time after completing administration of cisplatin (hr)[b)]										0.0	1.0	2.0	4.0	8.0
Administration of trastuzumab		←								→				
Administration of capecitabine		X												X
Hydration before and after administration of cisplatin[c)]		—								—				
Administration of cisplatin						←				→				
Sample collection	Capecitabine[b)]	X		X		X		X		X		X		X[d)]
	Cisplatin	X								X	X	X		X[d)]

a. Shows the case where cisplatin was administered 30 minutes after trastuzumab (HXP group) or 2 h after capecitabine (XP group)

b. Blood was collected based on the shaded times. From completion of infusion of cisplatin onward, the blood samples for measuring capecitabine and cisplatin were collected at the same times, apart from the sample at 1 h after completing infusion of cisplatin.

c. Shows the case where hydration before and after administration of cisplatin was carried out for 2 h before and after administration of cisplatin

d. Blood was collected before the evening meal.

Assessments

Plasma concentrations: The test variables were plasma concentrations of capecitabine and its metabolites (5′-DFCR, 5′-DFUR, 5-FU and FBAL); and plasma concentration of cisplatin (platinum in plasma and platinum in ultrafiltered plasma). The study did not include assessment of serum trastuzumab concentrations.

PK parameters of capecitabine and cisplatin: PK parameters (such as C_{max}, T_{max}, $t_{1/2}$, AUC, k_{el} and CL or CL/F) for capecitabine and its metabolites in plasma and for cisplatin (platinum in plasma and platinum in ultrafiltered plasma). The time course of the plasma

concentrations and the PK parameters of capecitabine and its metabolites and cisplatin in the XP and HXP groups were compared.

Patients

A total of 22 patients (8 in the XP group and 14 in the HXP group) were enrolled in Study JP19959. The baseline characteristics for the two groups were well balanced (see Table 6, below). All patients completed the study as stipulated and no patients were withdrawn from the study during the study period. Out of the 22 patients, one dose violation involving cisplatin was reported in 1 patient in the HXP group (cisplatin dose was 48 mg/m^2 and stipulated dose was 80 mg/m^2). The IV infusion time for trastuzumab in 5 patients and the IV infusion time for cisplatin in 9 patients deviated from the pre-specified times by 10 minutes or more, although these did not constitute protocol violations. In addition, 1 patient in the HXP group was hepatitis C virus positive and 1 patient in the XP group had gastro-oesophageal junction cancer.

Table 6: Study JP1999. Baseline characteristics XP and HXP groups.

	XP group	HXP group
Number (females/males)	8 (3/5)	14 (2/12)
Body weight (kg); mean±sd	53.9 ± 13.7	54.1 ± 9.31
Height (cm); mean±sd	160 ± 16.2	163 ± 7.49
Creatinine clearance (mL/min); mean±sd	85.7 ± 22.2	86.4 ± 24.0
Body surface area (m^2) ; mean±sd	1.55 ± 0.276	1.57 ± 0.161

PKs of capecitabine and its metabolites in the XP and HXP groups

The PK parameters for capecitabine and its metabolites in the XP and HXP groups are summarised below in Table 7.

Table 7: Study JP199959. PK parameters of capecitabine and its metabolites (mean±sd).

Group	Compound	N	T_{max} (h)	C_{max} (μg/mL)	AUC_{last} (μg*h/mL)	AUC_{inf} (μg*h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
XP	Capecitabine	8	1.36±0.753	2.21±0.848	3.65±1.42	3.65±1.54[1)]	0.441±0.116[1)]	252±141[1)]
	5'-DFCR	8	1.48±0.763	5.03±2.00	10.3±1.86	10.3±1.85	0.691±0.116	52.5±12.0
	5'-DFUR	8	1.62±0.751	4.81±2.74	8.34±2.19	8.72±2.17[2)]	0.738±0.419[2)]	61.6±20.1[2)]
	5-FU	8	1.61±0.922	0.191±0.135	0.324±0.140	0.364±0.144[2)]	0.725±0.384[2)]	924±569[2)]
	FBAL	8	2.72±0.694	3.80±0.848	15.1±5.14	16.9±6.61[1)]	2.07±0.524[1)]	14.9±5.14[1)]
HXP	Capecitabine	14	1.98±0.911	4.60±5.46	6.56±5.63	7.88±6.48[3)]	0.885±0.474[3)]	148±83.0[3)]
	5'-DFCR	14	2.05±0.866	5.08±2.70	12.0±5.58	11.9±5.72[4)]	0.933±0.323[4)]	54.1±28.1[4)]
	5'-DFUR	14	2.12±0.902	3.45±1.73	7.60±2.25	7.76±2.17[5)]	0.867±0.361[5)]	76.5±39.8[5)]
	5-FU	14	2.20±0.844	0.153±0.0957	0.315±0.120	0.334±0.137[5)]	0.878±0.389[5)]	972±523[5)]
	FBAL	14	3.04±0.955	3.55±1.02	13.9±3.84	17.2±5.02[5)]	2.41±0.586[5)]	14.6±5.06[5)]

Number of patients analysed: (1) N=7, (2) N=6, (3) N=9, (4) N=13, (5) N=10.

The ratios (HXP/XP) and 90% CI for the Ln(C_{max}), Ln(AUC_{last}) and Ln(AUC_{inf}) of capecitabine and its metabolites are summarised below in Table 8.

Table 8: Study JP199959. Ratios (HXP/XP) capecitabine and its metabolites.

Compound	Parameter	Ratio[%Ref]	CI_90_Lower	CI_90_Upper	Power
Capecitabine	Ln(C_{max})	130.53	66.96	254.46	0.1483
5'-DFCR	Ln(C_{max})	93.44	65.11	134.09	0.2642
5'-DFCR	Ln(C_{max})	72.87	51.09	103.92	0.2699
5-FU	Ln(C_{max})	82.76	52.91	129.43	0.2076
FBAL	Ln(C_{max})	91.89	75.32	112.09	0.5834
Capecitabine	Ln(AUC_{last})	140.39	77.41	254.59	0.1608
5'-DFCR	Ln(AUC_{last})	108.46	82.36	142.82	0.3763
5'-DFCR	Ln(AUC_{last})	89.68	71.50	112.47	0.4913
5-FU	Ln(AUC_{last})	99.38	73.24	134.85	0.3275
FBAL	Ln(AUC_{last})	93.69	76.30	115.02	0.5601
Capecitabine	Ln(AUC_{inf})	183.27	105.21	319.26	0.1685
5'-DFCR	Ln(AUC_{inf})	107.18	81.09	141.66	0.3695
5'-DFCR	Ln(AUC_{inf})	87.25	66.46	114.53	0.3811
5-FU	Ln(AUC_{inf})	92.11	62.20	136.40	0.2374
FBAL	Ln(AUC_{inf})	103.92	79.17	136.41	0.3815

Comment: Exposure to capecitabine and its metabolites was compared using the Ln(C_{max}) and the Ln(AUC_{last}[12]) as indicators, as these were able to be calculated in all patients. The Ln(AUC_{inf}[13]) was not used as an indicator of exposure because there were fewer than three points for the plasma concentration in the elimination phase for some of the patients and the kel could not be calculated. In the HXP group, the capecitabine mean Ln(C_{max}) and Ln(AUC_{last}) were approximately 31% and 40% higher than in the XP group, respectively. The mean time to the peak plasma concentration (T_{max}) was marginally longer in the HXP group (1.98 h) relative to the XP group (1.36 h) but this is not considered to be clinically significant. In both groups, the capecitabine mean elimination half-life ($t_{1/2}$) was rapid and marginally longer in the HXP group compared with the XP group (0.885 and 0.441 h, respectively). In the HXP group, the mean apparent clearance (CL/F) was slower than in the XP group (148 L/h and 252 L/h, respectively). The mean Ln(C_{max}), Ln(AUC_{last}) and Ln(AUC_{inf}) of the metabolites of capecitabine in the XP group were not markedly different from those in the HXP group. In both groups, the mean Ln(C_{max}) of capecitabine, 5′-DFCR, 5′-DFUR and 5-FU was reached rapidly and the compounds were then eliminated rapidly, while the Ln(C_{max}) of FBAL was reached slightly later after which the concentration decreased slowly. The log concentration - time course for capecitabine and its metabolites were similar in the XP and HXP groups. Overall, the results suggest that the differences between the XP and HXP groups as regards the PKs of capecitabine and its metabolites are unlikely to be clinically significant. The data supports the proposed PI statement that the PKs of capecitabine (and its metabolites) were not affected by concurrent use of cisplatin plus trastuzumab.

PKs of cisplatin in the XP and HXP groups

The PK parameters of cisplatin (platinum in plasma and platinum in ultrafiltered plasma) in the XP and HXP groups are summarised below in Table 9.

[12] AUC from time zero to the last time point.

[13] AUC from time zero to infinity.

Table 9: Study JP199959. PK parameters of cisplatin; mean±sd.

Group	Measured Variable	N	C_{max} (μg/mL)	AUC_{last} (μg*h/mL)	AUC_{inf} (μg*h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
XP	Platinum in plasma	8	4.00±0.511	14.8±2.20	60.1±13.4[1)]	13.9±4.84[1)]	2.26±0.652[1)]	41.5±10.7[1)]
	Platinum in ultrafiltered plasma	8	1.83±0.296	3.46±0.523	3.58±0.519	1.28±0.376	35.6±9.52	55.1±16.2
HXP	Platinum in plasma	14	3.70±0.887	13.4±2.95	71.1±91.2[2)]	17.9±23.9[2)]	2.89±1.39[2)]	43.0±4.53[2)]
	Platinum in ultrafiltered plasma	14	1.97±0.654	3.64±1.11	3.79±1.15[3)]	1.11±0.176[3)]	35.3±14.3[3)]	52.2±23.9[3)]

Number of patients analysed: (1) N=7, (2) N=12, (3) N=13.

The ratios (HXP/XP) and 90% CI for the Ln(C_{max}), AUC($_{last}$)and Ln(AUC_{inf}) of cisplatin (platinum in plasma and platinum in ultrafiltered plasma) are summarised below in Table 10.

Table 10: Study JP 199959. Ratio (HXP /XP) cisplatin.

Measured Variable	Parameter	Ratio[%Ref]	CI_90_Lower	CI_90_Upper	Power
Platinum in plasma	Ln(C_{max})	91.00	77.93	106.26	0.7715
Platinum in ultrafiltered plasma	Ln(C_{max})	103.89	83.69	128.96	0.5230
Platinum in plasma	Ln(AUC_{last})	88.92	76.32	103.60	0.7821
Platinum in ultrafiltered plasma	Ln(AUC_{last})	101.90	83.54	124.30	0.5836
Platinum in plasma	Ln(AUC_{inf})	85.50	51.08	143.10	0.1805
Platinum in ultrafiltered plasma	Ln(AUC_{inf})	102.67	84.01	125.48	0.5768

Comment: Exposure to cisplatin as assessed by the Ln(C_{max}), Ln(AUC_{last}) and Ln(AUC_{inf}) was similar in the XP and HXP groups. The data support the proposed PI statement that the PKs of cisplatin were not affected by capecitabine plus trastuzumab.

Effects of cisplatin and capecitabine on the PK profile of each other

The sponsor provided two cross-study comparisons which it claimed showed that the "pharmacokinetics of capecitabine are not affected by co-administration of cisplatin", and the "pharmacokinetics of cisplatin are not affected by co-administration of capecitabine."

The effect on the PKs of capecitabine when capecitabine is used with cisplatin or with trastuzumab and cisplatin was examined by comparing the PK parameters of capecitabine and its metabolites obtained in the XP and HXP groups in Study JP19959 with the PK parameters in three studies in which capecitabine was administered alone: JO15793 (late Phase II clinical study in Japanese patients with advanced or recurrent gastric cancer); JO15951 (Phase II clinical study in Japanese patients with advanced or metastatic colorectal cancer); and BP1583 (comparative PK study in Japanese and Caucasian patients with advanced or metastatic breast cancer from which only the data for Japanese patients were extracted and compared). The dose of capecitabine differed among the studies but the dose adjusted values for the C_{max}, AUC_{last} and AUC_{inf} were compared because it has been shown that the pharmacokinetics of capecitabine and its metabolites show dose proportionality. The results for the C_{max}/dose and the AUC_{last}/dose are provided in Tables 11 and 12 below.

The effect on the PKs of cisplatin when cisplatin is used with capecitabine or with trastuzumab and capecitabine was examined by comparing the PK parameters of platinum in ultrafiltered plasma obtained in the XP group and the HXP group in Study JP19959 with the PK parameters of ultrafiltered platinum after administration of cisplatin reported in 4

published papers: Kitajima et al., 1981[14]; Felici et al., 2006[15]; Urien et al., 2004[16]; and Hanada et al., 2001[17]. The results are provided in Table 13.

Table 11: JP199959. Cross study comparison of C_{max}/dose for capecitabine and its metabolites.

Compound		C_{max}/DOSE (ng/mL/mg/m^2)				
		CAPECITABINE/CISPLATIN	TRASTUZUMAB + CAPECITABINE/CISPLATIN	Monotherapy/ Gastric Cancer	Monotherapy/ Colorectal Cancer	Monotherapy/ Breast Cancer
	Dose (mg/m^2)	1000	1000	829	1250	825
	Study	JP19959	JP19959	JO15793	JO15951	BP15831 (Japanese patients only)
Capecitabine	N	8	14	7	20	19
	Mean	2.21	4.60	6.13	3.84	7.43
	SD	0.848	5.46	5.92	1.40	3.97
5'-DFCR	N	8	14	7	20	19
	Mean	5.03	5.08	3.94	4.76	6.09
	SD	2.00	2.70	3.31	2.00	2.53
5'-DFUR	N	8	14	7	20	19
	Mean	4.81	3.45	5.08	4.81	8.20
	SD	2.74	1.73	2.40	1.99	3.39
5-FU	N	8	14	7	20	19
	Mean	0.191	0.153	0.208	0.174	0.350
	SD	0.135	0.0957	0.130	0.0971	0.230
FBAL	N	8	14	7	20	19
	Mean	3.80	3.55	3.25	3.60	4.53
	SD	0.848	1.02	0.671	0.811	1.20

Table 12: JP199959. Cross study comparison of AUC_{last}/dose for capecitabine and its metabolites.

Compound		AUC_{last}/DOSE (ng*h/mL/mg/m^2)				
		CAPECITABINE/CISPLATIN	TRASTUZUMAB + CAPECITABINE/CISPLATIN	Monotherapy/ Gastric Cancer	Monotherapy/ Colorectal Cancer	Monotherapy/ Breast Cancer
	Dose (mg/m^2)	1000	1000	829	1250	825
	Study	JP19959	JP19959	JO15793	JO15951	BP15831 (Japanese patients only)
Capecitabine	N	8	14	7	20	19
	Mean	3.65	6.56	7.17	5.98	5.92
	SD	1.42	5.63	4.25	1.97	2.07
5'-DFCR	N	8	14	7	20	19
	Mean	10.3	12.0	8.72	12.5	9.23
	SD	1.86	5.58	7.42	3.55	3.45
5'-DFUR	N	8	14	7	20	19
	Mean	8.34	7.60	10.8	10.6	11.5
	SD	2.19	2.25	5.10	3.09	2.60
5-FU	N	8	14	7	20	19
	Mean	0.324	0.315	0.381	0.378	0.398
	SD	0.140	0.120	0.126	0.146	0.121
FBAL	N	8	14	7	20	19
	Mean	15.1	13.9	16.6	17.5	18.6
	SD	5.14	3.84	5.77	4.84	4.25

[14]Kitajima K, Fukuoka M, Kobayashi S, Kusunoki Y, Takada M, Negoro S, et al. Studies on the appropriate administration of cisplatin based on pharmacokinetics and toxicity. Japanese Journal of Cancer and Chemotherapy. 1987;14(8):2517-2523.

[15]Felici A, Loos WJ, Verweij J, Cirillo I, de Bruijn P, Nooter K, et al. A pharmacokinetic interaction study of docetaxel and cisplatin plus or minus 5-fluorouracil in the treatment of patients with recurrent or metastatic solid tumors. Cancer Chemother Pharmacol. 2006(Nov);58(5):673-680.

[16]Urien S, Lokiec F. Population pharmacokinetics of total and unbound plasma cisplatin in adult patients. Br J Clin Pharmacol. 2004 (Jun); 57(6): 756-763

[17]Hanada K, Nishijima K, Ogata H, Atagi S, Kawahara M. Population pharmacokinetic analysis of cisplatin and its metabolites in cancer patients: possible misinterpretation of covariates for pharmacokinetic parameters calculated from the concentrations of unchanged cisplatin, ultrafiltered platinum and total platinum. Jpn J Clin Oncol. 2001(May);31(5):179-184.

Table 13: JP19959. Cross study comparison of PK parameters for cisplatin.

		JP19959		Published Papers				
		XP Group	HXP Group	Kitajima et al.	Felici et al. TC Group	Felici et al. TCF Group	Urien et al.	Hanada et al.
Cisplatin dose	(mg/m^2)	80	80	80	75	75	15～80	60～100
AUC_{inf} (μg*h/mL)		3.58 ± 0.519	3.79 ± 1.15	2.0	3.72	3.67		
C_{max} (μg/mL)		1.83 ± 0.296	1.97 ± 0.654	3.08	1.22	1.18		
CL (L/h)		35.6 ± 9.52	35.3 ± 14.3		39.2	39.9	35.5	18.5

Mean ± standard deviation, or mean

TC group: Docetaxel and cisplatin
TCF group: Docetaxel, cisplatin and 5-FU

Comment: The submission included no formal PK drug-drug interaction studies investigating the effects of co-administration of capecitabine and cisplatin on the PKs of each agent when administered alone. It is considered that the cross-study comparisons do not provide convincing evidence that cisplatin and capecitabine do not affect the PK profile of each other. The cross-study comparison of dose corrected C_{max} and AUC_{last} for capecitabine and its metabolites showed significant variability for both parameters. Similarly, the cross-study comparison of AUC_{inf}, C_{max}, and CL for cisplatin (platinum in ultrafiltered plasma) also demonstrated variability in these parameters. It is considered that the submitted data are not strong enough to support the statements in the PI that the PKs of cisplatin were not affected by concurrent use of capecitabine and that the PKs of capecitabine were not affected by the concurrent use of cisplatin. Consequently, it is recommended that these statements be removed from the proposed PI statement.

Evaluator's overall comments on pharmacokinetics

Population-PK report 1034069 was submitted to support the changes to the *Pharmacokinetics* section of the PI relating to *Breast Cancer*. The report supports the changes relating to clearance (0.241 L) and volumes of distribution in the central (3.02 L) and peripheral (2.68 L) compartments. However, the data supporting the change in the elimination half-life from 28.5 (95% CI: 25.5, 32.8) days to 28-38 days could not be identified in the study report. Consequently, as the upper range of the elimination half life (38 days) could not be confirmed, the statement relating to the expected fall in serum trastuzumab levels to less than 5% of trough levels at steady state at approximately 27 weeks (190 days or 5 elimination half-lives [5 x 38 days]) after dose continuation) could not be confirmed.

Furthermore, in the population-PK report 1034069 the calculations could not be identified supporting the statement taken from the European Summary of Product Characteristics (SPC) that the parameters from the updated population PK analysis indicate that "steady state pharmacokinetics should therefore be reached by approximately 27 weeks, with median predicted AUC at steady state (over a three week period) of 1677 mg.day/L with weekly dosing and 1793 mg.day/L with 3 weekly (once every three weeks) dosing. The estimated median peak and trough concentrations were 104 mg/L and 64.9 mg/L (weekly) and 189 mg/L and 47.3 mg/L (3 weekly) respectively".

Population-PK report 1039626 was submitted to support the changes to the *Pharmacokinetics* section of the PI relating to *Gastric Cancer*. The submitted report supports most but not all of the proposed changes to the proposed PI (see above).

Study JP199959 showed that co-administration of trastuzumab with capecitabine and cisplatin had no significant effects on the PKs of the two chemotherapy agents compared with co-administration of the two agents without trastuzumab. However, the study did not

satisfactorily establish that the co-administration of the two chemotherapy agents did not affect the PKs of the agents when administered alone. Therefore, the proposed addition to the *Interactions With Other Medicines* section of the PI should be amended.

Pharmacodynamics

No new data.

Dosage selection for the pivotal studies

The rationales for dosage selection in the relevant clinical studies are satisfactory and are discussed below in the relevant sections of this CER.

Efficacy

Dossier 1 - Neoadjuvant treatment (extension of indication)

Pivotal efficacy study. NOAH (MO16432)

Study design, objectives, locations and dates

The *pivotal efficacy study* was a Phase III, multinational, multicentre, randomised, active-controlled, open label clinical trial comparing the safety and efficacy of a sequential neoadjuvant (pre-surgery) regimen involving doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and 5-fluorouracil, given with or without trastuzumab, in women with locally advanced breast cancer and HER2/c-erB-2 overexpression and amplification. The study also included a parallel observational arm in patients with HER2-negative tumours. The results of the study have been published. [18,19]

The *primary objective* was to compare event-free survival (EFS) in patients with HER2-positive disease who received chemotherapy alone compared with chemotherapy plus trastuzumab.

The *secondary objectives* were:

1. To compare the following in patients with HER2-positive disease who received chemotherapy alone compared with chemotherapy plus trastuzumab:
    - pathological complete response (pCR) rate;
    - overall clinical response rate (complete response (CR) plus partial response (PR) rate);
    - overall survival;
    - safety and tolerability; and
    - changes in left ventricular ejection fraction (LVEF).
2. To document the same efficacy parameters (event-free survival, overall response rate, overall survival) and safety parameters (safety, tolerability and LVEF) in patients with HER2-negative disease who received the same chemotherapy regimen without trastuzumab.

[18]Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer: primary efficacy analysis of the NOAH trial. 2008; SABCS. Abstract 31.

[19] Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010; 375: 377-384.

3. To describe the biological characteristics of tumours that might predict tumour response.

The *study period* was from 20 June 2002 (first patient randomised) to 30 March 2009 (clinical cut-off date). The study was undertaken in 6 countries (Russia, Spain, Italy, Germany, Austria and Portugal) and 25 centres.

The sponsor states that the study was conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong and South Africa), or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the patient. The study adhered to the principles outlined in "Guideline for Good Clinical Practice" International Conference Harmonisation (ICH) Tripartite Guideline (January 1997), or with the local law if it afforded greater protection to the patient. Site specific Independent Ethics Committees/Institutional Review Boards were responsible for approving the initial protocol and all subsequent amendments. All patients provided written informed consent.

> *Comment:* The pivotal study was conducted by the Michelangelo (Milan, Italy) and SOLTI (Madrid, Spain) collaborative groups and independent centres and sponsored by Roche. Initially, Roche was not involved in the data collection and analyses of the study, with the Michelangelo group being responsible for both of these aspects. However, between November 2009 and September 2010 Roche undertook a re-monitoring of the study with complete source data verification (with the exception of 21/330 patients, for whom source data were no longer available). In this process, some data were queried and subsequently changed based on investigators' responses. The updated case report form (CRF) data were then entered into a new database, which was used for the Roche Clinical Study Report (CSR) provided in the current submission. The results in the published data[20] differ from those provided in the sponsor's complete study report, and these differences are discussed later in this CER (see Section *Efficacy endpoints*).

Inclusion and exclusion criteria

The study included women aged ≥ 18 years of age presenting for the first time with locally advanced breast cancer who had not received any previous treatment for an invasive malignancy. Patients with evidence of metastases (with the exception of ipsilateral supraclavicular nodes) were excluded from the study. Patients were required to have a diagnosis of histologically proven breast cancer, and have HER2-positive or HER2-negative disease. Patients were required to be Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1 (asymptomatic, normal activity [ECOG = 0], or symptomatic but fully ambulatory [ECOG = 1]). Exclusion criteria included patients with New York Heart Association (NYHA) Class ≥ II heart disease, and patients with a left ventricular ejection fraction (LVEF) of < 55% by multiple-gated radionuclide angiography

[20]Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010; 375: 377-384.

(MUGA) or echocardiography (ECHO). ECOG[21] and NYHA[22] and Response Evaluation Criteria in Solid Tumours (RECIST) [23] criteria are summarised in footnotes below.

Tumours with HER2 overexpression by immunohistochemistry (IHC) or amplification by Fluorescence In Situ Hybridization (FISH), according to the local laboratory, were required to have central confirmation before randomisation. FISH was to be performed on all tumour samples but was not a primary eligibility criterion and patients were allowed to enter the study on the basis of a central IHC 3+ result. The study included a prospectively defined parallel observational group of patients with tumours that were HER2-negative (0 or 1+ by IHC). Women with HER2-negative disease were selected using the same criteria as women with HER2-positive disease and received the same chemotherapy regimen as the HER2-positive group but without trastuzumab.

The study included standard criteria providing for patient withdrawal. In the event of a patient withdrawing, all efforts were to be made to complete and report study observations. Survival status was to be reported yearly, unless the patient had withdrawn consent for the whole study. If a patient wished to stop treatment with trastuzumab and/or chemotherapy but did not have progressive disease, the patient was to remain within the study unless they had specifically withdrawn consent for the whole study (not just treatment). No patient prematurely withdrawn from the study for any reason was to

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ECOG Scale	
0	Asymptomatic, normal activity
1	Symptomatic but fully ambulatory
2	Symptomatic, in bed less than 50% of waking time
3	Symptomatic, in bed more than 50% of waking time, not bedridden
4	100% bedridden

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Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

[23] Objective tumour response, measured according to the RECIST criteria, was used as a secondary end-point in this trial. The response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and followed until disease progression. All other lesions are assessed according to the same schedule. Adequate investigations must be carried out at each disease evaluation to detect new lesions. For this trial, with the exception of T4d lesions, disease in the breast must be measurable according to RECIST criteria and this will count as a target lesion. Lymph nodes, if present, may be measurable or non-measurable. Ipsilateral axillary and supraclavicular nodes, if present, will be considered as target lesions, if they fulfil the RECIST criteria for target lesions.

be replaced. However, study centres could be replaced for excessively slow recruitment and/or poor protocol adherence.

Study treatments

a. Chemotherapy and trastuzumab treatments

The following sequential neoadjuvant (pre-surgery) chemotherapy regimen was administered to all patients:

- doxorubicin 60 mg/m^2 IV infusion and paclitaxel 150 mg/m$^{2\ IV}$ infusion every 3 weeks for 3 cycles, followed by;
- paclitaxel 175 mg/m^2 IV infusion every 3 weeks for 4 cycles, followed by;
- cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2 IV bolus and 5-fluorouracil 600 mg/m^2 IV bolus (CMF) starting on Day 21 after the last administration of paclitaxel on Days 1 and 8 every 4 weeks for 3 cycles.

In patients randomised to trastuzumab, neoadjuvant trastuzumab was administered every 3 weeks combined with the sequential neoadjuvant chemotherapy regimen, starting with a loading dose of 8 mg/kg on the first day of doxorubicin/paclitaxel treatment followed by a maintenance dose of 6 mg/kg every 3 weeks through to surgery. Following surgery, trastuzumab was re-started at a dose of 6 mg/kg every 3 weeks in patients in the neoadjuvant trastuzumab/chemotherapy group and continued for 1 year from the start of neoadjuvant treatment. Depending on when trastuzumab was re-started after surgery, up to a total of 17 cycles of trastuzumab might have been received over 1 year (neoadjuvant 10 cycles plus adjuvant 7 cycles).

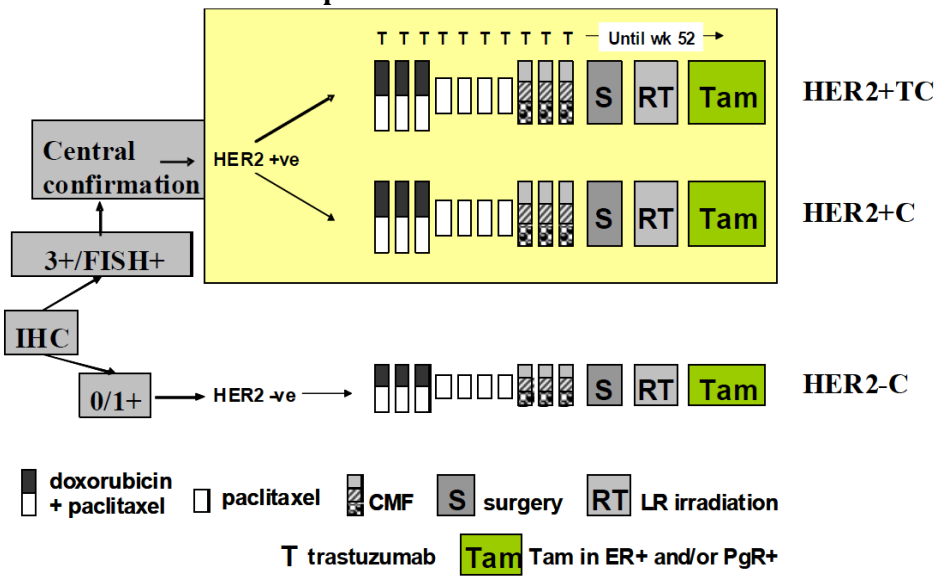
Adjuvant tamoxifen (20 mg/day) for 5 consecutive years was started in patients with tumours that were oestrogen receptor (ER) and/or progesterone receptor (PgR) positive in both the chemotherapy alone and the chemotherapy plus trastuzumab treatment arms.

Following protocol amendment version D (after announcement of positive results of studies of adjuvant trastuzumab treatment), all patients originally randomised to receive chemotherapy alone and who met specific eligibility criteria were offered access to adjuvant trastuzumab for a total of 1 year (8 mg/kg loading dose followed by 3 mg/kg every 3 weeks).

The treatment phase of the study is provided below in Figure 1. The following abbreviations were adopted in the study report and will be followed in this AusPAR:

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

Figure 1: NOAH Treatment phase.



Chemotherapy was to start as soon as possible after treatment assignment and not later than 5 working days after treatment assignment. It was intended that chemotherapy be administered in an outpatient setting. Doses were calculated according to the body surface area (BSA) using actual weights and heights. No downward adjustments to "ideal body weight" were allowed for patients who had a calculated BSA of ≤ 2.2 m^2 but in the few patients with a calculated BSA of > 2.2 m^2 a BSA of 2.2 m^2 was used.

Anti-emetogenic pre-medication was pre-specified for doxorubicin/paclitaxel for 3 cycles and paclitaxel alone for 4 cycles. The pre-medication regimen consisted of prednisone 25 mg (PO) on the evening before therapy and then on the day of therapy at 30 minutes prior to paclitaxel the following three medications were administered, hydrocortisone 250 mg (IV), chlorphenamine 10 mg (IV or IM), and cimetidine 300 mg (IV). If nausea and/or vomiting developed during treatment local investigators were responsible for administering the most appropriate management.

Comment: The study included an acceptable rationale for the choice of therapeutic agents. It was stated that at the time the study was designed, doxorubicin, paclitaxel and CMF were all well established treatments for patients with breast cancer and all had been used successfully as neoadjuvant therapy for patients with large operable or inoperable tumours. The strategy of using sequential, non cross-resistant, neoadjuvant treatment regimens for a few cycles was stated to be based on the observation that continued use of the same therapy beyond a few cycles did not generally result in further reduction in tumour size, risk of recurrence or improvement in survival. Use of different, sequential, non cross-resistant chemotherapy regimens was postulated to avoid the development of drug resistance.

The sponsor stated that the addition of trastuzumab to chemotherapy (paclitaxel, or an anthracycline plus cyclophosphamide) as adjuvant therapy in patients with HER2-positive breast cancer had been reported to improve not only response rate and time to progression but also survival in patients with metastatic HER2-positive breast cancer. This was supported by *in vitro* data, which suggested that trastuzumab enhances the antitumor activity of anthracyclines and taxanes. Therefore, the addition of trastuzumab to a neoadjuvant sequence of established chemotherapy regimens was expected to result in a "highly effective treatment" for patients with locally advanced, HER2-positive breast cancer.

The sponsor stated that inclusion of HER2-negative patients would help determine whether HER2-positive disease is a predictor of response to anthracyclines and taxanes, as well as providing additional comparative safety data on chemotherapy alone. These patients would receive the same neoadjuvant chemotherapy regimen as patients with HER2-positive disease, but would not receive trastuzumab.

b. Dose modification

The study included pre-specified chemotherapy dose modifications for haematological and non-haematological toxicities. The study also included pre-specified trastuzumab dose modifications for non-haematological toxicities, cardiac dysfunction and infusion related symptoms but no dose modifications or dose withholding of trastuzumab were to be undertaken for haematological toxicities.

c. Surgery

In this study, radical mastectomy was the standard surgical treatment and was mandatory for patients with inflammatory breast cancer, lesions with a diameter > 5 cm at diagnosis or micro-calcifications which involved more than one quadrant of the breast. However, the following were possible exceptions: (1) peripheral neoplasms (mammary fold, axillary tail) ≤ 4 cm in maximum diameter if a good cosmetic result could be expected, even if no objective response was recorded; and (2) breast saving surgical procedures could be undertaken based on patient request only if all the following conditions applied: no oedema or peau d'orange after chemotherapy; final good cosmetic results; and objective response > 50%.

Surgery had to be performed by Day 28 but not before Day 14 after the last cycle of chemotherapy or after resolution of all possible haematological or infective complications unless otherwise indicated. Lymph node axillary dissection should preferably have been performed up to the third level. Nodal sampling and the dissection of the first level only was not acceptable. Dissection of the first two levels should be considered. Surgical pathology was performed at local sites according to provided guidelines. After mastectomy, breast reconstruction with implants could be considered after assessment of the risks related to the subsequent radiotherapy on the chest wall.

d. Radiation therapy

All patients were to receive post-operative radiation therapy (techniques were detailed in pre-specified guidelines). Radiotherapy should have started within 4 weeks of completing surgery, and trastuzumab had to be administered concomitantly to patients randomised to this treatment group and not delayed until after completion of radiotherapy.

Assessment

a. Clinical assessment

In all cases, the primary breast lesion was assessed clinically by the study investigators. In addition, objective measurements were obtained using mammography and/or ultrasound to assess disease response. The imaging technique used was left to the discretion of the study investigators. However, it was recommended that the same imaging technique for evaluation of the lesion be used throughout the treatment period. Whenever possible, measurements were made by the same study investigator or reporter for all assessments for each patient. Response was assessed at the Michelangelo Operations Office using RECIST criteria, when applicable. Confirmatory clinical assessment was required before surgery. For mammography and ultrasound, disease response was based on the baseline and pre-surgery scans and confirmatory assessments were not required.

Recurrent disease included local, regional, distant recurrence and contralateral breast cancer, except lobular carcinoma in situ. During post-surgery and follow-up study periods, the diagnosis of first breast cancer relapse was made when clinical, radiological and laboratory findings met the specific criteria defined below.

Local recurrence: In the ipsilateral breast after surgery: (a) In case of conservative surgery (lumpectomy), defined as evidence of tumor, except lobular carcinoma in situ, in the ipsilateral breast after mass excision. Patients who developed clinical evidence of tumour recurrence in the remainder of the ipsilateral breast should have positive histology or cytology of the suspicious lesion to confirm the diagnosis; (b) In case of mastectomy, local recurrence (other than ipsilateral breast after lumpectomy), defined as evidence of tumour confirmed by positive histology or cytology in any soft tissue or skin of the ipsilateral chest wall after mastectomy.

Regional recurrence: Defined as the development of tumor in the ipsilateral internal mammary and/or ipsilateral axillary lymph nodes, as well as extranodal soft tissue of the ipsilateral axilla confirmed by positive histology or cytology, or by chest X-ray, computerised tomography (CT) scan or magnetic resonance imaging (MRI). Regional recurrence did not include supraclavicular lymph nodes or tumour in the opposite breast.

Distant recurrence: Defined as evidence of tumour in all areas, with the exception of those described for local recurrence. The following criteria applied skin, subcutaneous tissue, and lymph nodes (other than local or regional) confirmed by positive cytology, aspirate or biopsy or radiological (by CT scan or MRI or ultrasound); bone, confirmed by either X-ray, CT scan,or MRI evidence of lesions consistent with bone metastasis, or histological/cytological proof of bone metastases; bone marrow, confirmed by positive cytology or histology or MRI scan; lung confirmed by X-ray evidence of multiple pulmonary nodules consistent with pulmonary metastases or positive histology/cytology; liver, positive abdominal CT scan, liver scan, ultrasound or MRI consistent with liver metastases, or positive liver biopsy/fine needle aspiration; and central nervous system, positive MRI or CT scan, or positive cytology of the cerebrospinal fluid in case of meningeal involvement

Contralateral invasive breast cancer (confirmed by positive cytology or histology): The earliest date of the confirmed diagnosis of recurrent disease was used and recorded. This could be based on clinical, radiological, histological or cytological evidence.

> *Comment:* Assessment of disease response in this study was not centralised but was the responsibility of individual investigators. This has the potential to bias the results, particularly as neither investigators nor patients were blinded to treatment. Centralised unblinded assessment of disease response by the Michelangelo Operations Office appears to have only been undertaken in special circumstances (e.g., problems with data interpretation).

b. Assessment schedule

The assessment schedule was comprehensive and included: (a) screening; (b) on-therapy (c) 2 months after the end of first breast irradiation; (d) follow-up; and (e) on failure.

Efficacy variables and outcomes

a. Primary efficacy variable

The *primary efficacy variable* was event-free survival (EFS). This was defined as the time between randomisation 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, "randomisation" was defined as the date of study registration.

If there was any tumour assessment prior to surgery satisfying the criteria for progressive disease, the patient was evaluated as having an event even if the study 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, consequently, were not free of breast cancer at any time during the study, only disease progression or death was considered as an event during follow-up.

If no event was observed, censored observations were taken into account in the analyses. These were defined as the last date of "last tumour measurement", "last drug intake" or "last follow-up", whichever was latest. All events up to and including the cut-off date of 30 March 30 2009 were included in the analyses irrespective of whether there was missing follow-up information for the patient prior to the event. Patients without an event up to the cut-off date and with follow-up information after the cut-off date were censored at the cut-off date.

Comment: In this study, the primary efficacy endpoint was event free survival (EFS) defined as disease recurrence or progression (local, regional, distant or contralateral), or death of any cause. Initially, the protocol specified progression free survival (PFS) as the primary efficacy endpoint (defined as the time between randomisation and date of documented relapse or death due to any cause). The sponsor justified the change on the basis that EFS (as defined) covers all relevant events rather than a selection of these events caught by PFS (as defined). The sponsor commented that "the study characteristics: neoadjuvant treatment in patients with locally advanced breast cancer before surgical intervention, followed by observation or adjuvant Herceptin® therapy, and the exclusion from the study of patients with distant metastatic disease, except ipsilateral supraclavicular nodes, assumes the absence of residual primary tumour after surgery with or without radiotherapy in the majority of the patients". Therefore, the use of PFS as defined as the endpoint would capture only those patients in whom "progression of disease occurred [i.e., relapse of the primary tumour] despite receiving neoadjuvant chemotherapy and those patients who could not undergo surgery due to insufficient response". Furthermore, the sponsor commented that the protocol specified definition of PFS actually corresponds to the definition of recurrence free survival.

The TGA adopted EU clinical guideline on "The evaluation of anticancer medicinal products in man", indicates that acceptable primary endpoints in confirmatory trials include OS and PFS/DFS, and if "PFS/DFS is the selected primary endpoint then, OS should be reported as secondary and vice versa".[24] The guideline also state that "in situations where there is a large effect on PFS, a long expected survival time after progression, or a clearly favourable safety profile, precise estimates of OS may not be needed for approval". The guideline also state that "independent review and confirmation of best tumour response and progression should be undertaken if PFS is the primary endpoint", and alternative primary endpoints "such as....EFS might uncommonly be appropriate. This has to be fully justified and it is recommended that prior regulatory agreement is sought in these cases". The guidelines also state that the objectives of "neoadjuvant therapy may include improved overall outcome and organ preservation (e.g., more conservative surgery)".

[24] CPMP/EWP/205/95/Rev.3/Corr. http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf

Overall, in this particular study EFS is considered to be acceptable as the primary endpoint but the following limitations should be noted: (1) the study was open label in design which makes it subject to the well known biases associated with designs of this type (such as assessment bias); (2) while the EFS events were required to be confirmed by objective assessments (such as histology/cytology, X-ray, ultrasound, CT/MRI scan), the "reviewers" were not blinded to treatment allocation and assessments were undertaken at individual study sites rather than at a centralised site by blinded "reviewers".

b. Secondary efficacy variables

Pathological complete response rate (pCR) : The pCR was analysed in two ways: (1) pCR of the primary tumour (breast pCR [bpCR]) was defined as the absence of any invasive cancer cell of the primary tumor at major surgery after neoadjuvant chemotherapy ± trastuzumab; (2) pCR of the primary tumour and axillary nodes (total pCR [tpCR]) was associated with the presence or absence of positive axillary nodes at pathology; clinical assessment of ipsilateral supraclavicular lymph nodes could also be 0. The pCR was "not evaluable" for patients in whom response could not be assessed (i.e., patients who had not undergone surgery).

Comment: The pCR rate has been used as a surrogate endpoint for survival benefit in numerous neoadjuvant trials. In the more than the 30 additional neoadjuvant studies referenced as "supportive" in the submission nearly all used pCR as the primary efficacy outcome. There are data which suggest that pCR is significantly associated with outcome measures of OS, DFS and RFS.[25, 26] However, this endpoint is not specifically mentioned in the TGA adopted EU clinical guideline.[24] Furthermore, there is uncertainty about how large the size of the absolute difference in pCR rates between two neoadjuvant treatments needs to be before it translates into a clinically meaningful increased survival benefit and whether the association between pCR and survival are dependent on tumour type (such as ER status).

Overall clinical response rate: The response categories were calculated according to modified RECIST criteria based on the objective tumour measurements of the lesions as recorded in the CRF. In addition, study investigators were required to report whether they considered the disease to have progressed. With the exception of T4d lesions (inflammatory breast cancer), disease in the breast had to be measurable according to RECIST criteria and this counted as a target lesion. Ipsilateral axillary nodes and ipsilateral supraclavicular nodes, if present, were also considered as target lesions, if they fulfilled the RECIST criteria for target lesions. Patients with non-measurable disease at baseline (patients with non-inflammatory disease for whom the primary tumor, the axillary nodes or the ipsilateral supraclavicular nodes were classified as non-measurable) or patients without target lesions (patients with non-inflammatory disease having no lesion with a diameter of at least 2 cm) were excluded from the analysis of overall clinical response. Response was assessed as follows:

- Complete response (CR): defined as no progressive disease and a tumour assessment prior to surgery after the last CMF cycle satisfied the criteria for CR;

[25]Wolmark N, Wang J, Mamounas E. Preoperative chemotherapy in patients with operable breast cancer: nine year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr. 2001;30:96-102.

[26] Rastogi P, Andersen SJ, Bear HD, et al. Pre-operative chemotherapy updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008;26:778-85.

for patients with non-inflammatory breast cancer, all lesions needed to be measurable at this assessment, otherwise CR could not be concluded.
- Partial response (PR): defined as no progressive disease (PD) and no CR and there was a tumour assessment prior to surgery after the last CMF cycle satisfying the criteria for PR; for patients with non-inflammatory breast cancer, all lesions needed to be measurable at this assessment, otherwise PR could not be concluded.
- Progressive disease (PD): defined if at least one of the following two criteria were present: (1) the study investigator judged the patient as having progressed at any time prior to surgery; and (2) there was any tumour assessment prior to surgery satisfying the criteria for PD. For patients with non-inflammatory breast cancer, only measurable lesions were taken into account.
- Non-evaluable (NE): no PD and the last tumour assessment prior to surgery after the last CMF cycle had not been performed.
- Stable disease (SD): assigned if patients had none of the cases specified above.
- Overall response rate: defined as CR + PR.
- To assess the response in inflammatory carcinoma (T4d) the NOAH Protocol Steering Committee defined the following criteria based on the effect of treatment on the extent of breast oedema or erythema: CR (complete resolution of oedema and erythema); PR (oedema decrease or stable, erythema clear decrease); SD (oedema decrease or stable, erythema stable); and PD (progression of any of the two signs).

Overall Survival (OS): defined as the time from the date of randomisation to the date of death due to any cause. Patients that had not been reported as having died at the time of the cut-off date of 30 March 2009 were censored.

Randomisation and blinding methods

Approximately 332 patients were planned for the randomised part of the study (116 patients with HER2-positive disease in each of two treatment arms), and 100 patients with HER2-negative disease for the observational arm. There was no blinding as the study was open-label.

Before randomisation, patients with HER2-positive disease were stratified according to the following criteria: (1) geographical area (Austria/Germany, Italy, Russia, Spain/Portugal); (2) disease stage (TN1M0 or T4 non-inflammatory, N0-1, M0 versus inflammatory disease, M0 versus any T, N2 or ipsilateral supraclavicular nodes); and (3) hormonal receptor status (ER and/or PgR positive versus both negative). Randomisation was computerised and performed centrally at the Michelangelo Operation Office using a minimisation technique to assign patients to treatment arms.[27] Patients with HER2-positive disease were randomised in a 1:1 ratio to the HER2+TC or HER2+C treatment arms.

Patients with HER2-negative disease were also stratified according to the same factors mentioned above and then randomised to either the observational arm or to be excluded from the study. Randomisation was performed according to the same minimisation technique used for the primary analysis, but with a ratio of 1:3. Patients with HER2-negative disease randomised to the arm received the same chemotherapy treatment regimen (without trastuzumab) as patients with HER2-positive. Patients with HER-negative disease not randomised to the observational arm were excluded from the study and could be treated according to the investigator's usual practice.

[27]Taves DR. Minimization: a new method of assigning patients to treatment and control group. Clin Pharmacol Ther 1974; 15: 443-453.

Analysis populations

Full Analysis Set (FAS): The primary efficacy analysis was conducted using the FAS, following the intent-to-treat (ITT) principle. The FAS included all patients who were randomised in the main study or registered in the parallel observational arm. Patients with significant GCP problems were excluded from the FAS (patients without approval of any protocol amendment or with missing documentation of informed consent). Patients with partially or completely non-retrievable source data were not excluded from the FAS, as long as there was documentation of informed consent.

Per Protocol Set (PPS): The PPS ("evaluable patient set") included all patients in the FAS, excluding patients who fulfilled any of the following criteria: (1) no study medication received; (2) prior chemotherapy treatments specifically listed in the inclusion/exclusion criteria; (3) females who were pregnant or lactating at baseline; (4) failure to receive at least one dose of assigned treatment medication; (5) failure to meet the tumour assessment criteria specified in the inclusion/exclusion criteria; (6) absence of documentation of over-expression/amplification of HER2; (7) absence of documentation of protocol-specified tumour; (8) documented metastatic disease at study entry.

Safety Analysis Population and Post-Surgery Safety Analysis Populations will be discussed in the safety review section of this CER.

Sample size

The sample size was based on EFS (primary endpoint) comparison between the two HER2-positive treatment arms and the primary analysis was planned when a total of 86 events had occurred in the two HER2-positive arms. The number of events was based on the assumption that the chemotherapy alone arm would have a 50% EFS rate at 3 years. The study assumed that a clinically meaningful improvement in EFS with the addition of trastuzumab would be to increase the median EFS time to 5.5 years (corresponding to a 68.5% EFS rate at 3 years). With these assumptions, a log-rank test on the EFS required 86 EFS events in the two HER2-positive arms to achieve 80% power to detect a hazard ratio of 0.545 (absolute improvement of 18.5% in the EFS rate at 3 years) at a 2-sided significance level of 5%. It was estimated that about 116 patients in each HER2-positive treatment arm would be required to provide a total of 86 EFS events. It was assumed that there would be a 0% drop-out rate and that recruitment would take about 3.5 years (actual recruitment started in June 2002 and finished in December 2005). The sample size in the HER2-negative patients was chosen to be about 100, and the total sample size (HER2-positive and HER2-negative patients) was 322 patients.

> *Comment:* The sample size assumptions based on event-driven methodology are satisfactory. The study was initially designed using time-driven endpoint methodology, but this was changed after protocol amendment version D to event-driven endpoint methodology as this methodology was considered "state-of-the art" for statistical analysis of multicentre clinical trials.

Statistical methods

a. Null and alternative hypothesis

The null hypothesis for EFS and OS was that there was no difference between the two treatments in the hazard rates (HR) and the alternative hypothesis was that there was a difference between the two treatments in the HRs. The null hypothesis was tested with the log-rank test (2-sided).

The null hypothesis for the pCR and the ORR was that there was no difference between the two treatments in the response rates and the alternative hypothesis was that there was a

difference between the two treatments in the response rates. The null hypothesis was tested with the Chi-squared test (2-sided).

b. Analysis of the EFS (primary endpoint)

In the submitted CSR, the analysis was based on data at the clinical cut-off date of 30 March, 2009. The primary analysis of EFS was tested using a non-stratified log-rank test (2-sided) in the FAS population and this analysis was repeated in the PPS population to check the robustness of the results. Kaplan-Meier estimates were calculated giving the number of patients at risk at randomisation and every 6 months after randomisation. EFS rates (1, 2 and 3-years) and 95% confidence limits (CIs) were provided for each treatment arm and HRs and 95% CIs were provided for between-treatment comparisons.

Sensitivity analyses of the EFS included: censoring data from patients in the HER2+C arm known to have crossed over to receive adjuvant trastuzumab at the time of their first trastuzumab infusion; and Cox proportional hazards modelling adjusting for stratification variables (geographical area, disease stage and hormone receptor status).

Exploratory subgroup analyses examining the effect of additional factors on EFS included: inflammatory breast cancer (yes versus no); baseline age (≤ 49 yrs versus > 49 yrs); baseline age (< 65 yrs versus ≥ 65 yrs); clinical nodal status (cN0 versus other); outcome according to bpCR (yes versus no); outcome according to tpCR (yes versus no); hormone receptor status (ER and/or PgR positive versus both negative); and surgery versus no surgery. Descriptive analyses were also performed comparing HER2-negative patients treated with chemotherapy alone with HER2-positive patients treated with the same chemotherapy (HER2+C arm).

c. Analyses of the secondary endpoints

bpCR and tpCR rates

The bpCR and tpCR rates and 95% CIs (Pearson-Clopper) were calculated for each treatment arm and confidence limits were calculated for the difference (Hauck-Anderson method). The analyses were undertaken in the FAS and PPS populations and subgroup analyses were undertaken using similar groups as those used to analyse EFS.

The bpCR and tpCR rates in the subgroup of patients who crossed over to receive adjuvant trastuzumab were also provided to assess whether patients in this subgroup had a particularly favourable or unfavourable prognosis for EFS and OS.

Exploratory logistic regressions on bpCR, tpCR were modelled using the same stratification factors as the Cox regression on the EFS time-to-event data. Descriptive results were provided for a comparison between HER2-negative and HER2-positive patients treated with the same chemotherapy regimen.

ORR and *OS*

The ORR was analysed using methods similar to those used to analyse the bpCR and tpCR rates. OS was analysed using methods similar to those used to analyse EFS.

Participant flow

The first patient was randomised on 10 June 2002 and the last patient was randomised on 12 December 2005. The clinical cut-off date for the analysis presented in the CSR was 30 March 2009 and after data transfer and further data cleaning the database was locked on 27 July 2010. At the time of the clinical cut-off, patients had been followed up for a median time of about 3.5 years (see Table 14, below).

Table 14: NOAH. Duration of overall follow-up; FAS.

Parameter	HER2+TC (n=115)	HER2+C (n=116)	HER2-C (n=99)
Mean (SD) months	44.64 (16.371)	39.30 (18.518)	44.80 (18.487)
Media(range) months	45.9 (2.1, 76.8)	42.09 (0, 77.5)	48.13 (0.9. 75.5)

There were 333 enrolled patients. The number of patients screened but not enrolled was not collected. There were 6 patients who did not receive any study treatment: 1 in the HER2+TC arm (withdrew consent) and 5 in the HER2+C arm (4 withdrew consent, and 1 did not start study medication because of investigator's decision). 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%). Of the 333 enrolled patients, 3 patients were excluded from all statistical analyses because of missing informed consent (2 patients) or late site approval of a protocol amendment (1 patient). Consequently, the FAS consisted of 330 patients (115 in the HER2+TC arm, 116 in the HER2+C arm) and 99 in the HER2-C arm). Patient disposition in the FAS in the pre-operative and post-operative periods is summarised below in Table 15.

Table 15: NOAH. Patient disposition across the study periods; FAS.

Pre-operative period			Post-operative period		
Treatment	Status [1]	N	Treatment	Status [2]	N
HER2+TC	Completed	102	HER2+TC	Entered	112
	Discontinued	13		Completed	1
				Ongoing	79
				Withdrawn	32
HER2+C	Completed	96	HER2+C→T	Entered	20
	Discontinued	21		Ongoing	17
				Withdrawn	30
			HER2+C	Entered	68
				Completed	2
				Ongoing	36
				Withdrawn	30
HER2-C	Completed	82		Entered	79
	Discontinued	17		Completed	1
				Ongoing	54
				Withdrawn	24

[1] Completion status refers to neoadjuvant treatment only. Patients who did not complete neoadjuvant treatment were also to enter the follow-up (post-operative) period.
[2] A patient is considered to enter the post-operative phase if she received at least one dose of study medication and had at least one safety assessment after surgery (patients not undergoing surgery had to have at least one safety assessment after the first dose of adjuvant trastuzumab or more than 28 days after the last dose of neoadjuvant chemotherapy).

In the FAS population, a total of 279 patients (84.5% [279/330]) completed neoadjuvant treatment (88.7% [102/115) in HER2+TC; 81.9% [95/116] in HER2+C; 82.8% [82/99] in HER2-C); and 51 patients prematurely discontinued neoadjuvant treatment or did not receive study treatment (13 HER2+TC; 21 HER2+C; 17 HER2-C). The reasons discontinuation of neoadjuvant treatment are summarised in Table 16.

In the FAS population, 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).

There were 64 (19.4%) patients who 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 Russian site CRTN [47296] (13/17 patients in HER2+TC; 15/30 patients in HER2+C).

Table 16: NOAH. Summary of reasons for discontinuation of neoadjuvant treatment; FAS.

Time point	Discontinuation reason	HER2+TC (N=115) N %	HER2+C (N=116) N %	HER2-C (N= 99) N %
Overall	Discontinued	13 (11.3)	21 (18.1)	17 (17.2)
	Reason			
	Adverse event/intercurrent illness	1 (0.9)	1 (0.9)	3 (3.0)
	Death	0	0	1 (1.0)
	Insufficient therapeutic response/progressive disease	4 (3.5)	7 (6.0)	9 (9.1)
	Failure to return	0	0	1 (1.0)
	Violation of selection criteria at entry	0	0	1 (1.0)
	Other protocol violation	3 (2.6)	1 (0.9)	0
	Refused treatment/did not cooperate/withdrew consent	4 (3.5)	9 (7.8)	2 (2.0)
	Administrative/other	1 (0.9)	2 (1.7)	0
	Abnormality of laboratory test	0	1 (0.9)	0

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

In the FAS population, a total of 279 patients (84.5% [279/330]) entered the postoperative phase of the study (112 in HER2+TC; 20 in HER2+C→T; 68 HER2+C; and 79 in HER2-C). The reasons for discontinuation in the post-operative period are summarised in Table 17.

Table 17: NOAH. Summary of reasons for discontinuation in the post-operative period; FAS.

Time point	Discontinuation reason	HER2+TC (N=112) N %	HER2+C->T (N= 20) N %	HER2+C (N= 68) N %	HER2-C (N= 79) N %
During post-operative Period	Discontinued	32 (28.6)	3 (15.0)	30 (44.1)	24 (30.4)
	Reason				
	Death	21 (18.8)	3 (15.0)	20 (29.4)	10 (12.7)
	Insufficient therapeutic response/ progressive disease	8 (7.1)	0	6 (8.8)	5 (6.3)
	Failure to return	0	0	1 (1.5)	3 (3.8)
	Violation of selection criteria at entry	0	0	0	1 (1.3)
	Refused treatment/did not cooperate/ withdrew consent	1 (0.9)	0	2 (2.9)	2 (2.5)
	Administrative/other	2 (1.8)	0	1 (1.5)	3 (3.8)

Percentages are calculated with respect to the total number of patients in each treatment group.
Patient 32074/25 in the HER2+C group discontinued the follow-up period due to death - as this death occurred after the cut-off date it was not evaluated as event for the event-free and overall survival analysis.
Patient 47296/18 in the HER2+C group discontinued the follow-up period due to insufficient response/progressive disease. This was specified as ovarian cancer in the comment field and was not specified as an event on the CRF follow-up pages and thus not considered as an event in the analysis of event-free survival.

The majority of patients in the FAS population entered the follow-up stage and the percentage of patients entering this stage was higher in the HER2+TC (85.7% [96/112]) and HER2-C (86.3% [82/95]) arms than in the HER2+C arm (79.6% [86/108]). The major reason for the difference among the three treatment arms was the higher incidence of death in the HER2+C arm (27.8% [30/108]) than in the HER2+TC (30.4% [34/112]) and HER2-C (17.9% [17/95]) arms. The reasons for discontinuation in the follow-up period (FAS) are summarised in Table 18.

Table 18: NOAH. Patients entering follow-up and reasons for discontinuation; FAS.

Parameter	HER2+TC (N=115) N	%	HER2+C (N=116) N	%	HER2-C (N= 99) N	%
Patients having entered follow-up [1]	112	(100)	108	(100)	95	(100)
Patients who underwent surgery	96	(85.7)	86	(79.6)	82	(86.3)
Patients who completed neo-adjuvant treatment	101	(90.2)	95	(88.0)	82	(86.3)
Patients with any follow-up assessment regarding recurrence of breast cancer [2]	111	(99.1)	105	(97.2)	91	(95.8)
Patients with any follow-up assessment of survival status (dead/alive)	111	(99.1)	107	(99.1)	92	(96.8)
Patients having completed follow-up	1	(0.9)	2	(1.9)	1	(1.1)
Ongoing patients	77	(68.8)	60	(55.6)	58	(61.1)
Patients having discontinued follow-up	34	(30.4)	46	(42.6)	36	(37.9)
Reason						
Adverse event	0		0		0	
Death	21	(18.8)	30	(27.8)	17	(17.9)
Insufficient therapeutic response/progressive disease	10	(8.9)	9	(8.3)	8	(8.4)
Failure to return	0		2	(1.9)	4	(4.2)
Violation of selection criteria at entry	0		0		1	(1.1)
Other protocol violation	0		0		0	
Refused treatment/did not cooperate/withdrew consent	1	(0.9)	4	(3.7)	3	(3.2)
Administrative/other	2	(1.8)	1	(0.9)	3	(3.2)
Abnormality of laboratory test	0		0		0	

[1] Entering follow-up is defined as having any assessment recorded on the CRF follow-up pages.
[2] Patients 32067/46 and 32067/64 in the HER2+C group have been recorded as dead on their first follow-up assessment and are thus not included. Patient 33810/05 in the HER2-C group withdrew consent at the first follow-up assessment and was thus only assessed as alive.

Comment: The primary efficacy analysis was undertaken in the FAS population based on the ITT principle. This is considered to be the most appropriate population and method for the analysis. Following a protocol amendment, 20 patients in the HER2+C arm elected to receive adjuvant trastuzumab treatment (17.2% [20/116]).

The majority of patients (FAS) in both the HER2-positive treatment arms completed neoadjuvant treatment, but the percentage was higher in the HER2+TC arm than the HER2+C arm (88.7% and 81.9%, respectively). The major difference between the two treatment arms was the higher incidence in the HER2+C arm than in the HER2+TC arm of patients discontinuing neoadjuvant treatment due to insufficient therapeutic response/progressive disease (6.0% and 3.5%, respectively), and refused treatment/did not co-operate/withdrew consent (7.8% and 3.5%).

The majority of patients (FAS) in both the HER2-positive treatment arms underwent surgery but notably more patients in the HER2+TC arm than in the HER2+C were operated on (82.5% and 74.1%, respectively), and more patients in the HER2+TC arm (21.4%) had a quadrantectomy, lumpectomy or wide excision (less radical procedures than a mastectomy) than patients in the HER2+C arm (10.5%). The sponsor considers that these results reflect superior efficacy as regards surgical outcomes in the HER2+TC arm than in the HER2+C arm Unexpectedly, a high percentage of patients in both the HER2-positive treatment arms did not undergo surgery (14.8% [17/115] in HER2+TC arm, 25.9% [30/116] in HER2+C arm) and the majority of patients in the HER2-positive arms not undergoing surgery were from one Russian site.

Major protocol violations/deviations

The FAS included 330 patients and 7 patients were excluded from the PPS due to protocol violations (1 in the HER2+TC arm due to the administration of a specifically prohibited treatment; and 6 the HER2+C arm [4 due to no medications being received; 1 due to failure to meet tumour assessment criteria; 1 due to absence of documentation of over-expression/amplification of HER2]). There were 26 notable protocol violations that did not warrant exclusion from the PPS population. Examination of the listed violations showed a variety of reasons mainly relating to failure to modify the dose due to the presence of pre-specified toxicities.

Baseline data

a. Demographic characteristics

While the median age was similar in the three treatment arms (49 to 51.5 years), there were more patients aged < 50 years in the HER2-C arm (53.5%) than in the HER2+TC (48.7%) and HER2+C (44.0%) arms. At pre-treatment staging, the majority of patients had an ECOG performance status of 0 but notably more patients in the HER2+C arm (11.3%) had a performance status of 1 compared with the HER2+TC (4.3%) and HER2-C (4.0%) arms. No patient had an ECOG performance status worse than 1. All patients in the study were "White/Caucasian".

> *Comment:* The baseline demographic data were well balanced across the three treatment arms. The mean age of the patients in three treatment arms ranged from 50.2 to 51.9 years, indicating that the population with breast cancer in this study was relatively young. It has been estimated that the mean age of first diagnosis of women with breast cancer in Australia is about 60 years [AIHW, 2010].

b. Stratification factors

Patients were stratified according to geographical area, disease stage and hormone receptor status.

> *Comment:* In the FAS, the stratification factors of geographical area and receptor status were well balanced between the two HER2+ arms. However, there was an imbalance between the HER2+TC arm and the HER2+C arm in baseline stage "T3N1M0 or T4 non-inflammatory, N0-1, M0" (42.6% and 44.0%, respectively), baseline stage "inflammatory disease, M0" (16.5% and 20.7%, respectively) and baseline stage "any T, N2 or ipsilateral supraclavicular node" (40.9% and 35.3%, respectively).
>
> In the total study population there were fewer patients with baseline inflammatory disease compared with patients with baseline non-inflammatory disease (17.9% [59/330] versus 82.1% [271/330], respectively).

c. Baseline breast cancer disease characteristics

In the FAS, the median time from diagnosis to randomisation was less than one month and was shorter in the HER2-C arm (15.0 days; range 1-382) than in the HER2+TC (22.0 days; range 5-105) and the HER2+C (23.5 days; range 6-200) arms. The sponsor states that this might be partly due to the fact that patients in the HER2-positive arms were required to have IHC 2+ and 3+ status confirmed centrally after registration while patients with HER2-negative arm were randomised at the time of the registration.

In the two HER2-positive arms, patients were generally well balanced as regard baseline disease characteristics including tumour size and nodal status. None of the patients in the study had distant metastases. In nearly all patients, assessment of metastases was by chest X-ray, bone scan and liver ultrasound.

d. Baseline cardiac disease evaluation

Baseline LVEF met the protocol specified value (≥ 55%) in all patients, apart from 2 with missing values. Median LVEF was 63% in all three treatment arms and the majority of patients (> 65%) in each arm also had a normal ECG at baseline. The majority of patients in the three treatment arms had no baseline risk factors for cardiovascular disease (66.7%, 64.7% and 60.9% in the HER2-C, HER2+C and HER2+TC, arms, respectively). The incidence of at least one baseline cardiac risk factor was greater in the HER2+TC arm (39.1%) than in the HER2+C arm (35.3%), mainly due to a higher incidence of hypertension (25.2% and 20.7%, respectively).

Comment: The sponsor stated that the imbalance among the three treatment groups in baseline cardiovascular risk factors is "thought to have occurred by chance". This is a reasonable assumption.

e. Previous and concomitant disease other than breast cancer

In the FAS population, the incidence of history of disease (inactive) was similar in the HER2+TC (61.7%) and HER2+C (62.1%) arms and higher than that in the HER2-C arm (41.4%). The incidence of active disease at baseline was similar in the three arms (41.7% in HER2+TC; 46.6% in HER2+C; 47.5% in HER2-C).

f. Previous and concomitant medications

Overall, 27.9% (92/330) of patients (FAS) had at least one previous treatment not associated with breast cancer. The type and frequency of previously used medications were consistent with those expected in a patient population of the age distribution included in the study. Nearly all patients (FAS) received at least one concomitant treatment during the course of the study (95.7% in HER2+TC; 93.1% in HER2+C; 88.9% in HER2-C). The most commonly used medications were corticosteroids (91.3% in HER2+TC; 87.9% in HER2+C; 83.8% in HER2-C), histamine H2-receptor antagonists (91.3% in HER2+TC; 89.7% in HER2+C; 84.8% in HER2-C), anti-histamines (86.1% in HER2+TC; 85.3% in HER2+C; 81.8% in HER2-C), anti-emetics of the 5-HT3 antagonist class (73.0% in HER2+TC; 67.2% in HER2+C; 54.5% in HER2-C), other anti-emetics (25.2% in HER2+TC; 24.1% in HER2+C; 17.2% in HER2-C), analgesics (31.3% in HER2+TC; 18.1% in HER2+C; 17.2% in HER2-C) and benzodiazepines (18.3% in HER2+TC; 18.1% in HER2+C; 15.2% in HER2-C).

Overall, 8.7% [10/115] of patients (FAS population) in the HER2+TC arm, 5.2% [6/116] in the HER2+C arm and 7.1% [7/99] in the HER2-C arm received at least one concomitant medication related to breast cancer. The most frequently used concomitant medications were tamoxifen (3.5% in HER2+TC; 1.7% in HER2+C; 2.0% in HER2-C), aromatase inhibitors (2.6% in HER2+TC; 0.9% in HER2+C; 5.1% in HER2-C) and zoledronic acid (1.7% in HER2+TC; 0% in HER2+C; 0% in HER2-C).

Comment: Overall, the differences in previous and concomitant medication use between the two HER2-positive treatment arms appear to be relatively minor and are unlikely to have resulted in significant bias.

Results for the primary efficacy outcome

The results for the analysis (FAS) of the EFS (primary efficacy outcome) are summarised below in Table 19 and the Kaplan-Meier curves of EFS in HER2-positive patients are provided below in Figure 2. Results of all main efficacy endpoints are summarised in Table 20 below.

Table 19: NOAH. Summary of Event-Free-Survival (EFS); FAS.

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.

Figure 2: NOAH. Kaplan-Meier plot of EFS in HER2+ patients; FAS.

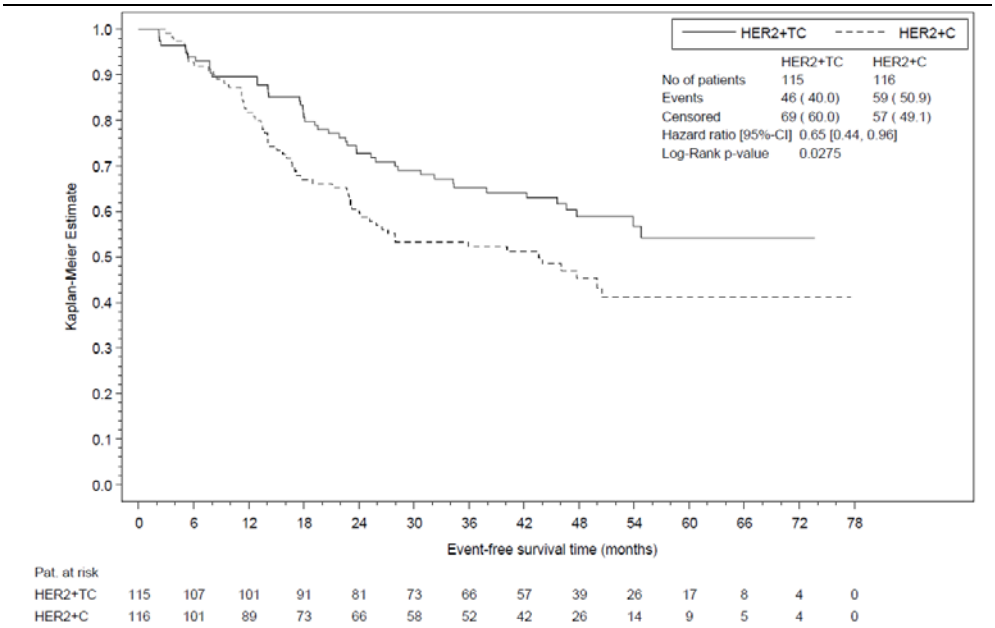


Table 20: NOAH. Summary of the main efficacy results at the clinical cut-off date (30 March 2009); FAS.

Parameter	HER2+TC N = 115	HER2+C N = 116	HER2-C N = 99
Event-Free Survival			
Total number of patients with EFS event	46 (40.0%)	59 (50.9%)	42 (42.4%)
HR (95%CI); p-value (Log-Rank test)			
Primary analysis: Unstratified (Log-Rank test)	0.65 (0.44, 0.96) p = 0.0275		
Stratified sensitivity analysis (Cox regression)	0.65 (0.44, 0.96) p = 0.0309		
EFS rate at 36 months (95% CI)	0.65 (0.56, 0.74)	0.52 (0.43, 0.62)	0.63 (0.53, 0.72)
Pathologival Complete Response			
bpCR			
% of patients (95% CI)	44.3 (35.1, 53.9)	26.7 (18.9, 35.7)	19.2 (12.0, 28.3)
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)	18.2 (11.1, 27.2)
Difference in tpCR rate (95%CI); p-value (Chi-square test)	19.3 (7.2, 31.4) p = 0.0014		
Overall Response Rate			
% of patients with measurable disease at baseline with			
Progressive disease	12 (10.9%)	11 (10.3%)	16 (16.7%)
Stable disease	9 (8.2%)	10 (9.3%)	11 (11.5%)
Partial response	21 (19.1%)	21 (19.6%)	32 (33.3%)
Complete response	59 (53.6%)	50 (46.7%)	31 (32.3%)
Not evaluable	9 (8.2%)	15 (14.0%)	6 (6.3%)
Overall Clinical Response (CR + PR)			
% of patients (95% CI)	72.7 (63.4, 80.8)	66.4 (56.6, 75.2)	65.6 (55.2, 75.0)
Difference in OR rates (95% CI); p-value (Chi-square test)	6.4 (-6.4, 19.1) p = 0.3077		
Overall Survival			
Number of patients (%) with event	22 (19.1%)	33 (28.4%)	21 (21.2%)
Median (months)	NR	NR	NR
HR (95%CI); p-value (Log-Rank test)	0.59 (0.35, 1.02) p = 0.0555		
36 months OS rate (95% CI)	0.85 (0.79, 0.92)	0.78 (0.70, 0.86)	0.85 (0.78, 0.92)

In the HER2+TC arm, 40.0% of patients experienced an EFS event (disease recurrence, progression or death) compared with 50.9% of patients in the HER2+C arm. Most of the events experienced by patients were disease recurrence (27.0% in HER2+TC; 37.1% in HER2+C), and disease progression (9.6% in HER2+TC; 10.3% in HER2+C). Of the patients who experienced recurrent disease, distant disease recurrence occurred in the majority patients (21.7% in HER2+TC; 27.6% in HER2+C).

EFS in the PPS population was consistent with the EFS in the FAS population. The risk of an EFS event in the PPS population was reduced by 35% in the HER2+TC arm relative to the HER2+C arm: HR = 0.65 [95% CI: 0.44, 0.96]; p=0.0300, log-rank test.

The Cox regression analysis of EFS adjusted for stratification factors (geographical area, disease stage and hormone receptor status) supported the primary analysis, with the results statistically significantly favouring the HER2+TC arm relative to the HE2+C arm: HR = 0.653 [95% CI: 0.443, 0.962]; p=0.0309, Wald's test. The analysis also showed that baseline disease stage was a predictor of EFS. Patients with "any T, N2 or ipsilateral supraclavicular nodes" baseline disease had a statistically significantly lower risk of experiencing an EFS event compared with patients with "inflammatory disease, M0" baseline disease (HR = 0.496 [95% CI: 0.288, 0.852]; p=0.0110, Wald's test).

Of the 20 patients who were originally randomised to the HER2+C arm and subsequently crossed over to receive adjuvant trastuzumab for up to 1 year, 5 patients experienced an EFS event after cross-over. However, the EFS benefit in the HER2+TC arm relative to the HER2+C arm was observed despite 20 patients crossing over from the HER2+C arm to receive adjuvant trastuzumab. When data from these 19 patients (1 of the 20 patients 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% in the HER2+TC arm relative to the HER2+C arm (unadjusted HR = 0.59 [95% CI: 0.40, 0.88]); p = 0.0084, log-rank test). The 3-year event free survival rate was 65% in the HER2+TC arm and 48% in the HER2+C arm.

Comment: There was a statistically significant 35% decreased risk of experiencing an EFS event (disease recurrence, progression or death) in patients in the HER2+TC arm relative to patients in the HER2+C arm: unadjusted HR = 0.65 [95% CI: 0.44, 0.96]; p = 0.0275, log-rank test. The median time to an EFS event was 43.6 months in patients in the HER2+C arm, but was not evaluable in the HER2+TC arm due to too few patients with events being reported at the time of the analysis. The EFS rate at 3 years was 65% in the HER2+TC arm and 52% in the HER2+C arm, and the 95% CIs are noted to overlap. In calculating the sample size it was estimated that an absolute difference between the two treatment arms of 18.5% in the EFS rate at 3 years represented a clinically meaningful improvement (i.e., 68.5% in the HER2+TC arm compared with 50% in the HER2+C arm; HR = 0.545). Consequently, the absolute difference in the EFS at 3 years of 13% between the two HER2-positive treatment arms (HR = 0.65) is not clinically significant, based on the assumption that a clinically meaningful difference between the two treatment arms is 18.5% (HR = 0.545).

Results for other efficacy outcomes

a. Pathological complete response (secondary efficacy endpoint)

The *bpCR rate* was statistically significantly higher in patients in the HER2+TC arm (44.3% [51/115]) compared to patients in the HER2+C arm (26.7% [31/116]), resulting in an absolute difference of 17.6% [95% CI: 5.0, 30.2]; p = 0.0051, Chi-square test. The *tpCR* rate was also statistically significantly higher in patients in the HER2+TC arm (40.0% [46/115]) than in patients in the HER2+C arm (20.7% [24/116]), resulting in an absolute difference of 19.3% [95% CI: 7.2, 31.4]; p=0.0014, Chi-square test.

In the exploratory *logistic regression analysis for bpCR* (unadjusted for the stratification factors) the odds ratio (OR) for the HER2+TC arm compared with the HER2+C arm was 2.18 [95% CI: 1.26, 3.79]; p=0.0055, Wald's test. After adjusting for each stratification factor separately (that is, geographical area, disease stage, hormone receptor status) the treatment effect on bpCR for the HER2+TC arm compared with the HER2-C arm remained statistically significant with similar ORs (2.20-2.29) to that for the unadjusted analysis (2.18). In addition, the also results showed that both baseline disease stage and hormone receptor status were predictors of bpCR.

In the *exploratory logistic regression analysis for tpCR* (unadjusted for the stratification factors), the OR for the HER2+TC arm relative to the HER2+C arm was 2.56 [95% CI: 1.43, 4.58]; p=0.0016, Wald's test. After adjusting for each stratification factor separately (geographical area, disease stage, hormone receptor status) the treatment effect for the HER2+TC arm compared with the HER2-C arm remained statistically significant with similar ORs (2.56 to 2.58) to that for the unadjusted analysis (2.56). In addition, the results also showed that hormone receptor status was a predictor of tpCR.

Comment: The bpCR and tpCR rates both statistically significantly favoured the HER2+TC arm relative to the HER2+C arm. However, there were a significant number of patients in the HER2+TC and the HER2+C arms who were not evaluable for bpCR or

tpCR (16.5% [19/115] in the HER2+TC arm and 26.7% [31/116] in the HER2+C arm). The major reason for patients being not evaluable was that no surgery had been performed (14.8% [17/115] in HER2+TC; 25.9% [30/116] in HER2+C). The pCR was assessed by local pathologists unblinded to treatment allocation (rather than blinded central pathology review), raising the possibility of assessment bias. However, the sponsor stated that "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".

NOAH provided no criteria defining a clinically significant difference in pCR rates between the two HER2+ treatment arms. However, the MDACC study[28] (nominated by the sponsor as a supportive study) was powered to detect a 2 fold increase in the pCR rate (=tpCR) from 21% in the HER2+C arm to 41% in the HER2+TC arm (pCR defined as no evidence of residual invasive cancer, both in breast and axilla). Consequently, it is reasonable to assume that the figures for the pCR rates used to power the MDACC study represent a minimum clinically significant difference between the two treatment arms. Therefore, applying the MDACC assumptions to the NOAH results suggests that the statistically significant absolute difference in the tpCR rate between the HER2+TC and the HER2+C treatment arms for the tpCR of 19.3% (40.0% and 20.7%, respectively) is of borderline clinical significance.

b. Overall clinical response rate (secondary efficacy endpoint)

The analysis of the overall clinical response rate (ORR = CP + PR) was determined in all patients with measurable disease at baseline (110 patients [95.6%] in HER2+TC; 107 patients [92.2%] in HER2+C; and 96 patients [97.0%] in HER2-C). The ORR was higher in the HER2+TC arm (72.7% [80/110]) than in the HER2+C arm (66.4% [71/107]) but the difference was not statistically significant: absolute difference of 6.4% [95% CI: -6.4, 19.1]; p=0.3077, chi-square test.

Comment: There was no statistically significant difference in the overall clinical response rate between the HER2+TC and HER2+C arms. The percentage of patients with progressive disease, stable disease and a partial response was similar for the two HER2-positive arms. However, the percentage of patients with complete response was higher in the HER2+TC arm (53.6%) than in the HER2+C arm (46.7%). The exploratory logistic regression analyses for the overall clinical response rate adjusted for each of the stratification factors showed no difference between the two treatment arms for any factor except for the comparison between the geographical regions Russia versus Germany/Austria. For this comparison, the odds ratio (OR) for the overall clinical response was 5.24 ([95% CI: 1.77, 15.57]; p=0.0001, Wald's test). The sponsor states that at the Russian site almost all patients were classified as complete responders.

c. *Overall survival (secondary efficacy endpoint)*

At the time of the analysis, a total of 76 randomised patients in the FAS population had died (22 [19.1%] in HER2+TC; 33 [28.4%] in HER2+C); 21 [21.2%] in HER2-C). The median survival time could not be estimated for patients in the three treatment arms due to the long survival time of all patients. The 3 year overall survival (based on Kaplan-Meier estimates) was 85.0% in the HER2+TC arm and 78.0% in the HER2+C arm: HR = 0.59

[28]Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomised trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005;23:3676-3685

[95% CI: 0.35, 1.02]; p=0.055, log-rank test. The Kaplan-Meier curves for the two HER2+ groups remained together for the first 6 months and then began to diverge. The result for OS survival in the PPS was similar to that in the FAS: HR = 0.59 [95% CI: 0.35, 1.02]; p=0.0546 log-rank test.

Comment: Overall survival was longer in the HER2+TC arm than in the HER2+C arm but the result was not statistically significant. The overall survival data were relatively immature at the time of analysis as shown by the large number of patients being censored (80.9% [93/115] in HER2+TC; 71.6% [83/115] in HE2+C).

d. Subgroup exploratory analyses

The exploratory subgroup analyses (HRs) for EFS in the two HER2+ treatment groups are were provided in a Forest plot. The HR statistically significantly favoured the HER2+TC arm relative to the HER2+C arm in the cN ≥1 subgroup, the ER and PgR both negative subgroup and the > 49 years of age subgroup.

Comment: The exploratory subgroup analyses should be interpreted with caution due to the relatively small number of patients in some subgroups with a relatively small number of events (underpowered analyses). Furthermore, no statistical adjustment was made for the multiplicity of pair-wise comparisons which means that the observed statistically significant results might have occurred by chance.

Comparison between published results and submitted results (CSR)

In the published results[29], patients had been followed for a median of 3.2 years compared with the CSR data provided in the submission in which patients in the HER2+TC, HER2+C, and HER2-C arms had been followed for a median of 3.8, 3.5 and 4.0 years, respectively. The comparative results of the analyses are provided in Table 21.

[29]Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010; 375: 377-384.

Table 21: NOAH. Main efficacy results (CSR and published) in HER2+ 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.

Comment: The published results favoured the HER2+TC arm compared with the HER2+C arm to a greater extent than the CSR results provided in the submission. However, the sponsor made some significant changes to the statistical analysis plan used for the CSR data from that used for the published data. The sponsor considers that the two most notable differences between the analyses were: (1) The criteria for overall clinical response were revised to ensure that objective tumour measurements were consistently used as the basis for response assessment, rather than subjective assessment of response by the investigators. This resulted in lower overall clinical response rates in the CSR analysis for both HER2+ treatment arms with the difference being not statistically significant (as compared to higher rates with the difference being statistically significant in the published analysis); (2) Based on responses to queries sent to the study sites during the re-monitoring of the data the initial disease stage category was changed in a number of patients (36/231 HER2-positive patients in the FAS). As a consequence, in the CSR, the proportion of patients classified as having inflammatory breast cancer (18.6% [43/231]) is smaller than that in the published analysis (26.8% [63/235]).

It is considered that the analysis submitted in the CSR is more robust than the analysis in the published data. This results in a more conservative estimate of the benefits of neoadjuvant trastuzumab therapy in women with locally advanced HER2-positive

breast cancer. In particular, in the CSR analysis the HR for EFS is closer to 1 (although still statistically significantly in favour of the HER2+TC arm), the absolute difference in the EFS rates at 36 months between the two HER2-positive treatment arms is smaller and the overall clinical response rates for the two HER2-positive treatments are lower and no longer statistically significant.

Supportive efficacy studies

MDACC Study [Buzdar et al., 2005; Buzdar et al., 2007].

Design

The MDACC study was nominated by the sponsor as a supportive study to extend the indications of trastuzumab to include neoadjuvant treatment in combination with chemotherapy for localised breast cancer. The results from this Phase III, prospective, randomised study were reported in two publications; an initial report[30] followed by an updated report.[31] The objective of the study was to determine whether the addition of trastuzumab to chemotherapy in the neoadjuvant setting could increase the pathologic complete response (pCR) rate in patients with HER2-positive disease. All patients provided written informed consent before entry into the study.

Comment: The published reports did not expressly state that the study was open-label. However, it can be inferred that this must have been the case as no trastuzumab placebo was provided for patients randomised to chemotherapy only and there were no statements in the report indicating that patients, investigators, or pathologists were blinded to treatment.

Following an extraordinary interim analysis requested by the Data Monitoring Committee (DMC) that took place prior to the scheduled interim analysis, the committee recommended that accrual be suspended after 42 patients had been registered, as the pCR rate (primary efficacy endpoint) in the first 34 patients significantly favoured the HER2+TC arm compared with the HER2+C arm. Consequently, the original study report includes comparative data on the 42 patients who had been randomised to treatment at the time the study was suspended (23 to the HER2+TC arm; 19 to the HER2+C arm). The study protocol was subsequently amended and randomisation to the chemotherapy arm alone was discontinued and an additional 22 patients were added to the chemotherapy plus trastuzumab arm. Therefore, it is considered that only the data from the original study can provide supportive data as patients were randomised to the HER2+TC arm or the HER2+C arm, while in the updated study additional patients were assigned to the HER2+TC arm. It is considered methodologically unsound to compare the HER2+C group (original data, randomised patients) with the HER2+TC group (original data, randomised patients plus additional data, non-randomised, assigned patients).

[30]Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomised trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005;23:3676-3685

[31] Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2–positive operable breast cancer: an update of the initial randomised study population and data of additional patients treated with the same regimen. Clin Cancer Res. 2007; 13:228-233

Patients

Patients with histologically confirmed Stage II to IIIa invasive but non-inflammatory carcinoma of the breast were included in the study. All tumours were HER2+ by FISH or showed 3+ overexpression by immunohistochemistry. Before initiation of therapy all patients underwent disease staging, which included a complete history, physical examination, complete blood count (CBC), chemistry profile, chest radiograph, ultrasound or CT scan of the liver and a bone scan. Mammography of both breasts was performed, and additional breast and axillary assessment of the tumour site was conducted by ultrasound. All patients were required to have adequate bone marrow function as defined by an absolute granulocyte count of more than 1,500/µL and platelet count of more than 100,000/µL. Patients were also required to have adequate liver function, with bilirubin within normal laboratory values and adequate renal function, which was defined as serum creatinine less than 2.5 mg/100 mL. Baseline cardiac evaluation included an ECHO or MUGA scan and patients with a history of uncompensated congestive heart failure or a cardiac ejection fraction less than 45% were excluded.

> *Comment*: This study excluded patients with non-inflammatory breast cancer, which contrasts with NOAH where patients with this disease were included.

Treatments

a. Chemotherapy

Patients were randomly assigned to chemotherapy alone (HER2+C) or chemotherapy with trastuzumab (HER2+TC) weekly for 24 weeks. The chemotherapy regimen for each patient was 4 cycles of paclitaxel 225 mg/m^2 as a 24 h continuous IV infusion repeated every 3 weeks, followed by 4 cycles of FEC consisting of fluorouracil 500 mg/m^2 IV on Days 1 and 4, cyclophosphamide 500 mg/m^2 IV on Day 1 only and epirubicin 75 mg/m^2 on Day 1 only. The study included dose modification for toxicities due to chemotherapy.

Each patient was pre medicated with either dexamethasone 20 mg (PO), 12 h and 6 h before administration of paclitaxel or dexamethasone 20 mg (IV) 30 minutes before chemotherapy. In addition, patients received diphenhydramine 50 mg (IV) and cimetidine 300 mg (IV) 30 minutes before paclitaxel infusions. The study report indicated that the dose and schedule of paclitaxel was based on information available at the time of study inception (1999) but that evidence at the time of the study report (2005) suggested that the most effective schedule may have been weekly rather than three weekly administration.

b. Trastuzumab

Patients randomised to trastuzumab received 4 mg/kg IV over 90 minutes on Day 1 of Cycle 1 and then weekly 2 mg/kg IV over 30 minutes for a total of 24 weekly doses. In the first cycle, trastuzumab was administered 1 day before paclitaxel to monitor any potential infusion reaction and in subsequent cycles therapies were administered on the same day if there had been no adverse event in the first cycle.

c. Local therapy and adjuvant therapies

After completion of 24 weeks of neoadjuvant therapy, patients were assessed to determine the most appropriate local therapy. Patients who were considered appropriate candidates for breast conservation therapy (BCT) were offered segmental mastectomy (lumpectomy). Patients who were considered inappropriate for BCT or who did not desire BCT underwent total mastectomy. All patients (total mastectomy and BCT) with persistent axillary disease detected by physical examination or by ultrasound and verified by ultrasound-guided fine-needle aspiration underwent axillary lymph node dissection.

Patients who were clinically node negative after neoadjuvant therapy proceeded to lymphatic mapping and sentinel lymph node biopsy. Clinically node negative patients who showed microscopic residual disease in the sentinel lymph node(s) were recommended for axillary lymph node dissection, although some patients elected to receive postoperative radiation therapy to the regional lymph nodes instead. All patients treated with a segmental mastectomy received radiotherapy with whole breast irradiation. Radiotherapy was not offered to patients with initial clinical Stage II breast cancer who had been treated with mastectomy and had negative lymph nodes. After completion of systemic and local therapy, patients with ER-positive tumours received tamoxifen at a dose of 20 mg daily or anastrozole 1 mg daily if the patient was postmenopausal. This was planned for 5 years, regardless of the menopausal status of the patient.

Assessments

Antitumor activity was evaluated with imaging studies after 4 cycles of chemotherapy (at the completion of paclitaxel) and before surgery (at the completion of FEC). Tumour measurements were documented after the first 12 weeks of paclitaxel and at the completion of FEC therapy to determine the best clinical response before local therapy. CBCs, differential counts and platelet counts were repeated weekly to monitor the myelotoxicity of chemotherapy in the first cycle and subsequently, blood counts were performed on Day 1 of each cycle. Cardiac evaluation was performed at baseline and then repeated after completion of paclitaxel and then again at the completion of FEC therapy. Follow-up ultrasound and mammography were performed after 4 cycles of paclitaxel and again after 4 cycles of FEC. In the adjuvant treatment phase, patients were evaluated at 4 month intervals during the initial 2 years and then at 6 month intervals for the third year. Mammograms were performed yearly.

Efficacy endpoints

The primary objective of the study was to compare the pathologic complete response (pCR) rate between the two HER2-positive treatment arms; pCR was defined as no evidence of residual invasive cancer, both in breast and axilla. The stated goal of the study was to demonstrate that the addition of trastuzumab to a complete 6 month preoperative chemotherapy regimen will increase the pCR rate 2 fold compared with chemotherapy alone.

Clinical complete remission was defined as disappearance of all clinical evidence of active tumour per evaluation by physical examination. Partial response was defined as equal or greater than 50% decrease in measurable lesions for a minimum of 4 weeks as determined by the product of the longest perpendicular diameters of the lesion(s). Minor response was defined as a decrease in the tumour size that did not qualify for partial response and progressive disease was defined as any increase in tumour size or appearance

Sample size and statistical methods

The primary objective of the study was to compare pCR rates between the two HER2-positive treatment arms. The projected pCR rate with the HER2+C arm was estimated to be 21% based on previous experience with similar chemotherapy. The study was powered to detect a 20% improvement in the pCR rate (from 21% to 41%). Accrual of 164 patients was planned and with this number of patients the study would have 80% power to detect a 20% difference (2-sided type I error = 0.05). Patients were assigned to treatment arms using stratified blocked randomisation, with strata based on age (< 50 years versus ≥ 50 years) and stage of disease. Toxicity was evaluated using National Cancer Institute Common Toxicity Criteria (NCI-CTC) (v2.0) criteria. Toxicity and response rates were compared using the Chi-square test.

One interim analysis was planned when pCR results were known for the first 82 patients. Stopping rules were provided in the event that evidence indicated a rate of cardiac toxicity more than 3%. However, in view of the apparently high pCR rate in the HER2+TC arm relative to the HER2-C arm in the first 34 patients, the DMC requested an extraordinary interim analysis based on Bayesian predictive probabilities addressing the question of how likely the final results of the study after the full planned sample size of 164 patients would show statistical significance favouring the HER2+TC arm. This analysis showed that the probability was 95% and the DMC found this to be compelling evidence that the study had reached its primary objective and recommended that accrual be suspended.

Comment: It is considered that the DMC's recommendation to suspend accrual based on the pCR data from the first 34 patients is unusual, given that the study was unblinded and the pCR is only a surrogate endpoint for clinical benefit. There were limited data on the statistical methods used in the study and no adjustments were made for multiple pairwise comparisons for secondary efficacy outcomes.

Results

a. Patients

The pre treatment characteristics of the three treatment groups are summarised below in Table 22.

Table 22: MADCC. Patient characteristics;

Characteristic	Randomised [2005		Assigned
	HER2+C (n=19)	HER2+TC (n=23)	HER2+TC (n=22)
Age (years), median (range)	48 (25-75)	52 (29-71)	51 (21-70)
Tumour: * T1/T2/T3/T4	2/13/4/0	2/15/5/1	3/14/5/0
Nodal status: No/N1/N2	7/12/0	10/12/1	9/13/0
Hormonal status: ER+,PR+/ER+,PR-/ER-,PR+/ER-,PR-	6/4/1/8	6/4/3/10	6/5/1/10
HER2 status: FISH+/IHC3+ only/IHC3+,FISH-/IHC3+,FISH+	17/1/1	19/3/1	4/1/0/17
White/Afro-American/Asian/Hispanic	13/3/2/1	13/1/4/5	14/3/1/4

Source: Buzdar et al., 2005 & Buzdar et al., 2007. * Two patients in the HER2+TC arm had synchronous bilateral disease.

Between June 2001 and October 2003, 42 patients were registered and randomised (19 to the HER2+C arm, and 23 to the HER2+TC arm). The second cohort of 22 patients reported in the updated study report and assigned to chemotherapy plus trastuzumab was treated between February 2004 and May 2005.

b. Pathologic complete response

In the original 42 patients, the pCR rate was 26.3% [95% CI: 9.1, 51.2] in the HER2+C arm (n=19) and 65.2% [95% CI: 43, 84] in the HER2+TC arm (n=23); p=0.016. The outcome achieved the stated goal of increasing the pCR 2 fold in the HER2+TC arm compared with the HER2+C arm. The pCR rate in patients with varying baseline characteristics were summarised in the sponsor's study report.

In the updated study, 22 additional patients were treated with chemotherapy plus trastuzumab. In this group, the pCR rate was 54.5% [95% CI: 32.2, 75.6]. In the 45 patients

who received chemotherapy plus trastuzumab (that is, original plus updated report), there were a total of 27 pCRs and the pCR rate was 60% [95% CI: 44.3-74.3%].

c. Clinical response

Complete clinical response was observed in 47.4% (9/19) of patients in the HER2+C arm and 91.3% (21/23) of patients in the HER2+TC arm; no statistical analysis was provided. Complete or partial clinical response was observed in 94.7% (18/19) in the HER2+C arm and 95.7% (22/23) of patients in the HER2+TC arm.

d. Disease free survival

The updated analysis included an assessment of disease free survival (DFS) measured from the date of study entry to the date of disease recurrence or last follow-up. However, this analysis does not appear to have been pre specified. In the two randomised group, median follow-up was 36.1 months (range 12.3, 54.8). In the HER2+C group (n=19), 3 patients developed recurrent disease and 1 of these patient died of progressive metastatic disease. In this group, DFS at 1 year was 94.7% [95% CI: 85.2, 100] and at 3 years was 85.3%[95% CI: 67.6-100]. In the HER2+TC group (n=23), there had been no recurrent disease and the estimated DFS at both 1 and 3 years was 100% (1-year DFS estimate [95% CI: 85.2, 100]). DFS was statistically significantly better in patients randomised to the HER2+TC arm compared with the HER2+C arm (p=0.041).

e. Breast surgery

Breast conservation therapy (BCT) (that is, segmental mastectomy [lumpectomy]) was performed in 52.6% (n=10) of patients in the HER2+C arm compared with 56.5% (n=13) in the HER2+C arm.

GeparQuattro Study [Untch et al., 2010]

Design

The GeparQuattro study was nominated by the sponsor as a supportive study to extend the indications of trastuzumab to include neoadjuvant treatment in combination with chemotherapy for localised breast cancer. The published study report was written on behalf of the German Breast Group and Arbeitsgemeinschaft Gynä-kologische Onkologie Breast Group Investigators. The study was Phase III, multicentre, non-randomise, and open-label in design. It postulated that the high efficacy of trastuzumab in the neoadjuvant setting could be confirmed if patients with HER2-positive tumours receiving chemotherapy plus trastuzumab achieved a much higher pathologic complete response (pCR) rate than a reference group of patients with HER2-negative tumours receiving the same chemotherapy without trastuzumab. This study design was adopted because a randomised study was not supported by the group members (presumably a study randomising HER2-positive patients to neoadjuvant chemotherapy with or without trastuzumab). The protocol was reviewed by all responsible local ethics committees. The study was supported by Roche, Germany and Sanofi-Aventis, Germany.

> *Comment*: The study was open-label and did not include a randomised comparison between neoadjuvant chemotherapy with and without trastuzumab in women with HER2-positive tumours. Therefore, it is considered to provide limited support for the efficacy of the proposed trastuzumab neoadjuvant treatment regimen in women with localised HER2-positive breast cancer.

Patients

Patients with either locally advanced (cT3 or cT4), hormone receptor–negative or hormone receptor–positive but lymph node–positive tumours were candidates for participation. Tumours were considered HER2-positive if staining intensity was 3+ and all

tumours with 2+ staining intensity were analysed by FISH. Normal cardiac function was confirmed by ECG and cardiac ultrasound (LVEF ≥ 55%) within the 3 months before registration.

Treatments

a. Chemotherapy

All patients were scheduled to receive 4 cycles of epirubicin/cyclophosphamide [EC] (90/600 mg/m^2), and were then randomly assigned to either 4 cycles of docetaxel 100 mg/m^2 [EC-T], 4 cycles of docetaxel 75 mg/m^2 plus capecitabine 1,800 mg/m^2 [EC-TX] or 4 cycles of docetaxel 75 mg/m^2 followed by 4 cycles of capecitabine 1,800 mg/m^2 on Days 1 through 14 (EC-T-X). All cycles lasted 3 weeks.

b. Trastuzumab

Patients with HER2-positive tumours received trastuzumab 6 mg/kg IV every 3 weeks concomitantly with all chemotherapy cycles, starting with a loading dose of 8 mg/kg IV on Day 1 of the first EC cycle. Trastuzumab 8 infusions (in the EC-T and EC-TX arm) or 12 infusions (in the EC-T-X arm) were given pre operatively. If chemotherapy was discontinued early, the skipped trastuzumab cycles were given post operatively. The total duration of trastuzumab treatment was 1 year.

Efficacy endpoints

The *co primary aim* of this study was to assess the pCR rate of neoadjuvant trastuzumab given concomitantly with epirubicin/cyclophosphamide followed by docetaxel with or without capecitabine (EC-T[X]) in patients with HER2-postive breast cancer. Efficacy of the same chemotherapy regimen given without trastuzumab in patients with HER2-negative disease was used as a reference.

Secondary *predefined aims* included assessment of the rate of breast conservation; clinical and pathologic response rate at surgery according to midcourse response after four cycles of EC and trastuzumab and the response rates in patients with cT4 tumours; toxic effects and compliance; and the influence of baseline factors in predicting pathologic response at surgery.

Assessment of endpoints

Pathologic response was assessed locally according to a modified regression grading (RG) system: Grade 5, no microscopic evidence of residual viable tumour cells (invasive or non-invasive) in breast and nodes; Grade 4, no residual tumour in breast tissue, but involved nodes; Grade 3, only residual non-invasive tumour in breast tissue irrespective of lymph node involvement; Grade 2 to 0, for all remaining scenarios. Regression Grades 4 and 5 were considered as pCR. *Clinical response* was assessed preferably by ultrasound, or mammography or physical examination in cases where ultrasound was not possible.

Sample size and statistical methods

All patients receiving at least one course of EC with trastuzumab were included in the efficacy analyses and all patients with HER2-negative tumours receiving at least one course of EC were the reference group. No sample size calculations were undertaken as the study was a descriptive comparison of different neoadjuvant treatments in HER2-positive and HER2-negative patients. Statistical analysis (2-sided, Pearson's Chi-square test) were performed for toxicity only, Patients with missing response data were considered as having no response. A sensitivity analysis of the primary endpoint was performed in patients who received all planned treatment cycles and had an available pCR assessment. Uni variable and multivariable analyses were performed to identify predictive factors for pCR in trastuzumab treated HER2-positive breast cancer.

Patients

a. Patient disposition

The study included 1,509 participants; 451 in the HER2-positive group and 1,058 in the HER2-negative group. There were 1,495 patient who received at least 1 cycle of EC and were analysed for efficacy; 445 in the HER2-positive group and 1,050 in the HER2-negative group. There were 1,158 patients who received all chemotherapy cycles in accordance with the protocol; 347 in the HER2-positive group and 811 in the HER2-negative group. Surgery was performed on a total of 1,460 patients; 436 in the HER2-positive group (98.0% of patients analysed for efficacy) and 1,024 in the HER2-negative group (97.5% of patients analysed for efficacy). There were 1,141 patients who completed treatment and surgery per protocol; 340 in the HER2-positive group (76.4% of patients analysed for efficacy) and 801 in the HER2-negative group (76.3% of patients analysed for efficacy).

b. Baseline characteristics

The patient group was relatively young with a median age of about 50 years and the majority of patients were in the 40 to 60 years age range. The majority of patients in both groups had stage cT2 tumours and cN0/CN1 status.

Efficacy results

a. Primary efficacy endpoint (pCR rate)

The pCR rate was 31.7% (141/445) in the HER2-positive group and 15.7% (165/1050) in the HER2- negative group. In the sensitivity analysis (patients who received all planned treatment cycles and had an available pCR) the pCR rate was 34.7% (118/340) in the HER2-positive group.

b. Other efficacy endpoint

Breast conserving surgery rates were similar in the HER2-positive (63.1%) and the HER2-negative groups (64.7%).

Complete clinical response after 4 cycles of EC was 10.8% (48/445) in the HER2-positive group and 4.8% (50/1050) in the HER2-negative group and the respective results for partial clinical response were 62.0% (276/445) and 61.1% (642/1050).

Complete clinical response at surgery was 34.6% (154/445) in the HER2-positive group and 18.7% (196/1050) in the HER2-negative group and the respective results for partial clinical response were 46.7% (208/115) and 56.9% (597/1050).

Uni variable and multivariable analyses for predetermined factors predicting a pCR were performed in the population with HER2-positive tumours. Negative hormonal status (ER -ve/PgR –ve) was the only factor associated with a pCR, with all other factors being not statistically significant (that is, age < 40 versus age ≥ 40; tumour size < 4 cm versus ≥ 4 cm; Grading 1 or 2 versus 3; and baseline clinical lymph node status negative versus positive. The histological type ductal invasive/other versus lobular invasive could not be tested as none of the 17 patients with lobular invasive tumours achieved a pCR.

Other studies

The submitted data included over 30 studies which the sponsor states provide supportive evidence of the efficacy of neoadjuvant trastuzumab when added to various chemotherapy regimens (single agent or combinations). The majority of the studies were submitted as published papers but a few were submitted in abstract or poster form. The studies were generally small, Phase II trials which differed in design, breast cancer disease characteristic, IHC and/or FISH criteria for establishing HER positivity, adherence to strict

pCR criteria and neoadjuvant treatment regimens. The most common primary efficacy endpoint in the studies was pCR but the criteria for this endpoint was not consistent among the studies and most studies also included the clinical overall response rate generally as a secondary efficacy endpoint. EFS/DFS and OS were generally not assessed in these studies. The most commonly used neoadjuvant trastuzumab regimen was 4 mg/m^2 (loading) followed by 2 mg/m^2 (weekly) and this regimen was combined with a variety of chemotherapy regimens. The studies also employed a variety of adjuvant (post operative) chemotherapy regimens.

The sponsor grouped the additional studies into patients with predominantly early breast cancer (operable disease) [10 studies], patients with local advanced breast cancer (inoperable disease) [13 studies] and patients with local advanced breast cancer and early breast cancer [16 studies]. The sponsor provided the published papers, abstracts or posters for all of listed studies, apart from one study[32] which appears to have been an inadvertent administrative oversight. In contrast to the MDACC and GeparQuattro studies, the sponsor did not expressly nominate any of the additional studies as supportive. It is considered that none of the additional 30 studies are formally evaluable for the purposes of the submission as none included the proposed patient population (women with localised breast cancer) treated with the proposed neoadjuvant trastuzumab in combination with chemotherapy regimen used in the pivotal study (NOAH). Nevertheless, a tabulated summary of 23 studies submitted by the sponsor identified as being peer reviewed (that is, excluding abstracts, poster presentations, letters to the editor) was included to provide an overview of the variety of studies and outcomes (pCR and ORR) that have been undertaken exploring neoadjuvant trastuzumab in combination with chemotherapy. In the studies tabulated, the pCR rate (breast/nodes [b/n]) ranged from 17% to 76% (in those studies in which the results could be identified) with neoadjuvant regimens containing trastuzumab, and the overall clinical response rate (ORR) ranged from 34% to 100%.

In addition to the more than 30 additional studies referred to above, the submitted data also included 4 poster and/or slide presentations from the San Antonio Breast Cancer Symposium 2010. These were:

(1) three year follow up data from the Taxol Epirubicin Cyclophosphamide Herceptin NeOadjuvant (TECHNO) study investigating the efficacy and safety of neoadjuvant therapy with epirubicin/cyclophosphamide followed by paclitaxel/trastuzumab in patients with HER2 overexpressing primary breast cancer (BC);

(2) the primary efficacy endpoint analysis from the GeparQuinto study comparing lapatinib with trastuzumab in combination with neoadjuvant anthracycline-taxane based chemotherapy;

(3) the antitumour and safety analysis from the randomised Phase II study (NeoSphere) comparing neoadjuvant pertuzumab and trastuzumab; and

(4) first results of the Phase III, randomised, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer (Neo-ALTTO trial).

[32]Gluck et al 2008: XeNA: Capecitabine plus docetaxel, with or without trastuzumab, as preoperative therapy for early breast cancer. International Journal of Medical Sciences (2008) 5:6 (341-346). 4 Nov 2008.

Sponsor comment: "Gluck et al 2008 was excluded since the same study (XeNa) as Gluck et al 2011. The most current reference was included in submission.".

None of these presentations are considered to be evaluable for the purposes of the submission as none of the complete study reports has been published in peer reviewed journals.

Analyses performed across trials (pooled analyses and meta-analyses)

There were no analyses performed across trials.

Evaluator's conclusions on clinical efficacy for neoadjuvant treatment.

The submission is supported by 1 pivotal study [NOAH] and 2 studies specifically nominated by the sponsor as being supportive [MDACC and GeparQuattro]. It is considered that the pivotal study [NOAH] does not provide adequate evidence to support a clinically meaningful treatment benefit for neoadjuvant trastuzumab plus chemotherapy beyond that observed with chemotherapy alone. While the supportive study MDACC is considered to show a clinically meaningful benefit for neoadjuvant trastuzumab plus chemotherapy compared with chemotherapy alone, patient numbers in the study were small and both the trastuzumab and chemotherapy regimens differed from those in the pivotal study. The supportive study GeparQuattro did not provide a comparison between patients with HER-positive disease randomised to neoadjuvant trastuzumab plus chemotherapy versus chemotherapy alone. Consequently, the descriptive results showing an efficacy benefit in favour of neoadjuvant trastuzumab plus chemotherapy in HER-positive disease compared with neoadjuvant chemotherapy alone in HER-negative disease are considered to be of limited support to the submission. In addition to the pivotal and specifically nominated supportive studies, the sponsor submitted more than 30 small, open-label and mostly single-arm published studies that are considered not to provide definitive efficacy data for the purposes of the submission. In these studies, the results for the efficacy outcomes (primarily pCR and ORR) were highly variable among the studies, as were the neoadjuvant chemotherapy regimens used in combination with trastuzumab.

In NOAH, the risk of experiencing an EFS event (disease progression, recurrence or death) was 35% lower in the HER2+TC arm relative to the HER2+C arm; unadjusted HR = 0.65 [95% CI: 0.44, 0.96]; p=0.0275 log-rank. The median time to an EFS event was 43.6 months in the HER2+C arm but was not evaluable in the HER2+TC arm due to too few events being reported in patients in this arm at the time of the analysis. In this study, EFS in the FAS population was the primary efficacy endpoint and the study was powered on a difference of 18.5% in the 36 month EFS rates between the two HER2-positive treatment arms (50% in the HER2+C arm and 68.5% in the HER2+TC arm). Furthermore, it is stated in the CSR that "a clinically meaningful improvement with the addition of trastuzumab would be to increase the median EFS time to 5.5 years, corresponding to 68.5% EFS rate at 3 years. This corresponds to a hazard ratio of 0.545". However, the observed difference in the 36 month EFS rates between the two HER2-positive treatment arms was 13% (52% in the HER2+C arm and 65% in the HER2+TC arm) and the HR was 0.65. Consequently, based on the assumptions used to power the study, it is considered that the observed difference between the two HER-positive treatment arms in EFS is not clinically significant despite being statistically significant.

In NOAH, the difference between the two treatment arms in the pCR (secondary efficacy endpoint) was statistically significant for both the bpCR (44.3% HER2+TC versus 25.7% HER2+C) and the tpCR (40.0% versus 20.7%). The absolute difference in bpCR between the two treatments was 17.6% ([95% CI: 5.0, 30.2]; p = 0.0051, Chi-square test) and the corresponding difference for tpCR was 19.3% ([95% CI: 7.2, 31.4]; p=0.0014, Chi-square test). The study did not specify a clinically meaningful absolute difference between the two treatment arms but data from the MDACC study suggests that a 2 fold increase in tpCR in the HER2+TC arm compared with the HER2+C arm (based on respective tpCR rates of

41% and 21%) is likely to be clinically significant. Consequently, based on the MDACC assumptions it can be reasonably inferred that the observed differences between the two HER2-positive treatment arms observed in NOAH for bpCR and tpCR are of borderline clinical significance.

In NOAH, neither the overall clinical response rate (secondary efficacy endpoint) nor the overall survival rate (secondary efficacy endpoint) were statistically significant for the comparison between the HER2+TC and HER2+C arms, although both favoured the HER2+TC arm. The exploratory subgroup analyses of EFS consistently favoured the HER2+ arm compared with the HER2+C arm but only the comparisons in the cN ≥ 1, ER and PgR both negative and age > 49 years subgroups were statistically significant. However, the subgroup analyses should be interpreted with caution as the analyses were not powered to detect statistically significant differences and no statistical adjustments were made to account for the multiplicity of pair-wise comparisons.

In addition to the problems relating to the clinical significance of the observed results, another significant problem relates to the inability of the pivotal study [NOAH] design to separate the effects of neoadjuvant trastuzumab plus chemotherapy from the effects of adjuvant trastuzumab. In the HER2+TC arm, all patients were treated with neoadjuvant trastuzumab plus chemotherapy followed after surgery by adjuvant trastuzumab for up to 1 year. Therefore, the effect of trastuzumab on EFS might be due to neoadjuvant trastuzumab plus chemotherapy, adjuvant trastuzumab or the combination of neoadjuvant trastuzumab plus chemotherapy and adjuvant trastuzumab.

In order to separate the effects, the sponsor analysed EFS in the 20 patients who were originally randomised to the HER2+C arm and subsequently crossed over to adjuvant trastuzumab. In this group, 5 patients experienced an EFS event after crossing over and 1 patient had an EFS event prior to crossing over. In an exploratory analysis, the risk of experiencing an EFS event was 41% lower in patients randomised to the HER2+TC arm compared with patients randomised to the HER2+C arm who subsequently crossed over to adjuvant trastuzumab (HR = 0.59 [95%CI: 0.40, 0.88]; p=0.0084, log-rank test). This result suggests that neoadjuvant trastuzumab plus chemotherapy is superior to adjuvant trastuzumab as regards EFS. However, there were only 19 patients in the group randomised to the HER2+C arm that crossed over to adjuvant trastuzumab and this number is considered too small for the results of the exploratory EFS to be meaningfully interpreted.

The pivotal study [NOAH] included a large proportion of patients from one Russian site that contributed 26% (26/115) of patients to the HER2+TC arm and 22.4% (26/116) of patients to the HER2+C arm. This site was unusual as it included a high number of patients who had not undergone surgery (due to the decision of the local surgeon not to operate on patients with persisting oedema) and a high number of patients in whom a complete clinical response had been reported. In view of the unusual features of the site the sponsor undertook an exploratory analysis of EFS and OS excluding patients from this site from the analyses. In the EFS analysis, the hazard ratio still favoured the HER2+TC arm compared with the HER2+C arm but was no longer statistically significant as the 95% CI included 1 (HR 0.65 = 95% CI [0.42, 1.00]; c.f., HR = 0.65 [95% CI: 0.44, 0.96] in the primary analysis). However, it is likely that the exploratory analysis was underpowered due to the smaller number of EFS events compared with the primary analysis. In the exploratory EFS analysis, the 36 month EFS rate was 64% in the HER2+TC arm and 49% in the HER2+C (compared to 65% and 52% respectively in the primary analysis). The results of the exploratory EFS analysis suggest that the inclusion of the relatively large number of patients from the unusual Russian site has not significantly biased the results of the primary EFS analysis. In the OS analysis, the hazard ratio still favoured the HER2+TC arm

compared with the HER2+C arm but was now statistically significant as the 95% CI excluded 1 (that is, HR = 0.52 [95% CI: 0.28, 0.96]; c.f., HR = 0.59 [95% CI: 0.35, 1.02] in the primary analysis).

The MDACC study in women with Stage II to IIa invasive (excluding inflammatory disease) HER2+ breast cancer was specifically nominated by the sponsor as a supportive study. The neoadjuvant chemotherapy regimen differed from that in NOAH as did the trastuzumab dosage regimen. In this study, the pCR rate (primary efficacy endpoint) was statistically significantly higher in the HER2+TC arm (65.2% [n=23]) compared with the HER2+C arm (26.3% [n=19]); p=0.016. The absolute difference between the two arms was 38.9%, which was higher than the approximately 2 fold increase (21% HER2+C and 41% HER2+TC) on which the study was powered. The results for complete clinical response rate, DFS and breast conservative therapy (lumpectomy rates), were numerically superior for the HER2+TC arm than for the HER2+2C arm but no statistical analyses were undertaken and the results for DFS and lumpectomy are of doubtful clinical significance. Overall, the results from this small study support a clinically meaningful benefit for neoadjuvant trastuzumab plus chemotherapy compared with neoadjuvant chemotherapy alone. The MDACC study[33] is specifically listed in the National Comprehensice Cancer Network (NCCN) Guidelines (v2.2011)[34] for Invasive Breast Cancer supporting the recommendation for neoadjuvant trastuzumab treatment but no other studies are listed supporting the recommendation. Furthermore, the guidelines specifically recommend the treatment regimen used in the MADCC study (with an additional alternative paclitaxel schedule) but refer to no other regimens.

The GeparQuattro study in women with locally advanced (cT3 or cT4) lymph node-positive, HER2-positive or HER2-negative breast cancer was specifically nominated by the sponsor as a supportive study. The neoadjuvant chemotherapy regimen differed from that in NOAH but the neoadjuvant trastuzumab dosage regimen was the same as that used in the pivotal study. However, the study was not designed to compare neoadjuvant trastuzumab plus chemotherapy with neoadjuvant chemotherapy alone in patients with HER2-positive tumours. Consequently, the study is considered to be of limited relevance to the submission. The study provided descriptive data supporting the efficacy of neoadjuvant trastuzumab plus chemotherapy in HER2-positive patients compared with neoadjuvant chemotherapy in HER2-negative patients as assessed by pCR and complete clinical response (after 4 cycles of EC and at surgery). However, the descriptive data suggested that there was no significant difference in efficacy between the two treatment groups based on breast conserving surgery or partial clinical response rates (after 4 cycles of EC and at surgery).

Addition of efficacy information to the *Clinical trial* section – Dossier 2

BCIRG 006 Study

Study design, objectives, locations and dates

The Breast Cancer International Research Group (BCIRG) Study (BCIRG 006) was a Phase III, multinational [43 countries], multicentre [433 sites], randomised, active-controlled, 3 parallel groups, open label clinical trial comparing adjuvant trastuzumab plus

[33]Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomised trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005;23:3676-3685

[34] http://www.jnccn.org/content/9/2/136.full.pdf and http://www.jnccn.org/content/9/2/136.figures-only

chemotherapy with chemotherapy alone in women with HER2-positive breast cancer following definitive surgery.

The *primary objective* was to compare disease free survival (DFS) after three different adjuvant treatments in node-positive and high-risk node-negative patients with operable HER2-positive breast cancer. The three adjuvant treatments were:

1. doxorubicin (Adriamycin®) and cyclophosphamide, followed by docetaxel (Taxotere®) [AC→T];
2. doxorubicin and cyclophosphamide, followed by docetaxel and trastuzumab (Herceptin®) [AC→TH]; and
3. docetaxel, carboplatin, and trastuzumab (TCH).

The *secondary objectives* were to compare overall survival and cardiac and non cardiac toxicity among the three treatment arms.

The study was submitted to support the addition of data from the study to the *Clinical Trials* section of the PI. The relevant approved indication allows for concurrent or sequential adjuvant trastuzumab therapy and no amendments to this indication were proposed by the sponsor based on the results of BCIRG 006. The relevant currently approved indication for trastuzumab is "for the treatment of patients with HER2 positive localised breast cancer following surgery and in association with adjuvant therapy chemotherapy and if, applicable, radiotherapy".

The study was initiated on 19 March 2001 and at the date of the CSR (14 June 2007) the study was still ongoing (data cut off was planned for 1 November 2006). The study complied with all TGA ethical requirements relating to approval and conduct.

Inclusion and exclusion criteria

The study included patients aged 18-70 with histologically proven breast cancer (HER2-positive confirmed with FISH) with definitive surgery consisting of either mastectomy with axillary lymph node involvement assessment or breast-conserving surgery with axillary lymph node involvement assessment. Patients were required to have lymph node-positive or high-risk lymph-node negative disease. Lymph node–positive patients were required to have invasive adenocarcinoma with at least one axillary lymph node showing evidence of tumor (pN1) of a minimum of six resected lymph nodes. High-risk lymph node–negative patients were required to have invasive adenocarcinoma with either

(1) no axillary lymph nodes showing evidence of tumour (pN0) of a minimum of six resected lymph nodes, or

(2) a negative sentinel node biopsy (pN0) and at least one of the following factors: tumour size > 2 cm, negative ER and PgR status, histological and/or nuclear Grade of 2 or 3 or age < 35 years.

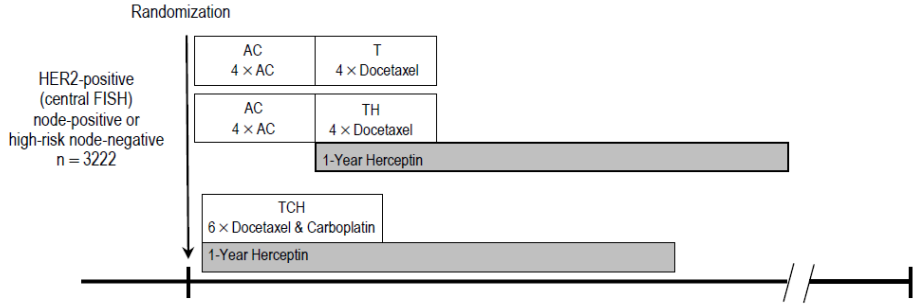
The interval between definitive surgery and registration in the study was required to be ≤60 days. The inclusion criteria required normal cardiac function confirmed by left ventricular ejection fraction (LVEF) 3 months prior to registration and adequate (criteria specified) haematologic, hepatic and renal function. The exclusion criteria included prior systemic anti-cancer therapy for breast cancer, prior radiation therapy for breast cancer, bilateral invasive breast cancer and cardiac disease (criteria specified). The inclusion and exclusion were comprehensive and were considered satisfactory. The study also included standard criteria allowing patients to be withdrawn from treatment.

Study treatments

Treatment plan

In the original protocol patients in both the AC→TH and TCH arms were to receive 2 mg/kg doses of Herceptin IV on a weekly basis following chemotherapy for a year from the date of first Herceptin administration. However, in Protocol Amendment 2 (30 July 2001), the frequency of Herceptin administration during monotherapy was changed from 2 mg/kg once every week to 6 mg/kg once every 3 weeks. There had been 43 patients who had started Herceptin monotherapy prior to the amendment and 32 of these patients continued to receive Herceptin monotherapy on a weekly basis while the remaining 11 switched to the once every 3 week schedule. The treatment plan is summarised below in Figure 3.

Figure 3: BCIRG 006. Treatment plan.



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

AC→T arm

Every 3 weeks for 4 cycles, patients in the AC→T arm received 60 mg/m^2 doxorubicin as a 5-15 minute IV bolus injection followed by 600 mg/m^2 IV cyclophosphamide as a 5-60 minute IV bolus injection. Beginning 3 weeks after the last cycle of AC, patients received 100 mg/m^2 docetaxel as a 1 h IV infusion every 3 weeks for 4 cycles.

AC→TH arm

Every 3 weeks for 4 cycles, patients in the AC→TH arm received 60 mg/m^2 doxorubicin as a 5-15 minute IV bolus injection followed by 600 mg/m^2 cyclophosphamide as a 5-60 minute IV bolus injection. Three weeks after the last treatment with AC (on Day 1 of Cycle 5), a 4 mg/kg trastuzumab loading dose was administered as a 90 minute IV infusion, followed by 2 mg/kg administered as a 30 minute infusion beginning on Day 8 of Cycle 5 and continuing every week. Docetaxel 100 mg/m^2 was administered as a 1 h IV infusion every 3 weeks for 4 cycles, beginning on Day 2 of Cycle 5 and then on Day 1 of all subsequent cycles. Beginning 3 weeks after the last treatment with docetaxel, 6 mg/kg trastuzumab was administered as a 30-minute IV infusion every 3 weeks. Trastuzumab was to continue for 1 year from the date of first administration, regardless of the number of doses received or missed.

TCH arm

Patients in the TCH arm received a 4 mg/kg trastuzumab loading dose as a 90 minute IV infusion on Day 1 of Cycle 1. Beginning on Day 8 of Cycle 1, 2 mg/kg trastuzumab was administered as a 30 minute IV infusion every week. Every 3 weeks for six cycles, beginning on Day 2 of Cycle 1 and then on Day 1 of all subsequent cycles, 75 mg/m^2

docetaxel was administered as a 1 h IV infusion followed by carboplatin at a target AUC of 6 mg/mL/min as a 30-60 minute IV infusion. Beginning 3 weeks after the last treatment with chemotherapy, 6 mg/kg trastuzumab was administered as a 30 minute IV infusion every 3 weeks. Trastuzumab treatment was to continue for 1 year from the date of first administration, regardless of the number of doses received or missed. For days on which docetaxel, carboplatin and trastuzumab were all scheduled to be administered, docetaxel was administered first followed by carboplatin and then trastuzumab.

Dosing modification for chemotherapy and trastuzumab

In cases of severe haematological and/or non-haematological toxicity occurring with chemotherapy, discontinuations, dose reductions or dosing delays were planned and specified in the protocol for each of the treatment arms. Toxicities were graded according to the NCI-CTC (v2) and dose adjustments were defined according to the body system showing the most severe toxicity. For patients with several toxicities that required conflicting dosing recommendations, the most conservative dose adjustment was to be made. Once a dose had been reduced for toxicity, it was not to be re-escalated except in the case of resolution of liver enzyme abnormalities.

No dose reductions were planned for trastuzumab. For patients who experienced trastuzumab related Grade 3 or 4 non-haematologic toxicities other than those related to cardiac dysfunction, trastuzumab was to be withheld until recovery to Grade 1 or 2. If recovery to Grade 1 or 2 did not occur, continuation of trastuzumab was left to the discretion of the investigator. If the same Grade 3 or 4 non-haematologic toxicity recurred, trastuzumab was permanently discontinued. Trastuzumab was not to be withheld for haematologic toxicity. The study included specific guidelines relating to the LVEF for initiating, continuing, withholding and discontinuing Herceptin treatment in the AC→TH and TCH arms.

Other protocol specified anti-tumour therapy

Hormonal therapy

Tamoxifen (20 mg PO daily) for 5 years was administered starting 3 to 4 weeks after the last course of chemotherapy for patients with positive ER and/or PgR status. After Protocol Amendment 4, post-menopausal patients were allowed to switch to anastrozole (1 mg PO daily) in case of tamoxifen related severe toxicities and the total treatment period of tamoxifen followed by anastrazole was not to exceed 5 years. Postmenopausal patients without contraindications to the use of tamoxifen and who had already started tamoxifen could receive a sequential therapy consisting of tamoxifen for 2–3 years followed by anastrozole or exemestane for a maximum of 5 years of hormonal therapy. Postmenopausal patients who had not yet started hormonal therapy could receive 5 years of anastrozole or sequential therapy, consisting of tamoxifen for 2 to 3 years followed by anastrozole or exemestane for a maximum of 5 years of hormonal therapy. Postmenopausal patients who had completed 5 years of tamoxifen were allowed to continue hormonal treatment with letrozole for a maximum of 3 years.

Radiation therapy

Radiation therapy was to begin 3 to 8 weeks after completion of chemotherapy. For patients receiving trastuzumab and/or tamoxifen, radiation was given while the patient was receiving the medicine. Radiotherapy was mandatory in case of breast-conserving surgery. It was allowed but not mandatory in case of mastectomy according to the policy in use at each participating centre.

Other

Except for protocol specified chemotherapy, hormonal therapy, radiotherapy and trastuzumab, no additional anti-tumour therapy was allowed (such as surgery, chemotherapy, immunotherapy) prior to documentation of tumour relapse. If patients were removed from the study because of disease relapse, further treatment was given at the discretion of the investigator.

Prior and concomitant therapies

The list of prior and concomitant therapies has been examined and is considered to be standard for oncology trials. Patients could be treated with granulocyte stimulating factor if required or at the study investigator's discretion (such as febrile neutropenia, infections, primary prophylaxis); anti-emetics; anti-allergy; antibiotics; and medically indicated ancillary treatments. Patients were not allowed to receive other investigational drugs or anti-cancer therapies during the study (that is, until relapse or for up to 10 years). In addition, the following therapies were not permitted during active treatment with chemotherapy and trastuzumab: corticosteroid (except as pre medication, anti-emetics, and treatment for acute hypersensitivity reactions and in cases of chronic treatments initiated as a low dose more than 6 months prior to surgery); bisphosphonates; amifostine; and "cardioprotectors".

Assessments and assessment schedules

The following assessments were performed 3 weeks after the last chemotherapy treatment (end of chemotherapy visit): physical examination, haematology, blood chemistry (liver function tests only), LVEF, quality-of-life questionnaires, socioeconomic evaluation (only in the United States, Canada, and Germany) and adverse events. Follow-up assessments after the end of chemotherapy were detailed.

The following adverse events (AEs) were also to be followed until resolution or until initiation of further anti-cancer therapy: ongoing AEs (not of a cardiac origin) possibly or probably related to study treatment at the time of the end of chemotherapy visit; ongoing AEs of a cardiac origin, regardless of their relationship to study treatment at the time of the end of chemotherapy visit; any delayed AE event starting during follow-up and considered to be possibly or probably related to study treatment; relevant non–cancer related signs and symptoms occurring after completion of chemotherapy (such as congestive heart failure (CHF) or toxicities related to hormonal therapy or radiation therapy).

Efficacy variables and outcomes

Primary efficacy outcome measure (DFS)

The *primary efficacy outcome measure* was disease free survival (DFS), defined as the time from the date of randomisation to the date of local, regional or distant relapse, or the date of second primary cancer, or death from any cause, whichever occurred first. Relapse was defined as any clinical or radiologic evidence of tumour recurrence. Histological or cytological proof of failure, if feasible, was to be obtained. Specific types of relapse are defined as follows:

- Local relapse: evidence of tumour in the breast surgical scar, ipsilateral breast (conservative surgery), ipsilateral anterior chest wall (mastectomy) or skin or soft tissue within the local area.
- Regional relapse: evidence of tumour in the ipsilateral nodal areas (axillary, internal mammary, or infraclavicular) as well as skin or soft tissue within the regional area

- Distant relapse: evidence of tumour beyond the local or regional level as previously defined; this includes the ipsilateral supraclavicular lymph nodes, contralateral breast, bone, liver, lung, central nervous system (CNS), skin or other sites.

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

Secondary efficacy outcome measures (OS)

The *secondary efficacy outcome measure* was overall survival (OS). Other secondary outcome measures (those related to quality of life and evaluation of pathologic and molecular markers for predicting efficacy) were not analysed in the submitted CSR.

Randomisation and blinding methods

Randomisation was via a centralised database system and was allowed as soon as all eligibility criteria (including positive HER2 result) were met. Treatment allocation was based on a dynamic minimisation procedure, taking into account the following stratification factors to achieve balance between the treatment arms: centre; number of axillary lymph nodes involved (0, 1–3, or ≥ 4); and hormonal receptor status (ER and/or PR positive versus negative).

The study was open-label and neither investigators nor patients were blinded to treatment allocation. However, there was a "blinded" independent cardiac review panel (ICRP) for adjudicating individual patient protocol defined symptomatic cardiac events.

Sample size

Updated data from BCIRG 001 (March 2005) were used to re-estimate the number of DFS events required for the interim and final analyses specified in the original protocol by assuming a 7% absolute advantage in 5 year DFS in favour of one of the Herceptin containing arms, with a power of 80% and a significance level of 0.05 as originally planned. The revised calculations were based on a presumed 5 year DFS of 70% in the AC→T arm of BCIRG 006 (Protocol amendment 4, March 2005). No unblinded analyses of efficacy data had been performed at the time the statistical considerations were revised. The revised analysis schedule called for three interim efficacy analyses to be conducted when 300, 450 and 650 DFS events, respectively, had been observed and a main analysis to be conducted when 900 DFS events had been observed. With the revised assumptions as well as the final number of 3222 randomised patients, the trial was powered to detect a 7% difference between the control arm (AC→T) and each Herceptin containing arm (that is, a 23.7% reduction in risk), assuming a 5 year DFS of 70% in the control arm. The statistical considerations relating to the revised analysis and the originally proposed analysis are summarised below in Table 23.

Table 23: BCIRG 006. Summarised original and final statistical considerations.

	Revised (March 2005)	Original (December 2000)
5 year DFS in AC→T or AC→TH or TCH	70% versus 77%	55% versus 62%
Absolute DFS benefit	7%	7%
Hazard ratio (relative to DFS benefit)	0.763	0.807
Interim analyses (number of DFS events)/significance level	300/0.0002 [a]	654/0.001 [b]
O'Brien-Fleming spending function [a]	450/0.0030 [a]	
Haybittle-Peto [b]	650/0.0111 [a]	
Number of events for main analysis among all patients	900/0.0461 [a]	1308/0.05 [b]

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; DFS = disease-free survival; TCH = docetaxel plus carboplatin plus Herceptin.

[a] O'Brien spending function with three interim analyses to occur when 300, 450, and 650 of a total 900 DFS events were observed.

[b] Haybittle-Peto boundary with a single interim analysis when 654 of the 1308 required events were observed.

In the submitted CSR, all analyses were based on data from the second planned interim analysis undertaken when 474 DFS events had occurred, representing 52.7% of the 900 planned events. The results at the time of the second interim analysis include a median follow-up of 36 months. The "main analysis" is planned when a total of 900 DFS events have occurred.

Statistical methods

The primary efficacy endpoint was DFS and the secondary efficacy endpoint was OS. In the calculation of DFS and OS (and all exploratory efficacy endpoints) data from patients not experiencing a particular endpoint were censored at the earliest of data cut-off date (1 November 2006), date of last follow-up assessment or date of last contact if lost to follow-up. Data from patients with no post randomisation follow-up were censored at Day 1.

The primary efficacy analysis was based on the ITT principle (that is, inclusion of all randomised patients, analysed according to randomised treatment assignment). The primary analysis of DFS was based on derivations from relevant components of the clinical database as opposed to the final evaluation of patients (FEVAL) dataset. The FEVAL dataset excluded DFS events from patients who upon further clinical review did not in fact have a per protocol DFS event. The majority of patients excluded in this dataset were found to have ductal carcinoma-in-situ (DCIS), which did not meet the protocol specified definition of a DFS event.

The Kaplan-Meier product limit method was used to estimate DFS and OS. The log rank test (2-sided), stratified for nodal status (N0 versus N1-3 versus N4+) and for hormonal receptor status (ER and/or PR positive versus negative) was used to perform all pair-wise comparisons between the three treatment arms with respect to DFS and OS. The hazard ratios (and 95% CI) for comparisons between the three treatment arms with respect to DFS and OS were estimated using Cox regression stratified by nodal status and hormonal receptor status (as for the log-rank test).

A "step-down" testing procedure was used to compare the control arm AC→T with each Herceptin arm (AC→TH and TCH), using the log-rank test stratified for nodal status (0 versus 1–3 versus ≥4) and hormone receptor status (ER and/or PR positive versus negative) at an $\alpha/2$ level to account for multiple testing. If both of the pair-wise comparisons were statistically significant, then comparison of the two trastuzumab

containing regimens could be conducted at the α level of significance. All tests of hypotheses were 2-sided. Landmark estimates (including 95% CIs) of 1 to 5 year DFS and OS were obtained using Kaplan-Meier product limit methodology.

Subgroup analyses based on baseline patient characteristics were performed to assess the consistency (and generalisability) of the treatment effect on DFS and OS. *Additional and sensitivity analyses* included: DFS using the FEVAL dataset; alternative definitions of DFS; time to first distant recurrence; exclusion of patients with baseline MBC and/or HER-negative disease; and time to first CNS metastasis.

Participant flow

Between 5 April 2001 and 31 March 2004, 3222 patients were randomised into the study: 1073 to the AC→T arm, 1074 to the AC→TH arm, and 1075 to the TCH arm. Of the 3222 randomised patients, 48 did not receive any study treatment: 28 in the AC→T arm, 2 in the AC→TH arm, and 18 in the TCH arm (see Table 24, below).

Table 24: BCIRG 006. Patient populations.

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

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

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

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

c Six patients were randomised to receive AC→TH but did not receive Herceptin.

d One patient was randomised to AC→T but received her first dose of Herceptin during the monotherapy phase of the study; 1 patient was randomised to receive TCH but received AC→TH.

e Two patients received Herceptin but no chemotherapy.

Of the patients randomised to receive AC→T and AC→TH, 97.4% and 99.8% respectively started AC and of the patients randomised to receive TCH, 98.1% began chemotherapy. The percentage of patients completing treatment in the AC→T, AC→TH and TCH arms was 88.8%, 92.3%, and 94.0%, respectively. The most frequent reasons for premature discontinuation of chemotherapy in all three arms were AEs (AC→T 4.3%; AC→TH 4.0%; and TCH 2.8%) and withdrawal of consent or patient refusal (AC→T 3.7%; AC→TH 2.8%; and TCH 0.9%).

Of the patients randomised to the AC→TH and TCH arms, 96.9% and 98.3% respectively received trastuzumab concurrent with chemotherapy and 90.2% and 93.8% respectively completed treatment. The most frequent reasons for discontinuation of Herceptin prior to completion of chemotherapy in the AC→TH arm were Herceptin toxicity (3.3%), and patient refusal and withdrawal of consent (2.1%). The most cited reasons for

discontinuation of Herceptin prior to completion of chemotherapy in the TCH arm were patient refusal and withdrawal of consent (1.6%), Herceptin toxicity (1.2%), and AEs (1.2%).

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

Patients were considered to have "completed" Herceptin therapy if the total duration from first to last Herceptin infusion exceeded 11 months and there was no report of early discontinuation of Herceptin. Of the patients randomised to receive AC→TH and TCH, 74.9% and 84.9% respectively completed the protocol specified year of Herceptin therapy. Of those randomised to receive AC→TH, 5.9% did not complete the protocol specified year of Herceptin therapy and no reason for discontinuation was available. Of those randomised to receive TCH, 3.5% did not complete the protocol specified year of Herceptin therapy and no reason for discontinuation was available. Of the 102 patients with incomplete Herceptin treatment, the time between the date of last Herceptin administration and the date of the last contact exceeded 180 days in 81 (79.4%).

Major protocol violations/deviations

In "all patients randomised", 77 (2.4%) had at least one major protocol eligibility violation and there was no notable difference in frequency among the three treatment arms. In "all patients randomised" (n=3222), the most common reasons for major protocol eligibility violation were "definitive surgery not performed or incorrect TNM stage, or margin involvement" (n = 25; 0.8%) and primary tumour classified as "T4, N2-N3, or M1" (n = 18; 0.6%). There were 12 patients (0.4%) who were HER2-negative by FISH.

Baseline data

A total of 433 centres in 43 countries enrolled patients in this study. The number of centres by country ranged from 1 centre (Bosnia, Cyprus, Greece, Sweden and Switzerland) to 177 centres (USA). The number of patients by country ranged from 2 to 990; the largest enrolling countries were the USA (n = 990; 30.7%), Germany (n = 313; 9.7%), Australia (n = 293; 9.1%) and Poland (n = 260; 8.1%).

There were no notable imbalances across treatment arms for any of the demographic characteristics. The mean age of patients was 48.8 years for the AC→T arm (range, 23–74 years), 48.7 years for the AC→TH arm (range, 22–74 years) and 48.6 years for the TCH arm (range, 23–73 years). The treatment arms were well balanced with respect to the type of primary breast cancer surgery and other tumour characteristics. All patients underwent primary surgery for breast cancer prior to study enrolment and randomisation and a total of 59.5% of patients in the AC→T arm, 62.8% in the AC→TH arm and 59.7% in the TCH arm had a mastectomy. A total of 99.6% of patients (3209 of 3222) were HER2+ (as assessed by the central laboratory). Nodal involvement was similar across the three treatment arms, with 28.8%, 28.5% and 28.6% of patients having node-negative disease and 13.4%, 11.4% and 11.3% of patients having 10 or more nodes involved in the AC→T, AC→TH, and TCH arms, respectively. Approximately half of the patients were ER-positive and/or PR-positive: 53.8% for the AC→T and AC→TH arms and 53.9% in the TCH arm. Infiltrating ductal carcinoma was the most common histopathological type in all treatment arms (~ 90%). Most tumours were poorly differentiated (~65%) and were excised with clear margins (~ 99.7%).

High-risk node-negative patients were defined as having invasive adenocarcinoma with either no axillary lymph nodes showing evidence of tumour of a minimum of six resected lymph nodes or a negative sentinel node biopsy and at least one of the following factors: tumour size > 2 cm, ER- and PR-negative, histologic and/or nuclear Grade of 2 or 3, or age < 35 years. In the AC→T, AC→TH, and TCH arms there were 309 (28.8%), 306 (28.5%) and 307 (28.6%) high-risk node negative respectively. The high-risk criteria for node-negative patients were well balanced among the three treatment arms.

Approximately 55% of patients in the three treatment arms had a medical history which included disease other than breast cancer. No notable differences in non-cardiac medical history were observed across the three treatment arms. Ongoing hypertension at baseline was observed for 16.2% of patients in the AC→T arm, 16.7% of patients in the AC→TH arm and 17.7% of patients in the TCH arm. Similarly, 12.9% of patients in the AC→T arm, 14.1% of patients in the AC→TH arm, and 14.8% of patients in the TCH arm reported prior use of a cardiovascular medication. Agents acting on the renin–angiotensin system (AC→T: 5.5%; AC→TH: 6.1%; and TCH: 6.5%) and β-blocking agents (AC→T: 3.6%; AC→TH: 4.2%; and TCH: 4.7%) were the agents used with the greatest frequency prior to and at study entry.

Results for the primary efficacy outcome

The primary efficacy analysis was based on data from the second interim analysis which included 474 DFS events (195 in AC→T, 134 in AC→TH and 145 in TCH) and corresponded to a median duration of follow-up of 36 months using the Kaplan-Meier method (see Table 25, below). The HR for a first event in the AC→TH arm relative to the AC→T arm was 0.61 ([95% CI: 0.49, 0.77]; p < 0.0001, stratified log-rank test). The HR for a first event in the TCH arm relative to the AC→T arm was 0.67 ([95% CI: 0.54, 0.83]; p = 0.0003, stratified log-rank test).

In the all randomised patient population, median duration of follow-up was 2.9 years in the AC→T (range: 0.0–5.2 years) arm and 3.0 years in both the AC→TH (range: 0.1–5.3 years) and TCH (range: 0.0–5.1 years) arms. The Kaplan-Meier analysis for DFS in all randomised patients show that the curves for the AC→TH and TCH arms are superimposable, while the curve for the AC→T begins to diverge from the other two curves at about 9 months and continues to diverge up to about 1.5 years after which time it remains parallel to the other two curves through to 4 years (see Figure 4).

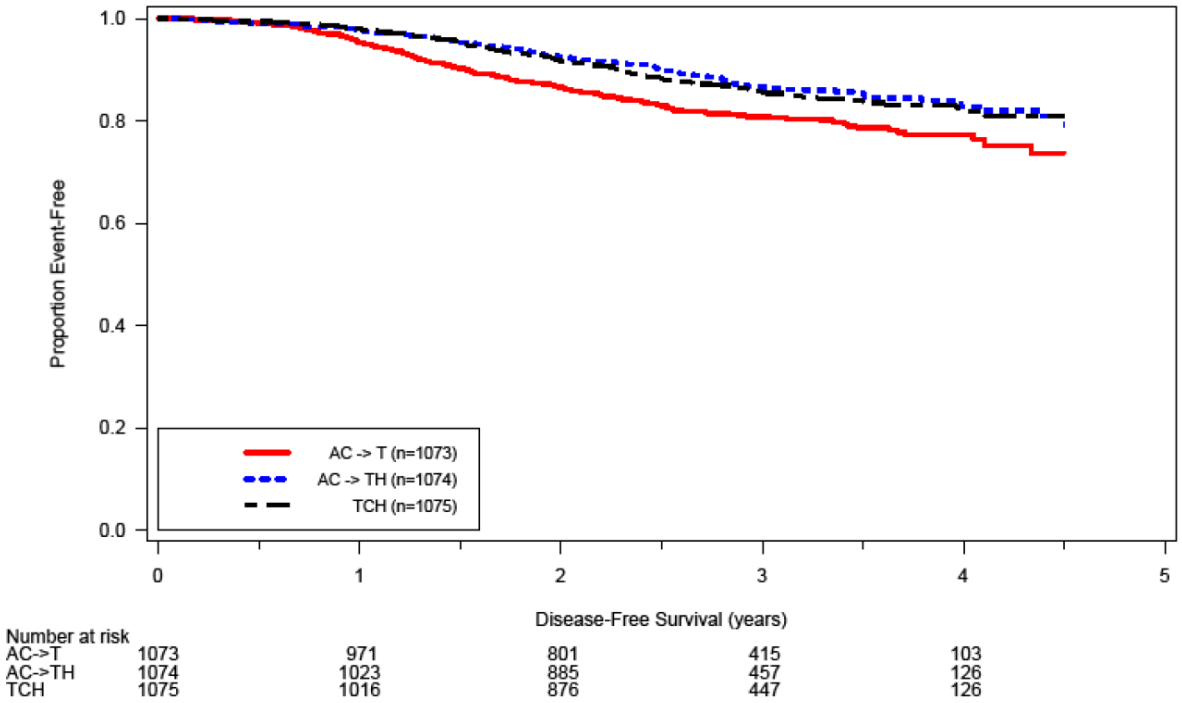
Table 25: BCIRG. Disease free survival (primary efficacy endpoint); all randomised patients.

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

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

a Earliest contributing event. A patient could be included in more than one event category; thus, the sum across rows may not equal the value in the "Major" row. b. Relative to AC→T. Estimated using Cox regression stratified by number of positive nodes and hormonal receptor status. c. Stratified log-rank p-value. d. Absolute benefit in percent event free compared with AC→T.

Figure 4: BCIRG. Kaplan-Meier curves for DFS; all randomised patients.



Results of other efficacy outcomes

Overall survival (secondary efficacy endpoint): At the time of the second interim analysis, deaths had been reported for 185 patients. There were 80 (7.5%) deaths in the AC→T arm, 49 (4.6%) in the AC→TH arm and 56 (5.2%) in the TCH arm. The HR for OS in the AC→TH arm relative to the AC→T arm was 0.58 ([95% CI: 0.40, 0.83]; p < 0.0024, stratified log-rank test). The HR for OS in TCH arm relative to the AC→T arm was 0.66 ([95% CI: 0.47, 0.93]; p = 0.0.182, stratified log-rank test). Kaplan-Meier curves for OS were included in the study report. The absolute difference in the estimated OS rates between the ACT→T arm and both the AC→TH and TCH arms increased from Year 1 to Year 5 from 0.3% to 5.5% and 0.2% to 4.4%, respectively.

DFS by nodal status: Of the 922 (28.6%) randomised patients classified as high-risk node-negative, the risk of DFS events was significantly lower in both Herceptin containing arms relative to the control arm (AC→T). Similarly, of the 2300 (71.4%) randomised patients classified as node-positive, the risk of DFS events was significantly lower in both Herceptin containing arms relative to the control arm (AC→T). The risk of experiencing a DFS event in the two Herceptin arms relative to the AC→T arm was lower in high-risk node negative patients than in node-positive patients.

Key exploratory DFS subgroup analyses of clinically important baseline factors (AC→T versus AC→TH) such as age, menopausal status, number of positive nodes, hormone receptor status, tumour size, tumour histopathology, nuclear grade, and type of surgery type and radiation therapy. These exploratory DFS subgroup analyses were generally consistent with the overall treatment effects as the relative HRs were generally < 1.0 and favoured AC→TH relative to AC→T.

Additional DFS and OS efficacy analyses were conducted for several additional endpoints and in general the results for the comparison between the AC→T versus AC→TH arms, and the AC→TH versus TCH arms were consistent primary analyses.

Evaluator's conclusions on clinical efficacy for Dossier 2 [BCIRG 006]

The evaluation of BCIRG 006 supports the proposed additions to the *Clinical Trials* section of the PI relating to the basic design features of the study and to the DFS and OS efficacy outcomes. BCIRG 006 is a large (n=3222), on-going, Phase III (multinational, multicentre), efficacy and safety study. The efficacy analyses in the submitted CSR were based on the data included in the pre specified second interim analysis. The efficacy analyses were based on 474 DFS events (52.7% of the planned 900 events) and a median duration of follow-up of approximately 3 years in each of the three treatment arms. The DFS data in the submitted analysis are not mature as the main analysis is planned to be undertaken using 5 year DFS data with a total of 900 events among all patients.

The study was open label in design which makes it subject to the well known biases associated with studies of this type. The inclusion and exclusion criteria were acceptable and reflect the characteristics of Australian women with localised breast cancer with HER2-positive tumours likely to be offered adjuvant treatment with trastuzumab in combination with chemotherapy. The primary efficacy outcome measure (DFS) and the secondary efficacy outcome measure (OS) are consistent with the measures recommended in the relevant TGA adopted guidelines on the clinical evaluating of anti-cancer medicinal products.[35]The use of these efficacy outcome measures, which are primarily objectively

[35] CPMP/EWP/205/95/Rev.3/Corr. Guideline On The Evaluation Of Anticancer Medicinal Products In Man. http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf

based for DFS and objectively based for OS is likely to have mitigated the potential biases associated with the open-label design of this study.

The adjuvant chemotherapy treatment used as a "control" (AC→T) is considered to be acceptable. This regimen was likely to have been used in clinical practice at the time the study was designed. The use of the two "experimental" adjuvant Herceptin plus chemotherapy treatment arms are considered acceptable: an anthracycline and a taxane together with cyclophosphamide (AC→TH), and a taxane together with carboplatin (TCH). In addition to adjuvant chemotherapy ± Herceptin, the study also allowed standard adjuvant treatments involving radiotherapy and hormonal therapy. The chemotherapy dosing modification regimens (reductions, interruptions, discontinuations) based on the occurrence of severe haematological and/or non-haematological toxicities were acceptable and are considered to reflect standard clinical practice. The regimens for withholding and/or discontinuing Herceptin based on the occurrence of non-haematological toxicities, including specific guidelines relating to reductions in the LVEF were considered to be acceptable.

The primary efficacy outcome measure was DFS, defined as the time from the date of randomisation to the date of local, regional, or distant relapse, or the date of second primary cancer, or death from any cause, whichever occurred first. Relapse was defined as any clinical or radiologic evidence of tumour recurrence. Histologic or cytological proof of failure, if feasible, was also to be obtained. The number of DFS events, at the time of the analysis in the AC→T, AC→TH, and TCH arms, were 195 (18.2%), 134 (12.5%) and 145 (13.5%), respectively. The absolute difference in DFS event rates at the time of the analysis favoured both adjuvant Herceptin containing regimens compared with adjuvant chemotherapy alone: that is, 5.7% (AC→TH versus AC→T) and 4.7% (TCH versus AC→T). The HR (stratified for number of positive nodes and hormonal receptor status) favoured both the adjuvant Herceptin plus chemotherapy arms (AC→TH and TCH) relative to the adjuvant chemotherapy alone arm (AC→T). Based on the HR, the risk of experiencing a DFS event was 39% lower in the AC→TH arm relative to the AC→T arm (HR = 0.61 [95% CI: 0.49, 0.77]; p<0.0001, stratified log-rank test) and 33% lower in the TCH arm relative to the AC→T arm (HR = 0.67 [95% CI: 0.54, 0.83]; p=0.0003 stratified log-rank test).

The secondary efficacy outcome measure reported in the CSR was OS, defined as the time from the date of randomisation to the date of death from any cause or last contact. The results showed an overall survival benefit in both the adjuvant Herceptin combined with chemotherapy treatment arms (AC→TH and TCH) compared with the adjuvant chemotherapy alone arm (AC→T). The number of patients alive in the AC→T, AC→TH and TCH arms at the time of analysis was 993 (92.5%), 1025 (95.4%) and 1019 (94.8%) respectively. The absolute differences in favour of OS in the adjuvant Herceptin combined with chemotherapy arms compared with adjuvant chemotherapy only arm were 2.9% (AC→TH versus AC→T) and 2.3% (TCH versus AC →T). Based on the HR, the risk of death was 42% lower in the AC→TH relative to the AC→T arm (HR = 0.58 [95% CI: 0.40, 0.83]; p<0.0024, stratified log-rank test), and 34% lower in the TCH arm relative to the AC→T arm (HR = 0.66 [95% CI: 0.47, 0.93]; p=0.0182, stratified log-rank test).

Safety

Extension of indication (Dossier 1)

Studies providing evaluable safety data

The safety data supporting the proposed extension of indication for trastuzumab are primarily derived from the pivotal study [NOAH]. In addition, supportive safety data are provided from the MDACC and the GeparQuattro studies. These three studies provide a total of over 600 patients with HER2-positive breast cancer treated with neoadjuvant

trastuzumab plus chemotherapy. The submission did not include pooled safety data from the three studies as the sponsor considered that pooling would not be clinically meaningful given that only limited safety data were reported in the published MDACC and GeparQuattro studies. The key safety related entry criteria for the three studies are summarised below in Table 26.

Table 26: Key safety related entry criteria.

Criteria	MO16432 (NOAH)	MDACC	GeparQuattro
Inclusion Criteria			
Normal hematological, liver, and renal function	√	√	√
LVEF ≥ LLN and normal ECG within 3 months prior to registration	√	√	√
Exclusion Criteria			
Prior chemotherapy, hormonal therapy, or anti-HER2 therapy for any malignancy	√	ns	√
Pregnancy or lactation	√	√	√

LVEF: left ventricular ejection fraction; LLN: lower limit of normal; ECG: electrocardiogram; ns: not specified.

In NOAH, safety and tolerability was a secondary objective as were changes in the LVEF. In this study, 115 patients with HER2-positive breast cancer were treated with trastuzumab (8 mg/kg loading dose, followed by a maintenance dose of 6 mg/kg every 3 weeks) in combination with neoadjuvant chemotherapy (doxorubicin 60 mg/m^2 and paclitaxel 150 mg/m^2 [AP] every 3 weeks for 3 cycles, followed by paclitaxel 175 mg/m^2 [P] every 3 weeks for 4 cycles, followed by cyclophosphamide 600 mg/m2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/kg^2[CMF] on Days 1 and 8 every 4 weeks for 3 cycles), and 112 patients with HER2-positive disease were treated with neoadjuvant chemotherapy alone. In addition, the study included a cohort of 99 patients with HER2-negative disease who received the same neoadjuvant chemotherapy regimen (without trastuzumab) as patients in the HER2-C arm. In the HER2+TC arm, trastuzumab was continued after surgery as adjuvant therapy for a total treatment duration of 1 year. In addition, patients in HER2+C arm were offered adjuvant trastuzumab for 1 year following surgery and 20 patients crossed-over.

In MDACC, 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 (paclitaxel 225 mg/m^2 [P] every 3 weeks for 4 cycles, followed by fluorouracil, epirubicin, and cyclophosphamide [FEC] every 3 weeks for 4 cycles), and 19 patients with HER2-positive disease received chemotherapy alone.

In GeparQuattro, 443 patients with HER2-positive breast cancer received trastuzumab (same regimen as NOAH) in combination with chemotherapy (epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 (EC) for 4 cycles and then random assignment to either 4 cycles of docetaxel 100 mg/m^2, 4 cycles of docetaxel 75 mg/m^2 plus capecitabine 1800 mg/m^2 or 4 cycles of docetaxel 75 mg/m^2 followed by 4 cycles of capecitabine 1800 mg/m2 (D[X]). In HER2-positive patients, trastuzumab was continued after surgery as adjuvant therapy for a total treatment duration of 1 year.

The safety analysis population (SAP)

NOAH Study

In NOAH, the SAP consisted of all patients who were randomised in the main study or registered in the parallel observational arm and received at least one dose of study medication for all assessments/events prior to and including surgery. The SAP comprised

326 patients (115 patients randomised to HER2+TC; 112 patients randomised to HER2+C; 99 patients allocated to parallel observational HER2-C).

NOAH included a second safety population defined as the post-surgery safety analysis population (SAP-P). This population comprised 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. There were 47 patients in the SAP who were excluded from the SAP-P due to having no safety assessment after surgery. The 20 patients in the HER2+C group who crossed over to adjuvant trastuzumab were analysed separately. The SAP-P comprised 279 patients (112 patients [HER2+TC]; 20 patients [HER2+C→T]; 68 patients [HER2+C]; and 79 patients [HER2-C]).

AEs and SAEs (regardless of the relationship to treatment) were collected until 4 weeks after the last dose of study medication. Thereafter, only SAEs that were considered treatment-related (remotely, possibly, probably or definitely) had to be reported. SAEs were defined according to the relevant EU guideline. Since trastuzumab was scheduled for a total of 1 year, the reporting period for safety data was considerably longer in patients receiving trastuzumab compared with patients receiving chemotherapy only. Therefore, the sponsor stated that no direct comparison should be performed in the postoperative period among the HER2+TC, HER2+C→T, HER2+C and HER2-C arms. Deaths occurring during the study or within 4 weeks after stopping study treatment, whether considered to be treatment-related or not, had to be reported. However, death was considered an outcome of an event, therefore, the event(s) that resulted in death had to be reported as an SAE unless death was directly related to progression of the underlying cancer.

The NCI-CTCAE (v2.0) was used to evaluate the severity of all AEs except for cardiac dysfunction which was graded according to the NYHA classification system. Owing to the design of the study only non-haematological AEs were to be recorded. Haematological toxicity on the day of treatment was recorded separately and was not considered an AE.

MDACC and GeparQuattro Studies

In *MDACC*, the safety population initially comprised 42 patients with HER2-positive disease randomised to neoadjuvant trastuzumab/chemotherapy (P-FEC+T [n=23]) or chemotherapy alone (P-FEC [n=19]) and subsequently included the 22 patients assigned to neoadjuvant trastuzumab (P-FEC+T [n=22]). Toxicity was evaluated using NCI-CTCAE (v2.0).

In GeparQuattro, the analysis population comprised 1495 patients (445 patients HER2+; 1050 patients HER2-). In the safety analysis, patients were evaluated according to having or not having received trastuzumab and 2 patients with HER2-positive disease did not receive trastuzumab while 6 patients with HER2-negative disease received trastuzumab. Therefore, the trastuzumab/chemotherapy arm (T+EC-D[X]) comprised 449 HER2-positive patients and the chemotherapy alone arm (EC-D[X]) comprised 1046 HER2-negative patients. Toxicity was evaluated using NCI-CTCAE (v3.0).

Overall extent of exposure

NOAH Study

In NOAH, at the time of the clinical cut-off (30 March 30, 2009), the median duration of follow-up was about 3.8 years (45.9 months in the HER2+TC arm, 42.6 months in the HER2+C arm and 48.1 months in the HER2–C arm).

Exposure to trastuzumab (pre and postoperative periods)

Overall exposure to trastuzumab in the pre and post operative periods was summarised in the sponsor's study report. The median cumulative trastuzumab dose in the HER2+TC arm was 6753 mg (range 812 – 11805). With the exception of one patient who was randomised but did not start study medication due to withdrawn consent, all randomised patients in the HER2+TC arm received at least 2 cycles of trastuzumab. The median number of cycles received was 16, indicating that the majority of patients in the HER2+TC arm completed one year of scheduled trastuzumab therapy. In the pre operative period, the median number of cycles was 11 (range 2–11) and during the post operative period the median number of cycles was 6 (range 1–8). Trastuzumab dose delays were reported in 64% (86/135) of patients, and trastuzumab dose adjustments of ≥ 10% were reported in 15.6% (21/135) of patients. During the pre operative period, 87.8% of patients had no dose adjustment of ≥ 10% or more for trastuzumab and 50.4% had no dose-delay.

> *Comment*: Dose delays were reported frequently in trastuzumab treated patients, with 64% of patients experiencing at least one dose delay. The sponsor comments that the relatively high percentage of dose delays was "consistent with the fact that treatment was given concurrently with 10 cycles of chemotherapy (which sometimes required a dose delay) and that during the total treatment period of one year most patients had surgery and/or radiotherapy".

Exposure to combination doxorubicin and paclitaxel

More than 98% of patients across the treatment arms received the 3 cycles of doxorubicin and paclitaxel as planned and exposure was similar in the three arms as indicated by the median cumulative doses of doxorubicin (range 306–312 mg) and paclitaxel (range 774–780 mg). Most patients in the three arms (94% to 97%) did not require dose adjustments or delays to doxorubicin plus paclitaxel chemotherapy. Only 4 patients in the HER2+TC arm, 7 in the HER2+C arm and 3 in the HER2-C arm required dose adjustments and these patients only required one dose adjustment. Dose delays were reported in 32 (27.9%) in the HER2+TC arm, 27 (24.1%) patients in the HER2+C arm and 19 (19.2%) patients in the HER2-C arm but most patients in all three arms required only one dose delay.

Exposure to paclitaxel alone

More than 96% of patients across the treatment arms received the 4 cycles of paclitaxel alone as planned and exposure was similar in the three arms as indicated by the median cumulative exposure of 1200 mg in all three groups. In the SAP, there was 1 patient in the HER2+TC arm, 2 in the HER2+C arm and 4 in the HER2-C arm who did not receive at least one cycle of paclitaxel alone. Only 4 patients in the HER2+TC arm, 7 in the HER2+C arm and 5 in the HER2-C arm required dose adjustments and most of these patients required only one dose adjustment. Dose delays were reported in 37 (32.2%) patients in the HER2+TC arm, 44 (39.3%) in the HER2+C arm and 31 (31.3%) in the HER2-C arm and most patients in all three arms required only one dose delay.

Exposure to cyclophosphamide, methotrexate and fluorouracil [CMF]

More than 93% across the treatment arms received the 3 cycles of CMF as planned and exposure was similar in the three treatment arms as indicated by the median cumulative doses (cyclophosphamide [6120-6198 mg], methotrexate [414-420 mg] and fluorouracil [6102-6162 mg]). Most patients in the three arms did not require a CMF dose adjustment (94% to 99%). Only 5 patients in the HER2+TC arm, 6 in the HER2+C arm and 1 in the HER2-C arm required dose adjustments. Patients in the HER2+C arm required more dose adjustments than patients in the other two arms (3 patients with 2 dose adjustments versus no patient with more than 1 dose adjustment in the other two arms). The number

of patients requiring a dose delay was similar in the three arms (45 [39.1%] patients in the HER2+TC arm, 43 [38.4%] patients in the HER2+C arm and 32 [32.3%] patients in the HER2-C arm).

MDACC and GeparQuattro studies

In *MDACC*, no specific exposure information was provided. For randomised patients, the median duration of patient follow-up was 20 months (range 8.8–36.6 months) at the time of the initial publication and 36.1 months (range 12.3-54.8 months) at the time of the updated publication. In HER2-positive patients in the additional cohort treated with trastuzumab plus chemotherapy, the median follow-up was 16.3 months (range 5.9–20.4 months).

In *GeparQuattro*, trastuzumab was given as planned to 78.0% of patients (347/445). In 20.9% of patients (93/445), trastuzumab plus chemotherapy was discontinued followed by immediate surgery with trastuzumab being restarted post operatively to complete the one year of scheduled trastuzumab therapy.

Adverse events

Overview

NOAH Study

The main features of safety in the pre-operative period (SAP) are summarised below:

- almost all patients in three treatment arms experienced at least one AE (range 98.3% to 100%);
- Grade 3 AEs were reported with similar frequencies in patients in the HER2+TC and HER2+C arms (37.4% and 39.3%, respectively) and more frequently than in patients in the HER2-C arm (32.3%);
- Grade 4 AEs were reported less frequently in patients in the HER2+TC arm (1.7%) compared with patients in the HER2+C (5.4%) and HER2–C (5.1%) arms;
- the incidence of SAEs was higher in the HER2+TC arm (10.4%) than in the HER2+C (7.1%) and HER2-C (6.1%) arms;
- the incidence of cardiac AEs (all types) was similar in the HER2+ arms (13.9% [HER2+TC]; 13.4% [HER2+C]) and notably lower in the HER2-C arm (3.0%);
- the number of patients with AEs leading to discontinuation was small in each of the three treatment arms (1 [0.9%] HER2+TC; 0 [0%] HER2+C; 3 [3.1%] HER2-C]; and
- there were no patients with AEs leading to death reported in any of the three treatment arms.

MDACC and GeparQuattro Studies

In *MDACC*, in the initial study Grade 4 neutropenia occurred significantly more frequently in the HER2+TC arm (91.3%) than in the HER2+C arm (57.9%), p=0.03. Most other reported AEs occurred with similar frequencies in the two HER2-positive arms. Overall, the study authors reported that no new safety concerns were observed in the study.

In *GeparQuattro*, neoadjuvant trastuzumab plus chemotherapy in the HER2-positive group did not result in clinically or statistically significant increases in Grade 3 and 4 AEs compared with neoadjuvant chemotherapy in the HER2-negative reference group.

Common adverse events

NOAH Study

a. During the pre-operative period, almost all patients experienced at least one treatment-emergent AE: 98.3% (113/115) in HER2+TC; 100% (112/112) in HER2+C; and 99.0% (98/99) in HER2-C. The most common AEs (in at least 50% of patients) by system organ class (SOC) were:
   - *Gastrointestinal disorders*: nausea, vomiting, stomatitis, diarrhoea, abdominal pain and constipation.
   - *Skin and subcutaneous tissue disorders*: alopecia and nail disorder.
   - *General disorders and administration site conditions*: asthenia, influenza-like illness, pyrexia, fatigue and mucosal inflammation.
   - *Nervous system disorders*: peripheral neuropathy, paraesthesia, peripheral sensory neuropathy, dysgeusia and headache.
   - *Musculoskeletal and connective tissue disorders*: myalgia, arthralgia, bone pain and pain in extremity.

b. In the pre operative period, the body systems (SOC) in which the HER2+TC arm recorded a higher incidence of treatment-emergent AEs (preferred term) compared with the HER2+C arm are summarised below (HER2+TC versus HER2+C):
   - *Gastrointestinal disorders (92.2% versus 88.4%)*: vomiting (47.0% versus 46.4%); stomatitis (40.0% versus 39.3%); diarrhoea (29.6% versus 28.6%); abdominal pain upper (16.5% versus 6.3%); dyspepsia (7.8% versus 2.7%).
   - *Skin and subcutaneous tissue disorders (92.2% versus 90.2%)*: alopecia (79.1% versus 77.7%); rash (7.0% versus 6.3%).
   - *General disorders and administration site conditions (75.7% versus 69.6%)*: influenzae like illness (22.6% versus 22.3%); pyrexia (20.0% versus 11.6%); fatigue (17.4% versus 13.4%); mucosal inflammation (13.0% versus 12.5%).
   - *Nervous system disorder (73.0% versus 75.9%)*: neurotoxicity (5.2% versus 3.6%).
   - *Musculoskeletal and connective tissue disorders (67.0% versus 50.0%)*: myalgia (27.8% versus 22.3%); arthralgia (24.3% versus 20.5%); pain in extremity (8.7% versus 4.5%); musculoskeletal pain (7.8% versus 3.6%).
   - *Infections and infestations (44.3% versus 36.6%)*: pharyngitis (6.1% versus 0.9%); rhinitis (6.1 % versus 0.9%); cystitis (5.2% versus 3.6%).
   - *Eye disorders (42.6% versus 30.4%)*: conjunctivitis (29.6% versus 19.6%); lacrimation increased (13.0% versus 4.5%).
   - *Respiratory, thoracic and mediastinal disorders (40.0% versus 22.3%)*: rhinorrhoea (18.3% versus 8.0%); epistaxis (13.9% versus 1.8%); cough (10.4% versus 2.7%); dyspnoea exertional (7.0% versus 2.7%).
   - *Vascular disorders (24.3% versus 22.3%)*: hot flush (13.0% versus 5.4%); hyperaemia (5.2% versus 3.6%).
   - *Reproductive and breast disorders (21.7% versus 28.6%)*: amenorrhoea (12.2% versus 11.6%); menstruation irregular (10.4% versus 7.1%).

- *Investigations (16.5% versus 8.0%)*: weight increase (5.2% versus 2.7%), ALT increase (2.6% versus 1.8%), AST increase (2.6% versus 0.9%); heart rate increase (2.6% versus 0.9%).
- *Psychiatric disorders (13.0% versus 11.5%)*: insomnia (6.1% versus 5.4%).
- *Blood and lymphatic system disorders (11.3% versus 8.0%)*: febrile neutropenia (7.0% versus 3.6%).

c. The results for the four treatment arms in the post operative period are were summarised in the sponsor's submission. Meaningful comparisons among the treatment arms are precluded due to the different durations of exposure. Examination of the treatment-emergent AEs reported in the HER2+TC treatment arm in which patients were exposed to trastuzumab for up to 1 year do not give rise to new or unexpected safety signals.

Grade 3/4 adverse events

NOAH Study

a. In the pre-operative period, most of the reported Grade 3 or 4 events were Grade 3 in severity. The proportion of patients reporting Grade 3 or 4 treatment-emergent AEs was similar in the HER2+TC (39.1% [45/115]) and HER2+C (41.1% [46/112]) treatment arms and higher than in the HER2-C arm (34.3% [34/99]). The most common Grade 3 or 4 AEs reported in the HER2+ treatment arms (≥ 5 % in at least one treatment arm) were in the SOCs (HER2+TC versus HER2+C): Skin and subcutaneous tissue disorders (15.7% versus 11.6%); Gastrointestinal disorders (3.5% versus 11.6%); General disorders and Administration site conditions (3.5% versus 5.4%); Musculoskeletal and connective tissue disorders (3.5% versus 5.4%); and Vascular disorders (1.7% versus 5.4%).

b. In the pre operative period, Grade 3 or 4 treatment-emergent AEs (preferred term) reported ≥ 2% more commonly in the HER2+TC arm than the HER2+C arm were: alopecia totalis (12.2% versus 9.8%); and febrile neutropenia (6.1% versus 2.7%).

c. In the pre operative period, treatment-emergent Grade 3 AEs occurred in 37.4% (43/115) of patients in the HER2+TC arm, 39.3% (44/112) of patients in the HER2+C arm, and 32.3% (32/99) of patients in the HER2-C arm. The most frequent Grade 3 AE in the HER2-positive arms was alopecia (reported as alopecia [4.3% in HER2+TC; 3.6% in HER2+C] and alopecia totalis [12.2% in HER2+TC; 9.8% in HER2+C]). Grade 3 alopecia was only reported in 2 patients with HER2-negative disease.

d. In the pre-operative period, treatment-emergent Grade 4 AEs were infrequent. In the HER2+TC arm, 2 patients (1.7%) experienced Grade 4 febrile neutropenia. In the HER2+C arm, 6 patients (5.4%) had at least one Grade 4 AE: febrile neutropenia (1 x patient); neutropenia (2 x patients); nausea and vomiting (1 x patient); pyrexia (1 x patient); and back pain (1x patient). In the HER2-C arm, 5 (5.1%) patients experienced a Grade 4 AE: febrile neutropenia (2 x patients); neutropenia (1 x patient); stomatitis (1 x patient); and pulmonary embolism (1 x patient).

e. In the post operative period, the proportion of patients reporting treatment-emergent Grade 3 or 4 AEs was similar across the four treatment arms (9.8% [11/112] in HER2+TC; 10% [2/20] in HER2+C→T; 8.8% [6/68] in HER2+C; 8.9% [7/79] in HER2-C).

MDACC and GeparQuattro Studies

In *MDACC*, the initial publication reported that a higher proportion of patients treated with chemotherapy plus trastuzumab experienced Grade 4 neutropenia during the paclitaxel

phase of the therapy: P-FEC (57.9% [11/99]) versus P-FEC+T (91.3% [21/23]); p=0.03. No further details about Grade ≥ 3 AEs were provided in either original or updated publications.

In *GeparQuattro*, the incidence of Grade 3 and 4 AEs were similar in the HER2-positive group (neoadjuvant trastuzumab plus chemotherapy) and the HER2-negative group (neoadjuvant chemotherapy alone). Statistically significant differences between the two groups were reported for AEs of febrile neutropenia (9.9% [44/449] HER2+ versus 6.1% [61/1046] HER2-, p=0.15) and conjunctivitis (2.5% [11/449] HER2+ versus 0.9% [9/1046] HER2-, p=0.024).

Treatment related adverse events (adverse drug reactions)

Noah Study

During the pre operative period, almost all patients experienced at least one treatment-emergent adverse event that was considered related to study treatment by the investigator (98.3% HER2+TC; 100% HER2+C; 99% HER2-C). The majority of the treatment-related AEs (HER2+TC, HER2+C, HER2-C, respectively) occurred within the SOCs of Gastrointestinal disorders (91.3%; 87.5%; 80.8%), Skin and subcutaneous tissue disorders (90.4%; 90.2%; 91.9%), General and administration site conditions (72.2%; 69.6%; 49.5%), Nervous system disorders (72.2%; 75.9%; 63.6%) and Musculoskeletal and connective tissue disorders (64.3%; 49.1%; 53.5%). Consistent with AEs (irrespective of relationship to treatment), the main treatment-related AEs within these SOCs were: nausea, diarrhoea, vomiting and stomatitis (Gastrointestinal disorders); alopecia (Skin and subcutaneous tissue disorders); asthenia (General and administration site conditions); parasthesia and peripheral neuropathy (Nervous system disorders); and arthralgia and myalgia (Musculoskeletal and connective tissue disorders). Overall, examination of the tabulated summary of treatment-related AEs in the pre-operative period showed no notable differences between the two HER2-positive treatment arms except for the increased incidence in the HER2+TC versus the HER2-C arm of upper abdominal pain (13.9% versus 3.6%), dyspepsia (7.8% versus 2.7%), pyrexia (13.0% versus 8.0%), conjunctivitis (28.7% versus 18.8%), increased lacrimation (13.0% versus 4.5%), rhinorrhoea (16.5% versus 7.1%), epistaxis (13.0% versus 0.9%), dyspnoea exertional (7.0% versus 1.8%) and hot flush (8.7% versus 3.6%).

MDACC and GeparQuattro studies

There were no data on treatment-related AEs in MDACC and GeparQuattro.

Deaths and other serious adverse events

Deaths

NOAH Study

In NOAH, at the time of clinical data cut-off, 76 patients had died. The main cause of death in the three treatment arms was disease progression (72/76 [94.7%] patients): 20 (17.2%) in the HER2+TC arm; 33 (28.0%) in the HER2+C arm; and 19 (19.2%) in the HER2–C arm. Of the 4 patients who died due to reasons other than disease progression, 2 were from the HER2+TC arm (1 of "unknown cause", 1 due to fatal myocardial infarction 34 months after being diagnosed with Grade 1 restrictive cardiomyopathy and 43 months after the last dose of trastuzumab) and 2 were from the HER2–C arm (1 "unknown cause"; 1 due to Grade 4 SAE thromboembolism of the lung arteria [surgical complication]).These 4 deaths were not reported as AEs or SAEs because they occurred after the mandatory AE/SAE reporting period. No treatment-related deaths were reported.

MDACC and GeparQuattro studies

In MDACC, at the time of the initial publication there were no treatment-related deaths. At the time of the updated publication, 1 patient in the chemotherapy alone group had died as a result of progressive metastatic disease. In GeparQuattro, 1 patient in the HER2-positive group died of unknown cause and 5 patients in the HER2-negative group died (4 due to sepsis and 1 due to disease progression).

Other serious adverse events

NOAH Study

a. During the pre operative period, a total of 40 SAEs in 26 patients were reported in the three treatment arms (18 in 12 patients [HER2+TC]; 14 in 8 patients [HER2+C]; 8 in 6 patients [HER2-C]). The incidence of SAEs was higher in patients in the HER2+TC arm (10.4%) compared with patients in the HER2+C (7.1%) and HER2–C (6.1%) arms. The most commonly reported SAEs were *Blood and lymphatic system disorders (SOC)* (8 [7.0%] patients in the HER2+TC arm; 5 [4.5%] patients in the HER2+C arm; 3 [3.0%] patients in the HER2-C arm). These SAEs were all diagnosed as febrile neutropenia, neutropenia or pancytopenia. Febrile neutropenia was reported more commonly in patients in the HER2+TC arm (6.1% [7/119]) than in patients in the HER2+C (2.7% [5/112]) and HER2-C (3.0% [3/99]) arms. In addition, 3 (2.6%) patients in the HER2+TC arm experienced SAE pyrexia (compared with none in HER2+C and HER2-C arms).

b. During the post operative period, a total of 12 SAEs in 11 patients were reported in the three treatment arms (8 in 7 patients [HER2+TC]; 1 in 1 patient [HER2+C]; 3 in 3 patients [HER2-C]). *Infections and infestations (SOC)* was the most commonly affected system: 4 patients in the HER2+TC arm experienced gastrointestinal infection (x1), pneumonia (x1), post operative wound infection (x1) and wound abscess (x1); and 2 patients in the HER2–C arm experienced pneumonia (x1) and herpes zoster (x1). The other SAEs reported in patients in the HER2+TC arm were seroma (1 patient), decreased ejection fraction (1 patient: this patient had also a post operative SAE of pneumonia), pulmonary embolism (1 patient) and hypertension (1 patient).

MDACC and GeparQuattro studies

No information on SAEs was reported in either the MDACC or GeparQuattro studies.

Discontinuations due to adverse events

NOAH Study

During the pre operative period, 1 patient in the HER2+TC arm discontinued treatment due to an AE (SAE Grade 3 decreased ejection fraction considered related to the study medication) and 3 patients in the HER2-C arm discontinued treatment due to an AE (1 x stomatitis, 1 x hypersensitivity, 1 x pruritus). No patients in the HER2+C arm discontinued in the pre operative period due to an AE.

During the post operative period, discontinuations due to AEs were reported in 2 patients in the HER2+TC arm (1 x pulmonary embolism, 1 x urticaria), 1 patient in the HER2+C→T arm (1 x fatigue) and 1 patient in the HER2+C arm (1 x idiopathic thrombocytopenic purpura).

Dose interruptions and modifications due to AEs

NOAH Study

In the pre operative period, AEs resulting in treatment interruptions were reported in 7.8% (9/115) of patients in the HER2+TC arm, 6.3% (7/112) of patients in the HER2+C

arm and 5.1% (5/99) of patients in the HER2-C arm. The most common reasons (SOC) for treatment interruptions in the three arms were Infections and infestations (4.3% in HER2+TC; 2.7% in HER2+C; 3.0% in HER2-C) and Blood and lymphatic system disorders (2.6% in HER2+TC; 0.9% in HER2+C; 0% HER2-C). During the post operative period, 2 patients experienced an AE which led to treatment interruption (1 in HER2+TC; 1 in HER2+C→T).

In the pre operative period, AEs resulting in dose modifications of at least one component of study treatment occurred in 13.0% (15/115), 9.8% (11/112) and 8.1% (8/99) of patients in the HER2+TC, HER2+C and HER2-C arms, respectively. In the HER2+TC arm, 3 (2.6%) patients with an increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and 2 (1.7%) patients with pyrexia had dose modifications, compared with no patients in the other two treatment arms for these AEs. More patients had peripheral sensory neuropathy leading to dose modification in the HER2+C and HER2-C arms (3 [2.7%] and 3 [3.0%], respectively) than in the HER2+TC arm (1 [0.9%]). During the post operative period, 2 patients had AEs resulting in dose modification (1 x bronchitis; 1 x influenzae).

MDACC and GeparQuattro studies

In MDACC, in the original study report chemotherapy dose was reduced because of neutropenia in 5 (26.3%) patients in the chemotherapy alone arm and 10 (43.5%) patients in the trastuzumab plus chemotherapy arm. In both treatment arms, 3 patients had dose reductions for reasons other than myelotoxicity. In *GeparQuattro*, no information on dose modification was identified.

Safety issues of special interest

Cardiac safety

Cardiac adverse events

NOAH Study

In NOAH, cardiac AEs were defined as all AEs in the SOCs of Cardiac disorders, and abnormal investigations associated with left ventricular dysfunction. The majority of patients in both the HER2+TC and HER2+C arms had a normal ECG at baseline (69.6% and 65.5%, respectively). During the pre operative period, 34 patients experienced 53 cardiac AEs (16 patients with 27 AEs [HER2+TC]; 15 patients with 21 AEs [HER2+C]; 3 patients with 5 AEs [HER2–C]). The proportion of patients with cardiac AEs was similar in the HER2+TC (13.9%) and the HER2-C (13.4%) arms (see Table 27, below). None of the Cardiac disorders (SOC) were reported as Grade 3 or 4 AEs or SAEs. One of the two patients with a decrease in ejection fraction was reported to have a Grade 3 decrease which was also reported as a SAE.

Table 27: NOAH. Treatment-emergent cardiac AEs in the pre-operative period; SAP.

SOC / Preferred term	HER2+TC n=115	HER2+C n=112	HER2-C n=99
Total patients with cardiac TEAEs	**16 (13.9)**	**15 (13.4)**	**3 (3.0)**
Cardiac Disorders N (%)	**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'.

In the post operative period, 16 patients experienced 22 cardiac adverse events (10 [8.9%] patients with 15 AEs [HER2+TC]; 2 [10.0%] patients with 2 AEs [HER2+C→T]; 4 [5.9%] patients with 5 AEs [HER2+C]). There were 2 (1.8%) patients in the HER2+TC arm with a decrease in LVEF.

MDACC and GeparQuattro studies

In *MDACC*, it was reported that none of the 45 patients treated with trastuzumab plus chemotherapy experienced clinical cardiac dysfunction and there were no cardiac deaths. In the second cohort of 22 patients treated with trastuzumab plus chemotherapy, 1 patient had a history of atrial arrhythmias and left bundle branch block on her initial electrocardiogram. After completion of therapy this patient developed Grade 1 cardiac dysfunction according to NYHA criteria but showed no further change in cardiac status during continued follow-up.

In *GeparQuattro*, congestive heart failure and cardiac ischaemia were each reported in 2 (0.2%) patients treated with chemotherapy alone (HER2-negative group) and in 1 (0.2%) patient treated with chemotherapy and trastuzumab (HER2-positive group).

Left ventricular ejection fraction

NOAH Study

In NOAH, a baseline LVEF of 55% or more (measured by ECHO or MUGA) was required for inclusion in the study. The median baseline LVEF was 63% in all three treatment arms, with the overall range being from 55% to 89%. In the pre operative period (evaluable patients), more patients in the HER2+TC arm had a decline in LVEF compared with patients in the HER2+C and HER2-C arms (86.7%: 72.5%; and 79.2%, respectively) (see Table 28, below). 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.

Table 28: NOAH. LVEF during the pre-operative patients in evaluable patients*; SAP.

Characteristic (worst pre operative value)	HER2+TC (n=113)	HER2+C (n=112)	HER2-C (n=96)
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

* Evaluable patients = patients with a non-missing baseline LVEF value and a non-missing post-treatment value. Note: Values are always summarised 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.

In the post operative period, decreases of ≥ 10 percentage points were observed in 24.4% (22/112), 6.3% (1/20), 57.6% (34/68) and 67.1% (47/79) of patients in the HER2+TC, HER2+C→T, HER2+C and HER2-C arms, respectively. In the HER2+TC arm, 4 (4.4%) patients had a decline in LVEF of ≥ 10 percentage points to ≥ 45% but < 50%, compared with no patients in the other 3 treatment arms.

LVEF values improved over time in all three treatment arms and at the 24 month follow-up the median LVEF was 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.

MDACC and GeparQuattro studies

In *MDACC*, the median LVEF was 65% (range 55-76) in patients initially randomised to the chemotherapy alone arm, 65% (range 50-71) in patients initially randomised to the chemotherapy plus trastuzumab arm and 65% (range, 55-70) in patients assigned to the chemotherapy plus trastuzumab arm in the updated study. After 6 months treatment, these values were 65% (range 55-70), 60% (range 52-70) and 60% (range 45-65), respectively. In patients randomised to chemotherapy plus trastuzumab in the initial study, the median LVEF decreased to 60% by the end of follow-up but the range remained nearly constant. In patients assigned to chemotherapy plus trastuzumab in the updated study, the median LVEF and range both decreased over time, although follow-up among these patients was shorter than that for the initially randomised patients.

In the initial study, a decrease in LVEF > 10% was observed in 5 (26.3%) patients in the chemotherapy alone arm and 7 (30.4%) patients in the trastuzumab plus chemotherapy arm. In patients treated with chemotherapy alone, 1 patient experienced a decrease in LVEF to 35% following an acute myocardial infarction. This patient had a history of hypertension, diabetes mellitus and mitral valve regurgitation. The LVEF returned to baseline values in those patients who had follow-up cardiac studies, except for 1 patient for whom the ejection fraction remained in the low normal range.

In *GeparQuattro*, LVEF measurement was repeated in 90.6% of patients during treatment and a decrease to ≤ 45% was reported in 5 patients. An LVEF decrease of more than 10%

from baseline was reported in 2 (0.4%) patients treated with trastuzumab. LVEF remained < 50% at the last measurement before surgery in 1 patient.

Infusion related adverse events

In NOAH, all AEs occurring during the first day of any cycle of trastuzumab treatment throughout the duration of the study (pre and post operative periods) were reviewed for evidence suggestive of infusion related reactions. In the HER2+TC arm, 5 (4.3%) patients experienced an AE during the combined doxorubicin/paclitaxel cycles (2 x flushing; 2 x rash; 1 x "infusion related reaction"), 1 (0.9%) patient experienced an AE in the paclitaxel cycles (1 x laryngospasm), 1 (0.9%) patient in the CMF cycles (1 x dyspnoea) and 1 (0.9%) patient in a trastuzumab monotherapy cycle (1 x urticaria). Overall, there were 8 (7.0%) patients who experienced an AE suggestive of an infusion related reaction during treatment.

Laboratory tests

Haematology

NOAH

Haematology values worsening in patients during therapy and shifting to Grade 3 or 4 AEs in the pre operative period are summarised below in Table 29. Only a limited number of patients (< 10) had available post-operative values.

Table 29: NOAH. Summary of newly occurring Grade 3 or 4 haematology values; SAP.

	HER2+TC (N=115)			HER2+C (N=112)			HER2-C (n=99)		
	N	n	%	N	n	%	N	n	%
Haemoglobin	115	0	0	112	2	1.8	99	0	0
White blood cells	115	3	2.6	112	8	7.1	99	4	4.0
Lymphocytes	0	-	-	1	0	0	2	1	50
Platelets	114	0	0	112	1	0.9	98	0	0
Neutrophils	115	14	12.2	110	12	10.9	98	12	12.2

MDACC and GeparQuattro studies

No information on laboratory parameters was provided in the MDACC or GeparQuattro studies.

Other laboratory tests

NOAH Study

Examination of the relevant tables for blood biochemistry parameters (AST, ALT, total bilirubin, lactate dehydrogenase and serum creatinine) showed few shifts to Grade 3/4 AEs and no notable differences between the three treatment arms.

MDACC and GeparQuattro studies

No information on laboratory parameters was provided in the MDACC or GeparQuattro studies.

Vital signs

NOAH Study

The study included information on weight change in the HER2+TC arm in the pre and post operative periods and information on weight change in the HER2+C→T arm in the post

operative period. Information on weight change was not collected for patients in the HER2+C and HER2-C arms. The majority of patients treated with trastuzumab maintained body weight (± 5% compared with baseline) during and after chemotherapy. Information on changes in vital signs from baseline to study end appear not to have been collected.

MDACC and GeparQuattro studies

No information on physical findings relating to safety was provided in the MDACC or GeparQuattro studies.

Other safety issues

Safety in special populations

Age

NOAH Study

AEs occurring during the pre operative period were analysed by age subgroup (< 65, ≥ 65 years). The majority of patients in each of the three treatment arms were aged < 65 years (range 82% to 92%). Comparison of the AE profile between the two age groups is likely to unreliable because of the marked imbalance in patient numbers.

MDACC and GeparQuattro studies

No information on age related to safety was provided in the MDACC or GeparQuattro studies.

Other safety issues

There was no other new safety information relating to race, genetic factors, drug-drug and other interactions.

Evaluator's overall conclusions on clinical safety (extension of indication)

The primary safety data in the submission was derived from the pivotal study [NOAH]. The safety data from the two supportive studies [MDACC, GeparQuattro] were consistent with the data from the pivotal study. The safety data in this submission do not give rise to new or unexpected safety signals associated with trastuzumab treatment. Overall, the safety data are consistent with the known safety profile for trastuzumab based on post marketing and clinical trial experience gathered over the 12 to 13 years since the drug was first marketed. The exposure data from the pivotal study in patients treated with neoadjuvant trastuzumab plus chemotherapy and patients treated with neoadjuvant chemotherapy alone are considered adequate to compare the safety profiles of the two treatments. Trastuzumab plus chemotherapy as neoadjuvant treatment for women with localised HER2-positive breast cancer was generally well tolerated. The data from the pivotal study [NOAH] suggests that the safety profile of neoadjuvant trastuzumab plus chemotherapy is generally similar to that of neoadjuvant chemotherapy alone apart from an increased risk of clinically significant reductions in LVEF with trastuzumab plus chemotherapy compared with chemotherapy alone. The review of the safety data provided below refers to the pivotal study [NOAH] unless otherwise stated.

In the pre operative period, nearly all patients in the HER2+TC and HER2+C arms experienced at least one AE (98.3% [113/115] and 100% [112/112], respectively). AEs (preferred term) in the pre operative period occurring with an incidence of at least 5% in either HER2+ treatment arm and at least 2% more frequently in the HER2+TC arm than in the HER2+C arm were (HER2+TC versus HER2+C): *Gastrointestinal disorders SOC (92.2% versus 88.4%);* abdominal pain upper (16.5% versus 6.3%) and dyspepsia (7.8% versus 2.7%); *General disorders and administration site conditions SOC (75.7% versus 69.6%);* pyrexia (20.0% versus 11.6%); *Musculoskeletal and connective tissue disorders SOC (67.0%*

versus 50.0%); myalgia (27.8% versus 22.3%); *Infections and infestations SOC (44.3% versus 36.6%);* pharyngitis (6.1% versus 0.9%) and rhinitis (6.1 % versus 0.9%); *Eye disorders SOC (42.6% versus 30.4%);* conjunctivitis (29.6% versus 19.6%) and lacrimation increased (13.0% versus 4.5%); *Respiratory, thoracic and mediastinal disorders SOC (40.0% versus 22.3%);* rhinorrhoea (18.3% versus 8.0%), epistaxis (13.9% versus 1.8%), and cough (10.4% versus 2.7%); and *Vascular disorders SOC (24.3% versus 22.3%);* hot flush (13.0% versus 5.4%).

In the pre operative period Grade 3 AEs occurred in 37.4% (43/115) of patients in the HER2+TC arm and 39.3% (44/112) of patients in the HER2+C arm. The most frequent Grade 3 AE in the HER2-positive arms was alopecia (alopecia [4.3% in HER2+TC, 3.6% in HER2+C] and alopecia totalis [12.2% in HER2+TC, 9.8% in HER2+C]). Grade 4 AEs in the pre operative period were infrequent and were reported in 2 patients (1.7%) in the HER2+TC arm and 6 patients (5.4%) in the HER2+C arm. Grade 3 or 4 AEs reported ≥ 2% more commonly in the HER2+TC arm than in the HER2+C arm in the pre operative period were alopecia totalis (12.2% versus 9.8%) and febrile neutropenia (6.1% versus 2.7%).

SAEs in the pre operative period were reported more frequently in the HER2+TC arm (10.4% [12/115]) than in the HER2+C arm (7.1% [8/112]). The most commonly reported SAEs were *Blood and lymphatic system disorders SOC* (8 [7.0%] patients in the HER2+TC arm, 5 [4.5%] patients in the HER2+C arm), consisting of febrile neutropenia, neutropenia or pancytopenia. Febrile neutropenia was reported more commonly in the HER2+C arm (6.1%) than in the HER2+C arm (2.7%). In addition, 3 (2.6%) patients in the HER2+TC arm experienced SAEs of pyrexia (compared with none in the HER2+C arm).

At the time of clinical data cut-off, 76 patients had died and the main cause of death in the three treatment arms was disease progression (72 patients): 20 (17.2%) in the HER2+TC arm; 33 (28.0%) in the HER2+C arm; and 19 (19.2%) in the HER2–C arm. Of the 4 patients who died for reasons other than disease progression, 2 were from the HER2+TC arm (1 "unknown cause", 1 fatal myocardial infarction 34 months after being diagnosed with Grade 1 restrictive cardiomyopathy and 43 months after the last dose of trastuzumab), and 2 were from the HER2–C arm (1 "unknown cause"; 1 Grade 4 SAE thromboembolism of the lung arteria [surgical complication]).

In the pre operative period 1 patient in the HER2+TC arm discontinued treatment due to an AE (Grade 3 SAE treatment-related decreased LVEF). No patients in the HER2+C arm discontinued. Dose interruptions were reported with similar frequencies in the HER2+TC and HER2+C arms (7.8% and 6.3%, respectively) and AEs resulting in dose modifications of at least one component of the treatment regime were reported more commonly in the HER2+TC arm than in the HER2+C arm (13.0% and 9.8%, respectively).

Cardiac safety is a major issue with trastuzumab. Heart failure has been observed in patients receiving trastuzumab alone and in combination with chemotherapy. In NOAH, cardiac AEs (including ejection fraction decreased) were reported with similar frequencies in the HER2+TC and HER2+C arms (13.9% [16/115] and 13.4% [15/112]), and injection fraction decrease was reported in 2 (1.7%) patients in the HER2+TC arm but not in any patients in the HER2+C arm group. However, clinically significant reductions in the LVEF (measured by ECHO or MUGA) occurred notably more frequently with trastuzumab in combination with chemotherapy compared with chemotherapy alone. LVEF decreases of ≥ 10 percentage points from baseline were reported more frequently in the HER2+TC arm than in the HER2+C arm (17.7% [20/113] and 12.8% [14/112], respectively). In addition, there were 4 (3.5%) patients in the HER2+TC group with LVEF < 50% and a decrease of ≥10 percentage points from baseline compared with 1 (0.95%) patient in the HER2+TC arm.

Safety BCIRG 006 study [Dossier 2]

Studies providing evaluable data

The main safety data relating to BCIRG was included in the CSR dated 13 June 2007 and updated cardiac safety data from the study was included in a review dated 11 March 2010. An independent data monitoring committee (IDMC) was responsible for the ongoing monitoring of safety data and the review of scheduled anti-tumour efficacy and cardiac safety analyses. An independent cardiac review panel (ICRP) was formed in September 2003 to review all cardiac AEs in a blinded manner.

The safety population included all patients who had received at least one dose of study treatment (chemotherapy or Herceptin) and was analysed according to treatment received. The safety population included 3174 patients (1050, 1068, and 1056 in the AC→T, AC→TH, and TCH arms, respectively). Safety was assessed by AEs, deaths, symptomatic cardiac AEs and asymptomatic declines in LVEF (MUGA scan or ECHO).

Overall extent of exposure

The median duration of follow-up among safety evaluable patients was 3.0 years for each treatment arm (see Table 30, below).

Table 30: BCIRG 006. Duration of follow up; safety population.

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
n	1050	1068	1056
Mean (SD) (yr)	2.9 (0.9)	2.9 (0.9)	2.9 (0.9)
Median (yr)	3.0	3.0	3.0
Range (yr)	0.0–5.2	0.1–5.3	0.0–5.1
<1 yr	39 (3.7%)	35 (3.3%)	31 (2.9%)
1 yr	127 (12.1%)	109 (10.2%)	102 (9.7%)
2 yr	415 (39.5%)	442 (41.4%)	438 (41.5%)
3 yr	353 (33.6%)	352 (33.0%)	352 (33.3%)
4 yr	114 (10.9%)	125 (11.7%)	125 (11.8%)
5 yr	2 (0.2%)	5 (0.5%)	8 (0.8%)

Doxorubicin exposure: More than 98% of patients treated with AC→T and AC→TH received the protocol specified 4 cycles of doxorubicin and the median duration of exposure for both arms was 84 days. For both arms, the median total doxorubicin dose was 240 mg/m^2 and the median relative dose intensity (RDI) was 100%. Dose reductions occurred in ≤ 1% of patients during a given cycle and were similar for both arms. The primary reason reported for dose reductions was the occurrence of an AE.
Cyclophosphamide exposure: More than 98% of patients treated with AC→T and AC→TH received the protocol specified 4 cycles of cyclophosphamide and the median duration of exposure for both arms was 84 days. For both arms, the median total dose of cyclophosphamide was 2400 mg/m^2 and the median RDI was 100%.

Docetaxel exposure: Approximately 90.9% and 92.5% of patients in the AC→T and AC→TH arms received the protocol specified 4 cycles of docetaxel, respectively, and in the TCH arm 95.3% of patients received the protocol specified 6 cycles. The median total dose of docetaxel was 400 mg/m^2 in the AC→T and AC→TH arms and 449.4 mg/m^2 in the TCH arm. The median duration of exposure was 84 and 83 days in the AC→T and AC→TH arms, respectively, and 126 days in the TCH arm. The median RDI was 100% for all three arms.

Platinum salts: Of the 1029 patients in the TCH arm who received carboplatin, 982 (95.4%) received the protocol specified 6 cycles. Of the 28 patients in the TCH arm who received cisplatin, 22 (78.6%) received the protocol specified 6 cycles. Of the 1054 patients in the TCH arm who received either type of platinum salt, 1006 (95.3%) received the protocol specified 6 cycles. The median total doses were 34.2 mg/mL/minute carboplatin, and 448.3 mg/m^2 for cisplatin. The median duration of exposure was 126 days for both carboplatin and cisplatin considered either separately or combined as platinum salt. The median RDI was 0.960, 1.000, and 0.964 for carboplatin only, cisplatin only and platinum salt, respectively.

Herceptin exposure: Patients were considered to have completed the protocol specified year of Herceptin therapy if the duration between first and last infusion exceeded 11 months. Of the patients in the AC→TH and TCH arms, 75.3% and 86.5%, respectively, received Herceptin therapy for more than 11 months. The median total dose of Herceptin in the AC→TH and TCH arms was 107.4 mg/kg and 109.5 mg/kg, respectively. The median RDI was 1.004 and the median duration of exposure was 378 days for patients in both the AC→TH and TCH arms. The majority of patients (90.9% and 95.4%) in the AC→TH and TCH arms completed planned Herceptin treatment administered concurrently with chemotherapy.

Adverse events

Overview

The period of observation for collection of AEs extended from the time patients started treatment with the study medication until 3 weeks after the last infusion of study medication (chemotherapy or Herceptin monotherapy). The severity of AEs was graded according to NCI CTC (v2.0) and AEs that could not be graded using these criteria were graded as mild (1), moderate (2), severe (3) or life-threatening (4). AEs were also graded as treatment related (remote, possible, probable). The key safety outcomes in the three arms are summarised in Table 31.

Table 31: BCIRG 006. Key safety outcomes at any time during the study; safety population.

Safety Outcome	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Deaths	78 (7.4%)	48 (4.5%)	55 (5.2%)
Death during chemotherapy	1 (0.1%)	0 (0.0%)	2 (0.2%)
Death during Herceptin monotherapy	0 (0.0%)	1 (0.1%)	1 (0.1%)
Death off study	77 (7.3%)	47 (4.4%)	52 (4.9%)
Grade 3/4 non-cardiac adverse event	704 (67.0%)	709 (66.4%)	670 (63.4%)
Grade 3/4 cardiac adverse event	41 (3.9%)	70 (6.6%)	76 (7.2%)
3-Year cumulative incidence of CHF following T, TH, TCH per the ICRP [a]	3 (0.3%)	20 (2.1%)	4 (0.4%)
Overall incidence of symptomatic cardiac events per the ICRP [b]	6 (0.6%)	23 (2.2%)	12 (1.1%)
Asymptomatic decline in LVEF of >15% below the LLN	43 (4.1%)	109 (10.2%)	36 (3.4%)
Grade 3/4 neutropenia	663 (63.1%)	761 (71.3%)	696 (65.9%)
Grade 3/4 leukopenia (WBCs)	540 (51.4%)	642 (60.1%)	507 (48.0%)
Grade 3/4 anemia (hemoglobin)	26 (2.5%)	34 (3.2%)	61 (5.8%)
Grade 3/4 thrombocytopenia (platelets)	10 (1.0%)	13 (1.2%)	57 (5.4%)
Grade 3/4 bilirubin toxicity	7 (0.7%)	5 (0.5%)	10 (0.9%)
Grade 3/4 alkaline phosphatase toxicity	7 (0.7%)	7 (0.7%)	6 (0.6%)
Grade 3/4 AST toxicity	2 (0.2%)	11 (1.0%)	13 (1.2%)
Grade 3/4 ALT toxicity	10 (1.0%)	21 (2.0%)	28 (2.7%)
Grade 3/4 creatinine toxicity	7 (0.7%)	6 (0.6%)	6 (0.6%)

a. CHF was confirmed by the ICRP and defined as a NCI-CTC, v2, Grade 3/4 cardiac left ventricular function (CLVF) adverse event.

b . Symptomatic cardiac events included cardiac death, Grade 3/4 CLVF, Grade 3/4 cardiac arrhythmia, Grade 3/4 cardiac ischaemia/infarction as confirmed by the ICRP.

Common adverse events

Nearly all patients in the three arms experienced at least one AE (99.9%, 100%, 99.7% in the AC→T, AC→TH, and TCH arms, respectively). AEs (any) occurring with an incidence of ≥ 5% occurring in any treatment arm were summarised the sponsor's study report. Overall, AEs occurred more commonly in the AC→TH arm than in the AC→T and TCH arms. The most commonly occurring AEs reported in ≥ 50% of patients in the AC→TH arm were: alopecia (98.6%); anaemia (97.0%); nausea (87.8%); leucocytes (87.0%); neutropenia (86.3%); fatigue (84.5%); stomatitis / pharyngitis (66.4%); vomiting (57.3%); myalgia (55.8%); ALT (54.4%); fluid retention (52.2%); diarrhoea (51.1%); and neuropathy sensory (50.9%).

Common non cardiac adverse events (overall) with a ≥ 2% higher incidence in both Herceptin containing arms compared with the AC→T arm (AC→T, AC→TH, TCH) included:

- abdominal pain or cramping (overall; 17.2%, 20.0%, 22.5%; Grade 3/4 - 0.7%, 0.8%, 0.8%);
- allergic reaction/hypersensitivity (overall; 9.3%, 12.5%, 14.8%; Grade 3/4 - 1.1%, 1.8%, 2.6%);
- diarrhoea (overall ; 43.1%, 51.5%, 62.8%; Grade 3/4 – 3.0%, 5.7%, 5.5%);
- dyspepsia/heartburn (overall; 19.2%, 24.3%, 24.1%; Grade 3/4 – 0.5%, 0.3%, 0.5%);
- epistaxis (overall; 6.1%, 13.0%, 16.1%; Grade 3/4 – 0%, 0%, 0.4%);
- rash/desquamation (overall; 28.5%, 34.1%, 32.7%; Grade 3/4 – 1.7%, 1.3%, 0.9%); and
- weight gain (overall; 19.9%, 23.5%, 24.0%; Grade 3/4 – 0.9%, 0.6%, 0.9%).

Common non cardiac adverse events with a ≥ 2% higher incidence in the AC→TH arm compared with the AC→T arm included allergic rhinitis/rhinitis, arthralgia, bone pain, dyspnoea, febrile neutropenia, infection without neutropenia, insomnia, mood alteration–depression, myalgia, pain, peripheral oedema and watery eyes.

Common non cardiac adverse events with a ≥ 2% higher incidence in the TCH arm compared with the AC→T arm included flushing and radiation dermatitis.

The most common non cardiac adverse events with a ≥ 2% higher incidence in the TCH arm compared with the AC→TH arm were: abdominal pain or cramping; allergic reaction/hypersensitivity; diarrhoea; epistaxis; irregular menses; and radiation dermatitis.

The most common non cardiac adverse events with a ≥ 2% higher incidence in the AC→TH arm compared with the TCH arm were: allergic rhinitis/rhinitis; alopecia; arthralgia; back pain; bone pain; pain; conjunctivitis; constipation; cough; dermatology/skin; dry skin; dyspnoea; peripheral oedema; fever in the absence of neutropenia; hand–foot skin reaction; hot flashes/flushes; infection (unknown absolute neutrophil count (ANC)); infection without neutropenia; myalgia; nail changes; motor neuropathy; sensory neuropathy; pharyngitis; stomatitis; watery eyes; nausea; and vomiting.

Grade 3 or 4 adverse events

Grade 3 or 4 non cardiac AEs (any) were reported in 66.1% (694/1050), 65.2% (696/1068) and 62.0% (655/1056) of patients in the AC→T, AC→TH and TCH arms, respectively. Grade 3 or 4 non cardiac AEs occurring in at least 10% of patients in any of the three treatment arms (AC→T, AC→TH, TCH) included: neutropenia (63.1%, 71.3%, 65.9%); leucopenia (51.4%, 60.1%, 48.0%); irregular menses (27.2%, 24.2%, 26.7%); infection with neutropenia (11.3%, 12.0%, 11.0%); febrile neutropenia (9.1%, 11.0%, 9.8%); and infection with unknown ANC (11.4%, 11.0%, 8.2%).

The increased incidence of AEs in the Herceptin containing arms compared with the chemotherapy only arm related primarily to the increased incidence of Grade 1 and 2 AEs. However, the incidence of Grade 3 or 4 AE diarrhoea was ≥ 2% higher in both Herceptin containing arms relative to the AC→T arm (that is, 3.0%, 5.7%, and 5.5% in the AC→T, AC→TH and TCH arms, respectively). The incidence of the following Grade 3 or 4 AEs was ≥ 2% higher in the AC→TH arm compared with the TCH arm: myalgia (5.2% versus 1.8%); infection with unknown ANC (11.0% versus 8.2%); and vomiting (6.8% versus 3.4%). The incidence Grade 3 or 4 AE irregular menses was ≥ 2% higher in the TCH arm compared with the AC→TH arm (26.7% versus 24.2%, respectively).

Deaths and other serious adverse events

Deaths

A total of 181 deaths were reported among the 3,174 treated patients. The overall incidence of death was highest in patients in the AC→T arm (7.4% [78/1050]), followed by the TCH (5.2% [55/1056]) and AC→TH (4.5% [48/1068]) arms. The majority of deaths occurred during the post treatment period and were the result of breast cancer. Deaths due to breast cancer in the post treatment period were reported 6.5% (68/1050), 4.5% (47/1050) and 4.0% (43/1068) of patients in the AC→T, TCH and AC→TH, and arms, respectively.

Other serious adverse events

Serious non cardiac AEs (NCI-CTC classification) occurring at any time in the study were reported in 19.2% (202/1050), 22.5% (240/1068) and 21.6% (228/1056) of patients in the AC→T, AC→TH and TCH treatment arms, respectively. Serious non cardiac AEs reported in ≥ 1% of patients in any of the three arms are summarised below in Table 32.

Table 32: BCIRG 006 – Non-cardiac SAES occurring in ≥ 1% of patients in any of the three arms; safety population.

NCI-CTC classification	AC→T	AC→TH	TCH
Febrile neutropenia	72 (6.9%)	90 (8.4%)	79 (7.5%)
Infection with Grade 3/4 neutropenia	47 (4.5%)	51 (4.8%)	47 (4.5%)
Infection without neutropenia	20 (1.9%)	24 (2.2%)	19 (1.8%)
Neutrophils/granulocytes	16 (1.5%)	21 (2.0%)	14 (1.3%)
Vomiting	13 (1.2%)	17 (1.6%)	17 (1.6%)
Fever	9 (0.9%)	19 (1.8%)	5 (0.5%)
Diarrhoea	2 (0.2%)	13 (1.2%)	15 (1.4%)

Discontinuations due to adverse events

Discontinuation of chemotherapy due to non cardiac AEs (NCI-CTC classification) were reported in 4.2% (44/1050), 3.6% (38/1068) and 2.1% (22/1056) of patients in the AC→T, AC→TH and TCH treatment arms, respectively. The most commonly reported AEs (≥ 0.2% in at least one of the three arms) in the AC→T, AC→TH and TCH treatment arms (respectively) resulting in discontinuation were: sensory neuropathy (0.9%, 1.1%, 0.3%); fatigue (0.7%, 0.3%, 0.1%); rash/desquamation (0.5%, 0.3%, 0.2%); allergic reaction / hypersensitivity (0.5%, 0.1%, 0.3%); infection with ≥ Grade 3 neutropenia (0.5%, 0%, 0.3%); hand-foot skin reaction (0.6%, 0.1%, 0%); myalgia (0.4%, 0.2%, 0.1%); ANC/AGC (0.4%, 0.1% 0.2%); diarrhoea in patients without colostomy (0.2%, 0.1%, 0.3%); motor neuropathy (0.1%, 0.2%, 0.1%); and oral/pharyngeal mucositis (0.3%, 0%, 0%).

Discontinuation of Herceptin due to non cardiac AEs (NCI-CTC classification) was reported in 1.1% (12/1068) and 1.2% (13/1956) of patients in the AC→TH and TCH arms, respectively. The most commonly reported AEs (≥ 0.2% in at least one of the two arms) in the AC→TH and TCH treatment arms (respectively) were dyspnoea (0.2%, 0.3%); fatigue (0.2%, 0.2%); diarrhoea in patients without colostomy (0%, 0.3%); allergic reaction/hypersensitivity (0%, 0.2%); and mood alteration – anxiety, agitation (0%, 0.2%).

Safety issues of special interest

Cardiac safety (5 year data – 11 March 2010)

The submission included cardiac safety data based on extended patient follow-up to 5 years. The safety evaluable population included all subjects who received at least one dose of study drug and analysis was according to actual treatment received. Analysis of clinically significant asymptomatic LVEF declines included patients who were evaluable for safety and who had at least one post-baseline LVEF assessment (ECHO or MUGA). The median duration of follow-up for cardiac safety for all patients was 5.5 years.

The protocol specified clinically significant symptomatic cardiac events included: cardiac death; confirmed CHF; NCI-CTC Grade 3-4 arrhythmia and NCI-CTC Grade 3-4 ischaemia/infarction. A clinically significant asymptomatic cardiac event was defined as an absolute decline in LVEF value of > 15 percentage points from baseline to a value that was below the institution's lower limit of normal (LLN). The key safety outcomes are summarised below in Table 33 and the following information relating to cardiac safety was provided in the updated analysis:

- Deaths (all cause) occurred more commonly in the AC→T arm (13.3%) compared with both the AC→TH (8.8%) and TCH (10.4%) arms. Cardiac events resulting in death were reported in 2 patients in the AC→T arm and 3 patients in the TCH arm. However, only 1 of these 5 patients was assessed by the ICRP as has having a cardiac death (1 x AC→T arm; Grade 4 CHF ~ 31 months after last dose chemotherapy with death about 3 weeks later).

Table 33: BCIRG 006 (updated analysis)/ Key safety outcomes at any time during the study; safety population.

	AC→T (n=1041)	AC→TH (n=1077)	TCH (n=1056)
Deaths	138 (13.3%)	95 (8.8%)	110 (10.4%)
Death during chemotherapy	1 (0.1%)	0	2 (0.2%)
Death during Herceptin monotherapy	0	1 (0.1%)	1 (0.1%)
Death off study	137 (13.2%)	94 (8.7%)	107 (10.1%)
Grade 3 or 4 non-cardiac adverse event	696 (66.9%)	717 (66.6%)	675 (63.9%)
Grade 3 or 4 cardiac adverse event	47 (4.5%)	75 (7.0%)	81 (7.7%)
5-year cumulative incidence of CHF following T, TH, TCH per the ICRP [a]	5 (0.56%)	20 (1.96%)	4 (0.39%)
Overall incidence of symptomatic cardiac events per the ICRP [b]	10 (1.0%)	25 (2.3%)	12 (1.1%)
Clinically significant asymptomatic cardiac events[c]	50 (4.8%)	111 (10.3%)	42 (4.0%)

a CHF was confirmed by the ICRP and defined as a NCI-CTC v2 Grade 3 or 4 CLVF adverse event.

b Symptomatic cardiac events included cardiac death, Grade 3 or 4 CLVF, Grade 3 or 4 cardiac arrhythmia, and Grade 3 or 4 cardiac ischaemia/infarction as confirmed by the ICRP.

c Clinically significant asymptomatic cardiac event was defined as a decline of > 15 percentage points in LVEF compared with baseline (with same assessment method) and to below the LLN.

- The overall incidence of cardiac AEs (any) was greater in the AC→TH (46.2%) and the TCH (43.4%) arms compared with the AC→T arm (36.3%). Cardiac AEs resulting in discontinuation of chemotherapy occurred in 0.4%, 0.2% and 0.7% of patients in the AC→T, AC→TH, and TCH arms, respectively and cardiac AEs resulting in discontinuation of Herceptin occurred in 1.5% of patients in both Herceptin plus chemotherapy arms. Cardiac AEs occurring in ≥ 1% of patients at any time during the study were summarised in the sponsor's study report.

- The most frequently occurring symptomatic cardiac event was CLVF (Grade 3–4), which corresponds to symptomatic CHF (see below in Table 34).

Table 34: BCIRG 006 (updated analysis). Symptomatic cardiac events (ICRP) occurring at any time during the study; safety population.

Event Type	AC→T (n = 1041)	AC→TH (n = 1077)	TCH (n = 1056)
CHF (Grade 3/4 CLVF)	6 (0.6%) [a]	20 (1.9%)	4 (0.4%)
Grade 3/4 cardiac ischemia/infarction	0	3 (0.3%)	2 (0.2%)
Grade 3/4 arrhythmia	6 (0.6%)	3 (0.3%)	6 (0.6%)
Cardiac death	0	0	0
Any symptomatic cardiac event [b]	10 (1.0%)	25 (2.3%)	12 (1.1%)

a Patient 33090 (assigned to the AC→T arm) was deemed by the ICRP to have had sudden cardiac death, associated with supraventricular tachycardia, and heart failure with cardiomyopathy

b A patient could be included in more than one event type category.

- The 5 year cumulative incidence of CHF in the AC→TH treatment arm (1.96%) was higher than in both the AC→T (0.56%) and TCH (0.39%) arms.
- The frequency of all Grade 3 and 4 cardiac AEs was greater in both the Herceptin plus chemotherapy arms than in the chemotherapy alone arm: 7.7%, 7.0%, and 4.5% in the TCH, AC→TH, and AC→T arms, respectively.
- The incidence of asymptomatic decline >15% in LEVF from baseline to a value below the institution's LLN was higher in the AC→TH arm (10.3% [111/1077) than in both the AC→T (4.8% [50/1041) and TCH (4.0% [42/1056]) arms.
- The incidence of absolute decline of > 10% from baseline to a value < 50% was higher in the AC→TH arm (12.7% [137/1077]) than in both the AC→T (6.8% [71/1041]) and TCH (4.7% [50/1056]) arms.
- The incidence of symptomatic and/or asymptomatic decline > 15% in LVEF was higher in the AC→TH arm (11.9% [128/1077]) than in both the AC→T (5.4% [56/1041]) and TCH (5.4% [72/1056]) arms.
- All patients were required to have LVEF measurements at baseline and at approximately 3, 4.5, 6, 9, 18, and 42 months after randomisation. There was a general decrease in the LVEF across arms from baseline to the 3 month evaluation point, which corresponded to the end of AC chemotherapy for the AC→T and AC→TH arms, and also the time point at which two thirds of TCH chemotherapy regimen had been received. The degree of decline in the LVEF was greater beginning at Month 6 and at all subsequent time points, in the AC→TH arm relative to both the AC→T and TCH arms. The means of the largest absolute decline in the LVEF from baseline were −7.6%, −9.9% and −7.3% in the AC→T, AC→TH, and TCH arms, respectively. Improvement in the LEVF started at 9 months in both the ACT→TH and TCH arms. By Month 42, the mean LVEF in the AC→TH arm was similar to that in the AC→T arm. The mean LVEF in the three treatment arms at all time points was above 60%.
- The following risk factors for cardiac AEs were analysed by treatment received (AC→T or AC→TH), age, nodal status, prior or current use of cardiovascular medications at baseline, ongoing hypertension at baseline, Karnofsky performance status, radiation (radiotherapy) to the left side of the chest, baseline LVEF value, on-study LVEF value as characterised by LVEF value at docetaxel baseline, LVEF value assessed at least 28 days prior to an event (continuous time-varying) and LVEF value < 55% at least 28 days prior to an event (continuous dichotomous).

- In univariate analyses (Cox proportional hazards models), the risk of a cardiac event was approximately 2.4-fold higher in the AC→TH arm than in the AC→T arm (HR = 2.38 [95% CI: 1.145, 4.963]; p=0.0203, Wald's test) and in the corresponding comparison the risk of a cardiac or LVEF was approximately 2.2-fold higher (HR = 2.19 [95% CI: 1.579, 3.037]; p<0.001, Wald's test). Univariate analyses identified the following patients to be at an increased risk of both symptomatic cardiac and asymptomatic LVEF events: older patients (> 50 years old versus ≤ 50 years); patients with absolute declines of > 15% in LVEF during AC chemotherapy; and patients with LVEF < 55% within 28 days before the event.
- In a multivariate analysis (Cox model of time to first cardiac event) exploring treatment effects (AC→TH and AC→T) and risk factors for the event, no significant treatment-by-covariate interaction effects were observed for the risk factors of age > 50 years and LVEF < 55% at least 28 days prior to an event. In a multivariate analysis (Cox model of time to first cardiac or LVEF event) exploring treatment effects (AC→TH and AC→T) and risk factors for the events, no significant treatment-by-covariate interaction effects were observed for the risk factors of age > 50 years, decline > 15% in LVEF during AC and LVEF < 55% at least 28 days prior to event.

Neutropenic complications and infections

Febrile neutropenia was defined as oral or tympanic temperature elevation ≥ 38.5°C in the presence of neutropenia (neutropenia defined as ANC < 1.0×10^9/L). The incidence of febrile neutropenic infection (irrespective of relationship to treatment) was higher in the AC→TH arm (13.0% [139/1068]) than in both the AC→T (12.2% [128/1050]) and the TCH (11.6% [123/1056]) arms. Similarly, febrile neutropenia (irrespective of relationship to treatment) was higher in the AC→TH arm (11% [117/1068] than in both the AC→T (9.3% [98/1050]) and the TCH (9.9% [105/1056]) arms.

Fluid retention

Fluid retention was defined as one or more of the following signs and symptoms: oedema, peripheral oedema, lung oedema, effusion (pleural effusion and ascites) or weight gain. The incidence of fluid retention was similar in the three treatment arms: 52.0% (558/1068), 50.8% (533/1050), and 51.0% (539/1056) in the AC→TH, AC→T and TCH arms, respectively. Fluid retention was defined as mild or moderate in the majority of cases and there was no notable difference among the three treatment arms in severity ratings.

Laboratory tests

Haematology

The protocol specified that blood counts were to be checked routinely every 3 weeks on Days 21 and 22 of the chemotherapy cycles. Additional blood counts were obtained during each cycle only if clinically indicated. Patients were evaluable for haematological toxicity if they had at least one blood count between Day 2 of a cycle and the next administration of chemotherapy. Haematology laboratory toxicities are summarised below in Table 35. Haematological toxicities were common in all three arms and occurred more frequently in the AC→TH arm than in the AC→T arm.

Table 35: BCIRG 006. Haematological laboratory toxicity (NCI-CTC, v2.0)

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

a Anaemia is defined as haemoglobin level < 12 g/dL.

b Neutropenia is defined as absolute neutrophil count < 1.0×10^9/L.

Chemistry

The blood chemistry assessment included AST, ALT, alkaline phosphatase, total bilirubin, creatinine and (if indicated) creatinine clearance. These parameters were assessed at baseline and then every 3 weeks throughout chemotherapy (within 3 days prior to chemotherapy). Liver function tests only were assessed 3 weeks after the last chemotherapy treatment. The results for blood chemistry toxicity are summarised below in Table 36. The incidence of creatinine toxicity, ALT and AST toxicity was higher in the AC→TH treatment arm than in the AC→T arm.

Table 36: BCIRG 006. Chemistry laboratory toxicity (NCI-CTC, v2.0)

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

Vital signs

Vital signs were not recorded.

Other safety issues

Age

Adverse events occurring at any time during the study were evaluated by age (< 65 versus ≥ 65). The majority of patients in the safety population were < 65 years old (AC→T: 93.9%; AC→TH: 94.6%; and TCH: 93.3%). There were 64 patients in the AC→T arm, 58 patients in the AC→TH arm, and 71 patients in the TCH arm aged ≥ 65 years. In general,

AEs occurred more commonly in the older age group in the three treatment arms. However, the relatively small proportion of patients who were aged ≥ 65 years limits the interpretation of the difference in safety profiles between the two age groups.

Other

There was no other safety data in special populations (such as racial groups, genetic factors, drug-drug interactions and other interactions,).

Evaluator's overall conclusions on clinical safety (BCIRC 006)

Overall, the safety profile of Herceptin in BCIRG 006 is consistent with the known safety profile of the medicine when used alone or in combination with chemotherapy. The sponsor is proposing no changes to the Adverse Effects (Clinical Trial Experience) of the PI based on the safety findings observed in BCIRG 006.

Nearly all patients in the safety population experienced at least one AE. Commonly occurring non-cardiac AEs reported more frequently (≥ 2%) in both Herceptin plus chemotherapy arms than in the chemotherapy alone arm were: diarrhoea; rash; weight gain; dyspepsia/heartburn; abdominal pain; allergic reaction/hypersensitivity; and epistaxis.

Commonly occurring non-cardiac AEs were generally reported more frequently in the AC→TH arm than in the TCH arm and events reported ≥ 2% more frequently: were allergic rhinitis/rhinitis; alopecia; arthralgia; back pain; bone pain; pain; conjunctivitis; constipation; cough; dermatology/skin; dry skin; dyspnoea; peripheral oedema; fever in the absence of neutropenia; hand–foot skin reaction; hot flashes/flushes; infection (unknown ANC); infection without neutropenia; myalgia; nail changes; motor neuropathy; sensory neuropathy; pharyngitis; stomatitis; watery eyes; nausea; and vomiting.

The overall incidence of non cardiac Grade 3 or 4 AEs was similar in the three treatment arms. However, the incidence of Grade 3 or 4 AE diarrhoea was increased by ≥ 2% in both the AC→TC and TCH arms relative to the AC→T arm (5.7%, 5.5% and 3.0%, respectively). The incidence of the following Grade 3 or 4 AEs was ≥ 2% in the AC→TH arm compared with the TCH arm: myalgia (5.2% versus 1.8%); infection with unknown ANC (11.0% versus 8.2%); and vomiting (6.8% versus 3.4%). The incidence of Grade 3 or 4 AE irregular menses was ≥ 2% in the THC arm compared with the AC→TH arm (26.7% versus 24.2%, respectively).

The incidence of death (all cause) was highest in patients in the AC→T arm (7.4% [n=78]), followed by the TCH (5.2% [n=55]) and AC→TH (4.5% [n=48]) arms. The majority of deaths occurred during the post treatment period and were the result of breast cancer. Three septic deaths were reported: 1 patient (AC→T arm) experienced bronchopneumonia after five cycles of chemotherapy; 1 patient (TCH arm) experienced renal failure secondary to dehydration, hypoglycaemic coma, sepsis, leukopenia and thrombocytopenia after two cycles of chemotherapy; and 1 patient (TCH arm) experienced bronchopneumonia after two cycles of chemotherapy. The updated cardiac disease data showed that only 1 of the 5 deaths was considered by the ICRP to be related to a cardiac AE (AC→T arm) and this death occurred post treatment. There were no cardiac deaths during treatment in any of the three treatment arms.

Non cardiac SAEs occurring at any time in the study were reported in patients with similar frequencies in the three treatment arms (19.2%, 22.5% and 21.6% in the AC→T, AC→TH, and TCH, respectively). The most commonly reported non cardiac SAE was febrile neutropenia and this event was reported more frequently in the AC→TH arm (8.4%) than in both the AC→T (6.9%) and the TCH (7.5%) arms. Discontinuation due to non cardiac

AEs occurred more frequently in the AC→T arm (4.2%) than in the AC→TH (3.6%) and the TCH (2.1%) arms.

The overall incidence of cardiac AEs (any) was greater in the AC→TH (46.2%) and TCH arms (43.4%) than in the AC→T arm (36.3%). Cardiac AEs resulting in discontinuation of chemotherapy occurred in 0.4%, 0.2% and 0.7% of patients in the AC→T, AC→TH and TCH treatment arms, respectively, and cardiac AEs resulting in discontinuation of Herceptin occurred in 1.5% of patients in both the Herceptin plus chemotherapy treatment arms.

The most frequently occurring symptomatic cardiac AE was CLVF (Grade 3–4), which corresponds to symptomatic CHF, and was reported more commonly in the in AC→TH arm (1.9%), than in the AC→T (0.6%) and TCH arms (0.4%). The frequency of all Grade 3 and 4 cardiac AEs was higher in both the TCH (7.7%) and the AC→TH (7.0%) arms than in the AC→T arm (4.5%). Key risk factors for development of a symptomatic cardiac event were identified as treatment with AC→TH, decrease in on-study LVEF and increased age (> 50 years).

The incidence of symptomatic and/or asymptomatic decline > 15% in LVEF was higher in the AC→TH arm (11.9%) than in both the AC→T (5.4%) and TCH (5.4%) arms. The incidence of absolute decline of > 10% from baseline and to a value < 50% was higher in the AC→TH (12.7%) arms than in both the AC→T (6.8%) and TCH (4.7%) arms.

Grade 3 or 4 AEs of anaemia and thrombocytopenia were ≥ 2% higher in the TCH arm relative to the AC→T and AC→TH arms (anaemia 5.8%, 2.5% and 3.2%; and thrombocytopenia 5.4%, 1.0% and 1.2%, respectively). Grade 3 or 4 neutropenia was ≥ 5% higher in the AC→TH arm relative to the AC→T and TCH arms (71.3%, 63.1% and 65.9%, respectively). There were no marked differences among the three treatment arms in Grade 3 or 4 AEs for creatinine, ALT, AST or bilirubin. However, creatine toxicity (all grades) was ≥ 2% higher in the TCH arm (9.7%) relative to both the AC→TH (6.8%) and AC→T (3.7%) arms. In addition, ALT toxicity (all grades) was ≥ 2% higher in both the AC→TH (54.4%) and TCH (53.2%) arms relative to the AC→T arm (48.4%).

Post marketing experience

Overview

The sponsor's Summary of Clinical Safety for Dossiers 1 and 2 included brief reviews of post marketing surveillance data accumulated for trastuzumab since initial marketing approval in the US on 25 September 1998. Cumulatively to 31 January 2010, 15,920 AEs meeting the criteria for inclusion in the Periodic Safety Update Reports (PSURs) have been reported to the sponsor. Of these events, 56% (n=8941) were considered to be serious adverse events and 44% (n=6979) were considered to be non serious adverse events.

The most frequently reported AEs [% of all AEs] were categorised under the following SOCs: General disorders and administration site conditions [18%]; Investigations [10%]; Cardiac disorders [10%]; and Respiratory, thoracic and mediastinal disorders [9.6%]. The most frequently reported AEs [% in the SOC] within the four SOC's were:

General disorders and administration site conditions: pyrexia [25%]; chills [16%]; and infusion-related reactions [8%]. Overall, there were 1081 SAEs and 1706 non-serious AEs.

Cardiac disorders: cardiac failure [19%]; cardiac failure congestive [13%]; and cardiomyopathy [6%].Overall, there were 1446 SAEs and 184 non-serious AEs.

Investigations: ejection fraction decreased [41%]. Overall, there were 907 SAEs and 747 non-serious AEs.

Respiratory, thoracic and mediastinal disorders: dyspnoea [29%]; pleural effusion [8.0%]; and interstitial lung disease [7%].Overall, there were 1142 SAEs and 387 non-serious AEs.

Drug Safety Report Number 104070. Pregnancy (post marketing)

This post marketing safety study was submitted to support the addition of text to the *Use in Pregnancy – Category B2* section of the PI.

The sponsor undertook a comprehensive search of the global safety database to 16 May 2010 using relevant search criteria aimed at identifying pregnant women who had been exposed to Herceptin and in whom foetal adverse events had been reported. The search returned 98 adverse events reported in 56 case reports. The sponsor reviewed all case reports for any evidence of oligohydramnios and renal hypoplasia. The resulting analysis identified 4 case reports in which oligohydramnios and evidence of renal hypoplasia were observed. These 4 cases all originated from the published literature and 2 of the cases were twins. In addition, 12 case reports of oligohydramnios without reported renal growth and/or functional impairment were identified, which the sponsor states "shows that there is not a definitive cause and effect relationship between foetal kidney function impairment and oligohydramnios". In addition, the sponsor states that the "case reports of renal growth and/or function impairment with oligohydramnios were confounded by other factors". The sponsor also commented on reports associated with the use of trastuzumab in which oligohydramnios was noted in associations with subsequent effects of low-set ears, pulmonary hypoplasia, renal function impairment and growth retardation. There was 1 report of renal disorder (born without one kidney) without oligohydramnios. The sponsor concluded that it is possible that trastuzumab may have an effect on foetal renal growth and/or function and that this may be a causative factor in the development of oligohydramnios. However, the sponsor qualified this conclusion by stating that "there are multiple cases of oligohydramnios without reported renal growth and/or functional impairment".

> *Comment*: Review of the tabulated summary of foetal and neonatal AEs and provided narratives of cases of oligohydramnios and renal abnormalities supports the addition of the proposed statement to the PI.

List of questions

After the initial clinical evaluation, a List of Questions to the sponsor is generated by the evaluator.

Additional expert input

Dossier 3 included an *in vitro* method validation study relating to HER2+ testing in gastric cancer tumours: Study D008548 "Method comparison study of CONFIRM anti-HER-2/neu (4B5) Primary Antibody and INFORM HER2 DNA Probe versus HercepTest and HER2 FISH PharmDx on human gastric cancer". This method validation study was submitted to support the addition of text to the *Dosage and Administration*, *Detection of HER2 Protein Overexpression or HER2 Gene Amplification* section of the PI. It is considered that this study should be reviewed by the TGA section responsible for the evaluation of *in vitro* diagnostic tests.

Clinical questions

Sponsor's covering letter

1. In the sponsor's covering letter of 8 August 2011, it is stated that "in the Australian clinical setting ~30% of patients with operable disease are being treated with neoadjuvant chemotherapy". What is the source for this claim?

Efficacy

2. Dossier 1: In the pivotal study [NOAH], it is stated that disease response was assessed, when applicable, at the Michelangelo Operations Office using RECIST (Response Evaluation Criteria in Solid Tumours) criteria. How many patients had disease response assessed centrally at the Michelangelo Operations Office rather than locally and what were the reasons for central assessment?

3. Dossier 1: In NOAH, the risk of experiencing an EFS event (disease progression, recurrence or death) was 35% lower (statistically significant) in the HER2+TC arm relative to the HER2+C arm; unadjusted HR = 0.65 [95% CI: 0.44, 0.96]; p=0.0275 log-rank. The study was powered on a difference of 18.5% in the 36 month EFS rates between the two HER2-positive treatment arms (50% in the HER2+C arm and 68.5% in the HER2+TC arm). It is stated in the CSR that "a clinically meaningful improvement with the addition of trastuzumab would be to increase the median EFS time to 5.5 years, corresponding to 68.5% EFS rate at 3 years. This corresponds to a hazard ratio of 0.545" (CSR). The observed difference in the 36 month EFS rates between the two HER2-positive treatment arms was 13% (52% in the HER2+C arm and 65% in the HER2+TC arm) and the HR was 0.65. Consequently, based on the assumptions used to power the study, it is considered that the observed difference between the two HER-positive treatment arms in EFS is not clinically significant (absolute difference in EFS rates at 3 years = 13% and EFS rate at 3 years 65% in the HER2+TC arm). What are the sponsor's reasons supporting the claim made in the submission that the improvement in EFS observed in the HER2+TC arm compared with the HER2+C arm is clinically significant?

4. In the pivotal study [NOAH], although the difference between the two treatment arms in the pCR (secondary efficacy endpoint) was statistically significant for both the bpCR and the tpCR, the absolute difference between the two treatment arms for these outcomes are considered to be of borderline clinical significance. While the study did not specify a clinically meaningful absolute difference between the two treatments for the bpCR and the tpCR, data from the MDACC study suggest that a 2 fold increase in the pCR (breast + axilla) in the HER2+TC arm compared with the HER2+C arm is likely to be clinically meaningful (based on respective pCR rates of 21% and 41%). Consequently, based on the MDACC assumptions it is considered that the absolute difference observed in NOAH between the two treatment arms in the bpCR of 17.6% [95% CI: 5.0, 30.2], (1.66-fold increase) and in the tpCR of 19.3% [95% CI: 7.2, 31.4] (1.93-fold increase) are of borderline clinical significance. Does the sponsor consider that the differences between the two HER2+ treatment arms in bpCR and tpCR in the pivotal study [NOAH] to be clinically significant? If so, on what grounds are the differences considered to be clinically significant?

5. In the pivotal study [NOAH], the Russian site was identified as an unusual site due to the fact that most of the patients did not undergo surgery and nearly all patients were complete responders. Furthermore, in both the HER2+ treatment arms a relatively large proportion of patients came from this one Russian site (CRTN 47296): 26% (26/115) of patients to the HER2+TC arm and 22.4% (26/116) of patients to the HER2+C arm. Was the Russian site monitored during the study and were any problems

identified? It is noted that re-monitoring by Roche resulted in a change in initial disease stage category in 44 patients from this site. Is the sponsor satisfied that the inclusion of data from this site in the primary EFS analysis in the FAS population has not biased the results of this study?

6. Dossier 1: In the pivotal study [NOAH], the exploratory logistic regression analysis for the overall clinical response rate adjusted for geographical region (Russia versus Germany/Austria) showed that the odds ratio (OR) for the overall clinical response was 5.24 ([95% CI: 1.77, 15.57]; p=0.0001, Wald's test), indicating that the chance of a Russian patient experiencing a clinical response was approximately 5 fold higher than a German/Austrian patient. The sponsor states that at the Russian site almost all patients were classified as complete responders. Have any reasons been identified for this unusual finding?
7. Dossier 1: In the pivotal study [NOAH], all HER2+TC patients received neoadjuvant and adjuvant trastuzumab. Consequently, it is not possible to separate the effects on EFS (primary efficacy endpoint) of neoadjuvant trastuzumab from those of adjuvant trastuzumab. Therefore, the statistically significant effect on EFS observed in the HER2+TC arm compared with the HER2+C arm might be due to neoadjuvant trastuzumab, adjuvant trastuzumab or the combination of neoadjuvant and adjuvant trastuzumab. While the analysis comparing the HER2+TC arm with the HER2+C→T [adjuvant] group showed that the risk of experiencing an EFS event was statistically significantly lower in the neoadjuvant/adjuvant trastuzumab arm than in the adjuvant trastuzumab arm, the number of patients who crossed-over from the HER2+C arm to adjuvant trastuzumab (n=19) is considered too small for the results to be meaningfully interpreted. Please justify why the pivotal study is considered to support neoadjuvant trastuzumab treatment over adjuvant trastuzumab treatment given the inability of the study design to isolate the two treatments.
8. Dossier 2: In BCIRG 006, all the efficacy analyses in the submitted CSR were based on data from the second planned interim analysis undertaken when 474 DFS events had occurred (median follow-up of 36 months), representing 52.7% of the 900 planned events. Consequently, the data on which the analysis was undertaken are immature. When will the efficacy results from the "main analysis" of the 900 planned events be submitted to the TGA for evaluation?

Several questions were also posed regarding the Risk Management Plan and PI but these are beyond the scope of this AusPAR.

Clinical summary and conclusions

First round benefit-risk assessment

Benefits

Extension of indication (Dossier 1)

The submission is considered to provide inadequate evidence supporting an additional clinically meaningful benefit for neoadjuvant trastuzumab plus chemotherapy above that observed with neoadjuvant chemotherapy alone in women with localised HER2-positive breast cancer. It is possible that the finalised reports of 4 recently completed relatively large Phase II/III studies in which neoadjuvant trastuzumab was administered in combination with chemotherapy and/or biological therapy might clarify the role of neoadjuvant trastuzumab in women with locally advanced breast cancer with HER2-positive tumours [NeoSphere, NeoALLTO GeparQuinto and Techno].

Inclusion of efficacy data from BCIRG 006 in the PI (Dossier 2)

The data from BCIRG 006 are considered to support the addition of the DFS and OS results from this study to the *Clinical Trials* section of the PI.

Risks

Extension of Indication Dossier 1

The pivotal study [NOAH] showed that trastuzumab in combination with chemotherapy as neoadjuvant treatment was generally well tolerated in women with localised breast cancer with HER2+ disease. The data from the pivotal study suggests that the overall safety profile of neoadjuvant trastuzumab plus chemotherapy is generally similar to that of neoadjuvant chemotherapy alone. However, the pivotal study shows that there is a notably increased risk of clinically significant reductions in LVEF with trastuzumab plus chemotherapy compared with chemotherapy alone. The safety data from the two supportive studies [MDACC, GeparQuattro] were consistent with the safety data from the pivotal study. Overall, the safety data in the submission are consistent with the known safety profile of trastuzumab alone and in combination with chemotherapy.

The major concern safety concern with trastuzumab relates to cardiac toxicity. It is known that moderate to severe heart failure can occur in patients treated with trastuzumab alone or in combination with chemotherapy and has been associated with death. Patients were excluded from the pivotal study if they had NYHA Class II heart disease, LVEF < 50%, a history of documented congestive cardiac failure, angina pectoris requiring anti-anginal medication, evidence of transmural infarction on ECG, poorly controlled hypertension (systolic > 180 mm Hg or diastolic > 100 mmHg), clinically significant valvular heart disease or high-risk uncontrolled arrhythmias.

In NOAH:

- Potential cardiac events were of particular concern as neoadjuvant treatment included trastuzumab in combination with doxorubicin (a known cardiotoxic agent). However, the incidence of cardiac AEs did not markedly differ between the HER2+TC arm and the HER2+C arm (13.9% [16/115] and 13.4% [15/112], respectively), with ejection fraction decrease AEs being reported in 2 (1.7%) patients in the HER2+TC arm and no patients in the HER2+C arm. In the HER2+TC arm, there was 1 reported death due to fatal myocardial infarction occurring 34 months after a diagnosis of Grade 1 restrictive cardiomyopathy and 43 months after the last dose of trastuzumab.
- Patients with LVEF < 50% (assessed by MUGA or ECHO) were excluded from the study. LVEF assessment was undertaken at baseline, in the pre operative period prior to the first cycle of paclitaxel alone, prior to the first cycle of CMF and before surgery. In the pre operative period, decreases in LVEF ≥ 10 percentage points from baseline occurred notably more frequently in patients in the HER2+TC arm (17.7% [20/113]) than in patients in the HER2+C arm (12.8%, [14/112]. In addition, decreases of ≥ 10 percentage points from baseline in LVEF together with a LVEF of < 50% occurred more frequently in patients in the HER2+TC arm (3.5% [n=4]) compared with patients in the HER2+C arm (0.9% [n=1), but the number of patients experiencing this event was small in both treatment arms. In clinical practice, LVEF reductions of ≥ 10 percentage points from baseline (and to below 50% in patients with a normal baseline measurement) with trastuzumab indicates that the medicine should be withheld and LVEF repeated within approximately 3 weeks with further treatment being determined by the response to withholding treatment (see Herceptin PI).
- In pre operative period, nearly all patients in the HER2+TC and HER2+C arms experienced at least one AE (98.3% [113/115] and 100% [112/112]. AEs (preferred

term) occurring with an incidence of at least 5% in either HER2+ treatment arm and at least 2% more frequently in the HER2+TC arm than in the HER2+C arm were (HER2+TC versus HER2+C): conjunctivitis (29.6% versus 19.6%); myalgia (27.8% versus 22.3%); pyrexia (20.0% versus 11.6%); rhinorrhoea (18.3% versus 8.0%); abdominal pain upper (16.5% versus 6.3%); epistaxis (13.9% versus 1.8%); hot flush (13.0% versus 5.4%); lacrimation increased (13.0% versus 4.5%); cough (10.4% versus 2.7%)dyspepsia (7.8% versus 2.7%); pharyngitis (6.1% versus 0.9%); and rhinitis (6.1 % versus 0.9%)

- In pre operative period, Grade 3 AEs occurred in 37.4% (43/115) of patients in the HER2+TC arm and 39.3% (44/112) of patients in the HER2+C arm. Grade 4 AEs occurred infrequently and were reported in 2 patients (1.7%) in the HER2+TC arm and 6 patients (5.4%) in the HER2+C arm. The most frequently occurring Grade 3 or 4 events occurring in ≥ 5% of patients in at least one of the HER2+ arms (HER2+TC versus HER2+C) were: alopecia totalis (12.2% versus 9.8%); neutropenia (6.1% versus 2.7%); amenorrhoea (6.1% versus 2.2%); and stomatitis (1.7% versus 5.4%).
- In pre operative period, SAEs were reported more frequently in the HER2+TC arm (10.4% [12/115]) than in the HER2+C arm (7.1% [8/112]). The most commonly reported SAEs were "blood and lymphatic system disorders" (8 [7.0%] patients in the HER2+TC arm, 5 [4.5%] patients in the HER2+C arm), consisting of febrile neutropenia, neutropenia or pancytopenia. Febrile neutropenia was reported more commonly in the HER2+C arm (6.1% [7/119]) than in the HER2+C arm (2.7% [5/112]). In addition, 3 (2.6%) patients in the HER2+TC arm experienced SAEs of pyrexia (compared with none in the HER2+C arm). There was 1 SAE Grade 3 decrease in LVEF in 1 patient in the HER2+TC arm reported after the database lock.
- At the time of clinical data cut-off, 76 patients had died and the main cause of death in the three treatment arms was disease progression (72 [94.7%]): 20 (17.2%) in the HER2+TC arm; 33 (28.0%) in the HER2+C arm; and 19 (19.2%) in the HER2–C arm. Of the 4 patients who died due to reasons other than disease progression, 2 were from the HER2+TC arm (1 "unknown cause", 1 fatal myocardial infarction 34 months after being diagnosed with Grade 1 restrictive cardiomyopathy and 43 months after the last dose of trastuzumab) and 2 were from the HER2–C arm (1 "unknown cause"; 1 Grade 4 SAE thromboembolism of the lung arteria [surgical complication]).
- In pre operative period, 1 patient in the HER2+TC arm discontinued treatment due to an AE (Grade 3 SAE treatment-related decreased LVEF) compared with no patients in the HER2+C arm. Dose interruptions were reported with similar frequencies in the HER2+TC and HER2+C arms (7.8% and 6.3%, respectively) and AEs resulting in dose modifications of at least one component of the treatment regime were reported more commonly in the HER2+TC arm than in the HER2+C arm (13.0% and 9.8%, respectively).
- In the pre operative period, haematology laboratory values shifting to Grade 3 or 4 AEs were similar in both the HER2+TC and HER2+C arms and there were few shifts to Grade 3 or 4 AEs in biochemical laboratory tests in both HER2-positive arms.

Inclusion of efficacy data from BCIRG 006 in the PI (Dossier 2)

It was considered that no new risks associated with adjuvant treatment with trastuzumab in combination with docetaxel, doxorubicin, cyclophosphamide, or carboplatin have been identified in BCIRG 006.

Benefit-risk balance

Extension of indication (Dossier 1)

It was considered that the data from the pivotal study [NOAH] show that the benefit-risk balance of neoadjuvant trastuzumab plus chemotherapy for the treatment of women with localised HER2-positive breast cancer is unfavourable. Neoadjuvant trastuzumab plus chemotherapy is considered not to provide an additional meaningful clinical benefit above that observed for neoadjuvant chemotherapy alone. Furthermore, while the risks of neoadjuvant trastuzumab plus chemotherapy were generally similar to those of neoadjuvant chemotherapy alone there was an increased risk of clinically significant reductions in LVEF with neoadjuvant trastuzumab plus chemotherapy.

Inclusion of efficacy data from BCIRG 006 in the PI (Dossier 2)

It was considered that the benefit-risk balance of the adjuvant trastuzumab combined with chemotherapy regimens used in BCIRG 006 for the treatment of women with localised HER2-positive breast cancer was favourable.

First Round Recommendation Regarding Authorisation

Extension of indication (Dossier 1)

It is recommended that the submission to extend the indications of trastuzumab to include the treatment of patients with HER2-positive localised breast cancer in association with neoadjuvant chemotherapy should be **rejected** on the grounds of inadequate demonstration of clinically meaningful increased efficacy compared with neoadjuvant chemotherapy alone. The reasons for this recommendation are that in NOAH:

- The risk of experiencing an EFS event (disease progression, recurrence or death) was 35% lower (statistically significant) in the HER2+TC arm relative to the HER2+C arm; unadjusted HR = 0.65 [95% CI: 0.44, 0.96]; p=0.0275 log-rank. EFS in the FAS population was the primary efficacy endpoint and the study was powered on a difference of 18.5% in the 36 month EFS rates between the two HER2-positive treatment arms (50% in the HER2+C arm and 68.5% in the HER2+TC arm). It is stated in the CSR that "a clinically meaningful improvement with the addition of trastuzumab would be to increase the median EFS time to 5.5 years, corresponding to 68.5% EFS rate at 3 years. This corresponds to a hazard ratio of 0.545" (CSR). The observed difference in the 36 month EFS rates between the two HER2-positive treatment arms was 13% (52% in the HER2+C arm and 65% in the HER2+TC arm) and the HR was 0.65. Consequently, based on the assumptions used to power the study it is considered that the observed difference between the two HER-positive treatment arms in EFS is not clinically significant (absolute difference in EFS rates at 3 years = 13%, and EFS rate at 3 years 65% in the HER2+TC arm).
- There was a statistically significant difference between the two treatment arms in the pCR rate (secondary efficacy endpoint) for both the bpCR (44.3% HER2+TC versus 26.7% HER2+C; p=0.0051, Chi square test) and the tpCR (40.0% versus 20.7%; p=0.0014). While the study did not specify a clinically meaningful absolute difference between the two treatments for bpCR and tpCR rates, data from the MDACC study suggests that a 2 fold increase in tpCR in the HER2+TC arm compared with the HER2+C arm is likely to be clinically significant (based on respective tpCR rates of 21% and 41%). Consequently, based on this assumption it is considered that the observed results in the tpCR and bpCR rates between the two HER2-positive treatment arms in favour of the HER2-TC arm are of borderline clinical significance (bpCR absolute difference = 17.6% [1.66 fold increase]; tpCR absolute difference = 19.3% [1.93 fold increase]).

- Neither the overall clinical response rate nor the overall survival rate (both secondary efficacy endpoints) showed statistically significance for the comparison between the HER2+TC and HER2+C arms.
- All HER2+TC patients received neoadjuvant and adjuvant trastuzumab. Consequently, it is not possible to separate the effects on EFS of neoadjuvant trastuzumab from those of adjuvant trastuzumab. Consequently, the statistically significant effect on EFS observed in the HER2+TC arm compared with the HER2+C arm might be due to neoadjuvant trastuzumab, adjuvant trastuzumab or the combination of neoadjuvant and adjuvant trastuzumab. While an exploratory EFS analysis showed that the risk of experiencing an EFS event was lower in the HER2+TC arm compared with HER2+C→T arm, the number of patients in the HER2+C→T arm (n=19) is considered too small for the results to be meaningfully interpreted.

In addition, in the supportive study [MDACC]:

The pCR rate (primary efficacy endpoint) was statistically significantly higher in the HER2+TC arm (65.2% [n=23]) compared with the HER2+C arm (26.3% [n=19]); p=0.016. Furthermore, the absolute difference between the two treatments was 38.9%, which was higher than the approximately 2 fold increase (21% HER2+C and 41% HER2+TC) on which the study was powered suggesting that the observed result is clinically meaningful. However, the neoadjuvant trastuzumab dosing regimen used in this study was different from that used in NOAH and is different from that being proposed for registration. In addition, the neoadjuvant chemotherapy regimen differed between the supportive study [MDACC] and the pivotal study [NOAH]. Furthermore, the patient numbers in MDACC randomised to treatment were relatively small (n=19 [HER2+C] and n=23 [HER2+TC]). Overall, it is considered that the MDACC data alone cannot support the submission.

Further, the supportive GeparQuattro study:

- Was not designed to compare neoadjuvant trastuzumab plus chemotherapy with neoadjuvant chemotherapy alone in patients with HER2-positive tumours. Consequently, the descriptive results of this study showing an efficacy benefit in women with HER2-positive disease treated with neoadjuvant trastuzumab plus chemotherapy compared with women with HER2-negative disease treated with neoadjuvant chemotherapy alone is considered to be of limited relevance to the submission.

Inclusion of efficacy data from BCIRG 006 in the PI (Dossier 2)

It is recommended that the proposed update of the *Clinical Trials* section of the PI relating to data from BCIRG 006 be accepted.

PI amendments (Dossier 3)

It was recommended that the PI amendments based on the studies submitted in Dossier 3 be accepted subject to the comments above and the sponsor's response to questions relating to the amendments raised above.

Second round clinical evaluation

Contents of the sponsor's subsequent data submission

The submitted data package consists of the sponsor's "*Response to Section 31 Request for Information (Milestone 3) Herceptin (trastuzumab)",* dated 27 February 2012.

The subsequent clinical data package included:

- Population-PK report 1018264;

- Rüschoff J, et.al. HER2 testing in gastric cancer: a practical approach. Mod Pathol. 2012 Jan 6. [Epub ahead of print];
- Toutain, P. L., Bousquet-Me´lou, A. Plasma terminal half-life. J. Vet. Pharmacol. Therap. (2004) 27: 427–439.

The sponsor's 27 February 2012 data package addressed the questions raised by the Therapeutic Goods Administration (TGA) in its letter to the sponsor of 31 January 2012, and included responses to the questions raised by the clinical evaluator following the first round clinical evaluation. The responses to the clinical questions are considered to be complete and fully address the first round clinical questions. The second round clinical evaluation report provides comment on the sponsor's response to the TGA questions (Section 3), the second round benefit-risk assessment (Section 4), the second round recommendation regarding authorisation (Section 5) and the second round comments on the product documentation (not included here as beyond the scope of this AusPAR). The first and second round clinical evaluation reports are complementary and should be considered together.

First round clinical questions, sponsor's response and second round clinical comments on the response

Question 1 (sponsor's covering letter)

In the sponsor's covering letter of 8 August 2011, it is stated that, "in the Australian clinical setting ~30% of patients with operable disease are being treated with neoadjuvant chemotherapy". What is the source for this claim?

Sponsor's response

The estimated utilisation of neoadjuvant chemotherapy for operable EBC was informed by expert opinion from Australian medical oncologists experienced in the treatment of patients with breast cancer. Following further recent consultation with six medical oncologists (in support of Pharmaceutical Benefits Advisory Committee (PBAC) submission this month), it is estimated that utilisation ranges between 0 to 40%. Utilisation of neoadjuvant chemotherapy varies greatly between centres and is dependent on local practices and the extent of interdisciplinary collaboration.

Clinical evaluator's comment (second round)

The sponsor's response is satisfactory. It illustrates the variability of Australian clinical practice as regards utilization of neoadjuvant chemotherapy for operable breast cancer.

Question 2 (Efficacy)

In the pivotal study [NOAH], it is stated that disease response was assessed, when applicable, at the Michelangelo Operations Office using RECIST (Response Evaluation Criteria in Solid Tumours) criteria. How many patients had disease response assessed centrally at the Michelangelo Operations Office rather than locally and what were the reasons for central assessment?

Sponsor's response

The key features of the sponsor's response were that in the NOAH study, clinical tumour response was assessed locally by the study investigator and there was no central assessment of clinical tumour response, neither by Michelangelo nor by Roche.

Clinical evaluator's comment (second round)

The sponsor's response clarifies the position. No central assessment of tumour response based on modified RECIST criteria was undertaken in NOAH. Investigator response of

clinical tumour response based on modified RECIST criteria in NOAH raises the potential for observer bias. Independent assessment of tumour response based on RECIST criteria is considered to be more persuasive than investigator assessment, particular in open-label studies such as NOAH.

Question 3 (Efficacy)

In NOAH, the risk of experiencing an EFS event (disease progression, recurrence or death) was 35% lower (statistically significant) in the HER2+TC arm relative to the HER2+C arm; unadjusted HR = 0.65 [95% CI: 0.44, 0.96]; p=0.0275 log-rank. The study was powered on a difference of 18.5% in the 36 month EFS rates between the two HER2-positive treatment arms (that is, 50% in the HER2+C arm and 68.5% in the HER2+TC arm). It is stated in the CSR that "a clinically meaningful improvement with the addition of trastuzumab would be to increase the median EFS time to 5.5 years, corresponding to 68.5% EFS rate at 3 years. This corresponds to a hazard ratio of 0.565" (CSR). The observed difference in the 36 month EFS rates between the two HER2-positive treatment arms was 13% (52% in the HER2+C arm and 65% in the HER2+TC arm) and the HR was 0.65. Consequently, based on the assumptions used to power the study, it is considered that the observed difference between the two HER-positive treatment arms in EFS is not clinically significant (absolute difference in EFS rates at 3 years = 13%, and EFS rate at 3 years 65% in the HER2+TC arm). What are the sponsor's reasons supporting the claim made in the submission that the improvement in EFS observed in the HER2+TC arm compared with the HER2+C arm is clinically significant?

Sponsor's response

Study design assumptions

The power considerations outlined in the CSR imply that the sample size considerations were based on assumed EFS rates at 3 years, namely 0.685 for HER2+TC and 0.5 HER+C. This would translate into median EFS times of 5.5 years for HER2+TC and 3 years for HER2+C assuming that EFS times are exponentially distributed as this is the model underlying the sample size computations. Table 37 summarises the observed rates at 3 years. The observed EFS rates at 3 years were 0.65 (95%CI: 0.56, 0.74) for HER2+TC and 0.53 (95%CI: 0.43, 0.62) for HER2+C in line with the rates used for determining the sample size. The Kaplan Meier Curve for EFS in the CSR implies that there are 66 and 52 patients at risk at 3 years, corresponding to about 50% of the initial study population. Hence the point estimates for EFS from this Kaplan Meier analysis for the 3 year EFS rate are subject to sampling variability (expressed by the corresponding confidence intervals). A 95% confidence interval using the Hauck-Anderson approach for the difference between the observed EFS rates is (-0.05, 0.30) as displayed in Table 37 [see below], thus in line with the initially assumed 3-years EFS rate of 0.185.

For the 1 and 2 years EFS rates, where more patients were at risk (1 year: 101 HER2+TC and 89 HER2+C; 2-years: 81 HER2+TC and 66 HER2+C), the comparisons between the EFS rates derived from the initially assumed median EFS rates of 5.5 years and 3 years in the HER2+TC and HER2+C arms respectively and the observed rates are also summarised in Table 37. The assumed rates (and the resulting rate difference) were well in line with the observed rates (and the resulting observed rate difference).

Table 37: Assumed rates and observed rates for 1-year, 2-years and 3-years EFS.

	HER2+TC rate[1]	HER2+C rate[1]	Rate difference[1]	Observed HER2+TC rate[2] (95%CI)	Observed HER2+C rate[2] (95%CI)	Observed rate difference (95% CI[3])
1 year EFS rates	0.882	0.794	0.088	0.89 (0.84,0.95)	0.82 (0.74,0.89)	0.07 (-0.03,0.17)
2 years EFS rates	0.777	0.630	0.147	0.73 (0.64,0.81)	0.61 (0.51,0.70)	0.12 (-0.03,0.27)
3 years EFS rates	0.685	0.500	0.185	0.65 (0.56,0.74)	0.52 (0.43,0.62)	0.13 (-0.05,0.30)

[1] Rates derived from the model assumed for the initial sample size considerations (exponential model with EFS rates of 0.685 and 0.5 for HER2+TC and HER2+C arms respectively which results in median EFS times of 5.5 years and 3 years for the two arms)

[2] CSR Table 22, page 98

[3] Computed based on the Hauck-Anderson approach for the difference between rates

Given that the observed data are in line with the assumptions made for detecting a clinically meaningful improvement in EFS and given that the study was able to show a statistically significant EFS benefit with respect to the HER2+TC arm, the study has shown a clinically significant benefit in terms of EFS when adding trastuzumab. For the primary endpoint EFS, the corresponding Kaplan-Meier curves show wide and sustained separation between the HER2-positive arms (Kaplan Meier plot in CSR).

Comparison of treatment benefit to other studies

The primary efficacy variable of the NOAH study is event-free survival (EFS), which was defined as the time between randomisation and date of documented disease recurrence [local, regional, distant or contralateral] or progression or death due to any cause. EFS is therefore very similar to disease-free-survival (DFS) which is the standard endpoint for trials of adjuvant therapy, the only difference being that EFS also includes events that occur in the neoadjuvant treatment period. DFS is a well accepted and widely used primary endpoint in adjuvant breast cancer trials.[36, 37]

In the trials that have led to the approval of trastuzumab in early breast cancer, the improvement of the DFS rate in the trastuzumab arm was in the range of 5.8 % (HERA study) to 11.3% (Joint Analysis), see Table 38 [below]. The observed difference in the 36 month EFS rates between the two HER2-positive treatment arms in the NOAH study was 13%, which is better than the best treatment effect seen in the adjuvant studies and therefore confirms the clinical significance of the improvement in EFS with trastuzumab in the NOAH study.

Table 38: DFS improvement in trastuzumab adjuvant trials.

		Trastuzumab arm	Control arm	Improvement in DFS rate
Joint Analysis (NCCTG N9831, NSABP B-31) [3]	4 y DFS rate	85.7 %	73.7 %	11.3 %
BCIRG-006 [4]	5 y DFS rate	84 %	75 %	9 %
HERA [5]	4 y DFS rate	78.6 %	72.2 %	5.8 %

Supportive evidence was provided by the total pathological response (tpCR) rate which was statistically significantly higher when adding trastuzumab to neoadjuvant

[36] Guidelines on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr)

[37] US FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

chemotherapy (tpCR rate: 40.0% HER2+TC, 20.7% HER2+C; rate difference 19.3% (95%CI: 7.2%, 31.4%), p-value chi-square test: 0.0014 (CSR). Achieving a tpCR has been shown to be associated with improved long-term outcome (EFS, disease-free survival [DFS]) in the MO16432/NOAH (CSR) and TECHNO studies. [38] The clear treatment benefit is supported by different sensitivity analyses.

Additional affirmation for the clinical finding in the primary endpoint EFS is provided by an update of the OS analysis (discussed in detail below under *Details on Performance of Overall Survival Update*)[see below] with an increase in median follow-up time of about 10 months in both arms. The unstratified hazard ratio for the updated overall survival data is 0.58 (95% CI: 0.35, 0.94; log-rank p-value: 0.0241), which is similar to the hazard ratio for the original survival analysis which was 0.59 (95% CI: 0.35, 1.02; log-rank p-value: 0.0555), implying a sustained OS benefit for the trastuzumab

Conclusion

The initial EFS rate assumptions used to power the study were in line with the observed rates (taking into account the associated sampling variability). The magnitude of treatment effect was comparable to other studies leading to approval in early breast cancer. Hence given the supportive evidence for EFS from the secondary endpoints as tpCR and OS, the NOAH trial demonstrated a clinically significant benefit when adding neoadjuvant-adjuvant trastuzumab to neoadjuvant chemotherapy.

Details on Performance of Overall Survival Update

The OS update was performed as follows: the survival data in the Roche MO16432/NOAH filing database was imputed with a data extract containing relevant survival information available in the Michelangelo Operations Office (MOO) database as of July 21, 2011. Beforehand, the imputed data was tested for its logical structure, including checks that the new death date of a patient with status "alive" in the Roche database from the MOO extract was not prior to the latest date on any of her follow-up forms. The follow-up time for a patient was updated by using the latest of the dates recorded on the "last follow-up" or "last drug intake" form from either the Roche database or the MOO data extract. The MAH considered "last drug intake" as a date for possible censoring since with protocol amendment D in 2005, an event-driven design was implemented. In the same amendment, patients randomised to receive chemotherapy alone were allowed to receive post operative trastuzumab (if certain criteria were met). Hence, in planning for the event-free survival (EFS) analysis, there was the necessity to account for the possibility that the required 106 events could be reached while some patients were still receiving drug therapy.

As described in the CSR MO16432, Roche performed a re-monitoring of the study with complete source data verification (with the exception of 21/330 patients, for whom source data were no longer available) to ensure the quality of the filing database met the regulatory submission standard.

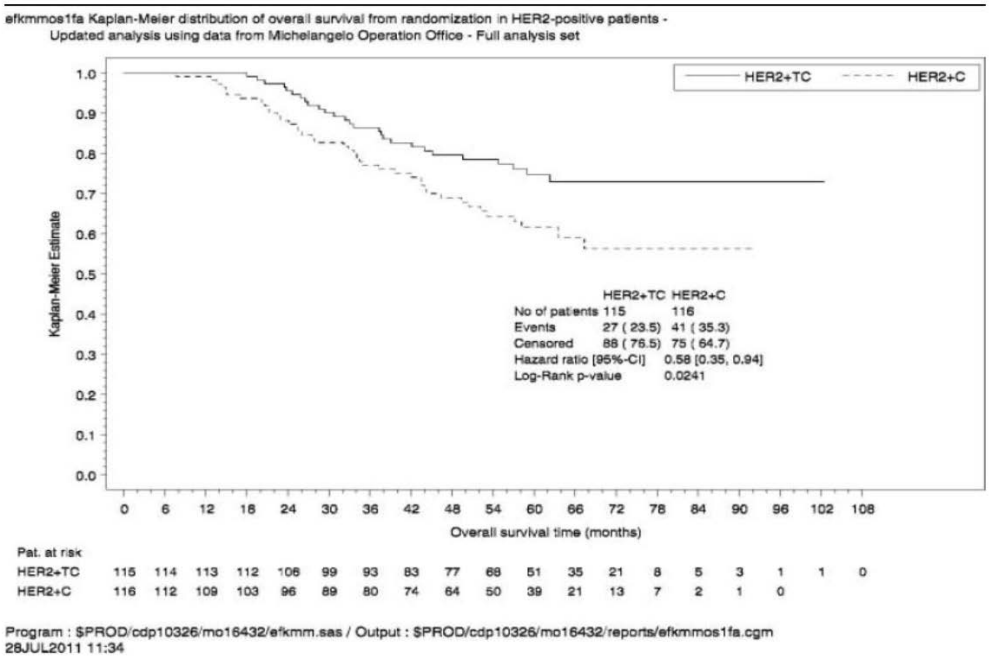
[38] Untch M, Fasching PA, Konecny GE, et al. Pathologic Complete Response After Neoadjuvant Chemotherapy Plus Trastuzumab Predicts Favorable Survival in Human Epidermal Growth Factor Receptor 2–Overexpressing Breast Cancer: Results From the TECHNO Trial of the AGO and GBG Study Groups, J Clin Oncol Published Ahead of Print

Table 39: Results for the updated overall survival analysis.

etsvmosfa Summary of overall survival (OS) from randomization (months) - Updated analysis using data from Michelangelo Operation Office - Full analysis set

Characteristic / Statistic	HER2+TC (N=115) N %	HER2+C (N=116) N %
Kaplan-Meier Estimate of OS (months) from randomization		
Number (%) of patients with events	27 (23.5)	41 (35.3)
Number (%) of patients censored	88 (76.5)	75 (64.7)
Third Quartile [95%-CI]	59.0 [42.1, -]	42.1 [32.2, 52.2]
Median [95%-CI]	- [- , -]	- [63.5, -]
Treatment effect - comparison vs. the HER2+C group		
Log-Rank p-value (two-sided)	0.0241	
Hazard ratio [95%-CI]	0.58 [0.35, 0.94]	
OS rate [95%-CI] at		
12 months	1.00 [1.00, 1.00]	0.99 [0.97, 1.00]
Patients at risk	113	109
24 months	0.96 [0.92, 0.99]	0.88 [0.82, 0.94]
Patients at risk	106	96
36 months	0.86 [0.80, 0.93]	0.77 [0.69, 0.85]
Patients at risk	93	80

Figure 5: Kaplan-Meier distribution of updated OS from randomisation in HER-2 positive patients..



Clinical evaluator's comment (second round)

It is considered that the sponsor's arguments supporting the clinical significance of the difference in EFS between HER2+TC and HER2+C are unconvincing for the following reasons:

1. The observed difference in EFS between the two treatment arms at 3 years was 13% (95% CI: -0.05, 0.30). This difference is notably smaller than the minimal clinically significance difference of 18.5% on which the study was powered.
2. The sponsor's argument that the initial EFS rate assumptions used to power the study were in line with the observed rates (taking into account the associated sampling variability) is not persuasive. The 95% CI using the Hauck-Anderson approach for the difference between the observed EFS rates at 3 years was (-0.05, 0.30). While this interval includes the rate difference of 0.185 in EFS at 3 years on which the study was

powered, the interval also includes zero which indicates that the observed rate difference in EFS between the two treatment arms was not statistically significant.

3. The use of cross-study comparisons of PFS rates to demonstrate the clinical significance of the observed difference in the year EFS rates between the two treatment arms should be interpreted cautiously because of the different study populations across the studies. Furthermore, the observed EFS rates at 3 years in the control (52%) and the trastuzumab (65%) arms in NOAH were both notably lower that the corresponding rates in the comparator studies (72.7% to 75% [control] versus 78.6% to 85.7% [trastuzumab]), raising further doubts about the validity of the comparisons.
4. The secondary efficacy endpoint of tpCR rate in NOAH is considered to support the efficacy of the HER2+TC regimen compared with HER2+C (see below) but supportive secondary endpoints cannot be considered to definitively establish efficacy. Furthermore, while the hazard ratio (HR) for the updated OS data statistically significantly favoured HER2+TC relative to HER2+C, it is considered that the data are too immature to conclude that that neoadjuvant trastuzumab plus chemotherapy provides a significant survival benefit compared with neoadjuvant chemotherapy alone. The immaturity of the data is evidenced by the high percentage of censored patients in both treatment arms (76.5% [88/115] HER2+TC arm; 64.7% [75/116] HER2+C arm) and the inability to calculate median survival duration in both treatment arms due to an insufficient number of events.

Question 4 (Efficacy)

In the pivotal study [NOAH], although the difference between the two treatment arms in the pCR (secondary efficacy endpoint) was statistically significant for both the bpCR and the tpCR, the absolute difference between the two treatment arms for these outcomes are considered to be of borderline clinical significance. While the study did not specify a clinically meaningful absolute difference between the two treatments for the bpCR and the tpCR, data from the MDACC study suggest that a 2 fold increase in the pCR (breast + axilla) in the HER2+TC arm compared with the HER2+C arm is likely to be clinically meaningful (based on respective pCR rates of 21% and 41%). Consequently, based on the MDACC assumptions it is considered that the absolute difference observed in NOAH between the two treatment arms in the bpCR of 17.6% [95% CI: 5.0, 30.2], (1.66 fold increase) and in the tpCR of 19.3% [95% CI: 7.2, 31.4] (1.93 fold increase) are of borderline clinical significance. Does the sponsor consider that the differences between the two HER2+ treatment arms in bpCR and tpCR in the pivotal study [NOAH] to be clinically significant? If so, on what grounds are the differences considered to be clinically significant?

Sponsor's response

The sponsor considers the differences between the two HER2+ treatment arms in bpCR and tpCR in the NOAH study to be clinically significant.

The NOAH study showed that pathological complete response (pCR) in breast (bpCR) and breast and axilla (tpCR) increased when adding neoadjuvant-adjuvant trastuzumab to neoadjuvant chemotherapy. Both pCR endpoints were specified as secondary endpoints in the study, hence no absolute or relative increment targets for the bpCR and tpCR rates have been defined a priori. The observed absolute increments of 17.6% (95%CI: 5.0%, 30.2%) in bpCR and 19.3% (95%CI: 7.2%, 31.4%) in tpCR correspond to a relative 1.66 fold increase for the bpCR rate and a 1.93 fold increase for the tpCR rate. The chi-square test applied to the data and reported in the CSR is a non-parametric test for differences of rates, with the null hypothesis of equal rates in the HER2+TC and HER2+C arms. The resulting p-values (0.0051 for bpCR and 0.0014 for tpCR) implied that the rates are statistically significantly higher in the HER2+TC arm for both pCR assessments.

The referenced pCR (in breast and axilla=tpCR) rate increase of 21% to 41% (corresponding to a 1.95 fold increment) in this question is reported from the randomised Phase III study of Buzdar et al. (2005, 2007)[39,40], referenced hereafter as MDACC study. The power consideration in that trial was based on this targeted 1.95 fold increase in tpCR. Given their initial sample size of 164 patients, the trial would have had 80% power to detect the difference of 20% (from 21% to 41%). Hence the minimum detectable difference in rates which corresponds to the smallest observed treatment effect that is statistically significant with the given sample size and a significance level of 5% would be 14% (can be derived mathematically). This corresponds to the relative increases presented in Table 40 [see below] for different assumed rates in the chemo alone arm.

Table 40: Relative pCR rate increments.

pCR rate in Chemo alone arm	Minimum pCR rate in Trastuzumab arm to achieve statistical significance*	Resulting x-fold increase
21%	35%	1.67
23%	37%	1.61
25%	39%	1.56
27%	41%	1.52

*pCR rate in Chemo alone plus the minimum detectable rate difference of 14%

Hence the relative 1.93 fold increment of tpCR in the NOAH trial (where the tpCR rate in the HER2+C arm was about 21%) is well in line with the targeted 1.95 fold increase in the MDACC study. Despite the fact that tpCR was used in the MDACC study, the 1.66 fold increase in bpCR in the NOAH trial with a corresponding rate in the HER2+C arm of about 27% is still higher than the corresponding value of 1.52 in Table 40, implying that the increment is in the range of values that do not exclude a (true) rate difference of 20%.

It is important to note that the actual sample size used in the MDACC study is relatively small and hence the inherent high variability does not allow a firm comparison to be made of the point estimates for the rate differences (tpCR) to the NOAH trial. In particular, the pCR rate that was observed in the NOAH study is in the same range as the pCR rates observed in other neoadjuvant trials with trastuzumab (Table 41 [see below]) that have employed a similar dose of anthracyclines and similar number of chemotherapy cycles. Of these only the MDACC study has a non-trastuzumab control arm, since at the time of the more recent studies trastuzumab had become standard of care and a non-trastuzumab control arm was no longer ethical. When comparing the pCR rates in Table 41, it can be seen that the pCR rates in the MDACC and NOAH control arms were in the same range, while the pCR rate in the MDACC trastuzumab arm is considerably higher than any pCR rate observed in other studies. Therefore, the sponsor believes that the pCR rate in the MDACC trastuzumab arm (small single institution study) should be interpreted with caution, as it could not be reproduced in larger multicenter studies.

[39] Buzdar AU, Ibrahim NK, Francis D et al., Significantly Higher Pathologic Complete Remission Rate After Neoadjuvant Therapy With Trastuzumab, Paclitaxel, and Epirubicin Chemotherapy: Results of a Randomized Trial in Human Epidermal Growth Factor Receptor 2–Positive Operable Breast Cancer, J Clin Oncol 23:3676-3685, 2005

[40] Buzdar AU, Valero V, Ibrahim NK et al., Neoadjuvant Therapy with Paclitaxel followed by 5-Fluorouracil, Epirubicin, and Cyclophosphamide Chemotherapy and Concurrent Trastuzumab in Human Epidermal Growth Factor Receptor 2-Positive Operable Breast Cancer: An Update of the Initial Randomized Study Population and Data of Additional Patients Treated with the Same Regimen, Clin Cancer Res 2007;13(1) January 1, 2007

Thus, the comparison of the NOAH trial with respect to the initial study design assumptions of Buzdar et al. as presented above is considered appropriate.

Table 41: pCR* rates in neoadjuvant trials with trastuzumab.

	n Trastuzumab arm	pCR rate Trastuzumab arm	pCR rate control arm
MDACC [1,2]	45	60%	26%
NOAH	115	40%	21%
GeparQuattro [3]	445	40%	n.a.
GeparQuinto [4]	307	44%	n.a.
TECHNO [5]	217	39%	n.a.

*pCR rate in Chemo alone plus the minimum detectable rate difference of 14%.

In conclusion, the observed rate increments in both tpCR and bpCR, (with a statistically significant rate increase in both endpoints in favor of the trastuzumab arm) of the NOAH trial are in line with a projected rate difference of 20% from the MDACC study. The increments are considered by the MAH as clinically meaningful since in the NOAH trial, achieving a pCR was associated with two clinical benefits:

1) Patients who achieved a pCR had a significantly better EFS outcome

Subgroup analyses of EFS according to response achieved (total pathological complete response or not) are summarised in Table 33 of the CSR [see below Table 42]. Irrespective of treatment arm, the EFS results were better in patients with tpCR than in those without tpCR. The Kaplan-Meier curves of EFS by outcome according to tpCR in HER2-positive patients are presented in Figure 7 of the CSR [see below Figure 6].

Twice as many patients in the HER2+TC arm were able to have breast-conserving surgery than in the HER2+C arm (21.4% versus 10.5%). Breast conserving surgery is considered one of the important advantages of neoadjuvant therapy, since one of the main objectives of neoadjuvant treatment is the down-staging of large tumours to avoid mastectomy.

Clinical evaluator's comment (second round)

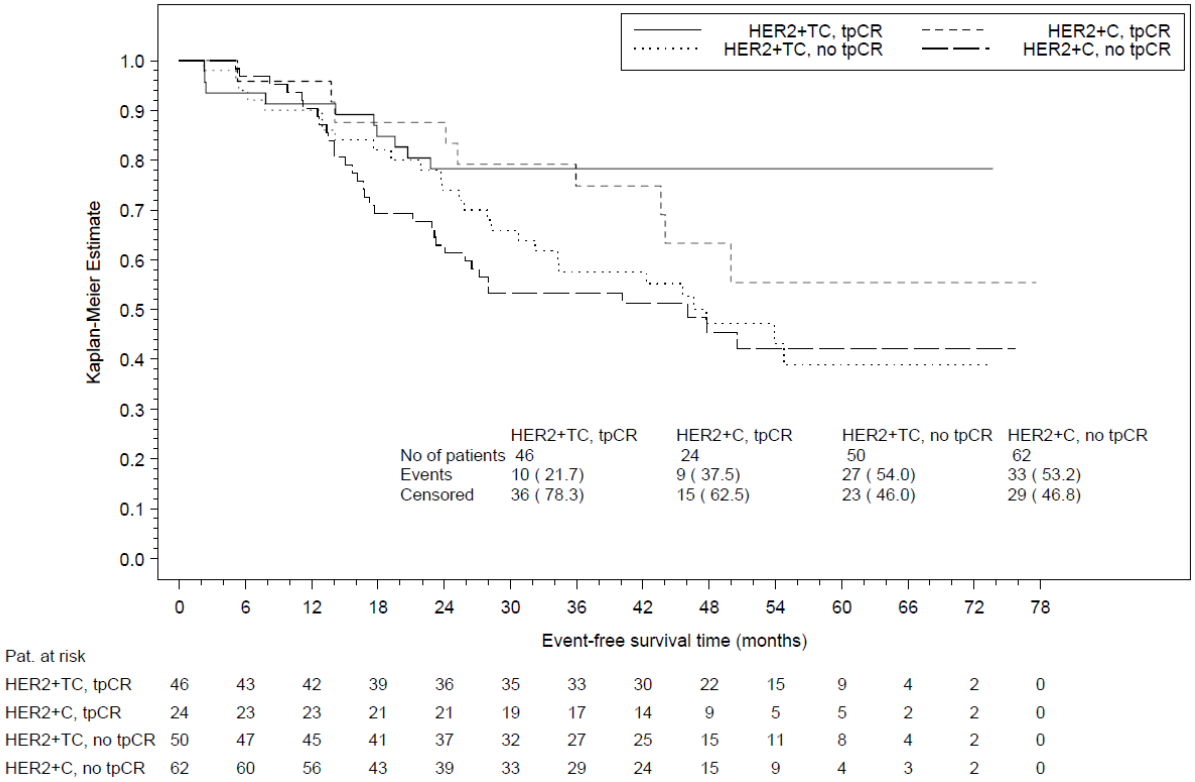
The sponsor's response is satisfactory. After consideration of the response it is considered that the results for the tpCR (absence of invasive cancer in the breast and axillary nodes) provide satisfactory supportive evidence for the efficacy of neoadjuvant trastuzumab plus chemotherapy compared with chemotherapy alone. However, it should be noted that the subgroup analyses of EFS according to response achieved (tpCR response or no tpCR response) referred to by the sponsor were not statistically significant for the comparisons between the HER2+TC and HER2+C (see Table 42). The analyses showed that in patients with a tpCR the risk of experiencing an EFS event was 42% lower in HER2+TC arm relative to the HER2+C arm (HR = 0.58 [95% CI: 0.24, 1.44], p=0.2355), and in patients without a tpCR the risk of experiencing an EFS event was 11% lower in the HER2+TC arm relative to the HER2+C arm (HR = 0.89 [95%CI: 0.54, 1.48]; p=0.6580). Kaplan-Meier curves of EFS by outcome according to tpCR in HER2-positive patients referred to in the sponsor's response are presented in Figure 6. The results of the subgroup EFS analyses in patients with and without a tpCR are considered to be exploratory.

Table 42: Summary of EFS by outcome according to tpCR; FAS.

tpCR	Characteristic / Statistic	HER2+TC (N=115) N %	HER2+C (N=116) N %	HER2-C (N=99) N %
tpCR	Total number of patients in subgroup	46 (40.0)	24 (20.7)	18 (18.2)
	Kaplan-Meier Estimate of EFS (months) from randomization			
	Number (%) of patients with events	10 (8.7)	9 (7.8)	2 (2.0)
	Number (%) of patients censored	36 (31.3)	15 (12.9)	16 (16.2)
	Third Quartile [95%-CI]	- [17.9, -]	35.9 [14.1, -]	- [11.6, -]
	Median [95%-CI]	- [-, -]	- [43.6, -]	- [-, -]
	Treatment effect - comparison vs. the HER2+C group			
	Log-Rank p-value (two-sided)	0.2355		
	Hazard ratio [95%-CI]	0.58 [0.24, 1.44]		
	EFS rate [95%-CI] at			
	12 months	0.91 [0.83, 0.99]	0.96 [0.88, 1.00]	0.89 [0.74, 1.00]
	Patients at risk	42	23	16
	24 months	0.78 [0.66, 0.90]	0.88 [0.74, 1.00]	0.89 [0.74, 1.00]
	Patients at risk	36	21	16
	36 months	0.78 [0.66, 0.90]	0.75 [0.57, 0.92]	0.89 [0.74, 1.00]
	Patients at risk	33	17	14
no tpCR	Total number of patients in subgroup	50 (43.5)	62 (53.4)	63 (63.6)
	Kaplan-Meier Estimate of EFS (months) from randomization			
	Number (%) of patients with events	27 (23.5)	33 (28.4)	26 (26.3)
	Number (%) of patients censored	23 (20.0)	29 (25.0)	37 (37.4)
	Third Quartile [95%-CI]	23.8 [14.1, 34.3]	16.7 [13.5, 23.3]	21.2 [15.3, 57.7]
	Median [95%-CI]	47.7 [32.2, -]	46.1 [24.0, -]	64.5 [57.7, -]
	Treatment effect - comparison vs. the HER2+C group			
	Log-Rank p-value (two-sided)	0.6580		
	Hazard ratio [95%-CI]	0.89 [0.54, 1.48]		
	EFS rate [95%-CI] at			
	12 months	0.90 [0.82, 0.98]	0.90 [0.83, 0.98]	0.89 [0.81, 0.97]
	Patients at risk	45	56	56
	24 months	0.74 [0.62, 0.86]	0.63 [0.51, 0.75]	0.75 [0.64, 0.85]
	Patients at risk	37	39	47
	36 months	0.58 [0.44, 0.71]	0.53 [0.41, 0.66]	0.66 [0.55, 0.78]
	Patients at risk	27	29	40

Percentages are calculated with respect to the total number of patients in each treatment group.
Total pathological complete response = pathological complete response of the primary tumor and axillary lymph nodes.

Figure 6: Kaplan-Meier distribution of event-free survival by outcome according to total pathological complete response in HER2-positive patients (FAS).



Pat. at risk

HER2+TC, tpCR	46	43	42	39	36	35	33	30	22	15	9	4	2	0
HER2+C, tpCR	24	23	23	21	21	19	17	14	9	5	5	2	2	0
HER2+TC, no tpCR	50	47	45	41	37	32	27	25	15	11	8	4	2	0
HER2+C, no tpCR	62	60	56	43	39	33	29	24	15	9	4	3	2	0

2) The higher likelihood of achieving a pCR in the trastuzumab arm corresponded with a higher likelihood of being eligible for breast-conserving surgery in the trastuzumab arm.

Question 5 (Efficacy)

In the pivotal study [NOAH], the Russian site was identified as an unusual site due to the fact that most of the patients did not undergo surgery and nearly all patients were complete responders. Furthermore, in both the HER2+ treatment arms a relatively large proportion of patients came from this one Russian site: 26% (26/115) of patients to the HER2+TC arm and 22.4% (26/116) of patients to the HER2+C arm. Was the Russian site monitored during the study and were any problems identified? It is noted that re-monitoring by Roche resulted in a change in initial disease stage category in 44 patients from this site. Is the sponsor satisfied that the inclusion of data from this site in the primary EFS analysis in the FAS population has not biased the results of this study?

Sponsor's response

The sponsor responded that the Russian site was regularly monitored throughout the duration of the study. Two specific findings were noted at this site which were not observed at any other site: (1) a high rate of patients who did not undergo surgery due to the surgeon at the site not operating in the presence of oedema. The sponsor commented that this was "clearly non-standard surgical practice" and the "judgment of the surgeon had to be respected"; and (2) a very high rate of clinical complete response which was confirmed by re-monitoring. The sponsor confirmed that all disease stage re-classifications "were carried out in a GCP-compliant way".

The sponsor undertook an analysis of tumour characteristics in three subgroups: (1) patients from the Russian site only; (2) patients from Russian sites excluding the Russian

site discussed aboev; and (3) patients from non-Russian sites. The sponsor noted that patients from the Russian site had smaller tumours than patients at other sites and that while the majority of patients from this site had T3 tumours the majority of patients from other Russian and non-Russian sites had T4 tumours. The sponsor also noted that at the Russian site "a very high number of patients were reported to have edema involving more than one third of the breast at baseline (80% in the HER2+TC arm and 68% in the HER2+C arm)" compared with the non-Russian sites "(26.4% in the HER2+TC arm and 25.5% in the HER2+C arm)". This might explain the unusually high number of patients not undergoing surgery at the Russian site, given that the surgeon at that site did not operate in the presence of oedema.

The sponsor undertook a sensitivity analysis of EFS to evaluate the potential bias arising from inclusion of patients from the site 47296 in the primary analysis. The sensitivity analysis excluded patients from the Russian site (26 patients [22.4%] in the HER2+TC arm and 26 patients [22%] in the HER2+C arm). The result of the sensitivity analysis gave the same point estimate of 0.65 of the efficacy effect as the primary analysis (see Table 43 below).

Table 43: EFS full analysis set and sensitivity analysis (excluding patients from site 47296).

PRIMARY ENDPOINT: EFS	**Full analysis set** (Mod 5, vol 1, section 5.3.5.1.1 NOAH CSR/MO16432, page 97)	**Excluding CRTN 47296** (Mod 5, vol 1, section 5.3.5.1.1 NOAH CSR/MO16432, page 276)
Unstratified analysis Hazard ratio (95%C; log-rank test)	0.65 (95%CI: 0.44, 0.96; p-value: 0.0275)	0.65 (95%CI: 0.42, 1.00; p-value: 0.0467)

The sponsor notes that the number of EFS events for the sensitivity analysis was lower than for primary analysis. In the sensitivity analysis there were a total of 86 EFS events (38 for HER2+TC and 48 for HER2+C), compared with a total of 105 EFS events (46 for HER2+TC and 59 for HER2+C) for the primary analysis. However, the p value for the sensitivity analysis was notably lower than the p-value for the primary analysis. Nevertheless, the sponsor commented that the study was still adequately powered (80%) for the analysis of EFS, excluding the Russian site, based on 86 events to demonstrate an absolute improvement of 18.5% in the EFS rate at 3 years from 50% to 68.5%, resulting in a hazard ratio of 0.545. The primary analysis conducted with 105 EFS events had an associated power of 86%. The sponsor states that "[t]herefore, the resulting p-value of 0.0467 implies that the hazard ratio is only slightly smaller as the minimum detectable difference, i.e. the smallest observed treatment effect which is statistically significant for the given sample size (full analysis set without CRTN 47296) and significance level (5%). It can be shown mathematically that the minimum detectable difference for the analysis excluding CRTN 47296 corresponds to a hazard ratio of 0.654, explaining why the p-value is borderline".

The sponsor also provided sensitivity analyses for the secondary efficacy endpoints of tpCR and OS excluding the data from site 47296 and these are summarised below in Table 44. The sponsor comments that "for tpCR and OS, the results when excluding CRTN 47296 [Russian site] are consistent with the results in the full analysis set, thus supporting the finding for the primary endpoint EFS that this particular center does not introduce bias into the inference from the full analysis set".

Table 44: Secondary endpoints. Full analysis set and sensitivity analysis (excluding patients from the Russian site).

SECONDARY ENDPOINTS	**Full analysis set** (Mod 5, vol 1, section 5.3.5.1.1 NOAH CSR/MO16432, p97)	**Excluding CRTN 47296*** tpCR: Computations based on output 1: "elpcrra". OS: (Mod 5, vol 1, section 5.3.5.1.1 NOAH CSR/ MO16432, p279)
Total pathological complete response (tpCR)	HER2+TC: 40% HER2+C: 20.7% **Difference: 19.3%** (95%CI: 7.2, 31.4; chi-square p-value: 0.0014)	HER2+TC: 41.1%* HER2+C: 18.7%* **Difference: 22.4%** (95%CI: 7.6, 35.6; chi-square p-value: 0.0010)
Overall Survival (OS) Hazard ratio (95% CI; log-rank p-value)	**0.59** (0.35, 1.02; p-value: 0.0555)	**0.52** (0.28, 0.96; p-value: 0.0340)

* Excluding the Russian site implies: For HER2+TC: Reduction of 25 patients in the denominator (90 instead of 115 in full analysis set); Reduction of 9 in tpCR responders (37 instead of 46) - For HER2+C: Reduction of 25 patients in the denominator (91 instead of 116) Reduction of 7 in tpCR responders (17 instead of 24)

Clinical evaluator's comment (second round)

The sponsor's conclusion that the results of the sensitivity analyses excluding the patients from the Russian site "does not introduce bias into the inference from the full analysis set" [primary analysis] is not convincing. It is considered that the sensitivity analysis of EFS excluding the Russian site introduces further uncertainty about the clinical significance of the observed difference in the primary analysis between the HER2+TC and HER2+C treatment arms. Although the point estimate of the HR from both the primary and the sensitivity analyses are identical (0.65), the 95% CI for the HR from the sensitivity analysis included 1 (HR not statistically significant) and the p-value was borderline statistically significant (p=0.0467). Overall, the result of the EFS sensitivity analysis suggest that the difference between the HER2+TC and HER2+C arms was of borderline statistical significance (at best) when patients from the Russian site with smaller tumours and/or less advanced disease stage and/or who had not undergone surgery were excluded from the analysis.

Question 6 (Efficacy)

In the pivotal study [NOAH], the exploratory logistic regression analysis for the overall clinical response rate adjusted for geographical region (Russia versus Germany/Austria) showed that the odds ratio (OR) for the overall clinical response was 5.24 ([95% CI: 1.77, 15.57]; p=0.0001, Wald's test), indicating that the chance of a Russian patient experiencing a clinical response was approximately 5 fold higher than a German/Austrian patient. The sponsor states that at the Russian site almost all patients were classified as complete responders. Have any reasons been identified for this unusual finding?

Sponsor's response and clinical evaluator's comment (second round)

See Question 5 (above).

Question 7 (Efficacy)

In the pivotal study [NOAH] all HER2+TC patients received neoadjuvant and adjuvant trastuzumab. Consequently, it is not possible to separate the effects on EFS (primary efficacy endpoint) of neoadjuvant trastuzumab from those of adjuvant trastuzumab. Therefore, the statistically significant effect on EFS observed in the HER2+TC arm compared with the HER2+C arms might be due to neoadjuvant trastuzumab, adjuvant trastuzumab or the combination of neoadjuvant and adjuvant trastuzumab.

While the analysis comparing the HER2+TC arm with the HER2+C→T [adjuvant] group showed that the risk of experience an EFS event was statistically significantly lower in the neoadjuvant/adjuvant trastuzumab arm than in the adjuvant trastuzumab arm, the number of patients who crossed over from the HER2+ to adjuvant trastuzumab (n=19) is considered too small for the results to be meaningfully interpreted. Please justify why the pivotal study is considered to support neoadjuvant trastuzumab treatment over adjuvant trastuzumab treatment, given the inability of the study design to isolate the two treatments.

Sponsor's response

The NOAH study was designed to answer the question whether neoadjuvant trastuzumab in combination with neoadjuvant chemotherapy, followed by adjuvant trastuzumab, was superior to neoadjuvant chemotherapy alone. The NOAH study does not address the question of whether neoadjuvant treatment with trastuzumab is superior to adjuvant treatment. The sponsor does not make such a claim. To clarify for the prescriber the nature of the neoadjuvant/adjuvant supportive clinical data, Roche proposes to include the following statement in the Australian PI (as per the approved EU Summary of product Characteristics (SmPC));

> *"To date, results are not available comparing the efficacy of Herceptin administered with chemotherapy in the adjuvant setting with that obtained in the neoadjuvant/adjuvant setting."*

As stated in the application cover letter..... the neoadjuvant-adjuvant treatment approach as studied in NOAH is intended for patients with large or locally advanced tumours who can benefit from down staging to enable surgery (for patients with inoperable disease) or less disfiguring surgery (for patients with large, operable tumours). This treatment approach also has the advantage of providing prognostic information associated with pCR, particularly in patients with HER2+ disease, where the NOAH and TECHNO[41] studies have shown a positive correlation of pCR with long term outcome. Patients who do not achieve a clinical response can be switched early to a different regimen and patients who do not achieve a pCR and who therefore have a higher risk for relapse can be included into trials of new therapies. These advantages of a neoadjuvant (or in the case of trastuzumab a neoadjuvant-adjuvant) treatment strategy have recently been confirmed by an international consensus panel.[42]

An updated copy of the proposed PI (annotated) including the above proposed statement was provided with this response package.

Clinical evaluator's comment (second round)

The sponsor's response confirms that there are no data from NOAH comparing neoadjuvant trastuzumab plus chemotherapy followed by trastuzumab adjuvant therapy with neoadjuvant chemotherapy alone followed by trastuzumab adjuvant therapy.

[41] Untch U, Fasching PA, Konecny GE et al., Pathologic Complete Response After Neoadjuvant Chemotherapy Plus Trastuzumab Predicts Favorable Survival in Human Epidermal Growth Factor Receptor 2–Overexpressing Breast Cancer: Results From the TECHNO Trial of the AGO and GBG Study Groups, J Clin Oncol 29:3351-3357, 2011

[42] Goldhirsch A, Wood WC, Coates AS et al., Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011, Ann Oncol. 2011 Aug;22(8):1736-47

Question 8 (Efficacy)

In BCIRG 006, all the efficacy analyses in the submitted CSR were based on data from the second planned interim analysis undertaken when 474 DFS events had occurred (median follow-up of 36 months), representing 52.7% of the 900 planned events. Consequently, the data on which the analysis was undertaken are immature. When will the efficacy results from the "main analysis" of the 900 planned events be submitted to the TGA for evaluation?

Sponsor's response

Please find below the currently projected dates for the clinical cut off and CSR availability for study BCIRG006.

Future analysis	Clinical cut-off/CSR	Number of DFS Events
Final Analysis	Q2 2014 (cutoff) Q1 2015 (CSR)	When 900 DFS is reached (approx. 10 years from last patient randomized)

Q1 2015=first quarter of 2015; Q2 2014=second quarter 2014.

Clinical evaluator's comment (second round)

The sponsor's response is satisfactory.

Second round benefit-risk assessment

Second round assessment of benefits

Extension of indication (Dossier 1)

After consideration of the responses to the clinical questions, it is considered the submission provides inadequate evidence supporting an additional clinically meaningful benefit for neoadjuvant trastuzumab plus chemotherapy above that observed with neoadjuvant chemotherapy alone in women with localised HER2-positive breast cancer.

In NOAH, the difference between the two treatment arms (HER2+TC and HER2+C) for the primary efficacy endpoint of event free survival (EFS) is considered to be not clinically significant for the reasons outlined in the initial CER and in the comments provided above. In addition, the sensitivity analysis of the EFS excluding patients from Russian clinical trial site adds weight to the conclusion that there are no meaningful clinical differences between the two neoadjuvant treatment arms. The patients from the Russian site appeared to have had less severe breast cancer disease and included a high percentage of patients who did not undergo surgery compared with patients from other sites. Therefore, it can be inferred that the sensitivity EFS analysis included patients with more advanced disease and/or who underwent surgery compared with patients in the primary EFS analysis. Furthermore, it appears that the patients in the sensitivity EFS analysis were more representative of those patients for whom the sponsor states neoadjuvant trastuzumab treatment is targeted (that is, patients with large or locally advanced tumours who can benefit from surgery). While the hazard ratio (HR) was identical for the sensitivity and primary analyses of the EFS, the result for the sensitivity analysis was of borderline statistical significance.

The secondary efficacy endpoint of tpCR is considered to support the efficacy of neoadjuvant trastuzumab. While the updated OS data (secondary efficacy endpoint) support the efficacy of neoadjuvant trastuzumab these data are considered to be too immature to allow a definitive conclusion to be made on the difference between the two treatment arms. In any event, statistically and clinically significant secondary efficacy

endpoints are considered to be insufficient to adequately support approval in submissions such as the current one where the primary efficacy endpoint analysis failed to demonstrate clinical significance for the proposed treatment.

Inclusion of efficacy data from BCIRG 006 in the PI (Dossier 2)

The data from BCIRG 006 are considered to support the addition of the DFS and OS results from this study to the *Clinical Trials* section of the PI (see the initial CER).

Second round assessment of risks

Extension of indication (Dossier 1)

After consideration of the responses to the clinical questions, it is considered that the risks of neoadjuvant trastuzumab are unchanged from those identified in the initial CER.

Inclusion of Efficacy data from BCIRG 006 in the PI (Dossier 2)

It is considered that no new risks associated with adjuvant treatment with trastuzumab in combination with docetaxel, doxorubicin, cyclophosphamide, or carboplatin have been identified in BCIRG 006 (see the initial CER).

Second round assessment of benefit-risk balance

Extension of Indication (Dossier 1)

The benefit-risk balance for the extension of indication to include neoadjuvant trastuzumab treatment is considered to be unfavourable for the reasons outlined in the initial CER.

Inclusion of efficacy data from BCIRG 006 in the PI (Dossier 2)

It is considered that the benefit-risk balance of the adjuvant trastuzumab combined with chemotherapy regimens used in BCIRG 006 for the treatment of women with localised HER2-positive breast cancer is favourable.

Second round recommendation regarding authorisation

Extension of indication (Dossier 1)

After consideration of the sponsor's responses to the clinical questions, it is considered that the submission to extend the indications of trastuzumab to include the treatment of patients with HER2-positive localised breast cancer in association with neoadjuvant chemotherapy should be rejected on the grounds of inadequate demonstration of clinically meaningful increased efficacy compared with neoadjuvant chemotherapy alone.

In NOAH, the risk of experiencing an EFS event (disease progression, recurrence or death) was 35% lower (statistically significant) in the HER2+TC arm relative to the HER2+C arm; unadjusted HR = 0.65 [95% CI: 0.44, 0.96]; p=0.0275 log-rank. EFS in the FAS population was the primary efficacy endpoint and the study was powered on a difference of 18.5% in the 36 month EFS rates between the two HER2-positive treatment arms (that is, 50% in the HER2+C arm and 68.5% in the HER2+TC arm). It is stated in the CSR that "a clinically meaningful improvement with the addition of trastuzumab would be to increase the median EFS time to 5.5 years, corresponding to 68.5% EFS rate at 3 years. This corresponds to a hazard ratio of 0.545" (CSR). The observed difference in the 36 month EFS rates between the two HER2-positive treatment arms was 13% (52% in the HER2+C arm and 65% in the HER2+TC arm), and the HR was 0.65. Consequently, based on the assumptions used to power the study, it is considered that the observed absolute difference in EFS (primary analysis) of 13% between the two HER-positive treatment arms is not clinically significant. The absolute difference between the two treatment arms indicates that, on average, approximately 8 patients would need to be treated with

neoadjuvant trastuzumab plus chemotherapy in order for 1 additional patient not to experience an EFS event.

After consideration of the sponsor's response to the clinical question relating to the clinical significance of the primary efficacy endpoint of EFS in NOAH it is concluded that:

- The observed difference in EFS between the two treatment arms at 3 years was 13% (95% CI: -0.05, 0.30), which is notably smaller than the minimal clinically significance difference of 18.5% on which the study was powered.
- The sponsor's argument that the initial EFS rate assumptions used to power the study were in line with the observed rates (taking into account the associated sampling variability) is not persuasive. The 95% CI using the Hauck-Anderson approach for the difference between the observed EFS rates at 3 years was (-0.05, 0.30). While this interval includes the rate difference of 0.185 in EFS at 3 years on which study was powered, the interval also includes zero (0) which indicates that the observed rate difference in EFS between the two treatment arms was not statistically significant.
- The use of cross-study comparisons of PFS rates by the sponsor to demonstrate the clinical significance of the observed difference in the year EFS rates between the two treatment arms should be interpreted cautiously because of the different study populations in the studies. Furthermore, the observed EFS rates at 3 years in the control (52%) and the trastuzumab (65%) arms in NOAH were both notably lower that the corresponding rates in the comparator studies (72.7% to 75% [control] versus 78.6% to 85.7% [trastuzumab]), raising further doubts about the validity of the comparison.
- The secondary efficacy endpoint of tpCR in NOAH is considered to support the efficacy of the HER2+TC regimen compared with HER2+C, but supportive secondary endpoints cannot be considered to definitively establish efficacy. Furthermore, while the hazard ratio (HR) for the updated OS data statistically significantly favoured HER2+TC relative to HER2+C, it is considered that the data are still too immature to conclude that that neoadjuvant trastuzumab plus chemotherapy provides a significant survival benefit compared with chemotherapy alone. The immaturity of the data is evidenced by the high percentage of censored patients in both treatment arms (76.5% [88/115] HER2+TC arm; 64.7% [75/116] HER2+C arm), and the inability of the analysis to calculate median survival duration in both treatment arms due to an insufficient number of events.

After consideration of the sponsor's response to the clinical question relating to the patients from the Russian clinical trial site, it is concluded that the sensitivity analysis of the EFS excluding patients from this site provides further evidence supporting the absence of meaningful clinical differences between the two neoadjuvant treatment arms in NOAH (that is, HT2+TC and HT2+C). The patients from the Russian site had less severe breast cancer disease and included a higher percentage of patients who did not undergo surgery compared with patients in the primary analysis. Therefore, it can be inferred that the EFS sensitivity analysis included patients with more advanced disease and/or who underwent surgery than patients in the primary EFS analysis. Consequently, it can be concluded that the patients in the EFS sensitivity analysis are more closely aligned to the target population for whom the sponsor states neoadjuvant trastuzumab is aimed (that is, patients with large or locally advanced tumours who can benefit from surgery). While the hazard ratio (HR) was identical for the sensitivity and primary analyses of the EFS, the result for the sensitivity analysis was of borderline statistical significance. The 95% CI for the HR included 1 (indicating non statistical significance), and the p value was 0.0467. The sensitivity analysis was adequately powered to detect a statistically significant difference

in EFS between the two treatment arms based on the assumptions used to power the primary analysis.

In the pivotal study [NOAH], all HER2+TC patients received neoadjuvant and adjuvant trastuzumab. Consequently, it is not possible to separate the effects on EFS of neoadjuvant trastuzumab from those of adjuvant trastuzumab. Consequently, the statistically significant effect on EFS observed in the HER2+TC arm compared with the HER2+C arm might be due to neoadjuvant trastuzumab, adjuvant trastuzumab or the combination of neoadjuvant and adjuvant trastuzumab. While an exploratory EFS analysis showed that the risk of experiencing an EFS event was lower in the HER2+TC arm compared with HER2+C→T arm, the number of patients in the HER2+C→T arm (n=19) is considered too small for the results to be meaningfully interpreted.

In the supportive study MDACC, the pCR rate (primary efficacy endpoint) was statistically significantly higher in the HER2+TC arm (65.2% [n=23]) compared with the HER2+C arm (26.3% [n=19]); p=0.016. Furthermore, the absolute difference between the two treatments was 38.9%, which was higher than the approximately 2 fold increase (21% HER2+C and 41% HER2+TC) on which the study was powered suggesting that the observed result is clinically meaningful. However, the neoadjuvant trastuzumab dosing regimen used in this study was different from that used in NOAH and is different from that being proposed for registration. In addition, the neoadjuvant chemotherapy regimen differed between the supportive study [MDACC] and the pivotal study [NOAH]. Furthermore, the patient numbers in MDACC randomised to treatment were relatively small (n=19 [HER2+C] and n=23 [HER2+TC]). Overall, it is considered that the MDACC data alone cannot support the submission.

The supportive study GeparQuattro was not designed to compare neoadjuvant trastuzumab plus chemotherapy with neoadjuvant chemotherapy alone in patients with HER2-positive tumours. Consequently, the descriptive results of this study showing an efficacy benefit in women with HER2-positive disease treated with neoadjuvant trastuzumab plus chemotherapy compared with women with HER2-negative disease treated with neoadjuvant chemotherapy alone is considered to be of limited relevance to the submission.

Inclusion of efficacy data from BCIRG 006 in the PI (Dossier 2)

It is recommended that the proposed update of the *Clinical Trials* section of the PI relating to data from BCIRG 006 be accepted.

PI amendments (Dossier 3)

It is recommended that the PI amendments based on the studies submitted in Dossier 3 be accepted subject to the comments provided by this evaluator.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification (SS)

The sponsor provided a summary of Ongoing Safety Concerns and subject to the evaluation of the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows in Table 45.

Table 45. Summary ongoing safety concerns

Important Identified Risks	• Cardiotoxicity • Infusion-Related reactions • Haematological Toxicity • [(1)] Oligohydramnios • Pulmonary Disorders
Important Potential Risks	• Infections

OPR reviewer comment

Pursuant to the evaluation of the clinical aspects of the SS, the above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance plan (PP)

The sponsor stated that routine pharmacovigilance activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03),* are proposed to monitor all the specified Ongoing Safety Concerns pertaining to the extension of indications.

No new additional pharmacovigilance activities have been proposed to further monitor the Important identified risks: 'Cardiotoxicity', 'Infusion related reactions', 'Oligohydramnios' & 'Pulmonary disorders'. Nevertheless Table 73 of the RMP: 'Summary of Safety Concern and Planned Pharmacovigilance Actions' now includes a reference to the American pregnancy registry Study H4621g AKA MotHER for the important identified risk: 'Oligohydramnios' to be consistent with Table 80 (of the RMP): 'Summary of the Risk Management Plan'.

OPR reviewer's summary in regard to the pharmacovigilance plan (PP) and appropriateness of milestones

The minor changes made to the PP are acceptable. However, the guided questionnaires used in an effort to better characterise the Important identified risks: 'Cardiotoxicity', 'Infusion related reactions' & 'Pulmonary disorders' associated with trastuzumab use do not appear to have been included in the RMP as indicated.

The sponsor's correspondence, dated 27 February 2012, did provide these guided questionnaires with their content unchanged from those accepted in the previous version of the Australian RMP. In addition, the sponsor advised that these guided questionnaires would be included in the RMP as Annex 6: 'Guided Questionnaires'. Consequently Annex 7 is now 'Other Supporting Data' and Annex 8 is 'Educational Material'.

Risk minimisation activities

The sponsor concluded that routine risk minimisation activities for all the specified Ongoing Safety Concerns are sufficient, as implied by Table 80: 'Summary of the Risk Management Plan'. However the summary table of Planned Risk Minimisation Actions has been deleted from this part of the RMP.

OPR reviewer comment

It is recommended that a summary table of Planned Risk Minimisation Actions, as per the EU-RMP template, addressing all the specified ongoing safety concerns be included in this part of the RMP.

Planned actions

Routine risk minimisation activities will include special warning and precaution statements, instructions for use and notification of undesirable effects in the product literature for all the specified Ongoing Safety Concerns.

The Table (79) 'Additional risk minimisation measures, cardiotoxicity' referred to the Trastuzumab Treatment Algorithm, which is described in the Australian PI. Consequently this table has been removed.

OPR reviewer comment

The sponsor's proposed application of routine risk minimisation activities would appear to be reasonable and therefore acceptable. In addition the removal of Table 79 is acceptable, as the clinical recommendation algorithm is correctly recognised as routine rather than as an additional risk minimisation activity. Nevertheless Section 7.3.1: 'HER2 Overexpression' of the Safety Specifications of the RMP states:

> *Common across all protocols was the prerequisite for HER2 over expression testing. Such tests are mandated in the Dosage and Administration section (proposed to be moved here from the Precautions section with this application) of the Australian Product Information (PI), as follows;*
>
> > *"Herceptin should only be used in patients whose tumours have HER2 protein overexpression or HER2 gene amplification.*
> >
> > *To ensure accurate and reproducible results, testing must be performed in a specialized laboratory, which can ensure validation of the testing procedures"*
>
> *The accuracy of HER-2 testing is crucial to selecting the right patient for HER-2 targeted therapy. The use of non-validated assays can affect the accuracy of test results and the quality of results can be affected by several pre-analytical factors. Through collaboration with pathologists and laboratories Roche monitors the appropriate use of validated assays (refer to Annex 6 – Other Supporting Data "QA Assurance of HER2 Testing in Australia" for further details).*
>
> *In addition to this, for advanced gastric cancer, the MAH has prepared educational material for prescribers (see Annex **7** Educational Material).*

The stated *"educational material for prescribers"* would be considered an additional risk minimisation activity that should be included in the Risk Minimisation Plan (RiMP). However, no detail was provided about how such educational material would be communicated and presented to prescribers and how the effectiveness of this additional risk minimisation activity as a measure to reduce medication error in the post market environment would be assessed.

The sponsor's correspondence, dated 27 February 2012, clarified that the *"educational material for prescribers (see Annex **7** Educational Material)"* is not intended for prescribers. The sponsor states that this was incorrectly referenced as such in the previous version of the Australian RMP. The gastric educational material is intended for pathologists and scientists participating within the five laboratories registered under the *in situ* hybridisation (ISH) program. Consequently it is agreed that this educational material is not considered an additional risk minimisation activity. The sponsor states that the

material will now be described as *"educational material for pathologists and scientists"* and included under Annex 7: 'Other Supporting Data', while Annex 8 is 'Educational Material' and not applicable.

In regard to the proposed routine risk minimisation activities, the draft PI document was considered satisfactory. However, the clinical evaluator has recommended amendments to the draft PI.

In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified:

If this application is approved the following specific condition of registration should be applied: "The Australian Risk Management Plan Version: 2.0, dated July 2011, to be revised as specified in the sponsor's correspondence dated 27 February 2012, must be implemented."

The minor changes made to the Pharmacovigilance Plan were considered acceptable.

It is recommended that a summary table of Planned Risk Minimisation Actions, as per the EU-RMP template, addressing all the specified Ongoing Safety Concerns be included in the RMP.

In regard to the proposed routine risk minimisation activities, the draft PI document is considered satisfactory. However, the clinical evaluator has recommended amendment to the draft PI.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacokinetics

- Three new pharmacokinetic (PK) studies were submitted to support changes to the Pharmacokinetics section of the PI. The studies were population PK analyses in breast and gastric cancer and an interaction study of trastuzumab with capecitabine and cisplatin.

- The population PK analysis in breast cancer (Report 1034069) was based on trials BO15899, BO15935, WO16229, M77004 and MO16982. A previous analysis was based on the first 4 trials. Trial MO16982 was new. The new analysis was generally consistent with the previous analysis. It supports the change to clearance to 0.241 L/day and volume of distribution to 3.02 L Vc and 2.68 L Vp.
- The population PK analysis in gastric cancer (Report 1039626) was based on a previously evaluated trial BO18255. The changes to the PI based on the report are generally supported except for the first paragraph (PI; Gastric Cancer) where an alternative statement is recommended.
- In the interaction Study JP19959 in Japanese patients, co-administration of trastuzumab with capecitabine and cisplatin did not significantly affect the pharmacokinetics of the two chemotherapy agents. There was insufficient data to determine if the pharmacokinetics of capecitabine and cisplatin were affected when the two drugs were co-administered. The evaluator recommended an alternative statement to that proposed.

Efficacy

Neoadjuvant plus adjuvant indication

- The pivotal efficacy study was a randomised, open label, parallel group trial (MO16432, also known as NOAH) conducted in Europe in patients with locally advanced (Stage III or inflammatory) breast cancer with HER2 overexpression.[43] The median age of patients was 50 years (range 25-80).
- HER2+ve patients received neoadjuvant chemotherapy with or without neoadjuvant trastuzumab (HER2+TC and HER2+C respectively). A HER2-ve group (HER2-C) received neoadjuvant chemotherapy alone. The chemotherapy consisted of doxorubicin and paclitaxel for three 3 week cycles, paclitaxel alone for four 3 week cycles, then cyclophosphamide, methotrexate and fluorouracil for three 4 week cycles. Trastuzumab was administered in a loading dose of 8 mg/kg IV on the first day of doxorubicin/ paclitaxel treatment, then 6 mg/kg every 3 weeks until surgery. Following surgery, trastuzumab was restarted at a dose of 6 mg/kg every 3 weeks. Trastuzumab was continued for a year (including the neoadjuvant period). Patients with oestrogen or progesterone receptor positive tumours also received adjuvant tamoxifen for 5 years. All patients received post-operative radiotherapy.
- The primary endpoint was investigator assessed event free survival (EFS). Events were disease progression, recurrence or death. Modified RECIST criteria were used. There was potential for bias because investigators were not blinded to treatment assignment. Statistically, based on the hazard ratio and log-rank test, trastuzumab (neoadjuvant + adjuvant) significantly increased EFS in HER2+ve subjects in the full analysis set (FAS) (Table 46). The FAS excluded three patients (two because of missing informed consent and one due to late site approval of a protocol amendment) (Table 46). There were no significant differences for overall response rate (ORR) or overall survival (OS). Similar results were obtained in the per protocol analysis. The median follow-up was 3.8 years in the trastuzumab + chemotherapy group (HER2+TC) and 3.5 years in the chemotherapy alone group (HER2+C).

[43] Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010; 375: 377-384.

- Results in the HER2-C group reflected the better prognosis of patients with HER2-ve breast cancer than HER2+ve breast cancer. These results are not discussed further since they are not relevant to trastuzumab efficacy.

Table 46: MO16432 Trial. Efficacy Results in HER2+ve Subjects. *Full Analysis Set*

	HER2+TC n=115	HER2+C n=116	Hazard Ratio or Difference [95% CI]
EFS median *mths*[1]	NR	43.6	0.65 [0.44, 0.96] p=0.028[3]
EFS at 3 yrs *%*[1]	65	52	13 [-5, 30][4]
OS median *mths*[1]	NR	NR	0.59 [0.35, 1.02]
OS at 3 yrs *%*[1]	85.0	78.0	NA
ORR *%*[2]	72.7 (n=110)	66.4 (n=107)	6.4 [-6.4, 19.1]

[1] Kaplan-Meier estimate. Hazard Ratio: HER2+TC/HER2+C. [2] Investigator-assessed using modified RECIST criteria in patients with measurable disease at baseline. [3] Log-rank test. [4]Hauck-Anderson difference in rates. NR-Not Reached. NA-Not Assessed.

- The absolute difference in EFS at 3 years between the treatment arms is 13 percentage points which was not statistically significant based on the Hauck-Anderson 95% CI. The sample size was calculated on the basis that a difference of 18.5 percentage points would be clinically significant. Thus, a clinically significant difference has not been achieved.
- In a protocol amendment, patients in the HER2+C (chemotherapy alone) arm could elect to receive adjuvant trastuzumab post-surgery (in a loading dose of 8 mg/kg then 3 mg/kg every 3 weeks). Twenty patients (17%) elected to receive adjuvant trastuzumab and 19 had an EFS event after commencing trastuzumab. If these 19 patients are censored at the time of crossover to trastuzumab, the EFS hazard ratio becomes 0.59, 95% CI [0.40, 0.88] and EFS at 3 years 65% in the HER2+TC group and 48% in the HER2+C group.
- An unexpectedly high number of subjects did not undergo surgery (15% in the HER2+ TC arm and 26% in the HER2+C arm), most being from a single Russian site. A sensitivity analysis excluding the Russian site found the same hazard ratio for EFS as the primary analysis (0.65); however, the 95% CI [0.42, 1.00] and log-rank p value 0.047 showed that the EFS increase with trastuzumab was now only marginally significant.
- An updated overall survival analysis was submitted during the evaluation. Overall survival was statistically significantly increased with trastuzumab; hazard ratio 0.58, 95% CI [0.35, 0.94] and log-rank p-value 0.024. Overall survival at 3 years was 86% in the HER2+TC group and 77% in the HER2+C group. Median survival had still not been reached in either group. Longer follow-up is needed to determine the clinical significance of the increase.
- In the published report based on a lesser median follow-up of 3.2 years, the magnitude of the EFS benefit in the HER2+TC group was greater (15 percentage points at 3 years).

However, assessment of clinical response was more subjective. The submitted analysis was considered more robust.

- The two supportive trials were of limited value. The MDACC trial was in a population with earlier stage disease (Stage II-IIIa invasive but non-inflammatory) and used a different treatment regimen to the pivotal trial. The trial showed marginally increased disease free survival with trastuzumab. The GeparQuattro trial was not designed to test the benefit of adding trastuzumab to neoadjuvant chemotherapy.

New adjuvant study

- BCIRG 006 was a randomised, open label trial of the addition of adjuvant trastuzumab (Herceptin) to adjuvant chemotherapy in patients with localised HER2 positive breast cancer. Three treatment regimens were compared:
    - AC→D: Adriamycin and cyclophosphamide followed by docetaxel (Note: instead of D, T for Taxotere is used in the clinical evaluation).
    - AC→DH: Adriamycin and cyclophosphamide followed by docetaxel (Taxotere) and Herceptin and
    - DCarbH: docetaxel, carboplatin and Herceptin.

After AC, docetaxel was given in a dose of 100 mg/m2 IV every 3 weeks for 4 cycles.

In the DCarbH regimen, docetaxel was given in a dose of 75 mg/m2 IV and carboplatin dosed at target AUC of 6 mg/mL/min IV, every 3 weeks for 6 cycles.

Herceptin was given IV in a loading dose of 4 mg/kg, then 2 mg/kg weekly whilst on chemotherapy, then 6 mg/kg every 3 weeks for a total duration of 12 months. Hormone receptor positive patients also received hormonal therapy and all patients received radiotherapy.

- The data submitted was of the second interim analysis which contained 53% of the planned 900 disease free survival (DFS) events. DFS, the primary endpoint, was defined as the time from randomisation to local, regional or distant relapse, second primary tumour or death from any cause. The two regimens containing trastuzumab significantly increased DFS and overall survival (OS) compared with the AC→D regimen (Table 47). The median duration of follow-up was 3 years. The final analysis is due in March 2015.

Table 47. BCIRG006 Trial. Efficacy Results. *Intent-to-Treat Population.*

	AC→D n=1,073	AC→DH n=1,074	DCarbH n=1,075	Hazard Ratio [95% CI]
DFS%[1]	81.8	87.5	86.5	*AC→DH versus AC→D* 0.61 [0.49, 0.77] *DCarbH versus AC→D* 0.67 [0.54, 0.83]
OS%[1]	92.5	95.4	94.8	*AC→DH versus AC→D* 0.58 [0.40, 0.83] *DCarbH versus AC→D* 0.66 [0.47, 0.93]

[1] Kaplan-Meier estimates.

Safety

- The safety data from the neoadjuvant plus adjuvant trastuzumab trials and the new adjuvant trastuzumab trial were consistent with the known safety profile of trastuzumab. In the pivotal neoadjuvant plus adjuvant trastuzumab Trial MO16432, serious and severe adverse events were not significantly increased when trastuzumab was administered in combination with chemotherapy.
- In regard to cardiac safety, in the pivotal neoadjuvant plus adjuvant trastuzumab trial MO16432, there were similar incidences of cardiac adverse events in the HER2+TC and HER2+C groups overall; however, clinically significant reductions in left ventricular ejection fraction (LVEF) were more frequent in the HER2+TC (trastuzumab) group.

The evaluator recommended rejection of the neoadjuvant plus adjuvant trastuzumab indication due to lack of clinically meaningful increased efficacy compared with neoadjuvant chemotherapy. The other changes to the PI were recommended for approval subject to some modifications.

Risk management plan

The Safety Specification was considered adequate. Implementation of the Australian RMP version 2.0, version 2.0, dated July 2011, revised as specified in the sponsor's correspondence dated 27 February 2012, was recommended as a condition of registration.

Risk-benefit analysis

Delegate considerations

The proposed neoadjuvant plus adjuvant trastuzumab indication was based on one pivotal and two supportive trials. In the pivotal trial MO16432, addition of neoadjuvant plus adjuvant trastuzumab to neoadjuvant standard chemotherapy in patients with HER2+ve breast cancer statistically significantly increased EFS, the primary endpoint, based on the hazard ratio and log-rank test. However when the Russian site, where potential bias occurred, was excluded, the increase was only marginally significant. The absolute increase in EFS at 3 years was neither statistically nor clinically significant. ORR was also not significantly increased and the overall survival data were immature. The supportive trials were of limited value. Therefore, based on the three trials, the efficacy of

neoadjuvant plus adjuvant trastuzumab in combination with neoadjuvant chemotherapy was uncertain.

The rationale for neoadjuvant trastuzumab and chemotherapy is to increase the chance of breast-conserving surgery or improve the operability of the tumour as well as increase overall survival. However, the trials were not designed to test this. The hazard ratio for overall survival in the pivotal neoadjuvant trial was similar to those in the four adjuvant trials. Based on this cross-trial comparison, overall survival appears comparable; however, there were no data for breast conservation or increased operability. Thus, any additional benefit from neoadjuvant and adjuvant trastuzumab with neoadjuvant chemotherapy is not evident (the Delegate accepts that the cross-trial comparison may be misleading). It is also not clear how much each component, neoadjuvant trastuzumab, adjuvant trastuzumab and neoadjuvant chemotherapy, is contributing to efficacy.

The population in the pivotal neoadjuvant trial had locally advanced (Stage III) or inflammatory disease whereas the proposed indication is for localised disease.

A potential safety concern with neoadjuvant trastuzumab is the risk of clinically significant reduction in LVEF which would increase the risk of subsequent breast cancer surgery. To avoid this risk, it would seem preferable to start trastuzumab after surgery (adjuvant).

The Delegate did not support approval of neoadjuvant plus adjuvant trastuzumab.

The new adjuvant trastuzumab Study BCIRG006 which assessed the use of trastuzumab in combination with new chemotherapy regimens confirmed the benefit of trastuzumab in adjuvant use in localised breast cancer.

Delegate's draft decision

The Delegate recommended that:

- the application for neoadjuvant plus adjuvant use of trastuzumab in combination with neoadjuvant chemotherapy in patients with HER2+ve localised breast cancer be rejected on the grounds that efficacy in this indication has not been satisfactorily established
- other changes to the PI including addition of the new adjuvant trastuzumab study to the Clinical Trials section be approved after amendments.

The Delegate proposed the following condition of registration:

- Implementation of the Australian Risk Management Plan, version 2.0, dated July 2011, revised as specified in the sponsor's correspondence dated 27 February 2012, and subsequent revisions as agreed with the Office of Product Review.

The application was submitted to the Advisory Committee on Prescription Medicines (ACPM) for advice.

Response from sponsor

Roche disagreed with the clinical evaluator and Delegate with respect to their conclusion of lack of clinical benefit, approval of indication globally and lack of evidence supporting a broader indication.

1. Clinically meaningful benefit

Roche does *not* agree with the clinical evaluator and Delegate that the pivotal study NOAH does not demonstrate a clinically meaningful benefit.

The clinical study report (CSR) defined: "*A clinically meaningful* improvement with the addition of trastuzumab would be to increase the median EFS (Event Free Survival) time

to 5.5 years, corresponding to 68.5% EFS rate at 3 years. This corresponds to a HR of 0.545". The clinical evaluator's conclusions that a difference in EFS at 3 years of 18.5% is the "minimal clinically significant difference" and that "the observed absolute difference of 13% is not clinically significant" are not valid. The evaluator suggested that there is an absolute cut off for clinical significance, which is not the case. The reference to the EFS rate at 3 years was only made to put the Hazard Ratio into context; it was not intended to be statistically tested. The study was not designed to test Kaplan-Meier estimates of event-free rates at this time point or at any other particular time during the study (for example, at 1 or 2 years). The study was designed and powered to compare the risk of an EFS event over the duration of the study between the HER2+ arms based on the log-rank test which is the appropriate tool to test for superiority of these time-to-event distributions. The magnitude of effect was measured by the hazard ratio as per current practice in clinical trials. Hence, any additional testing (in particular with respect to EFS rates at certain time points) would inflate the type 1 error in the trial.

The primary objective of the NOAH study was met, with a HR of 0.65 representing a 35% reduction in the risk of an EFS event and a statistically significant p-value (p=0.028, unstratified log-rank test) at the 5% significance level. Roche therefore disagreed with the Delegate's recommendation "that efficacy in this indication has not been satisfactorily established".

2. Approval of the neoadjuvant indication in other jurisdictions

The Delegate's Request for ACPM Advice states that the neoadjuvant-adjuvant indication has not been approved anywhere and that the European Commission adoption of the Committee for Medicinal Products for Human Use (CHMP) approval on 17 November 2011 was pending. Roche would like to confirm that the neoadjuvant-adjuvant indication has been approved in a number of countries. The EMA and SwissMedic granted approval in December 2011 and March 2012 respectively. These approvals were based primarily on the statistically significant and clinically meaningful results from the NOAH study.

3. Supportive trials justifying a broader indication

Roche was disappointed that the supportive trials provided with NOAH [key supporting studies MDACC and GeparQuattro and additional 53 publications] were not considered as intended and discussed with the TGA Delegate prior to submission. The additional supportive information was provided to justify the broad therapeutic indication (that is, localised breast cancer as opposed to only locally advanced breast cancer and inflammatory breast cancer) and the addition of trastuzumab to a broad range of neoadjuvant chemotherapy regimens (that is, current standard of care regimens not just those employed in the NOAH study). Roche therefore requested that the combined evidence of the supportive studies plus the NOAH trial be considered to support the use of neoadjuvant-adjuvant trastuzumab in combination with clinically proven neoadjuvant chemotherapy regimens for localised HER2+ breast cancer. Without consideration of the supportive studies, at the very least, a neoadjuvant-adjuvant indication based on the clinically meaningful results from NOAH should be considered.

Efficacy benefit demonstrated in Noah (pivotal study)

Event-Free Survival

As stated by the Delegate, the addition of neoadjuvant-adjuvant trastuzumab to neoadjuvant standard chemotherapy in HER2+ve breast cancer patients significantly increased EFS as demonstrated by the log-rank test and the Hazard Ratio.

Both the evaluator and Delegate commented on the potential bias occurring at the Russian site CRTN 47296 and the sensitivity analyses performed *("when the Russian site was*

excluded the increase was only marginally significant"). Roche performed extensive sensitivity analyses to investigate potential regional effects on EFS. The forest plot showed that treatment effects are consistent across the regions (including Russia) and in line with the overall treatment effect. Roche re-iterates the consistency demonstrated between the primary EFS analysis and the sensitivity EFS analysis excluding the Russian site CRTN 47296. The consequence of a smaller sample (and less EFS events) after excluding CRTN 47296 was increased variability of the HR, resulting in a slightly higher p-value (p = 0.0467) however, the results remained statistically significant at the 5% level and Roche do not believe a reduction in risk of 35% (HR =0.65) is only "*marginally significant*". Additionally, the secondary endpoints of the sensitivity analysis do not support a finding of bias, with the results also remaining in line with the overall analysis (tpCR rate difference of 22.4% in favour of HER2+TC vs.19.3% for overall analysis; OS HR=0.58 (excluding CRTN 47296) versus HR=0.59 for overall analysis).

In summary, Roche did not agree that the treatment effects seen with Herceptin in NOAH *"are uncertain*". The conclusion that *"the absolute increase in EFS at 3 years was neither statistically nor clinically significant"* is based on the inappropriate interpretation of the primary analysis based on the EFS rates at 3 years, together with the incorrect association between the 3 year rate which the evaluator assumed was used to power the study (referred to as: clinically meaningful difference) and threshold of clinical significance.

NOAH demonstrated a significant and clinically meaningful benefit in the primary endpoint (EFS). The corresponding Kaplan-Meier curves show wide and sustained separation between the HER2+ arms (HR 0.65, p=0.0275). Sensitivity analyses including Cox regression adjusted for stratification factors and selected baseline characteristics underline the robustness of the primary result.

Supportive evidence through secondary efficacy endpoints

The clinical evaluator acknowledged that the secondary endpoint, total pathological clinical response (tpCR) supports the efficacy of neoadjuvant Herceptin (CER). A compelling effect of trastuzumab was observed on pCR, with a doubling of the rate of total pCR (defined as absence of invasive breast cancer in the breast and axilla) from 21% in the HER2+C arm to 40% in the HER2+TC arm (p =0.0014, Chi-squared test). pCR has been shown to correlate to long term outcome (disease free and overall survival) after pre-operative treatment in patients with early breast cancer and provides an *in vivo* assessment of tumour chemosensitivity.[44, 45 ,46, 47, 48] Hence the significant difference in rates for pCR (bpCR and tpCR) and the exploratory analyses showing correlation of tpCR with EFS are supportive of the primary analysis in NOAH. Additionally, overall survival (OS) data, albeit immature (updated data submitted with RtQs) showed a sustained OS benefit over time for the Her2+TC arm relative to HER2+C, as demonstrated by HR (initial

[44]Bonadonna G, et al. Primary chemotherapy in operable breast cancer: Eight-year experience at the Milan Cancer Institute. J Clin Oncol 1998;16:93-100.

[45]Kuerer H, et al. Clinical Course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to Doxorubicin-Based Neoadjuvant chemotherapy. J Clin Oncol 1999.17:/460-/469.

[46] Rastogi P, et al. Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008;26:778-785.

[47] Fisher B, Bryant J, Wolmark Net al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998 16:2672-2685

[48]von Minckwitz G, et al. Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes, J Clin Oncol 2012, 30, 1-10

OS: HR=0.59 (95%CI: 0.35, 1.02; log-rank p-value=0.0555); updated OS: HR=0.58 (0.35, 0.94; p-value=0.0241)).

Hence, given the robustness of the pCR results as an objective endpoint for neoadjuvant treatment, the correlation of pCR with long-term outcome and the OS time dynamics (persistence of treatment effect over time which is in line with EFS), the additional efficacy endpoints support the positive treatment effect in the HER2+TC arm.

As well as improving long term outcomes (event free and overall survival), the rationale for neoadjuvant trastuzumab and chemotherapy is to increase the chance of breast-conserving surgery or improve the operability of the tumour. Improved efficacy with the addition of trastuzumab was reflected in NOAH with a doubling of breast conserving operations. Although the type of surgery performed was not a secondary endpoint in NOAH, in some patients, the choice of procedure performed probably reflected to some extent the clinical response to neoadjuvant therapy. Twice as many patients in the HER2+TC arm were able to have breast-conserving surgery (such as quadrantectomy, lumpectomy or wide excision) than patients in the HER2+C arm (21.4% [21/98]) versus 10.5% [9/86];). This is consistent with the higher clinical response and pCR rate in the HER2+TC arm and is an additional indicator of patient benefit, given that one of the main objectives of neoadjuvant treatment is the down-staging of large tumours to avoid mastectomy.

Safety

In the Delegate's overview it is stated that "*a potential safety concern with neoadjuvant trastuzumab is the risk of clinically significant reduction in LVEF which would increase the risk of subsequent breast cancer surgery. To avoid this risk, it would seem preferable to start trastuzumab after surgery (adjuvant).*"

As expected, combination therapy with trastuzumab led to a higher number of patients with a significant preoperative LVEF decrease (defined as decline of > 10 points from baseline and decrease to < 50%) in the HER2+TC arm than in the control arm, however, the overall number of such events was low (4 (3.5%) in the HER2+TC arm versus 1 (0.9%) in the HER2+C arm). In 1 of the 4 patients in the Herceptin arm the LVEF declined to <45%. This was also the only patient who developed symptoms of heart failure (in 115 patients overall). All 4 events were reversible (LVEF recovered to > 50% (2 of them to >55%)). The management of LVEF reductions is clearly stated in the current label.

Based on the current guidelines of the American College of Cardiology and the American Heart Association for perioperative cardiovascular evaluation and care for non-cardiac surgery[49], Roche does not consider decreased resting LVEF function in asymptomatic patients with no pre existing cardiac conditions to be associated with an increase of perioperative ischemic events. Symptomatic patients and those with pre-existing cardiac conditions are currently advised to be treated with caution (see the Precautions, Cardiotoxicity section of the Australian Product Information).

Further to this, following finalisation of this submission, Roche plans to update the PI with updated safety information for the concurrent administration of Herceptin and anthracyclines in the neoadjuvant-adjuvant setting to assist prescribers to manage this identified risk.

Importantly, and as confirmed by the Delegate ("*in the pivotal neoadjuvant-adjuvant trastuzumab trial, MO16432, serious and serious adverse events were not significantly*

[49] Fleisher LA, et al: ACC/AHA 2007 guidelines on Perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary. Journal of the American College of Cardiology 50:1707-1732, 2007

increased when trastuzumab was administered in combination with chemotherapy") the safety profile of neoadjuvant-adjuvant trastuzumab is consistent with the known adjuvant trastuzumab profile. And therefore the addition of Herceptin before surgery does not change the risk profile of Herceptin (also confirmed by the OPR review of the RMP).

Supportive studies

As described in the application cover letter (and pre-submission planning form), this dossier was considered a hybrid submission. NOAH is the pivotal study supporting the proposed indication and a well defined literature search was conducted to identify an additional 55 supportive references.

The relevance of the additional supportive data included in the submission (literature component) is considered by the sponsor to be significant, providing further evidence of the efficacy of neoadjuvant trastuzumab in the NOAH patient population (locally advanced breast cancer (LABC) and inflammatory breast cancer (IBC), that is, Stage III disease) and also to justify the broad therapeutic indication

a. in localised breast cancer (that is, Stage I, II and III patients) and

b. in association with a broad range of neoadjuvant chemotherapy regimens (that is, current standard of care regimens not just that employed in the NOAH study).

It was therefore disappointing that the clinical evaluator (and therefore the Delegate) considered them to be of "limited value".

1. Further support the efficacy demonstrated in the NOAH population (LABC and IBC)

Of the 55 supportive studies submitted, 4 are subsequently presented in more detail below because;

- they are either large (> 100 patients: GeparQuattro^, GeparQuinto*, TECHNO*) or
- have included a non-Herceptin control arm (MDACC) and

[The clinical evaluator acknowledged the MDACC study results as being clinically meaningful with "the primary efficacy endpoint pCR rate statistically significantly higher in the HER +TC arm (65.2% [n=23]) compared with the HER2+C arm (26.3% [n=19]); p=0.016".]

- they all employed a chemotherapy treatment regimen containing the same elements as the chemotherapy regimen in the NOAH study (i.e. at least 8 cycles of an anthracycline- and taxane-containing chemotherapy)

^Note the intent of submitting the GeparQuattro study was not to demonstrate superiority versus the HER2- arm but to consider the large number (n = 445) of HER2+ patients receiving neoadjuvant-adjuvant trastuzumab with neoadjuvant chemotherapy.

* Studies submitted as SABC abstracts but have now been fully published.

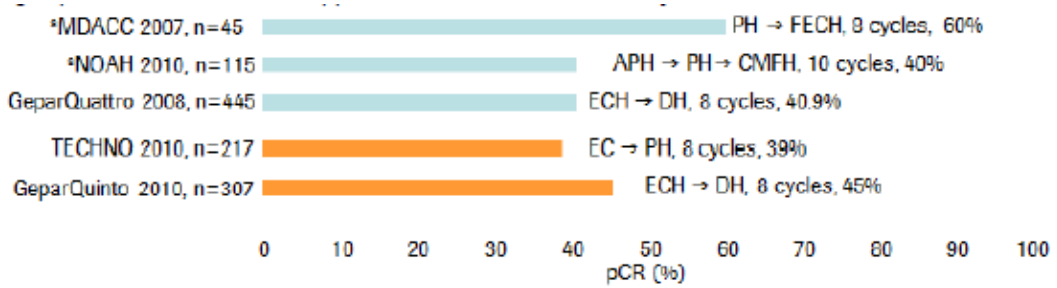
All 4 studies tabulated below (and several of the additional supportive studies) included a large percentage of patients with locally advanced disease. The pCR rates observed in these studies are consistent with the pCR rate in the NOAH study (Figure 7) and therefore provide further evidence of the efficacy of adding trastuzumab to neoadjuvant chemotherapy in HER2+ patients LABC and IBC.

Table 48. Patient population in supportive studies

Study	Study population as per protocol inclusion criteria	Distribution of tumour stage
MDACC[1]	invasive, but noninflammatory, carcinoma of the breast with stage II to IIIA disease	T1: 10.9% T2: 65.6% T3/4: 15.6% [4][1]
GeparQuattro[2]	either • locally advanced (cT3 or cT4), • hormone receptor (HR) –negative, or • HR+ but lymph node–positive tumours	T1: 15.1% T2: 55.1% T3/4: 29.9% [5][2]
GeparQuinto[3]	either • locally advanced (cT3 or cT4), • hormone receptor (HR) –negative, or • HR+ but lymph node–positive tumours	T1: 13.3% T2: 43.3% T3/4: 36.7% [3][3]
TECHNO[4]	tumours were either > 2 cm based on clinical or ultrasound assessment or were diagnosed clinically as inflammatory breast cancer	T1: 4.8% T2: 66.2% T3/4: 28.1% [1][4]

1: total n=64 pts, 2: total n=445 HER2+ pts, 3: total n=615 pts, tumour size by palpation 4: total n=217 pts,

Figure 7. pCR rates observed in supportive studies and NOAH study



Definition of pCR: Absence of invasive cancer in breast and axillary nodes

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; A, doxorubicin
Number of cycles reflects q3w regimen.

2) Expand the efficacy information for the proposed neoadjuvant-adjuvant indication (broad chemotherapy regimen and patient population)

As tabulated in Table 48 above, the MDACC, GeparQuattro, GeparQuinto and TECHNO studies (and many of the other supportive studies) included a large proportion of patients with operable breast cancer (tumour Stages T1 and T2) with a varied chemotherapy regimen, and demonstrated pCR rates consistent with the pCR rate observed in the NOAH study (Figure 7). Therefore, the benefits of adding trastuzumab to neoadjuvant chemotherapy apply regardless of whether the neoadjuvant therapy is required for disease that is technically inoperable (locally advanced, including inflammatory disease) or disease that is operable but requires down-staging of the tumour prior to surgery. Therefore the proposed indication for neoadjuvant-adjuvant trastuzumab also includes patients with HER2+ operable breast cancer, as is expressed in the term "*localised*". For this reason, Roche have not classified the use of neoadjuvant trastuzumab for locally advanced or inflammatory breast cancer, as per the NOAH patient population. If the ACPM and TGA do not believe the dossier supports the safe and efficacious use of neoadjuvant trastuzumab in patients with localised breast cancer (or non-metastatic disease) then an indication more aligned with the EU and Switzerland approvals (Stage II and III disease) could be considered.

The additional studies and publications also provide further supportive evidence of the safety and efficacy of trastuzumab when added to various chemotherapy regimens in the neoadjuvant setting. For this reason Roche have not specified the chemotherapy regimen to be used with neoadjuvant/adjuvant trastuzumab.

3) Expand the safety information for the proposed neoadjuvant-adjuvant indication (broad chemotherapy regimen and patient population)

Safety data from the key studies MDACC, TECHNO, GeparQuinto and GeparQuattro support the safety findings from NOAH, in that the addition of neoadjuvant trastuzumab was not associated with any unexpected safety issues or unmanageable additional toxicity.

Further safety data were also presented from a large number of the Phase II trials and retrospective reviews of trastuzumab given in combination with various chemotherapy regimens in the neoadjuvant setting.

Cardiac toxicity with neoadjuvant trastuzumab was low across the supportive studies. In particular, MDACC, GeparQuinto and GeparQuattro provide further supportive evidence of the cardiac safety of this treatment approach. All studies included concurrent treatment of Herceptin with low dose anthracycline regimens in 797 patients (in addition to the 115 patients from the NOAH study). The rate of symptomatic congestive heart failure or significant LVEF declines was low in all three studies (Table 49). No cardiac deaths were observed.

Table 49. Cardiac safety in supportive studies.

Study	n	Symptomatic CHF	LVEF decline[1]	Cardiac Deaths
MDACC	45	0 (0%)	1 (2.2%)	0 (0%)
GeparQuattro	445	1 (0.2%)	4 (0.9%)	0 (0 %)
GeparQuinto	309	1 (0.3%)	4 (1.4%)	0 (0%)

1. LVEF decline of > 10% and to below 50%

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall positive benefit–risk profile for the indication:

Current Indication

> *For the treatment of patients with HER2-positive localised breast cancer following surgery and in association with chemotherapy and, if applicable, radiotherapy.*

Additional extended indication

> *For the treatment of patients with HER2 positive locally advanced breast cancer in association with neo adjuvant chemotherapy and, if applicable, radiotherapy.*

In making this recommendation the ACPM agreed with the Delegate that the studies were not adequately designed to test the optimal timing for surgery in relation to the combined treatment regimen. However, the ACPM agreed that the data supports an indication to be extended to the locally advanced population subset.

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- A statement in the appropriate section of the (*Dosage and Administration / Clinical Trials / Precautions / Contraindications*) section of the PI and CMI to ensure accurate reflection of the data aligned with this new indication.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Herceptin (trastuzumab) for the new indication:

> *For the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin.*

Specific Conditions Applying to these Therapeutic Goods

1. The implementation in Australia of the trastuzumab Risk Management Plan (RMP) version 2.0, dated July 2011, included with submission PM-2011-01528-3-4, and revised as specified in the sponsor's correspondence dated 27 February 2012, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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