THE EU RISK MANAGEMENT PLAN FOR PERJETA® / PERTUZUMAB

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Rationale for submitting an updated risk management plan (RMP):

This version (V 13.1) of RMP is updated with completed status of Study MO28047 (PERUSE) in response to the RSI on submission of final Clinical Study Report for the Study MO28047 (PERUSE): A multicenter, open-label, single-arm study of pertuzumab in combination with trastuzumab and a taxane in first line treatment of patients with HER2- positive advanced (metastatic or locally recurrent) breast cancer. The Clinical Study Report (CSR) for this study shall be submitted along with this RMP as a Type II variation.

No new information was obtained for the safety concern Congestive heart failure/Left ventricular dysfunction. The safety concern of missing information risk in patients with cardiovascular impairment was not assessed as these patients were excluded from the study as stated in Peruse protocol and therefore is removed as an additional PV activity for this missing information

Summary of significant changes in this RMP

- Part III Module III.2 the references to PERUSE study from the pharmacovigilance plan was removed.
- Part III Module III.3 the reference to the PERUSE study was removed from the Table 24 and indicated as not applicable (NA) for category 1.
- Part IV the information regarding the APHINITY study was updated for the study status and further details were included in the Table 25.
- Part V Module V.3 the references made to the PERUSE study in Table 27 was deleted as the study is no longer ongoing.
- Part VI Module II.B and II.C the references to the PERUSE study were removed.

Other RMP versions under evaluation: None

RMP Version number: N/A
Submitted on: N/A
Procedure number: N/A

Details of Currently Approved RMP
Version number: 12.0
Approved with procedure: EMEA/H/C/002547/IB/0050
Date of approval (Commission Decision date): 9 July 2020

See page 1 for signature and date

[redacted] **(Deputy QPPV)** Date

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[redacted] Date

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PART I: PRODUCT OVERVIEW

Active Substance(s) (INN or common name)	Pertuzumab
Pharmacotherapeutic group(s) (ATC Code)	L01XC13
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Perjeta®
Marketing authorization procedure	Centrally authorized procedure
Brief description of the product including:	Chemical Class: Anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody.
	Summary of mode of action: Perjeta is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, Perjeta inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, Perjeta mediates antibody-dependent cell-mediated cytotoxicity (ADCC).While Perjeta alone inhibited the proliferation of human tumor cells, the combination of Perjeta and trastuzumab significantly augmented antitumor activity in HER2-overexpressing xenograft models.
	Important information about its composition: Pertuzumab is a humanised IgG1 monoclonal antibody produced in mammalian (Chinese

	hamster ovary) cells by recombinant DNA technology.
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	Current: **Early breast cancer** Perjeta is indicated for use in combination with trastuzumab and chemotherapy in: • the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence • the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence **Metastatic breast cancer** Perjeta is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended initial loading dose of Perjeta is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes. Perjeta and trastuzumab should be administered sequentially and can be given in any order. When administered with Perjeta the recommended initial loading dose of trastuzumab is 8 mg/kg body weight administered as an intravenous infusion followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight. In patients receiving a taxane, Perjeta and trastuzumab should be administered prior to the taxane.

	When administered with Perjeta the recommended initial dose of docetaxel is 75 mg/m^2 administered thereafter on a 3 weekly schedule. In patients receiving an anthracycline-based regimen, Perjeta and trastuzumab should be administered following completion of anthracycline (see section 4.4 of the SmPC). **Metastatic Breast Cancer** Perjeta should be administered in combination with trastuzumab and docetaxel until disease progression or unmanageable toxicity. Treatment with Perjeta and trastuzumab may continue even if treatment with docetaxel is discontinued. **Early breast cancer** **Neoadjuvant Treatment of Breast Cancer** In the neoadjuvant setting, Perjeta should be administered for 3 to 6 cycles in combination with trastuzumab and chemotherapy, as part of a complete treatment regimen for early breast cancer (see Section 5.1 of the SmPC). **Adjuvant Treatment of Breast Cancer** In the adjuvant setting, Perjeta should be administered in combination with trastuzumab for a total of one year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first) as part of a complete regimen for early breast cancer and regardless of the timing of surgery. Treatment should include standard anthracycline- and/or taxane-based chemotherapy. Perjeta and trastuzumab should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued.
	Proposed: Not applicable

Pharmaceutical form(s) and strengths	Current: Concentrate solution for infusion. One 14 ml vial of concentrate contains 420 mg of pertuzumab at a concentration of 30 mg/ml.
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the EU?	No

EEA=European economic area; EU=European Union; HER2=Human epidermal growth factor receptor 2; SmPC=Summary of Product Characteristics.

ABBREVIATIONS

AEGT	Adverse Event Grouped Term
AEs	Adverse events
ADAs	anti-drug antibodies
ALK	Alkaline phosphatase
ATAs	anti-therapeutic antibodies
CBR	clinical benefit rate
CHF	Congestive heart failure
CVD	Cerebrovascular disease
EBC	Early breast cancer
FEC	5 fluorouracil, epirubicin and cyclophosphamide
GD	gestation day
H	trastuzumab (Herceptin)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER	Human epidermal growth factor receptor
HIV	Human immunodeficiency virus
IHD	ischemic heart disease
IRF-PFS	independent review facility-assessed progression-free survival
IRR	infusion-related reactions
ITT	intent-to-treat
IV	intravenous
LVD	left ventricular dysfunction
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MBC	Metastatic breast cancer
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PFS	Progression-free survival
Pla	Placebo
Pla+H+D	Placebo + trastuzumab + docetaxel
Ptz+H+D	pertuzumab + trastuzumab + docetaxel
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PT	Preferred Term
Ptz	Pertuzumab

ABBREVIATIONS	
RMP	Risk Management Plan
SAEs	Serious adverse events
SEER	Surveillance Epidemiology and End Results
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
TEE	thromboembolic events

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 METASTATIC BREAST CANCER

Incidence:

The epidemiologic evidence specific to the human epidermal growth receptor 2 (HER2)-positive metastatic breast cancer (MBC) patient population is limited; we therefore present data from the general breast cancer population to supplement our findings.

Breast cancer was the second most commonly diagnosed cancer in the world and the most commonly diagnosed cancer among women with 2.09 million new cases and approximately 630,000 deaths in 2018 (IARC Breast Cancer 2018). In the more developed nations, it is the second most common cause of cancer death. This is a disease affecting 10 – 12% of women (Benson 2009). In 2018, it was estimated that there were 522,513 new cases of breast cancer in Europe, which represents 26% of all reported cases of cancer in women. (IARC Breast Cancer 2018. Since HER2-positive disease accounts for approximately 15% – 20% of cases of breast cancer (Wolff et al, 2007; Chia et al, 2008, Ross et al, 2009). It is estimated that approximately 264,000 new cases of HER2-positive breast cancer occur each year globally and 92,620 cases in the EU. Of these, around 94 – 95% would be non-metastatic at diagnosis and therefore potentially eligible for adjuvant or neoadjuvant treatment.

Depending on stage, tumor biology and the treatments utilized, between 20% and 85% of women with early breast cancer (EBC) develop distant metastases. The overall incidence of MBC (i.e., including patients initially presenting with early disease who subsequently relapse) is probably best indicated by annual mortality rates (refer to the mortality section below) since most patients who die from breast cancer die from metastatic disease.

There is limited data on the secular trends associated with the incidence of HER2-positive breast cancer. Köninki et al, 2009 reported the results from three cohorts (years 1982 to 1986 [n = 310], 1989 to 1992 [n = 108], and 2004 to 2005 [n = 713]) to estimate time trends of HER2-positive breast cancer: the age-adjusted incidence of HER2-positive breast cancer increased only slightly from 1982 to 2005 (12.2 per 100,000 to 13.0 per 100,000, respectively), whereas the incidence of HER2-negative breast cancer doubled over the same period (44.1 per 100,000 to 82.3 per 100,000, respectively). Numbers for incidence of HER2 positive breast cancer may vary as other factors like demographic parameters, histology/type of breast cancer and/or HER2 testing quality have an impact on positivity rates (Ruschoff et al, 2017; Wolff et al, 2007).

Prevalence

In 2008, the 5-year limited duration prevalence (i.e., breast cancer cases diagnosed between 2004 and 2008 who were still alive at the end of 2008) in the EU-27 was estimated to be 1,329,950 (Bray et al, 2013). To our knowledge, there have been no epidemiologic studies reporting on the prevalence of HER2-positive MBC. However, based on the prevalence of breast cancer in general, the 5-year limited duration prevalence of HER2-positive v is estimated to be 266,000 (or ~20% of all breast cancer cases) in the EU-27. It was suggested that improvements in treatment and aging of the population could lead to increased prevalence of MBC (Mariotto et al, 2017).

- Demographics:

The incidence rate of BC rises rapidly between 35 and 39 years of age and then levels off to a plateau after 80 years of age (Benson et al. 2009, Smigal et al. 2006). From US Surveillance Epidemiology and End Results (SEER) data 2005-2009, the median age at diagnosis for cancer of the breast was 61 years. HER2-positive BC tends to occur in the mid-50s (around 5 years younger than the general BC population (Neven et al. 2008, Kwan et al. 2009). Among patients newly diagnosed with BC, 28% of those aged 20-29 years were HER2-positive, while only about 10% of those aged >75 years were HER2-positive (Clarke et al. 2012).

The average age of diagnosis of breast cancer for men is 67 years, which is 5 – 10 years later than the average age of diagnosis for women. Estimation of HER2-positive breast cancer in men varies in the literature and may be as high as 5% – 56% (Onami et al, 2010; Barh 2009). Racial differences in the incidence of different breast cancer sub-types have been described (Kwan et al, 2009), notably for triple-negative breast cancer, but no particular racial differences have been described for HER2-positive disease.

The main existing treatment options:

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and systemic treatment of disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy, including HER2-targeted therapies, or combinations of these.

Risk factors for the disease:

Major risk factors for developing breast cancer (of all types) include age, sex and biomarker status (Hennigs et al, 2016; Ngyugen et al, 2008). It was reported that the number of involved lymph nodes at the time of breast cancer diagnosis are significant risk factors for distant metastases. The incidence rate rises rapidly after around 35 years of age, the increase slows around 50 years and then levels off to a plateau after 80 years of age (Benson et al 2009; Smigal et al 2006). HER2-positive breast cancer tends to occur in the mid-50s (around 5 years younger than the general breast cancer

population (Neven et al, 2008; Kwan et al, 2009). Breast cancer is rare in men, accounting for less than 1% of all malignancies in men (Fentiman et al, 2006).

Natural history of the indicated condition in the untreated population:

Mortality: Approximately 630,000 deaths due to breast cancer were recorded worldwide in 2018. Of these, 46,000 deaths in North America. and 138,000 deaths in the EU due to breast cancer were reported (IARC Breast Cancer 2018). According to Surveillance Epidemiology and End Results (SEER) database, from 2010 to 2014, the age-adjusted mortality due to breast cancer was reported to be 21.2 per 100,000 women per year (SEER website). According to an analysis of the SEER data (n = 1800), stage IV breast cancer is associated with a 27-fold increase in mortality compared to stage I disease (Yancik et al, 2001).

Discussion of the possible stages of disease progression to be treated: Most breast cancers in the Western world (around 94% – 95% of patients in the U.S. and Europe) are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Howlader et al, 2016; Sant et al, 2003) i.e. only around 5% – 6% of new cases are metastatic at diagnosis. Hence, around 94 – 95% would be non-metastatic at diagnosis and therefore potentially eligible for adjuvant or neoadjuvant treatment.

Outcome of the (untreated) target disease: MBC is almost always fatal. Five-year relative survival for newly diagnosed patients with distant disease is 24%, as compared to 99% for localized patients (Howlader et al, 2016). Depending on stage, tumor biology and the treatments utilized, between 20% and 85% of women with EBC develop distant metastases.

Important co-morbidities:

Diabetes, Obesity, Thromboembolic events (TEE), Cerebrovascular disease (CVD), Congestive Heart failure (CHF), Ischemic heart disease (IHD), Hypertension.

SI.2 EARLY BREAST CANCER

Incidence:

The epidemiologic evidence has been limited in the HER2-positive EBC patient population; therefore the data is presented from the general breast cancer population to supplement our findings. Refer to Section SI.1 for information regarding the incidence of overall BC and HER2-positive disease.

As mentioned in Section SI.1, most breast cancers in the Western world (around 94% – 95% of patients in the U.S. and Europe) are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Howlader et al, 2016; Sant et al, 2003) (i.e., EBC at diagnosis).

The age adjusted incidence rate of EBC among white women in the U.S. aged ≥20 years, from 2005 to 2009, was reported to be 163.2 per 100,000 person-years, while among non-white women, it was reported to be 56.6 per 100,000 person-years (Crabbe et al, 2015).The incidence of diagnosis of EBC increases with advanced age (De Glas et al, 2014).

Prevalence:

The prevalence of HER-2 positive breast cancers in 12 population-based SEER registries was estimated at 19% (95% confidence interval [CI]: 13; 25%) of women aged 49 years or younger and 15% (95%CI: 9; 21%) of women aged 50 years or older with early stage breast cancer. The overall prevalence estimate for the SEER population was 16% (95%CI: 12; 21%) for stage I, II, and IIIa breast cancer among women diagnosed in the year 2005 (Cronin et al, 2010).

Demographics:

The demographic profile of EBC is similar to that in MBC (refer to Section SI.1), although patients tend to be a few years younger. The incidence of breast cancer increases with age, and is higher in females than males and in Caucasians compared with other racial groups (Howlader et al, 2010; Anderson WF et al, 2009; Crabbe et al, 2015; Iqbal et al, 2015).

The main existing treatment options:

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and systemic treatment of disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy, including HER2-targeted therapies, or combinations of these. Data from recent observational studies using very large, prospectively collected, population-based studies suggested a detrimental impact for delayed time to surgery (Bleicher et al, 2015), or delayed initiation of adjuvant chemotherapy (Chavez-MacGregor et al, 2016).

Risk factors for the disease:

Major risk factors for developing breast cancer are described in Section SI.1.

Mortality: Mortality from breast cancer is typically due to metastatic disease. According to the SEER database, the mortality among patients with EBC due to breast cancer, from 2004 to 2012, was found to be 1.9% (3889/206,625) (Iqbal et al, 2017). Based on SEER data (2010), approximately 57% of deaths from breast cancer occur in those aged >65 years, and the median age at death from breast cancer is 68 years. Stage 4 breast cancer is associated with a 27-fold increase in mortality compared to stage I disease (Yancik et al, 2001).

Outcome of the (untreated) target disease: Based on a review of 107 published studies, Ross et al, 2009 reported that the relative risk for adverse clinical outcome of untreated

HER2-positive breast cancer is 2.74 (range, 1.39 – 6.93). It is estimated that up to 1 in 4 patients will experience recurrence within 10 – 11 years of diagnosis (Slamon et al, 2015; Cameron et al, 2017; Perez et al, 2014).

Important co-morbidities:

Important co-morbidities for EBC are similar to those for MBC and are described in Section SI.1.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 GENERAL SAFETY PHARMACOLOGY

SII.1.1 GENERAL FINDINGS

Relevance to human usage: Yes

Discussion: The pharmacokinetics (PK) of pertuzumab were consistent with trastuzumab and other IgG1 monoclonal antibodies that share the same Fc region as characterized by a distribution phase of less than 1 day, a terminal half-life of approximately 10 days, and volume of distribution of the central compartment of 30 to 50 mL/kg approximating the serum volume.

SII.1.2 DOSE ESCALATION

Relevance to human usage: Yes

Discussion:

In cynomolgus monkeys, weekly intravenous (IV) administration of pertuzumab at doses up to 150 mg/kg/dose were generally well tolerated. With doses of 15 mg/kg and higher intermittent mild treatment-associated diarrhea was noted. In a subset of monkeys chronic dosing (7 to 26 weekly doses) resulted in episodes of diarrhea-related dehydration which were managed with IV fluid replacement therapy. Diarrhea was observed in clinical trials.

SII.1.3 MECHANISMS FOR DRUG INTERACTIONS

Relevance to human usage: Yes

Discussion:

No PK interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel in a sub-study of 37 patients in the randomized, pivotal trial CLEOPATRA in MBC. In addition, no evidence of drug-drug interactions has been shown between pertuzumab and trastuzumab or between pertuzumab and docetaxel, paclitaxel, gemcitabine, capecitabine, carboplatin, or erlotinib. The absence of drug-drug interactions was confirmed by PK data from the NEOSPHERE trial in the neoadjuvant setting and by PK data from the APHINITY trial in the adjuvant setting.

SII.2 TOXICITY

SII.2.1 DEVELOPMENT TOXICITY

Placental transfer of pertuzumab was confirmed in cynomolgus monkeys. Systemic maternal and fetal exposure at clinically relevant pertuzumab concentrations was confirmed. Fetal to maternal pertuzumab serum concentration ratios were similar across a 10-fold range of doses at clinically relevant concentrations (20-fold greater than human clinical dose). Pertuzumab-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in a study when pertuzumab was administered intravenously from Gestation Day 19 (GD19) through GD50 to pregnant cynomolgus monkeys, the period of organogenesis in this species (GD20–50). In addition, consistent with fetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 30 mg/kg and 1 of 2 100 mg/kg), ventricular septal defects (1 of 6 30 mg/kg), thin ventricular wall 1 of 2 100 mg/kg) and minor skeletal defects (external - 3 of 6 30 mg/kg) were also noted.

Relevance to human usage: Yes

Discussion:

No clinical studies have been performed in pregnant women.

Women of childbearing potential and female partners of male patients of childbearing potential should use effective contraception while receiving pertuzumab and for 6 months following the last dose of pertuzumab (7 months after the last dose of trastuzumab, which is generally given concurrently with pertuzumab in clinical studies and routine practice).

SII.2.2 CARCINOGENICITY

Relevance to human usage: Yes

Discussion:

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of pertuzumab. In accordance with ICH guidance S6(R1) carcinogenicity tests are not required for the safety evaluation of monoclonal antibodies or recombinant human proteins such as pertuzumab.

SII.2.3 MUTAGENICITY

Relevance to human usage: Yes

Discussion:

Studies have not been performed to evaluate the mutagenic potential of pertuzumab. In accordance with ICH guidance S6(R1) standard mutagenicity tests are not required for

the safety evaluation of monoclonal antibodies or recombinant human proteins such pertuzumab.

SII.2.4 OTHER TOXICITY-RELATED INFORMATION OR DATA

Relevance to human usage: Yes

Discussion:

Since Perjeta is a biological medicine, general pharmacology, nephrotoxicity and hepatotoxicity were not studied.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Clinical trial exposure data are presented below for each indication by duration of exposure, age group, dose and racial origin in Table 1 to Table 9.

The clinical safety data presented are derived primarily from the following trials:

MBC indication: The pivotal, randomized, double-blind, placebo-controlled Phase III MBC study, WO20698/TOC4129g (CLEOPATRA), an exploratory Phase II study, BO17929 and Phase III MO28047 (PERUSE).

EBC indications: Three neoadjuvant treatment studies, WO20697 (NEOSPHERE, the pivotal, randomized, Phase II neoadjuvant study), BO22280 (TRYPHAENA) and WO29217 (BERENICE); and the pivotal, randomized, double-blind, placebo-controlled Phase III adjuvant study, BO25126 (APHINITY).

Table 1 Duration of Exposure to Perjeta in the PERUSE study

Duration of Exposure to Perjeta in the PERUSE study

	Pertuzumab + Trastuzumab + Chemotherapy (N=1435)
Total Patient cycles of Pertuzumab exposure	
n	1435
Mean (SD)	37.6 (33.6)
Median	24.0
Range	1, 126
Duration of Exposure	
n	1435
<= 1 months	40 (2.8%)
> 1 - <= 3 months	62 (4.3%)
> 3 - <= 6 months	161 (11.2%)
> 6 - <= 12 months	319 (22.2%)
> 12 - <= 24 months	292 (20.3%)
> 24 months	561 (39.1%)
Patient exposure duration (months per patient)	
n	1435
Mean (SD)	26.3 (23.9)
Median	16.2
Range	0, 86

Months = (days/365.25)x12

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dur_per.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dur_per_SE.out
24JUN2020 10:25

Table 2 **Duration of Exposure to Perjeta by Indication**

Duration of Exposure to Perjeta by Indication

	EBC (N=3282)	MBC (N=1983)	Total (N=5265)
Total Patient cycles of Pertuzumab exposure			
Mean (SD)	14.4 (5.7)	34.8 (31.6)	22.1 (22.2)
Median	17.0	22.0	18.0
Range	1, 22	1, 140	1, 140
Duration of Exposure			
n	3282	1983	5265
<= 1 months	110 (3.4%)	77 (3.9%)	187 (3.6%)
> 1 - <= 3 months	428 (13.0%)	109 (5.5%)	537 (10.2%)
> 3 - <= 6 months	210 (6.4%)	228 (11.5%)	438 (8.3%)
> 6 - <= 12 months	2178 (66.4%)	420 (21.2%)	2598 (49.3%)
> 12 - <= 24 months	356 (10.8%)	438 (22.1%)	794 (15.1%)
> 24 months	0	711 (35.9%)	711 (13.5%)
Patient exposure duration (months per patient)			
Mean (SD)	9.6 (4.1)	24.2 (22.6)	15.1 (15.9)
Median	11.7	15.2	11.7
Range	0, 17	0, 98	0, 98

Months = (days/365.25)x12

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dur.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dur_AP.out
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Table 3 Exposure to Perjeta by Dose and Indication

Exposure to Perjeta by Dose and Indication

	EBC (N=3282)	MBC (N=1983)	Total (N=5265)
Total pertuzumab exposure (mg)			
Mean (SD)	6516.9 (2429.53)	15083.5 (13324.51)	9743.4 (9368.05)
Median	7980.0	9660.0	7980.0
Range	300, 9660	420, 59640	300, 59640
Number of Patients Receiving Planned Dose Level	n (%) Person months	n (%) Person months	n (%) Person months
420mg (840mg loading dose)	3282(100.0)[33711.8]	1983(100.0)[49390.3]	5265(100.0)[83102.1]

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25)*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dose.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dose_AP.out
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Table 4 Exposure to Perjeta by Dose and Age-Group: Metastatic Breast Cancer

Exposure to Perjeta by Dose and Age-Group: Metastatic Breast Cancer

	Age 18-39 (N=252)	Age 40-64 (N=1354)	Age 65-74 (N=293)	Age >=75 (N=84)
Total pertuzumab exposure (mg)				
Mean (SD)	15347.7 (13616.21)	15650.1 (13507.18)	12928.0 (12186.68)	12675.4 (12437.78)
Median	10080.0	10500.0	7980.0	6930.0
Range	840, 51249	420, 53340	420, 59640	840, 48774
Number of Patients Receiving Planned Dose Level	n (%) Person months	n (%) Person months	n (%) Person months	n (%) Person months
420mg (840mg loading dose)	252(100.0) [6360.1]	1354(100.0) [35015.7]	293(100.0) [6251.6]	84(100.0) [1762.9]

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25)*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dose.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dose_AGEGRP_MBC_AP.out
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Table 5 Exposure to Perjeta by Dose and Age-Group: Early Breast Cancer

	Age 18-39 (N=495)		Age 40-64 (N=2394)		Age 65-74 (N=352)		Age >=75 (N=41)	
Total pertuzumab exposure (mg)								
Mean (SD)	6590.2 (2367.69)		6544.2 (2414.54)		6430.1 (2481.56)		4781.9 (2974.56)	
Median	7980.0		7980.0		7980.0		3780.0	
Range	420, 8400		300, 9660		420, 8400		420, 7980	
Number of Patients Receiving Planned Dose Level	n (%)	Person months	n (%)	Person months	n (%)	Person months	n (%)	Person months
420mg (840mg loading dose)	495(100.0)	[5154.4]	2394(100.0)	[24668.7]	352(100.0)	[3580.3]	41(100.0)	[308.4]

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25)*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: /opt/BIOSTAT/prod/cd11450w/t_ex_dose.sas / Output: /opt/BIOSTAT/prod/cd11450w/reports/t_ex_dose_AGEGRP_EBC_AP.out
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Table 6 Exposure to Perjeta by Dose and Age-Group: Metastatic and Early Breast cancer

Exposure to Perjeta by Dose and Age-Group: Metastatic and Early Breast cancer

	Age 18-39 (N=747)		Age 40-64 (N=3748)		Age 65-74 (N=645)		Age >=75 (N=125)	
Total pertuzumab exposure (mg)								
Mean (SD)	9544.5 (9124.69)		9833.8 (9420.19)		9381.8 (9009.96)		10086.3 (10965.71)	
Median	7980.0		7980.0		7980.0		6720.0	
Range	420, 51249		300, 53340		420, 59640		420, 48774	
Number of Patients Receiving Planned Dose Level	n (%)	Person months	n (%)	Person months	n (%)	Person months	n (%)	Person months
420mg (840mg loading dose)	747(100.0)	[11514.5]	3748(100.0)	[59684.4]	645(100.0)	[9831.9]	125(100.0)	[2071.3]

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25)*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dose.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dose_AGEGRP_AP.out
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Table 7 Exposure to Perjeta by Dose and Race: Metastatic Breast Cancer

Exposure to Perjeta by Dose and Race: Metastatic Breast Cancer

	Asian (N=243)	Black (N=22)	White (N=1388)	Other (N=329)	Missing (N=1)
Total pertuzumab exposure (mg)					
Mean (SD)	14574.0 (11713.09)	11798.2 (9757.26)	14992.0 (13480.94)	16110.1 (13941.00)	420.0
Median	10920.0	9030.0	9500.0	10500.0	420.0
Range	840, 45780	840, 34860	420, 59640	840, 52500	420, 420
Number of Patients Receiving Planned Dose Level	n (%) Person months	n (%) Person months	n (%) Person months	n (%) Person months	n (%) Person months
420mg (840mg loading dose)	243(100.0) [5805.2]	22(100.0) [426.9]	1388(100.0) [34383.5]	329(100.0) [8773.9]	1(100.0) [0.7]

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25)*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dose.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dose_RACEGR1_MBC_AP.out
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Table 8 Exposure to Perjeta by Dose and Race: Early Breast Cancer

	Asian (N=700)		Black (N=58)		White (N=2380)		Other (N=89)		Missing (N=55)	
Total pertuzumab exposure (mg)										
Mean (SD)	6814.2 (2283.97)		5257.2 (2836.87)		6446.3 (2458.17)		6418.0 (2577.41)		7277.5 (1381.34)	
Median	7980.0		6300.0		7980.0		7980.0		7560.0	
Range	420, 8400		840, 8400		300, 9660		840, 7980		1680, 7980	
Number of Patients Receiving Planned Dose Level	n (%)	Person months	n (%)	Person months	n (%)	Person months	n (%)	Person months	n (%)	Person months
420mg (840mg loading dose)	700(100.0)	[7447.8]	58(100.0)	[480.3]	2380(100.0)	[24236.4]	89(100.0)	[896.4]	55(100.0)	[651.0]

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25)*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: /opt/BIOSTAT/prod/cd11450w/t_ex_dose.sas / Output: /opt/BIOSTAT/prod/cd11450w/reports/t_ex_dose_RACEGR1_EBC_AP.out
03MAY2017 12:05 Page 1 of 1

Table 9 Exposure to Perjeta by Dose and Race: Metastatic and Early Breast cancer

Exposure to Perjeta by Dose and Race: Metastatic and Early Breast cancer

	Asian (N=943)	Black (N=80)	White (N=3768)	Other (N=418)	Missing (N=56)
Total pertuzumab exposure (mg)					
Mean (SD)	8813.8 (7116.68)	7056.0 (6304.92)	9594.2 (9366.26)	14046.5 (13040.45)	7155.0 (1647.16)
Median	7980.0	7140.0	7980.0	7980.0	7560.0
Range	420, 45780	840, 34860	300, 59640	840, 52500	420, 7980
Number of Patients Receiving Planned Dose Level	n (%) Person months	n (%) Person months	n (%) Person months	n (%) Person months	n (%) Person months
420mg (840mg loading dose)	943(100.0)[13253.0]	80(100.0)[907.2]	3768(100.0)[58619.9]	418(100.0)[9670.3]	56(100.0)[651.7]

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25)*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dose.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dose_RACEGR1_AP.out
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Special Population Exposure (by Indication)

There are currently no specific exposure data available for special population groupings, which are, by definition, excluded from the clinical trial program. As of 7 June 2020, it is estimated that 784 male patients have been exposed to Perjeta in the clinical trial program.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 10 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Hypersensitivity	Patients with known hypersensitivity to pertuzumab or to any of its excipients were excluded from clinical trials to avoid risk of anaphylactic shock/reaction.	No	Patient with hypersensitivity to the active substance or to any of the excipients is contraindicated as per EU SmPC. A statement regarding severe hypersensitivity, including anaphylaxis and events with a fatal outcome, have been observed with Perjeta has been added in Section 4.4 of the EU SmPC. In addition, a statement regarding permanent discontinuation of pertuzumab for any patient who experiences a NCI CTCAE Grade 4 reaction, will remain in Section 4.4 of the EU SmPC.
Pregnancy	Pregnant patients were excluded in clinical trials as Studies in animals have shown reproductive related toxicity (see Module II-Toxicity).	Yes Please refer to section SVII.3 for additional details on the missing information “Use during pregnancy and lactation”.	Not applicable
Patients with poor performance status	Such patients are unlikely to be able to tolerate taxane- or anthracycline-based therapy	No	No warning or exclusion included in the EU SmPC for Perjeta. Assessment of a patient’s fitness for chemotherapy is part of routine oncology practice

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients with known Central nervous system metastases	Pertuzumab and trastuzumab are monoclonal antibodies and therefore are thought to cross the blood-brain barrier poorly. Such patients also tend to have aggressive disease and may have insufficient time to benefit from treatment in a trial setting	No	Section 5.1 of the EU SmPC for Perjeta indicates that patients with brain metastases were excluded from the CLEOPATRA trial and that no data are available on Perjeta activity on brain metastases.
Patients exposed to cumulative doses of doxorubicin >360 mg/m^2 (or equivalent cumulative doses of other anthracyclines) or prior radiotherapy to the chest area.	Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents.	No	Included in Section 4.4, Special Warnings and Precautions for Use, in the EU SmPC for Perjeta
Patients with uncontrolled hypertension, a history of congestive heart failure, a serious cardiac arrhythmia requiring treatment (other than atrial fibrillation or paroxysmal supraventricular tachycardia), angina requiring anti-angina medication, clinically significant valvular heart disease, or a myocardial infarction within the last 6 months	Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents.	Yes. Please refer to section SVII.3 for additional details on the missing information “Cardiac impairment”.	Not applicable

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients with low left ventricular ejection fraction (<50% or <55%, depending on the patient population)	Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents	Yes. Please refer to section SVII.3 for additional details on the missing information “Cardiac impairment”.	Not applicable
Patients with inadequate renal or hepatic function or with impaired bone marrow reserve (manifest as anemia, neutropenia or thrombocytopenia)	Such patients are unlikely to be able to tolerate taxane- or anthracycline-based therapy	No	EU SmPC for Perjeta indicates that there is no information on patients with severe renal impairment EU SmPC for Perjeta indicates that Perjeta has not been studied in patients with hepatic impairment. EU SmPCs for cytotoxic agents commonly used in patients with breast cancer (e.g. docetaxel, paclitaxel, doxorubicin and epirubicin) indicate that clearance may be reduced and/or toxicity increased in patients with hepatic impairment. EU SmPCs for docetaxel and paclitaxel do not include information on patients with severe renal impairment; for doxorubicin and epirubicin, SmPCs indicate that dose reductions may be required for renal impairment. The SmPCs for these agents also clearly indicate the high risk of myelosuppression and the need to monitor blood counts before and during therapy

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients with other severe, uncontrolled systemic diseases or known to be infected with HIV, HBV or HCV	Such patients may not be able to tolerate taxane- or anthracycline-based therapy and are at increased risk of infectious complications associated with myelosuppression	No	No specific warning or exclusion included in the EU SmPC for Perjeta since assessment of a patient's fitness for chemotherapy is part of routine oncology practice. This concern is not considered by the MAH to be a sufficient reason to limit physician options in treatment of patients with active infections with Perjeta. However, Section 4.4 of the Perjeta SmPC indicates that patients treated with Perjeta, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel. The SmPCs of cytotoxic agents commonly used in patients with breast cancer (e.g., docetaxel, paclitaxel, doxorubicin and epirubicin) provide extensive warnings about the risks of neutropenia and its complications.
Patients with current dyspnea at rest due to advanced malignancy or other diseases that require continuous oxygen therapy	Such patients may not be able to tolerate the infusion reactions associated with pertuzumab, trastuzumab, docetaxel and paclitaxel	No	No specific warning or exclusion included in the EU SmPC for Perjeta since this is considered part of routine assessment of a patient's fitness for treatment (part of routine oncology practice). The EU SmPC for Perjeta, Herceptin, docetaxel and paclitaxel all include details of infusion reactions in Section 4.4, Special Warnings and Precautions for Use.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients requiring chronic daily treatment with corticosteroids (other than inhaled or topical steroids)	Such patients may not be able to tolerate taxane- or anthracycline--based therapy and are at increased risk of infectious complications associated with myelosuppression	No	No specific warning or exclusion included in the EU SmPC since this is considered part of routine assessment of a patient's fitness for treatment (part of routine oncology practice).
Patients who have had recent major surgical procedures or significant traumatic injury	Such patients may not be able to tolerate taxane- or anthracycline-based therapy and may be at increased risk of infectious complications associated with myelosuppression	No	No specific warning or exclusion included in the EU SmPC since this is considered part of routine assessment of a patient's fitness for treatment (part of routine oncology practice).
Patients with other malignancies in the last 5 years (other than curatively-treated non-melanomatous skin cancer or in situ carcinomas treated with curative intent)	Such patients were excluded from clinical trials because relapse or progression of the other malignancy could confound interpretation of trial efficacy data.	No	Such patients should still benefit from treatment with Perjeta, Herceptin and chemotherapy. No warning or exclusion included in the EU SmPC.
Patients receiving other investigational treatments	Such patients were excluded from clinical trials because the other investigational agent could confound interpretation of trial safety and efficacy data.	No	No warning or exclusion included in the EU SmPC. Co-administration of investigational agents is beyond the scope of the EU SmPC.

EU=European Union; HER2=Human epidermal growth factor receptor 2; HIV=Human immunodeficiency virus; HBV=Hepatitis B virus; HCV=Hepatitis C virus; LVEF= Left ventricular ejection fraction; MAH=Marketing authorization holder; SmPC=Summary of Product Characteristics.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAM

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 11 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in the clinical development program, including: • Patients with known severe hepatic impairment; • Patients with current known infection with HIV, HBV or HCV were excluded.
Patients with renal impairment	Patients with a serum creatinine > 2.0 mg/dL or 177 µmol/L or > 1.5 × upper limit of normal were not included in the clinical development program.
Patients with cardiovascular impairment	• Not included in the clinical development program, including following groups: Patients with a left ventricular ejection fraction < 50 % or 55 % in history or at screening. • Patients with a clinically significant cardiovascular disease, such as uncontrolled hypertension, unstable angina, a history of CHF or serious cardiac arrhythmias. Patients with a cumulative dose of prior anthracyclines > 360 mg/m^2 of doxorubicin or equivalent.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	
Children:	Children and adolescents below the age of 18 years were not included in the clinical development program.
Elderly aged ≥75 years :	These patients were not excluded from the clinical trial program for Perjeta. The number of patients aged > 75 years exposed via participation in clinical trials remains small (refer to Table 6), however the data regarding use of Perjeta in patients aged 75 years or older is growing.
Male breast cancer patients	Male breast cancer patients were not excluded from the clinical trial program for Perjeta. However, the number of male breast cancer patients exposed via participation in clinical trials remains relatively small as compared to female breast cancer patients. Refer to Part II-Module SIII-clinical trial exposure–Special Population Exposure for male patients' exposure. Of note, a considerable number of male patients have now been exposed to Perjeta in the post-marketing setting (Table 12).

CHF= congestive heart failure; HBV= Hepatitis B virus; HCV= Hepatitis C virus HIV = Human immunodeficiency virus.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-authorization exposure

SV.1.1 Method used to calculate exposure

Worldwide Exposure from Marketing Experience (Excluding the United States)

Exposure is based on Roche internal data on the number of commercial product vials shipped to each country and Roche market research with oncologists to estimate patients receiving therapy.

In keeping with the methodology, data by sex and age are only shown for the five largest European countries.

Exposure in the EBC setting is currently estimated based on projected adoption and verification of usage from Roche market research with oncologists.

Patient Exposure from Marketing Experience in the United States

The patient exposure data presented are based on a patient model that assumes U.S. sales are split such that 65% of usage was in patients with EBC and 35% in the MBC setting. Patient exposure is calculated from actual vials sold, divided by estimated historical vials per patient from the patient model.

According to data obtained via patient tracking activities, approximately 25% of patients receiving Perjeta for EBC and 41% of patients receiving Perjeta for MBC in the U.S. are aged 65 years or older. Epidemiology data indicates 0.8% of patients with breast cancer are male.

No estimates of pediatric exposure are provided but exposure is expected to be very low in view of the rarity of breast cancer in the pediatric age group.

Patient Exposure from Marketing Experience in Japan

The estimated exposure in Japan was calculated using the following algorithm:

1) the ratio of the total dose for each indication was calculated from 2018 Sales Assumption data,

2) the total dose for the indication being studied was calculated using the ratio of each indication (calculated in “(1)” above) and total sales data during the period,

3) the dose per patient per indication was calculated from 2018 Sales Assumption data, and

4) the patient exposure for indication was then calculated by dividing the results in “(2)” by the results in “(3)”.

SV.1.2 Exposure

From the international birth date (IBD: 8 June 2012) up to 7 June 2020, an estimated total of 475,041patients have received Perjeta from marketing experience (Perjeta PBRER Report 1101895 [Reporting interval: 8 June 2019 to 7 June 2020]). The estimated cumulative exposure to Perjeta is presented in Table 12.

Table 12 Cumulative Exposure to Perjeta from Marketing Experience

Indication	Sex			Age (years)				Region				Total
	M	F	Unk	0 to ≤ 16	> 16 to ≤ 65	> 65	Unk	EEA	U.S.	RoW	Japan	
EBC	1,943	232,037	65,306	0	174,767	59,215	65,306	71,942	162,039	56,886	8,420	299,287
MBC	944	110,034	64,776	0	73,871	37,107	64,776	55,959	55,019	33,573	31,203	175,754
Total	2,887	342,072	130,082	0	248,638	96,322	130,082	127,901	217,058	90,459	39,623	475,041
Grand Total[a]	475,041			475,041				475,041				

EBC = early breast cancer; EEA = European Economic Area; F = female; M = male; MBC = metastatic breast cancer; n/a = Not applicable; RoW = Rest of World; Unk = unknown.

[a] Sum of exposure numbers in each category may not equal the totals due to rounding errors.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have potential for misuse for illegal purposes are expected to share some general characteristics, such as psychoactive effects or, less commonly, anabolic effects or enhancement of hemoglobin levels. There is no evidence that Perjeta has such effects which makes it highly unlikely that Perjeta will be misused for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns have been identified since this module of the RMP was last submitted.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of important identified risks and important potential risks

1. INFORMATION ON IMPORTANT IDENTIFIED RISKS

1.1 INFUSION-RELATED REACTIONS, HYPERSENSITIVITY REACTIONS/ANAPHYLAXIS

MedDRA Terms:

Infusion-related reactions (IRRs):

In Study WO20698 (CLEOPATRA), a conservative definition was initially used to identify potential infusion-associated events. IRR was subsequently defined as any event in the MedDRA SMQ “Anaphylactic reaction (wide)”, Roche Standard Adverse Event Grouped Term (AEGT) “Anaphylaxis and hypersensitivity” and, the Roche Standard AEGT “Infusion Related Reactions + Hypersensitivity” that occurred on the day of a Perjeta (or placebo) infusion, irrespective of Investigator causality. This definition was also used for the NEOSPHERE, TRYPHAENA, APHINITY and PERUSE studies (see Table 14).

Hypersensitivity reactions/Anaphylaxis:

Identified using the Roche standard AEGT, 'Anaphylaxis and Hypersensitivity', containing the MedDRA SMQ (narrow) 'Anaphylactic reaction' plus all MedDRA Preferred Terms containing the term, 'hypersensitivity.'

Note that analysis of hypersensitivity reactions/anaphylaxis is not time-restricted (i.e., includes events occurring at any time) or restricted to events considered related to study treatment. Thus, the figures include occasional unrelated events such as hypersensitivity reactions to other medication (e.g. antibiotics) or food.

Potential mechanisms:

IRRs are thought to be due to release of cytokines and/or other chemical mediators. Anaphylactic or hypersensitivity reactions to the IV administration of protein may also play a part in some patients, for example monoclonal antibodies. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms of these reactions overlap (Lenz 2007).

Evidence source(s) and strength of evidence:

Randomized clinical trial data

Based on safety results from WO20698 (CLEOPATRA), WO20697 (NEOSPHERE), BO22280 (TRYPHAENA), BO25126 (APHINITY) and MO28047 (PERUSE).

Characterization of the risk:

Background Incidence/Prevalence

Infusion-associated reactions are known to occur with monoclonal antibodies. The frequency of infusion-associated reactions is variable depending on the molecule and the definition used for an infusion-associated reaction, the time window reviewed and whether the first or later cycles are assessed. These differences mean that comparison of incidence figures for different antibodies should be interpreted with caution.

In general antibody infusion-associated AEs are more frequent and severe with the first infusion, and decrease in number and severity over time, and the majority of AEs resolve fully.

Infusion-associated reactions typically occur during or shortly after infusions of monoclonal antibodies but may also show a delayed onset. The true relation of an event to infusion of study treatment is therefore difficult to ascertain, particularly when treatment regimens involve combination therapy. The potential incidence of infusion-associated reactions has been considered using a number of approaches in

studies involving Perjeta. A conservative approach was initially used in the CLEOPATRA study, in which all events occurring on the day of the infusion and the day following Perjeta infusion were presented as infusion-associated AEs, whether considered related or unrelated to Perjeta by the investigator. This definition is likely to result in inclusion of events that are not truly Perjeta infusion-related. Therefore, the definition was revised to include any event in the AEGT/SMQ for 'Anaphylactic Reactions (wide)', 'Roche Standard AEGT Anaphylaxis and Hypersensitivity', 'AEGT - Rituximab-Specific AEGT Hypersensitivity Infusion Reaction (MabThera RA), plus the Preferred Term (PT) Cytokine Release Syndrome 'occurring on the day of the Perjeta (or placebo), whether considered related or unrelated to Perjeta by the investigator.

Hypersensitivity reactions to trastuzumab are described as common (≥ 1/100 to < 1/10 patients).

Although not a monoclonal antibody, taxanes are also associated with infusion-related reactions, hypersensitivity reactions and anaphylaxis, and these reactions also typically start during the first or second infusion. The incidence of hypersensitivity reactions with 75 mg/m^2 of docetaxel alone is described as common (≥ 1/100 to < 1/10 patients). With 100 mg/m^2, such reactions are described as very common (≥ 1/10) and include Grade ≥ 3 reactions in 5.3% of cases (Docetaxel SmPC).

Frequency with 95% CI

The great majority of patients included received Ptz + H + chemotherapy. The details are provided in Table 13 below:

Table 13 Summary of Infusion-Related Reactions in Early and Metastatic Breast Cancer

	EBC (N=3282)	MBC (N=548)	Total (N=3830)
Infusion-associated reaction n(%)	208 (6.3%)	34 (6.2%)	242 (6.3%)
95% Clopper-Pearson Confidence Interval	[5.5; 7.2]	[4.3; 8.6]	[5.6; 7.1]

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Seriousness / Outcomes

Please refer to Table 14, Table 15 and Table 16 below in clinical trials.

Events with a fatal outcome in clinical trials: There have been no infusion reactions with a fatal outcome.

Table 14 Summary of Infusion-Related Reactions (AEGT/SMQ) Occurring on the Day of a Pertuzumab Infusion in the NEOSPHERE, TRYPHAENA, and APHINITY Studies

Early Breast Cancer

Cycle	NEOSPHERE						TRYPHAENA					
	Ptz+H+D (n=107)		Ptz+H (n=108)		Ptz+D (n=94)		Ptz+H+FEC/ Ptz+H+D (n=72)		FEC/Ptz+H+D (n=75)		Ptz+TCH (n=76)	
	All	Gr ≥ 3	All	Gr ≥ 3	All	Gr ≥ 3	All	Gr ≥ 3	All	Gr ≥ 3	All	Gr ≥ 3
All	38.3%	0	38.0%	2.8%	35.1%	0	37.5%	1.4%	25.3%	4.0%	46.1%	3.9%
1[a]	23.4%	0	33.3%	1.9%	8.5%	0	25.0%	1.4%	18.6%	4.3%	23.7%	3.9%
2[a]	12.4%	0	7.4%	0.9%	17.2%	0	12.7%	0	13.6%	0	17.6%	0

Cycle	APHINITY			
	Ptz+H+Chemo n=2364		Pla+H+Chemo n=2405	
	All	Gr ≥ 3	All	Gr ≥ 3
All	54.7%	2.7%	51.3%	2.1%
1	20.9%	1.2%	18.0%	0.7%
2	13.3%	0.3%	12.6%	0.4%

Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel; TCH=docetaxel (Taxotere), carboplatin, Herceptin, Ptz+H+FEC: Perjeta+Herceptin + 5-fluorouracil, epirubicin, cyclophosphamide

Shaded columns show incidence of AEs (all Grades) in the AEGT/SMQ for anaphylactic reactions, hypersensitivity reactions and infusion reactions that occurred on the day of a Perjeta infusion. [a]Cycle 1 and 2 indicate the first and second cycle at which Perjeta was scheduled (ie. Cycle 4 and 5 for patients in the FEC/Ptz+H+D arm).

Sources: Tables 66 and 69 in the Summary of Clinical Safety (neoadjuvant); APHINITY Primary CSR, t_ae_ppinf_TRT1A_IREA_SE. Data cut off dates WO20697 NEOSPHERE (12 July 2012), BO22280/TRYPHAENA (04 July 2012), APHINITY (19 Dec 2016).

Table 15 Summary of Infusion-Related Reactions (AEGT/SMQ) Occurring on the Day of a Pertuzumab Infusion in the CLEOPATRA and PERUSE Studies

Metastatic Breast Cancer

Cycle	CLEOPATRA				PERUSE	
	Ptz+H+D (n=408)		Pla+H+D (n=396)		Ptz+H+Taxane+Chemo N=1436	
	All	Gr ≥ 3	All	Gr ≥ 3	All	Gr ≥ 3
All	60.8%	4.7%	53.0%	4.0%	73.1%	7.9%
1	13.2%	0.2%	9.8%	0.3%	30.7%	2.3%
2	13.8%	0.3%	15.9%	1.0%	19.3%	0.9%

Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel

Shaded columns show incidence of AEs (all Grades) in the AEGT/SMQ for anaphylactic reactions, hypersensitivity reactions and infusion reactions that occurred on the day of a Perjeta infusion. Source: Table 23 of CSR Update 2 and t_fae1_iar_hday_ua_aepr_s. Data cut-off date WO20698 CLEOPATRA (11 Feb 2014).

Table 16 Summary of Anaphylaxis/Hypersensitivity Reactions

Early Breast Cancer

Safety parameter	Patients experiencing event								
	NEOSPHERE				TRYPHAENA			APHINITY	
	T+D n=107	Ptz+H+D n=107	Ptz+H n=108	Ptz+D n=94	Ptz+H+FEC/ Ptz+H+D (n=72)	FEC/Ptz+H +D (n=75)	Ptz+TCH (n=76)	Ptz+H+Chemo n=2364	Pla+H+Chemo n=2405
Anaphylaxis/ hypersensitivity All Grades	1.9%	5.6%	5.6%	7.4%	9.7%	1.3%	13.2%	4.9%	3.6%
Anaphylaxis/ hypersensitivity Grade ≥ 3[a]	0	0.9%	1.9%	0	2.8%	0	2.6%	0.8%	0.7%

Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel; TCH=docetaxel (Taxotere), carboplatin, Herceptin, Ptz+H+FEC: Perjeta+Herceptin + 5-fluorouracil, epirubicin, cyclophosphamide

Table 16 Summary of Anaphylaxis/Hypersensitivity Reactions (cont.)

Metastatic Breast Cancer

Safety parameter	Patients experiencing event		
	CLEOPATRA		PERUSE
	Ptz+H+D n=408	Pla+H+D n=396	Ptz+H+Taxane+Chemo N=1436
Anaphylaxis/ hypersensitivity All Grades	11.3%	9.3%	8.6%
Anaphylaxis/ hypersensitivity Grade ≥ 3[a]	2.0%	2.5%	1.3%

Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel

Sources: Tables 19 and 23 of the Summary of Clinical Safety (neoadjuvant); APHINITY Primary CSR. Table 44; CLEOPATRA CSR Update Table17. Data cut off dates WO20697 NEOSPHERE (09 March 2012), BO22280/TRYPHAENA (04 July 2012), APHINITY (19 Dec 2016) and WO20698 CLEOPATRA (11 Feb 2014, , ROCHE\PERTUZUMAB\XSA84478_QSTR\BIOSTATISTICS\PRODUCTION\TABLES\ADHOC\T_AE_HYP_ADHOC.SAS] IQVIA 30APR2020.

[a] No Grade 5 events occurred

Severity and Nature of Risk:

Infusion-related reactions (IRRs):

Perjeta has been associated with IRRs, including events with fatal outcomes. Overall, the incidence and severity of IRRs was similar across treatment arms and studies. Less than 5% of patients in any treatment arm experienced Grade ≥ 3 reactions. The incidence of IRRs was generally highest in the first cycle of therapy and declined thereafter, as is typical of infusion reactions with monoclonal antibodies.

Hypersensitivity and Anaphylaxis:

The incidence and severity of events was similar in Study WO20698 in MBC and in studies in the neoadjuvant treatment of EBC (NEOSPHERE/ TRYPHENA), and in the adjuvant setting (APHINITY), with the majority of events being Grade $1-2$ in severity.

Hypersensitivity reactions are typically associated with pre-formed antibodies and therefore require prior exposure to the drug or a cross reacting agent. Thus hypersensitivity reactions would be expected to worsen with repeated doses (Lenz 2007). This distinguishes them from infusion-associated events, which are typically worst with the first dose and become less severe with repeated doses. However, symptoms overlap, and in practice it can be difficult to distinguish between infusion-associated events and hypersensitivity reactions in individual patients.

Impact on quality of life:

Patients may experience considerable discomfort during a reaction (e.g., chills, rigors, flushing, breathing difficulty, vomiting, itching, headache), although symptoms are likely to resolve completely following the infusion. Hence, such reactions are likely to have no long-term impact on quality of life.

On the other hand, although severe infusion reactions, hypersensitivity and anaphylactic reactions to pertuzumab are rare events, such reactions would prevent the patient from continuing treatment.

Risk factors and risk groups:

There are currently no reliable predictors of patients who may or may not be susceptible to infusion-associated reactions, hypersensitivity or anaphylaxis to pertuzumab. Patients with a history of asthma, eczema or hay fever (atopy) had a slightly increased risk of developing an IRR (on the day of or the day after a Perjeta infusion) than patients who did not have a history of atopy but the number of patients with a history of atopy was too small for any firm conclusions to be drawn. Moreover, patients with a history of atopy did not appear to be at increased risk of anaphylaxis or hypersensitivity reactions. Importantly, prior and concomitant trastuzumab exposure did not appear to reduce or exacerbate the infusion-associated events seen with Perjeta.

Anti-Drug Antibodies (ADA) in Study WO20698

Serum samples were assayed for ADAs to pertuzumab, also known as anti-therapeutic antibodies (ATAs) or human anti-human antibodies (HAHA). The incidence of ADA was calculated from the total number of patients who tested positive for ADA against pertuzumab after dosing, divided by the total number of patients who had post dose ADA samples available for the ADA analysis. A conservative approach was taken for calculating the incidence of ADA so that any patient confirmed to have an ADA positive sample after dosing was considered positive for ADA, regardless of baseline status.

Since trastuzumab and pertuzumab share the same framework structure, differing only in the complementarity-determining region, it is possible that the positive ADA findings in patients treated with Placebo + trastuzumab (Herceptin) + docetaxel (Pla + H + D) were due to antibodies directed toward the common framework portion of pertuzumab and trastuzumab.

In Study WO20698, at the second clinical data cutoff (14 May 2012), 6.7% (25/372 patients) of placebo-treated patients and 3.3% (13/389 patients) of Perjeta-treated patients tested positive for ADA. Of these 38 patients, none experienced anaphylactic/ hypersensitivity reaction that was clearly related to the ADA. Most patients with detectable ADA were able to continue study treatment, sometimes for prolonged periods.

Preventability:

Infusion reactions, hypersensitivity and anaphylactic reactions to pertuzumab cannot be reliably predicted or prevented. However, the incidence and severity of infusion reactions may be reduced by premedication and appropriate monitoring of the patient during infusions, with slowing or discontinuation of the infusion if needed.

Impact on the benefit-risk balance of the product:

The impact of infusion- associated reactions to the benefit-risk balance of Perjeta is considered to be low since the symptoms generally resolve completely once the infusion has been discontinued, slowed or completed. IRRs are commonplace in oncology practice and patients are already at higher risk of reactions due to the concomitant administration of taxanes and trastuzumab. Due to this increased risk, oncology patients are routinely monitored for the typical symptoms of an infusion related event.

Current pharmacovigilance plans and product labels include guidance for patient management in the event of a hypersensitivity or infusion related reaction (Section 4.4 of the EU SmPC, “Infusion reactions” and “Hypersensitivity reactions/anaphylaxis” provides recommendations on risk management approach) and these measures are considered adequate to manage the risk.

Public health impact:

The potential public health impact of Perjeta-related IRRs is considered low. Patients receiving trastuzumab or taxanes are already at risk of IRRs and monitoring and treatment of IRRs is a routine part of oncology clinical practice.

In studies in MBC and EBC, the incidence of events coded to the AEGT “Anaphylaxis and Hypersensitivity” Grade ≥3 was low. Therefore, the potential public health impact associated with this safety concern is considered to be low.

1.2 CONGESTIVE HEART FAILURE/LEFT VENTRICULAR DYSFUNCTION

MedDRA Terms:

Serious adverse events (SAEs) in the MedDRA SMQ Cardiac failure-wide

LVEF declines (significant LVEF declines were defined as any LVEF decline of ≥10%-points from baseline to an absolute value of <50%). Note that reporting of cardiac dysfunction is based on a single LVEF decline, which is a conservative approach, as many LVEF declines are not confirmed at the next assessment.

Potential mechanisms:

Since pertuzumab targets HER2, like trastuzumab, there is a potential risk of cardiac dysfunction, particularly in patients who have received prior anthracycline treatment. HER2 signaling is required for the growth, repair and survival of cardiomyocytes. These repair mechanisms involve HER2-HER4 heterodimeric receptors which trigger the myocyte survival pathways required during the activation of acute stress signals mainly by anthracyclines (Crone et al, 2002; Swayer et al, 2002; Negro et al, 2004). Available clinical evidence to date from studies in MBC and EBC suggests a similar or only slightly increased risk of cardiotoxicity with the addition of Perjeta to trastuzumab. It is possible that the maximum effect on cardiomyocytes is already exerted by trastuzumab and that the addition of Perjeta does not add to this (Stortecky & Suter 2010; Zuppinger & Suter 2010; Carver 2010).

Evidence source(s) and strength of evidence:

Clinical trial data

Based on safety results from WO20697 (NEOSPHERE), WO20698 (CLEOPATRA), BO22280 (TRYPHAENA), WO29217 (BERENICE), BO25126 (APHINITY), and MO28047 (PERUSE).

Characterization of the risk:

Background Incidence / Prevalence:

First-line HER2-positive MBC:

The incidence of symptomatic CHF (Grades 3 or 4) for:

Non-trastuzumab containing regimens:

- Without anthracyclines: 0.3% to 1% (Slamon et al, 2001, Johnston 2009)
- With anthracyclines: 3% to 4.7% (Slamon et al, 2001, O'Brien 2004).

Trastuzumab containing regimens:

- Without anthracyclines: 2% to 4% (Slamon et al, 2001, Seidman et al, 2002)
- With anthracyclines: 16% (Slamon et al, 2001).

Long-term trastuzumab therapy: Among 173 patients who received ≥1 year of trastuzumab-based therapy (median length of treatment was 21.3 months), 10.9% experienced Grade 3 cardiac toxicity (85% were exposed to anthracyclines).

Second-line HER2-positive MBC:

Based on three lapatinib studies, the incidence of symptomatic CHF (Grades 3 or 4) was <1% for non-trastuzumab containing regimens (Blackwell 2010, Capri at al. 2010, Burstein at al. 2003). In a pooled analysis of 3689 lapatinib patients enrolled in clinical trials, the incidence of symptomatic cardiac toxicity by prior treatment was:

Anthracyclines: 0.5%

Trastuzumab: 0.1%

Neither anthracyclines nor trastuzumab: 0.1%.

Based on data from Study MO22324 (PHEREXA), the most common AE that led to withdrawal of all study treatment was left ventricular dysfunction (LVD):

Treatment Arm A (Herceptin+capecitabine): 0.9%

Treatment Arm B (Perjeta+Herceptin+capecitabine): 3.1%.

The incidence of AEs reported during the study in the SOC 'Cardiac Disorders' was higher in treatment Arm B (8.7% vs. 14.0%), with LVD being the most commonly reported and occurred more frequently in treatment Arm B (3.2% vs. 7.5%). The proportion of patients that experienced cardiac disorders as SAEs was low in both treatment arms but higher in treatment Arm B (2.3% vs. 6.1%). Grade ≥3 LVD was also reported more frequently in treatment Arm B (0.9% vs. 2.2%).

The incidence of event to monitor LVD (both asymptomatic and symptomatic left ventricular systolic dysfunction [LVSD] New York Heart Association [NYHA class

II/III/IV]) was higher in treatment Arm B (asymptomatic: 3.2% in Arm A and 6.6% in Arm B; symptomatic: 0 in Arm A and 2.2% in Arm B); however, these findings were consistent when compared to prior experience with Perjeta. All five events of symptomatic LVSD in Arm B were considered as possibly related to study treatment by the investigator. Of the five patients with symptomatic LVSD, three had central LVEF assessment at baseline lower than 50% however, their local LVEF readings were all above 50%, making them eligible for the study. Four of the five patients reported cardiac medical history, all five received anthracycline therapy, and three received radiotherapy to the chest. At the time of the clinical cut-off date, four of the five symptomatic LVSD events had resolved. The mean LVEF at baseline was balanced between the two treatment arms (60.8% in Arm A and 60.0% in Arm B). The incidence of asymptomatic LVEF-drops reported as AEs was low (2.3% of patients in Arm A vs. 5.3% in Arm B).

Based on a review of three adjuvant trastuzumab trials (NASBP B-31, NCCTG N9831, HERA) with anthracycline and non-anthracycline containing regimens, the incidence of symptomatic CHF (defined as NYHA Class III or IV) was:

0.6% to 3.8% for trastuzumab containing regimens

0% to 0.9% for non-trastuzumab containing regimens.

In a meta-analysis of eight randomized clinical trials (B31, BCIRG006, Buzdar, FinHer, HERA, NOAH, N9831, PACS-04) involving 10,281 patients, 2.5% of patients treated with a trastuzumab containing regimen and 0.4% of patients treated with a non-trastuzumab containing regimen experienced CHF. In a Phase III trial of 615 women with HER2-positive operable or locally advanced breast cancer (median age = 50 years) treated with epirubicin, cyclophosphamide, and docetaxel with lapatinib (n = 308) or trastuzumab (n = 307) (Untch et al, 2012), the incidence of Grade 3 – 4 CHF (NCI-CTC version 3) was 0% with trastuzumab containing regimens and 0.3% with lapatinib containing regimens.

In a randomized, open label multi-centre Phase III study comparing the activity of lapatinib alone versus trastuzumab alone versus trastuzumab followed by lapatinib versus lapatinib concomitantly with trastuzumab in the adjuvant treatment of patients with ErbB2 overexpressing and/or amplified breast cancer (ALTTO), although approximately 90% of patients received anthracycline-based chemotherapy, which has raised concerns regarding cardiotoxicity, congestive heart failure occurred in less than 1% across all arms (Piccart-Gebhart et al, 2014).

The incidence of CHF was reported to be 3.3% in HER2-positive EBC patients treated with anthracycline prior to trastuzumab (Anthony et al, 2015).

Frequency with 95% CI

Refer to Table 17 below:

Table 17 Summary of Congestive Heart Failure in Early and Metastatic Breast Cancer

	EBC (N=3282)	MBC (N=548)	Total (N=3830)
Congestive Heart Failure n(%)	76 (2.3%)	7 (1.3%)	83 (2.2%)
95% Clopper-Pearson Confidence Interval	[1.8; 2.9]	[0.5; 2.6]	[1.7; 2.7]

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Note: Congestive Heart Failure is defined by SAEs in the SMQ (wide) Cardiac Failure.

Seriousness/Outcomes

Please refer to Table 18 and Table 19 below.

Events with a fatal outcome in clinical trials: There were two fatal CHF events in Study BO25126 (APHINITY): an event of cardiogenic shock in the Ptz + H + Chemo arm and an event of cardiac failure in the Pla + H + Chemo arm.

Table 18 Key Cardiac Safety Data from the NEOSPHERE, TRYPHAENA, APHINITY, CLEOPATRA and PERUSE Studies

Early Breast Cancer

Safety Parameter	Patients Experiencing Event								
	NEOSPHERE (overall treatment period)				TRYPHAENA (overall treatment period)			APHINITY (overall treatment period)	
	H+D n=107	Ptz+H+D n=107	Ptz+H n=108	Ptz+D n=94	Ptz+H+FEC/ Ptz+H+D n=72	FEC/ Ptz+H+D n=75	Ptz+TCH n=76	Ptz+H+Chemo n=2364	Pla+H+Chemo n=2405
Any cardiac AE[a]	7.5%	20.6%	14.8%	12.8%	15.3%	16.0%	21.1%	11.4%	10.6%
LVD/EFD/CF[b] (PT)	1.9%	7.5%	0	5.3%	8.3%	9.3%	6.6%	6.4%[e]	6.8%[e]
Gr≥3 LVD/EFD/CF (PT)	0	0.9%[c]	0	0	0	2.7%	1.3%	2.3%[f]	2.0%[f]
LVEF decline[c]	1.9%	7.5%	0.9%	5.3%	6.9%	13.3%	7.9%	5.7%[g]	7.0%[g]
CHF SAE	0	2.8%[d]	0.9%	0	1.4%	2.7%	1.3%	1.8%	1.1%
Grade 5 CHF	0	0	0	0	0	0	0	0.04	0.04

Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel; TCH=docetaxel (Taxotere), carboplatin, Herceptin, Ptz+H+FEC: Perjeta+Herceptin + 5-fluorouracil, epirubicin, cyclophosphamide

Table 18 Key Cardiac Safety Data from the NEOSPHERE, TRYPHAENA, APHINITY, CLEOP]ATRA and PERUSE Studies (cont.)

Metastatic Breast Cancer

Safety Parameter	Patients Experiencing Event		
	CLEOPATRA (overall treatment period)		PERUSE
	Ptz+H+D n=408	Pla+H+D n=396	Ptz+H+Taxane+Chemo N=1436
Any cardiac AE[a]	16.9%	17.4%	15.2%
LVD/EF (PT)[b]	6.6%	8.6%	13.6%
Gr ≥ 3 LVD (PT)	1.5%	3.3%	2.9%
LVEF decline[c]	5.9%	7.1%	9.4%
CHF SAE	1.7%	2.0%	2.4%
Grade 5 CHF	0	0	0.2%

AE=adverse event; CF=cardiac failure; CHF=congestive heart failure (symptomatic left ventricular dysfunction) SAEs analyzed by SMQ (wide) 'Cardiac failure'; EFD=ejection fraction decrease; FEC=5-fluorouracil, epirubicin, LVEF=left ventricular ejection fraction; LVD=left ventricular dysfunction; Pla+H+D=placebo+Herceptin+docetaxel; PT=preferred term; Ptz+H+D= Perjeta+Herceptin+docetaxel; SAE=serious adverse event.

[a] Any AE in the Cardiac Disorder SOC.

[b] APHINITY based on PTs 'cardiac failure' and 'ejection fraction decreased'. All other studies based on LVD PT only, due to differences in MedDRA coding.

[c] LVEF decline of ≥ 10% from baseline to an absolute value <50%.

[d] Reported as an SAE suggestive of CHF, however, events were asymptomatic.

[e] APHINITY based on PTs 'cardiac failure' and 'ejection fraction decreased'.

[f] Based on grade ≥ 3 events of 'cardiac failure' and 'ejection fraction decreased'. Note that a primary cardiac event (defined as either Heart Failure [NYHA Class III or IV] and a drop in LVEF of at least 10 EF points from baseline AND to below 50%, or Cardiac Death) was reported in 0.7% of patients in the Ptz+H+Chemo arm and 0.3% of patients in the Pla+H+Chemo arm.

[g] Rate for the whole study period, not just the treatment period.

Source: Tables 34, 35, 37, and 39 and t_ae11_345 in the Update CSR for NEOSPHERE; Tables 7, 14, 15, and 17 in the Update CSR for TRYPHAENA; APHINITY Primary CSR, Table 56, t_ae_TRT1A_SE, t_ae_TRT1A_CFEFD_SE, t_ae_TRT1A_CFEFD_CTC3_SE, t_ae_TRT1A_CFN_SER_SE and t_saf_lvefc_TRT1A_SE and Tables 27, 30, 32, 34 and t_ae11_345_pr in the Update CSR2 for CLEOPATRA. Data cut off dates WO20697 NEOSPHERE (12 July 2012), BO22280 TRYPHAENA (04 July 2012), APHINITY (19 Dec 2016) and WO20698 CLEOPATRA (11 Feb 2014),ROCHE\PERTUZUMAB\XSA84478_QSTR\BIOSTATISTICS\PRODUCTION\TABLES\ADHOC\T_AE_CARDIAC_CI_ADHOC.SAS] IQVIA 30APR2020.

Table 19 Cardiac Events, LVD/EFD and LVEF Declines with Confidence Intervals in the NEOSPHERE, TRYPHAENA, APHINITY, CLEOPATRA and PERUSE Studies

Early Breast Cancer

Safety Parameter	Patients Experiencing Event								
	NEOSPHERE (overall treatment period)				TRYPHAENA (overall treatment period)			APHINITY (overall treatment period)	
	H+D n=107	Ptz+H+D n=107	Ptz+H n=108	Ptz+D n=94	Ptz+H+FEC/ Ptz+H+D n= 72	FEC/ Ptz+H+D n=75	Ptz+TCH n=76	Ptz+H+ Chemo n=2364	Pla+H+Chemo n=2405
Cardiac Disorder AE[a]									
Incidence (% pts)	7.5	20.6	14.8	12.8	15.3	16.0	21.1	11.4	10.6
95% CI	3.3;14.2	13.4;29.5	8.7;22.9	6.8;21.2	7.9;25.7	8.6;26.3	12.5;31.9	10.1; 12.7	9.4; 11.9
LVD/EFD/CF[b]									
Incidence (% pts)	1.9	7.5	0.9	5.3	8.3	9.3	6.6	6.4[d]	6.8[d]
95% CI	0.2;6.6	3.3;14.2	0.0;5.1	1.7;12.0	3.1;17.3	3.8;18.3	2.2;14.7	5.4; 7.5	5.8; 7.9
LVEF Decline[c]									
Incidence (% pts)	1.9	8.4	0.9	7.4	6.9	14.7	10.5	5.7[e]	7.0[e]
95% CI	0.2;6.6	3.9;15.4	0.0;5.1	3.0;14.7	2.3;15.5	7.6;24.7	4.7;19.7	4.8; 6.7	6.0; 8.1

Table 19 Cardiac Events, LVD/EFD and LVEF Declines with Confidence Intervals in the NEOSPHERE, TRYPHAENA, APHINITY and CLEOPATRA and PERUSE Studies (cont.)

Metastatic Breast Cancer

Safety Parameter	Patients Experiencing Event		
	CLEOPATRA (overall treatment period)		PERUSE
	Ptz+H+D n=408	Pla+H+D n=396	Ptz+H+Taxane+Chemo N=1436
Cardiac Disorder AE[a]			
Incidence (% pts)	16.9	17.4	15.2
95% CI	13.4;20.9	13.8;21.5	13.4, 17.1
LVD[b]			
Incidence (% pts)	6.6	8.6	13.6
95% CI	4.4;9.5	6.0;11.8	11.9, 15.5
LVEF Decline[c]			
Incidence (% pts)	6.4	7.6	9.4
95% CI	4.2;9.2	5.2;10.6	7.9, 11.0

AE = adverse event; EFD = ejection fraction decrease; FEC= 5 fluorouracil, epirubicin and cyclophosphamide; LVEF = left ventricular ejection fraction; LVD = left ventricular dysfunction; Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel; TCH=docetaxel (Taxotere), carboplatin, Herceptin.

[a] Incidence of any cardiac events where the SOC of the reported AE is 'Cardiac Disorders' - treatment period only.

[b] Incidence of any LVD event where the reported AE preferred term is 'Left Ventricular Dysfunction' - treatment period only. For NEOSPHERE, the preferred term 'Cardiac Failure Congestive' was also included. For APHINITY the incidence is based only on the PTs 'cardiac failure and 'ejection fraction decreased' due to changes in MedDRA coding.

[c] Incidence of any significant LVEF declines where LVEF $<$ 50% and $\geq$10% decrease from baseline - including treatment-free follow-up period. The reporting period is different to that given for LVEF declines in the previous table.

[d] Based on PTs 'cardiac failure' and 'ejection fraction decreased'.

[e] Rate for the whole study period, not just the treatment period.

Source: Table 64 in the Summary of Clinical Safety (neoadjuvant); APHINITY Primary CSR, t_ae_TRT1A_SE, t_ae_TRT1A_CFEFD_SE and t_saf_lvefc_TRT1A_SE and Tables 30 and 34 of CLEOPATRA CSR Update 2. Data cut off dates: WO20697 NEOSPHERE (09 March 2012), BO22280/TRYPHAENA (04 July 2012), APHINITY (19 Dec 2016) and WO20698 CLEOPATRA (11 Feb 2014),ROCHE\PERTUZUMAB\XSA84478_QSTR\BIOSTATISTICS\PRODUCTION\TABLES\ADHOC\T_AE_CARDIAC_CI_ADHOC.SAS] IQVIA 30APR2020.

Severity and Nature of Risk:

Cardiac dysfunction may manifest as an asymptomatic or mildly symptomatic decrease in LVEF (NCI CTCAE Grade 1 and Grade 2; NYHA Class I – II) or as a symptomatic decrease in LVEF/CHF (NCI CTCAE $\geq$ Grade 3; NYHA Class III or IV). In line with trastuzumab, a clinically relevant drop in LVEF has been defined as a decline $\geq$ 10%-points from baseline to an absolute value of $<$ 50% for Perjeta studies. However, the clinical importance of asymptomatic declines in LVEF is currently not known.

In the TRYPHAENA study, patients in Arm A received 5-fluorouracil, epirubicin, cyclophosphamide (FEC), Herceptin and Perjeta for three cycles, followed by docetaxel, Herceptin and Perjeta for three cycles (Ptz + H + FEC/Ptz + H + D); patients in Arm B received FEC for three cycles, followed by docetaxel, Herceptin and Perjeta for three cycles (FEC/Ptz + H + D); and patients in Arm C received Herceptin, carboplatin, docetaxel and Perjeta for six cycles (Ptz + TCH). During the post-treatment follow-up period, symptomatic left ventricular dysfunction (LVD) was observed in 1 patient in Arm B (no events were observed in Arms A and C). LVEF declines of at least 10%-points from baseline to below 50% were observed in 15 patients (5 in Arm A, 5 in Arm B, and 5 in Arm C), based on local and central data. At the end of the study, the LVEF measurements had improved to ≥ 50% in all but 4 patients: one symptomatic LVD patient who subsequently improved (this patient was asymptomatic at the last assessment with an LVEF of 47%) and 3 asymptomatic patients whose LVEF values were below 50% at the last assessment, based on either local or central readings.

In the APHINITY study, Grade ≥3 events of cardiac failure and ejection fraction decreased (EFD) were observed in 2.3% of patients in the Ptz + H + Chemo arm and in 2.0% of patients the Pla + H + Chemo arm. Note that a primary cardiac event (defined as either Heart Failure [NYHA Class III or IV] and a drop in LVEF of at least 10 EF points from baseline AND to below 50%, or Cardiac Death) was reported in 0.7% of patients in the Ptz + H + Chemo arm and 0.3% of patients in the Pla + H + Chemo arm.

In the BERENICE study, the rates of cardiac toxicity during the neoadjuvant period were as expected in the two treatment arms:

Cohort A (ddAC→TPH): NYHA Class III/IV heart failure incidence of 1.5% (n = 3 [95% CI: 0.31 – 4.34]) plus 1 patient with NYHA Class II heart failure.

Cohort B (FEC→DPH): No patients experienced (0% [95% CI: 0.00 – 1.85]) NYHA III/IV heart failure.

The rates of declines in LVEF (of at least ≥10% points from baseline to a value of < 50%) as measured by echocardiography or MUGA were also as expected (6.5% [n = 13; 95% CI: 3.5 – 10.9] of patients in Cohort A and 2.0% [n = 4; 95% CI: 0.6 – 5.1] in Cohort B).The rates of asymptomatic LVEF decline (reported as an AE with the term 'ejection fraction decreased') were 7.0% (n = 14) of patients in Cohort A and 3.5% [n = 7] in Cohort B.

Impact on quality of life:

Cardiac failure may have a significant impact on the quality of life on individual patients and the presence of pre-existing risk factors or co-morbidities need to be taken into account when determining the benefit risk evaluation for individual patients.

Risk factors and risk groups:

Risk factors such as age of 60 years or older, prior chemotherapy, registration left ventricular ejection fraction (LVEF) less than 65%, hypertension and use of antihypertensive medications such as angiotensin-converting-enzyme inhibitor, angiotensin II receptor blockers and β-blockers were associated with an increased risk of cardiac events in patients with HER2-positive breast cancer (Russo et al, 2014; Anthony et al, 2015; Advani et al, 2015).

Anthracycline exposure: Risks for anthracycline-induced heart failure include cumulative dosage, age over 70 years, earlier or simultaneous radiation to the chest, concurrent treatment with other chemotherapeutic cardiotoxic agents, examples, taxanes, capecitabine or trastuzumab and pre-existing heart disease (Geiger et al, 2010; Fiuza 2009). The most important risk factor for late cardiac toxicity is reported as the cumulative anthracycline dose (Yeh et al, Keefe quoted in Senkus & Jassem 2011).

Concurrent trastuzumab: The cardiac changes associated with trastuzumab are mostly reversible, do not appear to be dose-related and do not involve histological changes in cardiac tissue. Identified risk factors include exposure to anthracyclines or paclitaxel, low LVEF at baseline, age >60 years, obesity, previous heart disease and hypertension. Current monitoring of cardiac function uses changes in LVEF as a reference for cardiotoxicity. Age, anthracycline exposure, and the presence of cardiovascular risk factors predicted cardiac AEs in trastuzumab recipients (Hudis, quoted in Guglin et al, 2009). No clear relation to a cumulative dose of trastuzumab has been described (Geiger et al, 2010). After treatment interruption, clinical and subclinical signs of heart failure are mostly reversible and reinitiating of trastuzumab after recovery is often well tolerated (Geiger et al, 2010).

Adjuvant breast radiotherapy: A relative increase of 30% in cardiac deaths was found in women treated with radiotherapy before the 1980s (Clark et al, quoted in Chargari et al, 2011). Among patients treated during 1973–82 and receiving radiotherapy, the cardiac mortality ratio (left vs. right tumor) was 1.58 (1.29-1.95) after 15 years or more and for patients diagnosed during 1993–2001, the cardiac mortality ratio was 0.96 (0.82-1.12) less than 10 years afterwards (Darby et al, quoted in Chargari et al, 2011). Internal mammary chain irradiation increases heart dose exposure particularly when outdated techniques are used or in patients with left-sided tumors, potentially translating into increased long-term heart disease (Chargari et al, 2011).

Preventability:

Careful monitoring and early detection of (asymptomatic) LVEF reduction from baseline is a reliable screening mechanism for the individual patient decisions to continue or stop treatment with anticancer agents in general (Geiger et al, 2010). All patients enrolled in Perjeta trials undergo routine cardiac monitoring by ECHO or MUGA scan.

Impact on the benefit-risk balance of the product:

The impact of congestive heart failure/left ventricular dysfunction on the benefit-risk balance of Perjeta is considered to be low. The incidence of CHF in patients receiving Perjeta, Herceptin and chemotherapy is low. Careful monitoring and following the dose management algorithm suggested in the product label further reduces the likelihood of a heart failure/left ventricular dysfunction event. The current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

The potential public health impact of this safety concern is considered to be low because of the low frequency of CHF in patients with advanced malignancy receiving Perjeta, Herceptin and chemotherapy and because most cardiac events appear to be asymptomatic reversible declines in LVEF.

2. INFORMATION ON IMPORTANT POTENTIAL RISKS

2.1 OLIGOHYDRAMNIOS

MedDRA terms:

MedDRA PTs coded to SMQ Pregnancy and neonatal topics.

Potential mechanisms:

Pertuzumab-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in an embryo-fetal study when pertuzumab was administered intravenously from GD 19 through GD50 to pregnant cynomolgus monkeys (the period of organogenesis in this species is GD20–50). In addition, consistent with fetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 30 mg/kg and 1 of 2 100 mg/kg), ventricular septal defects (1 of 6 30 mg/kg), thin ventricular wall 1 of 2 100 mg/kg) and minor skeletal defects (external - 3 of 6 30 mg/kg) were also noted. Systemic maternal and fetal exposure at clinically relevant pertuzumab concentrations, were confirmed.

The embryo-fetal effects observed with pertuzumab and trastuzumab are consistent with the role HER-family members play in the development and differentiation of ectodermal/epithelial tissues, including that of renal tissue (Bader et al, 2007).

Evidence source(s) and strength of evidence:

Non-clinical study in pregnant cynomolgus monkeys. Placental transfer of pertuzumab was confirmed in cynomolgus monkeys. Fetal to maternal pertuzumab serum concentration ratios were similar across a 10-fold range of doses at clinically relevant concentrations (20-fold greater than human clinical dose). Pertuzumab-related embryo-

fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in a study when pertuzumab was administered intravenously from GD19 through GD50 to pregnant cynomolgus monkeys, the period of organogenesis in this species (GD20 – 50). In addition, consistent with fetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 30 mg/kg and 1 of 2 100 mg/kg), ventricular septal defects (1 of 6 30 mg/kg), thin ventricular wall 1 of 2 100 mg/kg) and minor skeletal defects (external - 3 of 6 30 mg/kg) were also noted. Systemic maternal and fetal exposure at clinically relevant pertuzumab concentrations was confirmed.

No clinical studies have been performed in pregnant women.

Characterization of the risk:

Background Incidence/Prevalence:

There is no accepted standard definition for oligohydramnios. However, the incidence has been estimated as being between 0.4 and 1.7 % of pregnancies (Stoll et al, 1998; Alfirevic et al, 1997, Macharey et al, 2017). Stoll et al, (1998) reviewed 225,669 consecutive pregnancies births and concluded that 0.99/1000 pregnancies were complicated by oligohydramnios.

Frequency with 95% CI:

No events of oligohydramnios have been reported in patients receiving Perjeta in the MotHER pregnancy registry as of 31 January 2018 (cut-off date for the Final annual data summary [ADS] for this registry). Three patients exposed to Perjeta plus Herceptin enrolled in the registry; two patients had a live birth, and one patient was lost to follow-up).

Cumulatively, up to 7 June 2020 (data lock point for Perjeta PBRER Report 1101895, six initial cases of oligohydramnios were reported:

- AER [redacted] normal baby [redacted] delivered;
- AER [redacted] pregnancy outcome: [redacted];
- AER [redacted] pregnancy outcome: lost to follow-up;
- AER [redacted] pregnancy outcome: [redacted];
- AER [redacted] baby with [redacted];
- AER [redacted] no pregnancy.

One relevant follow-up case reported PT Amniotic fluid volume decreased (AER [redacted]; pregnancy outcome not reported).

In addition, AEs were reported for 2 initial child cases: [redacted] (AER [redacted] [redacted] week of gestation) and [redacted] (AER [redacted]; event outcome reported as resolved).

Seriousness/Outcomes

Oligohydramnios is associated with serious risks to fetal development. Perjeta-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development were observed in cynomolgus monkeys. Further clinical complications of oligohydramnios could include renal and pulmonary hypoplasia (which could be lethal) and skeletal malformations due to intrauterine growth restriction.

No cases of oligohydramnios have been reported in patients receiving Perjeta in the MotHER pregnancy registry, which includes both clinical and post-marketing cases as of 31 January 2018 (cut-off date for the Final ADS for this registry). Three patients exposed to Perjeta plus Herceptin have enrolled in the registry. Of these, two patients had a live birth; no specific SAE has been reported for these patients. One patient was lost to follow-up.

A summary of the seven initial cases of oligohydramnios and AEs reported for 2 initial child cases reported cumulatively up to 7 June 2020 (data lock point for Perjeta PBRER Report 1101895) is presented above.

In conclusion, the available data are consistent with the known information in the Perjeta SmPC.

Events with a fatal outcome in clinical trials: No events of fatal oligohydramnios have been reported in patients receiving Perjeta.

Severity and Nature of Risk:

Oligohydramnios is classified as a potential risk based on non-clinical data and because cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab and because of findings in non-clinical studies. No events of oligohydramnios have been reported in patients receiving Perjeta.

Impact on quality of life:

Oligohydramnios is associated with serious risks to fetal development and therefore may have a significant impact on an individual patient. Women of childbearing potential are advised to use effective contraceptive measures during treatment and for 7 months after the last dose of Perjeta.

The need to avoid pregnancy during and for 7 months after Perjeta treatment may affect patients' quality of life. However, patients are likely to face the same restrictions even if Perjeta were not given, since most treatment for breast cancer (chemotherapy, Herceptin, hormone therapy and radiotherapy) are associated with significant risks to the developing fetus.

Risk factors and risk groups:

Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive breast cancer is the mid-50s, at least half the patients likely to receive Perjeta treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the antiproliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur.

Opioid abuse or dependence during pregnancy markedly increased the odds of oligohydramnios (Maeda et al, 2014). Pregnant women with sickle cell disease are at increased risk of oligohydramnios (Kuo and Caughey 2016). Primiparity is associated with an increased rate of oligohydramnios (Wielgos et al, 2015).

Preventability:

The risk of oligohydramnios is avoidable providing effective contraceptive measures are applied by women of childbearing potential during treatment and for 7 months after the last dose of Perjeta in combination with Herceptin.

Impact on the benefit-risk balance of the product:

Current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

The public health impact associated with this safety concern is considered to be low. Pregnancies are usually contraindicated in patients with advanced malignancy due to the risks of cytotoxic drugs, hormone therapy and/or radiotherapy, as well as the limited life expectancy of the mother.

2.2 RISK IN FERTILITY IN HUMANS

MedDRA terms:

MedDRA HLT Fertility analyses, Sexual function and fertility disorders NEC.

Potential mechanisms:

There is no known mechanism for the risk in fertility in humans as a result of treatment with Perjeta. No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab on fertility. Only very limited data are available from repeat-dose toxicity studies with respect to the risk for adverse effects on the male reproductive

system. No adverse effects were observed in sexually mature female cynomolgus monkeys exposed to pertuzumab. However, a non-clinical reproductivity study in cynomolgus monkeys showed embryo/fetal losses, oligohydramnios, delayed renal development (renal hypoplasia) and intrauterine death with a dose-related increase in incidence and severity.

Evidence source(s) and strength of evidence:

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab.

The Roche Global Safety Database has been reviewed for any cases of risk in fertility in humans or fertility disorders.

Characterization of the risk:

Frequency with 95% CI:

Cumulatively, no cases of the risk in fertility in humans or fertility disorders have been reported to the Roche global safety database (up to 3 May 2017).

Seriousness/Outcomes

Cumulatively, no cases of the risk in fertility in humans or fertility disorders have been reported to the Roche Global Safety Database (up to 3 May 2017).

SAEs of the risk in fertility in humans or fertility disorders in clinical trials: No SAEs of the risk in fertility in humans or or fertility disorders have been reported in patients receiving Perjeta in clinical trials.

Severity and Nature of Risk:

No cases of the risk in fertility in humans or fertility disorders have been reported in patients receiving Perjeta.

Impact on quality of life:

Attention to future fertility following diagnosis of breast cancer in younger patients who are pre-menopausal or of child-bearing age are extremely important. Both ESMO and ASCO guidelines recommend referral to a fertility specialist for women interested in preserving their fertility (Loren et al. 2013; Peccatori et al. 2013).

Standard options for fertility preservation such as embryo and oocyte cryopreservation or other treatments for fertility in patients who may develop fertility disorders may have an impact on the quality of life of the patient. However, younger women are more likely to present with a more advanced stage of disease and are also more likely to develop more aggressive subtypes of breast cancer (including HER2-positive breast cancer) and have lower survival rates compared to older women. Therefore, it is more likely that the benefit of treatment for the underlying disease outweighs the impact in younger women.

Risk factors and risk groups:

The median age at diagnosis of HER2-positive breast cancer is the mid-50s, therefore at least half the patients likely to receive Perjeta treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the anti-proliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur.

Preventability:

Currently there is no data of risk of fertility in humans following the use of Perjeta. Perjeta labelling indicates that women of child bearing potential and female partners of male patients of child bearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta. Chemotherapies are likely to reduce the chances of conception, implantation and embryogenesis and clinical guidelines recommend referral to a fertility specialist for women of childbearing potential with breast cancer interested in preserving their fertility (Loren et al. 2013; Peccatori et al. 2013).

Impact on the benefit-risk balance of the product:

Current routine risk minimization measures in place recommend avoidance of pregnancy during the use of Perjeta.

Public health impact:

The public health impact associated with this safety concern is considered to be low since to date there is no indication of the risk in fertility in humans following the use of Perjeta.

2.3 RISK IN PATIENTS AGED 75 YEARS OR OLDER

MedDRA terms:

Not applicable.

Potential mechanisms:

The elderly population is more susceptible to AEs, including those related to their co-morbidities.

Evidence source(s) and strength of evidence:

Adults were not excluded from participating in Perjeta trials on the grounds of age if they met the other eligibility criteria (i.e., no upper age limit was applied). No dedicated PK studies were performed in elderly patients. No Perjeta dose adjustment is required for adult patients of any age, including patients aged 65 years or older.

Characterization of the risk:

Background Incidence/Prevalence:

A considerable number of older patients have now been treated in Perjeta clinical trials. No upper age limit was applied and adult patients of any age could enter the trials if they met the other eligibility criteria. The relative lack of patients in the ≥75 year age category likely reflects the higher incidence of comorbidities (such as cardiac failure or renal impairment) in older patients and concerns about administration of chemotherapy to elderly patients. A total of 464 patients aged ≥65 years have been evaluated in key Perjeta clinical studies, including 47 patients aged ≥75 years (~10% of patients aged ≥65 years) (Table 20). An estimated cumulative total of 75,800 patients aged ≥65 years have received Perjeta in routine clinical practice (Table 12), and assuming a similar ratio to that seen in clinical trials, approximately 7,500 of these patients may have been aged ≥75 years.

Table 20 Number of Patients Aged ≥65 years and ≥75 years Exposed to Perjeta by Study

Study number (Study name)	Aged ≥65 years	Aged ≥75 years
BO22280 (TRYPHAENA)	26	4
BO25126 (APHINITY)	302	30
WO20697 (NEOSPHERE)	22	2
WO20698 (CLEOPATRA)	68	5
WO29217 (BERENICE)	46	6
MO28047 (PERUSE)	269	Not available
Total	**733**	**47**

Source: BO22280 (TRYPHAENA, Primary CSR [Report 1046609; May 2012]); BO25126 (APHINITY, Primary CSR [Report 1075429, July 2017]); WO20697 (NEOSPHERE Primary CSR [Report 1032196; June 2011]); WO20698 (CLEOPATRA Primary CSR [Report 1046288; October 2011]); WO29217 (BERENICE Primary CSR [Report 1070920; December 2016])and Final CSR Study MO28047, (PERUSE) [Report 1101598;July 2020]

Seriousness/Outcomes

Analyses have been conducted comparing the safety of Perjeta in patients aged 65 – 75 years and adult patients aged below 65 years. To date, no significant differences in safety of Perjeta have been observed between elderly patients aged 65 – 75 years and patients aged below 65 years, with the exception of decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhea which had at least 5% higher in patients aged 65 years of age or higher, compared to patients aged less than 65 years of age. There are no distinct biological differences between patients aged 65 – 75 years and patients aged ≥ 75 years, and patients in these two age categories are likely to show considerable overlap in biological characteristics such as cardiac, renal and hepatic function, performance status and presence of comorbidities.

Severity and nature of risk

Accordingly, no differences in safety of Perjeta are expected for patients aged ≥ 75 years compared to patients aged 65 – 75 years. Also, as reported in the current Perjeta PBRER (reporting interval: 8 June 2019 to 7 June 2020), no meaningful increase in frequency, severity or specificity or a pattern of the reported events in patients aged 75 years and older was observed during the reporting interval. Subgroup analyses of efficacy based on age groups have also been conducted in all the key Perjeta studies, and no differences in efficacy have been observed.

Impact on quality of life

Not applicable.

Risk factors and risk groups:

Patients aged ≥75 years.

Preventability:

In elderly patients (≥65 years), diarrhea has been observed at a higher rate (increased risk of diarrhea in elderly patients is already included in Perjeta product label). Early intervention with loperamide, fluids and electrolyte replacement should be considered, particularly in elderly patients.

Impact on the benefit-risk balance of the product:

The impact of the risk of use of Perjeta in patients 75 years or older on the overall benefit-risk balance of the product is considered low. Age-related information is already included in the product label for Perjeta, notably the warning about increased risk of diarrhea in elderly patients. Current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

The potential public health impact of Perjeta-related AEs in patients aged 75 years or older is considered low, due to the small number of these patients receiving Perjeta. The event of diarrhea which is seen at a higher rate in these patients is manageable with treatment.

2.4 LACK OF EFFICACY DUE TO IMMUNOGENICITY

MedDRA terms:

PTs Neutralising antibodies; neutralising antibodies positive; Drug specific antibody present.

Potential mechanisms:

The production of ADAs is considered to occur via well-understood humoral responses to foreign antigens, namely coordination between antigen presenting cells, T-helper cells and B-cells.

Nearly all biopharmaceuticals may induce antibodies by various mechanisms, however, the frequency of these antibodies and the clinical impact, if any, varies widely (Schellekens 2003). The mechanisms by which ADAs may impact efficacy include increased clearance of ADA/drug immune complexes thereby lowering drug exposure, as well as directly interfering with drug/target interactions (so-called neutralizing ADA).

Evidence source(s) and strength of evidence:

The immunogenicity of pertuzumab has been assessed in pertuzumab clinical trials by evaluating the incidence of ADAs to pertuzumab at baseline and following exposure to

pertuzumab and a low incidence of ADA formation has been observed (2.4% in all studies to date).

Characterization of the risk:

Background Incidence/Prevalence:

The immunogenicity of pertuzumab has been assessed in many clinical trials by evaluating the incidence of ADAs to pertuzumab at baseline and following exposure to pertuzumab. ADA data available for Perjeta-treated patients in Phase I/II and Phase III studies are summarized in Table 21 and Table 22, respectively.

The incidence of ADA in the Phase I/II studies was lower (0.5%) than in the Phase III studies (2.9%) but the duration of therapy/observation was relatively short, reflecting the Phase I/II patient populations (which generally include patients with advanced refractory disease after failure of standard therapies) and the inclusion of patients with tumor types now known not to respond to Perjeta-based therapy.

Table 21 Summary of ADA Data for Perjeta-Treated Patients in Phase I /II Studies

Study Number	Study Phase	Number of Patients with Evaluable ADA Result [a]	Number of Patients with Positive ADA Response [b]
TOC2297g	I	17	0
JO17076	I	18	0
WO20024	I	8	0
BO16934	II	61	0
TOC2682g	II	31	0
BO17004	II	59	0
BO17931	II	46	1
TOC2689g	II	72	0
TOC3258g	II	26	0
TOC2572g	II	27	1
TOC2664g	II	1	0
Total		366	2

[a] Number of patients with at least one post-dose (post− Perjeta treatment) ADA time point available for analysis.

[b] Number of patients who had a positive, confirmed ADA sample after Perjeta treatment.

Table 22 Summary of ADA Data for Perjeta-Treated Patients in Phase III Studies

Study Number (Study Name)	Indication	Incidence of ADA to date[a], Number of Patients (%)
WO20698 (CLEOPATRA)	First-line HER2-Positive Metastatic Breast Cancer	13/389 (3.3%)
MO28113 (PENELOPE)	Recurrent platinum-resistant epithelial ovarian cancer with low HER3 mRNA expression	4/63 (6.3%)
BO25114 (JACOB)	First-line HER2-positive metastatic gastric cancer	2/347 (0.6%)
WO29217 (BERENICE)	Locally advanced, inflammatory, or early-stage HER2-positive breast cancer	16/392 (4.1%)
	Total	35/1191 (2.9%)

[a] CSRs reporting the most recent ADA data available.

Source: WO20698 (CLEOPATRA Primary CSR [Report 1046288; October 2011]); MO28113 (PENELOPE Final CSR [February 2017]); BO25114 (JACOB Primary CSR [Report 1078586; 1078586]); WO29217 (BERENICE Update CSR [Report 1077424]).

Seriousness/Outcomes

ADAs were extensively evaluated in the pivotal CLEOPATRA study in patients with metastatic breast cancer. Post-hoc exploratory analyses of the effects of ADAs on key efficacy parameters were also conducted (Primary CSR [Report 1046288; October 2011]). Exploratory analyses of independent review facility-assessed progression-free survival (IRF-assessed PFS) in Perjeta-treated patients with at least one post-baseline positive ADA assessment indicated shorter IRF-assessed PFS in comparison with IRF-assessed PFS in the overall intent-to-treat (ITT) population. The median PFS was 12.5 months (95% CI: 2; 14) for Perjeta-treated patients in the ADA positive subgroup, which was consistent with results of the ITT population in the control arm (12.4 months [95% CI： 10; 13]), whereas the median PFS for the Perjeta-treated/ADA negative subgroup was 18.7 months (95% CI： 16; 25). Overall response rate (ORR) was also lower in Perjeta-treated patients with ADA-positive samples than in the Perjeta-treated patients who were ADA-negative (ORR 45.5% [95% CI: 16.7; 76.6] vs. 80.2% [95% CI: 77.1; 85.7], respectively). However, these results should be viewed with caution since a low number of patients tested positive for ADA and the CIs were wide for PFS and ORR in the ADA positive subgroup. In addition, examination of individual IRF-assessed PFS data for each patient revealed that several of the patients with a positive ADA response receiving Perjeta treatment achieved prolonged disease control and there was no clear temporal association between development of a positive ADA response and IRF-assessed progressive disease.

In the BERENICE study, the incidence of ADAs at the time of primary analysis was considered too low (1/383 [0.3%]) to conduct efficacy analyses in the subgroup of patients determined to be positive for ADAs, however, the patient was determined to have achieved pCR. At the latest clinical cut-off date, 16/392 [4.1%] patients were positive for ADAs, however, there were no updates to efficacy endpoints in the study, and therefore, the impact of ADA to efficacy was not assessed at the time. In the other two studies (PENELOPE and JACOB), which were conducted in patients with ovarian cancer and gastric cancer respectively, there was insufficient evidence of Perjeta efficacy in the study overall (ITT population) to warrant subgroup analyses of efficacy based on ADA status. In addition, the number and/or frequency of ADAs were too low in these studies to warrant evaluation of efficacy in the subgroup of patients who developed ADA. However, 2 (of 2) patients in the JACOB study with ADAs achieved a partial response to therapy with PFS and overall survival in the expected range, suggesting that the presence of ADAs had no detrimental effect on efficacy in these 2 patients.

A search of the post-marketing data did not identify any cases of lack of efficacy due to reported ADA or immunogenicity from clinical and post-marketing sources (Perjeta PBRER [reporting interval: 8 June 2019 to 7 June 2020]). However, this is to be expected given that patients are rarely tested for ADAs outside of clinical trials.

Severity and nature of risk

The presence of ADA at baseline or post-baseline has not been found to be associated with hypersensitivity/anaphylaxis. Although cases of Grade 3 hypersensitivity reactions have been reported in patients with ADAs, most patients with ADAs do not develop severe reactions and have continued Perjeta treatment as planned.

The immunogenicity of Perjeta has now been assessed in more than 1500 Perjeta-treated patients in clinical trials. Based on data available to date, the incidence of ADA formation is low (~2.4%). ADA formation is also not generally associated with hypersensitivity reactions or anaphylaxis. Although an adverse effect of ADA formation on Perjeta efficacy cannot be excluded, other causes of treatment failure (inherent or acquired resistance to HER2-targeted therapy) are likely to be much more common. Further investigation of ADA formation in Perjeta clinical trials is not likely to yield significant new information or to change this conclusion.

Impact on quality of life

The impact of lack of efficacy due to immunogenicity on quality of life is considered low.

Risk factors and risk groups:

Risk factors for the development of ADAs have been described in various regulatory guidance documents and industry white papers (EMEA 2007; Koren et al. 2008; FDA 2014), and includes genetic factors, patient immune status, and concomitant medications. However, there is currently no way to predict which patients will generate ADAs and of these which (if any) will lose drug benefits as a result.

Preventability:

Based on data available to date, the incidence of ADA formation is low (~2.4%). When ADAs are detected, they are often transient and titers also tend to be low, and are not generally associated with hypersensitivity reactions or anaphylaxis. Although an adverse effect of ADA formation of pertuzumab PK and/or efficacy cannot be excluded, other causes of treatment failure (inherent or acquired resistance to HER2-targeted therapy) are likely to be much more common. Further investigation of ADA formation in Perjeta clinical trials is not likely to yield significant new information or to change this conclusion. The low incidence of ADA formation in Perjeta-treated patients and the lack of apparent clinical consequences in most patients mean that ADA testing is unlikely to be introduced into routine clinical practice in the future. No additional pharmacovigilance or specific risk minimization measures are planned for patients receiving Perjeta.

Impact on the benefit-risk balance of the product:

The impact of the risk of lack of efficacy due to immunogenicity on the overall benefit-risk balance of the product is considered low given the risk factors cited above and because

of the low incidence of ADA formation observed to date. In particular, pertuzumab is a humanized monoclonal antibody with no endogenous counterpart is administered intravenously to cancer patients whose immune systems are generally suppressed, and does not have immunomodulatory activity further supporting its low immunogenic potential.

Public health impact:

The potential public health impact of lack of efficacy due to immunogenicity is considered low, due to the low incidence of ADA formation in Perjeta-treated patients.

SVII.3.2. Presentation of the Missing Information

3. INFORMATION ON MISSING INFORMATION:

3.1 RISK IN PATIENTS WITH CARDIOVASCULAR IMPAIRMENT

Evidence source:

Perjeta has not been studied in patients with: a pretreatment LVEF value of $<50\%$; a prior history of congestive heart failure (CHF); LVEF declines to $<50\%$ during prior trastuzumab adjuvant therapy; or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction (MI), serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to >360 mg/m^2 of doxorubicin or its equivalent.

Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents. Cardiac dysfunction may manifest as an asymptomatic or mildly symptomatic decrease in LVEF (NCI CTCAE Grade 1 and Grade 2; NYHA Class I-II) or as a symptomatic decrease in LVEF/CHF (NCI CTCAE $\geq$Grade 3; NYHA Class III or IV). In line with Herceptin, a clinically relevant drop in LVEF has been defined as a decline $\geq 10\%$-points from baseline to an absolute value of $<50\%$ for Perjeta studies. However, the clinical importance of asymptomatic declines in LVEF is currently not known.

3.2 RISK IN PREGNANT OR LACTATING WOMEN

Evidence source:

Pregnant or lactating women were excluded from all Perjeta trials. A non-clinical reproductivity study in cynomolgus monkeys showed embryo/fetal losses, oligohydramnios, delayed renal development (renal hypoplasia) and intrauterine death with a dose-related increase in incidence and severity. These findings were consistent with evidence that antibodies can be transported across the placenta during the period of organogenesis in the cynomolgus monkey. Cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have also been reported in pregnant women receiving trastuzumab, which (like Perjeta) is an antibody that targets the HER2 receptor. Professional labeling documents indicate that Perjeta should be

avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. Women of child bearing potential and female partners of male patients of child bearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta.

Because human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, a recommendation should be made to discontinue nursing during and after Perjeta treatment, taking into account the importance to the mother and the half-life of pertuzumab.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 23 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infusion-related reactions, Hypersensitivity reactions / anaphylaxis Congestive heart failure / Left ventricular dysfunction
Important potential risks	Oligohydramnios* Risk in fertility in humans Risk in patients aged 75 years or older Lack of efficacy due to immunogenicity
Missing information	Risk in patients with cardiovascular impairment Risk in pregnant or lactating women

*Oligohydramnios has not been reported in patients treated with Perjeta but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. Due to age, prior adjuvant treatment, concurrent chemotherapy, the advanced stage of disease and poor prognosis in the patient population, the MAH assesses the likelihood of pregnancies to be low.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Guided Questionnaire – Pregnancy-Related Adverse Events

Oligohydramnios has been classified as an important potential risk for Perjeta. The guided questionnaire was implemented as part of the Global Enhanced Pharmacovigilance Pregnancy Program to request additional information on the mother's medical and obstetric history, the current pregnancy, fetal and infant condition, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life (Annex 4).

Other forms of routine pharmacovigilance activities:

Presentation of cumulative data in Periodic Safety Update Reports (PSURs) for the following risks:

Infusion-related reactions, Hypersensitivity reactions/anaphylaxis

Congestive heart failure/Left ventricular dysfunction

Patients aged 75 years or older

Lack of efficacy due to immunogenicity

Risk in patients with cardiovascular impairment

Global Enhanced Pharmacovigilance Pregnancy Program for safety concern:

Oligohydramnios

Risk in fertility in humans

Risk in pregnant or lactating women.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not Applicable

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

TABLE 24 ONGOING AND PLANNED ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Study Status	**Summary of Objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
NA	NA	NA	NA	NA
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance activities				
NA	NA	NA	NA	NA

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table 25 Planned and Ongoing post-authorization Imposed efficacy studies that are conditions of the marketing authorization or that are specific obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
NA	NA	NA	NA	NA
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
BO25126 (APHINITY)	To provide long term efficacy data for Perjeta in the treatment of HER2-positive EBC	Long-term efficacy	Submission of final CSR	2024 (Approximately)

CSR = Clinical study report, EBC = early breast cancer.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 26 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Infusion-related reactions, Hypersensitivity reactions/anaphylaxis	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.4 of the EU SmPC, “Infusion reactions” and “Hypersensitivity reactions/anaphylaxis” part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Perjeta is a prescription only medicine
Congestive heart failure / Left ventricular dysfunction	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.2 of the EU SmPC, “Left ventricular dysfunction” part and Section 4.4 “Left ventricular dysfunction (including congestive heart failure)” provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Perjeta is a prescription only medicine

Safety concern	Routine risk minimization activities
Oligohydramnios	**Routine risk communication:** Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.6 of the EU SmPC: “Fertility, pregnancy and lactation” part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Perjeta is a prescription only medicine
Risk in fertility in humans	**Routine risk communication:** Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.6 of the EU SmPC: “Fertility, pregnancy and lactation” part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Perjeta is a prescription only medicine
Risk in patients aged ≥ 75 years	**Routine risk communication:** Section 4.2 of the EU SmPC: “Elderly patients” part **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.4 “Diarrhoea” part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:**

Safety concern	Routine risk minimization activities
	Legal Status: Perjeta is a prescription only medicine
Risk of lack of efficacy due to immunogenicity	**Routine risk communication:** Section 5.1 of the EU SmPC: “Immunogenicity” part **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Perjeta is a prescription only medicine
Risk in patients with cardiovascular impairment	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.2 of the EU SmPC, “Left ventricular dysfunction” part and Section 4.4 “Left ventricular dysfunction (including congestive heart failure)” provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Perjeta is a prescription only medicine
Risk in pregnant or lactating women	**Routine risk communication:** Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.6 of the EU SmPC: “Fertility, pregnancy and lactation” part provides recommendations on risk management approach.

Safety concern	Routine risk minimization activities
	Other risk minimization measures beyond the Product Information: None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

None

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 27 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion-related reactions, Hypersensitivity reactions/anaphylaxis	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.4 of the EU SmPC, "Infusion reactions" and "Hypersensitivity reactions/anaphylaxis" part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Congestive heart failure / Left ventricular dysfunction	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.2 of the EU SmPC, "Left ventricular dysfunction" part and Section 4.4 "Left ventricular dysfunction (including congestive heart failure)" provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Oligohydramnios	**Routine risk communication:** Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4. 6 of the EU SmPC: "Fertility, pregnancy and lactation" part provides recommendations on risk management approach.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Global Enhanced Pharmacovigilance Pregnancy Program **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other risk minimization measures beyond the Product Information: None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None	
Risk in fertility in humans	**Routine risk communication:** Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4. 6 of the EU SmPC: "Fertility, pregnancy and lactation" part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Global Enhanced Pharmacovigilance Pregnancy Program *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Risk in patients aged ≥ 75 years	**Routine risk communication:** Section 4.2 of the EU SmPC: "Elderly patients" part **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.4 "Diarrhoea" part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Risk of lack of efficacy due to immunogenicity	**Routine risk communication:** Section 5.1 of the EU SmPC: Pharmacodynamic properties under Immunogenicity part **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Risk in patients with cardiovascular impairment	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.2 of the EU SmPC, "Left ventricular dysfunction" part and Section 4.4 "Left ventricular dysfunction (including congestive heart failure)" provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Risk in pregnant or lactating women	**Routine risk communication:** Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4. 6 of the EU SmPC: "Fertility, pregnancy and lactation" part provides	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Global Enhanced Pharmacovigilance Pregnancy Program *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs

Safety concern	Risk minimization measures	Pharmacovigilance activities
	recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** None

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR PERJETA (PERTUZUMAB)

This is a summary of the risk management plan (RMP) for Perjeta. The RMP details important risks of Perjeta, how these risks can be minimized, and how more information will be obtained about Perjeta risks and uncertainties (missing information).

Perjeta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Perjeta should be used.

This summary of the RMP for Perjeta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Perjeta RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Perjeta is authorized for Metastatic Breast Cancer as well as Neoadjuvant & Adjuvant Treatment of Early Breast Cancer (see SmPC for the full indication). It contains pertuzumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Perjeta benefits can be found in Perjeta's EPAR, including in its plain-language summary, available on the European Agency for the Evaluation of Medicinal Products (EMA) website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Perjeta, together with measures to minimize such risks and the proposed studies for learning more about Perjeta's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

Important advice on the medicine's packaging;

The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Perjeta is not yet available, it is listed under 'missing Information' below.

II.A List of Important Risks and Missing Information

Important risks of Perjeta are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Perjeta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Infusion-related reactions, Hypersensitivity reactions / anaphylaxis Congestive heart failure / Left ventricular dysfunction
Important potential risks	Oligohydramnios* Risk in fertility in humans Risk in patients aged 75 years or older Lack of efficacy due to immunogenicity
Missing information	Risk in patients with cardiovascular impairment Risk in pregnant and lactating women

*Oligohydramnios has not been reported in patients treated with pertuzumab but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. Due to age, prior adjuvant treatment, concurrent chemotherapy, the advanced stage of disease and poor prognosis in the patient population, the MAH assesses the likelihood of pregnancies to be low.

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risk-Infusion-related reactions, Hypersensitivity reactions/anaphylaxis	
Evidence for linking the risk to the medicine	Randomized clinical trial data Based on safety results from WO20698 (CLEOPATRA), WO20697 (NEOSPHERE), BO22280 (TRYPHAENA) and BO25126 (APHINITY)
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not be susceptible to infusion-associated reactions, hypersensitivity or anaphylaxis to pertuzumab. Patients with a history of asthma, eczema or hay fever (atopy) had a slightly increased risk of developing an IRR (on the day of or the day after a pertuzumab infusion) than patients who did not have a history of atopy but the number of patients with a history of atopy was too small for any firm conclusions to be drawn. Moreover, patients with a history of atopy did not appear to be at increased risk of anaphylaxis or hypersensitivity reactions. Importantly, prior and concomitant trastuzumab exposure did not appear to reduce or exacerbate the infusion-associated events seen with pertuzumab. *Anti-Drug Antibodies (ADA) in Study WO20698* Serum samples were assayed for anti-drug antibodies (ADAs) to pertuzumab, also known as anti- therapeutic antibodies (ATAs) or human anti-human antibodies (HAHA). The incidence of ADA was calculated from the total number of patients who tested positive for ADA against pertuzumab after dosing, divided by the total number of patients who had post dose ADA samples available for the ADA analysis. A conservative approach was taken for calculating the incidence of ADA so that any patient confirmed to have an ADA positive sample after dosing was considered positive for ADA, regardless of baseline status. Since trastuzumab and pertuzumab share the same framework structure, differing only in the complementarity determining region, it is possible that the positive ADA findings in patients treated with Pla+H+D were due to antibodies directed toward the common framework portion of pertuzumab and trastuzumab.

	In Study WO20698, at the second clinical data cutoff (14 May 2012), 6.7% (25/372 patients) of placebo-treated patients and 3.3% (13/389 patients) of pertuzumab-treated patients tested positive for ADA. Of these 38 patients, none experienced anaphylactic/ hypersensitivity reaction was clearly related to the ADA. Patients with detectable ADA were able to continue study treatment, sometimes for prolonged periods.
Risk minimization measures	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.4 of the EU SmPC, “Infusion reactions” and “Hypersensitivity reactions/anaphylaxis” part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** **Medicine’s legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Identified Risk - Congestive heart failure / Left ventricular dysfunction	
Evidence for linking the risk to the medicine	Clinical trial data Based on safety results from WO20697 (NEOSPHERE), WO20698 (CLEOPATRA), BO22280 (TRYPHAENA), WO29217 (BERENICE),BO25126 (APHINITY)and MO28047 (PERUSE)
Risk factors and risk groups	Risk factors such as age of 60 years or older, prior chemotherapy, registration left ventricular ejection fraction (LVEF) less than 65%, hypertension and use of antihypertensive medications such as angiotensin-converting-enzyme inhibitor, angiotensin II receptor blockers and β-blockers were associated with an increased risk of cardiac

	events in patients with HER2-positive breast cancer (Russo et al 2014, Anthony et al 2015, Advani et al 2015). **Anthracycline exposure:** Risks for anthracycline-induced heart failure include cumulative dosage, age over 70 years, earlier or simultaneous radiation to the chest, concurrent treatment with other chemotherapeutic cardiotoxic agents, examples, taxanes, capecitabine or trastuzumab and pre-existing heart disease (Geiger et al, 2010; Fiuza 2009). The most important risk factor for late cardiac toxicity is reported as the cumulative anthracycline dose (Yeh et al,, Keefe quoted in Senkus & Jassem 2011). **Concurrent trastuzumab.** The cardiac changes associated with trastuzumab are mostly reversible, do not appear to be dose-related and do not involve histological changes in cardiac tissue. Identified risk factors include exposure to anthracyclines or paclitaxel, low LVEF at baseline, age > 60 years, obesity, previous heart disease and hypertension. Current monitoring of cardiac function uses changes in LVEF as a reference for cardiotoxicity. Age, anthracycline exposure, and the presence of cardiovascular risk factors predicted cardiac AEs in trastuzumab recipients (Hudis, quoted in Guglin et al 2009). No clear relation to a cumulative dose of trastuzumab has been described (Geiger et al, 2010). After treatment interruption, clinical and subclinical signs of heart failure are mostly reversible and reinitiating of trastuzumab after recovery is often well tolerated (Geiger et al, 2010). **Adjuvant breast radiotherapy**: A relative increase of 30% in cardiac deaths was found in women treated with radiotherapy before the 1980s (Clark et al quoted in Chargari et al 2011). Among patients treated during 1973-82 and receiving radiotherapy, the cardiac mortality ratio (left vs. right tumor) was 1.58 (1.29-1.95) after 15 years or more and for patients diagnosed during 1993-2001, the cardiac mortality ratio was 0.96 (0.82-1.12) less than 10 years afterwards (Darby et al, quoted in Chargari et al 2011). Internal mammary chain irradiation increases heart dose exposure particularly when outdated techniques are used or in patients with left-sided tumors, potentially translating into increased long-term heart disease (Chargari et al 2011).

Risk minimization measures	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.2 of the EU SmPC, “Left ventricular dysfunction” part and Section 4.4 “Left ventricular dysfunction (including congestive heart failure)” provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** **Medicine’s legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risks - Oligohydramnios	
Evidence for linking the risk to the medicine	Non-clinical study in pregnant cynomolgus monkeys. Placental transfer of pertuzumab was confirmed in cynomolgus monkeys. Fetal to maternal pertuzumab serum concentration ratios were similar across a 10-fold range of doses at clinically relevant concentrations (20-fold greater than human clinical dose). Pertuzumab-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in a study when pertuzumab was administered intravenously from Gestation Day 19 (GD19) through GD50 to pregnant cynomolgus monkeys, the period of organogenesis in this species (GD20＝50). In addition, consistent with fetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 30 mg/kg and 1 of 2 100 mg/kg), ventricular septal defects (1 of 6 30 mg/kg), thin ventricular wall 1 of 2 100 mg/kg) and minor skeletal defects (external - 3 of 6 30 mg/kg) were also noted. Systemic maternal and fetal exposure at clinically relevant pertuzumab concentrations was confirmed. No clinical studies have been performed in pregnant women.
Risk factors and risk groups	Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive breast cancer is the mid-50s, at least half the patients likely to receive pertuzumab treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the anti-proliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur. Opioid abuse or dependence during pregnancy markedly increased the odds of oligohydramnios (Maeda et al 2014). Pregnant women with sickle cell disease are at increased risk of oligohydramnios (Kuo and Caughey 2016). Primiparity is associated with an increased rate of oligohydramnios (Wielgos et al 2015).

Risk minimization measures	**Routine risk communication:** Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.6 of the EU SmPC: “Fertility, pregnancy and lactation part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** **Medicine’s legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risks – Risk in fertility in humans	
Evidence for linking the risk to the medicine	No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. The Roche Global Safety Database has been reviewed for any cases of risk in fertility in humans or fertility disorders.
Risk factors and risk groups	The median age at diagnosis of HER2-positive breast cancer is the mid-50s, therefore at least half the patients likely to receive Perjeta treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the anti-proliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur.
Risk minimization measures	**Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risks – Risk in patients aged 75 years or older	
Evidence for linking the risk to the medicine	Adults were not excluded from participating in Perjeta trials on the grounds of age if they met the other eligibility criteria (i.e., no upper age limit was applied). No dedicated pharmacokinetcic studies were performed in elderly patients. No Perjeta dose adjustment is required for adult patients of any age, including patients aged 65 years or older.
Risk factors and risk groups	Patients aged $\geq$ 75 years.
Risk minimization measures	**Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risks – Lack of efficacy due to immunogenicity	
Evidence for linking the risk to the medicine	The immunogenicity of pertuzumab has been assessed in Perjeta clinical trials by evaluating the incidence of anti-drug antibodies (ADAs) to pertuzumab at baseline and following exposure to pertuzumab (or placebo), and a low incidence of ADA formation has been observed.
Risk factors and risk groups	Risk factors for the development of ADAs have been described in various regulatory guidance documents and industry white papers (EMEA 2007; Koren et al. 2008; FDA 2014). Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products, and include genetic factors, patient immune status, and concomitant medications. However, there is currently no way to predict which patients will generate ADAs and of these which will lose drug benefits as a result.
Risk minimization measures	**Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information- Risk in patients with cardiovascular impairment	
Evidence for linking the risk to the medicine	Perjeta has not been studied in patients with: a pretreatment LVEF value of $<50\%$; a prior history of congestive heart failure (CHF); LVEF declines to $<50\%$ during prior trastuzumab adjuvant therapy; or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to >360 mg/m^2 of doxorubicin or its equivalent. Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents. Cardiac dysfunction may manifest as an asymptomatic or mildly symptomatic decrease in LVEF (NCI CTCAE Grade 1 and Grade 2; NYHA Class I-II) or as a symptomatic decrease in LVEF/CHF (NCI CTCAE $\geq$Grade 3; NYHA Class III or IV). In line with trastuzumab, a clinically relevant drop in LVEF has been defined as a decline $\geq 10\%$-points from baseline to an absolute value of $<50\%$ for pertuzumab studies. However, the clinical importance of asymptomatic declines in LVEF is currently not known.
Risk minimization measures	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.2 of the EU SmPC, “Left ventricular dysfunction” part and Section 4.4 “Left ventricular dysfunction (including congestive heart failure)” provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** **Medicine’s legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information – Risk in pregnant and lactating women	
Evidence for linking the risk to the medicine	Pregnant or lactating women were excluded from all Perjeta trials. A non-clinical reproductivity study in cynomolgus monkeys showed embryo/fetal losses, oligohydramnios, delayed renal development (renal hypoplasia) and intrauterine death with a dose-related increase in incidence and severity. These findings were consistent with evidence that antibodies can be transported across the placenta during the period of organogenesis in the cynomolgus monkey. Cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have also been reported in pregnant women receiving trastuzumab, which (like pertuzumab) is an antibody that targets the HER2 receptor. Professional labeling documents indicate that Perjeta should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. Women of child bearing potential and female partners of male patients of child bearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta. Because human Immunglobulin G is secreted in human milk, and the potential for absorption and harm to the infant is unknown, a recommendation should be made to discontinue nursing during and after Perjeta treatment, taking into account the importance to the mother and the half-life of pertuzumab.
Risk minimization measures	**Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

Study short name: BO25126 (APHINITY)

Purpose of the study: To provide long term efficacy data for Perjeta in the treatment of HER2-positive EBC.

II.C.2 Other studies in post-authorization development plan

There are no other studies in post-authorization development plan for Perjeta.

ANNEX 1:

EUDRAVIGILANCE INTERFACE

ANNEX 1 – EUDRAVIGILANCE INTERFACE

Available in electronic format only

ANNEX 2:

TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

ANNEX 2: TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table 1 Planned and ongoing studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
NA	NA	NA	NA

Table 2 Completed studies

Study	Summary of Objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
PERUSE study (MO28047)* A Phase IIIb study to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane Category 1 Completed	**Primary Objective** • To evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane.	Congestive heart failure / Left ventricular dysfunction. Risk in patients with cardiovascular impairment.	Final CSR submission – Sept 2020*

Study	Summary of Objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
	Secondary Objectives • To evaluate pertuzumab in combination with trastuzumab and a taxane with respect to: – Progression-free survival (PFS) – Overall survival (OS) – Overall response rate (ORR) – Clinical benefit rate (CBR) – Duration of response – Time to response Quality of life (Functional Assessment of Cancer Therapy-Breast [FACT-B] questionnaire for female patients only).		
MO22324 (PHEREXA) Phase III study –in patients with HER2-positive metastatic breast cancer that have progressed after one line of trastuzumab- based therapy in the metastatic setting. Category 1	Investigate combination of pertuzumab with trastuzumab and capecitabine (known for a potential cardiac ischemic effect).	Congestive heart failure / Left ventricular dysfunction.	July 2016 (PV commitment fulfilled).
BO22280 (TRYPHAENA)- A phase II study to evaluate the overall safety and cardiac toxicity of pertuzumab plus trastuzumab in combination with both anthracycline containing and	After completion of trastuzumab LVEF to be performed every 6 months for 2 years then annually, for a further 2 years.	Congestive heart failure / Left ventricular dysfunction.	2014 (update). 2016 (PV commitment fulfilled and study completed).

Study	Summary of Objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
anthracycline-free regimens in neoadjuvant treatment of HER2-positive EBC. Category 3			
WO20698 (CLEOPATRA)- A Phase III, randomized, double blind,Placebo controlled clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab +docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2- positive metastatic breast cancer. Category 3	Long-term follow up of cardiac events.	All safety concerns.	2014; CSR with final OS data submitted (PV commitment fulfilled).
BERENICE- A phase II study to evaluate the cardiac safety of two neoadjuvant anthracycline/taxane based regimens given in combination with Perjeta and Herceptin in patients with locally advanced, inflammatory, or early stage HER2-positive breast cancer (with primary tumors $>$ 2 cm in diameter or node-positive disease) who were scheduled to receive neoadjuvant therapy. Category 1	To evaluate the cardiac safety of neoadjuvant treatment with pertuzumab in combination with trastuzumab and anthracycline/ taxane-based chemotherapy regimens.	Congestive heart failure / Left ventricular dysfunction.	Submission of primary analysis in May 2017 (PV commitment fulfilled).

Study	Summary of Objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
MotHER (Study H4621g) An observational study of pregnancy and pregnancy outcomes in women with breast cancer treated with Herceptin, Perjeta in combination with Herceptin, or Kadcyla during pregnancy or within 7 months prior to conception. Category 3	The objective of this study was to describe adverse pregnancy complications (e.g., oligohydramnios), delayed renal development) pregnancy outcomes (i.e., live births, stillbirths, and abortions), fetal/infant outcomes (e.g., major malformations, deformations, and disruptions), and fetal or infant functional deficits among women with breast cancer treated with Herceptin (either in combination with chemotherapies, or as a single agent),and the subset of women treated with Perjeta plus Herceptin or with Kadcyla during pregnancy or within 7 months prior to conception.	Oligohydramnios.	2018; Submission of Final annual data summary (PV commitment fulfilled)

*The PERUSE final CSR was submitted to the EMA in September 2020 together with EU RMP version 13.0. This study is moved to completed studies in current RMP updates.m

ANNEX 3:

PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

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3. PART C: PREVIOUSLY AGREED PROTOCOLS FOR ON-GOING STUDIES AND FINAL PROTOCOLS NOT REVIEWED BY THE COMPETENT AUTHORITY 118

1. PART A: REQUESTED PROTOCOLS OF STUDIES IN THE PHARMACOVIGILANCE PLAN, SUBMITTED FOR REGULATORY REVIEW WITH THIS UPDATED VERSION OF THE RMP

Not applicable.

2. PART B: REQUESTED AMENDMENTS OF PREVIOUSLY APPROVED PROTOCOLS OF STUDIES IN THE PHARMACOVIGILANCE PLAN, SUBMITTED FOR REGULATORY REVIEW WITH THIS UPDATED VERSION OF THE RMP

Not applicable.

3. PART C: PREVIOUSLY AGREED PROTOCOLS FOR ON-GOING STUDIES AND FINAL PROTOCOLS NOT REVIEWED BY THE COMPETENT AUTHORITY

Approved Protocols

Study	Protocol Title	Protocol Number / Version	Protocol Date	Procedure Number
PERUSE (MO28047)	A Multicenter, Open-Label, Single-Arm Study of Pertuzumab in combination with Trastuzumab and a Taxane in First Line Treatment of Patients With HER2-positive Advanced (Metastatic or Locally Recurrent) Breast Cancer.	MO28047 Version 5.0	20 November 2015	EMEA/H/C/002547/II/0021/G

PROTOCOL

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY OF PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AND A TAXANE IN FIRST LINE TREATMENT OF PATIENTS WITH HER2- POSITIVE ADVANCED (METASTATIC OR LOCALLY RECURRENT) BREAST CANCER**
PROTOCOL NUMBER:	MO28047
VERSION NUMBER:	5.0
EUDRACT NUMBER:	2011-005334-20
TEST PRODUCT:	Pertuzumab (RO 43-68451)
MEDICAL MONITOR:	[redacted], MD
SPONSOR:	F. Hoffmann-La Roche Ltd.
DATE FINAL:	20 November 2015

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	07-Dec-2015 13:37:35

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY OF PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AND A TAXANE IN FIRST LINE TREATMENT WITH HER2- POSITIVE ADVANCED (METASTATIC OR LOCALLY RECURRENT) BREAST CANCER**
PROTOCOL NUMBER:	MO28047
VERSION NUMBER:	5.0
EUDRACT NUMBER:	2011-005334-20
TEST PRODUCT:	Pertuzumab (RO 43-68451)
MEDICAL MONITOR:	[redacted], MD
SPONSOR:	F. Hoffmann-La Roche Ltd.

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature Date

Please return a copy of the form as instructed by your local study monitor. Please retain the original for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY OF PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AND A TAXANE IN FIRST LINE TREATMENT OF PATIENTS WITH HER2- POSITIVE ADVANCED (METASTATIC OR LOCALLY RECURRENT) BREAST CANCER**
PROTOCOL NUMBER:	MO28047
EUDRACT NUMBER:	2011-005334-20
TEST PRODUCT:	Pertuzumab (RO 43-68451)
PHASE:	IIIb
INDICATION:	Advanced breast cancer (metastatic or locally recurrent)
SPONSOR:	F. Hoffmann-La Roche Ltd.

Objectives

Primary Objective

The primary objective for this study is as follows:

- To evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane.

Secondary Objectives

The secondary objectives for this study are as follows:

- To evaluate pertuzumab in combination with trastuzumab and a taxane with respect to:
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Overall response rate (ORR)
  - Clinical benefit rate (CBR)
  - Duration of response
  - Time to response
  - Quality of life (Functional Assessment of Cancer Therapy-Breast [FACT-B] questionnaire for female patients only).

Study Design

Description of Study

Multicenter, open-label, single-arm, Phase IIIb trial.

Number of Patients

Approximately 1500 patients will be enrolled in the study.

Target Population

Patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer (metastatic or locally recurrent) who have not previously received systemic non-hormonal anticancer therapy in the metastatic setting.

Patients must meet the following criteria for study entry according to the timing specified in the Schedule of Assessments:

1. Signed written informed consent approved by the relevant Institutional Review Board (IRB), or Independent Ethics Committee (IEC).
2. Male or female patients aged 18 years or over.
3. Histologically or cytologically confirmed and documented adenocarcinoma of the breast with metastatic or locally recurrent disease not amenable to curative resection.
4. HER2-positive (defined as either immunohistochemistry [IHC] 3+ or *in situ* hybridization [ISH] positive) as assessed by local laboratory on primary tumor and/or metastatic site if primary tumor not available (ISH positivity is defined as a ratio of 2.0 or greater for the number of HER2 gene copies to the number of signals for CEP17, or for single probe tests, a HER2 gene count greater than 4).
5. At least one measurable lesion and/or non-measurable disease evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
7. Left ventricular ejection fraction (LVEF) of at least 50%.
8. Negative serum pregnancy test in women of childbearing potential (WOCBP; premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization).
9. For WOCBP and male patients with partners of CBP who are sexually active, agreement to use a highly effective, non-hormonal form of contraception (such as surgical sterilization) or two effective forms of non-hormonal contraception (such as a barrier method of contraception in conjunction with spermicidal jelly) during and for at least 7 months post-study treatment (refer to Section 4.5.2.1 for details).
10. Life expectancy of at least 12 weeks.

Patients who meet any of the following exclusion criteria will not be eligible for this study. Assessments must be performed according to the timing specified in the Schedule of Assessments:

1. Previous systemic non-hormonal anticancer therapy for the metastatic or locally recurrent disease. Note: Prior to study entry, up to two lines of hormonal therapy for metastatic or locally recurrent disease are permitted, one of which may be in combination with Everolimus.
2. Disease-free interval from completion of adjuvant or neoadjuvant systemic non-hormonal treatment to recurrence within 6 months.
3. Previous approved or investigative anti-HER2 agents in any breast cancer treatment setting, except trastuzumab and/or lapatinib in the adjuvant or neoadjuvant setting.
4. Disease progression while receiving trastuzumab and/or lapatinib in the adjuvant or neoadjuvant setting.
5. History of persistent Grade 2 or higher (NCI-CTC, Version 4.0) hematological toxicity resulting from previous adjuvant or neoadjuvant therapy.
6. Patients with radiographic evidence of central nervous system (CNS) metastases as assessed by computed tomography (CT) or magnetic resonance imaging (MRI) that are not well controlled (symptomatic or requiring control with continuous corticosteroid therapy (eg dexamethasone)). Note: Patients with CNS metastases are permitted to participate in the study if they are stable in the 3 months prior to screening (as assessed by the investigator) after receiving local therapy (irradiation, surgery etc) but without anti-HER2 therapy.
7. Current peripheral neuropathy of Grade 3 or greater (National Cancer Institute [NCI]-Common Toxicity Criteria [CTC], Version 4.0).
8. History of other malignancy within the last 5 years prior to 1st study drug administration (dosing), except for carcinoma *in situ* of the cervix or basal cell carcinoma.
9. Serious uncontrolled concomitant disease that would contraindicate the use of any of the investigational drugs used in this study or that would put the patient at high risk for treatment-related complications.
10. Inadequate organ function, evidenced by the following laboratory results:
    - Absolute neutrophil count <1,500 cells/mm^3

- Platelet count <100,000 cells/mm^3
- Hemoglobin <9 g/dL
- Total bilirubin greater than the upper limit of normal (ULN; unless the patient has documented Gilbert's syndrome)
- Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) >2.5 × ULN (> 5 × ULN in patients with liver metastases)
- Alkaline phosphatase levels > 2.5 × the ULN (> 5 × ULN in patients with liver metastases, or >10 × ULN in patients with bone metastases)
- Serum creatinine >2.0 mg/dL or 177 µmol/L
- International normalized ratio (INR) and activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) >1.5 × ULN (unless on therapeutic anti-coagulation)

11. Uncontrolled hypertension (systolic >150 mm Hg and/or diastolic >100 mm Hg) or clinically significant (i.e. active) cardiovascular disease: cerebrovascular accident/stroke or myocardial infarction within 6 months prior to first study medication, unstable angina, congestive heart failure (CHF) of New York Heart Association (NYHA) Grade II or higher, or serious cardiac arrhythmia requiring medication.
12. Current known infection with HIV, Hepatitis B virus, or Hepatitis C virus.
13. Dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy.
14. Major surgical procedure or significant traumatic injury within 14 days prior to 1st study drug administration (dosing) or anticipation of need for major surgery during the course of study treatment. Note: Should surgery be necessary during the course of the study, patients should be allowed to recover for a minimum of 14 days prior to subsequent pertuzumab and trastuzumab treatment.
15. Receipt of intravenous (IV) antibiotics for infection within 7 days prior to enrolment.
16. Current chronic daily treatment (continuous for >3 months) with corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids.
17. Known hypersensitivity to any of the study medications or to excipients of recombinant human or humanized antibodies.
18. History of receiving any investigational treatment within 28 days prior to 1st study drug administration (dosing).
19. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
20. Concurrent participation in any interventional clinical trial.

Length of Study

It is planned to enroll approximately 1500 patients over approximately 18 months.

Patients will receive study medication until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurs first. Roche will continue to provide pertuzumab for those patients who are still receiving the IMP at the end of the study and who are willing and considered suitable to enter an extension study for the purpose of collecting safety data and pre-specified efficacy measures.

All patients will continue to be followed up until at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, whichever occurs first.

End of Study

The study will end at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

Efficacy Outcome Measures

- PFS
- OS
- ORR
- CBR

- Duration of response
- Time to response

Safety Outcome Measures

- Incidence and severity by NCI-CTCAE version 4.0 of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of CHF
- LVEF over the course of the study
- Laboratory test abnormalities

Patient-Reported Outcome Measures

- Quality of life (FACT-B questionnaire, completed by female patients).

Investigational Medicinal Products

Pertuzumab is considered to be the investigational medicinal product in this study.

Pertuzumab (intravenous infusion)

Administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 840 mg, followed by 420 mg on Day 1 or Day 2 of each subsequent 3 weekly cycle (pertuzumab, trastuzumab and taxanes can be administered in any order but for the first cycle at least, it is recommended to administer pertuzumab on day 1 and trastuzumab and taxane on day 2).

Initial infusions of pertuzumab will be administered over 60 (± 10) minutes and patients observed for a further 60 minutes from the end of infusion for infusion-associated symptoms such as fever, chills etc. Interruption or slowing of the infusion may reduce such symptoms. If the infusion is well tolerated, subsequent infusions may be administered over 30 to 60 (± 10) minutes with patients observed for a further 30 minutes.

Non-Investigational Medicinal Products

Trastuzumab and taxane chemotherapy (docetaxel, paclitaxel or nab-paclitaxel) are considered to be non-investigational medicinal products in this study.

Trastuzumab

Trastuzumab will be administered in line with approved local Product Information and/or recognized clinical practice guidelines.

Taxane Chemotherapy

Chemotherapy can be administered before or after monoclonal antibody (pertuzumab and trastuzumab) infusions (pertuzumab, trastuzumab and taxanes can be administered in any order but for the first cycle at least, it is recommended to administer pertuzumab on day 1 and trastuzumab and taxane on day 2). The administration will follow the respective local Product Information for each taxane and/or recognized clinical practice guidelines.

Statistical Methods

Primary Analysis

All AEs, AEs Grade 3 or higher, AEs leading to treatment interruption and discontinuation, SAEs, cause of death, incidence of CHF, LVEF, premature discontinuation from study and treatment, laboratory parameters and study medication will be the safety variables. Our primary interest in this study will be AEs Grade 3 or higher related to pertuzumab.

There are no formal statistical hypothesis tests to be performed. There are no adjustments for multiplicity of endpoints or within-subgroups comparisons.

Safety Data Analysis

All safety variables described below will be analyzed for the safety population that will include all patients who have received at least one dose of study medication.

All AEs will be assessed according to the NCI-CTCAE version 4.0 grading system. The analysis of AEs will focus on treatment-emergent AEs i.e., AEs occurring on the day of or after first administration of study drug. Non-treatment-emergent AEs only (i.e. those occurring during screening) will be listed.

The incidence, type and severity of AEs will be summarized. Time to onset of the first episode of CHF will also be summarized.

AEs Grade 3 or higher, AEs leading to treatment interruption and discontinuation, AEs of special interest (AESI), and SAEs will be analyzed in a similar way to all AEs. Cause of death will also be summarized and listed.

The number of patients prematurely discontinued from the treatment with corresponding reason for discontinuation will be summarized and listed. The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative study medication doses and duration of exposure.

LVEF over time will be analyzed using descriptive statistics for continuous variable and presented graphically over time with associated 95% confidence interval.

Laboratory parameters, hematology, serum biochemistry and coagulation will be presented in shift tables of NCI-CTCAE version 4.0 grade at baseline versus worst grade during treatment period. The summary of laboratory parameters presented by means, standard deviation, minimum, and maximum will be also presented. Selected laboratory parameters will be also graphically presented over time.

Efficacy analyses

The efficacy analyses are the secondary endpoints in this study. The efficacy variables will be: PFS, OS, ORR, CBR, duration of response, and time to tumor response. These will be summarized for the intent-to-treat (ITT) population defined as a population that includes all patients enrolled in the study.

Estimates for the survivor function for PFS, OS, duration of response and time to tumor response will be obtained by the Kaplan-Meier (KM) approach.

The analysis of ORR is based on the best (confirmed) overall response (BOR). The BOR will be assessed by the number and proportion of responders and non-responders in each treatment group, together with two-sided 95% confidence intervals. Only patients with measurable disease at baseline will be included in the analysis of the BOR. Patients without a post-baseline tumor assessment will be considered to be non-responders.

Logistic analysis will be used for ORR to assess the influence of baseline covariates, e.g. country, region, age (>65, ≤65), ECOG (0, 1 vs. 2), type of taxane (docetaxel, paclitaxel, nab-paclitaxel), visceral disease at baseline (yes vs. no) and prior (neo) adjuvant chemotherapy (yes vs. no), in an exploratory manner. More details will be specified in the statistical analysis plan.

CBR includes patients whose BOR was PR, CR or SD that lasted at least 6 months. CBR will be summarized in a similar way to ORR.

Other analyses

Baseline and disease characteristics such as demographics, medical history, etc. will be summarized by descriptive statistics (frequency tables for categorical variables and mean, median, range, standard deviation, and 25th-75th quartiles for the continuous variables). The summaries will be presented for the ITT population.

Quality of Life

FACT-B (in female patients only): physical well-being, social/family well-being, functional well-being, and disease-specific concerns, will be summarized by descriptive summary tables at baseline and over time for the ITT population. Mean changes from baseline will also be summarized using descriptive statistics (including 95% CIs). More details will be provided in the statistical analysis plan.

Subgroups analyses

The following subgroup will be performed for AEs Grade 3 or higher and other selected safety variables: by country, region, >65 vs. ≤65, ECOG 0, 1 vs. ECOG 2, type of taxane (docetaxel, paclitaxel or nab-paclitaxel) visceral disease at baseline (yes vs. no) and prior (neo) adjuvant chemotherapy (yes vs. no).

Determination of Sample Size

A sample size of approximately 1500 patients is planned for this study. For the purpose of the estimation of sample size, the incidence of AEs with Grade 3 or higher related to pertuzumab was chosen as a safety endpoint of primary interest.

If the observed incidence of AEs Grade 3 or higher related to pertuzumab is between 1% and 50% (see Section 6.1), the precision for the estimating incidence of AE is presented below by 95% Clopper-Pearson confidence intervals.

Table 1: Clopper-Pearson 95% Confidence Intervals for the incidence of AEs Grade 3 or higher based on 1500 patients

Number of AE events/observed AE incidence	*95% Clopper Pearson Confidence Interval*
15 (1%)	0.6% - 1.6%
30 (2%)	1.4% - 2.8%
45 (3%)	2.2% - 4.0%
60 (4%)	3.1% - 5.1%
75 (5%)	4.0% - 6.2%
90 (6%)	4.9% - 7.3%
105 (7%)	5.8% - 8.4%
120 (8%)	6.7% - 9.5%
135 (9%)	7.6% - 10.6%
150 (10%)	8.5% - 11.6%
300 (20%)	18.0% - 22.1%
450 (30%)	27.7% - 32.4%
600 (40%)	37.5% - 42.5%
750 (50%)	47.4% - 52.6%

Interim Analyses

In addition to the final analysis, there will be five interim analyses for safety reporting and publication of safety and efficacy results, after approximately 100, 350, 700, 1100 and 1500 patients have been enrolled.

There will also be an annual review of safety data by the Independent Data Monitoring Committee (IDMC) following completion of enrollment.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
AST (SGOT)	Aspartate aminotransferase
BOR	Best overall response
CBP	Child bearing potential
CBR	Clinical benefit rate
CHF	Congestive heart failure
CR	Complete response
CRO	Clinical research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVAD	Central venous access device
ECHO	Echocardiogram
ECOG	Eastern Cooperative oncology group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	Epidermal growth factor receptor
FACT-B	Functional Assessment of Cancer Therapy-Breast
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
HER2	Human epidermal growth factor receptor 2
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMP	investigational medicinal product
IRB	Institutional Review Board
ISH	*In situ* hybridization
ITT	Intent-to-treat
IxRS	Interactive voice response system
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
MRI	Magnetic resonance imaging

MUGA	Multi gate acquisition
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for adverse events
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
PRO	Patient reported outcome
PTT	Partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
SOC	System-organ class
ULN	upper limit of normal
WOCBP	Women of childbearing potential

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

Breast cancer is the most common cancer in women, with a global prevalence of more than 1.6 million patients and an annual mortality rate of approximately 520,000 deaths (International Agency for Research on Cancer 2012). Factors associated with poor survival include age ≥ 50 years, visceral disease, shorter disease-free interval, aneuploid tumors, tumors with a high S-phase fraction, p53 accumulation, low bcl-2 expression, negative hormone receptor status, and positive human epidermal growth factor receptor 2 (HER2) status (Chang 2003).

Although the treatment of MBC is palliative rather than curative in intent, improvement in survival is an important treatment goal. There is a significant need for new agents with novel mechanisms of action and non-overlapping toxicity, which can be combined with established treatment for breast cancer.

1.2 BACKGROUND ON STUDY TREATMENTS

1.2.1 Human Epidermal Growth Factor Receptors (HER)

Evidence suggests that dysregulation of ligands and receptors of the HER family are important in the pathogenesis of cancer. The HER tyrosine kinase receptor family is comprised of four receptors: HER1 (epidermal growth factor receptor [EGFR]), HER2, HER3, and HER4. These receptors mediate tumor cell growth, survival, and differentiation (Sundaresan et al. 1999; Yarden and Sliwkowski 2001). HER receptors normally exist as inactive monomers.

Activation of HER receptors occurs following ligand binding, leading to receptor dimerization and cell signaling through the PI3-kinase/AKT pathway for promotion of tumor cell survival and through the mitogen-activated protein kinase pathway for cellular proliferation.

HER2 has no known ligand and, in a state of overexpression, can form active homodimers and initiate tyrosine kinase signaling without ligand stimulation. Additionally, as HER2 concentrations increase, the incidence of HER2 interactions with other receptors is also increased, resulting in a broad recruitment of a number of proteins (Jones et al. 2006). Recent data obtained using micro-array technology suggest that the HER2 receptor can bind to more than 17 different proteins and may recruit proteins that other HER receptors cannot recruit. These activities highlight the promiscuity of HER2 in its ability to bind to other HER receptors and initiate tyrosine kinase signaling through several mechanisms (Jones et al. 2006).

Approximately 18-25% of patients overexpress HER2. Overexpression of HER2 in breast cancer has been correlated with high histologic grade, increased mitotic activity, p53 mutation, negative estrogen receptor (ER) status, absence of bcl2, and absence of lobular architecture. Despite associations with other known negative

prognostic factors, HER2 overexpression has been independently associated with poorer disease-free survival and overall survival (OS) compared with tumors that do not overexpress HER2 (Pauletti et al. 2000). Approximately 65% of breast cancers are ER-positive and progesterone receptor-positive (American Cancer Society).

1.2.1.1 Pertuzumab (RhuMAb 2C4)

Pertuzumab (the study drug) is a fully humanized monoclonal antibody based on the human immunoglobulin (Ig)G1(κ) framework sequences and consisting of two heavy chains (449 residues) and two light chains (214 residues). Similar to trastuzumab, pertuzumab is directed against the extracellular domain of HER2; however, it differs from trastuzumab in the epitope-binding regions of the light chain (12 amino acid differences) and heavy chain (29 amino acid differences). As a result, pertuzumab binds to an epitope within what is known as sub-domain 2 of HER2, while the epitope for trastuzumab is localized to sub-domain 4 (Cho et al. 2003; Franklin et al. 2004).

Pertuzumab acts by blocking the dimerization of HER2 with other HER family members, including HER1 (epidermal growth factor receptor [EGFR]), HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, MAP-kinase and PI3-kinase. Inhibition of these signaling pathways can result in growth arrest and apoptosis, respectively (Baselga 2010). Data from a clinical trial of lapatinib support the hypothesis that HER2 plays an active role in tumor biology, with progression of MBC occurring even after treatment with trastuzumab (Geyer et al. 2006). The results obtained suggest that a more comprehensive blockade of HER2 through interruption of heterodimerization may provide clinical benefit.

Due to the different binding sites of pertuzumab and trastuzumab, ligand-activated downstream signaling is blocked by pertuzumab, but not by trastuzumab. Due to their complementary modes of action, there is a potential role for the combination of pertuzumab and trastuzumab in HER2-overexpressing diseases.

The randomized, double-blind, placebo-controlled Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study assessed the efficacy and safety of the combination of pertuzumab and trastuzumab with docetaxel as first-line treatment for patients with HER2-positive metastatic breast cancer. This phase III study established that targeting HER2-positive tumors with two anti-HER2 monoclonal antibodies that have complementary mechanisms of action along with chemotherapy, as compared with placebo plus trastuzumab plus docetaxel, significantly increased median overall survival by 15.7 months (hazard ratio [HR] 0.68; 95% CI 0.56, 0.84; p<0.001) and median PFS by 6.3 months (HR 0.68; 95% CI 0.58, 0.80; p<0.001). The combination therapy with pertuzumab did not increase the rates of symptomatic or asymptomatic cardiac dysfunction. AEs (any grade) of diarrhea, rash, upper respiratory tract infection, pruritus, and muscle spasm were reported more frequently in the pertuzumab group than in the control group (Swain et al. 2015).

Pertuzumab in combination with trastuzumab and docetaxel is currently indicated for the treatment of adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or

chemotherapy for their metastatic disease. Pertuzumab is also approved in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

See the pertuzumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1.2 Trastuzumab (rhuMAb HER2, Herceptin®)

Trastuzumab is a humanized monoclonal antibody directed at the HER2 receptor and is indicated for the treatment of patients with HER2-positive breast cancer both in the adjuvant and metastatic setting. The addition of trastuzumab to standard chemotherapy increases time to progressive disease or the length of progression-free survival (PFS), and improves survival when given with chemotherapy to women with HER2-positive breast cancer (Romond et al. 2005; Slamon et al. 2001).

Clinical benefits are greatest in patients with tumors strongly overexpressing HER2, as described by a 3+ score by immunohistochemistry (IHC) or a positive FISH or CISH result (see Herceptin® Summary of Product Characteristics, 2015).

A randomized Phase II study evaluated trastuzumab and docetaxel vs. docetaxel alone as a first line treatment for HER2-positive MBC. The addition of trastuzumab to 100 mg/m^2 docetaxel for at least six cycles resulted in superior clinical efficacy with improved overall response rates (ORR), time to progressive disease, time to treatment failure, and duration of response. Grade 3 to 4 neutropenia was seen more commonly with the combination than with docetaxel alone, and there was a slightly higher incidence of febrile neutropenia in the combination arm. More patients in the combination arm had left ventricular ejection fraction (LVEF) decreases ≥ 15% compared with the docetaxel alone arm (Marty et al. 2005).

Trastuzumab is well tolerated both as a single agent and in combination with standard chemotherapy (Cobleigh et al. 1998; Slamon et al. 2001). The most significant adverse event (AE) observed in patients who received trastuzumab was cardiac dysfunction, reflected by asymptomatic decreases in LVEF and, less frequently, by clinically symptomatic congestive heart failure (CHF). Risk factors for cardiac failure in the setting of trastuzumab treatment include co-administration with anthracycline-based chemotherapy, increasing age, declining LVEF during treatment to below the lower limit of normal, and the use of anti-hypertensive medications (Tan-Chiu et al. 2005).

See the local prescribing information for trastuzumab for details on nonclinical and clinical studies.

1.2.2 Taxanes

Taxanes are anti-neoplastic agents that bind to free tubulin within the cell and promote the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This mode of action leads to the production of

microtubule bundles without normal function and to the stabilization of microtubules, blocking cells in the M-phase of the cell cycle and leading to cell death. Extensive Phase II and III data have led to regulatory approvals for its use either in combination or as monotherapy for the treatment of breast cancer.

Docetaxel is a semi-synthetic analog of paclitaxel, which was the first taxane to be identified. Both trastuzumab and pertuzumab have been successfully administered with docetaxel in doses ranging between 60 mg/m^2 and 100 mg/m^2.

See the local prescribing information for taxanes such as docetaxel, paclitaxel, and nab-paclitaxel for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Pertuzumab, a humanized monoclonal antibody to the HER2 receptor, represents a promising new anti-HER2 agent with a novel mechanism of action targeting inhibition of HER2 dimerization. Nonclinical and clinical data to date indicate that pertuzumab provides a broader HER2 blockade through inhibition of HER2 heterodimerization. Pertuzumab has been shown in preclinical experiments to have superior anti-tumor effects when combined with other anti-HER2 treatments such as trastuzumab than when used as monotherapy.

Trastuzumab and pertuzumab monoclonal antibodies bind to distinct epitopes on the HER2 receptor without competing with each other, resulting in distinctive mechanisms for disrupting HER2 signaling. These mechanisms are complementary and result in augmented therapeutic efficacy when pertuzumab and trastuzumab are given in combination.

Preclinical data indicate at least additive efficacy when the two agents are administered together, resulting in significantly reduced tumor volume compared with either agent alone. Clinically, pertuzumab may have optimal therapeutic effects when given in combination with trastuzumab to patients with HER2-positive cancers, evidenced by data generated in a Phase II study of patients with previously treated HER2-positive MBC (Baselga et al. 2007). A recently published meta-analysis of pertuzumab Phase II trials concluded that pertuzumab has a low cardiac risk and there is no notable increase in cardiac events when pertuzumab is used in combination with other anticancer agents (Lenihan et al. 2012).

In CLEOPATRA, treatment with pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, significantly improved independently assessed PFS. The median independently assessed PFS was prolonged by 6.1 months, from 12.4 months in the control group to 18.5 months in the pertuzumab group (hazard ratio for progression or death, 0.62; 95% CI 0.51, 0.75; P<0.001) (Figure 1) (Baselga et al 2012).

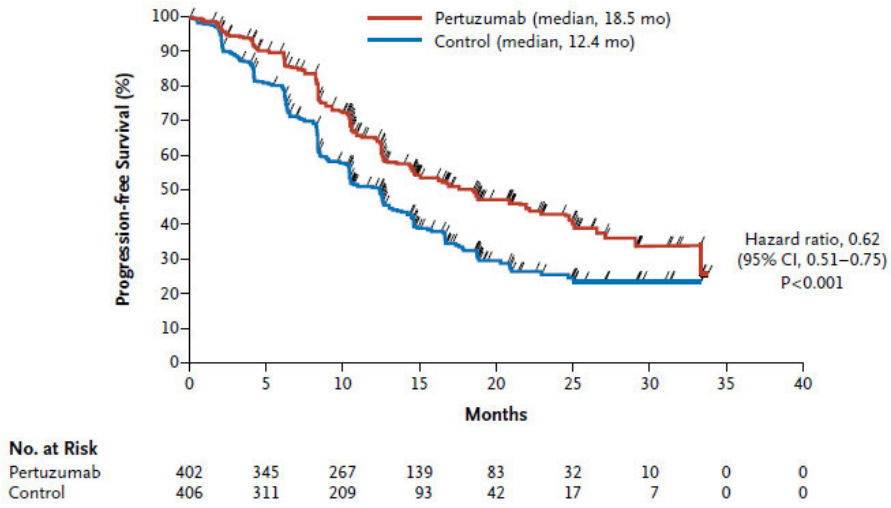


Figure 1Independently assessed progression-free survival in the CLEOPATRA trial

The benefit of pertuzumab–trastuzumab–docetaxel therapy with respect to PFS was observed across all predefined subgroups. Among the 88 patients who had received adjuvant or neoadjuvant chemotherapy with trastuzumab, the median independently assessed PFS was 10.4 months in the control group, as compared with 16.9 months in the pertuzumab group (hazard ratio, 0.62; 95% CI, 0.35 to 1.07). Among the 288 patients who had received adjuvant or neoadjuvant chemotherapy without trastuzumab, the median independently assessed PFS was 12.6 months in the control group, as compared with 21.6 months in the pertuzumab group (hazard ratio, 0.60; 95% CI, 0.43 to 0.83). The median investigator-assessed PFS was 12.4 months in the control group, as compared with 18.5 months in the pertuzumab group (hazard ratio, 0.65; 95% CI, 0.54 to 0.78; P<0.001) (Baselga et al 2012).

The combination of pertuzumab, trastuzumab and docetaxel significantly improved overall survival in patients with HER2-positive MBC, compared with placebo, trastuzumab and docetaxel alone (HR for overall survival, 0.68; 95% CI 0.56, 0.84; p<0.001) (Swain et al 2015).

The objective response rate was 69.3% in the control group, as compared with 80.2% in the pertuzumab group. The difference in response rates was 10.8 percentage points (95% CI, 4.2 to 17.5; P=0.001). A fixed-sequence testing hierarchy was prespecified: independently assessed PFS was to be tested first, followed by the secondary end point of overall survival and then by the secondary end point of objective response rate (Baselga et al 2012).

The combination of pertuzumab and trastuzumab plus docetaxel increased rates of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin. These adverse events were primarily grades 1–2, manageable, and occurred during docetaxel therapy. There was no increase in cardiac adverse events or LVSD (Baselga et al 2012).

In CLEOPATRA, left ventricular systolic dysfunction (any grade) was reported more frequently in the control group than in the pertuzumab group (8.3% vs. 4.4%). Left ventricular systolic dysfunction of grade 3 or higher was reported in 2.8% of the patients in the control group and in 1.2% of the patients in the pertuzumab group. Among patients in whom the left ventricular ejection fraction was assessed after the baseline assessment, 6.6% in the control group and 3.8% in the pertuzumab group had declines of 10 percentage points or more from baseline that resulted in a left ventricular ejection fraction of less than 50% (Baselga et al 2012).

In CLEOPATRA, 45.8% of patients in the placebo plus trastuzumab plus docetaxel arm experienced neutropenia and 7.6% experienced febrile neutropenia of grade ≥3; by comparison, 48.9% and 13.8% of patients, respectively, experienced neutropenia or febrile neutropenia of grade ≥3 in the pertuzumab plus trastuzumab plus docetaxel arm. (Baselga et al 2012)

A taxane (docetaxel, paclitaxel, or nab-paclitaxel) will be included in the standard treatment plan, as docetaxel has been shown to be efficacious when combined with trastuzumab in women with HER2-positive MBC, and should, therefore, provide clinical benefit independent of pertuzumab.

As a potent inhibitor of HER receptor signaling, and as inducers of antibody-dependent cell-mediated cytotoxicity, the combination of pertuzumab and trastuzumab may have potential mechanistic advantages over trastuzumab alone. Taxanes in combination with trastuzumab have been shown to be effective in the treatment of HER2-positive breast cancer and to be generally well tolerated. Results of phase III CLEOPATRA trial have shown a significant efficacy benefit with a manageable tolerability profile and no new safety signals with a regimen consisting of pertuzumab, trastuzumab and a taxane (docetaxel). The benefit/risk of the combination of pertuzumab, trastuzumab and taxanes is therefore anticipated to be favorable.

Considering that the incorporation of pertuzumab in a trastuzumab-chemotherapy regimen should have a low additional impact on tolerability and quality of life, and together with rigorous monitoring of the known toxicities of the agents, the proposed study poses an acceptable risk in this patient population. The complementary mechanisms and good tolerability profile of each of the HER2-directed antibodies, pertuzumab and trastuzumab, strongly supported by the results of the randomized, double-blind phase III CLEOPATRA study, provide a strong rationale to further explore and better characterize the safety and tolerability profiles of the combination of the two anti-HER2 antibodies pertuzumab and trastuzumab with taxanes.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective for this study is as follows:

- To evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane.

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

- To evaluate pertuzumab in combination with trastuzumab and a taxane with respect to:
  - Progression-free survival (PFS).
  - Overall survival (OS).
  - Overall response rate (ORR).
  - Clinical benefit rate (CBR).
  - Duration of response.
  - Time to response.
  - Quality of life (Functional Assessment of Cancer Therapy-Breast [FACT-B] questionnaire for female patients only).

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

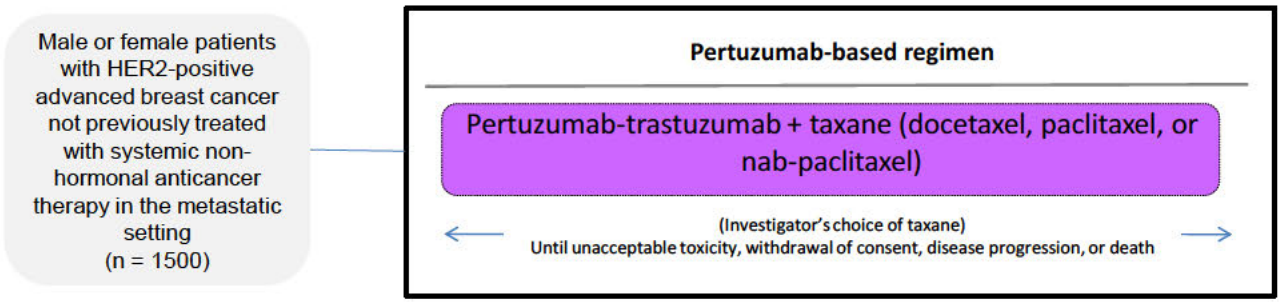
This study is an open-label, single-arm, multicenter Phase IIIb study to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane. Patients with HER2-positive advanced breast cancer (metastatic or locally recurrent) who have not previously received systemic non-hormonal anticancer therapy in the metastatic setting are eligible to participate in the study.

Approximately 1500 patients will be enrolled into the study in approximately 250-300 centers worldwide. Details of the treatment are given in Section 4.3.

Patients will receive study medication until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death whichever occur first. Roche will continue to provide pertuzumab for those patients who are still receiving the IMP at the end of the study and who are willing and considered suitable to enter an extension study for the purpose of collecting safety data and pre-specified efficacy measures.

The study design is presented in Figure 2. A Schedule of Assessments is provided in Appendix 1.

Figure 2Study Design



3.1.1 Independent Data Monitoring Committee

In addition to the final analysis, there will be five interim analyses for safety reporting and publication of safety and efficacy results, after approximately 100, 350, 700, 1100 and 1500 patients have been enrolled.

There will also be an annual review of safety data by the IDMC following completion of enrollment.

3.2 END OF STUDY

The end of the study is defined as at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

3.3 RATIONALE FOR STUDY DESIGN

This is a multi-center, open-label, non-randomized study to assess the safety of pertuzumab. The study design employs standard methods for Phase IIIb safety studies in patients with cancer.

The primary objective is to assess the safety and tolerability of pertuzumab in patients with HER2 positive metastatic breast cancer. Good efficacy and a manageable safety profile have been demonstrated in clinical trials of pertuzumab in this patient population. As this is a safety study where all patients must receive the active treatment, the study design will be open-label and non-randomized.

Safety will be carefully evaluated, and the type of data collected and the frequency with which patients are monitored will ensure the safety of the patients at all times, as well as fulfilling international regulatory requirements.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- PFS, defined as the time from enrollment until the first radiographically documented progression of disease or death from any cause, whichever occurs first.
- OS, defined as the time from the date of enrollment to the date of death, regardless of the cause of death. Patients who were alive at the time of the analysis will be censored at the date of the last follow-up assessment.
- ORR (partial response [PR] plus complete response [CR]), which is defined as the best response recorded from the start of study treatment until disease progression/recurrence or death and confirmed ≥ 4 weeks later.
- CBR includes patients whose best (confirmed) response was PR or CR or stable disease that lasts at least 6 months.
- Duration of response, defined as the period from the date of initial confirmed PR or CR until the date of progressive disease or death from any cause.

- Time to response, for patients with a best overall response of CR or PR, defined as the time from the date of enrolment to the date of first CR or PR.

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity by NCI-CTC for AEs (NCI-CTCAE) version 4.0 of adverse events (AEs) and serious AEs (SAEs).
- Incidence of congestive heart failure (CHF).
- Left ventricular ejection fraction (LVEF) over the course of the study.
- Laboratory test abnormalities.

3.4.3 Patient-Reported Outcome Measures

The patient reported outcome (PRO) measures for this study are as follows:

- Quality of life, which will be assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire for female patients only (Appendix 6).

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population for this study is patients with HER2-positive advanced (metastatic or locally recurrent) breast cancer.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry according to the timing specified in the Schedule of Assessments:

1. Signed written informed consent approved by the relevant Institutional Review Board (IRB), or Independent Ethics Committee (IEC).
2. Male or female patients aged 18 years or over.
3. Histologically or cytologically confirmed and documented adenocarcinoma of the breast with metastatic or locally recurrent disease not amenable to curative resection.
4. HER2-positive (defined as either IHC 3+ or *in situ* hybridization [ISH] positive) as assessed by local laboratory on primary tumor and/or metastatic site if primary tumor not available (ISH positivity is defined as a ratio of 2.0 or greater for the number of HER2 gene copies to the number of signals for CEP17, or for single probe tests, a HER2 gene count greater than 4).
5. At least one measurable lesion and/or non-measurable disease evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix 5).
6. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2 (Appendix 3).
7. LVEF of at least 50%.

8. Negative serum pregnancy test in women of childbearing potential (WOCBP; premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization).
9. For WOCBP and male patients with partners of CBP who are sexually active, agreement to use a highly effective, non-hormonal form of contraception (such as surgical sterilization) or two effective forms of non-hormonal contraception (such as a barrier method of contraception in conjunction with spermicidal jelly) during and for at least 7 months post-study treatment (refer to Section 4.5.2.1 for details).
10. Life expectancy of at least 12 weeks.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry. Assessments must be performed according to the timing specified in the Schedule of Assessments:

1. Previous systemic non-hormonal anticancer therapy for the metastatic or locally recurrent disease. Note: Prior to study entry, up to two lines of hormonal therapy for metastatic or locally recurrent disease are permitted, one of which may be in combination with Everolimus.
2. Disease-free interval from completion of adjuvant or neoadjuvant systemic non-hormonal treatment to recurrence within 6 months.
3. Previous approved or investigative anti-HER2 agents in any breast cancer treatment setting, except trastuzumab and/or lapatinib in the adjuvant or neoadjuvant setting.
4. Disease progression while receiving trastuzumab and/or lapatinib in the adjuvant or neoadjuvant setting.
5. History of persistent Grade 2 or higher (National Cancer Institute [NCI]-Common Toxicity Criteria [CTC], Version 4.0) hematological toxicity resulting from previous adjuvant or neoadjuvant therapy.
6. Patients with radiographic evidence of central nervous system (CNS) metastases as assessed by computed tomography (CT) or magnetic resonance imaging (MRI) that are not well controlled (symptomatic or requiring control with continuous corticosteroid therapy (eg dexamethasone)). Note: Patients with CNS metastases are permitted to participate in the study if they are stable in the 3 months prior to screening (as assessed by the investigator) after receiving local therapy (irradiation, surgery etc) but without anti-HER2 therapy.
7. Current peripheral neuropathy of Grade 3 or greater (NCI-CTC, Version 4.0).
8. History of other malignancy within the last 5 years prior to 1st study drug administration (dosing), except for carcinoma *in situ* of the cervix or basal cell carcinoma.
9. Serious uncontrolled concomitant disease that would contraindicate the use of any of the investigational drugs used in this study or that would put the patient at high risk for treatment-related complications.
10. Inadequate organ function, evidenced by the following laboratory results:
    - Absolute neutrophil count <1,500 cells/mm^3.
    - Platelet count <100,000 cells/mm^3.
    - Hemoglobin <9 g/dL.
    - Total bilirubin greater than the upper limit of normal (ULN; unless the patient has documented Gilbert's syndrome).
    - AST (SGOT]) or ALT (SGPT) >2.5 × ULN (> 5 × ULN in patients with liver metastases)

- Alkaline phosphatase levels > 2.5 × the ULN (> 5 × ULN in patients with liver metastases, or >10 × ULN in patients with bone metastases)
- Serum creatinine >2.0 mg/dL or 177 µmol/L.
- International normalized ratio (INR) and activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) >1.5 × ULN (unless on therapeutic anti-coagulation).

11. Uncontrolled hypertension (systolic >150 mm Hg and/or diastolic >100 mm Hg) or clinically significant (i.e. active) cardiovascular disease: cerebrovascular accident/stroke or myocardial infarction within 6 months prior to first study medication, unstable angina, congestive heart failure (CHF) of New York Heart Association (NYHA) Grade II or higher, or serious cardiac arrhythmia requiring medication.
12. Current known infection with HIV, Hepatitis B virus, or Hepatitis C virus.
13. Dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy.
14. Major surgical procedure or significant traumatic injury within 14 days prior to 1st study drug administration (dosing) or anticipation of need for major surgery during the course of study treatment. Note: Should surgery be necessary during the course of the study, patients should be allowed to recover for a minimum of 14 days prior to subsequent pertuzumab and trastuzumab treatment.
15. Receipt of intravenous antibiotics for infection within 7 days prior to enrolment.
16. Current chronic daily treatment (continuous for >3 months) with corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids.
17. Known hypersensitivity to any of the study medications or to excipients of recombinant human or humanized antibodies.
18. History of receiving any investigational treatment within 28 days prior to 1st study drug administration (dosing).
19. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
20. Concurrent participation in any interventional clinical trial.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Not applicable, the study is open-label.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Study drug packaging will be overseen by the Sponsor clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication will be in accordance with Sponsor standards and local regulations.

The study drug must be stored according to the details on the Product Information. The drug label indicates the storage temperature.

Local packaging in some countries may be different.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the Monitor upon discovery.

4.3.1.1 Pertuzumab

Pertuzumab is provided as a single-use formulation containing 30 mg/mL pertuzumab formulated in 20 mM L-histidine (pH 6.0), 120 mM sucrose, and 0.02% polysorbate 20. Each 20-cc vial contains approximately 420 mg of pertuzumab (14.0 mL/vial). Pertuzumab is intended for use only in clinical trials.

For further details, see the pertuzumab Investigator's Brochure.

4.3.1.2 Trastuzumab

Commercial Herceptin (trastuzumab) will be obtained directly by the site for intravenous use during this study.

Trastuzumab will be a freeze-dried preparation at a nominal content of either 440 mg or 150 mg per vial. Vial size will also vary by country.

Trastuzumab is formulated in histidine, trehalose, and polysorbate 20. Once reconstituted, each solution contains 21 mg/mL of active drug at a pH of approximately 6.0.

For further details, see the local prescribing information for trastuzumab and/or recognized clinical practice guidelines.

4.3.1.3 Taxanes

Commercial docetaxel and/or paclitaxel and nab-paclitaxel will be obtained locally by the investigational sites.

For further details, see the local prescribing information for docetaxel, paclitaxel, and nab-paclitaxel and/or recognized clinical practice guidelines.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Pertuzumab

Pertuzumab will be administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 840 mg, followed by 420 mg on Day 1 or Day 2 of each subsequent 3 weekly cycle (pertuzumab, trastuzumab and taxanes can be administered in any order but for the first cycle at least, it is recommended to administer pertuzumab on day 1 and trastuzumab and taxane on day 2).

Initial infusions of pertuzumab will be administered over 60 (± 10) minutes and patients observed for a further 60 minutes from the end of infusion for infusion-associated symptoms such as fever, chills etc. Interruption or slowing of the infusion

may reduce such symptoms. If the infusion is well tolerated, subsequent infusions may be administered over 30 to 60 (± 10) minutes, with patients observed for a further 30 minutes.

Pertuzumab administration may be delayed to assess or treat AEs such as cardiac AEs, myelosuppression, or other events. No dose reduction will be allowed for pertuzumab or trastuzumab (see Section 5.1.1).

In the case of surgery during the study, there is no evidence that the HER2 antibodies delay wound healing, but patients should have recovered from surgery and anesthesia (including liver functions) for a minimum of 14 days before antibody treatment.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 Trastuzumab

Trastuzumab will be administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 8 mg/kg, followed by 6 mg/kg on Day 1 or Day 2 of each subsequent 3-weekly cycle; in line with approved local Product Information and/ or recognized clinical practice guidelines (pertuzumab, trastuzumab and taxanes can be administered in any order but for the first cycle at least, it is recommended to administer pertuzumab on day 1 and trastuzumab and taxane on day 2).

Trastuzumab administration may be delayed to assess or treat AEs such as cardiac AEs, myelosuppression, or other events. No dose reduction will be allowed for pertuzumab or trastuzumab (see Section 5.1.1).

Any overdose or incorrect administration of trastuzumab should be noted on the trastuzumab Administration eCRF. Adverse events associated with an overdose or incorrect administration of trastuzumab should be recorded on the Adverse Event eCRF.

4.3.2.3 Taxanes

A taxane (docetaxel or paclitaxel or nab-paclitaxel) will be administered in line with the respective product Information and/ or recognized clinical practice guidelines. The taxane can be administered before or after the monoclonal antibody (pertuzumab and trastuzumab) infusions (pertuzumab, trastuzumab and taxanes can be administered in any order but for the first cycle at least, it is recommended to administer pertuzumab on day 1 and trastuzumab and taxane on day 2).

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.1.6.

Any overdose or incorrect administration of a taxane should be noted on the taxane Administration eCRF. Adverse events associated with an overdose or incorrect administration of a taxane should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

Pertuzumab is considered to be the investigational medicinal product (IMP) in this study.

Trastuzumab and taxanes (docetaxel, paclitaxel, nab-paclitaxel) are considered to be non-IMPs in this study.

All IMP required for completion of this study (pertuzumab) will be provided by The Sponsor. The investigational site will acknowledge receipt of IMP, using the interactive voice response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to The Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by The Sponsor. The site must obtain written authorization from The Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMP and non-IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Pertuzumab

Roche will not provide pertuzumab or other study interventions to patients after conclusion of the study or any earlier patient withdrawal; except for patients who are still receiving pertuzumab at the end of the study and who are willing and considered suitable to enter an extension study for the purpose of collecting safety data and pre-specified efficacy measures.

The study will be concluded at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, whichever occurs first.

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 28 days prior to 1st study drug administration (dosing) to the one month post-treatment safety follow-up visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

Patients should receive full supportive care including transfusion of blood and blood products and antibiotics, etc., according to standard of care when necessary.

All protocol-allowed medications taken by the patient for concomitant disease(s) should be continued as necessary during the study and be recorded on the eCRF. The following list of allowed medications is provided as guidance. Treatments prescribed to patients should be adapted according to the local standard of care practice.

The following treatments/procedures are permitted:

- Paracetamol (acetaminophen) or other analgesics, and diphenhydramine, chlorpheniramine, or other antihistamines can be used according to local clinical practice for the prevention and treatment of infusion reactions associated with pertuzumab and/or trastuzumab.
- Medication to treat diarrhea (e.g., loperamide).
- Granulocyte colony stimulating factor (G-CSF) may be used according to the product license and according to the currently approved prescribing information for docetaxel and ASCO clinical guidelines (Smith et al. 2006).
- Steroids for docetaxel premedication and anti-emetics according to routine practice at each clinical site.
- Steroids, antihistamines, and H2-receptor antagonists for paclitaxel premedication according to routine practice at each clinical site.
- Inhaled steroids for asthma.
- Bisphosphonates may be given according to their product license and routine clinical practice, at the investigator's discretion.
- Palliative surgical procedures. Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded including the dates, description of the procedure(s), and any clinical findings. In the case of surgery during the study, patients should have recovered from surgery and anesthesia (including liver functions) for a minimum of 14 days before antibody treatment.
- As a precautionary measure, it is recommended, but not strictly required, that if patients require placement of a central venous access device (CVAD), the procedure should be done 7 days prior to first study treatment start.
- The date of CVAD placement should be noted in the medical record and recorded in the eCRF. Episodes of CVAD replacement should be recorded, as should CVAD-related thrombosis, infection, or dysfunction.
- Anti-coagulation therapy for maintenance of patency of permanent indwelling intravenous catheters is permitted.
- Palliative radiotherapy. Radiotherapy will be allowed during the study treatment period for the indication of bone or breast lesions present at baseline as long as the lesion is not a target lesion. If a patient requires

radiation therapy to a new lesion, that new lesion would, per RECIST, qualify as progressive disease. Radiotherapy will also be permitted for new brain metastases that are treatable with radiation in patients who have visceral disease control (defined as patients having received clinical benefit (i.e., PR or CR of any duration, or stable disease for ≥ 4 months). These patients will be allowed to continue to receive study therapy until they either experience systemic progression of their disease and/or further progression in the brain (based on investigator assessments). Patients must not miss more than one cycle for the treatment of their brain disease and must have an ECOG performance status of 0 or 1 to continue on therapy. For the purposes of the PFS analysis, progression will be recorded on the date when the isolated brain metastasis was documented.

- Approved endocrine therapies only after discontinuation of chemotherapy.

4.4.2 Prohibited Therapy

The following treatments are not permitted:

- Treatment with other systemic anticancer agents (e.g., chemotherapy, immunotherapy) or other treatments not part of protocol-specified anticancer therapy. Note: Approved endocrine maintenance therapies will be permitted only after discontinuation of chemotherapy.
- Radiotherapy for unequivocal progressive disease with the exception of new brain metastases (see Section 4.4.1).
- Any oral, injected or implanted hormonal methods of contraception.
- Concurrent investigational agents of any type.
- Initiation of herbal remedies for cancer treatment. Herbal remedies initiated prior to study entry and continuing during the study are permitted and must be reported on the appropriate eCRF.

The following treatments should be avoided because of the risk of immunosuppression:

- Chronic or high-dose oral corticosteroid therapy.
- Tumor necrosis factor-α inhibitors.
- Anti-T cell antibodies.

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

Details of the timing of assessments are presented in the Schedule of Assessments (Appendix 1).

4.5.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and all medications used by the patient within 28 days prior to the screening visit.

Demographic data will include age, sex, and self-reported ethnicity.

4.5.1.2 Vital Signs

Vital signs recorded will include measurements of pulse rate while the patient is in a seated position, body temperature and blood pressure (systolic and diastolic).

4.5.1.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eye, ear, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.1.4 Tumor and Response Evaluations

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor response will be assessed by the investigator on the basis of CT or MRI scans, and (if indicated) isotope bone scan, using RECIST. An objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions.

For patients with non-measurable disease only, qualitative evaluation of the burden of non-measurable disease with reproducible imaging techniques will be required at the fixed time points in the protocol. In such cases, response to treatment should be assessed as meaningful change in the tumor burden defined as persistence, disappearance or unequivocal progression of the tumor as per RECIST.

Consistency of consecutive CT scans, X-rays or MRIs should be ensured during all assessments for each patient, with the same technique being used for evaluating lesions throughout the treatment period (use of spiral CT or MRI is required for baseline lesions <20 mm and must be documented in medical records and used consistently throughout the study). The use of oral and intravenous contrast etc. should, as long as it is clinically possible, be kept consistent. Tumor measurements should be made by the same investigator/radiologist for each patient during the study to the extent that this is feasible. In case of clinically measurable superficial (such as

skin) lesions, repeated photographs should be used to document tumor response. These photographs must include a ruler for documentation purposes.

CT scans should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected. Brain CT or MRI scans should be performed at screening in patients with clinical suspicion of brain metastases, and during the study if clinically indicated.

Patients who have demonstrated control of their visceral disease, defined as having received clinical benefit (CR or PR of any duration or SD ≥4 months per RECIST 1.1) from study therapy, but who have newly developed isolated brain metastases that are treatable with radiation will be allowed to continue with study treatment until they either experience systemic progression of their disease and/or further progression in the brain based on investigator assessment. Patients should not miss more than one cycle for the treatment of their brain disease and must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 to continue on therapy. Brain MRI should be performed along with regularly scheduled tumor assessments in these instances. For the purposes of the PFS analysis, progression will be recorded on the date when the isolated brain metastasis was documented.

Tumor response will be confirmed a minimum of 4 weeks after the initial response was noted, or at the next scheduled tumor assessment if it is to occur more than 4 weeks after the initial response.

See the RECIST version 1.1 (Appendix 5) for further details of criteria for differentiating between response, stable disease, and progressive disease.

Scheduling of tumor assessments

Baseline total tumor burden must be assessed within a maximum of 28 days before first dose of study drug treatment. Post-baseline assessments are to be performed every three treatment cycles up to 36 months, and every six cycles thereafter for patients who remain progression free after 36 months. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.

All tumor assessments after baseline will be done within 7 days of the scheduled visit. If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present.

Instructions for scans in the event of isotope shortage

Two key suppliers of Tc-99m generators (Chalk River Reactor, Canada and High Flux Reactor, the Netherlands) are expected to close. Supplies from other reactor sources will be unable to meet the expected world-wide patient-care needs. As a

result, significant shortages of Tc-99m are expected, and the instructions listed below should be followed:

- Echocardiogram (ECHO) will be the preferred imaging modality over multi gate acquisition (MUGA) scans to evaluate cardiac function.
- Tc-99m bone scans should only be obtained if the presence of bone lesions is clinically suspected. If a bone scan cannot be performed because of the Tc-99m shortage, the investigator may choose F-18 NaF or FDG-PET scan as an alternative.
- If bone lesions are selected as index non-target lesions, they must be apparent on baseline CT scans or other radiographic modalities (e.g., skeletal X-rays that can be repeated in subsequent tumor assessments). Additional scans may be obtained to follow clinically important bone lesions if not visualized on the chest, abdomen, or pelvic CT scan. These measures are intended to ensure that the same method of assessment and the same imaging technique is used throughout the study for each patient. If there is a question regarding the choice of alternatives in the event that a standard bone scan cannot be obtained during screening and/or during the study, please contact the Medical Monitor.

4.5.1.5 Left Ventricular Ejection Fraction Assessment

LVEF assessments will be assessed within 42 days of enrollment and every three treatment cycles ≤7 days (with results available) prior to administration of study drug by either ECHO or MUGA scan (with ECHO as the preferred method). Patients will be reassessed with the same technique used for baseline cardiac evaluation throughout the study and, to the extent possible, be obtained at the same institution for an individual patient. All pre-study LVEF values during and following trastuzumab adjuvant treatment for all patients will be collected.

4.5.1.6 Performance Status

Performance status will be measured using the ECOG performance status scale (see Appendix 3).

It is recommended, where possible, that a patient's performance status will be assessed by the same person throughout the study.

Performance status will be assessed at baseline, every three cycles of treatment, and at the 28-days post-treatment safety follow-up visit.

4.5.1.7 Laboratory Assessments

Samples for laboratory tests will be assessed locally.

Hematology, biochemistry, and coagulation tests will be done as part of regular safety assessments at screening/baseline, every treatment cycle, and at the 1-month post-treatment safety follow-up. Assessments must be performed at each cycle within 3 days (with results available) prior to the administration of study medication.

Specifically:

- Hematology: Hemoglobin, hematocrit, platelet count, red blood cells, white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and other cells).
- Biochemistry: Sodium, potassium, calcium, chloride, magnesium, blood urea nitrogen (or urea), uric acid, total protein, albumin, ALP, ALT, AST, GGT, LDH, total bilirubin, creatinine, and blood glucose. Calculated creatinine clearance to be determined at baseline only.
- Coagulation: INR and aPTT or PTT. Tests should be repeated at each treatment cycle in all patients receiving therapeutic doses of anti-coagulants.
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at baseline. The result must be available prior to enrolment. Urine or serum pregnancy tests will be performed every 3rd cycle within 3 days (with results available) prior to the administration of study medication, at the 1-month post-treatment safety FU visit, and at 4 and 7 months after the last dose of study medication. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

4.5.1.8 Electrocardiograms

Two standard 12-lead ECG recordings, taken two minutes apart, must be obtained every three cycles of monoclonal antibody therapy during the treatment period (where possible at the time of LVEF measurement) ≤3 days (with results available) prior to administration of study treatment. The average of the two readings will be used to determine ECG intervals (e.g., PR, QT). ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. Where available, digital recordings will be stored at the site. ECG characteristics, including heart rate, QRS duration, and RR, PR, and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction) and QTcF (Fridericia's correction) will be calculated. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF.

4.5.1.9 Patient-Reported Outcomes

PRO data will be elicited from the patients in this study to more fully characterize the clinical profile of pertuzumab. The PRO instruments (FACT-B), translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health

authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study (approved by the relevant IRB or IEC) must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 28 days prior to 1st administration of study medication (dosing), unless the procedures have already been conducted during this time period as part of the patient's routine clinical care. Results of LVEF assessments performed prior to obtaining informed consent and within 42 days prior to enrollment may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Patients must have HER2 positive status established prior to entering the study. Demonstrated evidence from previous testing is acceptable; otherwise HER2-positive status on fixed tissue blocks from the primary tumor (and/or metastatic site, if primary tumor not available) will be assessed locally by IHC and/or ISH according to institutional criteria.

WOCBP and male patients with partners of CBP who are sexually active will have to agree to use a highly effective, non-hormonal form of contraception (such as surgical sterilization) or two effective forms of non-hormonal contraception (such as a barrier method of contraception in conjunction with spermicidal jelly) during and for at least 7 months post-study treatment.

Pretreatment tests and evaluations will be performed within 7 days prior to first study drug administration, after confirmation of other eligibility criteria, unless the procedures have already been conducted during this time period as part of the patient's routine clinical care.

Please see Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.2.2 Assessments during Treatment

During the treatment period, the following assessments must be performed

- Vital signs and weight: every treatment cycle prior to administration of study drug with pulse rate, body temperature and blood pressure again after infusion during the observation period of each study medication.

- Infusion reactions: every treatment cycle during infusion and observation period
- Hematology, biochemistry and coagulation (if indicated): every treatment cycle ≤3 days (with results available) prior to administration of study drug
- Concomitant medication and SAEs/AEs: every treatment cycle
- Pregnancy test and ECG: every 3 cycles of monoclonal antibody ≤3 days (with results available) prior to administration of study drug
- LVEF: every 3 cycles of monoclonal antibody ≤7 days (with results available) prior to administration of study drug
- ECOG performance status and quality of life: every 3 cycles of monoclonal antibody (±7 days)
- Tumor evaluation: every 3 cycles of monoclonal antibody up to 36 months and every 6 cycles thereafter in those who remain progression free
- Physical examination and brain CT/MRI: if clinically indicated

Please see Appendix 1 for the schedule of assessments performed during the treatment period.

4.5.2.3 Assessments at Post-treatment Safety Follow-up

Patients will receive study medication until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death. Roche will continue to provide pertuzumab for those patients who are still receiving the IMP at the end of the study and who are willing and considered suitable to enter an extension study for the purpose of collecting safety data and pre-specified efficacy measures.

All patients will continue to be followed up for at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, whichever occurs first.

Patients who discontinue from study treatment will be asked to return to the clinic approximately 28 days after the last dose of study drug for a follow-up visit. The visit at which response assessment shows progressive disease may be used as the post-treatment safety follow-up visit.

Please see Appendix 1 for the schedule of assessments performed at the study completion/early termination visit.

4.5.2.4 Follow-Up Assessments

After the post-treatment safety follow-up visit, AEs should be followed as outlined in Sections 5.5 and 5.6.

After disease progression, patients will be followed for survival every 3 months until the end of the study, which is at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, whichever occurs first.

After confirmed disease progression, anticancer medical or surgical procedures and therapies including biologics and patient outcomes/survival, will be recorded in the eCRF for as long as is reasonably possible.

Please see Appendix 1 for the schedule of follow-up assessments.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time.
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the patient.

4.6.1.1 Discontinuation from Study Drug

Patients must discontinue study drug if they experience any of the following:

- Clinical signs and symptoms suggesting CHF.
- Dyspnea or clinically significant hypotension (defined per investigator discretion).
- Symptomatic left ventricular dysfunction (NCI-CTCAE version 4.0 Grade 3 or 4) with a drop in LVEF consistent with cardiac failure.

Details of discontinuation due to toxicity are given in Section 5.1.1.

Patients who discontinue study drug prematurely will be asked to return to the clinic for a post-treatment safety follow-up visit (see Section 4.5.2.3) and may undergo follow-up assessments (see Section 4.5.2.4). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

4.6.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn unless a separate consent has been given for further survival data collection. Patients who withdraw from the study will not be replaced.

4.6.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment.
- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Non-compliance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

If any of the individual study medications must be delayed for 1 day or more, all three agents (pertuzumab, trastuzumab, and the taxane) should be delayed for the same timeframe.

Baseline body weight is used to calculate required dose of trastuzumab. The trastuzumab dose should be recalculated only if the patient's weight changes by more than ±10% from baseline.

The pertuzumab dose should not be adjusted for body weight.

5.1.1 Toxicity Management Guidelines

The NCI-CTCAE version 4.0 will be used to Grade toxicity.

Pertuzumab, trastuzumab, and taxanes will be given as specified in Section 4.3.2.

Before starting a new treatment cycle, toxicity must have resolved as specified in the following sections.

Pertuzumab and trastuzumab administration may be delayed to assess or treat AEs such as cardiac AEs, myelosuppression, or other events. No dose reduction will be allowed for pertuzumab or trastuzumab.

5.1.1.1 Cardiac Safety

All patients must have a baseline LVEF ≥ 50%. LVEF will be monitored regularly according to the Schedule of Assessments (Appendix 1). If an investigator is concerned that an AE may be related to cardiac dysfunction, an additional LVEF measurement should be performed. Pertuzumab, trastuzumab, paclitaxel, and docetaxel will be discontinued in any patient who develops clinical signs and symptoms suggesting CHF, with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA. CHF should be treated and monitored according to standard medical practice.

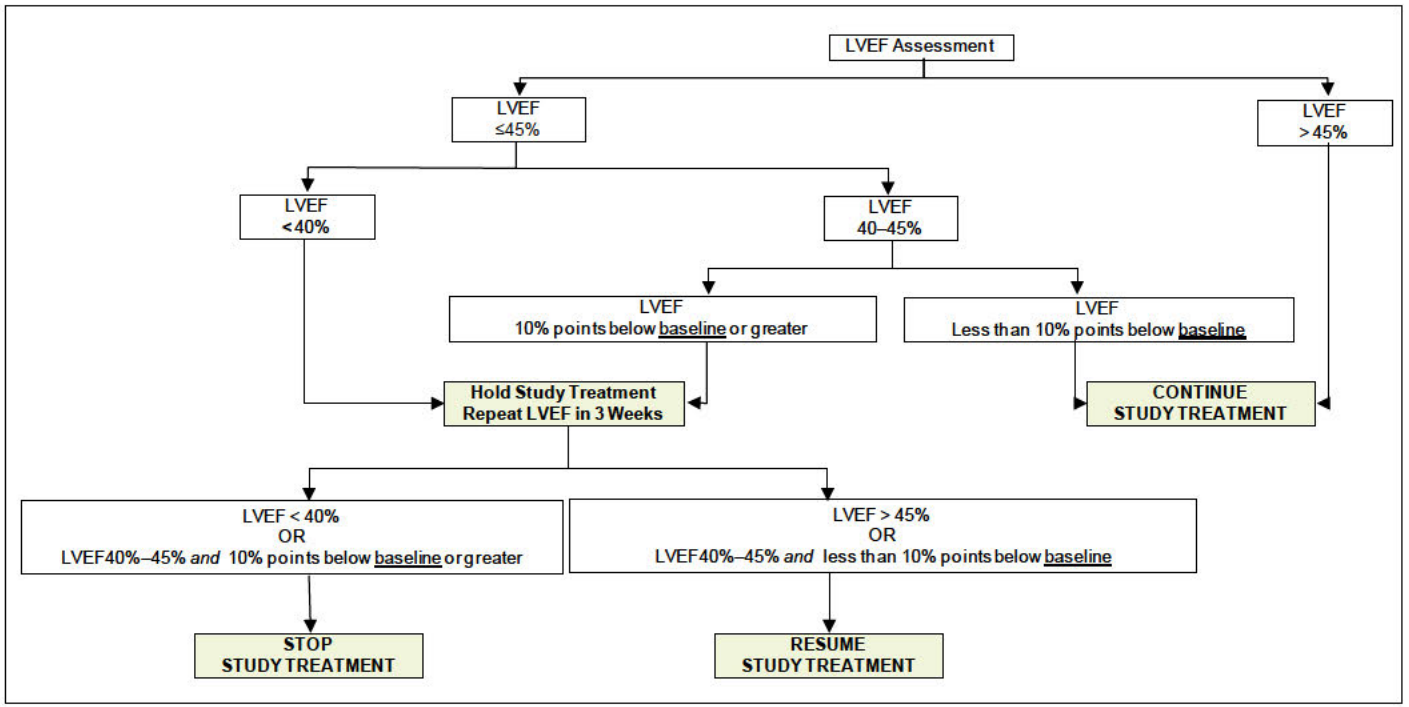
At present, there are inadequate data available to assess the prognostic significance of asymptomatic drops of LVEF. However, to ensure the safety of patients in the trial, pertuzumab and trastuzumab must be discontinued in all patients for whom a drop of LVEF to a value lower than 40% is documented and confirmed with a repeat assessment within 3 weeks of the first assessment, using the same assessment method.

For patients whose LVEF drops to values ≤ 45% (50% is required for entry into the study), the decision to stop or continue study treatment is based on the algorithm shown in Figure 3.

The incidence of CHF will also be recorded throughout the study.

See Appendix 4 for details of the NYHA classification and left ventricular systolic dysfunction NCI-CTCAE version 4.0 grading.

Figure 3Asymptomatic decline in LVEF: Algorithm for Continuation and Discontinuation of Pertuzumab and Trastuzumab Based on LVEF Assessments



5.1.1.2 Infusion-Associated Symptoms and Allergic Reactions

Administration of monoclonal antibodies, including pertuzumab and trastuzumab, may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rashes, headache, nausea, vomiting, or allergic reactions. Patients with extensive pulmonary disease, e.g., lymphangitis, multiple metastases, recurrent pleural effusions, and those with preexisting pulmonary compromise who are treated with trastuzumab, may be at increased risk of serious infusion-associated symptoms. Therefore, careful consideration must be made before enrolling patients with chronic lung disease into the study.

Study treatment will be administered in a setting with emergency equipment and staff that is trained to monitor for and respond to medical emergencies. Patients who experience an NCI-CTCAE version 4.0 Grade 4 allergic reaction, acute respiratory distress syndrome (ARDS), or bronchospasm will be discontinued from study treatment.

Patients who experience infusion-associated symptoms may be managed by:

- Slowing or stopping the trastuzumab or pertuzumab infusion.
- Supportive care with oxygen, beta-agonists, antihistamines, antipyretics, or corticosteroids as appropriate at the investigator's discretion.

Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent trastuzumab or pertuzumab infusions at the investigator’s discretion.

If infusion-associated symptoms occur, patients will be monitored until complete resolution of signs and symptoms.

5.1.1.3 Incomplete Loading Dose

In case the whole loading dose of pertuzumab cannot be administered due to an infusion reaction or other reason, the following guidelines apply. The same guidelines apply if the whole loading dose of trastuzumab cannot be administered:

The patient should receive at least 50% of the loading dose in the first week. Therefore, if the patient receives less than 50% of the Cycle 1 dose, the patient should receive the remainder before Day 22, preferably within the first week. Thereafter, the patient should receive the usual maintenance dose 3 weeks after the first interrupted dose, as routinely scheduled. For example, if a patient received only approximately 50% of the scheduled loading dose (i.e., only 420 mg instead of 840 mg of pertuzumab, or only 4 mg/kg instead of 8 mg/kg of trastuzumab), the patient should receive the remaining dose (420 mg of pertuzumab or 4 mg/kg of trastuzumab), preferably in the first week, and then regular maintenance doses (420 mg of pertuzumab; 6 mg/kg of trastuzumab) on Day 22, as routinely scheduled.

If the patient receives between 50-75% of the dose, the patient should receive the remainder before Day 22, preferably within the first two weeks of Cycle 1. For

example, if a patient received only approximately 60% of the scheduled loading dose, the patient should receive the remaining 40%, within 2 weeks after the interrupted loading dose. Thereafter, the patient should receive the regular maintenance doses on Day 22, as routinely scheduled.

If the patient received ≥75% of the loading dose, additional loading is probably not necessary. However, the remainder of the loading dose may be given at the investigator's discretion. In such a case, the remainder may be given at any time before the next scheduled dose or the patient may be given an additional loading dose on Day 22. If, after receiving an incomplete loading dose on Day 1, the patient cannot attend the site until Day 22, the patient should receive a second loading dose on Day 22. However, every effort should be made to give the remainder of the dose prior to Day 22.

If a dose is delayed (i.e. the time between two sequential infusions is less than 6 weeks), the 420 mg dose of pertuzumab should be administered. If a dose is missed (i.e. the time between two sequential infusions is 6 weeks or more), a re-loading dose of pertuzumab (840 mg) should be given as described in the product labeling. If re-loading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1. Subsequent maintenance pertuzumab doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.

If the patient misses a dose of trastuzumab by more than one week, re-loading of trastuzumab should follow approved local Product Information and/or recognized clinical practice guidelines. If re-loading is required for a given cycle, the 3 study therapies should be given on the same schedule as Cycle 1. Subsequent maintenance trastuzumab doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later.

In case of a delay to the administration of study treatments, the schedule of drug administration will always refer to the first drug to be administered.

5.1.1.4 Pertuzumab

Risk of Allergic Reactions, Including Anaphylaxis and Infusion-Associated Symptoms

Infusion-associated reactions typically occur during or shortly after infusions of monoclonal antibodies but may also show a delayed onset. The true relation of an event to infusion of study treatment is therefore difficult to ascertain, particularly when treatment regimens involve combination therapy. The potential incidence of infusion-associated reactions has been considered using a number of approaches in studies involving pertuzumab. In some studies, a conservative approach was used, in which all events occurring

- on the day of the infusion and the following day or

- within 24 hours following pertuzumab infusion

were presented as infusion-associated AEs, whether considered related or unrelated to pertuzumab by the investigator.

This definition is likely to result in inclusion of events that are not truly pertuzumab infusion-related; therefore some studies reported only treatment-related AEs (as assessed by the investigator) during the time periods above. Finally, in some studies, data have been collected only on AEs that started during the infusion itself.

In general antibody infusion-associated AEs are more frequent and severe with the first infusion, and decrease in number and severity over time, and the majority of AEs resolve fully.

Administration of pertuzumab should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. Patients will be monitored during each pertuzumab infusion and for 60 minutes following the completion of the infusion for any adverse effects. If infusion-associated symptoms occur, patients will be monitored until complete resolution of signs and symptoms. Patients who experience infusion-associated symptoms may subsequently be premedicated with acetaminophen, diphenhydramine, or meperidine.

Infusion of pertuzumab should be stopped in patients who develop dyspnea or clinically significant hypotension (defined per investigator discretion). Patients who experience an NCI-CTCAE v 4.0 Grade 3 or 4 allergic reaction or ARDS should not receive additional pertuzumab.

The investigator brochure should be referred to for most recent data relating to risk of allergic reactions.

Risk of Cardiotoxicity

Like trastuzumab, pertuzumab is directed at the HER2 receptor and may be associated with a risk of cardiac dysfunction.

All patients enrolled in pertuzumab studies undergo regular LVEF monitoring by echocardiography or MUGA scan.

Patients with significant cardiac disease or baseline LVEF below 50% are not eligible for this study. Risk factors for pertuzumab-associated cardiac dysfunction are not known at this time, and this risk should be carefully weighed against the potential benefit in patients who have received prior anthracyclines. During the screening/baseline period, complete medical history information will be collected from all patients to explore possible risk factors for treatment-CHF, including all prior LVEF assessments.

Monitoring of LVEF is required while patients are receiving study treatment. If symptomatic left ventricular dysfunction develops (NCI-CTCAE version 4.0 Grade 3 or 4) with a drop in LVEF consistent with cardiac failure, the patient must discontinue

study treatment. Left ventricular dysfunction, whether symptomatic or not, should be treated and followed according to standard medical practice.

The investigator brochure should be referred to for most recent data relating to risk of cardiotoxicity.

Risk of EGFR-Related Toxicities

Although pertuzumab targets HER2, because of its role in heterodimerization with other members of the HER family (e.g., EGFR), it may cause toxicities associated with the use of EGFR tyrosine kinase inhibitors. In the 7-week intravenous and 26-week toxicity studies in cynomolgus monkeys, there was a treatment-related increase in the incidence of diarrhea.

Diarrhea has been observed in patients being treated with pertuzumab in Phase II single-agent studies, and in combination therapy studies. For patients experiencing diarrhea, early intervention with loperamide should be considered.

Rash has also been observed with EGFR tyrosine kinase inhibitors.

The investigator brochure should be referred to for most recent data relating to risk of EGFR-related toxicities.

5.1.1.5 Trastuzumab

Trastuzumab therapy should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

Serious adverse reactions including cardiotoxicities, infusion reactions, hypersensitivity, allergic-like reactions, and pulmonary events have been observed in patients receiving trastuzumab therapy. These severe reactions were usually associated with the first infusion of trastuzumab and generally occurred during or immediately following the infusion. For some patients, symptoms progressively worsened and led to further pulmonary complications. Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported.

Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than 6 hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur. Patients who have dyspnea at rest due to co-morbidities may be at increased risk of a fatal infusion reaction.

Infusion Reactions, Allergic-Like Reactions, and Hypersensitivity

Serious adverse reactions to trastuzumab infusion that have been reported infrequently include dyspnea, hypotension, wheezing, bronchospasm, asthma

tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, and angioedema. The majority of these events occur during or within 2.5 hours of the start of the first infusion.

Should an infusion reaction occur, the trastuzumab infusion should be discontinued and the patient monitored until resolution of any observed symptoms. The majority of patients experienced resolution of symptoms and subsequently received further infusions.

Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions were associated with a clinical course culminating in a fatal outcome. Patients with dyspnea at rest due to co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab.

Pulmonary Events

Dyspnea, bronchospasm, asthma, and hypoxia can occur as part of an infusion reaction. These are most common with the first infusion, and their severity decreases with subsequent infusions. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. Single cases of pulmonary infiltrates, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, and respiratory insufficiency have been reported rarely. ARDS has been reported with fatal outcome.

Cardiotoxicity

Heart failure (NYHA Class II-IV) has been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel or docetaxel following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death.

Risk factors for trastuzumab-associated cardiotoxicity include increased age, concomitant administration with anthracyclines, and declining LVEF while on trastuzumab treatment. If symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with the standard medications for this purpose.

The half-life of trastuzumab is approximately 28.5 days (range: 25.5-32.8 days). Trastuzumab may persist in the circulation for up to 24 weeks (range: 18-24 weeks) after stopping trastuzumab treatment. Patients who receive anthracyclines during this period may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy up to 24 weeks after stopping trastuzumab. If anthracyclines are used then the patient should have careful cardiac surveillance.

Most patients who developed heart failure in the Phase III trials of trastuzumab in MBC improved with standard medical treatment. This treatment included diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab

treatment continued on weekly therapy with trastuzumab without additional clinical cardiac events.

5.1.1.6 Taxanes

Docetaxel, paclitaxel, and nab-paclitaxel should only be administered under the supervision of a physician experienced in the use of cancer cytotoxic agents.

Significant hypersensitivity reactions can occur in patients receiving taxanes, even after receiving adequate premedication. In the case of severe hypersensitivity reactions, taxane infusion should be discontinued immediately, symptomatic therapy should be initiated, and the patient should not be rechallenged with the taxane. In particular, macrogolglycerol ricinoleate, an excipient in paclitaxel, can cause hypersensitivity reactions. Localized skin erythema of the palms of the hands and soles of the feet with edema followed by desquamation has been observed with docetaxel.

Neutropenia can occur with docetaxel, paclitaxel, and nab-paclitaxel. In the case of neutropenia, patients should not be retreated until the neutrophil count is ≥1,500 cells/mm^3.

Patients with severe fluid retention such as pleural effusion, pericardial effusion, and ascites should be monitored closely.

Dose reduction should occur in the case of development of severe peripheral neurotoxicity with docetaxel, paclitaxel, or nab-paclitaxel.

Heart failure has been observed in patients receiving docetaxel in combination with trastuzumab. Cardiac function should be carefully monitored in patients receiving trastuzumab with docetaxel, paclitaxel, and nab-paclitaxel. Details on monitoring of cardiac toxicity are given in Section 5.1.1.1).

Limited, non-comparative data from Phase I/II studies suggest that the combination of pertuzumab and docetaxel may also result in myelosuppression. Given these data, it is expected that patients in this trial could experience hematologic AEs while receiving treatment. For this reason, all patients will be monitored for hematologic events, and dose reductions of docetaxel with or without growth factor support will be allowed in this protocol.

For further information, please refer to the local prescribing information for docetaxel, paclitaxel, and nab-paclitaxel.

5.1.2 Management of Specific Adverse Events

5.1.2.1 Pregnancy

See Section 5.4.3 for details of pregnancy during the study.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-SAEs of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.2.2 Serious Adverse Events (Immediately Reportable to The Sponsor)

An SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death).
- Life-threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death).

  This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10).
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.

- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to NCI-CTCAE version 4.0 criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to The Sponsor)

Non-serious adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

AESI for this study include the following:

- Asymptomatic declines in LVEF requiring treatment or leading to discontinuation of monoclonal antibodies
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy’s law (see Section 5.3.5.6).
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs considered to be related to a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies).

After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug. Thereafter, the patient will be followed 3-monthly, during which time all study drug-related SAEs should continue to be collected, until completion of the study, which is at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

Any pregnancy will be reported until 7 months after the last dose of pertuzumab and trastuzumab (see Section 5.4.3.1).

During post-treatment survival follow-up, deaths attributed to progression of breast cancer should be recorded only on the Survival eCRF.

After completion of the study, the investigator is not required to actively monitor patients for adverse events; however the Sponsor should be notified if the investigator becomes aware of any post-study serious adverse events (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI-CTCAE (version 4.0) will be used for assessing adverse event severity. The following table (Table 1) will be used for assessing severity for adverse events that are not specifically listed in the NCI-CTCAE.

Table 1 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the NCI CTCAE (version 4.0), which can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable).
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Associated Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

For AEs other than infusion-associated reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Clinically significant in the investigator's judgment.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the investigator's judgment.

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT and/or AST (>3 × baseline value) in combination with either an elevated total bilirubin (>2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (defined as a potential Hy's law case). Therefore, investigators must report to the Sponsor immediately (within 24 hours after learning of the event) as an SAE the occurrence of either of the following:

- Treatment-emergent ALT and/or AST >3 × baseline value in combination with total bilirubin >2 × ULN (of which ≥35% is direct bilirubin).
- Treatment-emergent ALT and/or AST >3 × baseline value in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Serious Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor within 24 hours after learning of the event.

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of breast cancer should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. If the cause of death is disease progression, this should be recorded on the Study Completion/Early Discontinuation eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care.

- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not suffered an AE.
- Hospitalization due solely to progression of the underlying cancer.

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from patient-reported outcome data (FACT-B questionnaire in women only). However, if any patient responses suggestive of a possible AE are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an AE have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an AE, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report the following events to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events.
- Non-SAEs of special interest.
- Pregnancies.

The investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.

- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB or IEC.

5.4.1 Emergency Medical Contacts

MEDICAL MONITOR (SPONSOR MEDICAL RESPONSIBLE) CONTACT INFORMATION

Primary Contact

Medical Monitor: [redacted] MD

Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: [redacted], MD

Telephone No.:

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of SAEs and non-SAEs of special interest, investigators should record all case details that can be gathered within 24 hours on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to The Sponsor Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to The Sponsor Safety Risk Management or its designee within 24 hours after learning of the event, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Reproductive toxicity data were recently published in the Investigator Brochure, and of particular interest is that pertuzumab caused oligohydramnios, delayed renal development and embryo-fetal deaths in pregnant cynomolgus monkeys. There are no clinical studies of trastuzumab or pertuzumab in pregnant women. IgGs are known to cross the placental barrier. Therefore, neither pertuzumab nor trastuzumab should be used during pregnancy.

Therefore, as a precaution, female patients of childbearing potential are required to use one highly effective form of contraception (such as surgical sterilization) or use two effective forms of contraception (such as a barrier method of contraception in conjunction with spermicidal jelly). Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or 7 months after the last dose of study drug. Additional information on any pertuzumab-exposed pregnancy and infant will be requested by the Sponsor's Drug Safety Department at specific time points (i.e., at the end of second trimester, 2 weeks after expected date of delivery, and at 3, 6 and 12 months of the infant's life). A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to The Sponsor Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drugs and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to The Sponsor Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

It is not known whether trastuzumab or pertuzumab are excreted in human milk. As maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or trastuzumab therapy and not to breastfeed for at least 6 months following the last dose of pertuzumab and for at least 7 months following the last dose of trastuzumab.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Experimental studies have reported that IgGs are present in both the pre-ejaculate and the seminal plasma (Moldoveanu et al. 2005). To date, there have been no clinical studies to assess the IgG profile in the pre-ejaculate and seminal plasma in male patients receiving pertuzumab or trastuzumab. Therefore, as a precaution, male patients with female partners of childbearing potential are required to use to use

one highly effective form of contraception (such as surgical sterilization) or use two effective forms of contraception (such as a barrier method of contraception in conjunction with spermicidal jelly).Similarly, vaginal absorption of pertuzumab is unknown and therefore male patients with pregnant partners are required to use condoms for the duration of the pregnancy, and then revert to contraceptive methods as outlined above. This is to ensure that the fetus is not exposed to the study medication through vaginal absorption. Similarly, sperm donation should not occur for at least 7 months after the last dose of study treatment.

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all

SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For SAEs, non-SAEs of special interest, and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period/completion of the study, which is at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first. However, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period/end of the study.

The investigator should report these events directly to Roche Safety Risk Management via telephone or via fax machine using the Serious Adverse Event Reporting Form and fax cover sheet (see "Protocol Administrative and Contact Information & List of Investigators").

5.7 REVIEW OF SAFETY BY AN INDEPENDENT DATA MONITORING COMMITTEE

An IDMC will be established for the study and specific policies on the operation of the IDMC will be documented in an IDMC Charter. The IDMC will be lead by a biostatistician and the other members will consist of physicians experienced in the treatment of breast cancer and a cardiologist to specifically review cardiac data. The IDMC will meet on a regular basis over the course of the study and may also meet on an unscheduled basis if any unexpected safety concerns arise. These meetings may occur via videoconference, teleconference, or in person. The IDMC Chair or a designated member will prepare minutes within two weeks following each IDMC meeting.

The IDMC will be responsible for independently evaluating the safety of the patients participating in the trial which includes an independent cardiologist to review cardiac safety data. If the IDMC has safety concerns they may recommend suspending or discontinuing the study.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final analysis will be done at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

In addition to the final analysis, there will be five interim safety analyses for review by the IDMC, after approximately 100, 350, 700, 1100 and 1500 patients have been enrolled. There will also be an annual review of safety data by the IDMC following completion of enrollment.

Further details will be provided in the statistical analysis plan.

6.1 DETERMINATION OF SAMPLE SIZE

A total of approximately 1500 patients will be enrolled in this study. For the purpose of the estimation of sample size, the incidence of AEs with Grade ≥3 related to pertuzumab was chosen as a safety endpoint of primary interest.

If the observed incidence of AEs Grade ≥ 3 related to pertuzumab is between 1% and 50%, the precision for the estimating incidence of AE is presented below by 95% Clopper-Pearson confidence intervals (Table 2).

Table 2 Clopper-Pearson 95% Confidence Intervals for the Incidence of AEs ≥ 3 Based on 1500 Patients

Number of AE events/observed AE incidence	*95% Clopper Pearson Confidence Interval*
15 (1%)	0.6% - 1.6%
30 (2%)	1.4% - 2.8%
45 (3%)	2.2% - 4.0%
60 (4%)	3.1% - 5.1%
75 (5%)	4.0% - 6.2%
90 (6%)	4.9% - 7.3%
105 (7%)	5.8% - 8.4%
120 (8%)	6.7% - 9.5%
135 (9%)	7.6% - 10.6%
150 (10%)	8.5% - 11.6%
300 (20%)	18.0% - 22.1%
450 (30%)	27.7% - 32.4%
600 (40%)	37.5% - 42.5%
750 (50%)	47.4% - 52.6%

6.2 SUMMARIES OF CONDUCT OF STUDY

The major protocol deviations will be summarized by frequency tables.

The median follow up on treatment and study will be summarized and estimates with corresponding 95% confidence interval provided using the Kaplan-Meier approach.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

There is only one treatment group in this study. There are no formal statistical hypothesis tests to be performed and there will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

Baseline and disease characteristics such as demographics, medical history, etc. will be summarized by descriptive statistics (frequency tables for categorical variables and mean, median, range, standard deviation, and 25th-75th quartiles for the continuous variables). These characteristics will be summarized for the intent-to-treat (ITT) population, which is defined as the population that includes all patients enrolled in the study.

6.4 EFFICACY ANALYSES

Analysis of efficacy is a secondary endpoint in this study.

6.4.1 Efficacy Endpoints

The efficacy secondary variables will be summarized for the ITT population.

Estimates for the survivor function for PFS, OS, duration of response and time to tumor response will be obtained by the Kaplan-Meier approach.

The analysis of ORR is based on the best (confirmed) overall response (BOR). The BOR will be assessed by the number and proportion of responders and non-responders in each treatment group, together with two-sided 95% confidence intervals (see Appendix 5). Only patients with measurable disease at baseline will be included in the analysis of the BOR. Patients without a post-baseline tumor assessment will be considered to be non-responders. Logistic analysis will be used for ORR to assess the influence of baseline covariates, e.g. country, region, age (>65, ≤65), ECOG performance status (0, 1 vs. 2), type of taxane (docetaxel, paclitaxel, nab-paclitaxel), visceral disease at baseline (yes vs. no) and prior (neo) adjuvant chemotherapy (yes vs. no), in an exploratory manner.

CBR includes patients whose BOR was PR, CR or SD that lasted at least 6 months. CBR will be summarized in a similar way to ORR.

6.5 SAFETY ANALYSES

The safety analyses will include all enrolled patients who received at least one dose of study drug, with patients grouped according to the treatment actually received.

Interim analyses of safety data will be performed on a regular basis and reviewed by the IDMC of the study (see Section 5.7).

The safety variables are all AEs, AEs Grade ≥3 according to the NCI CTCAE version 4.0, AEs leading to treatment interruption and discontinuation, AESI, SAEs, cause of death, incidence of CHF, LVEF, premature discontinuation from study and treatment, laboratory parameters, and study medication. The primary interest in this study will be AEs Grade ≥3 related to pertuzumab.

The analysis of AEs will focus on treatment-emergent AEs i.e. AEs occurring on the day of or after first administration of study drug. Non-treatment-emergent AEs (i.e. those occurring during screening) will only be listed.

The incidence, type and severity of AEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by MedDRA preferred term. Time to onset of the first episode of CHF will also be summarized using the Kaplan-Meier approach.

AEs Grade ≥3, AEs leading to treatment interruption and discontinuation, AESI, and SAEs will be analyzed in a similar way to all AEs. Cause of death will also be summarized and listed.

LVEF over time will be analyzed using descriptive statistics for continuous variable and presented graphically over time with associated 95% confidence interval.

The number of patients prematurely discontinued from the treatment with corresponding reason for discontinuation will be summarized and listed. The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative study medication doses and duration of exposure.

The following subgroup will be performed for AEs Grade ≥ 3 and other selected safety variables: by country, region, >65 vs. ≤65, ECOG 0, 1 vs. ECOG 2, type of taxane (docetaxel, paclitaxel or nab-paclitaxel), visceral disease at baseline (yes vs. no), and prior (neo) adjuvant chemotherapy (yes vs. no).

Laboratory parameters, hematology, serum biochemistry and coagulation will be presented in shift tables of NCI-CTCAE version 4.0 grade at baseline versus worst grade during treatment period. The summary of laboratory parameters presented by means, standard deviation, minimum, and maximum will be also presented. The selected laboratory parameters will be also graphically presented over time.

6.6 PATIENT-REPORTED OUTCOME ANALYSES

Quality of life will be assessed by FACT-B (in female patients only): physical well-being, social/family well-being, functional well-being, and disease-specific concerns, will be summarized by descriptive summary tables at baseline and over

time for the ITT population. Mean changes from baseline will also be summarized using descriptive statistics (including 95% CIs).

6.7 INTERIM ANALYSES

In addition to the final analysis, there will be five interim safety analyses for review by the IDMC, after approximately 100, 350, 700, 1100 and 1500 patients have been enrolled. There will also be an annual review of safety data by the IDMC following completion of enrollment. This is one single arm study with primary safety endpoints, hence there will be no adjustment for interim analysis.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

Roche will perform oversight of the data management of this study. Roche will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Other electronic data will be sent directly to the CRO, using Roche's standard procedures, as agreed, to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Roche and records retention for the study data will be consistent with Roche's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and a have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes (PRO questionnaires), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the Roche policy for retention of records.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB or IEC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer.

After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; Appendix 2). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB or IEC submission. The final IRB or IEC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB or IEC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB or IEC policy) during their participation in the study. For any updated

or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INDEPENDENT ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB or IEC by the Principal Investigator and reviewed and approved by the IRB or IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB or IEC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB or IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB or IEC. Investigators are also responsible for promptly informing the IRB or IEC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB or IEC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB or IEC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (where study completion is defined as at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB or IEC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by The Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB or IECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

An IxRS system will be used for enrollment of patients into the study.

A CRO will be used for data management (see Section 7.1).

Assessment of laboratory test results will be performed locally.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Investigators are responsible for promptly informing the IRB or IEC of any amendments to the protocol. Approval must be obtained from the IRB or IEC before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Assessments

	Screening	Baseline* (Enrolment)	Treatment period (all visits within ± 7 days of scheduled treatment day)	Post-treatment follow-up after study treatment termination	
	Day -28 to Day 1	Day -7 to Day 1	Each Treatment Cycle**	One month post-treatment safety follow-up (28 days [±5 days] after end of study treatment)[14]	~3-monthly post-treatment follow-up visits
Informed consent	X				
Demographics & medical history[1]	X				
Concomitant medication[2]	X	X	X	X	
Physical examination[3]		X	If clinically indicated	X	
Vital signs and blood pressure[3]		X	X	X	X
Height		X			
Weight[3]		X	X		
Pregnancy test[4]		X	Every 3 cycles of monoclonal antibody ≤3 days (with results available) prior to administration of study drug	X	4 and 7 months after treatment discontinuation

	Screening	Baseline* (Enrolment)	Treatment period (all visits within ± 7 days of scheduled treatment day)	Post-treatment follow-up after study treatment termination	
	Day -28 to Day 1	Day -7 to Day 1	Each Treatment Cycle**	One month post-treatment safety follow-up (28 days [±5 days] after end of study treatment)[14]	~3-monthly post-treatment follow-up visits
HER2 [5]	If positive HER2 result not available				
Tumor evaluation[6]	X		Every 3 cycles of monoclonal antibody up to 36 months, and every 6 cycles thereafter for patients who remain progression free after 36 months)	If disease progression not yet established	If disease progression not yet established
Hematology[7]		X	≤3 days (with results available) prior to administration of study drug	X	
Biochemistry[7]		X	≤3 days (with results available) prior to administration of study drug	X	

	Screening	Baseline* (Enrolment)	Treatment period (all visits within ± 7 days of scheduled treatment day)	Post-treatment follow-up after study treatment termination	
	Day -28 to Day 1	Day -7 to Day 1	Each Treatment Cycle**	One month post-treatment safety follow-up (28 days [±5 days] after end of study treatment)[14]	~3-monthly post-treatment follow-up visits
Coagulation[7]		X	If clinically indicated: ≤3 days (with results available) prior to administration of study drug	X	
Standard 12-lead ECG[8]	X		Every 3 cycles of monoclonal antibody ≤3 days (with results available) prior to administration of study drug	X	
LVEF[9]	X		Every 3 cycles of monoclonal antibody ≤7 days (with results available) prior to administration of study drug	X	
Brain CT/MRI[10]	X		If clinically indicated	If clinically indicated	If clinically indicated
ECOG performance status		X	Every 3 cycles of monoclonal antibody	X	

	Screening	Baseline* (Enrolment)	Treatment period (all visits within ± 7 days of scheduled treatment day)	Post-treatment follow-up after study treatment termination	
	Day -28 to Day 1	Day -7 to Day 1	Each Treatment Cycle**	One month post-treatment safety follow-up (28 days [±5 days] after end of study treatment)[14]	~3-monthly post-treatment follow-up visits
SAEs and AEs[11]	X	X	X	X	X
Quality of life (FACT-B)[12]		X	Every 3 cycles of monoclonal antibody	X	X
Administration of study medication			X		
Infusion reactions during infusion and observation period			X		
Survival[13]	X	X	X	X	X
Record anticancer medical or surgical procedures and therapies					X

* Baseline/ Screening assessments are allowable on Day 1 of first treatment cycle pre-dose as long as the results are available prior to enrolment

** Cycle = 3 weeks for monoclonal antibodies

Notes

1. Complete medical history and demographics (i.e. age, sex, race, and ethnicity, if applicable) and all medications taken the last 28 days prior to 1st study drug administration (dosing) will be collected.

2. Current concomitant medication will be recorded at baseline and on an ongoing basis.

3. Physical examination, including vital signs will be performed prior to enrolment with particular care taken with regard to cardiovascular signs and symptoms (e.g. elevated jugular venous pressure, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.). Vital signs will be assessed before treatment on Day 1 of every treatment cycle (pertuzumab, trastuzumab, and chemotherapy), with blood pressure, pulse rate, and body temperature recorded again after infusion during the observation period of each study medication.

4. Pregnancy tests must be performed for all WOBP (premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization). Baseline pregnancy test must be performed by serum β-HCG. Urine or serum pregnancy test must be performed every 3rd cycle within 3 days (with results available) prior to the administration of study medication, at the 1-month post-treatment safety FU visit, and at four and seven months after last dose of study medication. Any positive urine pregnancy test to be confirmed by serum β-HCG.

5. Demonstrated evidence of HER2 positive status from previous testing is acceptable, otherwise HER2-positive status on fixed tissue blocks from the primary tumor (and/or metastatic site, if primary tumor not available) to be assessed locally by IHC and/or ISH according to institutional criteria.

6. A CT or MRI and (if indicated) isotope bone scan (evaluation according to RECIST criteria) should be performed at screening and as clinically indicated. Scans at screening should not be older than 28 days prior to first study medication administration. To be performed post-study treatment only if disease progression has not yet been established. NB: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.

7. Assessment must be performed within 3 days (with results available) prior to the administration of study medication. Hematology will include hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, other cells). Biochemistry will include sodium, potassium, calcium, chloride, magnesium, BUN (or urea), uric acid, total protein, albumin, alkaline phosphatase, ALT, AST, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin, creatinine, and blood glucose. Calculated creatinine clearance to be determined at baseline only. All patients will have INR and aPTT or PTT testing at baseline. Tests will be repeated at each treatment cycle in all patients receiving therapeutic doses of anti-coagulants. Assessment of coagulation must be performed within 3 days (with results available) prior to the administration of study medication.

8. Two ECG recordings, taken two minutes apart, must be obtained at the screening visit, and every three cycles of monoclonal antibody therapy during the treatment period, ≤3 days (with results available) prior to administration of study drug (where possible at the time of LVEF measurement). ECG at safety follow-up visit to mirror ECHO/MUGA.

9. LVEF ≥ 50% at Screening period to be determined by either ECHO or MUGA scan (with ECHO as the preferred method). The same method of LVEF assessment (ECHO or MUGA) must be used for the same patient throughout the study and, to the extent possible, be obtained at the same institution. All pre-study LVEF values during and following trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrolment into the study will be collected.

LVEF assessment (ECHO or MUGA) done within 42 days prior to screening does not need to be repeated. To be performed every three cycles of monoclonal ant body therapy ≤7 days (with results available) prior to administration of study drug during the treatment period and at safety follow-up. If the previous assessment showed any abnormality, assessments should be performed until resolved.

10. A CT or MRI brain scan is to be performed at screening only in patients with clinical suspicion of brain metastases, and during the study if clinically indicated. If the patient has had recent radiotherapy (within 28 days prior to 1st study drug administration (dosing), the existing CT scan can be used for baseline.
11. After informed consent, but prior to initiation of study medications, only SAEs considered to be related to a protocol-mandated intervention will be collected. Adverse events to be monitored continuously during the treatment period. All AEs occurring during the study and until the treatment discontinuation visit 28 days after last study medication are to be recorded with grading according to NCI-CTCAE, Version 4.0, and thereafter all study drug-related SAEs should continue to be collected.
12. Quality of life will be assessed using the FACT-B questionnaires completed by the patient (FACT-B only by female patients). FACT-B has a 28-item generic score for all patients, plus nine items specific to breast cancer. Patients rate items on a five-point scale ranging from 'not at all' to 'very much'. FACT-B provides a total QoL score as well as information about physical well-being, social/family well-being, functional well-being, and disease-specific concerns. FACT-B provides supplemental domain valuative ratings or utility weights thus providing an estimate of the relative importance of each quality of life domain to an individual patient.
13. Survival status will be recorded during the treatment period and every 3 months after the one month post-treatment safety follow-up visit until at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by Roche, whichever occurs first.
14. The visit at which response assessment shows progressive disease may be used as the post-treatment safety follow-up visit.

Appendix 2 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- Is fatal; [results in death] [NOTE: death is an outcome, not an event].
- Is life-threatening [NOTE: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe].
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For SAEs, possible causes of the event **are** indicated by selecting one or more options. (Check all that apply)

- Preexisting/underlying disease - specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g. accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

Such preliminary reports will be followed by detailed descriptions later, which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For SAEs, the following must be assessed and recorded on the AEs page of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the IRB or IEC of an SAE in writing as soon as is practical and in accordance with international and local laws and regulations.

SPONSOR LOCAL COUNTRY CONTACT for SAEs: Local Monitor.

SPONSOR HEADQUARTERS CONTACT for SAEs and other medical emergencies: Contact information for the Contract Research Organization responsible for drug safety will be provided separately.

24 HOUR MEDICAL COVERAGE

Identification of a contact for 24 Hour Medical Coverage is mandatory to be compliant with worldwide Regulatory Agencies and to ensure the safety of study patients.

An Emergency Medical Call Center Help Desk will access the Sponsor Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with the Sponsor medical contact for this study and track all calls. The Emergency Medical Call Center Help Desk will be manned 24 hours 7 days a week. Toll-free numbers will be distributed to all investigators participating in this clinical trial. The Help Desk will be used for medical emergencies outside regular business hours, or when the regular International Medical Leader cannot be reached.

See the Protocol Administrative and Contact Information & List of Investigators form for details of administrative, contact information, and Emergency Medical Call Center Help Desk toll-free numbers. This information will be provided separately.

Appendix 3 ECOG Performance Status

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 4 NYHA Classification and Left Ventricular Systolic Dysfunction NCI CTCAE version 4.0 Grading

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain.
Class II	Patients with cardiac disease resulting in slight limitations 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 limitations 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 angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Oxford textbook of internal medicine. Vol 2, pp 2228. Oxford University Press. 1997	

Left Ventricular Systolic Dysfunction NCI-CTCAE Version 4.0 Grading

Grade 1	-
Grade 2	-
Grade 3	Symptomatic due to drop in ejection fraction responsive to intervention.
Grade 4	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated.
Grade 5	Death.
Common Terminology Criteria for Adverse Events. Version 4.0. Published May 28, 2009 (v4.03: June 14, 2010). US Department of Health and Human Services, National Institutes of Health, National Cancer Institute (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE-4.03-2010-06-14-QuickReference-5x7.pdf).	

Appendix 5 Tumor Assessments (RECIST) version 1.1 (Eisenhauer et al. 2009)

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot accurately be measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease-specific, instructions for their measurement should be incorporated into protocols on a disease-specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease: To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above). In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is

restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm·x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

Evaluation of target lesions:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation.

The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Appendix 6 FACT-B

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Guided Questionnaire Pregnancy-Related Adverse Events

Guided Questionnaire
Pregnancy-Related Adverse Events

AER:	
Site No:	
Patient ID/Initials:	
Patient Gender:	❑ M ❑ F

Local Case ID:	
Patient Date of Birth (dd-MMM-yyyy):	
Other Patient Identifiers	

Oligohydramnios, some associated with fatal pulmonary hypoplasia, and fetal renal impairment have been observed in some patients treated with Herceptin in the post-marketing setting. Oligohydramnios has been identified as an important identified risk for Herceptin, while for Perjeta and Kadcyla, oligohydramnios has been classified as an important potential risk.

By filling out this questionnaire, you will help us to understand more fully the risk factors for this condition and associated abnormalities, to communicate potential adverse pregnancy complications and fetal/infant outcomes to Health Authorities, Healthcare Professionals and patients.

Reporter Information	
Name of reporter completing this form ***(if other than addressee, please provide contact information below)***:	
Health Care Provider? ❑ Yes ❑ No - Please Specify:	
Phone number:	Fax number:
Email address:	

☐ Drug: **Herceptin** Lot Number(s):_____
☐ Drug: **Perjeta** Lot Number(s):_____
☐ Drug: **Kadcyla** Lot Number(s):_____

Maternal Information

	Selected Medical History		Comment
☐	None	☐ Unknown	
☐	Hypertension		
☐	Diabetes; if yes, please, specify type		
☐	Seizure disorders		
☐	Thyroid disorder		
☐	Smoking / use of alcohol; specify		
☐	Family history of diabetes mellitus		
☐	Family history of congenital renal anomalies; if yes, please specify		
☐	Other; specify		

	Selected Obstetric History (*previous pregnancies*)		Please, provide specifics including contributing factors
☐	None	☐ Unknown	
☐	Gestational hypertension/preeclampsia/eclampsia		
☐	Gestational diabetes		
☐	Spontaneous or induced abortions; if yes and known, please specify cause		
☐	Oligohydramnios		
☐	History of other pregnancy complications; specify		
☐	Other; specify		

Guided Questionnaire
Pregnancy-Related Adverse Events

	Fetal Abnormalities in Previous Pregnancies		Please, provide specifics including contributing factors
☐	None	☐ Unknown	
☐	Delayed renal development		
☐	Death in utero; if yes/known, specify reason		
☐	Birth defects; if yes, specify		
☐	Family history of birth defects; if yes, specify		
☐	Other; specify		

Current Pregnancy

Pre-pregnancy weight and height	Weight:	Height:
Blood pressure prior to conception	Date:	BP:

Prenatal Imaging and Aneuploidy Screening/testing (e.g., ultrasound, amniocentesis, etc.)
Was a prenatal test performed? ☐ Yes ☐ No

If yes, Prenatal Test Type	Date	Indication for test	Was a defect noted?	Specify

Ultrasound Assessment Log

Date	Gestational Age	Amniotic Fluid (AF) Measurement	Provider's Assessment of AF	Estimated Fetal Weight	Reported Percentile Growth	Provider's Assessment of Growth
	_____ weeks	AF Index _____ cm Maximum Vertical Pocket _____ cm Other _____ ☐ AF not measured	1 Normal 2 Abnormal 3 Oligohydramnios 4 Anhydramnios 5 Polyhydramnios 6 Delayed renal development 7 Other: _____ 8 Not assessed	_____ grams ☐ Not estimated	_____ ☐ Not reported ☐ Growth not measured	☐ Normal ☐ Abnormal ☐ IUGR* (< 10%ile) ☐ Severe IUGR (< 3%ile) ☐ Large for Gestational Age (> 90%ile) ☐ Growth not measured

* IUGR=Intrauterine growth retardation

Guided Questionnaire
Pregnancy-Related Adverse Events

Concomitant Medications, including ACE inhibitors and prostaglandin synthase inhibitors and all known teratogens up to 6 months prior to conception or during pregnancy:				
Product Name	**Indication**	**Total daily dose**	**Start date**	**Stop date/Ongoing**

	Maternal Medical Conditions During Current Pregnancy *Please check all that apply and provide detailed information on pregnancy-related complications on last page*			
☐	Gestational Hypertension/ Preeclampsia/Eclampsia ☐ chronic hypertension ☐ pregnancy-induced hypertension ☐ Preeclampsia-eclampsia ☐ Preeclampsia superimposed on chronic hypertension	Diagnostic tests:	Start date / Gestational age	Contr buting factors
☐	Gestational Diabetes	Diagnostic tests:	Start date / Gestational age	Contr buting factors
☐	Spontaneous or induced abortions; if yes/known, specify cause	Pathology results:	Start date / Gestational age	Contr buting factors
☐	Chronic leakage of amniotic fluid	Start date / Gestational age		Contributing factors
☐	Other; specify	Pathology results:	Start date / Gestational age	Contr buting factors
	Fetal Conditions During Current Pregnancy *Please check all that apply and provide detailed information on fetal complications on last page*			
☐	Renal abnormalities in fetus ☐ Normal fetal kidneys and fluid filled bladder ☐ Delayed renal development ☐ Renal agenesis ☐ Cystic dysplasia ☐ Ureteral obstruction	Diagnostic tests: ☐ Ultrasonography	Start date / Gestational age	Contr buting factors
☐	Fetal abnormalities, including genetic disorders; if yes, specify	Diagnostic tests: ☐ Ultrasound ☐ Alpha-fetoprotein ☐ Amniocentesis ☐ Aneuploidy screening ☐ Other	Date / Gest. age	Specify

Guided Questionnaire
Pregnancy-Related Adverse Events

☐	Post-maturity syndrome	Evidence:	Start date / Gestational age	Contr buting factors
☐	Death in utero; if yes/known, specify reason	Pathology results:	Date / Gestational age	Contr buting factors
☐	Other; specify			

Infant information

Mode of birth	☐ Spontaneous vaginal delivery ☐ Forceps / vacuum ☐ Cesarean section	Date	
Gestational age at birth		Apgar score	

Please check all that apply and provide detailed information on complications in infants on last page

	Date of Assessment			Contr buting factors
☐	Birth outcome	☐ Live birth ☐ Neonatal death	Cause	
☐	Small for gestational age at birth (SGA)	☐ Gestational age ☐ Weight/length	Date of assessment	
☐	Congenital anomalies	☐ Major malformation A defect that has either cosmetic or functional significance to the child	Specify	
		☐ Minor malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify	
		☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify	
		☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify	
☐	Abnormal renal function	☐ Proteinuria ☐ Electrolyte imbalance ☐ Other	Lab results	
☐	Other; specify			

Guided Questionnaire
Pregnancy-Related Adverse Events

FOR INTERNAL USE ONLY
Company Awareness Date:
MCN:

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: ..... Tel. No.: .....

Contact name for further information on pregnancy and/or on the infant:

Function ..... Tel. No.: .....

Contact Address: ..... Fax No.: .....

..... Email: .....

.....

Guided Questionnaire
Pregnancy-Related Adverse Events

Detailed information on pregnancy-related complications

Please enter text in dynamic box below:

ANNEX 5

PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

ANNEX 5: PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

F. HOFFMANN-LA ROCHE LTD
CLINICAL STUDY PROTOCOL
PROTOCOL NUMBER: BIG 4-11 / BO25126 / TOC4939G
EUDRACT NUMBER: 2010-022902-41
IND NUMBER: BB-IND 9900

PROTOCOL APPROVAL

Protocol Number / Version: **BIG 4-11 / BO25126 / TOC4939g**
Amendment D
Date: See last date in electronic signature manifestation below.
Protocol approved by: See electronic signature manifestation below.

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	02-Feb-2015 22:46:31

This protocol is intended for use in a life-threatening indication: Yes ☑ No ☐

PROTOCOL AMENDMENT, VERSION D: RATIONALE

Protocol BO25126 has been amended to include details of the enhanced measures for reporting of pertuzumab-exposed pregnancies that occur during study treatment and within 6 months after completion of pertuzumab treatment. Additionally, changes were made to extend the washout period of Herceptin® to 7 months based on updates to the data relating to the half-life of Herceptin; updates to relevant warnings have been made based on the updated washout period of 7 months (pregnancy exclusion and cardiac toxicity risk).

Additional changes to the protocol are as follows:

- Endocrine therapy can be administered as per local clinical practice
- An additional plasma sample is mandated to be collected at disease recurrence
- Clarification that the serum sample at the 28-day safety follow-up visit is mandatory
- Clarification of definitions for second primary malignancy, disease recurrence
- Clarification regarding reporting of AEs and SAEs during follow-up

No other changes have been made. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION D: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2.3: Pertuzumab Safety Data

As of 10 November 2010 (data cut-off date for the ~~current~~ IB *version current at the time of the original protocol*), approximately 1327 patients have been exposed to pertuzumab (excluding studies that are still blinded). The majority of adverse events (AE)s experienced by these patients were NCI-CTCAE (National Cancer Institute – Common Terminology Criteria for AEs) Grade 1 or 2 in severity. The most commonly reported AEs in single-agent Phase II studies, regardless of causality, were diarrhea, fatigue, nausea, abdominal pain, and vomiting (>20% of patients).

Further d~~D~~details ~~of the~~*and updated* safety data can be found in the *current* IB. A high-level summary *based on the 10 November 2010 cutoff* is presented below.

SECTION 1.3.2: Pharmacokinetic Data Supporting Trastuzumab Administration Every 3 Weeks

Analyses in clinical studies showed that trastuzumab has dose-dependent, nonlinear PK, with dose-dependent clearance and half-life. The volume of distribution approximates the serum volume *and steady-state is reached by approximately 20 weeks (95% CI 18–24 weeks). Based on population PK analyses,* ~~A~~*a*t therapeutic doses, the half-life is approximately ~~28.5~~*28–38* days. ~~(95% confidence interval [CI] 25.5–32.8 days) and steady-state is reached by approximately 20 weeks (95% CI 18–24 weeks).~~ *Accordingly, the recommended washout period (5 elimination half-lives, based on a conservative estimate of half-life) is 27 weeks (190 days).* ~~*The estimated trough concentrations for 3-weekly and weekly dosing are 52.9 mg/L and 69.6 mg/L, respectively.*~~

Data to support the q3w regimen are available from two studies evaluating the safety, tolerability, and PK of trastuzumab administered to women with HER2-positive (immunohistochemistry [IHC] 3+ or fluorescence in situ hybridization [FISH] +) metastatic breast cancer and from the 1-year arm of the HERA study (BO16348). Data from these three trials indicate that serum concentrations of trastuzumab increased until steady-state trough concentrations (median 47.3 ng/mL, 95% CI 19.6-51.2 ng/mL). Serum trough levels appeared to be comparable over the study periods, although trough concentrations were slightly lower with the q3w regimen *(52.9 mg/L)* compared with previous studies of the qw regimen *(69.6 mg/L)*. The average exposure at any time during the treatment is comparable between the two treatment regimens.

SECTION 1.4.4: Rationale for Dose Selection of Trastuzumab and Pertuzumab

The half-life of trastuzumab has been determined to be approximately 28~~.5~~ *–38* days, which supports a dosing of q3w (see also Section 1.3.2).

SECTION 3.1: Overview of Study Design:

For patients with tumors that are estrogen receptor (ER) and/or progesterone receptor (PgR) positive, hormonal agents should be started at the end of chemotherapy consisting of tamoxifen or an aromatase inhibitor for post-menopausal patients; or tamoxifen with or without ovarian suppression *or an aromatase inhibitor with ovarian suppression* for pre-menopausal patients. Hormonal therapy should be given for at least 5 years in accordance with the protocol recommendations (see Section 4.4.3.1 for details).

SECTION 4.2: Inclusion Criteria:

Patients must meet ALL of the following criteria in order to be eligible for this study:

9. Women of childbearing potential and male participants with partners of childbearing potential must agree to use a highly-effective, non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner. Contraception must continue for the duration of study treatment and for at least ~~6~~*7* months after the last dose of study treatment (Section 7.2.5).

SECTION 4.3: Exclusion Criteria

Patients meeting any ONE of the following criteria are not eligible for this study:

12. Women of childbearing potential or less than one year after menopause (unless surgically sterile) who are unable or unwilling to use the contraceptive measures required by this protocol during and *7*~~6~~ months after the last dose of study medication (see Section 7.2.5).

SECTION 4.4.3: Concomitant Hormonal Therapy

Before actively enrolling patients, each center must set a policy for the use of tamoxifen, ovarian ablation~~, or both~~ *and aromatase inhibitors* for patients in the trial. ~~Study sites must also set their local policy for the use of registered aromatase inhibitors.~~ *Table 7 contains recommendations for accepted hormonal therapy. However, as of protocol amendment D, sites may prescribe hormonal therapy per standard local clinical practice.* ~~Aromatase inhibitors will be allowed as adjuvant hormonal therapy for post-menopausal patients who are hormone receptor positive with early invasive breast cancer, in countries where it has been registered for this indication. Its use must be consistent with the registered label.~~

~~No other hormonal therapy for primary breast cancer is allowed, including pure anti-estrogens and progestational agents. The use of any other hormonal therapy that becomes approved for adjuvant therapy during the conduct of the trial must be approved by the study steering committee.~~

SECTION 5.3.2: Targeted Treatment Period – Required Assessments and Procedures

Additional blood samples (serum) for biomarker research must be collected for all patients during treatment if the site has appropriate storage facilities (as described in Section 5.6.2.1). A serum sample is to be collected at the end of taxane treatment, either prior to Cycle 4 or Cycle 5 of targeted treatment for patients who received taxanes sequentially after anthracyclines; or prior to Cycle 7 of targeted treatment for patients

receiving TCH therapy. ~~For patients who drop out of the targeted treatment before Week 52,~~. a*A* serum sample must be collected during the safety follow-up visit 28 days from the last dose of targeted treatment*, including patients who drop out of the targeted treatment before Week 52*.

SECTION 5.5.1: Acceptable Procedures for Confirmation of Disease Recurrence

e) Second primary malignancy (breast or other cancer)

Any positive diagnosis of a second (non-breast) primary cancer*, with the exception of non-melanoma skin cancers and carcinoma in situ of any site,* ~~other than basal or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix~~ will be considered an event in the analysis of the invasive disease-free survival including second primary non-breast cancer endpoint, however, they will not be included in the IDFS primary endpoint.

SECTION 5.5.2: Tumor Tissue*,* ~~and~~ Serum, *and Plasma* Sample Collection at Disease Recurrence

Likewise for regional or distant metastases, an FFPE tumor block from the biopsy or surgery (preferred) *or if biopsy or surgical samples are not available, a fine-needle aspiration sample* should be obtained and sent to the central laboratory for central review and future translational research.

Serum *and plasma* collection at disease recurrence

~~Wherever possible, a~~*A*n additional serum *and plasma* sample (*each* prepared from 10 mL of peripheral blood) should be collected at disease recurrence *or a timepoint close to diagnosis of disease recurrence* (see Section 5.6.2.1 for further details) *but prior to the initiation of any new lines of therapy for disease recurrence.*

SECTION 5.6.1.1: *FFPE Tumor Block (Mandatory)*

FFPE tumor blocks (screening ~~and recurrence samples~~) will be returned to site.

SECTION 5.6.2.1: *Additional Serum and Plasma Samples (Subject to the Site Having Appropriate Storage Facilities)*

Samples will be collected at the following time points:

- At disease recurrence (if any)*, both serum and plasma samples will be collected*

SECTION 7.1.1: Clinical Adverse Events

Per the ICH, an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during a study are to be reported as AEs. *After informed consent has been obtained but prior to initiation of study drug, only SAEs*

caused by a protocol-mandated intervention (such as biopsies) should be reported.

SECTION 7.1.1.4: *Disease Recurrence*

Non-breast-related secondary primary malignancies are to be reported as SAEs at any time regardless of the time elapsed since the last dose of investigational product. *Myelodysplastic syndrome is not considered a progression event but is to be reported as an SAE.*

SECTION 7.1.2:Treatment and Follow-up of Adverse Events

~~The terminal half-life of trastuzumab, derived from population PK analysis of three studies in patients with metastatic breast cancer and one trial in patients with NSCLC, is approximately 28 days. The terminal half-life of pertuzumab, derived using similar methods, is similar. Therefore, pertuzumab and trastuzumab may be present in the circulation for 20 weeks (range 18-24 weeks) after the last treatment.~~

All adverse events (related and unrelated) occurring during the study conduct and up to 28 days after the last dose of study medication must be reported on the eCRF and followed until resolution or end of study, whichever occurs first. *If a non-serious-related adverse event becomes serious after the reporting period, this should be reported as per the SAE process.*

SECTION 7.2.1: Reporting of Adverse Events

During the period after signing the informed consent and *prior to* study Day 1 (administration of study treatment), any non-serious AEs that occur will be reported in the medical history, unless AE reporting is deemed more appropriate; SAEs caused by a protocol mandated Intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

All adverse events (related and unrelated) occurring during the study conduct and up to 28 days after the last dose of study medication must be reported on the eCRF and followed until resolution or end of study, whichever occurs first. *If a non-serious-related adverse event becomes serious after the reporting period, this should be reported as per the SAE process.*

Thereafter only the following events should continue to be both followed and recorded up to 10 years after the last administration of study medication.

- Non–breast-related second primary malignancies*, (irrespective of casual relationship) and myelodysplastic syndrome* (irrespective of causal relationship)

See Section 7.1.2 for further information on~~f~~ the follow-up of AEs.

SECTION 7.2.2: Reporting of Serious Adverse Events (Immediately Reportable)

Related SAEs and suspected, unexpected serious adverse reaction (SUSARs) **MUST** be collected and reported regardless of the time elapsed from the last study treatment administration, even if the study has been closed. *If a non-serious-related adverse*

event becomes serious after the reporting period, this should be reported as per the SAE process.

Unrelated SAEs must be collected and reported during the study and for up to 28 days after the last dose of study medication.

SAEs occurring during screening will also be reported *if they are considered related to a protocol-mandated procedure.*

SECTION 7.2.3: Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious Adverse Events of Special Interest (AESI) are required to be reported on an SAE form by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

AESI for this study include the following:

- *An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment, as defined in Section 7.2.4*

SECTION 7.2.5: Pregnancy and Pregnancy Prevention

According to the ICH M3 Guideline, precautions need to be taken to minimize risk to a fetus or embryo when including women of childbearing potential in clinical trials. These include highly effective contraceptive measures, excluding pregnancy at baseline (serum test), continued pregnancy *testing*~~monitoring~~ *during study treatment*~~,~~ and ~~continued pregnancy testing~~ up to 6 months following last dose of targeted treatment. *In addition, women of childbearing potential are required to use highly effective contraceptive measures during study treatment and for at least 7 months following their last dose of study drug (washout period) based on PK considerations for trastuzumab. See trastuzumab IB for details.*

It is not known whether trastuzumab or pertuzumab is excreted in human milk. As maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or trastuzumab therapy and not to breastfeed for at least ~~6~~7 months following the last dose of either ~~monoclonal antibody~~*trastuzumab or pertuzumab*.

Additional information for any pertuzumab-exposed pregnancies that occur during study treatment and within 6 months after completion of pertuzumab treatment will be requested by Roche Drug Safety at specific timepoints (i.e., at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

SECTION 7.2.5.1: *Pregnancy Prevention*

For women of childbearing potential (who have not undergone surgical sterilization), and the female partners of male participants; agreement must be obtained to use one highly effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner *during study treatment and for at least*

7 months following the last dose of study drug. Specific country and/or local requirements for contraception will be followed.

Timing and duration of contraception

Based on PK considerations, contraception methods should start a minimum of 14 days prior to first administration of study treatment and continue for the duration of study treatment and for at least ~~6~~*7* months after the last dose of study treatment.

SECTION 7.4.3: Risk of EGFR-Related Toxicities

Although pertuzumab targets HER2, because of its role in heterodimerization with other members of the HER family (e.g., epidermal growth factor receptor [EGFR]), it may cause toxicities associated with the use of EGFR TKIs. Diarrhea has been observed in approximately 60% of patients being treated with pertuzumab in Phase II single-agent studies, and up to 70% of patients in combination therapy studies, and was of Grade 1 or 2 in the majority of cases. For patients experiencing diarrhea, early intervention with loperamide *as well as fluid and electrolyte replacement* should be considered.

SECTION 7.5.3: Risk of Cardiotoxicity

Cardiac dysfunction

The half-life of trastuzumab is approximately 28*–38* days ~~(range 25.5–32.8 days)~~. Trastuzumab may persist in the circulation for up to *27*~~24~~ weeks ~~(range 18–24 weeks)~~ after *the last dose of*~~stopping~~ trastuzumab treatment. Patients who receive anthracyclines during this period may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy up to *27*~~24~~ weeks *(7 months)* after stopping trastuzumab. If anthracyclines are used then the patient should have careful cardiac monitoring. For the purposes of this study, a minimum of 3 weeks separates the *trastuzumab plus* pertuzumab/placebo *dosing* and the ~~epirubicin~~ *anthracycline* dosing. The patient will be closely monitored, including LVEF assessments prior to and after completion of the anthracycline.

TABLE 7: Recommendations for Hormonal Therapy

Table 7 has been revised to reflect changes made to the protocol.

TABLE 8: Schedule of Assessments – Screening and Treatment Period

Table 8 has been revised to reflect changes made to the protocol.

TABLE 9: Schedule of Assessments – Follow-Up Period

Table 9 has been revised to reflect changes made to the protocol.

TABLE 10: Schedule of Assessments – Treatment Period (Patients Who Discontinue Study [Targeted Treatment])

Table 10 has been revised to reflect changes made to the protocol.

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BIG 4-11 / BO25126 / TOC4939G SYNOPSIS

TITLE:	A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer
SPONSOR	F. Hoffmann-La Roche Ltd. and Genentech, Inc. CLINICAL PHASE III
INDICATION	HER2-positive primary breast cancer
OBJECTIVES	PRIMARY OBJECTIVES To compare invasive disease-free survival (IDFS) in patients with HER2-positive breast cancer randomized to chemotherapy plus one year of trastuzumab plus placebo or chemotherapy plus one year of trastuzumab plus pertuzumab. SECONDARY OBJECTIVES To compare invasive disease-free survival including second non-breast cancers, disease-free survival (DFS), overall survival (OS), recurrence-free interval (RFI), distant recurrence-free interval (DRFI), cardiac safety, overall safety and health-related quality of life (HRQL) in the two treatment arms.
TRIAL DESIGN	A prospective, two-arm, randomized, multicenter, multinational, double-blind, placebo-controlled study in patients with HER2-positive primary breast cancer who have had excision of their tumor.
NUMBER OF PATIENTS	A planned total of approximately 4800 evaluable patients will be enrolled into the study.
TARGET POPULATION	Patients newly diagnosed with primary invasive breast cancer that is HER2-positive (immunohistochemistry [IHC] 3+ or FISH/CISH positive determined by central review) who will be treated with adjuvant systemic chemotherapy *within* 8 weeks following surgery.
INCLUSION CRITERIA	Patients must meet ALL of the following criteria in order to be eligible for this study: • Age ≥ 18 years. • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. • Non-metastatic operable primary invasive carcinoma of the breast that is: a) Histologically confirmed; b) Adequately excised: – Patients must have undergone either a total mastectomy or breast conserving surgery – For patients who undergo conservative surgery, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates

tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible without additional resection.

– For patients who undergo mastectomy, margins must be free of gross residual tumor. Patients with microscopic positive margins are eligible (see radiation therapy requirements).

c) pTNM staging:

Pathological classification of regional lymph nodes: micrometastases (tumor deposits >0.2 mm) are considered pN1, but isolated tumor cells (ITC) are considered pN0.

– For patients with node-positive disease (pN ≥1), any tumor size except T0.

Node-negative patients are NOT allowable under Protocol B. Below applies to Protocol A ONLY:

For patients with node-negative disease (pN0) (Protocol A ONLY):

Tumor size must be > 1.0 cm OR

For tumor size between > 0.5 cm and ≤ 1.0 cm, at least one of the following features must be present: histologic/nuclear grade 3 OR negative for ER and PgR OR age < 35 years.

Enrollment of patients with node negative tumors ≤ 1.0 cm will be limited to <10% of the total number of randomized patients.

– For multifocal (the presence of two or more tumor foci within a single quadrant of the breast) or multicentric disease (the presence of two or more tumor foci within different quadrants of the same breast), the size of the largest invasive tumor is to be used to determine T stage.

– Patients with synchronous bilateral invasive disease are eligible so long as both lesions are HER2-positive.

- Known hormone receptor status (estrogen receptor [ER] and progesterone receptor [PgR]).
- The interval between definitive surgery for breast cancer and the first dose of chemotherapy must be no more than 8 weeks (56 days). All procedures, including randomization, must occur during this period. The first cycle of chemotherapy must be administered within 7 days of randomization or on Day 56, whichever occurs first.
- Baseline LVEF ≥55% measured by echocardiography (preferred) or MUGA scan.
- HER2-positive breast cancer confirmed by a central

	laboratory and defined as: – IHC 3+ in >10% immunoreactive cells OR c-erbB2 gene amplification by in situ hybridization [ISH] (ratio of c-erbB2 gene signals to centromere 17 signals ≥2). Availability of formalin-fixed paraffin-embedded (FFPE) tissue block with at least 5-mm invasive tumor and, wherever possible, a minor component of non-neoplastic breast tissue for central confirmation of HER2 eligibility, hormone receptor status and biomarker evaluation is mandatory (a minimum of 4 and up to 7 × 1-mm cores will be taken for translational research and the block returned to the site). • Completion of all necessary baseline laboratory and radiologic investigations prior to randomization • Women of childbearing potential and male participants with partners of childbearing potential must agree to use a "highly-effective", non-hormonal form of contraception or two "effective" forms of non-hormonal contraception by the patient and/or partner. Contraception must continue for the duration of study treatment and for at least 7months after the last dose of study treatment. • Signed informed consent
EXCLUSION CRITERIA	Patients meeting any ONE of the following criteria are not eligible for this study: • History of any prior (ipsi- and/or contralateral) invasive breast carcinoma • History of non-breast malignancies within the 5 years prior to study entry*, except for the following: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinomas of the skin (*malignancies occurring more than 5 years prior to study entry are permitted if curatively treated with surgery alone). • Any "clinical" T4 tumor as defined by TNM, including inflammatory breast cancer • Any node-negative tumor • Any previous systemic chemotherapy (e.g., neoadjuvant or adjuvant) for cancer OR radiation therapy for cancer: – Patient with a past history of DCIS and/or LCIS are not allowed to enter the study if they have received any form of systemic therapy for its treatment; OR radiation therapy to the ipsilateral breast where invasive cancer subsequently develops. – Patients who had their DCIS/LCIS treated with surgery only are allowed to enter the study. – High risk patients who have received chemoprevention drugs in the past are not allowed to enter the study. • Prior use of anti-HER2 therapy (e.g., lapatinib, neratinib or

other tyrosine kinase inhibitors [TKIs]) for any reason or other prior biologic or immunotherapy for cancer.

- Concurrent anti-cancer treatment in another investigational trial, including hormone therapy, bisphosphonate therapy and immunotherapy.
- Serious cardiac illness or medical conditions including but not confined to:
  - History of documented heart failure or systolic dysfunction (LVEF <50%)
  - High-risk uncontrolled arrhythmias i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block)
  - Angina pectoris requiring anti-anginal medication
  - Clinically significant valvular heart disease
  - Evidence of transmural infarction on ECG
  - Poorly controlled hypertension (e.g., systolic >180 mm Hg or diastolic >100 mm Hg)
- Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness (e.g., infections or poorly controlled diabetes).
- Any of the following abnormal laboratory tests immediately prior to randomization:
  - Serum total bilirubin >1.5 upper limit of normal (ULN); in cases of known Gilberts syndrome a total bilirubin of 2 × ULN is permitted
  - Alanine amino transferase (ALAT) and/or aspartate amino transferase (ASAT) >1.25 × ULN
  - Alkaline phosphatase (ALP) >2.5 × ULN
  - Serum creatinine >1.5 × ULN
  - Total white blood cell count (WBC) 2,500 / mm^3 (<2.5 × 10^9/L)
  - Absolute neutrophil count (ANC) <1,500 / mm^3 (<1.5 × 10^9/L)
  - Platelets < 100,000 / mm^3 (< 100 × 10^9/L)
- Pregnant, lactating or women of childbearing potential without a negative pregnancy test (serum), within 7 days prior to randomization, irrespective of the method of contraception used.
- Women of childbearing potential or less than one year after menopause (unless surgically sterile) who are unable or unwilling to use the contraceptive measures required by this protocol during and 7 months after the last dose of

	study medication. • Sensitivity to any of the study medications or any of the ingredients or excipients of these medications, including sensitivity to benzyl alcohol.
LENGTH OF STUDY	Recruitment is expected to last approximately 25 months. The primary analysis for IDFS will take place after patients have been followed for a minimum of 30 months or after 379 events have occurred, whichever occurs later. Post treatment, patients will be followed at approximately 3 monthly intervals for 2 years, then every 6 months during years 3 to 5 and annually thereafter. Overall, patients will be followed until approximately 10 years have elapsed since the last patient was enrolled into the study.
INVESTIGATIONAL MEDICAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	Pertuzumab 840 mg loading dose administered intravenously (IV) followed by 420 mg IV every three weeks (q3w).
COMPARATOR "DRUG" (or STANDARD OF CARE) DOSE/ ROUTE/ REGIMEN	Standard of care: Investigators' choice of trastuzumab-containing adjuvant chemotherapy for early stage breast cancer, either with an anthracycline-containing regimen or a non-anthracycline-containing regimen. Treatments should include 6−8 cycles of: **ANTHRACYCLINE-BASED CHEMOTHERAPY** **FEC (or FAC) →TH** 3 or 4 cycles of FEC (or FAC) administered IV q3w – 5-Fluorouracil (5-FU) 500−600 mg/m^2 – Epirubicin 90−120 mg/m^2 (doxorubicin 50 mg/m^2 is acceptable) – Cyclophosphamide 500−600 mg/m^2 Followed by 3 or 4 cycles of TH – Docetaxel 100 mg/m2 IV q3w for 3 cycles OR 75 mg/m^2 IV at the first docetaxel cycle (escalating to 100 mg/m^2 for subsequent cycles) as per local practice OR 75 mg/m^2 IV q3w for 4 cycles – Paclitaxel instead of docetaxel is acceptable and must be given at doses of 80 mg/m^2 once weekly (qw) for 12 weekly cycles – Trastuzumab 8 mg/kg for the first cycle of HER2-targeted treatment (beginning with the first cycle of taxane therapy), then 6 mg/kg IV q3w in subsequent cycles Alternatively: AC (or EC) →TH 4 cycles of AC (or EC) administered q3w OR dose-dense every 2 weeks (q2w) with G-CSF support

- Doxorubicin 60 mg/m^2 (or epirubicin 90–120 mg/m^2)
- Cyclophosphamide 500–600 mg/m^2

Followed by 3 or 4 cycles of TH

- Docetaxel 100 mg/m^2 IV q3w for 3 cycles OR 75 mg/m^2 IV at the first docetaxel cycle (escalating to 100 mg/m2 for subsequent cycles) as per local practice OR 75 mg/m^2 IV q3w for 4 cycles
- Paclitaxel instead of docetaxel is acceptable and must be given at doses of 80 mg/m^2 qw for 12 weekly cycles
- Trastuzumab 8 mg/kg for the first cycle of HER2-targeted treatment (beginning with the first cycle of taxane therapy), then 6 mg/kg IV q3w in subsequent cycles

OR

NON-ANTHRACYCLINE-BASED CHEMOTHERAPY

TCH administered IV q3w for 6 cycles

- Docetaxel 75 mg/m^2
- Carboplatin AUC 6 (maximum dose 900 mg)
- Trastuzumab 8 mg/kg at Cycle 1, then 6 mg/kg IV q3w in subsequent cycles.

Randomized targeted treatment (trastuzumab plus pertuzumab OR trastuzumab plus placebo) must start concurrently with the taxane component of chemotherapy. Randomized targeted treatment is to be administered for a total duration of 52 weeks plus a window of 3 days (i.e., maximum of 18 cycles within 1 year).

For patients with tumors that are ER and/or PgR positive, hormonal agents should be started at the end of chemotherapy (tamoxifen or an aromatase inhibitor for post-menopausal patients; or tamoxifen with or without ovarian suppression for pre-menopausal patients) and given for at least 5 years in accordance with protocol recommendations (Section 4.4.3).

Radiotherapy is to be given as clinically indicated at the end of chemotherapy in accordance with protocol recommendations (Appendix 2).

Patients treated with anthracyclines must have an LVEF ≥50% prior to commencing the HER2-targeted component of therapy.

STRATIFICATION	The following stratification factors will be used: • Nodal status • Type of adjuvant chemotherapy regimen (anthracycline-based versus non-anthracycline-based) • Hormone receptor status • Geographical region • Protocol version
ASSESSMENTS OF:	
EFFICACY	**Primary efficacy variable** IDFS defined as the time from randomization until the date of the first occurrence of one of the following events: – Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion); – Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall and/or skin of the ipsilateral breast) – Distant recurrence (i.e., evidence of breast cancer in any anatomic site−other than the two abovementioned sites−that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer) – Contralateral invasive breast cancer – Death attributable to any cause including breast cancer, non-breast cancer or unknown cause (but cause of death should be specified if at all possible).
SAFETY	Clinical and laboratory adverse events (AE)s will be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. In addition, cardiovascular side effects will be reported according to prespecified criteria (NCI-CTCAE and New York Heart Association [NYHA]). Left ventricular ejection fraction (LVEF) will be assessed using either echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans. Cardiac reassessment throughout the study will be performed using the same technique as at baseline.
PHARMACOKINETICS (Substudies)	A subset of principal investigators and patients will participate in pharmacokinetic and drug-drug interaction substudies as detailed in separate protocols. Separate Institutional Review Board/Independent Ethics Committee approval and Informed Consent Form will be required for participation in each substudy.

PROCEDURES (Summary):	Eligible and consenting patients will be randomized and will undergo 6−8 cycles of adjuvant chemotherapy with a regimen chosen by the Investigator, with the addition of pertuzumab or placebo. Patients will receive the randomized targeted treatment (trastuzumab plus pertuzumab OR trastuzumab plus placebo) for a total duration of one year (52 weeks + 3-day window). During adjuvant therapy, patients will be assessed for safety and efficacy (see Schedule of Assessments tables).
STATISTICAL ANALYSES	**Primary Efficacy Endpoint** The primary efficacy variable is IDFS and is defined as the time between randomization and date of first occurrence of an IDFS event (as described in the efficacy assessments above). Patients who have not had an event at the time of data analysis will be censored at the date they were last known to be alive and event free. Note: this definition of IDFS (which excludes second primary non-breast cancers as events) is not the same as IDFS defined by Hudis et al. [2007] (which includes second primary non-breast cancers as events). The stratified log-rank test will be used to compare IDFS between the two treatment arms. The unstratified log-rank test results will also be provided as a sensitivity analysis. The Kaplan-Meier approach will be used to estimate 3-year IDFS rates for each treatment arm. The stratified Cox proportional hazards model will be used to estimate the hazard ratio (HR) between the two treatment arms (i.e., the magnitude of treatment effect) and its 95% confidence interval (CI). The primary analysis will be based on the intent-to-treat (ITT) population. Cox proportional hazards regression models will be performed in an exploratory manner, to determine if adjustment for additional covariates will modify the conclusions from the primary analysis. Variables to be considered in addition to the stratification factors are other disease or patient-related prognostic or predictive factors. **Secondary Efficacy Endpoints** **Invasive Disease-Free Survival including second primary non-breast cancer** will be defined the same way as the primary endpoint IDFS but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site). **Disease Free Survival (DFS)** is defined as the time between randomization and the date of the first occurrence of an invasive disease-free survival event including second primary non-breast cancer event or contralateral or ipsilateral DCIS. Patients who have not had an event at the time of data analysis will be censored at the date they were last known to be event free. **Overall Survival (OS)** is defined as the time from randomization to death due to any cause. Patients still alive at the time of analysis (including lost to follow-up) will be censored at the last known alive date. **Recurrence-Free Interval (RFI)** is defined as the time between randomization and the date of local, regional or distant breast cancer recurrence. Patients who are recurrence-free at the time

of analysis will be censored at the date of death or last known alive date.

Distant Recurrence-Free Interval (DRFI) is defined as the time between randomization and the date of distant breast cancer recurrence. Patients without distant disease recurrence at the time of analysis will be censored at the date of death or last known alive date.
Secondary variables will be analyzed in a similar manner as the primary endpoint to estimate 3-year event rates (5-year event rates are planned for OS) for each treatment arm and the HR between the two treatment arms with 95% CI. A testing hierarchy (detailed in the Statistical Analysis Plan) will be used to control the overall type I error rate at 5%.
Analyses will be based on the ITT population.

Exploratory Analyses for Efficacy

Exploratory analyses will be performed for IDFS to ascertain whether the magnitude of the effectiveness of the addition of pertuzumab might differ according to patient sub-populations.

HRQL

HRQL data will be captured using the following questionnaires: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, the breast symptom module QLQ-BR23, and the EQ-5D.
Analysis will be conducted to investigate the changes in HRQL over time. HRQL assessments will be conducted at baseline, at the end of the anthracycline treatment period, at weeks 13 and 25 of the targeted treatment period, at the end of study treatment and 18 months, 2 years, and 3 years after randomization.

Safety Analyses

Patients who receive any amount of study treatment will be included in safety analyses. Safety results will be summarized by the treatment patients actually received.

The safety of pertuzumab in combination with trastuzumab and chemotherapy will be assessed through summaries of AEs, serious AEs (SAEs), cardiac-specific AEs, LVEF measurements, and laboratory test results.

Cardiac-specific AEs will focus on the incidence of patients with heart failure (NYHA, NCI-CTCAE [heart failure] Grades 2, 3, 4, and 5). LVEF data summaries will include the incidence of patients with significant LVEF decreases defined as an absolute decrease of at least 10 percentage points from baseline and to below 50%.

Cardiac AEs will be categorized according to the following endpoint criteria:

Primary cardiac endpoint:

Heart failure NYHA Class III or IV and a drop in LVEF of at least 10 EF points from baseline and to below 50%.

Cardiac death defined as either:

- Definite cardiac death due to heart failure, myocardial infarction or documented primary arrhythmia;

- Probable cardiac death defined as sudden, unexpected death within 24 hours of a definite or probable cardiac event (e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia) without documented etiology.

Secondary cardiac endpoint:

Defined as an asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF by MUGA scan or ECHO, confirmed by a second LVEF assessment within approximately 3 weeks showing also a significant drop OR as confirmed by the APHINITY Cardiac Advisory Board.

Interim Safety Analyses

The IDMC will monitor patient safety, including cardiac criteria at pre-specified times, as well as, at ad hoc meetings if requested.

After the first 200 and 800 patients have been enrolled and treated for 6 months, the IDMC will perform a planned review of heart failure data. If an absolute difference of more than 3% (expected rate of heart failure on trastuzumab plus standard of care chemotherapy = 3%) in the incidence of heart failure NYHA Classes III to IV or definite or probable cardiac death is observed between treatment groups, the IDMC will make recommendations based on the data which may include amending or stopping the trial.

Full details of format and frequency of Interim Safety Analyses for the IDMC are given in the protocol.

Sample Size Calculation

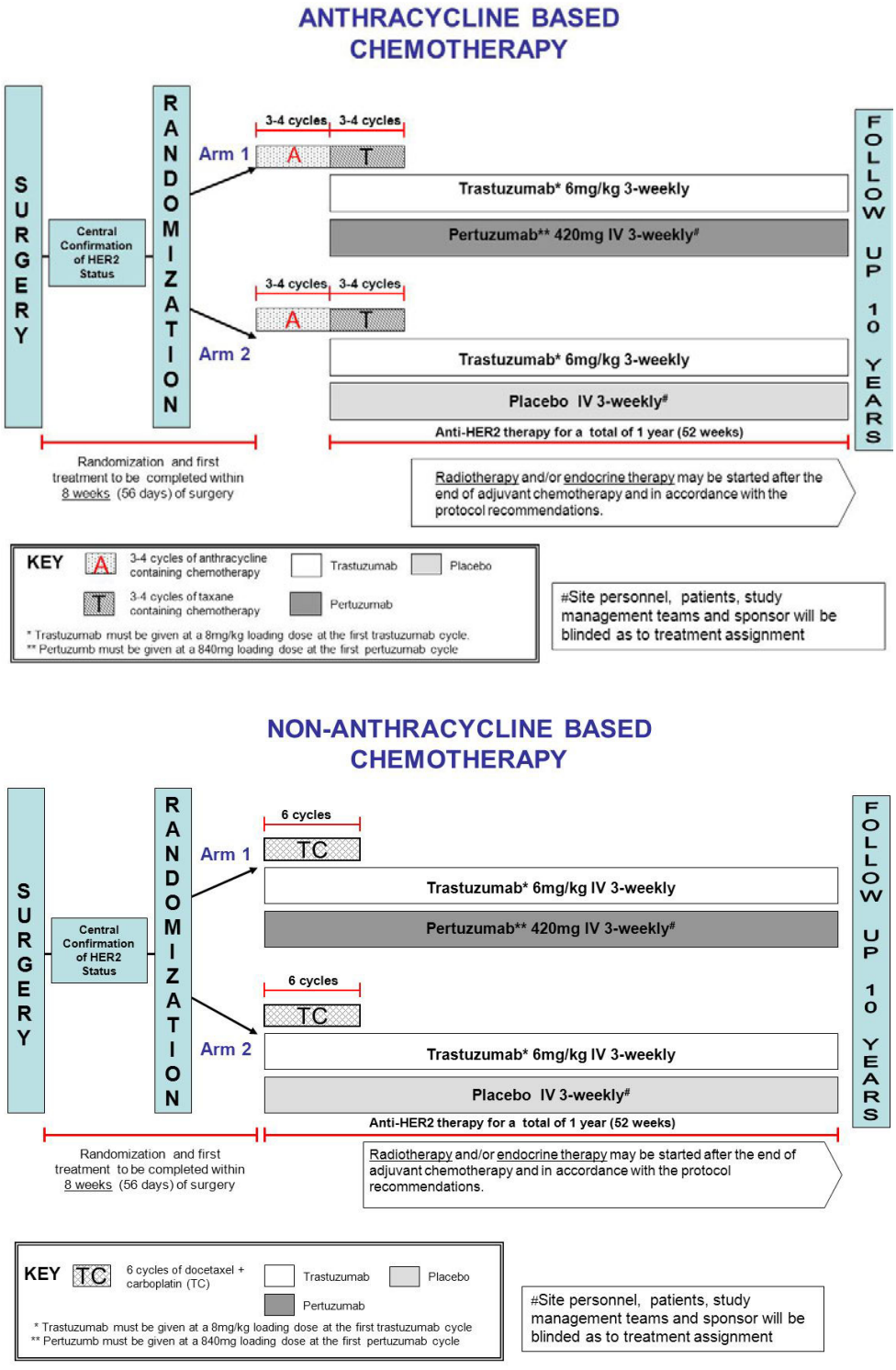
The study is designed to have 80% power to test the null hypothesis of no true difference in risk of an IDFS event (HR = 1) versus the alternative hypothesis of a difference (HR = 0.75) in hazard ratios with a 5%, 2-sided significance level. Under these assumptions approximately 379 IDFS events are required for the primary analysis of IDFS.

The annual decrease in Kaplan-Meier estimates of the invasive disease-free survival function in the trastuzumab control group (regardless of the chemotherapy regimen) is anticipated to be 1.9% during the first year after randomization, 4.5% during Year 2, 4.4% during Year 3, and 1.8% during Year 4 and beyond. Therefore the Kaplan-Meier estimate of IDFS at 3 years for the trastuzumab control group is 89.2%. These assumptions are based on 5 year follow up data from BCIRG006. Under the alternative hypothesis and with the assumption that IDFS for both groups is exponentially distributed, the magnitude of treatment effect in terms of increase in IDFS at 3 years will be 2.6%, meaning a Kaplan-Meier estimate of IDFS at 3 years for the pertuzumab group of 91.8%. The smallest estimated difference detectable at a 5%, 2-sided significance level is HR = 0.818, under which the magnitude of treatment effect will be 1.9%.

As of end of September2012, approximately 1900 patients have been enrolled, at a peak rate of approximately 350 patients per month. It is estimated that following the implementation of protocol Amendment B, the enrollment rate will reduce by

	approximately 50%, as node-negative patients will no longer be enrolled. Under these assumptions, it is planned that 4800 patients will be enrolled over an estimated 25 months, and assuming a 10% drop-out rate, the 379 IDFS events required for the primary analysis will have occurred at 46 months. In order to ensure sufficient data maturity (particularly in patients enrolled after the protocol amendment), in the event that 379 IDFS events are reached sooner than 30 months after last patient enrolled (as is anticipated based on the revised IDFS assumptions), the primary analysis will be delayed until 30 months after last patient randomized.
BIOMARKER RESEARCH SAMPLES	Biomarkers will be evaluated in order to potentially identify patients whose disease is more likely to respond to treatment or those who are more likely to experience toxicity. All patients must consent to fully participate in principle to the translational research project. The following samples will be collected for every patient: – 1 whole blood, 1 serum and 1 plasma sample at baseline (mandatory). – Minimum of 4 and up to 7 × 1-mm cores of FFPE tumor, taken from the definitive surgery sample of the primary tumor containing at least 5 mm of invasive tumor (mandatory). If the disease recurs, the patient will be expected to undergo biopsy for use in central assessment and biomarker analysis unless there is a medical contra-indication • At sites where there is appropriate collection and storage facilities (as determined by the Joint Study Management Team [JSMT]): – Additional serum samples prepared from 10 mL of blood will be collected at defined intervals through study treatment and follow-up until year 10. Non-mandatory blood sample (10 mL) will be collected for genetic analysis (e.g., *FCγR3A, FCγR2A* and *FCγR2B* polymorphisms). If the blood sample is not collected during the scheduled visit, it may be collected at any time (after randomization) during the conduct of the clinical study (subject to additional consent).

Figure 1 Study Design



Schedule of Assessments – Screening and Treatment Period

Non-mandatory assessments are shown in parentheses [ ]	Screening	Base-line	Anthracyclines Treatment Period*	Targeted Treatment Period Within 3 days prior to Day 1 of Cycle Number X											Safety follow-up at the end of treatment 28 days from the last dose of Study medication (a)
Cycle			1-3 or 1-4	1	2	3	4	5	6	7	8	9	13	18	
Beginning of Week			1, 4, 7 or 1, 4, 7, 10	1	4	7	10	13	16	19	22	25	37	52	
Informed Consent (b)	X														
HER2 Determination (c)	X														
Tumor tissue sample (Mandatory) (d)	X														
Whole blood, serum, and plasma sample (biomarker analysis, mandatory) (e)		X	X (end of treat.)				X (s)	X (s)		X (s)		X	X	X	X (t)
Full blood sample for PGx analysis (subject to additional consent) (f)		[X]													
Frozen tissue (optional)	[X]														
Demographic, Medical History	X														
Radiologic Examinations (g): - Mammogram or breast MRI - Chest X-ray or chest CT/MRI/PET - Bone scan (h) - Liver imaging	X (within 6 mos) X (within 6 mos) [X] [X]											[X] [X] [X] [X]		[X] [X] [X] [X]	
Pregnancy Test (i)	X (within 7 d)			Continuously (Every 9 weeks/3 cycles)											[X] (i)
Physical Examination (j)	X		X (cycle 1)	X				X				X	X	X	X
ECOG status (j)	X		X (cycle 1)	X				X				X	X	X	X
Cardiac Monitoring: - ECG (k) - LVEF (l)(m) - Signs/symptoms(m)	X X (within 14 d) X		Every 12 weeks, ideally just prior to the next scheduled cycle in order to confirm adequate cardiac function.												
Quality of Life Assessment (n)	X		X (end of treat.)				X	X		X		X			X
Hematology & Biochemistry (o)	X (within 7 d)		X	X	X	X	X	X	X	X	X	X	X	X	X
Liver function test (p)	X (within 7 d)		X	X	X	X	X	X	X			X	X	X	X
Menopausal status													X		

Non-mandatory assessments are shown in parentheses [ ]	Screening	Base-line	Anthracyclines Treatment Period*	Targeted Treatment Period Within 3 days prior to Day 1 of Cycle Number X	Safety follow-up at the end of treatment 28 days from the last dose of Study medication (a)
Adverse Events (q)	X (if appl.)		Continuously		
Serious Adverse Events (q)	X (if appl.)		Continuously		
Concomitant medications (r)	X		Continuously		

DISEASE RECURRENCE: Patients with local, regional, distant recurrence or contralateral breast cancer should be assessed according to the procedures outlined in Section 5.5.1. Where possible, tumor tissue samples should be collected (see Section 5.5.2). *Serum and plasma samples are MANDATORY*. Thereafter the patient should be followed once a year until Year 10 as described in Section 5.4.1.

* Only applicable to patients receiving anthracycline-based chemotherapy regimens (FEC [FAC] →TH or AC [EC] →TH).

a) 2- day safety follow up visits will optimally be scheduled for 28 days following the last dose of study medication.
b) Written informed consent must be obtained before any study specific screening assessments are performed.
c) HER2 determination should be applied as per the HER2 screening algorithm (Figure 3).
d) FFPE tumor tissue sample is MANDATORY and will also be used for biomarker analysis. A tissue sample collected at definitive breast cancer surgery is acceptable. Sections and/or slides will not be acceptable.
e) A whole blood sample, serum sample and plasma sample for biomarker analysis are MANDATORY and must be collected after randomization, but before the first dose of study treatment is administered. Refer to Section 5.6.2.1.
f) Full blood sample for clinical genotyping, e.g., assessment of Fc-γ receptor polymorphism is OPTIONAL.
g) A bilateral mammogram or breast MRI will be completed yearly from that performed at screening/surgery as per clinical practice, and as clinically indicated upon finding from physical examination. Bilateral mammogram or breast MRI and chest x-ray/CT/MRI/PET is to be performed within 6 months prior to randomization. Bone scan and liver imaging is to be performed if clinically indicated to exclude metastatic disease and within a timeline as per current standard of practice.
h) In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.
i) For all women of childbearing potential, and for all women not meeting the definition of postmenopausal (see Protocol Table 6), and who have not undergone surgical sterilization: a serum β-human chorionic gonadotropin (HCG) test must be performed within 7 days prior to randomization. During the treatment period, a urine pregnancy test must be performed every 9 weeks during targeted treatment (approximately every 3 cycles) and as clinically indicated. For patients that discontinue the targeted treatment before Week 52, a urine pregnancy test must be done at the safety follow-up visit (28 days from the last dose of targeted treatment), and then at 3 months and 6 months post-discontinuation of targeted treatment. Any positive urine pregnancy test must be confirmed via a serum β-HCG test. Treatment period pregnancy test results must be available prior to drug infusion. (See Protocol Table 9 for pregnancy tests required during the follow-up period).

j) Physical examination and ECOG performance status should be measured at baseline and monitored throughout the study. As a minimum these assessments must be done every 3 months, at Cycle 1, Week 13, Week 25, Week 37 and Week 52 of targeted treatment and at the end of treatment safety follow-up visit. These assessments may be done at more frequent intervals if clinically indicated. Physical examination includes height (at baseline only), weight and vital signs (blood pressure, pulse rate and body temperature). Weight is to be measured on Day 1 of the specified cycles and compared to baseline. If ± 10% variation occurs then trastuzumab and chemotherapeutic doses will be recalculated.

k) ECGs are required to allow assessment prior to Cycle 1 and after the completion of therapy or at the week 52 visit in conjunction with the other cardiac assessments. Additional ECGs to be performed as clinically indicated.

l) LVEF assessment by ECHO is preferred, but LVEF can also be assessed by MUGA. The same method should be used throughout the study for each patient and preferably performed and assessed by the same assessor. At baseline, LVEF must be done within 14 days prior to randomization. During study treatment, all assessments will be performed between Days 15-21 of the previous cycle to allow evaluation of the results before the indicated cycle. (Please note that the LVEF should be done as close to the assigned week as possible but prior to the next infusion). For patients receiving anthracyclines, an additional LVEF assessment must be performed before commencing anti HER2 therapy. The Week 52 assessment should occur at Week 52±7days. The assessment should be done at the indicated week, not at the cycle.

m) For patients receiving anthracycline therapy: cardiac signs/symptoms and an additional LVEF assessment must be completed after the last cycle of anthracycline is administered, but prior to the first cycle of targeted treatment. Patients treated with anthracyclines must have an LVEF ≥50% prior to commencing the HER2-targeted component of therapy.

n) Quality of life assessments are MANDATORY and include three questionnaires: EORTC QLQ-C30, QLQ-BR23 and EQ-5D. Quality of life assessment to be collected at the end of taxane treatment, either prior to Cycle 4 or Cycle 5 of targeted treatment for patients who receive taxanes sequentially after anthracyclines; or prior to Cycle 7 of targeted treatment for patients receiving TCH therapy.

o) Hematology and biochemistry should be completed pre-dose on Day 1 of each indicated cycle (or up to 3 days before). Hematology tests (complete blood count) include counts of hemoglobin, white blood cells, neutrophils and platelets. Biochemistry tests include serum creatinine, blood urea nitrogen and electrolytes (P-, Ca2+, Mg2+, Na+, K+, Cl-). At baseline, hematology and biochemistry should be completed within 7 days prior to randomization (and do not need to be repeated within 3 days before first infusion only).

p) Liver function tests include: ALP, ASAT, ALAT, LDH; and total, direct and indirect bilirubin. At baseline, liver function tests should be completed within 7 days prior to randomization.

q) AE and SAEs will be collected from the start of study screening procedures. All non-serious AEs occurring prior to study Day 1 (administration of study treatment) will be reported in the medical history, unless AE reporting is deemed more appropriate. Adverse events are to be monitored continuously during study treatment. All AEs occurring during the study and until the end of treatment/treatment discontinuation visit 28 days after the last dose of study medication are to be recorded and followed up until resolution or until the end of study, whichever occurs first; thereafter only drug-related SAEs and AEs/SAEs that qualify for long-term reporting should continue to be collected (see Section 7.1.2 for details).

r) Concomitant medication will be recorded in the interval beginning 7 days prior to the patient being randomized into the study until the end of the treatment period, and thereafter followed-up as specified in Section 4.4. If a patient has a recurrence, any anti-cancer medication given after the date of diagnosis must be recorded on the post treatment anti-cancer medication page.

s) Refer to Section 5.6.2.1.

t) *A serum sample must be collected for all patients* during the safety follow-up visit 28 days from the last dose of targeted treatment*, including those* patients who drop out of the targeted treatment before Week 52.

Schedule of Assessments – Follow-Up Period*

Assessments shown in parentheses [ ] to be performed as clinically indicated	Follow-up Every three months (± 28 days)				Follow-up Every six months (± 28 days)						Follow-up Every 12 months (± 42 days)
	Month 15	Month 18	Month 21	Month 24	Month 30	Month 36	Mon h 42	Month 48	Mon h 54	Month 60	Year 6 until Year 10 *
Radiologic Examinations: - Chest X-ray - Bone scan (a) - Liver imaging - Mammogram (b)		[X] [X] [X]		[X] [X] [X] X	[X] [X] [X]	[X] [X] [X] X		[X] [X] [X] X		[X] [X] [X] X	[X] [X] [X] X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X
Serum sample (biomarker analysis)						[X]				[X]	[X] (h)
Pregnancy Test (urine)	X	X									
Menopausal Status		*X*									
Quality of Life Assessment (c)		X		X		X					
Cardiac Monitoring: - ECG - LVEF - Signs/symptoms		[X] X X		[X] X X	[X] X X	[X] X X		[X] X X		[X] X X	[X] X X
Hematology and Biochemistry (d) - Liver function tests (e)		X X		X X	X X	X X	X X	X X	X X	X X	X X
SAEs (f)	Con inuously										
Concomitant medications (i)	Con inuously										
Record post recurrence anticancer related therapies	Continuously post recurrence (g)										
Survival*	Yearly										

This table applies to all patients who either complete all study treatment (chemotherapy and targeted) or who discontinue chemotherapy early (i.e. who have not received a dose of targeted treatment). For those patients who discontinue targeted treatment early, the Schedule of Assessments—Follow-up Period applies once they have completed the 28-day follow-up visit and the subsequent Schedule of Assessments—Treatment Period (Patients Who Discontinue Study [(Targeted) Treatment]). Visits are scheduled relative to C1D1 of targeted treatment. Patients who discontinue treatment at the chemotherapy stage, once they have completed the 28-day follow-up visit will then follow the Schedule of Assessments—Follow-

up Period, but are only followed for SAEs, concomitant medications, subsequent anticancer therapies and survival. For these patients, visits are scheduled relative to last dose of study medication.

DISEASE RECURRENCE: Patients with local, regional, distant recurrence or contralateral breast cancer should be assessed according to the procedures outlined in Section 5.5.1. Where possible, tumor tissue samples should be collected (see Section 5.5.2). *Serum and plasma samples are MANDATORY*. Thereafter the patient should be followed once a year until Year 10 as described in Section 5.4.1.
*All patients irrespective of treatment allocation should be followed for survival yearly from completion/ discontinuation of treatment period (28 days following the last dose of study medication) until 10 years after the original randomization of the last patient. For this reason patients recruited early in the study may be followed for more than 10 years. For these patients annual follow-up should continue beyond 10 years, as per the assessment schedule specified in this table for 'Years 6 until Year 10'.

a) In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.
b) Mammogram to be performed annually as per local practice.
c) Quality-of-life assessments include the EORTC QLQ-C30, QLQ-BR23 and EQ-5D questionnaire.
d) Hematology tests (complete blood count) include counts of hemoglobin, white blood cells, neutrophils and platelets. Biochemistry tests include serum creatinine, blood urea nitrogen and electrolytes.
e) Liver function tests include: ALP, ASAT, ALAT, LDH; and total, direct and indirect bilirubin.
f) Any AEs and SAEs that are ongoing 28 days after the last dose of study treatment, or new AEs or SAEs requiring long-term reporting, should be followed and reported as described in Section 7.1.2.
g) Information on treatment for breast cancer should be collected for all patients with disease recurrence until 10 years from the original randomization of the last patient. Follow-up after study treatment termination includes survival follow-up and reporting of post study anticancer treatments until the patient withdraws from the study including survival follow up, lost to follow up or death.
h) Serum sample for biomarker analysis *is only* taken at Year 10.
i) Concomitant medications requiring reporting in the follow up period are specified in Section 4.4 (medication applicable for long-term reporting).

Schedule of Assessments –Treatment Period (Patients Who Discontinue Study [Targeted Treatment])

Non-mandatory assessments are shown in parentheses [ ]		Weeks											
Beginning of Week		1	4	7	10	13	16	19	22	25	37	52	
Serum, sample (biomarker analysis) (a)						X		X		X	X	X	
Radiologic Examinations (b): - Mammogram or breast MRI - Chest X-ray or chest CT/MRI/PET - Bone scan (c) - Liver imaging										[X] [X] [X] [X]		X [X] [X] [X]	
Pregnancy Test (d)		Continuously (Every 9 weeks/3 cycles) until 6 months after *study drug* discontinuation											
Physical Examination (e) ECOG status (e)						X X				X X	X X	X X	
Cardiac Monitoring: - ECG (f) - LVEF (g) - Signs/symptoms						[X] X X				[X] X X	[X] X X	X X X	
Quality of Life Assessment (h)						X				X			
Hematology & Biochemistry (i) Liver function test (j)						X X				X X	X X	X X	
Menopausal status											X		
Adverse Events (k)	Record continuously until 28 days after discontinuation												
Serious Adverse Events (k)	Record continuously until 28 days after discontinuation												

This table lists the Schedule of Assessments for patients discontinuing targeted treatment early. Safety follow-up should be conducted 28 days after the last dose of targeted treatment. Thereafter the patient should follow Schedule of Assessments—Treatment Period (Patients Who Discontinue Study [(Targeted) Treatment]) until week 52 from the start of targeted treatment dosing has been reached; the patient will then follow the Schedule of Assessments—Follow-Up Period.

DISEASE RECURRENCE: Patients with local, regional, distant recurrence or contralateral breast cancer should be assessed according to the procedures outlined in Section 5.5.1. Where possible, tumor tissue samples should be collected (see Section 5.5.2). *Serum and plasma samples are MANDATORY*. Thereafter the patient should be followed once a year until Year 10 as described in Section 5.4.1.

a. Additional serum sample collection during treatment and at the 28-day safety follow-up visit must be done for all patients if the site has appropriate storage facilities. Refer to the lab manual. See Section 5.6.2.1.

b. Bilateral mammogram or breast MRI and chest x-ray/MRI/PET/CT is to be performed within 6 months prior to randomization. Bone scan and liver imaging is to be performed if clinically indicated to exclude metastatic disease and within a timeline as per current standard of practice.
c. In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.
d. For patients that discontinue the targeted treatment before Week 52, a urine pregnancy test must be done at the safety follow-up visit (28 days from the last dose of targeted treatment), and then every 3 months thereafter until 6 months after the discontinuation of targeted treatment. Any positive urine pregnancy test must be confirmed via a serum β-HCG test. (See Protocol Table 9 for pregnancy tests required during the follow-up period).
e. Physical examination and ECOG performance status should be measured at baseline and monitored throughout the study. As a minimum these assessments must be done every 3 months, at Cycle 1, Week 13, Week 25, Week 37 and Week 52 of targeted treatment and at the end of treatment safety follow-up visit. These assessments may be done at more frequent intervals if clinically indicated. Physical examination includes height (at baseline only), weight and vital signs (blood pressure, pulse rate and body temperature).
f. ECGs are required to allow assessment prior to and after the completion of therapy. Additional ECGs to be performed as clinically indicated.
g. LVEF assessment by ECHO is preferred, but LVEF can also be assessed by MUGA. The same method should be used throughout the study for each patient and preferably performed and assessed by the same assessor. At baseline, LVEF must be done within 14 days prior to randomization. During study treatment, all assessments will be performed between Days 15-21 of the cycle to allow evaluation of the results before the next treatment cycle. For patients receiving anthracyclines, an additional LVEF assessment must be performed before commencing anti HER2 therapy. The Week 52 assessment should occur at Week 52 ±7days.
h. Quality of life assessments are MANDATORY and include three questionnaires: EORTC QLQ-C30, QLQ-BR23 and EQ-5D.
i. Hematology tests (complete blood count) include counts of hemoglobin, white blood cells, neutrophils and platelets. Biochemistry tests include serum creatinine, blood urea nitrogen and electrolytes. At baseline, hematology and biochemistry should be completed within 7 days prior to randomization.
j. Liver function tests include: ALP, ASAT, ALAT, LDH; and total, direct and indirect bilirubin.
k. AEs and SAEs are to be monitored continuously during study treatment. All AE/SAEs occurring during the study and until the end of treatment/treatment discontinuation visit 28 days after the last dose of study medication are to be recorded, but are to be followed up until resolution or until the end of study, whichever occurs first; thereafter only drug-related SAEs and AEs/SAEs that qualify for long-term reporting should continue to be collected (see Section 7.1.2 for details).

GLOSSARY OF ABBREVIATIONS: BIG 4-11 / BO25126 / TOC4939G

AC →T	Standard chemotherapy regimen comprised of 3–4 cycles of anthracycline and cyclophosphamide followed by 3–4 cycles of a taxane treatment. This type of treatment is described as sequential treatment.
ACE	Angiotensin-converting enzyme
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activities of daily living
AE	Adverse event
ALND	Axillary lymph node dissection
ALP	Alkaline phosphatase
ALAT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
ARDS	Acute Respiratory Distress Syndrome
ASAT (SGOT)	Aspartate aminotransferase
AUC	Area Under the Plasma Concentration–Time Curve
BIG	Breast International Group
BWFI	Bacteriostatic water for injection
CHF	Congestive heart failure
CHO	Chinese hamster ovary
CI	Confidence interval
CISH	Chromogenic in situ hybridization
CR	Complete response
CT	Computer tomography
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DRFI	Distant recurrence-free interval

GLOSSARY OF ABBREVIATIONS: BIG 4-11 / BO25126 / TOC4939G

ECD	Extra-cellular domain (of the HER2 receptor)
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalogram
e-Form	Electronic Form (page)
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
ER	Estrogen receptor
ESF	Eligibility screening form
EU	European Union
FAC	A standard therapy for breast cancer consisting of 5-fluorouracil, doxorubicin and cyclophosphamide
FEC	A standard therapy for breast cancer consisting of 5-fluorouracil, epirubicin and cyclophosphamide
FEC →T	Sequential chemotherapy, consisting of courses of FEC chemotherapy followed by courses of taxane
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
5-FU	5-fluorouracil
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate

GLOSSARY OF ABBREVIATIONS: BIG 4-11 / BO25126 / TOC4939G

H_0	Null hypothesis
H_1	Alternative hypothesis
HCG	Human chorionic gonadotropin
HER1	Human epidermal growth factor receptor 1
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQL	Health-related quality of life
IB	Investigator's brochure
ICH	International Conference on Harmonization
IDFS	Invasive disease-free survival
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
INN	International non-proprietary name
IMP	Investigational medicinal product
IWRS	Interactive Web Based Response System
JSMT	Joint study management team
JVP	Jugular venous pressure
TKI	Tyrosine kinase inhibitor
IDCC	Independent Data Coordinating Center
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITC	Isolated tumor cells
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous

GLOSSARY OF ABBREVIATIONS: BIG 4-11 / BO25126 / TOC4939G

LCIS	Lobular carcinoma in situ
LDH	Lactic dehydrogenase
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MBC	Metastatic breast cancer
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance image
MTD	Maximum tolerated dose
MUGA	Multiple-gated acquisition
NCI	National Cancer Institute
NCI–CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NSABP	National Surgical Adjuvant Breast Project
NSAIDS	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
pCR	Complete pathological response
PD	Progressive disease or pharmacodynamic
PET	Positive emission tomography
PgR	Progesterone receptor
PK	Pharmacokinetic
PR	Partial response
PRO	Patient reported outcome
qw	Every week
q3w	Every 3 weeks

GLOSSARY OF ABBREVIATIONS: BIG 4-11 / BO25126 / TOC4939G

RFI	Recurrence-free interval
RT	Radiotherapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SNB	Sentinel lymph node biopsy
SND	Sentinel lymph node dissection
SOP	Standard operating procedure
SUSAR	Suspected, Unexpected Serious Adverse Reaction
SWFI	Sterile water for injection
TAC	Standard chemotherapy regimen comprising **t**axane, **a**nthracycline and **c**yclophosphamide given separately on one day, known as concurrent chemotherapy
TCH	Commonly used chemotherapy regimen for HER2 positive breast cancer combination comprising taxane (Taxotere®), carboplatin and trastuzumab (Herceptin®)
TNM	Primary tumor/regional lymph nodes/distant metastasis
T_{max}	Time to maximum plasma concentration
TR	Translational research
ULN	Upper Limit of Normal
WBC	White blood cell

1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Breast Cancer

Breast cancer is the most common cancer in women and the second most common cause of cancer-related death in women worldwide. The GLOBOCAN 2008 data show that breast cancer is by far the most frequent cancer among women with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and ranks second overall (10.9% of all cancers). It is the most commonly occurring neoplasm in women, accounting for over one fifth of the estimated annual 4.7 million cancer diagnoses in females, and the second most common tumor, after lung cancer, in both sexes. It is also the most common female cancer in both developing and developed countries, with most (55%) occurring in the latter regions, where age-standardized rates are three times higher than in developing areas [Ferlay, 2008] [16]. Mammographic screening for women aged 50–69 years is effective in reducing breast cancer mortality, and reductions in mortality have been observed where screening has been introduced [Shapiro, 1998; IARC, 2002] [55, 35].

1.1.2 Role of HER Family of Receptors

The human epidermal growth factor receptor (HER) family of membrane receptors are important mediators of normal cell growth, survival and differentiation (see the trastuzumab Investigator's Brochure [IB]). The HER family of receptors are activated by the action of external ligands, interactions (dimerization) with other HER family members, and specifically in the case of HER2, by proteolytic cleavage of the extracellular domain (shedding) or by dimerization with one or other of the HER receptors, particularly HER3. About 18% of breast cancers overexpress HER2 and these tumors appear to be driven by HER2 signaling as they have a poor prognosis when treated with standard chemotherapy regimens compared to the prognosis associated with breast cancers that do not overexpress HER2 [Slamon, 1987] [60]. Breast cancers that overexpress HER2 have been shown to be susceptible to treatment with the monoclonal antibody trastuzumab (Herceptin®). Trastuzumab binds to the juxta-membrane epitope (domain IV) of the HER2 extracellular domain, preventing cleavage and signal transduction. Trastuzumab is registered in many countries for the adjuvant treatment of breast cancer.

HER2 is also known to play a role in the normal development of myocardial tissue and in the repair of damaged myocardium [Sawyer et al 2002; Zhao et al 2006; Timolati et al 2006] [54, 72, 64].

1.2 Study Treatment: Pertuzumab

Pertuzumab (rhuMab 2C4) is a humanized monoclonal antibody based on human immunoglobulin G1 (IgG1) framework sequences and consists of two heavy chains (449 amino acid residues) and two light chains (214 residues). Like trastuzumab, pertuzumab is produced in Chinese hamster ovary (CHO) cells and is directed against the extracellular domain of HER2. However, it differs from trastuzumab in the epitope-binding regions of the light chain (12 amino acid differences) and heavy chain

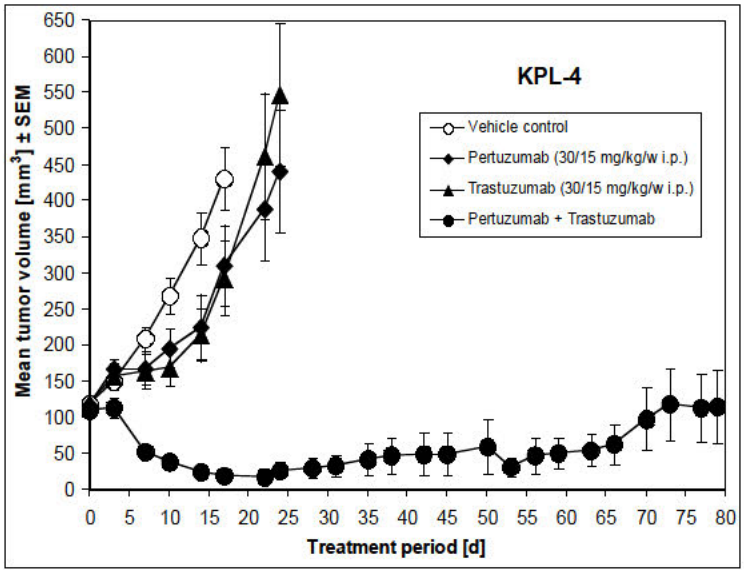
(29 amino acid differences). As a result, pertuzumab binds to the dimerization epitope of the HER2 receptor, thereby inhibiting dimerization of HER2 with HER2 and other HER family receptors. The modes of action of trastuzumab and pertuzumab are complementary.

In addition to blocking signal transduction, both pertuzumab and trastuzumab are capable of inducing antibody-dependent cell-mediated cytotoxicity (ADCC). Pertuzumab is an investigational compound.

1.2.1 Nonclinical Experience with Pertuzumab

Pertuzumab showed activity in xenograft models of various tumor origins, like breast, lung and prostate cancer. In addition, pertuzumab demonstrated synergistic anti-tumor activity in combination with trastuzumab in HER2-positive breast and lung cancer xenograft models (see Figure 1; [Friess, 2005] [21]). The synergistic efficacy can be explained by the two antibodies' complementary mechanisms of action: while trastuzumab inhibits HER2 extracellular domain shedding, an activation mechanism of HER2, pertuzumab can inhibit the dimerization of HER2 with ligand-activated HER family members like HER3 and HER1.

Figure 1 Pertuzumab plus Trastuzumab Combination Therapy in a HER2-Positive Human Breast Cancer Xenograft Model



Teratology findings in the nonclinical reprotoxicity study in cynomolgus monkeys showed embryo/fetal losses, low amniotic fluid volume (oligohydramnios), and microscopic evidence of delayed renal development (renal hypoplasia) in all pertuzumab-treated groups. The findings were consistent with evidence that antibodies can be transported across the placenta during the period of organogenesis in the cynomolgus monkey (for more information, see the pertuzumab IB).

1.2.2 Clinical Experience with Pertuzumab in HER2-Positive Breast Cancer

Study BO17929 was a two-stage, Phase II study of patients with HER2-positive metastatic breast cancer whose disease had progressed on trastuzumab therapy [Gelmon, 2008; Baselga, 2009] [23, 6]. Patients received a combination of trastuzumab (either weekly or three weekly dosing) and pertuzumab with a loading dose of 840 mg and maintenance dose of 420 mg every three weeks (q3w). The data from the first two cohorts of this study showed good clinical activity (complete response [CR]: 6%, partial response [PR]: 18% and stable disease [SD] ≥ 6 months: 26%). Tolerability was good with no patients withdrawn for treatment-related adverse experience. In a study of similar design [Portera, 2007] [49], a similar level of efficacy (18% response rate) was observed. A third cohort of patients was added to BO17929, in which patients received only pertuzumab, but were allowed to have trastuzumab re-introduced if the tumor did not respond to pertuzumab alone, or responded and then relapsed. The data from this cohort showed that pertuzumab without trastuzumab has anti-tumor activity, but that the two antibodies together are better than either alone [Baselga, 2009] [6].

The primary analysis of a Phase II study (Study WO20697 "NEOSPHERE") has been completed. In this study, eligible patients with newly diagnosed HER2-positive breast cancer were randomized to receive either A) trastuzumab/docetaxel (reference treatment) or B) trastuzumab/docetaxel and pertuzumab (primary comparison arm) or C) trastuzumab/pertuzumab without chemotherapy or D) pertuzumab/docetaxel. After four cycles of study treatment, patients then underwent surgery, the primary endpoint of the study being pathological complete response (pCR) rate at surgery. Following surgery, patients completed chemotherapy and treatment to one year with trastuzumab so that all patients received overall standard therapy as a minimum. The main therapeutic result showed a very high rate of tumor eradication in the breast when pertuzumab was added to conventional trastuzumab and docetaxel treatment: 45.8 % for the triplet regimen (arm B) and 29% for the comparator arm (arm A). pCR accounted for 16.8% in women receiving the two monoclonals (arm C) without chemotherapy, and 24% in arm D when pertuzumab and docetaxel were used [Gianni, 2010] [26].

The data from NeoSphere confirm that both trastuzumab and pertuzumab are active against HER2-positive breast cancer when given with docetaxel, and that the two antibodies given together are more active than either alone when given with docetaxel.

The pathological complete response data from this study are shown in Table 1.

Table 1 Pathological Complete Response Rates, Study WO20697 / NEOSPHERE

	Arm A trastuzumab/docetaxel n = 107	Arm B trastuzumab/docetaxel /pertuzumab n = 107	Arm C trastuzumab /pertuzumab n = 107	Arm D pertuzumab /docetaxel n = 96
pCR rate in the breast	29.0%	45.8%	16.8%	24.0%
		Primary statistical comparison: Arm B vs. Arm A P = 0.0141		

A further Phase II tolerability study, BO22280 (TRYPHAENA) has been initiated – in this study the tolerability of pertuzumab in combination with standard chemotherapy regimens, (i.e., anthracycline/cyclophosphamide then taxane with trastuzumab [AC→T with trastuzumab] and Taxotere®/carboplatin/Herceptin® [TCH]) will be investigated.

In the Phase III pivotal study WO20698/TOC4129g (CLEOPATRA), a randomized, multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive metastatic breast cancer, patients were randomized in a 1:1 ratio to receive placebo plus trastuzumab and docetaxel or pertuzumab plus trastuzumab and docetaxel.

The primary endpoint of the randomized trial was progression-free survival (PFS) as assessed by an independent review facility (IRF). The randomized trial demonstrated a statistically significant improvement in IRF-assessed PFS in the pertuzumab-treated group compared with the placebo-treated group (hazard ratio [HR] =0.62 [95% CI: 0.51, 0.75, $p < 0.0001$]) and an increase in median PFS of 6.1 months (median PFS of 18.5 months in the pertuzumab-treated group vs. 12.4 months in the placebo-treated group). A second interim analysis of overall survival (OS) was performed 1 year after the primary PFS analysis, applying the Lan-DeMets α-spending function with the O'Brien-Fleming (OBF) stopping boundary to maintain the overall Type I error at 5%. Based on the number of OS events observed, the OBF boundary for statistical significance at this analysis was $p \leq 0.0138$. The results showed a statistically significant improvement in OS in favor of the pertuzumab + trastuzumab + docetaxel arm compared with the placebo + trastuzumab + docetaxel arm (HR, 0.66; p=0.0008; 95% CI, 0.52–0.84). This analysis has achieved statistical significance. The median OS was 37.6 months in the placebo + trastuzumab + docetaxel and has not yet been reached in the pertuzumab + trastuzumab + docetaxel arm.

Another randomized study with pertuzumab is ongoing: Study MO22324/(PHEREXA), in which pertuzumab is added to trastuzumab and capecitabine as second-line therapy in patients with metastatic HER2-positive breast cancer.

1.2.3 Pertuzumab Safety Data

As of 10 November 2010 (data cut-off date for the IB *version current at the time of the original protocol*), approximately 1327 patients have been exposed to pertuzumab (excluding studies that are still blinded). The majority of adverse events (AE)s

experienced by these patients were NCI-CTCAE (National Cancer Institute – Common Terminology Criteria for AEs) Grade 1 or 2 in severity. The most commonly reported AEs in single-agent Phase II studies, regardless of causality, were diarrhea, fatigue, nausea, abdominal pain, and vomiting (>20% of patients).

*Further d*etails *and updated* safety data can be found in the *current* IB. A high-level summary *based on the 10 November 2010 cutoff* is presented below.

1.2.3.1 Pertuzumab in Combination with Trastuzumab

Pertuzumab in combination with trastuzumab has been generally well tolerated (Study BO17929). The most common AEs reported were diarrhea (64%), fatigue (33%), nausea (27%) and rash (26%). In this study there were no clinically significant cardiac events. However, in a study of similar design, conducted in the United States, a patient with extensive invasion of the chest wall by breast cancer experienced congestive cardiac failure [Portera, 2007] [49]. In this study, the selection criteria with respect to baseline cardiac function and prior therapy differed from those in Study BO17929.

1.2.3.2 Pertuzumab in Combination with Docetaxel

Based on data from a Phase Ib study (Study BO17021), pertuzumab appears to be well tolerated in combination with docetaxel up to a dose of 75 mg/m^2. Table 2 shows the dose levels assessed in this study.

Table 2 Dose Levels in Study BO17021

Dose Level	Pertuzumab (mg)	Docetaxel (mg/m² q3w)	Planned no. of Patients	Patients Treated
1	1050	60	3–6	6
2	1050	75	6	2
2A	420*	75	6	6
3A	420*	100	6	5

*Loading dose of 840 mg in Cycle 1. The 420 mg dose was introduced by amendment after results of Phase II single-agent studies suggested no difference in toxicity or efficacy between the 420 mg and 1050 mg doses.

Dose-limiting toxicities (DLTs) were observed in the first two patients treated in Dose Level 2: Grade 3 diarrhea and fatigue in one patient and febrile neutropenia (absolute neutrophil count [ANC] 0.4 x 109/L) in the second patient. An additional three patients were enrolled to Dose Level 1. No dose-limiting toxicities were observed in these three additional patients. In Dose Level 3A, two patients developed DLTs in Cycle 1 (Grade 4 febrile neutropenia in one patient, and Grade 3 fatigue in the second patient). Thus, in the BO17201 study, the maximum tolerated dose (MTD) of docetaxel in combination with pertuzumab (420 mg dose) was determined to be 75 mg/m^2.

It is recognized that:

a) the registered dose of docetaxel in combination with trastuzumab is 100 mg/m^2 and there is evidence that outcomes might be improved when higher doses of docetaxel are given [Harvey, 2006] [31]

b) the DLTs in study BO17021 were not life threatening.

c) the exposure to docetaxel is highly variable between patients.

1.2.3.3 Pertuzumab in Combination with Carboplatin and Taxane (Paclitaxel)

Pertuzumab has been used in combination with carboplatin and paclitaxel in a study in patients with relapsed, platinum-sensitive ovarian cancer (Study BO17931). Although this study did not meet its efficacy endpoint, the tolerability was found to be generally good (details are provided in the IB).

1.2.4 Serious Adverse Events

Amongst the approximately 1327 patients exposed to pertuzumab, there have been 156 serious adverse events (SAEs) assessed as related to pertuzumab by Investigators and/or the Sponsor (see IB for further details). Eight of these treatment-related SAEs were reported as life-threatening: congestive cardiac failure and anaphylactic reaction in a patient with platinum-resistant ovarian cancer in study TOC3258g; myocardial infarction in a patient enrolled in the Phase I dose escalation study TOC2297g; pulmonary embolism in the Phase Ib study BO17003; cardiac failure (left ventricular ejection fraction [LVEF] 27%) in a patient with relapsed non-small cell lung cancer (NSCLC) and a baseline LVEF of 51% in study TOC4603g; hypersensitivity reaction with bronchospasm and hypertensive derailment after administration of pertuzumab in study BO22280; cardiac arrest in a patient with advanced metastatic breast cancer (MBC) in study TDM4688g; and ventricular fibrillation in a patient in study WO20698/TOC4129g.

Eight SAEs reported as treatment-related had a fatal outcome: acute respiratory distress syndrome (ARDS) in a patient with advanced NSCLC in study TOC2572g (considered an infusion-associated event); gastrointestinal hemorrhage in a patient with platinum-sensitive ovarian cancer in study BO17931; hemolytic uremic syndrome in a patient with prostate cancer in study BO17004; hepatitis in a patient with breast cancer in study WO20697 who was concomitantly receiving drugs known to have hepatotoxic potential including docetaxel and an antihypertensive treatment (the investigator assessed the hepatitis to be related to both drugs); somnolence in a patient with metastatic breast cancer in study WO20698/TOC4129g; cardiac ischemia and cardiac infarction in a patient with metastatic colorectal cancer in study TOC4163s; and malignant neoplasm progression in a patient with MBC in study TOC3487s.

An additional case (cardiotoxicity) was extracted from a publication by Portera et al 2008 [50], where it was stated that the patient died of progressive disease with congestive heart failure two months after treatment termination. This corresponds to a non-fatal SAE of ejection fraction decrease (Grade 3) reported by the principal investigator of the National

Cancer Institute (NCI)-sponsored study, TOC3487s, of pertuzumab and trastuzumab in HER2 positive breast cancer.

1.2.4.1 Decrease in LVEF and Heart Failure

Because pertuzumab targets HER2, as with trastuzumab, there is a potential risk of cardiac side effects, particularly in patients who have received prior anthracycline treatment. All patients enrolled in pertuzumab studies undergo routine cardiac monitoring by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan. Overall, the data so far show that pertuzumab as a single agent, or combined with other therapies (trastuzumab or cytotoxic chemotherapy) has an acceptable cardiac safety profile.

The cardiac side-effect profile appears to be similar to that of trastuzumab, and combination of the two antibodies has not increased the rate of cardiac events in patients studied so far.

The incidence of cardiac dysfunction has been assessed using the following criteria: an absolute decrease from baseline of ≥10 percentage points in left ventricular ejection fraction (LVEF) to a value of <50% at any post-baseline LVEF assessment. Using this definition, the majority of patients with cardiac dysfunction were asymptomatic and have shown improvement or return to baseline function on follow-up, in line with the experience with trastuzumab.

The rate of asymptomatic declines was similar across all studies where the primary analysis has been completed:

- 5.9% (20/341) for all Phase I and II single agent studies.
- 0% (0/15) for pertuzumab in combination with erlotinib.
- 1.9% (5/269) for pertuzumab in combination with cytotoxic chemotherapy.
- 3.0% (6/202) for pertuzumab in combination with trastuzumab.
- 2.8% (3/107) for pertuzumab in combination with cytotoxic chemotherapy and trastuzumab.

To minimize the risk of cardiac problems, only patients who have adequate cardiac function at baseline (LVEF ≥55%) will be enrolled into the planned study. In addition, patients who have particular cardiac risk factors will be excluded.

1.2.4.2 Infusion-Associated Reactions

Infusion-associated reactions typically occur during or shortly after infusions of monoclonal antibodies.

Ten treatment-related SAEs (in <1% of all treated patients) occurring during, or on the day of pertuzumab infusion, have been identified as compatible with infusion-associated reactions/hypersensitivity/anaphylaxis reactions based on individual medical review of all completed and ongoing studies (excluding those for which treatment is still blinded) Disease progression and co-administered chemotherapy (gemcitabine) were possible contributing factors in several of these cases (see the IB for details of each case).

1.2.5 Pharmacokinetics of Pertuzumab

Pertuzumab has shown a similar pharmacokinetic (PK) profile across studies, with no change in clearance at doses from 2.0–15.0 mg/kg (140 mg–1050 mg for a 70-kg patient). A two-compartment model adequately describes the concentration–time data with a systemic serum clearance of ~0.24 L/day and a terminal half-life of ~17.3 days for a typical patient. Based on these data, a dosing interval of 3 weeks is supported in clinical studies. In the Phase II studies, a loading dose of 840 mg (followed by 420 mg q3w), was capable of attaining steady-state trough and peak concentrations by the second cycle. Population PK modeling of data from Phase Ia and Phase II studies supports the continued use of fixed, non–weight-based dosing in female patients [Ng, 2006] [44]. In Phase Ib and II studies completed thus far, there was no evidence of an impact of pertuzumab on the pharmacokinetics of co-administered gemcitabine, docetaxel, capecitabine or erlotinib.

1.3 Study Treatment: Trastuzumab

Trastuzumab (Herceptin®) is a recombinant humanized anti-p185^{HER-2} monoclonal antibody that binds with high affinity to the HER2 protein. In most of the world, trastuzumab is licensed in combination with docetaxel as first-line therapy of HER2-positive metastatic breast cancer, where a significant survival benefit has been demonstrated for the combination compared with chemotherapy alone [Slamon, 2001; Marty, 2005] [61, 42]. Based on the data generated in the HERA Study [Study BO16348] [Piccart-Gebhart, 2005] [47], trastuzumab is registered in the European Union (EU) and in many other countries for use following adjuvant chemotherapy. Other data confirm that trastuzumab in combination with chemotherapy is associated with improved outcomes following adjuvant therapy of HER2-positive breast cancer, and that the improvement is possibly greater when the trastuzumab is integrated with the taxane part of the adjuvant therapy as compared to the sequential use [Romond, 2005; Perez, 2009] [52, 46].

Details of the use of trastuzumab are to be found in the trastuzumab IB and in the Herceptin® prescribing information.

1.3.1 Trastuzumab Safety Data

Details of the adverse experience associated with the clinical use of trastuzumab are to be found in the trastuzumab IB. In order to minimize the risk of cardiac dysfunction, only patients who have adequate cardiac function (LVEF ≥55%) will be enrolled, and patients with particular cardiac risk factors will be excluded.

1.3.2 Pharmacokinetic Data Supporting Trastuzumab Administration Every 3 Weeks

Analyses in clinical studies showed that trastuzumab has dose-dependent, nonlinear PK, with dose-dependent clearance and half-life. The volume of distribution approximates the serum volume *and steady-state is reached by approximately 20 weeks (95% CI 18–24 weeks). Based on population PK analyses, a*t therapeutic doses, the half-life is approximately *28–38* days. *Accordingly, the recommended washout*

period (5 elimination half-lives, based on a conservative estimate of half-life) is 27 weeks (190 days).

There are two approved dose regimens of trastuzumab: 4 mg/kg initial dose followed by a 2 mg/kg dose qw (every week); and 8 mg/kg initial dose followed by a 6 mg/kg dose q3w. The approval of the qw dosing regimen was based on clinical efficacy demonstrated in a randomized Phase III study.

Data to support the q3w regimen are available from two studies evaluating the safety, tolerability, and PK of trastuzumab administered to women with HER2-positive (immunohistochemistry [IHC] 3+ or fluorescence in situ hybridization [FISH] +) metastatic breast cancer and from the 1-year arm of the HERA study (BO16348). Data from these three trials indicate that serum concentrations of trastuzumab increased until steady-state trough concentrations (median 47.3 ng/mL, 95% CI 19.6-51.2 ng/mL). Serum trough levels appeared to be comparable over the study periods, although trough concentrations were slightly lower with the q3w regimen *(52.9 mg/L)* compared with previous studies of the qw regimen *(69.6 mg/L)*. The average exposure at any time during the treatment is comparable between the two treatment regimens.

Please refer to the trastuzumab IB for further information.

1.3.3 Trastuzumab in Combination with Anthracyclines

Because anthracyclines are potentially cardiotoxic, the trastuzumab prescribing information specifically excludes the use of the two agents concomitantly. However, anthracyclines have a central role in the management of breast cancer and so evaluation of the combinations has been undertaken in carefully managed clinical studies. Published data are summarized in Table 3.

Table 3 Anthracyclines Given with Concurrent Trastuzumab in Breast Cancer Patients

Author	Indication	Dose (mg/m^2)	n=	Response Rate	Cardiac LVEF/CHF
Bianchi, 2003 [8]	1st/2nd line	Doxo 60	16	87.5% ORR	??*
Buzdar, 2005 [12]	Neoadjuvant	FEpi75/cyclo	64	60% pCR	remains clinically adequate
Untch, 2004 [66]	1st line MBC	Epi 60–90	75	>60% ORR	remains clinically adequate
Untch, 2008 [65]	Neoadjuvant	Epi 90	452	41.3% pCR	remains clinically adequate
Gianni, 2008 [26]	Neoadjuvant	Doxo 60	115	43% tumor pCR	remains clinically adequate
Venturini, 2006 [67]	1st line MBC	Epi 75	45	66.7% ORR	10 / 45 CHF (all recovered)
Thomssen, 2002 [63]	1st line MBC	Epi 60 or 90	133	~65% ORR	??**
Joenssu, 2006 [36]	Adjuvant	FEpi60C	116	0.42: HR for recurrence	remains clinically adequate
			N = 1016		

?? – Authors express reservations; * –2 cohorts with comparison; ** – randomized study.
MBC – metastatic breast cancer; ORR – objective response rate; LVEF – left ventricular ejection fraction; CHF – congestive heart failure; HR – hazard ratio

The overall data on over 1000 patients indicate that with proper selection and with careful cardiac monitoring, the combination of anthracyclines and trastuzumab in patients with early breast cancer is feasible and that the incidence of symptomatic cardiac events is relatively low, albeit higher than the non-trastuzumab containing arms [Bozovic-Spasojevic, 2011] [11]. In addition, these trials lacked long-term follow-up. Thus, this approach remains investigational.

1.3.4 Trastuzumab in Combination with Carboplatin Regimens

Trastuzumab has been used successfully in combination with carboplatin in a number of studies [Slamon, 2007; Robert, 2006] [58, 51]. A negative study showing no increase in additional activity associated with carboplatin but with good tolerability has also been conducted [Forbes, 2006] [19].

1.4 Rationale for the Study

1.4.1 Post-Surgery Adjuvant Anti-HER2 Therapy

HER2-positivity is associated with a poor prognosis. Trastuzumab targets the extracellular domain of HER2 and its use in the adjuvant therapy of HER2-positive breast cancer reduces the risk of relapse by about 50% and the risk of death by about 30%. Trastuzumab is generally given in combination with chemotherapy either as sequential

therapy (as in the HERA trial) or as concurrent therapy (as in the NSABP B-31, NCCTG N9831 and BCIRG 006 trials).

Two large trials have investigated concurrent trastuzumab and adjuvant chemotherapy. The NSABP B-31 and NCCTG N9831 (both conducted principally in North America) were broadly similar in design. The NSABP B-31 trial compared doxorubicin and cyclophosphamide followed by paclitaxel (AC→T), with the same regimen with 1 year of trastuzumab (AC→TH) starting concurrently with paclitaxel. The NCCTG N9831 trial included a third arm which gave trastuzumab on completion of paclitaxel therapy (AC→T→H). The combined results of the two trials [Romond, 2005] [52] demonstrated that the addition of trastuzumab to AC→T significantly improved disease-free survival (DFS) and OS in women with HER2-positive breast cancer. At the time of the first scheduled interim efficacy analysis, a total of 394 patients had experienced a DFS event. Of these, 261 patients had received chemotherapy alone and 133 patients received trastuzumab + chemotherapy. There was a significant increase in DFS in patients that received trastuzumab + chemotherapy compared with those that revived chemotherapy alone. The hazard ratio for a first event for trastuzumab + chemotherapy relative to chemotherapy alone was 0.48 (95% CI: 0.39, 0.59), $p < 0.0001$, corresponding to a relative risk reduction for recurrence of 52%. There was also an increase in overall survival for patients who received trastuzumab+chemotherapy. For OS, the hazard ratio for trastuzumab+chemotherapy relative to chemotherapy alone was 0.67 (95% CI: 0.48, 0.92), $p = 0.014$.

In the HERA trial, women had surgery and had completed standard chemotherapy and radiotherapy before they were entered into the study and randomly allocated to observation only or to receive trastuzumab q3w for either 1 or 2 years. Analyses were planned after 1 and 2 years' median follow-up. The efficacy analysis of the 1-year treatment arm versus observation demonstrated that treatment with trastuzumab is associated with improved outcomes [Piccart-Gebhart, 2005] [47]. Patients treated with trastuzumab for 1 year experienced a 46% lower risk of a first event than patients under observation (HR = 0.54; $p < 0.0001$), corresponding to an absolute disease-free survival (DFS) benefit favoring trastuzumab of 8.4% at 2 years. Following this interim analysis in 2005, the protocol was modified to allow women who had been randomized to receive no treatment to crossover to trastuzumab therapy. A second analysis of patients who received 1 year of trastuzumab treatment after a 2-year follow-up showed improved OS and distant recurrence event-free survival benefit for patients in the trastuzumab group compared with those in the observation group [Smith, 2007] [27]. No further improvement in DFS was observed in patients randomized to the 2-year trastuzumab arm [Goldhirsch, 2013] [30].

The Phase III randomized trial BCIRG 006 [Slamon 2006; Slamon, 2009] [57, 59] compared doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin, and trastuzumab (TCH) for the adjuvant treatment of women with early breast cancer. The study population consisted of 3222 women who were stratified by tumor size, nodal status, and hormone receptor status prior to randomization. Since 2005, 23 patients initially randomized to the control arm (AC→T) crossed over to

receive trastuzumab, leaving 97.9% of the control arm intact for subsequent analyses. The results of the third efficacy analysis from this trial were presented at SABCS 2009. At a median follow-up time of 65 months, there have been 348 deaths. The DFS rates were 84% for the AC→TH arm and 81% for the TCH arm, compared with 75% for the control arm, similar to the rates in the first efficacy analysis in 2005, but now with higher HRs (0.64 for AC→TH, $P < 0.001$; 0.75 for TCH, $P = 0.04$). Overall survival rates were 92% for the AC→TH arm, 91% for the TCH arm, and 87% for the control arm, with HRs of 0.63 ($P < 0.001$) for the AC→TH arm and 0.77 ($P = 0.038$) for the TCH arm.

In summary, there are compelling data to support the addition of trastuzumab to adjuvant chemotherapy, and clinicians now have a variety of trastuzumab-based options for treating early breast cancer. A number of questions remain unanswered, however, regarding treatment duration and exactly how to combine trastuzumab with chemotherapy.

1.4.2 Rationale for Incorporating Pertuzumab and Trastuzumab into Anthracycline and Taxane-Based Regimens

The combination of intravenous pertuzumab and trastuzumab is scientifically compelling based on their complementary mechanisms of action and the available nonclinical data, as described. This rationale is supported by the clinical data from studies WO20698, WO20697 and BO17929 [Gelmon, 2008; Baselga, 2009; Baselga, 2011] [23, 6, 5].

Anthracyclines (generally used in combination with 5-fluorouracil [5-FU] and cyclophosphamide) have a central role in the management of breast cancer [Romond, 2005; Poole, 2006] [52, 48]. More specifically, there might be a particular activity associated with the use of anthracyclines in patients whose tumors overexpress chromosome 17. Polysomy 17 is associated with overexpression of HER2, overexpression of topoisomerase II (topoisomerase II being the target for anthracyclines) and with the overexpression of other potentially relevant proteins such as p53 [Gennari, 2008; Bartlett; 2008] [24, 4].

Taxanes are also integral in standard regimens for the treatment of breast cancer, used in combination with anthracyclines in a regimen known as TAC (docetaxel plus doxorubicin and cyclophosphamide) [Martin, 2005] [41] or in sequence with anthracyclines in a regimen known as AC→T [Romond, 2005; Joennsu, 2006] [52, 36].

Carboplatin is both an active and well-tolerated chemotherapy agent and there are studies in breast cancer which show clear efficacy in combination with a taxane and trastuzumab in a regimen known as TCH [Robert 2006; Slamon 2009] [51, 59]. However, in metastatic breast cancer, there are negative data [Forbes, 2006] [19]. Carboplatin is not directly cardiotoxic and the potential long term risk and benefit associated with carboplatin makes it an attractive chemotherapy agent.

The clinical data pertaining to pertuzumab suggest that it has a promising benefit and risk profile and could be a suitable additional agent for use in early, potentially curable, breast cancer.

1.4.3 Rationale for Dose Selection of Docetaxel, 5-Fluorouracil, Carboplatin, Epirubicin, Cyclophosphamide, Paclitaxel and Doxorubicin

The intravenous chemotherapy regimens to be used in this protocol are based on published data and routine clinical usage as well as well-established clinical practice guidelines (National Comprehensive Cancer Network [NCCN] guidelines; [Goldhirsch 2009] [29]).

It is recognized that docetaxel at a dose of 100 mg/m^2 in combination with trastuzumab has been associated with a positive benefit-risk ratio in patients with HER2-overexpressing metastatic breast cancer compared to docetaxel alone (100 mg/m^2 given every 3 weeks) [Marty, 2005] [42]. The risks and benefits associated with different docetaxel doses (single agent) have been established in randomized studies [Harvey, 2006, Bono, 2009] [31, 10].

The clinical utility of docetaxel 100 mg/m^2 used in sequence with an anthracycline and cyclophosphamide for 3 cycles has been previously demonstrated in the BCIRG006 early breast cancer study [Slamon 2006, Slamon 2009] [57, 59]. In order to ensure that all patients are treated optimally, where local practice dictates, 4 cycles of docetaxel at 75 mg/m^2 may be given. Alternatively, the dose of docetaxel may be started at 75 mg/m^2 in the first cycle and escalated to 100 mg/m^2 in subsequent cycles according to individual tolerability; a minimum of 3 cycles will be given for this dosing regimen.

Docetaxel in combination with carboplatin and trastuzumab will be given at 75 mg/m^2; this is based on the clinical experience of the BCIRG 001/2 and BCIRG006 [Slamon 2006] [57] studies that investigated the combination of docetaxel, together with carboplatin and trastuzumab (Herceptin®). The dose of docetaxel can be reduced according to toxicity experienced. Carboplatin will be given at AUC (area under the plasma concentration–time curve) 6. The total dose of carboplatin should not exceed 900 mg.

The use of paclitaxel in combination with trastuzumab is supported by a number of studies in the adjuvant and neo adjuvant settings [Buzdar, 2005; Romond, 2005; Paluch-Shimon, 2008;] [12, 52, 45], both the NCCTG N9831 and NSABP B31 studies utilized q3w or weekly paclitaxel in combination with trastuzumab.

Weekly paclitaxel given at a dose 80 mg/m^2 has been shown to have advantages in terms of tolerability, while displaying increased efficacy compared to 3 weekly paclitaxel [Sparano, 2008] [62]. Therefore, if paclitaxel is used it should be administered at 80 mg/m2 weekly for 12 weekly cycles.

The dose of doxorubicin 60 mg/m^2 in combination with cyclophosphamide was established by the NSABP B15 study [Fisher, 1990] [17]. The combination of doxorubicin at a dose of 60 mg/m^2 together with cyclophosphamide was also utilized in the anthracycline component of the 3 principal studies that investigated trastuzumab in combination with chemotherapy in the adjuvant setting [Romond 2005; Slamon 2006] [52, 57].

There is a body of evidence supporting the use of epirubicin in breast cancer [Poole, 2006] [48]. Higher doses of epirubicin are preferred [Poole, 2006; de Azambuja, 2009] [48, 15], and so the dose of epirubicin used in this study will be 90-120 mg/m^2. The cyclophosphamide dose to be used is 500-600 mg/m^2 IV, (note: oral cyclophosphamide is not acceptable). In addition, the use of 5-FU at 500-600 mg/m^2 IV in combination with an anthracycline and cyclophosphamide is considered a standard regimen [Henry, 2007] [32].

For all the regimens, the number of treatment cycles will be between 6 and 8 cycles (Table 4). Thus, patients will receive either FEC (FAC) → T (sequential IV treatment comprising of 5-FU, anthracycline and cyclophosphamide followed by taxane therapy; in this regimen the anthracycline will be epirubicin [or doxorubicin] and the taxane will be docetaxel [or paclitaxel]); or AC (EC) → T (sequential IV treatment comprising of doxorubicin [or epirubicin] and cyclophosphamide followed by taxane [docetaxel or paclitaxel] therapy); or TCH (intravenous docetaxel, carboplatin and trastuzumab) for 6 cycles. There are data supporting the use of 6 cycles of therapy, both as neoadjuvant therapy [von Minckwitz, 2008] [68] and as adjuvant therapy [Joennsu, 2006; Slamon, 2009] [36, 59], and 8 cycles as adjuvant therapy [Romond, 2005] [52].

1.4.4 Rationale for Dose Selection of Trastuzumab and Pertuzumab

Based on the PK data and clinical data, an intravenous dosing interval of 3 weeks was determined for pertuzumab. A loading dose of 840 mg followed by 420 mg q3w is capable of attaining steady-state trough and peak concentrations by the second cycle. For further details of the PK profile of pertuzumab, see Section 1.2.5.

The half-life of trastuzumab has been determined to be approximately 28-*38* days, which supports a dosing of q3w (see also Section 1.3.2).

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare invasive disease-free survival (IDFS) in patients with HER2-positive breast cancer randomized to chemotherapy plus 1 year of trastuzumab plus placebo or chemotherapy plus 1 year of trastuzumab plus pertuzumab.

2.2 Secondary Objectives

To compare invasive disease-free survival including second non-breast cancers, DFS, OS, recurrence-free interval (RFI), distant recurrence-free interval (DRFI), cardiac safety, overall safety and health-related quality of life (HRQL) in the two treatment arms.

3. STUDY DESIGN

3.1 Overview of Study Design

A prospective, two-arm randomized, multicenter, multinational, double-blind, placebo-controlled study in patients with HER2-positive primary breast cancer who have had excision of their primary tumor (Figure 2). HER2-positive status of the primary tumor will be confirmed by central pathology laboratory prior to enrollment of the patient in the trial.

To participate in the trial, a patient must fulfill all inclusion criteria, must not meet any of the exclusion criteria, and will need to consent to collection and storage of blood samples and tumor tissue samples for biomarker research as specified in Section 5.6.

The Investigator should select one of the protocol approved adjuvant chemotherapy regimens (described below) with which to treat the patient. Once the Investigators' choice of chemotherapy has been made and eligibility confirmed, the patient will be randomized to receive trastuzumab plus placebo OR trastuzumab plus pertuzumab.

The Investigators' choice of adjuvant chemotherapy must be recorded on the electronic Case Record Form (eCRF) and this choice must be maintained throughout adjuvant chemotherapy. In the event of significant toxicity associated with the assigned adjuvant chemotherapy, the investigator should discuss the possibility to switch the patient to another approved chemotherapy regimen.

The Investigator must select one of the following protocol approved chemotherapy regimens:

Table 4 Protocol Approved Chemotherapy Regimens (Investigators' Choice)

All study treatments will be given intravenously.
For all regimens, the maximum allowed cumulative dose of doxorubicin is 360 mg/m^2 and of epirubicin is 720 mg/m^2.
Key: A (doxorubicin), C (cyclophosphamide), E (epirubicin), F (5-fluorouracil), T (taxane)

REGIMEN	DOSE	FREQUENCY
Anthracycline therapy: FEC (or FAC) → T		
3 or 4 cycles x FEC (or FAC) → 3 or 4 cycles x docetaxel	F: 500 to 600mg/m^2 E: 90 to 120mg/m^2 or A: 50mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Docetaxel: 100mg/m^2 OR Docetaxel: 75mg/m^2 for 4 cycles[1] OR Docetaxel: 75mg/m^2 in the first cycle, escalating to 100mg/m^2 in subsequent cycles	q3w q3w q3w
3 or 4 cycles x FEC (or FAC) → 12 weekly cycles of paclitaxel	F: 500 to 600mg/m^2 E: 90 to 120mg/m^2 or A: 50mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Paclitaxel: 80mg/m^2	q1w
Anthracycline therapy: AC (or EC) → T		
4 cycles x AC[2] (or EC) → 3 or 4 cycles x docetaxel	A: 60mg/m^2 or E: 90 to 120mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Docetaxel: 100mg/m^2 OR Docetaxel: 75mg/m^2 for 4 cycles[1] OR Docetaxel: 75mg/m^2 in the first cycles, escalating to 100mg/m^2 in subsequent cycles	q3w
4 cycles x AC2 (or EC) → 12 weekly cycles of paclitaxel	A: 60mg/m^2 or E: 90 to 120mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Paclitaxel: 80mg/m^2	q1w

1 If docetaxel 75 mg/m2 is used and not escalated to 100mg/m^2, then 4 cycles must be given.
2 EC or AC can be given at the same dose (A: 60mg/m^2 or E: 90 to 120mg/m^2) every 2 weeks (dose dense) with G-CSF support, for a total of 4 cycles.

Table 4 Protocol Approved Chemotherapy Regimens (Investigators' Choice) (Cont.)

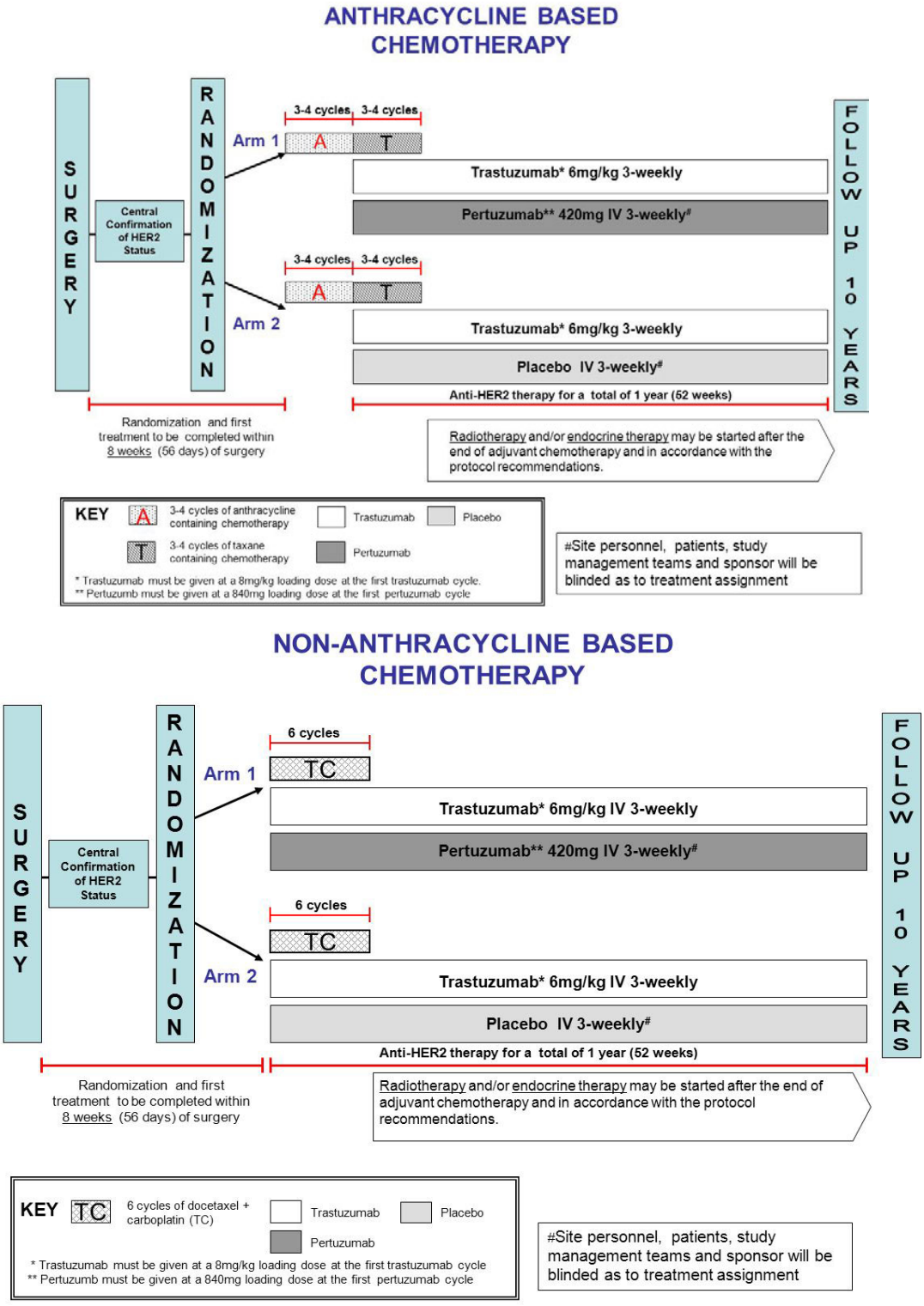
Non-Anthracycline therapy: Docetaxel/carboplatin as in BCIRG 006		
6 x docetaxel plus carboplatin	Docetaxel: 75 mg/m^2 Carboplatin: AUC 6 (900-mg maximum dose)	q3w

Randomized targeted treatment (trastuzumab plus placebo OR trastuzumab plus pertuzumab) must start concurrently with the taxane component of chemotherapy. Randomized targeted treatment is to be administered for a total of 52 weeks plus a window of 3 days (i.e., maximum of 18 cycles within 1 year).

For patients with tumors that are estrogen receptor (ER) and/or progesterone receptor (PgR) positive, hormonal agents should be started at the end of chemotherapy consisting of tamoxifen or an aromatase inhibitor for post-menopausal patients; or tamoxifen with or without ovarian suppression *or an aromatase inhibitor with ovarian suppression* for pre-menopausal patients. Hormonal therapy should be given for at least 5 years in accordance with the protocol recommendations (see Section 4.4.3.1 for details).

Radiotherapy is to be given as clinically indicated at the end of chemotherapy in accordance with protocol recommendations (see Appendix 2 for details).

Figure 2 Study Design



3.1.1 End of Study

The study will formally end approximately 10 years from the date the last patient is randomized into the study provided the study objectives have been met by this time. This may or may not coincide with the time of the event-driven OS analysis, depending on the event rate.

3.2 Number of Patients/Assignment to Treatment Groups

Approximately 4800 patients are planned to be enrolled from approximately 600 sites. It is expected that the accrual will take approximately 25 months to complete. A web-based randomization system will be used to collect patient screening information and to randomize eligible patients in a 1:1 ratio between trastuzumab plus placebo adjuvant therapy and trastuzumab plus pertuzumab adjuvant therapy.

A permuted blocks randomization procedure will be used for which patients will be randomized between the two treatment arms and stratified using the criteria specified in Table 5.

Table 5 Stratification Factors

Nodal Status:	0 positive nodes and tumor ≤1 cm [a] 0 positive nodes and tumor >1 cm [a] 1-3 positive nodes ≥4 positive nodes
Adjuvant chemotherapy regimen:	Anthracycline containing regimen Non-anthracycline containing regimen
Hormone receptor status [b]	ER and PgR negative ER and/or PgR positive [c]
Geographical Region	USA Canada/Western Europe/Australia-New Zealand/South Africa Eastern Europe Asia-pacific Latin America
Protocol Version [d]	Protocol A Protocol Amendment B

[a] Nodal status may take any of these four categories under protocol A, but only the two categories with positive nodes after protocol amendment B has been implemented

[b] Hormone receptor status must be known for each patient and will be confirmed by the central laboratory. Hormone receptor status ('negative' or 'positive') will follow the definition of the central laboratory.

[c] ER or PgR positive is defined as ≥ 1% immunoreactive cells.

[d] The inclusion of protocol version reflects the actual study design, and as with all stratification variables is included to allow a valid and robust statistical analysis taking into account the protocol version randomized under.

A patient may only be randomized once in this trial.

3.3 Centers

Patients will be enrolled from approximately 600 centers worldwide.

4. STUDY POPULATION

4.1 Overview

The study population for this trial is patients who are newly diagnosed with primary invasive breast cancer that is HER2-positive (determined by IHC3+ or FISH/chromogenic in situ hybridization [CISH] positive as determined by central review) who will be treated with adjuvant systemic chemotherapy following definitive surgery.

Adjuvant systemic chemotherapy should commence within 8 weeks of definitive surgery. All procedures, including randomization, must occur during this period.

4.2 Inclusion Criteria

Patients must meet ALL of the following criteria in order to be eligible for this study:

1. Age ≥18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status ≤1 (Appendix 3).
3. Non-metastatic operable primary invasive carcinoma of the breast that is:
   a) Histologically confirmed
   b) Adequately excised
   - Patients must have undergone either a total mastectomy or breast conserving surgery.
   - For patients who undergo conservative surgery, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible without additional resection.
   - For patients who undergo mastectomy, margins must be free of gross residual tumor. Patients with microscopic positive margins are eligible (see radiation therapy requirements).
     c) pTNM staging:
     Pathological classification of regional lymph nodes: micrometastases (tumor deposits >0.2 mm) are considered pN1, but isolated tumor cells (ITC) are considered pN0.
     - For patients with node-positive disease (pN ≥1), any tumor size except T0

Node-negative patients are NOT allowable under Protocol Amendment B. Below applies to Protocol A ONLY:

For patients with node-negative disease (pN0) (Protocol A ONLY):

- Tumor size must be >1.0 cm
  OR
- For tumor size between >0.5 cm and ≤1.0 cm, at least one of the following features must be present: histologic/nuclear grade 3 OR negative for ER and PgR OR age <35 years.
- Enrollment of patients with node negative tumors ≤1.0 cm will be limited to <10% of the total number of randomized patients

- For multifocal (the presence of two or more tumor foci within a single quadrant of the breast) or multicentric disease (the presence of two or more tumor foci within different quadrants of the same breast), the size of the largest invasive tumor is to be used to determine T stage.
- Patients with synchronous bilateral invasive disease are eligible so long as both lesions are HER2 positive.

4. Known hormone receptor status (ER and PgR)
5. The interval between definitive surgery for breast cancer and the first dose of chemotherapy must be no more than 8 weeks (56 days). All procedures, including randomization, must occur by this time. The first cycle of chemotherapy must be administered within 7 days of randomization or on Day 56, whichever occurs first.
6. Baseline LVEF ≥55% measured by ECHO (preferred) or MUGA scan
7. HER2-positive breast cancer confirmed by a central laboratory and defined as:

- IHC 3+ in >10% immunoreactive cells OR c-erbB2 gene amplification by in situ hybridization [ISH] (ratio of c-erbB2 gene signals to centromere 17 signals ≥2).

  Availability of formalin-fixed paraffin-embedded (FFPE) tissue block with at least 5 mm of invasive tumor and, wherever possible, a minor component of non-neoplastic breast tissue for central confirmation of HER2 eligibility, hormone receptor status and biomarker evaluation is mandatory (a minimum of 4 and up to 7 × 1-mm cores will be taken for translational research (TR) and the block returned to site).

8. Completion of all necessary baseline laboratory and radiologic investigations prior to randomization (see Section 5 for the Schedule of Assessments)
9. Women of childbearing potential and male participants with partners of childbearing potential must agree to use a highly-effective, non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner. Contraception must continue for the duration of study treatment and for at least *7* months after the last dose of study treatment (Section 7.2.5).
10. Signed informed consent

4.3 Exclusion Criteria

Patients meeting any ONE of the following criteria are not eligible for this study:

1. History of any prior (ipsi- and/or contralateral) invasive breast carcinoma
2. History of non-breast malignancies within the 5 years prior to study entry*, except for the following: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinomas of the skin (*malignancies occurring more than 5 years prior to study entry are permitted if curatively treated with surgery alone).
3. Any "clinical" T4 tumor as defined by TNM, including inflammatory breast cancer.
4. Any node-negative tumor.
5. Any previous systemic chemotherapy (e.g., neo-adjuvant or adjuvant) for cancer OR radiation therapy for cancer.
    - Patient with a past history of DCIS and/or LCIS are not allowed to enter the study if they have received any form of systemic therapy for its treatment; OR radiation therapy to the ipsilateral breast where invasive cancer subsequently develops.
    - Patients who had their DCIS/LCIS treated with surgery only are allowed to enter the study.
    - High risk patients who have received chemoprevention drugs in the past are not allowed to enter the study.
6. Prior use of anti-HER2 therapy (e.g., lapatinib, neratinib or other tyrosine kinase inhibitors [TKIs]) for any reason or other prior biologic or immunotherapy for cancer.
7. Concurrent anti-cancer treatment in another investigational trial, including hormone therapy, bisphosphonate therapy and immunotherapy.
8. Serious cardiac illness or medical conditions including but not confined to:
    - History of documented heart failure or systolic dysfunction (LVEF <50%),
    - High-risk uncontrolled arrhythmias i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block),
    - Angina pectoris requiring anti-angina medication,
    - Clinically significant valvular heart disease,
    - Evidence of transmural infarction on electrocardiogram (ECG),
    - Poorly controlled hypertension (e.g., systolic > 180 mm Hg or diastolic > 100 mm Hg).
9. Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness (e.g., infections or poorly controlled diabetes).
10. Any of the following abnormal laboratory tests immediately prior to randomization:
    - Serum total bilirubin >1.5 × upper limit of normal (ULN); in cases of known Gilberts syndrome a total bilirubin of 2 × ULN is permitted.
    - Alanine amino transferase (ALAT) and/or aspartate amino transferase (ASAT) >1.25 × ULN
    - Alkaline phosphatase (ALP) >2.5 × ULN

- Serum creatinine >1.5 × ULN
- Total white blood cell count (WBC) <2,500 / mm3(<2.5 × 109/L)
- ANC <1,500 / mm3 (<1.5 × 109/L)
- Platelets <100,000 / mm3 (<100 × 109/L).

11. Pregnant or lactating women or women of childbearing potential without a negative pregnancy test (serum), within 7 days prior to randomization, irrespective of the method of contraception used.
12. Women of childbearing potential or less than one year after menopause (unless surgically sterile) who are unable or unwilling to use the contraceptive measures required by this protocol during and *7* months after the last dose of study medication (see Section 7.2.5).
13. Sensitivity to any of the study medications or any of the ingredients or excipients of these medications, including sensitivity to benzyl alcohol.

4.4 Concomitant Medication and Treatment

All concomitant medications and prior treatments for breast cancer (undertaken or used within 7 days prior to randomization) must be reported in the eCRF, including:

- Date and extent of primary surgery
- Any loco-regional radiation therapy (extent or volume and total dose)
- Any hormonal therapy and/or surgical and radiation-induced ovarian ablation and drug induced ovarian suppression (type, drug name, dose and schedule, anticipated duration of therapy)
- Bisphosphonate therapy
- Any additional medication that is necessary for the management of the patient may be used at the discretion of the Investigator.

All concomitant medications are to be reported until the end of targeted treatment visit (28 days after the last dose of targeted treatment). Thereafter, only medication applicable for long-term reporting must be reported, including:

- Breast cancer treatments (e.g., hormonal therapy)
- Anti-cancer treatments given to treat a recurrence
- Medications related to the treatment of SAEs that are applicable for long-term reporting (e.g., treatment for heart failure; see Section 7.1.2).

End dates for all recorded concomitant medications started during the treatment period should be obtained and reported in the eCRF.

4.4.1 Adjuvant Radiotherapy

Before actively enrolling patients, each center must define a radiotherapy policy for treating patients in the trial. Guidelines are given in Appendix 2. Radiotherapy is to be given at the end of chemotherapy whilst targeted treatment is being administered.

4.4.2 Minimum requirements for Patients Undergoing Sentinel Lymph Node Biopsy

Patients with positive sentinel lymph node biopsy (SNB) should undergo axillary dissection unless the following characteristics apply [Giuliano, 2011] [28]:

- No palpable nodes
- No more than 2 positive lymph nodes
- Breast conserving surgery
- Tangential whole breast irradiation
- Clinical tumor size ≤T2 (5 cm)

In the case that all of the above are applicable, it is not mandatory to have the axillary dissection but it is left at the discretion of the investigator as per site standard practice.

4.4.3 Concomitant Hormonal Therapy

Before actively enrolling patients, each center must set a policy for the use of tamoxifen, ovarian ablation *and aromatase inhibitors* for patients in the trial. *Table 7 contains recommendations for accepted hormonal therapy. However, as of protocol amendment D, sites may prescribe hormonal therapy per standard local clinical practice.*

4.4.3.1 Recommendations for Administering Hormonal Therapy

Female patients must be classified according to one of the menopausal status definitions described in Table 6.

Table 6 Menopausal Status Definitions

A	**Premenopausal:** <12 months since last menstrual period AND no prior bilateral ovariectomy AND not receiving estrogen replacement OR biochemical evidence of premenopausal status, according to local policies
B	**Post-menopausal:** ≥12 months since last menstrual period with no prior hysterectomy, OR prior bilateral ovariectomy OR biochemical evidence of postmenopausal status, according to local policies

Female patients should be treated according to the recommendations in Table 7.

NOTE: Endocrine therapy in male patients is to be given according to local policies.

Table 7 Recommendations for Hormonal Therapy

CLINICAL SCENARIO	HORMONAL THERAPY
Hormone receptor negative	Not permitted
Hormone receptor positive[1] PREMENOPAUSAL[2]	• Tamoxifen for 5 years with or without ovarian suppression as per local policy • Aromatase inhibitors, with ovarian suppression (luteinizing-hormone-releasing hormone [LHRH]analogue)
Hormone receptor positive[1], POSTMENOPAUSAL[2]	• Aromatase inhibitor for 5 years • Aromatase inhibitor for 2-3 years, followed by tamoxifen to complete a total of 5 years • Tamoxifen for 2-3 years, followed by an aromatase inhibitor to complete a total of 5 years • Tamoxifen for 5 years • Tamoxifen for 5 years followed by an aromatase inhibitor for 5 years A longer duration of endocrine therapy is acceptable if this is a locally-recognized policy.

[1] Hormone receptor "positive" is defined as positive estrogen receptor and/or progesterone receptor. Hormone receptor status ('negative' or 'positive' will follow the definition of the central laboratory. In case of discrepancy between local and central results of hormone receptors, then the investigator can decide treatment policy according to local practice.

[2] Menopausal status criteria: see Table 6.

4.4.4 Allowed Therapies

Concomitant treatments are any prescription medications, over-the-counter preparations, herbal medications/remedies or radiotherapy used by a patient in the interval beginning 7 days prior to the patient being randomized into the study and continuing through the study treatment period. All concomitant medications should be reported to the Investigator and recorded on the eCRF. In general, all medications taken by the patient for concomitant diseases should continue during the study treatment period and should be recorded on the eCRF.

The following treatments are permitted during the study:

- Acceptable methods of contraception must be used when the patient is not surgically sterilized or does not meet the study definition of post-menopausal. For further details see Section 7.2.5.
- H1 and H2 antagonists (e.g., diphenhydramine, cimetidine)
- Cardiovascular medications: angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers and diuretics (for treatment of arterial hypertension with a goal to reduce blood pressure < 140/90mmHg); beta blockers, calcium channel blockers and digoxin (for heart rate control); thrombocyte aggregation inhibitors.

- Analgesics/anti-inflammatories (e.g., paracetamol/acetaminophen, meperidine, opioids)
- Short term use of corticosteroids to treat or prevent allergic or infusion reactions,
- Anti-emetics (approved prophylactic serotonin-antagonists, benzodiazepines, ondansetron, etc.)
- Medication to treat diarrhea (e.g., loperamide)
- Colony-stimulating factors (e.g., granulocyte colony-stimulating factor [G-CSF])
- Estrogen receptor antagonists (e.g., tamoxifen) or aromatase inhibitors (e.g., anastrazole, letrozole or exemestane) after completion of post-operative chemotherapy as per local practice
- LHRH/GnRH analogues
- Vitamin and mineral supplements
- Bisphosphonates (to be used in accordance with the approved labeled indication and/or nationally recognized treatment guidelines)

4.4.5 Excluded Therapies

The following therapies are excluded during the treatment period of the study:

- Anti-cancer therapies other than those administered in this study, including cytotoxic chemotherapy, radiotherapy (except for adjuvant radiotherapy for breast cancer after completion of chemotherapy), immunotherapy, and biological anti-cancer therapy and anti-cancer agents used for the treatment of rheumatoid arthritis (e.g., methotrexate).
- Any targeted anti-cancer therapy (e.g., lapatinib, neratinib)
- Regular treatment with steroids. Exceptions include: short-term corticosteroid ONLY to treat and prevent allergic or infusion reactions. In the case of short-term corticosteroid administration, the dose must not exceed >20 mg of dexamethasone a day (or equivalent) for >7 consecutive days.
- Any investigational agent, except for those used for this study.
- Initiation of herbal remedies. Note: herbal remedies initiated prior to study entry and continuing during the study are permitted and must be reported on the appropriate eCRF.
- Any systemically active oral, injected or implanted hormonal method of contraception (see Section 7.2.5.1 for acceptable contraception methods) except for progesterone-coated IUDs that had been previously implanted
- Estrogen-replacement therapy (HRT)

4.5 Criteria for Premature Withdrawal

A patient may withdraw from the study or study specific procedures at any time during the entire duration of the study for any reason and without prejudicing future medical treatment.

Whilst a patient can withdraw without needing to give a reason, as soon as a patient has triggered a withdrawal, the investigator has the responsibility to establish that the patient's decision is an informed choice and to ascertain to what extent the patient might

be willing to continue limited participation in the trial, (e.g., willing to continue being contacted or seen to providing follow-up information).

The outcome of the discussion should be documented in both the patient's medical records and the eCRF.

It is therefore important to clarify that patient's withdrawal is defined within three different scenarios that have a different impact on the study analysis and data collection:

- Withdrawal from study treatment: the decision to withdraw from treatment can be taken by the patient or by the investigator. Patients must be kept on study and followed up according to the protocol schedule of assessments until study completion. The reason for treatment discontinuation must be recorded on the eCRF.

If the patient decides to withdraw from treatment because of an AE, the reason for treatment discontinuation should be reported as Adverse Event even in the case the investigator does not consider the AEs as qualifying for treatment withdrawal as per protocol.

Investigators may withdraw patients from study treatment in the event of intercurrent illness, AEs, treatment failure, protocol violation, administrative reasons or for other reasons.

When study treatment is prematurely discontinued, patients should complete the end of treatment visit 28 days after the last administration of study treatment.

- Withdrawal from the entire study: should a patient decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible. No further data will be collected after the date of withdrawal from study.

The Investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

- Partial withdrawal from the study, with consent to allow collection of information regarding disease recurrence, survival status, and reportable toxicity: all of the above point is applicable to this scenario with the exception that the patient accepts to be contacted for further information on recurrence as per the primary study endpoint and survival status. It should be documented in both the medical records and in the eCRF that the patient accepted to be contacted for survival despite she/he withdrew the study consent.

In the case of patients who fail to attend scheduled visits, several attempts should be made by the site to contact these patients for follow up information. The collection of follow up data is extremely important in regards to the reliable estimation of study endpoints, therefore at least 3 attempts within a reasonable extent of time should be made to try to contact the patients if they do not attend clinic visits.

If any of the trial patients are lost to follow up, contact will initially be attempted through the trial research nurse and the lead investigator at each center. Where these attempts are unsuccessful, the patient's GP will be contacted and asked to contact the patient or her/his family and provide follow-up information to the recruiting center.

It is only after sufficient attempts at contact have been unsuccessful, that a patient may be declared "Lost to follow-up".

An excessive rate of withdrawals and loss to follow-up can render the study uninterpretable; therefore, unnecessary patient attrition should be avoided.

4.6 Replacement Policy

4.6.1 For Patients

Patients randomized into the study will not be replaced. Patients who choose to withdraw after screening but before randomization will be replaced.

4.6.2 For Centers

A center may be replaced for the following reasons:

- Excessively slow recruitment (no randomizations within 6 months of activation)
- Poor protocol adherence (major protocol violations)
- Noncompliance with the principles of the International Conference On Harmonization – Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki
- Investigator decision to withdraw the center's participation.

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The complete schedule of assessments is presented in Table 8, Table 9, and Table 10. These outline the schedule of assessments before and during the treatment period including the 28-day follow-up period.

All patients will be followed from the first day of treatment (either first anthracycline administration or first targeted treatment for the non-anthracycline patients) through to Week 52 of targeted treatment according to the assessment schedule outlined in Table 8. Thereafter, Table 9 outlines the schedule of assessments during the follow-up period after week 52.

In the case where the patient prematurely discontinues targeted treatment (trastuzumab plus pertuzumab/placebo) before week 52 for reason other than Study consent withdrawal or disease recurrence, safety follow-up should be conducted 28 days from the last dose of targeted treatment and thereafter the patient should be followed according to Table 10 until the patient reaches week 52. Thereafter, the schedule of assessment per Table 9 is applicable.

For patients who discontinue anthracycline early (i.e., who have not received a dose of targeted treatment) for any reason other than consent withdrawal or disease recurrence, safety follow-up should be conducted 28 days from the last dose of chemotherapy. Thereafter, they should follow the schedule of assessments in Table 9, but are only

followed for SAEs, concomitant medications, additional anticancer related therapies and survival.

Patients will be followed for approximately 10 years from the date of randomization of the last patient.

A bullet–point description for patients who discontinue targeted treatment early is as follows:

- Complete 28-day safety follow-up visit
- Follow Table 10

A bullet-point description for patients who discontinue anthracycline early is as follows:

- Complete 28-day safety follow-up visit
- Follow Table 9, but only SAEs, concomitant medications, additional anticancer related therapies and survival.

Table 8 Schedule of Assessments – Screening and Treatment Period

Non-mandatory assessments are shown in parentheses [ ]	Screening	Base-line	Anthracyclines Treatment Period*	Targeted Treatment Period Within 3 days prior to Day 1 of Cycle Number X											Safety follow-up at the end of treatment 28 days from the last dose of Study medication (a)
Cycle			1-3 or 1-4	1	2	3	4	5	6	7	8	9	13	18	
Beginning of Week			1, 4, 7 or 1, 4, 7, 10	1	4	7	10	13	16	19	22	25	37	52	
Informed Consent (b)	X														
HER2 Determination (c)	X														
Tumor tissue sample (Mandatory) (d)	X														
Whole blood, serum, and plasma sample (biomarker analysis, mandatory) (e)		X	X (end of treat.)				X (s)	X (s)		X (s)		X	X	X	X (t)
Full blood sample for PGx analysis (subject to additional consent) (f)		[X]													
Frozen tissue (optional)	[X]														
Demographic, Medical History	X														
Radiologic Examinations (g): - Mammogram or breast MRI - Chest X-ray or chest CT/MRI/PET - Bone scan (h) - Liver imaging	X (within 6 mos) X (within 6 mos) [X] [X]											[X] [X] [X] [X]		[X] [X] [X] [X]	
Pregnancy Test (i)	X (within 7 d)			Continuously (Every 9 weeks/3 cycles)											[X] (i)
Physical Examination (j)	X		X (cycle 1)	X				X				X	X	X	X
ECOG status (j)	X		X (cycle 1)	X				X				X	X	X	X
Cardiac Monitoring: - ECG (k) - LVEF (l)(m) - Signs/symptoms(m)	X X (within 14 d) X		Every 12 weeks, ideally just prior to the next scheduled cycle in order to confirm adequate cardiac function.												
Quality of Life Assessment (n)	X		X (end of treat.)				X	X		X		X			X
Hematology & Biochemistry (o)	X (within 7 d)		X	X	X	X	X	X	X	X	X	X	X	X	X
Liver function test (p)	X (within 7 d)		X	X	X	X	X	X	X			X	X	X	X
Menopausal status													X		
Adverse Events (q)	X (if appl.)		Continuously												

Non-mandatory assessments are shown in parentheses [ ]	Screening	Base-line	Anthracyclines Treatment Period*	Targeted Treatment Period Within 3 days prior to Day 1 of Cycle Number X	Safety follow-up at the end of treatment 28 days from the last dose of Study medication (a)
Serious Adverse Events (q)	X (if appl.)		Continuously		
Concomitant medications (r)	X		Continuously		

DISEASE RECURRENCE: Patients with local, regional, distant recurrence or contralateral breast cancer should be assessed according to the procedures outlined in Section 5.5.1. Where possible, tumor tissue samples should be collected (see Section 5.5.2). *Serum and plasma samples are MANDATORY*. Thereafter the patient should be followed once a year until Year 10 as described in Section 5.4.1.

* Only applicable to patients receiving anthracycline-based chemotherapy regimens (FEC [FAC] →TH or AC [EC] →TH).

a) 28-day safety follow up visits will optimally be scheduled for 28 days following the last dose of study medication.

b) Written informed consent must be obtained before any study specific screening assessments are performed.

c) HER2 determination should be applied as per the HER2 screening algorithm (Figure 3).

d) FFPE tumor tissue sample is MANDATORY and will also be used for biomarker analysis. A tissue sample collected at definitive breast cancer surgery is acceptable. Sections and/or slides will not be acceptable.

e) A whole blood sample, serum sample and plasma sample for biomarker analysis are MANDATORY and must be collected after randomization, but before the first dose of study treatment is administered. Refer to Section 5.6.2.1.

f) Full blood sample for clinical genotyping, e.g., assessment of Fc-γ receptor polymorphism is OPTIONAL.

g) A bilateral mammogram or breast MRI will be completed yearly from that performed at screening/surgery as per clinical practice, and as clinically indicated upon finding from physical examination. Bilateral mammogram or breast MRI and chest x-ray/CT/MRI/PET is to be performed within 6 months prior to randomization. Bone scan and liver imaging is to be performed if clinically indicated to exclude metastatic disease and within a timeline as per current standard of practice.

h) In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.

i) For all women of childbearing potential, and for all women not meeting the definition of postmenopausal (see Table 6), and who have not undergone surgical sterilization: a serum β-human chorionic gonadotropin (HCG) test must be performed within 7 days prior to randomization. During the treatment period, a urine pregnancy test must be performed every 9 weeks during targeted treatment (approximately every 3 cycles) and as clinically indicated. For patients that discontinue the targeted treatment before Week 52, a urine pregnancy test must be done at the safety follow-up visit (28 days from the last dose of targeted treatment), and then at 3 months and 6 months post-discontinuation of targeted treatment. Any positive urine pregnancy test must be confirmed via a serum β-HCG test. Treatment period pregnancy test results must be available prior to drug infusion. (See Table 9 for pregnancy tests required during the follow-up period).

j) Physical examination and ECOG performance status should be measured at baseline and monitored throughout the study. As a minimum these assessments must be done every 3 months, at Cycle 1, Week 13, Week 25, Week 37 and Week 52 of targeted treatment and at the end of treatment safety follow-up visit. These assessments may be done at more frequent intervals if clinically indicated. Physical examination includes height (at baseline only), weight and vital signs (blood pressure, pulse rate and body temperature). Weight is to be measured on Day 1 of the specified cycles and compared to baseline. If ± 10% variation occurs then trastuzumab and chemotherapeutic doses will be recalculated.

k) ECGs are required to allow assessment prior to Cycle 1 and after the completion of therapy or at the week 52 visit in conjunction with the other cardiac assessments. Additional ECGs to be performed as clinically indicated.

l) LVEF assessment by ECHO is preferred, but LVEF can also be assessed by MUGA. The same method should be used throughout the study for each patient and preferably performed and assessed by the same assessor. At baseline, LVEF must be done within 14 days prior to randomization. During study treatment, all assessments will be performed between Days 15-21 of the previous cycle to allow evaluation of the results before the indicated cycle. (Please note that the LVEF should be done as close to the assigned week as possible but prior to the next infusion). For patients receiving anthracyclines, an additional LVEF assessment must be performed before commencing anti HER2 therapy. The Week 52 assessment should occur at Week 52±7days. The assessment should be done at the indicated week, not at the cycle.

m) For patients receiving anthracycline therapy: cardiac signs/symptoms and an additional LVEF assessment must be completed after the last cycle of anthracycline is administered, but prior to the first cycle of targeted treatment. Patients treated with anthracyclines must have an LVEF ≥50% prior to commencing the HER2-targeted component of therapy.

n) Quality of life assessments are MANDATORY and include three questionnaires: EORTC QLQ-C30, QLQ-BR23 and EQ-5D. Quality of life assessment to be collected at the end of taxane treatment, either prior to Cycle 4 or Cycle 5 of targeted treatment for patients who receive taxanes sequentially after anthracyclines; or prior to Cycle 7 of targeted treatment for patients receiving TCH therapy.

o) Hematology and biochemistry should be completed pre-dose on Day 1 of each indicated cycle (or up to 3 days before). Hematology tests (complete blood count) include counts of hemoglobin, white blood cells, neutrophils and platelets. Biochemistry tests include serum creatinine, blood urea nitrogen and electrolytes (P-, Ca2+, Mg2+, Na+, K+, Cl-). At baseline, hematology and biochemistry should be completed within 7 days prior to randomization (and do not need to be repeated within 3 days before first infusion only).

p) Liver function tests include: ALP, ASAT, ALAT, LDH; and total, direct and indirect bilirubin. At baseline, liver function tests should be completed within 7 days prior to randomization.

q) AE and SAEs will be collected from the start of study screening procedures. All non-serious AEs occurring prior to study Day 1 (administration of study treatment) will be reported in the medical history, unless AE reporting is deemed more appropriate. Adverse events are to be monitored continuously during study treatment. All AEs occurring during the study and until the end of treatment/treatment discontinuation visit 28 days after the last dose of study medication are to be recorded and followed up until resolution or until the end of study, whichever occurs first; thereafter only drug-related SAEs and AEs/SAEs that qualify for long-term reporting should continue to be collected (see Section 7.1.2 for details).

r) Concomitant medication will be recorded in the interval beginning 7 days prior to the patient being randomized into the study until the end of the treatment period, and thereafter followed-up as specified in Section 4.4. If a patient has a recurrence, any anti-cancer medication given after the date of diagnosis must be recorded on the post treatment anti-cancer medication page.

s) Refer to Section 5.6.2.1.

t) *A serum sample must be collected for all patients* during the safety follow-up visit 28 days from the last dose of targeted treatment*, including those* patients who drop out of the targeted treatment before Week 52.

Table 9 Schedule of Assessments – Follow-Up Period*

Assessments shown in parentheses [ ] to be performed as clinically indicated	Follow-up Every three months (± 28 days)				Follow-up Every six months (± 28 days)						Follow-up Every 12 months (± 42 days)
	Month 15	Month 18	Month 21	Month 24	Month 30	Month 36	Mon h 42	Month 48	Mon h 54	Month 60	Year 6 until Year 10 *
Radiologic Examinations: - Chest X-ray - Bone scan (a) - Liver imaging - Mammogram (b)		[X] [X] [X]		[X] [X] [X] X	[X] [X] [X]	[X] [X] [X] X		[X] [X] [X] X		[X] [X] [X] X	[X] [X] [X] X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X
Serum sample (biomarker analysis)						[X]				[X]	[X] (h)
Pregnancy Test (urine)	X	X									
Menopausal Status		*X*									
Quality of Life Assessment (c)		X		X		X					
Cardiac Monitoring: - ECG - LVEF - Signs/symptoms		[X] X X		[X] X X	[X] X X	[X] X X		[X] X X		[X] X X	[X] X X
Hematology and Biochemistry (d) - Liver function tests (e)		X X		X X	X X	X X	X X	X X	X X	X X	X X
SAEs (f)	Con inuously										
Concomitant medications (i)	Con inuously										
Record post recurrence anticancer related therapies	Continuously post recurrence (g)										
Survival*	Yearly										

*This table applies to all patients who either complete all study treatment (chemotherapy and targeted) or who discontinue chemotherapy early (i.e., who have not received a dose of targeted treatment). For those patients who discontinue targeted treatment early, the Schedule of Assessments—Follow-up Period applies once they have completed the 28-day follow-up visit and the subsequent Schedule of Assessments—Treatment Period (Patients Who Discontinue Study [(Targeted) Treatment]). Visits are scheduled relative to C1D1 of targeted treatment. Patients who discontinue treatment at the chemotherapy stage, once they have completed the 28-day follow-up visit will then follow the Schedule of Assessments—Follow-up Period, but are only followed for SAEs, concomitant medications, subsequent anticancer therapies and survival. For these patients, visits are scheduled relative to last dose of study medication.

DISEASE RECURRENCE: Patients with local, regional, distant recurrence or contralateral breast cancer should be assessed according to the procedures outlined in Section 5.5.1. Where possible, tumor tissue samples should be collected (see Section 5.5.2). *Serum and plasma samples are MANDATORY*. Thereafter the patient should be followed once a year until Year 10 as described in Section 5.4.1.
*All patients irrespective of treatment allocation should be followed for survival yearly from completion/ discontinuation of treatment period (28 days following the last dose of study medication) until 10 years after the original randomization of the last patient. For this reason patients recruited early in the study may be followed for more than 10 years. For these patients annual follow-up should continue beyond 10 years, as per the assessment schedule specified in this table for 'Years 6 until Year 10'.

a) In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.
b) Mammogram to be performed annually as per local practice.
c) Quality-of-life assessments include the EORTC QLQ-C30, QLQ-BR23 and EQ-5D questionnaire.
d) Hematology tests (complete blood count) include counts of hemoglobin, white blood cells, neutrophils and platelets. Biochemistry tests include serum creatinine, blood urea nitrogen and electrolytes.
e) Liver function tests include: ALP, ASAT, ALAT, LDH; and total, direct and indirect bilirubin.
f) Any AEs and SAEs that are ongoing 28 days after the last dose of study treatment, or new AEs or SAEs requiring long-term reporting, should be followed and reported as described in Section 7.1.2.
g) Information on treatment for breast cancer should be collected for all patients with disease recurrence until 10 years from the original randomization of the last patient. Follow-up after study treatment termination includes survival follow-up and reporting of post study anticancer treatments until the patient withdraws from the study including survival follow up, lost to follow up or death.
h) Serum sample for biomarker analysis *is only* taken at Year 10.
i) Concomitant medications requiring reporting in the follow up period are specified in Section 4.4 (medication applicable for long-term reporting).

Table 10 Schedule of Assessments –Treatment Period (Patients Who Discontinue Study [Targeted Treatment])

Non-mandatory assessments are shown in parentheses [ ]		Weeks											
Beginning of Week		1	4	7	10	13	16	19	22	25	37	52	
Serum, sample (biomarker analysis) (a)						X		X		X	X	X	
Radiologic Examinations (b): - Mammogram or breast MRI - Chest X-ray or chest CT/MRI/PET - Bone scan (c) - Liver imaging										[X] [X] [X] [X]		X [X] [X] [X]	
Pregnancy Test (d)		Continuously (Every 9 weeks/3 cycles) until 6 months after *study drug* discontinuation											
Physical Examination (e) ECOG status (e)						X X				X X	X X	X X	
Cardiac Monitoring: - ECG (f) - LVEF (g) - Signs/symptoms						[X] X X				[X] X X	[X] X X	X X X	
Quality of Life Assessment (h)						X				X			
Hematology & Biochemistry (i) Liver function test (j)						X X				X X	X X	X X	
Menopausal status											X		
Adverse Events (k)	Record continuously until 28 days after discontinuation												
Serious Adverse Events (k)	Record continuously until 28 days after discontinuation												

This table lists the Schedule of Assessments for patients discontinuing targeted treatment early. Safety follow-up should be conducted 28 days after the last dose of targeted treatment. Thereafter the patient should follow Schedule of Assessments—Treatment Period (Patients Who Discontinue Study [(Targeted) Treatment]) until week 52 from the start of targeted treatment dosing has been reached; the patient will then follow the Schedule of Assessments—Follow-Up Period.
DISEASE RECURRENCE: Patients with local, regional, distant recurrence or contralateral breast cancer should be assessed according to the procedures outlined in Section 5.5.1. Where possible, tumor tissue samples should be collected (see Section 5.5.2). *Serum and plasma samples are MANDATORY*. Thereafter the patient should be followed once a year until Year 10 as described in Section 5.4.1.

a. Additional serum sample collection during treatment and at the 28-day safety follow-up visit must be done for all patients if the site has appropriate storage facilities. Refer to the lab manual. See Section 5.6.2.1.

b. Bilateral mammogram or breast MRI and chest x-ray/MRI/PET/CT is to be performed within 6 months prior to randomization. Bone scan and liver imaging is to be performed if clinically indicated to exclude metastatic disease and within a timeline as per current standard of practice.
c. In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.
d. For patients that discontinue the targeted treatment before Week 52, a urine pregnancy test must be done at the safety follow-up visit (28 days from the last dose of targeted treatment), and then every 3 months thereafter until 6 months after the discontinuation of targeted treatment. Any positive urine pregnancy test must be confirmed via a serum β-HCG test. (See Table 9 for pregnancy tests required during the follow-up period).
e. Physical examination and ECOG performance status should be measured at baseline and monitored throughout the study. As a minimum these assessments must be done every 3 months, at Cycle 1, Week 13, Week 25, Week 37 and Week 52 of targeted treatment and at the end of treatment safety follow-up visit. These assessments may be done at more frequent intervals if clinically indicated. Physical examination includes height (at baseline only), weight and vital signs (blood pressure, pulse rate and body temperature).
f. ECGs are required to allow assessment prior to and after the completion of therapy. Additional ECGs to be performed as clinically indicated.
g. LVEF assessment by ECHO is preferred, but LVEF can also be assessed by MUGA. The same method should be used throughout the study for each patient and preferably performed and assessed by the same assessor. At baseline, LVEF must be done within 14 days prior to randomization. During study treatment, all assessments will be performed between Days 15-21 of the cycle to allow evaluation of the results before the next treatment cycle. For patients receiving anthracyclines, an additional LVEF assessment must be performed before commencing anti HER2 therapy. The Week 52 assessment should occur at Week 52 ±7days.
h. Quality of life assessments are MANDATORY and include three questionnaires: EORTC QLQ-C30, QLQ-BR23 and EQ-5D.
i. Hematology tests (complete blood count) include counts of hemoglobin, white blood cells, neutrophils and platelets. Biochemistry tests include serum creatinine, blood urea nitrogen and electrolytes. At baseline, hematology and biochemistry should be completed within 7 days prior to randomization.
j. Liver function tests include: ALP, ASAT, ALAT, LDH; and total, direct and indirect bilirubin.
k. AEs and SAEs are to be monitored continuously during study treatment. All AE/SAEs occurring during the study and until the end of treatment/treatment discontinuation visit 28 days after the last dose of study medication are to be recorded, but are to be followed up until resolution or until the end of study, whichever occurs first; thereafter only drug-related SAEs and AEs/SAEs that qualify for long-term reporting should continue to be collected (see Section 7.1.2 for details).

5.1 Eligibility Screening

All patients must provide written informed consent before any study specific assessments or procedures are performed.

An Eligibility Screening Form (ESF) documenting the patient's fulfillment of the entry criteria is to be completed by the Investigator/designee for all individuals considered for the study and subsequently included or excluded from the study. Patients who are considered for study entry but fail to meet the eligibility requirements should also have an ESF completed with the reason for lack of eligibility given, since this provides information on the selected trial population. All ESFs should be kept in the study files at the sites.

5.1.1 HER2 Screening for Eligibility

Patients should be initially screened for HER2 status by the local laboratory; and should have a HER2 score of 3+ by IHC or HER2 (c-erbB2) gene amplification by in situ hybridization (FISH, SISH or CISH) to qualify for central laboratory screening (Figure 3).

For local assessments, HER2 positivity is defined as the following: IHC 3+ in >10% immunoreactive cells OR c-erbB2 gene amplification by ISH (as defined by local standards).

For central confirmation, HER2 positivity is defined as IHC 3+ in >10% immunoreactive cells OR c-erbB2 gene amplification by ISH (ratio of c-erbB2 gene signals to centromere 17 signals ≥ 2.0).

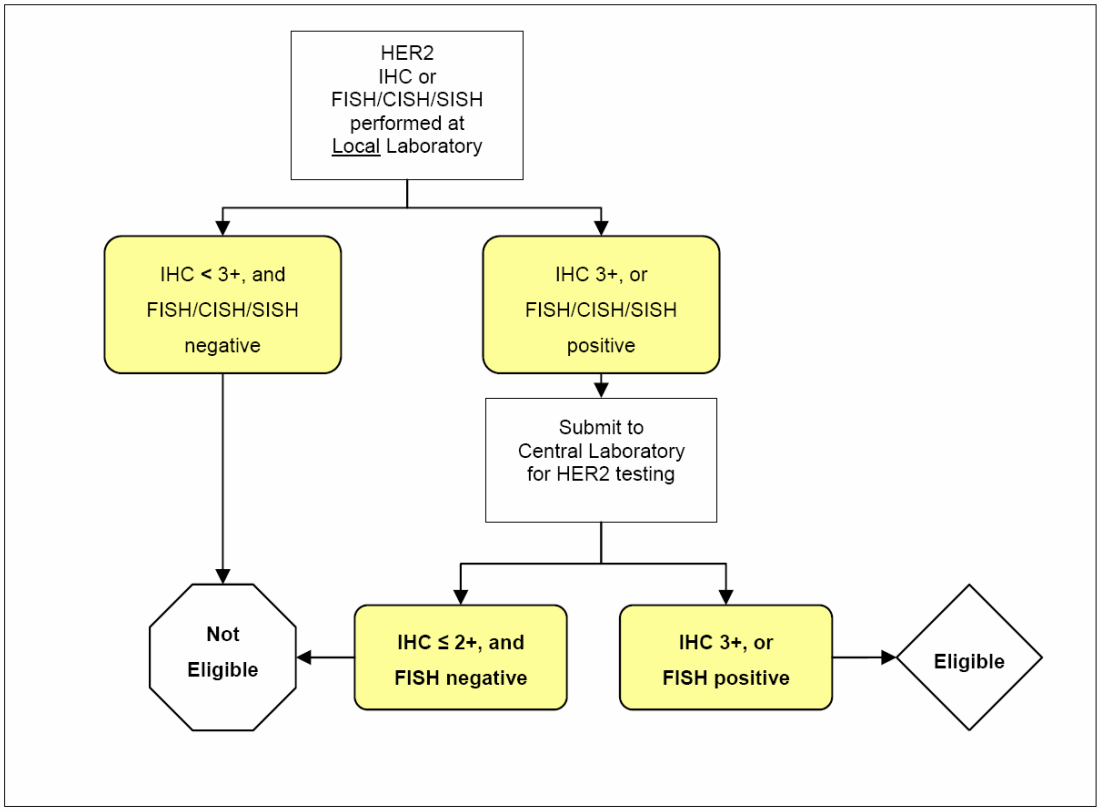
Central laboratory confirmation of a positive HER2 status is required prior to randomization to the study. The outcome of this assessment will be communicated to the investigator and the applicable data also transferred directly into the randomization system.

In addition, central assessment of hormone receptor status (ER and PgR) will be conducted for the purpose of stratification, the results of which will also be communicated to the investigator.

Only patients who are HER2 positive by central determination will be allowed to enter the study; patient with overall negative and equivocal scores will be excluded from entry to the study.

After completion of HER2 testing for eligibility criteria applying pre-specified HER2 tests, patient samples may also be tested with other HER2 assays to establish performance characteristics of these assays for diagnostic development. Testing could be performed on all screened patients (screen-failed and enrolled). These testing data will have no impact on eligibility and testing will be performed only after eligibility is established for each patient.

Figure 3 HER2 Screening Procedure



HER2 positivity is defined as the following: IHC 3+ in > 10% immunoreactive cells OR c-erbB2 gene amplification by ISH (ratio of c-erbB2 gene signals to centromere 17 signals ≥ 2).

5.1.2 Cardiac Function Screening

All patients must have an LVEF measurement of at least 55% by echocardiography (preferably) or MUGA scan a maximum of 14 days prior to randomization. Investigators must be aware of local institution regulations regarding the maximum allowable frequency of repeat MUGA scans. The repeated administration of radioisotopes is limited in some nuclear medicine laboratories and some patients in this study could require monitoring on four or more occasions within one year.

Patients must also be assessed for history of cardiac events, physical exam, and a baseline ECG prior to enrollment to exclude any cardiac condition that would render them ineligible for participation in this trial, as outlined in Sections 4.2 and 4.3.

5.1.3 Other Eligibility Screening

All other investigations (e.g., chest X-ray, MRI, PET, computer tomography [CT] scan, etc.) which were performed as part of standard patient care prior to primary surgery or within the appropriate screening window prior to study entry, and prior to signing the definitive informed consent form for the study, may be used to fulfill inclusion/exclusion criteria as outlined in Table 8.

Investigations which are regarded as 'standard patient care' for this study are:

- Bilateral mammogram or breast MRI (within 6 months prior to randomization)
- Chest X-ray/MRI/PET (within 6 months prior to randomization)
- CT scan (within 6 months prior to randomization)
- Bone scan

The following items should be reviewed and recorded at screening (after surgery and prior to randomization), unless otherwise specified:

- HER2 determination by the Central Laboratory (any time after written informed consent has been signed).
- Complete medical history including breast cancer history, clinically significant diseases and surgical procedures within the last 5 years, smoking history and significant prior or concomitant medications.
- Demographic data: date of birth, race and ethnicity, gender
- ECOG performance status (see Appendix 3).
- Physical examination must include assessment of vital signs (blood pressure, pulse rate, and body temperature) and physical measurements (body weight in kilograms and height in centimeters). In the physical examination, particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated Jugular Venous Pressure [JVP], sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc).
- Cardiac monitoring to include: ECG, LVEF (within 14 days prior to randomization), and signs and symptoms of cardiac disease.
- Radiological examinations to rule out metastatic and contralateral disease: Chest X-ray (MRI, PET, and CT are acceptable) (within 6 months prior to randomization) and bilateral mammogram or breast MRI (within 6 months prior to randomization) are mandatory. Breast imaging must be performed on both breasts, unless a mastectomy has been performed.
- Assessment of skeletal status using radioisotope bone scan, skeletal MRI or F18 PET, if clinically indicated (e.g., if there is an area of localized pain).
- Liver imaging if there are symptoms or clinical suspicion of liver metastasis present.
- Hematology and blood biochemistry tests (within 7 days prior to randomization):
    - Hematology: counts of hemoglobin, total WBC, neutrophils, platelets.
    - Biochemistry: serum creatinine, blood urea nitrogen, electrolytes (P-, Ca2+, Mg2+, Na+, K+, Cl-)
    - Liver function tests: ALP, ASAT, ALAT, LDH, bilirubin (total, direct and indirect).
- Pregnancy Test: a serum β-HCG test must be performed for all women of childbearing potential and for all women not meeting the definition of postmenopausal (see Table 6), and who have not undergone surgical sterilization. Testing must be performed at a local laboratory within 7 days prior to randomization. For all other women, documentation must be present in the medical history confirming that the patient is not of childbearing potential.

Additional requirements at baseline:

- Patient-reported outcomes (PRO): PRO of HRQL, symptoms and global quality of life/health status measured using the EORTC QLQ—C30, QLQ—BR23, and EQ-5D questionnaires (for further details see Section 8.1.5). It is mandatory for all 3 questionnaires to be completed by the patient during the screening period or after randomization, as long as they are completed before the first dose of study (targeted) treatment is administered.
- A mandatory blood sample (whole blood, serum, and plasma) for biomarker research must be collected at baseline for all patients as described in Section 5.6.2. This sample must be collected after randomization, but before the first dose of study treatment is administered.
- If the patient has consented to the pharmacogenetic substudy, a whole blood sample should be collected at baseline as described in Section 5.6.3.

5.2 Procedures for Enrollment of Eligible Patients

Once HER2 positivity is confirmed by the Central Laboratory and the patient is considered eligible for the trial after completing all required assessments, the Investigator will choose which type of adjuvant therapy the patient should receive (Investigators' Choice). Patients will then be randomly assigned to receive trastuzumab plus pertuzumab OR trastuzumab plus placebo. Patients, investigators, study staff and the sponsor will be blinded to therapy. Patient identification numbers will be allocated sequentially in the order in which patients are screened via the web-based randomization system.

The Investigator or designee will then enter the patients' data into the eCRF, which will be used for electronic data capture (EDC). A Patient Enrollment and Identification Code List must be maintained by the Investigator.

Randomization allocations will be generated by the web-based randomization system.

5.3 Treatment Period Assessments and Procedures

The following assessments and procedures will be completed for randomized patients as shown in Table 8. Specific data points to be collected will be detailed in the eCRF.

During the treatment period, a window of ± 3 days will apply to all visits; total treatment duration for targeted treatment (defined as day 1 from first cycle until day 1 of last cycle) will not exceed 365 days +3 days.

All assessments must be performed before study treatment administration on Day 1 of the cycle or up to 3 days prior, unless otherwise specified.

Patients receiving ANTHRACYCLINE-BASED chemotherapy must be followed in accordance with the assessments and procedures outlined in:

- Section 5.3.1 during anthracycline treatment
- Section 5.3.2 during HER2-targeted treatment

Patients receiving NON-ANTHRACYCLINE-BASED chemotherapy must be followed in accordance with the assessments and procedures outlined in:

- Section 5.3.2 (HER2- targeted treatment) only.

5.3.1 Anthracycline Treatment - Required Assessments and Procedures

The following assessments must be completed while the patient is receiving anthracycline-based chemotherapy (3-4 cycles).

- Symptom-directed physical examination including assessment of vital signs and weight must be performed on Day 1 of the first cycle of anthracyclines. These assessments may be performed at more frequent intervals if clinically indicated.
    - Vital signs including blood pressure, pulse rate, and body temperature.
    - Weight must be compared to the baseline weight. If a ± 10% variation occurs then chemotherapeutic doses will be recalculated.
    - Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc).
- Hematology and blood biochemistry tests on Day 1 of each cycle:
    - Hematology: counts of hemoglobin, total WBC, neutrophils, platelets.
    - Biochemistry: serum creatinine, blood urea nitrogen, electrolytes (P-, Ca2+, Mg2+, Na+, K+, Cl-)
    - Liver function tests: ALP, ASAT, ALAT, LDH, bilirubin (total, direct and indirect).
- Serum samples (end of anthracycline treatment)
- ECOG performance status before administration of the first cycle of anthracyclines.
- Cardiac monitoring: LVEF (same method to be used throughout), and signs and symptoms must be assessed after the last dose of anthracycline therapy is administered (Days 15-21), but prior to the first cycle of targeted treatment. ECG should be performed if clinically indicated.
- Patients who receive anthracycline chemotherapy must have an additional LVEF assessment at the end of anthracycline treatment in order to ensure they are fit to receive HER2- targeted treatment. Patients treated with anthracyclines must have an LVEF ≥ 50% prior to commencing the HER2-targeted component of therapy.
- AEs including SAEs documented according to NCI-CTCAE v 4.0.

Concomitant medications and cancer-related surgery or procedures documented.

- Patient-reported outcomes (PRO): All 3 questionnaires (EORTC QLQ-C30, QLQ-BR23, and EQ-5D) must be completed by the patients at the end of the anthracycline treatment period.

5.3.2 Targeted Treatment Period – Required Assessments and Procedures

The following assessments must be completed and recorded during the HER2-targeted treatment period. During this time, the patient will receive 3 to 6 cycles of concurrent taxane therapy, according to the Investigators' choice of chemotherapy specified at the

time of randomization (NOTE: 1 cycle equals 3 weeks [or 2 weeks in the case of dose-dense treatment]).

All patients will be followed from the first day of targeted treatment (either first anthracyclines administration or first targeted treatment for the non-anthracycline patients) through to Week 52 of targeted treatment, according to the assessment schedule outlined in Table 8. Thereafter, Table 9 outlines the schedule of assessments during the follow-up period after Week 52.

- Symptom-directed physical examination must include assessment of vital signs and weight on Day 1 of Cycle 1, Week 13, Week 25, Week 37 and Week 52 of targeted treatment and at the end of treatment safety follow-up visit. These assessments may be performed at more frequent intervals if clinically indicated.
    - Vital signs including blood pressure, pulse rate, and body temperature.
    - Weight must be compared to the baseline weight. If a ± 10% variation occurs then the trastuzumab and taxane doses will be recalculated. The pertuzumab/placebo dose should not be adjusted.
    - Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc).
- ECOG performance status before study treatment administration at Cycle 1, Week 13, Week 25, Week 37, Week 52 and at the end of treatment safety follow-up visit.
- Cardiac monitoring will occur 13, 25, 37 and 52 weeks from the first dose of targeted treatment and will include assessment of LVEF (same method to be used throughout), and signs and symptoms. ECG will be done at Week 52, and as clinically indicated (at Weeks 13, 25 and 37). ECG and LVEF assessments will be performed between Days 15–21 of the previous cycle to allow evaluation of the results before the next treatment cycle.
- Radiological examinations: A bilateral mammogram or breast MRI will be completed yearly from that performed at screening/surgery as per clinical practice, and as clinically indicated upon finding from physical examination. Breast imaging must be performed on both breasts unless a mastectomy was done. Chest X-ray/MRI/PET, CT scan, bone scan and liver imaging should be done if clinically indicated.
- All AEs including SAEs during targeted treatment until 28 days after the last dose must be documented according to NCI-CTCAE version 4.0. Thereafter, only SAEs related to investigational medicinal product (IMP, pertuzumab), or AEs/SAEs qualifying for long-term reporting should be reported. See Section 7.1.2 for AE and SAE reporting requirements.
- Concomitant medications, and any cancer-related surgery or procedures performed must be documented at each visit including: prescription, over-the-counter, and herbal/homeopathic remedies and/or therapies; and any cancer-related diagnostic, therapeutic, or surgical procedures.

- Hematology and blood biochemistry tests:

Hematology and biochemistry tests will be performed within 3 days of Day 1 of every indicated cycle (see Schedule of Assessments) until Week 25 then at Weeks 37 and 52. Liver function test will be performed at the start of every cycle during taxane chemotherapy and then at Weeks 13, 25, 37 and 52.

  - Hematology: counts of hemoglobin, total WBC, ANC, platelets.
  - Biochemistry: serum creatinine, blood urea nitrogen, electrolytes (P-, Ca2+, Mg2+, Na+, K+, Cl-)
  - Liver function tests: ALP, ASAT, ALAT, LDH, bilirubin (total, direct and indirect).
- Blood or urine pregnancy test for all women of childbearing potential, and for all women not meeting the definition of postmenopausal (Table 6) and who have not undergone surgical sterilization, pregnancy tests must be performed as described below:
  - Prior to the first dose of targeted treatment (pre-dose Cycle 1)(serum) approximately every 9 weeks (3 treatment cycles), and as clinically indicated (urine; if urine test is positive, confirm with serum test)
  - For patients who discontinue the targeted treatment before Week 52, a pregnancy test must be done at the safety follow-up visit (28 days from the last dose of targeted treatment), and at 3 months, 6 months after the discontinuation of study treatment (urine; if urine test is positive, confirm with serum test)

Any positive urine pregnancy test must be confirmed via a serum β-HCG test. Treatment period pregnancy test results must be available prior to the administration of the next treatment cycle.

- Patient-reported outcomes (PRO): All 3 questionnaires EORTC QLQ-C30, QLQ-BR23, and EQ-5D) must be completed by the patients at the following time points during the targeted treatment period (see Section 8.1.5 for further details):
  - Weeks 13 and 25
  - Safety follow-up at the end of study treatment which corresponds to 28 days from the last dose of targeted treatment.

Additional blood samples (serum) for biomarker research must be collected for all patients during treatment if the site has appropriate storage facilities (as described in Section 5.6.2.1). A serum sample is to be collected at the end of taxane treatment, either prior to Cycle 4 or Cycle 5 of targeted treatment for patients who received taxanes sequentially after anthracyclines; or prior to Cycle 7 of targeted treatment for patients receiving TCH therapy. *A* serum sample must be collected during the safety follow-up visit 28 days from the last dose of targeted treatment*, including patients who drop out of the targeted treatment before Week 52*.

5.4 Post–Treatment Follow-Up Assessments and Procedures

Once the HER2-targeted treatment period (52 weeks + 3-day window) is complete (including the end of study treatment safety follow-up visit), all patients should continue

to be followed up according to the schedule outlined in Table 9. In the case of premature discontinuation of the targeted treatment, patients should continue to be followed up as per Table 10; once 52 weeks has then elapsed from the time targeted treatment has been commenced, patients are to be followed up as per Table 9.

All patients must be followed until approximately 10 years after the randomization of the last patient, irrespective of their treatment arm, even if the assigned treatment is discontinued permanently. For this reason, some patients will be followed for more than 10 years (due to the 25 month projected recruitment period). For example, if the first patient is enrolled on 1 October 2011 and the last patient is enrolled on 1 December 2013, the follow-up period for all patients will end on 1 December 2023. Therefore, the first patient enrolled will actually complete approximately 12 years of follow-up.

All participating sites will be informed of the end of follow-up date for the study shortly after the last patient is enrolled.

The schedule of follow-up visits and tests for this study (Table 9) is the minimum required; investigators may wish to see their patients more frequently according to their routine practice.

5.4.1 Survival Follow-up

In cases of disease recurrence (please refer to events described in Section 5.5) diagnosed at any time during the study, patients will be out of the study schedule (Table 8 and Table 10) and will be followed once a year (starting 1 year after first relapse) until Year 10 after randomization of the last patient for survival and new relapse events as per secondary endpoints. In addition, post-recurrence anticancer related therapies, SAEs and cardiac events will continue to be collected.

5.5 Recurrence of Disease – Acceptable Procedures for Confirmation

5.5.1 Acceptable Procedures for Confirmation of Disease Recurrence

The diagnosis of a first breast cancer recurrence or second primary cancer can be made only when clinical, radiological and laboratory findings meet specific ‘acceptable’ criteria as defined below:

Suspicious findings do not usually constitute criteria for breast cancer recurrence, nor are they an indication to alter protocol therapy. Under certain circumstances, however, suspicious findings that remain suspicious may be so clinically relevant that they lead to the indication for a change in the therapy.

In cases of diagnostic doubt (e.g., ill-defined, palpable mass in an irradiated breast), histological or cytological confirmation of recurrence should be obtained whenever possible.

Some patients may develop a suspicious recurrence that leads to death quite quickly without having the possibility to confirm relapse of disease. Efforts should be made to obtain an autopsy report in such patients.

The earliest date of diagnosis of recurrent disease should be used and recorded. This should be based on clinical, radiological, histological or cytological evidence. The recurrence of disease has to be backdated to the date of the first diagnosis of lesion (i.e., an objective finding), not to the date of occurrence of the first symptom.

For example, a patient presenting with abdominal pain is found to have a possible lesion on liver CT scan of uncertain significance. If a subsequent CT scan confirms disease progression, the date of the first diagnostic CT scan should be taken as the date of recurrence (not the date of presentation with abdominal pain). Thus, the actual date of relapse of disease is the time of first appearance of a suspicious lesion (in a radiological procedure in this case), later proven to be a definitive recurrence or metastasis.

Recurrent disease includes: local, regional, distant recurrence and contralateral breast cancer. Patients who are diagnosed with in situ breast disease or second (non-breast) malignancies should be maintained in regular follow-up wherever possible in order to fully capture any subsequent recurrent disease events.

NOTE: Types of recurrent disease are listed below, along with acceptable methods of confirmation of recurrence. Invasive disease must be positively identified in accordance with the pathology guidance given in Appendix 6.

a) Local invasive recurrence

- **In the ipsilateral breast after previous lumpectomy**

Defined as evidence of invasive tumor (except DCIS and LCIS) in the ipsilateral breast after lumpectomy. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast should have a biopsy of the suspicious lesion to confirm the diagnosis. See Section 6.2 for treatment options.

– positive histology or cytology

- **Ipsilateral after previous mastectomy**

Defined as evidence of invasive tumor in any soft tissue or skin of the ipsilateral chest wall. This includes the area bounded by the midline of the sternum, extending superiorly to the clavicle, and inferiorly to the costal margin. Soft tissue recurrences in this area extending into the bony chest wall or across the midline will be considered as evidence of local recurrence.

– positive histology or cytology

b) Regional recurrence

Defined as the development of tumor in the ipsilateral internal mammary lymph nodes, ipsilateral axillary lymph nodes or supraclavicular lymph nodes as well as extranodal soft tissue of the ipsilateral axilla. Regional recurrence does not include tumor in the opposite breast.

– Positive histology or cytology, or

– Chest-x-ray, CT-scan or MRI (especially in case of internal mammary lymph nodes if no biopsy was performed)

c) Distant recurrence
Defined as evidence of tumor in all areas, with the exception of those described in Sections a) and b) above

The following criteria apply:

- **Skin, subcutaneous tissue, and lymph nodes (other than local or regional)**

– positive cytology, aspirate or biopsy, or

– radiological (by CT scan or MRI or ultrasound) evidence of metastatic disease.

- **Bone**

– X-ray, CT scan, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, or

– Bone scan (requires additional radiological investigation, alone not acceptable in case of diagnostic doubt), or

– Biopsy proof of bone metastases or cytology

- **Bone marrow**

– positive cytology or histology or MRI scan

- **Lung**

– Radiologic evidence of multiple pulmonary nodules consistent with pulmonary metastases

– Positive cytology or histology (practically rarely performed with the exception of solitary nodules)

NOTE: For solitary lung lesions, cytological or histological confirmation should be obtained in case of diagnostic doubt. Proof of neoplastic pleural effusions should be established by cytology or pleural biopsy.

- **Liver**

– Abdominal CT scan, liver scan, ultrasound, or MRI consistent with liver metastases, or

– Liver biopsy or fine needle aspiration.

NOTE: If radiological findings are not definitive (especially with solitary liver nodules) a liver biopsy is recommended; however, if a biopsy is not performed, serial scans should be obtained if possible to document stability or progression.

- **Central nervous system (please note that these recurrences should be reported at any time)**

– Positive MRI or CT scan, usually in a patient with neurologic symptoms, or

– Biopsy or cytology (e.g., for a diagnosis of meningeal involvement). However, meningeal involvement may also be diagnosed by CT scan or MRI and depending from the general status of the patient additional investigations (including cytology of the cerebrospinal fluid).

d) Contralateral invasive breast cancer

– positive cytology or histology

e) Second primary malignancy (breast or other cancer)

Any positive diagnosis of a second (non-breast) primary cancer*, with the exception of non-melanoma skin cancers and carcinoma in situ of any site,* will be considered an event in the analysis of the invasive disease-free survival including second primary non-breast cancer endpoint, however, they will not be included in the IDFS primary endpoint.
LCIS of the breast and myelodysplastic syndrome are not considered progression events.
The diagnosis of a second primary cancer must be confirmed histologically.

All second primary malignancies are to be reported whenever they occur during the study.

NOTE: Patients diagnosed with a second primary malignancy not requiring systemic therapy (i.e., chemotherapy, hormonal therapy, targeted treatment, etc) and with no evidence of breast cancer recurrence will remain on study and should continue with study treatment according to the protocol and schedule of assessment, if considered by the investigator to be in the patient's best interest, whenever possible.

f) Death without recurrence

Any death occurring without prior breast cancer recurrence or second (non-breast) malignancy is considered an event for the following endpoints: IDFS, invasive disease-free survival including second primary non-breast cancer, DFS, and OS.

g) Other noteworthy events

The following events should be recorded on the follow-up eCRF. These events are NOT considered recurrent disease, but must be recorded.

– Ipsilateral and contralateral LCIS

– Ipsilateral and contralateral DCIS

– Carcinoma in situ of the cervix

– Basal or squamous cell carcinoma of the skin

Please note: Following recurrence, all patients should be followed for survival as described in Section 5.4.1. In addition, safety follow-up visit(s) should be performed. Please refer to Section 5.4 for further details.

5.5.2 Tumor Tissue, Serum, *and Plasma* Sample Collection at Disease Recurrence

Tissue collection at disease recurrence

For patients diagnosed with a local or contralateral breast cancer, the study team request submission of an FFPE tumor block from the biopsy or surgical sample (preferred) that was used to diagnose recurrent disease, for central pathology review and subsequent translational research.

Likewise for regional or distant metastases, an FFPE tumor block from the biopsy or surgery (preferred) *or if biopsy or surgical samples are not available, a fine-needle aspiration sample* should be obtained and sent to the central laboratory for central review and future translational research.

Serum *and plasma* collection at disease recurrence

*A*n additional serum *and plasma* sample (*each* prepared from 10 mL of peripheral blood) should be collected at disease recurrence *or a timepoint close to diagnosis of disease recurrence* (see Section 5.6.2.1 for further details) *but prior to the initiation of any new lines of therapy for disease recurrence.*

5.6 Biomarker Research Samples

The tissue and blood samples collected will be used to identify biomarkers that may be predictive of response or toxicity to pertuzumab/trastuzumab treatment and/or prognostic for breast cancer. Since the knowledge of new markers that may correlate with disease activity and the efficacy or safety of the treatment is evolving, the analytes may change during the course of the study and may include determination of additional markers of tumorigenesis pathways and mechanisms of response to anti-HER2 therapies. The collected tumor tissue and blood samples may also be used to develop and validate diagnostic assays and allow the generation of statistically meaningful biomarker data. Remaining sample materials after the completion of the initial biomarker assessments (e.g., aliquots of tumor RNA or DNA) may be used for re-testing, developing and validating diagnostic assays, or for further assessment of expanded marker panels. Samples will be stored at a study's central biological samples repository for up to 15 years after database closure, with the additional option of further long-term storage (see Section 5.6.4).

For sampling procedures and shipment see instructions in the Sample Collection, Handling and Logistics Manual.

5.6.1 Tumor Tissue Samples

5.6.1.1 FFPE Tumor Block (Mandatory)

Submission of a tumor block from the primary tumor (definitive surgery sample) is mandatory and will be collected for study eligibility testing (central confirmation of HER2 status, see Section 5.1.1).

Note: For a patient with bilateral breast cancer, two FFPE tissue blocks, one from each breast, must be provided to the central laboratory for confirmation of HER2 eligibility.

In addition, a minimum of 4 and up to 7 x 1mm cores of tissue will be taken from the tumor block of each patient that enters the study for biomarker research, provided that this does not exhaust the invasive tumor in the block.

FFPE tumor blocks (screening) will be returned to site.

A variety of methodologies may be applied in the above biomarker evaluation, including, but not limited to, qRT-PCR, immunohistochemistry, ELISA, in situ hybridization, and gene expression profiling. The most suitable analytical methodologies will be selected and employed. All samples should be prepared and stored as detailed in the Sample Collection, Handling and Logistics Manual.

Extraction of nucleic acids (DNA and RNA) may be required to perform these analyses.

See Section 5.5.2 for details on tissue collection at disease recurrence.

5.6.1.2 Fresh Frozen Tissue (Optional)

Sites that routinely collect fresh frozen tissue at surgery will have the option to allocate this material, if available, to the study. This will be subject to additional patient consent.

A variety of methodologies may be applied in the biomarker evaluation, including, but not limited to, analysis of proteins and phospho-proteins, analyses involving RNA (gene expression, microRNA, methylation) and Next Generation Sequencing NGS.

The most suitable analytical methodologies will be selected and employed. All samples should be prepared and stored as detailed in the Sample Collection, Handling and Logistics Manual.

In cases of bilateral breast cancer, a sample from each breast is requested.

5.6.2 Baseline Whole Blood, Serum and Plasma Samples (Mandatory)

At baseline (prior to the start of cycle 1), a mandatory whole blood, serum and plasma sample (each prepared from 10 mL of peripheral blood) will be collected for biomarker assessment for pertuzumab/trastuzumab response prediction and assessment of cardiac markers. The biomarkers evaluated may include levels of shedded HER2 and selected HER ligands, and/or markers thought to be important for HER family signaling, or response to HER inhibitors and HER activation, as well as, markers of cardiac dysfunction.

5.6.2.1 Additional Serum and Plasma Samples (Subject to the Site Having Appropriate Storage Facilities)

Where possible, additional serum samples (prepared from 10 mL of peripheral blood) will be collected throughout the treatment and follow-up phases of the study for biomarker assessment of pertuzumab/trastuzumab response prediction and assessment of cardiac markers.

Samples will be collected at the following time points:

- After the last dose of anthracycline therapy, but prior to starting targeted treatment;
- At the completion of taxane therapy (end of Cycle 3 or 4 of targeted treatment for patients who receive FEC → T or AC → T; or end of Cycle 6 for patients who receive TCH);
- At weeks 25, 37 and 52;
- At years 3 (Month 36), 5 (Month 60), and 10 from the start of targeted treatment;
- At disease recurrence (if any)*, both serum and plasma samples will be collected*

The biomarkers evaluated with serum samples may include levels of shedded HER2 and selected HER ligands, and/or markers thought to be important for HER family signaling, or response to HER inhibitors and HER activation. In addition, biomarkers of cardiac dysfunction will be evaluated and may include troponin T, troponin I and BNP.

5.6.3 Pharmacogenetic Analysis (Subject to Additional Patient Consent)

Specimens for genetic-based biomarker discovery and validation will be collected from consenting patients.

The pharmacogenetic information gathered through the analysis of these specimens is hoped to improve patient outcome by predicting which patients are more likely to respond to specific drug therapies, predicting which patients are susceptible to developing adverse side effects, and/or predicting which patients are likely to progress to more severe disease states. Such genetic samples collected for analysis of heritable (germline) DNA variations will be double-coded: a new independent code will be added to the first code to increase confidentiality and data protection.

The results of specimen analysis from the pharmacogenetic analysis will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Collection of blood samples requires separate patient consent. Individual patients may refuse the collection, storage and use of their blood for genetic analysis, however this will not exclude them from this study.

If the patient consents, the following sample should be submitted:

Blood (approximately 10 mL in K3 EDTA) for DNA isolation will be collected. If, however, the genetic blood sample is not collected at screening/baseline or during the scheduled visit, it may be collected at any time (after randomization) during the conduct of the clinical study. See the Sample Collection, Handling and Logistics Manual for more details.

5.6.4 Retention and Destruction of Samples

The specimens in the study repository will be made available for future biomarker research towards further understanding of treatment with pertuzumab and trastuzumab, of

breast cancer, related diseases and adverse events, and for the development of potential associated diagnostic assays. The implementation and use of the study repository specimens is governed by the Study Steering Committee, with guidance from a dedicated translational advisory committee to ensure the appropriate use of the study specimens.

All biomarker specimens will be retained for new research related to this study and/or disease in accordance with the recommendations and approval of the Study Steering Committee. Samples will be only destroyed if required by local laws relating to the collection, storage and destruction of biological specimens. Samples will be destroyed if the patient withdraws consent, but data from the analysis performed until then will be retained.

5.7 Pharmacokinetic and Drug-Drug Interaction Substudies

A subset of principal investigators and patients will participate in pharmacokinetic and drug-drug interaction substudies as detailed in separate protocols.

Separate Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval and Informed Consent Form will be required for participation in each substudy.

For sampling procedures and shipment see instructions in the Sample Collection, Handling and Logistics Manual.

6. INVESTIGATIONAL MEDICINAL PRODUCT

Study treatment is defined as adjuvant (post-operative surgery) treatment. The procedures for randomization and blinding are detailed in Sections 3.2 and 6.7, respectively.

Throughout the study, the investigational medicinal product is pertuzumab. A pertuzumab matched placebo will also be provided.

5-FU, epirubicin, doxorubicin, cyclophosphamide, carboplatin and paclitaxel are considered standard of care (Table 4). Trastuzumab and docetaxel are administered in accordance with their local prescribing information so these drugs are not regarded as Investigational Medicinal Products. A typical nomogram is provided for the determination of body surface area (see Appendix 7).

The choice of which adjuvant chemotherapy is given will be determined by the Investigator prior to randomization. Randomization will determine whether a patient receives adjuvant therapy with trastuzumab plus pertuzumab OR trastuzumab plus placebo. Patients, investigators, study staff and the sponsor will be blinded as to this assignment.

Prescribing of hormone therapy post-chemotherapy, where applicable, is in accordance with the protocol recommendations (see Section 4.4.3), local prescribing information and/or standard practice.

Radiotherapy should be applied as clinically indicated in accordance with the protocol recommendations (see Appendix 2).

6.1 Adjuvant Chemotherapy and Trastuzumab plus Pertuzumab/Placebo Therapy

The Investigator can choose to treat the patient with either an anthracycline-based chemotherapy (Sections 6.1.1 and 6.1.2) or a non-anthracycline-based chemotherapy (Section 6.1.3) following the procedures below.

6.1.1 Anthracycline-Based Chemotherapy: FEC (or FAC) →TH + P (Pertuzumab/Placebo)

3 or 4 cycles of FEC (or FAC): Cycles 1-3 (or 1-4)

5-FU 500-600 mg/m^2, epirubicin 90-120 mg/m^2 (doxorubicin 50 mg/m^2 is acceptable) and cyclophosphamide 500-600 mg/m^2 IV q3w.

Followed by:

3 to 4 cycles of TH + P (pertuzumab/placebo): Cycles 4-6 (4-7, 5-7, or 5-8)

Trastuzumab IV, followed by pertuzumab/placebo IV will be administered on Day 1 of the first taxane-containing cycle. Docetaxel or paclitaxel will be administered after the pertuzumab/placebo infusion is completed.

Trastuzumab will be given at a loading dose of 8 mg/kg, and pertuzumab/placebo at 840 mg. For all subsequent cycles, trastuzumab will be given as a maintenance dose of 6 mg/kg and pertuzumab/placebo at 420 mg q3w.

Intravenous docetaxel when used in sequence with an anthracycline and cyclophosphamide will be used at 100 mg/m^2 for a minimum of 3 cycles. To ensure that all patients are treated optimally and where local practice dictates, 4 cycles of docetaxel at 75 mg/m^2 may be given. Alternatively the dose of docetaxel may be started at 75 mg/m^2 in the first cycle, and escalated to 100 mg/m^2 if no dose limiting toxicity occurs (see Section 6.6.2.1).

Paclitaxel may also be used instead of docetaxel and must be given at 80 mg/m^2 qw for 12 weekly cycles.

6.1.2 Anthracycline-Based Chemotherapy: AC→TH + P (Pertuzumab/Placebo)

4 cycles of AC (or EC): Cycles 1-4

Doxorubicin 60 mg/m^2 (or epirubicin 90-120 mg/m^2) and cyclophosphamide 500-600 mg/m^2 IV q3w OR q2w for four cycles (dose dense) with G-CSF support.

Followed by:

3 or 4 cycles of TH + P (pertuzumab/placebo): Cycles 5–7 (or 5–8)

Trastuzumab IV followed by pertuzumab/placebo IV will be administered on Day 1 of the first taxane-containing cycle. Docetaxel or paclitaxel will be administered after the pertuzumab/placebo infusion is completed.

Trastuzumab will be given at a loading dose of 8 mg/kg and pertuzumab/placebo at 840 mg. For subsequent cycles, trastuzumab will be given as a maintenance dose of 6 mg/kg and pertuzumab/placebo at 420 mg q3w.

Intravenous docetaxel when used in sequence with an anthracycline and cyclophosphamide will be used at 100 mg/m^2 for a minimum of 3 cycles. Where local practice and/or guidelines dictate, 4 cycles of docetaxel at 75 mg/m^2 may be given. Alternatively the dose of docetaxel may be started at 75 mg/m^2 in the first cycle, and escalated to 100 mg/m^2 if no dose limiting toxicity occurs (see Section 6.6.2.1).

Alternatively paclitaxel may be used instead of docetaxel and must be given at 80 mg/m^2 qw for 12 weekly cycles.

6.1.2.1 Notes on Adjuvant Chemotherapy

5-Fluorouracil

5-FU will be administered at 500-600 mg/m^2 on day 1 of each cycle of FEC/FAC treatment. It will be given as an IV bolus or infusion in accordance with local policy. Patients should be dose capped at 1200 mg. Dose delays and dose reductions for toxicity are permitted. 5-FU will be administered q3w for three cycles.

Epirubicin

Epirubicin will be administered at 90-120 mg/m^2 on Day 1 of FEC/EC treatment. It may be given as an IV bolus over 3–5 minutes or as an infusion over 15–30 minutes. Dose delays and dose reductions for toxicity are permitted. Epirubicin will be administered q3w for three cycles OR q2w for four cycles (dose dense) with G-CSF support.

Doxorubicin

Doxorubicin will be administered at 50–60 mg/m^2 on Day 1 of AC/FAC treatment. It may be given as an IV bolus over 3–5 minutes or as an infusion over 15–30 minutes. Dose delays and reduction for toxicity are permitted. Doxorubicin will be administered q3w for four cycles OR q2w for four cycles (dose dense).

Cyclophosphamide

Cyclophosphamide will be administered at 500-600 mg/m^2 on Day 1 of treatment. It should be given as an IV bolus over 3–5 minutes or as an infusion, in accordance with local policy. Patients should be dose capped at 1200 mg. Dose delays and dose reductions for toxicity are permitted. Cyclophosphamide will be administered q3w for three/four cycles OR q2w (dose dense). Note: Oral cyclophosphamide is not permitted.

Docetaxel

Docetaxel will be administered at 100 mg/m^2 as an IV infusion over 60 (± 10) minutes, after the trastuzumab plus pertuzumab or trastuzumab plus placebo infusion observation period.

Docetaxel may also be administered at 75 mg/m^2 as an IV infusion and may be escalated in the subsequent cycle(s) (from Cycle 2 onwards) to 100 mg/m^2, if no limiting toxicity

occurs OR docetaxel may be administered at 75 mg/m^2 for 4 cycles q3w (see Section 6.6.2.1).

If a Grade 3 or 4 non-hematological toxicity is experienced, docetaxel may be reduced from 100 mg/m^2 to 75 mg/m^2; and again to 60 mg/m^2 if required.

Patients must be closely observed from the start of the infusion for hypersensitivity reactions which may occur within minutes. Severe hypotension, bronchospasm or generalized rash/erythema requires immediate discontinuation of docetaxel and appropriate treatment. The infusion may be slowed for minor symptoms like flushing or local cutaneous reactions. Patients experiencing severe hypersensitivity reactions should be discontinued from the study treatment, but maintained in the schedule of assessments unless consent is withdrawn. Pre-medication consisting of a corticosteroid according to institutional guidelines.

Dose reduction (and dose delays if necessary) and/or prophylactic G-CSF may be used to mitigate the risk of hematological toxicities. Treatment of neutropenia with G-CSF is permitted according to local policies. In all cases, G-CSF will not be considered as a study treatment and will not be provided by the Sponsor.

Paclitaxel

Paclitaxel must be administered at a dose of 80 mg/m^2 as an IV infusion over a minimum of 1 hour, qw for 12 weekly cycles, after the trastuzumab/pertuzumab or trastuzumab/placebo infusion observation period. Premedication with corticosteroids should be administered as clinically indicated (please see Section 4.4.4).

6.1.2.2 Notes on HER2 Targeted Treatment

Trastuzumab

Trastuzumab will be administered for a total of 52 weeks (+ 3-day window) of targeted treatment; the recommended treatment schedule for trastuzumab is 3-weekly.

Trastuzumab will be administered on Day 1 of the first taxane-containing cycle at the required loading dose of 8 mg/kg, as an IV infusion. Three weeks (21 days) after the first dose of trastuzumab, and every three weeks thereafter, trastuzumab will be administered at a dose of 6 mg/kg as an IV infusion.

The initial dose of trastuzumab will be administered over 90 (± 10) minutes and patients observed for at least 30 minutes from the end of the infusion for infusion-related symptoms such as fever, chills etc. Interruption or slowing of the infusion may help control such symptoms and may be resumed when symptoms abate. If the infusion is well tolerated, subsequent infusions may be administered over 30 (± 10) minutes and patients will be observed for a further 30 minutes.

All infusion-related symptoms must have resolved before the remaining study treatment is given or the patient is discharged. Patients who experience infusion-related symptoms may be pre-medicated with paracetamol and anti-histamines for subsequent infusions.

Dose reduction for toxicity is not permitted.

Pertuzumab/Placebo

Pertuzumab/placebo will be administered on Day 1 of the first taxane-containing cycle at the required loading dose of 840 mg as an IV infusion. Three weeks (21 days) after the first dose of pertuzumab/placebo, and every three weeks thereafter, pertuzumab will be administered at a dose of 420 mg as an IV infusion.

The initial dose of pertuzumab/placebo will be given after the infusion of trastuzumab (following the observation period) and administered over 60 (± 10) minutes with patients to be observed for a further 60 minutes. The infusion should be slowed or interrupted if the patient experiences infusion-related symptoms. If the infusion is well tolerated, subsequent doses may be administered over 30 (± 10) minutes and patients will be observed for a further 30 minutes for infusion-related symptoms such as fever, chills.

All infusion-related symptoms must have resolved before any docetaxel (or paclitaxel) is given or the patient is discharged. Patients who experience infusion-related symptoms may be pre-medicated with paracetamol and anti-histamines for subsequent infusions.

Dose reduction for toxicity is not permitted.

Pertuzumab/placebo will be administered for a total of 52 weeks (+ 3-day window) of targeted treatment.

6.1.3 Non-Anthracycline-Based Chemotherapy (TCH)

Trastuzumab IV followed by pertuzumab/placebo IV, followed by docetaxel q3w then carboplatin AUC 6 (the total dose should not exceed 900 mg) will be administered for 6 cycles. The order of administration of docetaxel and carboplatin can be adjusted per standard practice.

A loading dose of 8 mg/kg of trastuzumab and 840 mg of pertuzumab/placebo is required on Day 1 Cycle 1. Thereafter a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab/placebo is required for subsequent cycles.

The dose for docetaxel is 75 mg/m^2 for all 6 cycles of treatment.

6.1.3.1 Notes on Adjuvant Chemotherapy

Docetaxel

Docetaxel will be administered at 75 mg/m^2 as an IV infusion over 30–60 (± 10) minutes, after the pertuzumab/placebo infusion observation period.

Patients will be closely observed from the start of the infusion for hypersensitivity reactions which may occur within minutes. Severe hypotension, bronchospasm or generalized rash/erythema requires immediate discontinuation of docetaxel and appropriate treatment. The infusion may be slowed for minor symptoms like flushing or local cutaneous reactions. Patients experiencing severe hypersensitivity reactions should be discontinued from the study. Pre-medication consisting of a corticosteroid, such as dexamethasone 16 mg per day in divided doses for 3 days starting 1 day prior to docetaxel administration, unless contra-indicated, must be used.

Dose reduction (and dose delays if necessary) and/or prophylactic G-CSF may be used to mitigate the risk of hematological toxicities. Treatment of neutropenia with G-CSF is permitted according to local policies. In all cases, G-CSF will not be considered as a study treatment and will not be provided by the Sponsor.

Carboplatin

Carboplatin should be administered by IV infusion at a target AUC = 6 mg/mL/min over 30–60 minutes and repeated every 3 weeks for a total of six cycles.

The Calvert formula will be used to calculate the dose of carboplatin:

Dose (mg) = target AUC (mg/mL × min) × [GFR mL/min + 25]

Dose (mg) = 6 × [GFR mL/min + 25]

NOTE: the Calvert formula gives the dose in **mg**, not mg/m^2.
GFR, glomerular filtration rate

The maximum dose of carboplatin must not exceed 900 mg.

6.1.3.2 Notes on HER2-Targeted treatment

Trastuzumab

Trastuzumab will be administered for a total of 52 weeks (+ 3-day window) of targeted treatment; the recommended treatment schedule for trastuzumab is 3-weekly.

Trastuzumab will be administered at the start of the taxane-based chemotherapy (Day 1 of Cycle 1) at the required loading dose of 8 mg/kg, as an IV infusion. Three weeks (21 days) after the first dose of trastuzumab, and q3w thereafter, trastuzumab will be administered at a dose of 6 mg/kg as an IV infusion.

The initial dose of trastuzumab will be administered over 90 (± 10) minutes and patients observed for at least 30 minutes from the end of the infusion for infusion-related symptoms such as fever, chills etc. Interruption or slowing of the infusion may help control such symptoms and may be resumed when symptoms abate. If the infusion is well tolerated, subsequent infusions may be administered over 30 (± 10) minutes and patients will be observed for a further 30 minutes.

All infusion-related symptoms must have resolved before the remaining study treatment is given or the patient is discharged. Patients who experience infusion-related symptoms may be pre-medicated with paracetamol and anti-histamines for subsequent infusions.

Dose reduction for toxicity is not permitted.

Pertuzumab/Placebo

Pertuzumab/placebo will be administered at the start of the taxane-based chemotherapy (Day 1 of Cycle 1) at the required loading dose of 840 mg as an IV infusion. Three weeks (21 days) after the first dose of pertuzumab/placebo, and every three weeks thereafter, pertuzumab/placebo will be administered at a dose of 420 mg as an IV infusion.

The initial dose of pertuzumab/placebo will be given after the infusion of trastuzumab (following the observation period) and administered over 60 (± 10) minutes with patients to be observed for a further 60 minutes. The infusion should be slowed or interrupted if the patient experiences infusion-related symptoms. If the infusion is well tolerated, subsequent doses may be administered over 30 (± 10) minutes and patients will be observed for a further 30 minutes for infusion-related symptoms such as fever, chills.

All infusion-related symptoms must have resolved before docetaxel is given or the patient is discharged. Patients who experience infusion-related symptoms may be pre-medicated with paracetamol/acetaminophen and anti-histamines for subsequent infusions.

Dose reduction for toxicity is not permitted.

Pertuzumab/placebo will be administered for a total of 52 weeks (+3-day window) of targeted treatment.

6.2 Treatment after Local Recurrence

Under rare circumstances the investigator may decide to re-initiate treatment with trastuzumab in individual patients after operable local relapse in the ipsilateral conserved breast. Details of such treatment (e.g., trastuzumab, surgery) must be recorded on the post-study treatment page in the eCRF.

Initiation, re-initiation or discontinuation of treatment with trastuzumab, will be at the discretion of the investigator.

Note: trastuzumab for such therapy will not be provided as part of the study protocol but may be given to the patient outside of this clinical study. Patients who develop a local other than an operable relapse in the ipsilateral conserved breast should be treated according to the decision of the investigator and the patient.

6.3 Formulation of Pertuzumab/Placebo and Trastuzumab

Each lot of the recombinant antibodies or placebo produced for clinical purposes meets the United States Pharmacopeia and the European Pharmacopoeia for sterility, and meets viral safety requirements. Each lot meets the required specifications for identity, purity, and potency.

6.3.1 Pertuzumab

Pertuzumab is provided as a single-use formulation containing 30 mg/mL pertuzumab formulated in 20 mM L-histidine-acetate (pH 6.0), 120 mM sucrose, and 0.02% polysorbate 20. Each 20-cc vial (14.0 mL solution per vial) contains approximately 420 mg of pertuzumab. This medication will be blinded as “Pertuzumab/placebo” and is intended for use only in clinical trials.

For further details, see the pertuzumab IB.

6.3.2 Trastuzumab

For details, see the trastuzumab local prescribing information.

6.3.3 Placebo Pertuzumab

The formulation of the placebo pertuzumab is equivalent to pertuzumab, without the active agent. This medication will be blinded.

6.4 Labeling of Pertuzumab/Placebo and Trastuzumab

Pertuzumab/placebo and trastuzumab will be labeled according to the regulatory requirements in each country, as well as in accordance with ICH-GCP topic E6.

6.4.1 Pertuzumab/Placebo

The study Sponsor will provide pertuzumab/placebo to all study sites labeled for investigational use only.

6.4.2 Trastuzumab

Where permitted by regulatory requirements, sites will obtain and utilize commercially available trastuzumab.

6.5 Storage, Preparation, and Administration of Pertuzumab/Placebo and Trastuzumab

6.5.1 Storage of Pertuzumab/Placebo and Trastuzumab

Vials of pertuzumab/placebo and trastuzumab are shipped at a temperature ranging from 2°C–8°C (36°F–46°F), and must be placed in a refrigerator (at the same temperature range) immediately upon receipt to ensure optimal retention of physical and biochemical integrity and should remain refrigerated until immediately prior to use. Temperature logs must be maintained (in accordance with local pharmacy practice) on the refrigerator to ensure proper storage conditions. If a temperature deviation from the allowed 2°C–8°C is found either during shipment or storage, contact the Sponsor to determine if the drug is still appropriate for use.

DO NOT FREEZE and DO NOT SHAKE the pertuzumab/placebo or trastuzumab vials. Store all vials within the outer carton, and protect them from light.

The medication must not be used beyond the use by date provided on the outer carton.

6.5.2 Preparation of Pertuzumab/Placebo and Trastuzumab

6.5.2.1 Pertuzumab/Placebo

Because the pertuzumab formulation does not contain a preservative, the vial seal may only be punctured once. Any remaining solution should be discarded.

The indicated volume (14 mL for 420-mg pertuzumab or for two vials [820-mg loading dose] use 2 x 14-mL 420-mg pertuzumab vials) of pertuzumab/placebo solution should be withdrawn from the vials and added to a 250-cc IV bag of 0.9% sodium chloride injection. Gently invert the bag to mix the solution. DO NOT SHAKE VIGOROUSLY. Visually inspect the solution for particulates and discoloration prior to administration. The entire volume within the bag should be administered as a continuous IV infusion. The volume contained in the administration tubing should be completely flushed using a 0.9% sodium chloride injection.

The solution of pertuzumab/placebo for infusion diluted in PVC or non-PVC polyolefin bags containing 0.9% sodium chloride injection may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use. Diluted pertuzumab/placebo has been shown to be stable for up to 24 hours at room temperature (2°C–25°C). However, since diluted pertuzumab/placebo contains no preservative, the aseptically diluted solution should be stored refrigerated (2°C–8°C) for no more than 24 hours.

A rate-regulating device may be used for all study-drug infusions. When the IMP IV bag is empty, 50 mL of 0.9% Sodium Chloride Injection may be added to the IV bag or an additional bag will be hung, and the infusion may be continued for a volume equal to that of the tubing to ensure complete delivery of the IMP.

Should extravasation of the IMP infusion occur, the following steps should be taken:

- Discontinue the infusion,
- Treat the extravasation according to institutional guidelines for extravasation of a non-caustic agent,
- If a significant volume of the IMP infusion remains, restart the infusion at a more proximal site in the same limb or on the other side.

6.5.3 Pertuzumab/Placebo Dose and Schedule

Pertuzumab/placebo will be administered as an IV loading dose of 840 mg for the first cycle of HER2-targeted treatment, and 420 mg for subsequent cycles.

Pertuzumab/placebo will be administered q3w for 52 weeks (+ 3-day window) OR until Investigator-assessed radiographic or clinical recurrence of disease, or unmanageable toxicity (up to a maximum of 52 weeks). Administration may be delayed to assess or treat AEs such as cardiac AEs or myelosuppression. No dose reduction will be allowed.

If the patient misses a dose of pertuzumab/placebo for any cycle and the time between doses is 6 weeks or more, a re-loading dose of pertuzumab/placebo (840 mg) should be given. If re-loading is required for a given cycle, the three study therapies should be given at the same schedule. Subsequent maintenance pertuzumab/placebo doses of 420 mg will then be given q3w, starting 3 weeks later.

6.5.4 Trastuzumab Dose and Schedule

Trastuzumab will be administered as an IV loading dose of 8 mg/kg for Cycle 1, and 6 mg/kg for subsequent cycles. The dose of trastuzumab does not need to be re-calculated unless the body weight has changed by more than ± 10% from baseline.

Trastuzumab will be administered q3w for 52 weeks (+ 3-day window) or until Investigator-assessed radiographic or clinical recurrence of disease, or unmanageable toxicity occurs (up to a maximum of 52 weeks). Administration may be delayed to assess or treat AEs such as cardiac AEs or myelosuppression. No dose reduction will be allowed.

If the patient misses a dose of trastuzumab for any cycle, (i.e., the 2 sequential administration times are 6 weeks or more apart), a re-loading dose of 8 mg/kg of

trastuzumab should be given. If re-loading is required for a given cycle, the study therapies should be given at the same schedule.

6.6 Dose Delays and Modifications

If any of the individual study drugs must be delayed for a day or more, all agents should be delayed for the same timeframe.

Patients who discontinue chemotherapy due to toxicity should not systematically be withdrawn from all study treatments. The following recommendation is given:

– Anthracycline and non-anthracycline-based chemotherapy: in the case of discontinuation of chemotherapy, targeted treatment should be completed as per protocol.

6.6.1 Pertuzumab/Placebo and Trastuzumab Dose Delays and Modifications

Pertuzumab/placebo and trastuzumab doses may be delayed due to toxicities.

If pertuzumab/placebo or trastuzumab are held for more than two cycles or need to be permanently discontinued, the patient will be withdrawn from all study treatment and treated at the discretion of the investigator as clinically indicated. The patient will continue to be followed post-treatment as described in Section 5.4.

Pertuzumab/placebo or trastuzumab dose modifications are not permitted.

6.6.2 Chemotherapy Delays and Modifications

Dose modifications for chemotherapies other than those recommended in this section are to be performed as per local product information and according to standard clinical practice.

6.6.2.1 Dose Modifications and Delays for Taxanes (Docetaxel/Paclitaxel)

All dose modifications for docetaxel/paclitaxel alone are based on the dose level changes outlined below (Table 11).

Table 11 Dose Levels for Docetaxel/Paclitaxel

	Dose Level 0 Starting Dose	Dose Level 1	Dose Level 2	Dose Level 3
Docetaxel (mg/m^2)	100	75	60	Discontinue
Paclitaxel (mg/m^2)	80	64	Discontinue	

A dose limiting toxicity to docetaxel is defined as the occurrence of 1 or more of the following:

- Febrile neutropenia
- Grade 4 neutropenia (neutrophils $< 0.5 \times 10^9$/L) for > 5 days or neutrophil count $< 0.1 \times 10^9$/L for more than 1 day

- Grade 2 non-hematological AEs (NCI-CTCAE, version 4.0), such as peripheral neuropathy, unless the toxicity is deemed manageable by the Investigator, e.g., nausea and vomiting.

General dose modification guidelines

- If a Grade 3 or 4 non-hematological toxicity is experienced, docetaxel may be reduced from 100 mg/m^2 to 75 mg/m^2, and again to 60 mg/m^2 if required. For paclitaxel, the dose may be reduced from 80 mg/m^2 to 64 mg/m^2
- If a taxane-related hypersensitivity reaction occurs despite pre-medication, treatment as medically indicated will be instituted.
  - For hypersensitivity reaction ≤ NCI–CTCAE Grade 3, continuation of docetaxel/paclitaxel is at the Investigator's discretion.
  - If Grade 4 hypersensitivity is experienced, docetaxel/paclitaxel must be permanently discontinued.
- Taxane-related fluid retention will be treated as per the Investigator's discretion.
- If the taxane must be discontinued before completion of the scheduled cycles, the remaining trastuzumab and pertuzumab/placebo doses should be administered.

See Table 12 for the management of taxane-related neurosensory toxicity and Table 13 for taxane-related musculoskeletal pain. Instructions for management of all other toxicities related to docetaxel/paclitaxel are listed in Table 14.

Table 12 Dose Modifications for Taxane-Related Neurosensory Toxicity

Paresthesias/Dysesthesias	1–7 Days Duration	Persistent for >7 Days or Caused the Next Cycle to be Delayed
Grade 1 Paresthesias/dysesthesias that do not interfere with function	Maintain docetaxel/paclitaxel dose	Maintain docetaxel/paclitaxel dose
Grade 2 Paresthesias/dysesthesias interfering with function, but not activities of daily living	Maintain docetaxel/paclitaxel dose[a]	Decrease docetaxel/paclitaxel one dose level[b]
Grade 3 Paresthesias/dysesthesias with pain or with function impairment interfering with activities of daily living[c]	First episode: Decrease docetaxel/paclitaxel one dose level[a] Second episode: Discontinue docetaxel/paclitaxel	Discontinue docetaxel/paclitaxel

[a] Must be resolved to ≤ Grade 1 on Day 1 of the next cycle.

[b] Hold chemotherapy (docetaxel/paclitaxel and, for non-anthracycline treatment group, carboplatin) for persistent Grade 2 neurotoxicity. When ≤ grade 1, resume treatment with dose modification for docetaxel/paclitaxel (no dose reduction for carboplatin). If grade 2 toxicity persists after 3 weeks of delay, discontinue docetaxel/paclitaxel.

[c] For persistent paresthesias/ dysesthesias that are disabling or life-threatening, docetaxel/paclitaxel should be discontinued.

Table 13 Dose Modifications for Taxane Musculoskeletal Pain Not Controlled by Analgesics[a]

Musculoskeletal Pain	1–7 Days Duration	Persistent for >7 Days or Caused the Next Cycle to be Delayed
Grade 1	Maintain docetaxel/paclitaxel dose	Maintain docetaxel/paclitaxel dose
Grade 2	Maintain docetaxel/paclitaxel dose	Maintain docetaxel/paclitaxel dose OR Decrease docetaxel/paclitaxel one dose level[b]
Grade 3	First episode: Decrease docetaxel/paclitaxel one dose level Second episode: Discontinue docetaxel/paclitaxel	First episode: Decrease docetaxel/paclitaxel one dose level[b] OR Discontinue docetaxel/paclitaxel Second episode: Discontinue docetaxel/paclitaxel

[a] Use of narcotics and NSAIDs is encouraged to maintain dose of docetaxel/paclitaxel if possible.

[b] Hold docetaxel/paclitaxel for persistent Grade 2 or 3 musculoskeletal pain. When ≤ grade 1, resume treatment with dose modification for docetaxel/paclitaxel. If Grade 2 or Grade 3 toxicity persists after 3 weeks of delay, discontinue docetaxel/paclitaxel.

Table 14 Dose Modifications and Delays for Docetaxel/Paclitaxel Alone

NCI CTCAE v 4.0 [Category] Grade	Modifications for AEs that occur during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE[a]	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE[b]
HEMATOLOGICAL:		
Neutrophils count decreased [Investigations]		
Grades 2, 3, 4	Maintain dose	For Docetaxel Hold until ≥ 1500/mm^3. If recovery takes: ▪ 1-3 wks: maintain dose and add G-CSF If receiving G-CSF and recovery takes: ▪ 1 wk: maintain dose ▪ 2-3 wks: ↓ one dose level For Paclitaxel Hold until ≥ 1000/mm^3. If recovery takes: • 1-3 wks: maintain dose and add G-CSF If receiving G-CSF and recovery takes: ▪ 1 wk: maintain dose ▪ 2-3 wks: ↓ one dose level
Platelet count decreased [Investigations]		
Grades 2, 3 Grade 4	Maintain dose ↓ one dose level	Hold until ≥ 75,000/mm^3. If recovery takes: ▪ 1 wk: maintain dose ▪ 2-3 wks: ↓ one dose level ↓ one dose level
BLOOD AND LYMPHATIC SYSTEM DISORDERS:		
Febrile neutropenia		
Grade 3, 4	↓ one dose level, add G-CSF support or discontinue.	
GASTROINTESTINAL DISORDERS (if related to chemotherapy):		
Diarrhea		
Grade 2 Grade 3 Grade 4	Maintain dose ↓ one dose level ↓ two dose levels or discontinue	↓ one dose level ↓ one dose level ↓ two dose levels or discontinue
Mucositis oral (stomatitis)		
Grade 2 Grade 3 Grade 4	Maintain dose ↓ one dose level ↓ two dose levels or discontinue	↓ one dose level ↓ one dose level ↓ two dose levels or discontinue
Vomiting (despite antiemetics)		
Grade 2 Grades 3, 4	↓ one dose level (optional) ↓ one dose level or discontinue	↓ one dose level ↓ two dose levels or discontinue

Table 14 Dose Modifications and Delays for Docetaxel/Paclitaxel Alone (cont.)

HEPATIC FUNCTION:		
Bilirubin or AST or ALP increased [Investigations]		
Grade 2	↓ one dose level	Hold until bilirubin returns to the baseline grade, and AST and alkaline phosphatase have returned to ≤ grade 1. Then ↓ one dose level
Grade 3 Grade 4	↓ two dose levels Discontinue	↓ two dose levels Discontinue
OTHER CLINICALLY SIGNIFICANT AEs[c]:		
Grade 3 Grade 4	↓ one dose level ↓ two dose levels or discontinue	↓ one dose level Discontinue

Dose modifications must be based on AEs that occur during the cycle (column 2) and AEs present on the scheduled cycle Day 1 (column 3).
Dose modifications must be based on the AE requiring the greatest modification.

[a] Resolved means that all requiring dose modification are ≤ grade 1 (except ANC/AGC [which must be ≥ 1500/mm3] and bilirubin [which must be ≤ the baseline grade]) on Day 1 of the next scheduled cycle (i.e., treatment can be given without delay).

[b] Hold and check weekly. With exception of ANC/AGC and bilirubin, resume treatment when toxicity is ≤ grade 1. If toxicity has not resolved after 3 weeks of delay, discontinue docetaxel and proceed with targeted treatment as planned to complete 52 weeks (+ 3-day window) of treatment.

[c] Determination of "clinically significant" AEs is at the discretion of the investigator.

6.6.2.2 Dose Modification and Delays for Docetaxel and Carboplatin

All dose modifications for docetaxel/carboplatin are based on the dose level changes outlined in Table 15.

Table 15 Dose Levels for Docetaxel and Carboplatin

	Dose Level 0 Starting Dose	Dose Level 1	Dose Level 2	Dose Level 3
Docetaxel (mg/m^2)	75	60	50	Discontinue
Carboplatin (AUC)	6	5	4	Discontinue

If a docetaxel-related hypersensitivity reaction occurs despite pre-medication, treatment as medically indicated will be instituted. For < Grade 3 hypersensitivity reactions, continuation of docetaxel should be at the investigator's discretion. Following Grade 4 hypersensitivity, docetaxel must be permanently discontinued.

Docetaxel-related fluid retention will be treated as per the Investigator's discretion.

6.7 Blinding and Unblinding

The Sponsor will NOT routinely unblind the investigator as to the identity of the study medication for SAEs, unexpected or otherwise.

Unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the patient's care by their physician or a regulatory body. In general,

unblinding of participants during the conduct of the clinical trial is not allowed unless there are compelling medical or safety reasons to do so.

The investigator may wish to contact the central study team if they believe that there are compelling circumstances where unblinding of the treatment assignment is in the best interests of a patient. Under these circumstances, arrangements may be made in conjunction with the randomization center to unblind only the treating physician as to the treatment assignment of that patient.

The clinical management of the patient should be identical, irrespective of blinded treatment assignment.

Any serious adverse event considered by the investigator to be related to the blinded IMP (pertuzumab/placebo) should be reported as such to the sponsor via the appropriate SAE reporting form.

Unblinding for ongoing safety monitoring by an Independent Data Monitoring Committee (IDMC), will be performed through an Independent Data Coordinating Center (IDCC) to ensure integrity of the study.

All other entities including the sponsor who are directly involved in this study will remain blinded until the definitive analysis of the primary efficacy endpoint.

The Randomization List will not be available at the study center, to the study monitors, to the sponsor, the project statisticians or to the project team.

The password-protected and/or encrypted electronic Master Randomization List is kept by Clinical Supply in their secure system and is only accessible to the Randomization List Managers. No open key to the code will be available at the study center, to the monitors, the sponsor (Roche), the project statisticians, the joint Study Management Team, the BrEAST Data Center or the Study Steering Committee.

As per regulatory reporting requirement, Roche safety will unblind the identity of the IMP for all unexpected SAEs that are considered by the investigator to be related to IMP as per safety reference document(s), e.g., IB, CDS, and SPC. Details of subjects who are unblinded during the study will be included in the Clinical Study Report.

6.8 Assessment of Compliance

Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records for all study treatments. Any dose reductions and titrations must be recorded.

Accurate records must be kept for each study drug provided by the Sponsor, pertuzumab/placebo and trastuzumab used as part of the study-defined treatment. These records must contain at least the following information:

- Documentation of drug shipments received from the Sponsor (date received and quantity).

A Drug Dispensing Log must be kept current and contain the following information:

- The study number of the patient to whom the study drug was dispensed
- The date(s), drug kit number, and quantity of the study drug dispensed to the patient.

Copies of the dispensing and inventory logs must be available for inspection by the monitor. Instructions for the destruction of unused, partially used or empty vials of pertuzumab/placebo, are detailed in Section 6.9.

6.9 Destruction of Study Drug

All pertuzumab, placebo and trastuzumab supplies, including unused, partially used or empty vials, must be destroyed either on site or as per the site's specific procedures for handling and disposing of hazardous drugs. The specific procedures for destruction of investigational pertuzumab/placebo are to be provided to the monitor who will verify them as acceptable and in line with the Sponsor's standard operating procedures (SOPs).

6.9.1 Partially Used or Empty Vial Destruction

To assist with storage capacity and functionality, it is acceptable for sites to destroy the partially used or empty pertuzumab and placebo vials before inspection by the site monitor so that only the empty boxes stating the drug kit number and patient information and dispensing date written on the label can be used for reconciliation of destroyed supplies.

6.9.2 Unused Vial Destruction

Unused pertuzumab, placebo and trastuzumab drug supplies, including medication that has been exposed to storage temperatures outside of the protocol-specified range, may only be destroyed upon written approval from the Sponsor, provided that such disposition does not expose humans to risks from the drug.

Written authorization must be obtained from the Sponsor before destruction of unused pertuzumab and placebo.

Written documentation of destruction must contain the following:

- Identity (drug kit numbers or patient numbers) of investigational product(s) destroyed.
- Quantity of investigational product(s) destroyed.
- Date of destruction (date discarded in designated hazardous container for destruction).
- Method of destruction (the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs).
- Name and signature of the responsible person who discarded the investigational product in a hazardous container for destruction.

7. SAFETY INSTRUCTIONS AND GUIDANCE

Emergency Medical Contact

Medical Monitor (Roche Medical Responsible) Contact Information

Primary Contact

Medical Monitor: [redacted], FFPM

Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

7.1 Adverse Events and Laboratory Abnormalities

7.1.1 Clinical Adverse Events

Per the ICH, an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during a study are to be reported as AEs. *After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention (such as biopsies) should be reported.*

7.1.1.1 Intensity

Intensity of all AEs will be graded according to the NCI-CTCAE version 4.0 on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF. Adverse events not listed in CTCAE should be graded as listed in Table 16.

Table 16 Grading for Adverse Events Not Listed in NCI-CTCAE

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*
Grade 3	Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life threatening/disabling	Life threatening consequences; urgent intervention required
Grade 5	Death	Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.1.1.2 Adverse Event Relationship to Drug

The causality relationship of the AE to the study treatment will be assessed by the Investigator as either:
Yes or No

If there is a reasonable suspected causal relationship to the study treatment, i.e., there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as "Yes".

The following criteria should be considered in order to assess the relationship as **Yes:**

– Reasonable temporal association with drug administration.

– It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

– Known response pattern to suspected drug.

– Disappears or decreases on cessation or reduction in dose.

– Reappears on rechallenge.

The following criteria should be considered in order to assess the relationship as **No**:

– It does not follow a reasonable temporal sequence from administration of the drug.

– It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

– It does not follow a known pattern of response to the suspected drug.

– It does not reappear or worsen when the drug is re-administered.

7.1.1.3 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any adverse event that at any dose fulfills at least one of the following criteria:

– is fatal (results in death; NOTE: death is an outcome, not an event);

– is life-threatening (NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused death had it been more severe);

– requires in-patient hospitalization or prolongation of existing hospitalization;

– results in persistent or significant disability/incapacity;

– is a congenital anomaly/birth defect;

– is medically significant or requires intervention to prevent one or other of the outcomes listed above.

The study will comply with all local regulatory requirements. The full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A (Appendix 1) will be adhered to.

7.1.1.4 Disease Recurrence

Recurrence or progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected recurrence or progression of the underlying cancer. Hospitalization due solely to the recurrence or progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of recurrence or progression may be reported as AEs if the symptom cannot be determined as exclusively due to the recurrence or progression of the underlying malignancy, or does not fit the expected pattern of recurrence or progression for the disease under study.

If there is any uncertainty about an AE being due to the disease under study, it should be reported as an AE or SAE as appropriate.

See Section 5.5 for the acceptable procedures for confirming disease recurrence.

Non-breast-related secondary primary malignancies are to be reported as SAEs at any time regardless of the time elapsed since the last dose of investigational product.

Myelodysplastic syndrome is not considered a progression event but is to be reported as an SAE.

7.1.2 Treatment and Follow-up of Adverse Events

AEs are to be monitored continuously during study treatment. All AEs occurring during the study and until the treatment discontinuation visit 28 days after last study medication are to be recorded; thereafter only drug-related SAEs, cardiac AEs (e.g., heart failure), non–breast-related second primary malignancies, all irrespective of causal relationship, and pregnancies, should continue to be collected.

AEs are to be followed as described below:

Related AEs:

Follow until one of the following occurs:

– Resolves or improves to baseline levels

– Relationship is reassessed as unrelated

– Death

– Start of new anti-cancer regimen

– Investigator confirms that no further improvement can be expected

– Clinical or safety data will no longer be collected, or final database closure

Unrelated severe or life-threatening AEs:

Follow until one of the following occurs:

– Resolves or improves to baseline levels

– Severity improves to Grade 2

– Death

– Start of new anti-cancer regimen

– Investigator confirms that no further improvement can be expected

– Clinical or safety data will no longer be collected, or final database closure

All adverse events (related and unrelated) occurring during the study conduct and up to 28 days after the last dose of study medication must be reported on the eCRF and followed until resolution or end of study, whichever occurs first. *If a non-serious-related adverse event becomes serious after the reporting period, this should be reported as per the SAE process.*

The final outcome of each AE must be recorded on the eCRF.

Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results eForms of the eCRF.

Any abnormal laboratory result fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, must be recorded as a single diagnosis on the AE eForm in the eCRF:

– Accompanied by clinical symptoms,

– Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation),

– Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

7.1.3 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed until they have returned to the normal range, baseline value and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

7.2 Handling of Safety Parameters

7.2.1 Reporting of Adverse Events

During the period after signing the informed consent and *prior to* study Day 1 (administration of study treatment), any non-serious AEs that occur will be reported in the medical history, unless AE reporting is deemed more appropriate; SAEs caused by a protocol mandated Intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

All adverse events (related and unrelated) occurring during the study conduct and up to 28 days after the last dose of study medication must be reported on the eCRF and followed until resolution or end of study, whichever occurs first. *If a non-serious-related adverse event becomes serious after the reporting period, this should be reported as per the SAE process.*

Thereafter only the following events should continue to be both followed and recorded up to 10 years after the last administration of study medication.

- Study treatment-related SAEs
- Cardiac adverse events (irrespective of causal relationship)
- Pregnancies

- Non–breast-related second primary malignancies, *(irrespective of casual relationship) and myelodysplastic syndrome* (irrespective of causal relationship)

See Section 7.1.2 for further information on the follow-up of AEs.

7.2.2 Reporting of Serious Adverse Events (Immediately Reportable)

Any clinical AE or abnormal laboratory test value that is serious and which occurs during the course of the study (as defined in Section 7.1.1.3 above), regardless of the treatment arm, must be reported to Roche within 24 hours of the Investigator becoming aware of the event (expedited reporting).

Related SAEs and suspected, unexpected serious adverse reaction (SUSARs) **MUST** be collected and reported regardless of the time elapsed from the last study treatment administration, even if the study has been closed. *If a non-serious-related adverse event becomes serious after the reporting period, this should be reported as per the SAE process.*

Unrelated SAEs must be collected and reported during the study and for up to 28 days after the last dose of study medication.

SAEs occurring during screening will also be reported *if they are considered related to a protocol-mandated procedure.*

This study adheres to the definition and reporting requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting Topic E2A (Appendix 1).

The reporting of SAEs and SUSARs may be subject to change to comply with updated regulations and/or company procedures.

Please see Section 7.2.3 for reporting of study specific SAEs.

7.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious Adverse Events of Special Interest (AESI) are required to be reported on an SAE form by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

AESI for this study include the following:

- *An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment, as defined in Section 7.2.4*

7.2.4 Reporting of Study-Specific Adverse Events and Serious Adverse Events

Heart failure

Symptomatic left ventricular systolic dysfunction (otherwise referred to as heart failure) should be reported as an SAE. If the diagnosis is heart failure it should be reported as such and not as individual signs and symptoms thereof. In the eCRF, signs and symptoms should be recorded. Heart failure should be graded according to NCI-CTCAE v 4.0 for "heart failure" (Grade 2, 3, 4 or 5) and in addition the New York Heart Association (NYHA) classification (Appendix 4). 'Left ventricular systolic dysfunction' should not be used to describe symptomatic dysfunction as per NCI –CTCAE v.4.0.

Heart failure occurring during the study and up to 10 years after last administration of study medications must be reported irrespective of causal relationship and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

Asymptomatic Left Ventricular Systolic Dysfunction

Asymptomatic declines in LVEF should not be reported as AEs since LVEF data are collected separately in the eCRF. Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF ≥10 percentage-points from baseline to an LVEF < 50% must be reported as an adverse event with the term of 'ejection fraction decreased' as per NCI-CTCAE v4.0 and, in addition, a comment in the AE comments field should confirm that this was asymptomatic.
- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab/placebo and trastuzumab must also be reported.
    - Please note that this AE should also be captured as a non-serious event of special interest on the SAE form.

Table 17 summarizes the reporting conventions for left ventricular systolic dysfunction.

Table 17 Reporting Conventions for Left Ventricular Systolic Dysfunction/Heart Failure

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decline in LVEF < 10%-points from baseline or to an LVEF ≥ 50%	No additional reporting required, LVEF results to be reported on eCRF	N/A	N/A
Asymptomatic decline in LVEF ≥ 10%-points from baseline to an LVEF < 50%	AE (eCRF AE e-form)	ejection fraction decreased (a)	NCI CTCAE for "ejection fraction decreased"
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab/placebo and trastuzumab	AE (eCRF AE e-form) and complete SAE form and indicate as AE of special interest	"ejection fraction decreased" (a)	NCI CTCAE for "ejection fraction decreased"
Heart failure (symptomatic left ventricular systolic dysfunction)	AE (eCRF AE e-form) and SAE (SAE form)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA Class

Any symptomatic Left Ventricular Systolic Dysfunction event must be reported as "heart failure"

[a] Report the status "asymptomatic" and the LVEF value in the comments field as appropriate

Please refer to the algorithm to assist the decision as to whether to initiate (after completion of anti-HER2 therapy), continue or discontinue anti-HER2 study medication based on LVEF assessment in asymptomatic patients (see Appendix 5).

7.2.5 Pregnancy and Pregnancy Prevention

According to the ICH M3 Guideline, precautions need to be taken to minimize risk to a fetus or embryo when including women of childbearing potential in clinical trials. These include highly effective contraceptive measures, excluding pregnancy at baseline (serum test), continued pregnancy *testing during study treatment* and up to 6 months following last dose of targeted treatment. *In addition, women of childbearing potential are required to use highly effective contraceptive measures during study treatment and for at least 7 months following their last dose of study drug (washout period) based on PK considerations for trastuzumab. See trastuzumab IB for details.*

Nonclinical reprotoxicity data in cynomolgus monkeys treated with pertuzumab showed embryo/fetal losses, oligohydramnios, and renal hypoplasia (see Section 1.2.1 and the IB).

There are no clinical studies of trastuzumab or pertuzumab in pregnant women. IgGs are known to cross the placental barrier. Therefore, neither pertuzumab nor trastuzumab should be used during pregnancy.

It is not known whether trastuzumab or pertuzumab is excreted in human milk. As maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or trastuzumab therapy and not to breastfeed for at least *7* months following the last dose of either *trastuzumab or pertuzumab*.

Reporting of a Pregnancy

A female patient who becomes pregnant during the study must be instructed to stop taking study medication and immediately inform the Investigator. Likewise, a male patient whose female partner becomes pregnant during the study must inform the Investigator. The Investigator should report all pregnancies within 24 hours to the Sponsor using the appropriate form. The Investigator should counsel the patient, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring should continue until conclusion of the pregnancy and the outcome reported.

Pregnancies occurring up to 10 years after the completion of study medication must also be reported.

Additional information for any pertuzumab-exposed pregnancies that occur during study treatment and within 6 months after completion of pertuzumab treatment will be requested by Roche Drug Safety at specific timepoints (i.e., at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

7.2.5.1 Pregnancy Prevention

For women of childbearing potential (who have not undergone surgical sterilization), and the female partners of male participants; agreement must be obtained to use one highly effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner *during study treatment and for at least 7 months following the last dose of study drug*. Specific country and/or local requirements for contraception will be followed.

Please refer to Table 6 for the definition of pre- and post-menopausal for this study.

Highly Effective Non-Hormonal Contraception

Methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are considered highly effective forms of contraception.

The following non-hormonal methods of contraception are acceptable:

- True abstinence when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal post-ovulation methods] and withdrawal are not acceptable methods of contraception).

- Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomized male partner should be the sole partner.
- Female surgical sterilization

Effective Non-Hormonal Contraception

Alternatively two of the following effective forms of contraception may be used instead:

- Placement of a non-hormonal intrauterine device (IUD). Consideration should be given to the type of device being used, as there is higher failure rates quoted for certain types, e.g., steel or copper wire. Patients who have had a progesterone-coated device in place prior to screening are not required to have it removed. However, newly inserted devices after screening should not contain estrogen or progesterone.
- Condom with spermicidal foam/gel/film/cream/suppository.
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection.

It should be noted that two forms of effective contraception are required. A double barrier method is acceptable, which is defined as condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream /suppository.

Spermicides are not a barrier method of contraception and should not be used alone.

Timing and duration of contraception

Based on PK considerations, contraception methods should start a minimum of 14 days prior to first administration of study treatment and continue for the duration of study treatment and for at least 7 months after the last dose of study treatment.

7.3 Death

A death occurring during treatment with investigational drug or within 28 days after stopping treatment, whether considered to be treatment-related or not, must be reported.

- All deaths thought to be related to study treatment at any time should be reported as a SAE regardless of the time elapsed since the last dose of investigational product.
- Deaths related to progression of the underlying disease during the course of the study will not be reported as a SAE, but should be reported on the appropriate eCRF page (unless the patient has withdrawn consent).
- Deaths from other causes should be reported on the appropriate eCRF page.

7.4 Warnings and Precautions for Pertuzumab

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate, other than those noted in the IB.

Pertuzumab should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

7.4.1 Risk of Allergic Reactions, Including Anaphylaxis and Infusion-Associated Symptoms

Monoclonal antibodies may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and/or vomiting. Such reactions typically occur during, or very shortly after, an infusion. In the single-agent Phase II studies, 41% of patients experienced treatment-related AEs occurring during or within 24 hours of an infusion. The true rate of infusion-associated reactions may be considerably lower since less than 5% of patients had such events during an infusion.

To date, 10 treatment-related SAEs (in < 1% of all treated patients) that occurred during or on the day of pertuzumab infusion have been identified as compatible with infusion-associated reactions/hypersensitivity/anaphylaxis reactions on the basis of individual medical review of all completed and ongoing studies (excluding those for which treatment is still blinded). Disease progression and co-administered chemotherapy (gemcitabine) were possible contributory factors in several other of these cases – see the pertuzumab IB for further details. One patient (an [redacted]-year-old [redacted] in Study TOC2572g) experienced fatal ARDS, which was investigator-assessed as infusion-related; however disease progression with tumor growth occurring in the mediastinum and lung, compressing the trachea, was a significant contributing factor. Of the 10 SAEs identified, at least 4 occurred in the context of the first pertuzumab infusion.

Administration of pertuzumab should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. Patients will be monitored during each pertuzumab infusion and at least 60 minutes following the completion of the first infusion for any adverse effects. If infusion-associated symptoms occur, patients should be monitored until complete resolution of signs and symptoms. Patients who experience infusion-associated symptoms may subsequently be pre-medicated with analgesia and anti-histamines. If the infusion is well tolerated, patients will be observed for 30 minutes following subsequent infusions.

Infusion of pertuzumab should be stopped in patients who develop dyspnea or clinically significant hypotension (defined per Investigator discretion). Patients who experience an NCI-CTCAE Grade 3 or 4 allergic reaction or ARDS should be discontinued from treatment.

7.4.2 Risk of Cardiotoxicity

There is a risk of cardiac dysfunction with pertuzumab, as with trastuzumab, it is directed at the HER2 receptor.

All patients enrolled in pertuzumab studies undergo regular LVEF monitoring by echocardiography or MUGA scan. A decrease in LVEF has been observed in patients receiving pertuzumab; however, the majority of patients show improvement or return to baseline function on follow-up. A total of 8 patients (<1%) have experienced symptomatic cardiac failure across all studies to date. Three of these events were reported in patients with MBC, two in patients with ovarian cancer, two in patients with early breast cancer and one in a patient with NSCLC. Of these 8 patients, 3 had received prior or concurrent anthracyclines and 2 had a history of heart disease or other cardiac risk factors. Of the 8 patients, 4 were receiving pertuzumab in combination with trastuzumab.

Patients with significant cardiac disease or baseline LVEF below 55% (50% when measured after anthracycline therapy) should not start treatment with anti-HER2 drugs. Risk factors for pertuzumab-associated cardiac dysfunction are not known at this time; and this risk should be carefully weighed against the potential benefit. For patients who experience an asymptomatic decrease in LVEF after anthracycline therapy, they may continue to receive the taxane component of chemotherapy at the discretion of the investigator. HER2-targeted treatment may be subsequently initiated in accordance with the algorithm (Appendix 5); the delay in initiating HER2-targeted treatment should not exceed 6 weeks.

Monitoring of LVEF is advised while patients are receiving pertuzumab/placebo as per the schedule of assessments. If severe heart failure symptoms develop (NYHA Class III or IV) or there is a significant LVEF decrease (LVEF decrease ≥ 10 percentage points and below an LVEF value of 50 the patient must discontinue anti-HER2 therapy. Heart failure or left ventricular dysfunction should be treated and monitored according to standard medical practice. These patients should be evaluated by a certified cardiologist and the results of this evaluation should be reported on the eCRF.

Appendix 5 summarizes the management of study medication for patients who have an asymptomatic decrease in LVEF. The decision to initiate therapy (as for patients completing anthracycline treatment) or whether to continue or stop study medication should be based on two factors: measured LVEF and changes in LVEF from baseline.

7.4.3 Risk of EGFR-Related Toxicities

Although pertuzumab targets HER2, because of its role in heterodimerization with other members of the HER family (e.g., epidermal growth factor receptor [EGFR]), it may cause toxicities associated with the use of EGFR TKIs. Diarrhea has been observed in approximately 60% of patients being treated with pertuzumab in Phase II single-agent studies, and up to 70% of patients in combination therapy studies, and was of Grade 1 or 2 in the majority of cases. For patients experiencing diarrhea, early intervention with loperamide *as well as fluid and electrolyte replacement* should be considered.

Rash has also been observed with EGFR TKIs. The rash was generally mild to moderate in intensity and appeared to be treatable in some patients with standard acne therapies, including topical and oral antibiotics. To date, rash has been observed in approximately 17% of patients receiving pertuzumab in Phase II single-agent studies and up to 40% of patients in pertuzumab–combination studies and was generally of Grade 1 or 2.

7.5 Warnings and Precautions for Trastuzumab

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the IB for trastuzumab.

Trastuzumab should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

7.5.1 Infusion Reactions, Allergic-Like Reactions and Hypersensitivity

Serious adverse reactions to trastuzumab infusion that have been reported infrequently include dyspnea, hypotension, wheezing, bronchospasm, asthma tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, and angioedema. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur, the trastuzumab infusion should be discontinued and the patient monitored until resolution of any observed symptoms. The majority of patients experienced resolution of symptoms and subsequently received further infusions. Serious reactions are usually associated with the first infusion and have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients have experienced the onset of infusion symptoms or pulmonary symptoms more than 6 hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur. Patients with dyspnea at rest due to co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab.

7.5.2 Pulmonary Events

Dyspnea, bronchospasm, asthma and hypoxia can occur as part of an infusion reaction. These are most common with the first infusion and their severity decreases with subsequent infusions. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. Single cases of pulmonary infiltrates, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema and respiratory insufficiency have been reported rarely. ARDS has been reported with fatal outcome.

7.5.3 Risk of Cardiotoxicity

Cardiotoxicity has been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel, most frequently following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. Other important risk factors include age (> 50 years), pre-existing arterial hypertension and potentially the time between anthracycline and trastuzumab treatment. These effects may be moderate to severe and seldom have resulted in death.

If cardiotoxicity develops during trastuzumab therapy, it should be treated with the standard medications for this purpose. These patients should be evaluated by a certified cardiologist, and the results of this evaluation should be reported on the eCRF.

Discontinuation of anti-HER2 therapy

Heart failure

Anti-HER2 therapy will be discontinued in any patient who develops clinical signs and symptoms suggesting heart failure or a confirmed drop in LVEF (LVEF drop ≥10% and below 50%) (see Appendix 5). Confirmation should be done within ±3 weeks (7 to 35 days).

Cardiac dysfunction

Appendix 5 summarizes the management of study medication for patients who have an asymptomatic decrease in LVEF. The decision to initiate therapy (as for patients completing anthracycline treatment) or whether to continue or stop study medication should be based on two factors: measured LVEF and changes in LVEF from baseline.

The half-life of trastuzumab is approximately 28–*38* days. Trastuzumab may persist in the circulation for up to *27* weeks after *the last dose of* trastuzumab treatment. Patients who receive anthracyclines during this period may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy up to *27* weeks *(7 months)* after stopping trastuzumab. If anthracyclines are used then the patient should have careful cardiac monitoring. For the purposes of this study, a minimum of 3 weeks separates the *trastuzumab plus* pertuzumab/placebo *dosing* and the *anthracycline* dosing. The patient will be closely monitored, including LVEF assessments prior to and after completion of the anthracycline.

Most patients who developed heart failure in the adjuvant trastuzumab breast cancer trials improved with standard medical treatment. This included ACE-inhibitors or angiotensin receptor blockers, beta-blockers and diuretics when needed. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on weekly therapy with trastuzumab without additional clinical cardiac events.

7.6 Warnings and Precautions for Docetaxel, Paclitaxel, Carboplatin, Doxorubicin, Epirubicin, 5-Fluorouracil and Cyclophosphamide

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the currently approved prescribing information for docetaxel, paclitaxel, carboplatin, doxorubicin, epirubicin, 5-FU, and cyclophosphamide.

* Please note that there are special precautions for dihydropyrimidine dehydrogenase (DPD) deficiency patients and 5-FU (please refer to label for further information).

7.7 Warnings and Precautions for Anti-Estrogen Therapy and Radiotherapy

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the currently approved prescribing information for anti-estrogen therapy and radiotherapy.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary Study Variables

8.1.1 Primary Efficacy Variable

The primary endpoint of the trial is IDFS. It is a composite endpoint which is defined as the time from randomization until the date of the first occurrence of one of the following events:

- Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion);
- Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall and/or skin of the ipsilateral breast);
- Distant recurrence (i.e., evidence of breast cancer in any anatomic site – other than the two abovementioned sites – that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer);
- Contralateral invasive breast cancer;
- Death attributable to any cause including breast cancer, non-breast cancer or unknown cause (but cause of death should be specified if at all possible).

All second primary non-breast cancers and in situ carcinomas (including DCIS and LCIS) and non-melanoma skin cancers are excluded as an event in this endpoint.

Patients who have not had an event at the time of data analysis will be censored at the date last known to be alive and event free.

Note: this definition of IDFS (which excludes second primary non-breast cancers as events) is not the same as IDFS defined by Hudis et al. [2007] (which includes second primary non-breast cancers as events).

8.1.2 Secondary Efficacy Variables

The secondary endpoints of the present trial include OS, DFS, IDFS, including second primary non-breast cancer, RFI and DRFI.

- IDFS, including second primary non-breast cancer will be defined in the same way as IDFS but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site). This definition of IDFS is often the primary endpoint for breast cancer adjuvant therapy trials to acknowledge i) difficulty in distinguishing second primaries from breast cancer metastasis and ii) that second cancers may be treatment related.
- DFS is defined as the time between randomization and the date of the first occurrence of an invasive disease-free survival event including second primary non-breast cancer event or contralateral or ipsilateral DCIS. Patients who have not had an event at the time of data analysis will be censored at the date last known to be alive and event free. DFS is included to address the question that DCIS does not affect prognosis of primary disease and bridge to the definition applied in the HERA trial.

- OS is defined as the time from randomization to death attributable to any cause. Patients who are alive (including lost to follow-up) at the time of the analysis will be censored at the last known alive date.
- RFI is defined as the time between randomization and the date of local, regional or distant breast cancer recurrence. Patients who have not had a recurrence event at the time of data analysis will be censored at the date last known to be alive or at date of death.
- DRFI is defined as the time between randomization and the date of distant breast cancer recurrence. Patients who have not had a distant recurrence event at the time of data analysis will be censored at the date last known to be alive or at date of death. DRFI is included since based on previous published trials, distant recurrence is anticipated to account for the majority of first disease recurrence events.

8.1.3 Safety Variables

Safety of the treatment will be evaluated as a secondary objective as follows:

- Incidence of a symptomatic ejection fraction decrease (otherwise referred to as heart failure), defined as the occurrence of symptomatic left ventricular ejection fraction decrease or definite or probable cardiac death;
- Incidence of left ventricular systolic dysfunction will be evaluated (defined as an absolute decrease in LVEF of at least 10 percentage points below the baseline measurement and to below 50%);
- LVEF measurements over the course of the study;
- Incidence and severity of AEs and SAEs;
- Laboratory test abnormalities.

Primary cardiac endpoint:

Heart failure NYHA Class III or IV and a drop in LVEF of at least 10 EF points from baseline and to below 50%.

Cardiac death (identified by the APHINITY Cardiac Advisory Board), defined as either

- Definite cardiac death: due to heart failure, myocardial infarction or documented primary arrhythmia.
- Probable cardiac death: sudden unexpected death within 24 hours of a definite or probable cardiac event (e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia) without documented etiology.

Secondary cardiac endpoint:

Defined as an asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF by MUGA scan or echocardiogram, confirmed by a second LVEF assessment within approximately 3 weeks showing also a significant drop OR as confirmed by the APHINITY Cardiac Advisory Board.

A significant LVEF drop is defined as an absolute decrease of at least 10 EF points below the baseline measurement and to below 50%.

The assessment of the secondary cardiac endpoint will be based on data from randomization until the start of any new therapy for recurrence of disease. Therefore, any asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF should be confirmed within approximately 3 weeks, even during follow-up phase.

Other Cardiac events: Acute coronary syndrome, acute myocardial infarction, and severe rhythm disturbances requiring treatment.

8.1.4 Other Variables

Biomarker analysis: Possible relationships between molecular markers, efficacy and safety outcomes will be evaluated.

8.1.5 Patient-Reported Outcomes

The EORTC cancer-specific and EUROQOL (EQ-5D) general health indexes have been chosen in this comparative study. The patient should complete the questionnaire by themselves at the center prior to physician assessment and prior to receiving treatment at the study visit.

It is recommended that a key person (e.g., research nurse) at each center be responsible for questionnaire data collection in order to optimize the compliance of the patient and to ensure the completeness of the data.

- The EORTC QLQ-C30 (Appendix 8) is a validated and reliable self-report measure [Aaronson, 1993; Aaronson, 1996; Fitzsimmons, 1999] [2, 3, 18] which consists of 30 questions that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), symptom scales: (fatigue, nausea and vomiting, pain; and the global health/quality of life) and single-items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales. The QLQ—C30 takes 5-10 minutes to complete.
- The QLQ-BR23 (Appendix 9) consists of 5 multiple-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning. In addition, single items assess sexual enjoyment, hair loss and future perspective.
- EQ-5D (Appendix 10) has 5 questions and categorizes health states according to the following dimensions: mobility, self-care, usual activities (e.g., work, study, homework or leisure activities), pain/discomfort and anxiety/depression.

Patient Reported Outcomes will be assessed by calculating scores associated for each questionnaire at each time point. The scores will be described absolutely and in terms of change from baseline for the two treatment arms. The endpoints are i) absolute scores for each questionnaire and ii) change from baseline for these questionnaires by time points.

8.2 Statistical and Analytical Methods

8.2.1 Statistical Model

8.2.1.1 Analysis of Primary Variable

The primary objective is to compare IDFS in patients with HER2-positive breast cancer who have been randomized to chemotherapy plus 1 year of trastuzumab plus placebo OR

chemotherapy plus 1 year of trastuzumab plus pertuzumab. The final analysis will take place when approximately 379 IDFS events have occurred. In order to ensure sufficient data maturity (particularly in patients enrolled after the protocol amendment B), in the event that 379 IDFS events are reached sooner than 30 months after last patient enrolled (as is anticipated based on the revised IDFS assumptions), the primary analysis will be delayed until 30 months after last patient randomized. A data cut-off date will be determined when this number of events occurs, and the clinical data on or prior to the data cut-off date will be thoroughly cleaned.

The stratified log-rank test, will be used to compare IDFS between the two treatment arms. The strata levels will be as defined in Table 5; however, region will be excluded. The unstratified log-rank test results will also be provided as a sensitivity analysis.

The Kaplan-Meier approach will be used to estimate 3-year IDFS rates for each treatment arm. The stratified Cox proportional hazards model will be used to estimate the HR between the two treatment arms (i.e., the magnitude of treatment effect) and its 95% CI.

Analyses will be based on the intent-to-treat (ITT) population (see Section 8.2.3.1).

An expanded analysis for IDFS will be performed using Cox proportional hazards regression models to determine if adjustment for covariates will modify the conclusions from the primary analysis. Variables to be considered are the stratification factors as well as other disease or patient-related prognostic or predictive factors (e.g., menopausal status, race, loco-regional radiotherapy, type of surgery, tumor size and histological grade).

The aforementioned analyses will be performed in demographic subgroups of interest as appropriate as detailed in Section 8.2.1.4.

Further sensitivity analyses defined in the Statistical Analysis Plan will be performed to assess the robustness of the primary analysis.

8.2.1.2 Secondary Efficacy Variables

Secondary variables will be analyzed in a similar manner as the primary endpoint to compare the two treatment arms using the stratified log rank test, estimate 3-year event rates (5-year event rates for OS) and the HR between treatment arms with 95% CI. Analyses will be based on the ITT population.

An event driven OS analysis is planned when 640 deaths have occurred, estimated to be around nine and a half years after last patient randomized. This will provide approximately 80% power to detect a hazard ratio of 0.8, using a two-sided log-rank test at an α-level of 5%. Assuming the primary analysis for IDFS occurs after 379 events then the first interim OS analysis will be made available at this time (estimated to be 4 to 5 years after the first patient is randomized). Two subsequent interim analyses of OS will be performed approximately 2.5 and 5 years later, with the final event-driven OS analysis defined above. For regulatory purposes, the alpha-level will be controlled at 5% (details will be provided in the SAP). Exploratory follow up analyses of IDFS in overall ITT population and in key demographic subgroups will also be performed at the time of the OS analyses.

8.2.1.3 Biomarker Analyses

To evaluate the correlation between the baseline molecular markers and efficacy, efficacy outcomes will be summarized for all patients, and by treatment arm, within each subgroup determined by exploratory markers. Markers to be considered include the status of HER receptors, HER ligands, Fc-γ receptors, shed antigens (e.g., ECD/HER2), and other markers relevant for the HER family pathway. Special emphasis will be put on markers that have shown association with clinical outcome in patients treated with pertuzumab in previous studies. Efficacy outcomes considered for this analysis will include IDFS and OS.

The biomarker analyses at the time of protocol development do not take the form of testing fixed hypotheses involving specific cut-offs or other pre-specified prediction rules. It is planned for all available scientific evidence from independent studies or publications to be used to determine any testable prediction rules prior to unblinding of this trial. In addition, detail will be provided of any data-adaptive prediction rules will be derived (e.g., systematic cutoff search) and how the inherent multiplicity/bias will be corrected in order to prevent biased conclusions.

The difference in treatment benefit across biomarker statuses defined by a suitable prediction rule will be evaluated, including exploratory testing of the interaction effect of treatment and the prediction status using Cox regression for IDFS and OS. These models involving an interaction term will also be used to estimate the conditional efficacy outcomes, conditional on biomarker prediction status or treatment arm, including and excluding the stratification factors into the model.

Clinical covariates can be of prognostic value and could interact with treatment benefit and with biomarker status. Candidates here are baseline variables of prognostic value describing tumor properties and morbidity status or common lab values. Biomarker prediction will be checked involving relevant clinical covariates, which could be part of the biomarker prediction function, if necessary.

8.2.1.4 Exploratory Efficacy Analyses

Exploratory analyses will be performed for IDFS to ascertain whether the magnitude of the effectiveness of the addition of pertuzumab might differ according to patient sub-populations.

Variables used to define subgroups of interest include the randomization stratification factors as well as other disease or patient-related prognostic or predictive factors. Based on information available at the time of protocol amendment B, attention will be given to the following factors:

- Nodal status categorized as 0 positive nodes versus ≥1 positive nodes
- Menopausal status at randomization
- Type of surgery for primary tumor
- Tumor size
- Histological grade
- Race
- Loco-regional radiotherapy

- Hormonal receptor status (ER, PgR).

Additional factors may also be considered based on results from other trials that will be reported prior to the primary analysis.

Treatment effects – 3-year IDFS percentages and HRs with CIs – will be estimated separately for the defined subgroups. Tests of interactions between treatment effect and subgroup will be reported.

8.2.2 Hypothesis Testing

The null hypothesis for the primary endpoint is that the survival distributions of IDFS in the two treatment groups are the same. The alternative hypothesis is that the survival distributions of IDFS in the treatment and the control arm are different:

$$\mathbf{H_0: S_{<pertuzumab>} = S_{<placebo>} \quad vs. \quad H_1: S_{<pertuzumab>} \neq S_{<placebo>}}$$

Provided that the null hypothesis is rejected, for regulatory purposes, formal treatment comparisons will be performed for secondary endpoints using a testing hierarchy in order to control the overall type I error rate at 5% (details are provided in the SAP).

8.2.3 Types of Analyses

Analysis of primary and secondary efficacy variables will be based on the ITT population, defined as all patients who have been randomized. All efficacy analyses will be based on the treatment arm to which patients were randomized.

Safety analyses will be performed based on the safety population consisting of all patients randomized and who received any study treatment. Safety analyses will be based on the treatment received.

8.2.3.1 Analysis Populations

Intent-to-Treat Population:

All randomized patients will be included in the ITT population.

Safety population:

Patients who do not receive any amount of study medication (chemotherapy, pertuzumab/placebo, trastuzumab) will be excluded from the safety population.

8.2.4 Safety Data Analysis

The safety of pertuzumab in combination with trastuzumab and chemotherapy will be assessed through summaries of AEs, cardiac-specific AEs, LVEF measurements, and laboratory test results. Patients who receive any amount of study treatment will be included in the safety analyses. Safety results will be summarized for the safety population, by actual treatment received.

Cardiac data analyses

The incidence of all cardiac events including those not qualifying for the primary or secondary cardiac endpoints will be summarized.

LVEF data analyses will include the following:

The baseline LVEF value and the maximum absolute decrease (or minimum absolute increase if patients' post-baseline LVEF measures are all larger than the baseline value) in LVEF measure from baseline will be summarized. The 95% two-sided confidence limits for the maximum absolute decrease in LVEF measure and the difference between the two treatment arms will be presented. LVEF measurements and change in LVEF from baseline will be summarized by treatment arm and time point in graphical and tabular format.

In addition, LVEF will be summarized by presenting frequencies over time by treatment group for the following categories:

- Absolute value < 50% and decrease from baseline ≥ 15 percentage points
- Absolute value ≥ 50% and decrease from baseline ≥ 10 percentage points.

To account for amount of follow-up, the cumulative incidence of heart failure and asymptomatic heart failure will be summarized using Cox regression model of time to first event. Risk factors for cardiac dysfunction may be investigated.

Adverse Events

Verbatim descriptions of treatment-emergent AEs will be mapped to MedDRA (medical dictionary for regulatory activities) terminology thesaurus terms and graded according to the NCI-CTCAE, Version 4.0. All AEs, including SAEs, will be summarized by treatment arm and CTCAE grade. In addition, AEs leading to discontinuation of study treatment will be summarized by treatment arm. For each patient's AEs, the maximum severity recorded will be used in the summaries.

Laboratory data

Clinical laboratory tests will be performed at local laboratories. Laboratory toxicities will be defined based on local laboratory normal ranges and NCI-CTCAE, Version 4.0. Select laboratory abnormalities such as worst toxicity grade and toxicity grade shift from baseline will be summarized by treatment arm.

Patient-Reported Outcomes

Data will be collected from patients in this study to more fully characterize the clinical profile of pertuzumab. These PRO measurements are described in Section 8.1.5 and Section 8.2.5.1 below. The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered AEs. Due to these differences, PRO data will not be reported as AEs and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered AEs. The PRO data will be presented in separate tables, figures, and data listings from the AE data, and will be included in the appropriate section of the final study report (i.e., efficacy, exploratory).

8.2.5 Other Analyses

8.2.5.1 Patient-Reported Outcomes

The EORTC QLQ-C30 and QWLQ-BR23 data will be scored according to the EORTC QLQ-C30 and QLQ-BR23 Scoring Manual. For the QLQ—C30 and QLQ—BR23, scales with more than 50% of the constituent items completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing. Summary statistics of absolute scores of the QLQ-C30 and QLQ-BR23 scales and their changes from baseline will be calculated at each assessment time point for the two treatment arms. The mean (and 95% CI) and median (and inter-quartile ranges) of the absolute scores and the changes from baseline will be reported.

Frequencies and percentages of missing data for the PRO endpoints will be compared between the two treatment arms. Differences in the proportion of dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) between the two treatment arms will be tested using the χ^2 test.

Repeated measures mixed-effects models will be the primary models for the analysis of the EORTC QLQ-C30 and QLQBR23. Each model will have an intercept term, a linear time trend term (in weeks), a term for treatment group, a term for treatment-by-time interaction. A baseline score and appropriate covariates will also be added. The repeated measures mixed-effects model assumes that the missing data mechanism is ignorable.

EQ-5D data will be evaluated at the level of the entire study population and will follow patients over time to describe utility values for the entire population. Results will be used for pharmaco-economic modeling purposes.

8.2.5.2 Interim Safety Monitoring and Interim Safety Analyses

The IDMC will monitor patient safety, including cardiac criteria at pre-specified times, as well as, at ad hoc meetings if requested.

After the first 200 and 800 patients have been enrolled and treated for 6 months, the IDMC will perform a planned review of heart failure data. If an absolute difference of more than 3% (expected rate on trastuzumab standard of care =3%) in the incidence of heart failure NYHA Classes III to IV or definite or probable cardiac death is observed between treatment groups, the IDMC will consider recommending stopping or modifying the trial (if only seen in a subset of patients, the IDMC may recommend continuation of the trial with an amendment).

The IDMC will work according to the guidelines defined in the IDMC charter. The decision of the IDMC will be made based on looking at the difference in rates of heart failure between the groups, and the 95% two-sided confidence limits for the difference, as well as the rates in each group. If the assumed rate of heart failure NHYA classes 3–4 is 3% in non-pertuzumab-treated patients, then a 3% observed increase in this rate among the pertuzumab-treated patients would give the following confidence limits for each of the interim analyses (Table 18):

Table 18 Confidence Intervals for Interim Analyses

Number of Patients		Two-sided 95% Confidence Limits Based on Hauck-Anderson Method
Control	Pertuzumab	
100	100	-3.26%, 9.26%
400	400	0.00%, 5.99%

The IDMC will also consider cumulative incidence estimates of heart failure calculated over time and the incidence of secondary/other cardiac endpoints (asymptomatic left ventricular systolic dysfunction [LVSD] events, rate of significant LVEF drops of an absolute decrease of at least 10% from baseline and to below 50%).

8.2.5.3 Updated Analyses

In order to capture additional data from patients followed for the full duration of the protocol and to report more mature OS data, further updated analyses will be performed. Formal analyses of OS and updated analyses of other key data will be performed at the time points detailed in Section 8.2.1.2. These additional analyses will be reported separately to the final study report.

8.3 Sample Size

The study is designed to have 80% power to test the null hypothesis of no true difference in risk of an IDFS event (HR = 1) versus the alternative hypothesis of a difference (HR = 0.75) in HRs with a 5%, 2-sided significance level. Under these assumptions approximately 379 IDFS events are required for the primary analysis of IDFS.

Original protocol recruitment rate and event rate assumptions:

It was foreseen when the protocol was designed that this study would enroll a similar population to the adjuvant trastuzumab trial BCIRG [Slamon 2006; Slamon, 2009] [57, 59]. Therefore based on the data from that trial, the Kaplan–Meier estimate of IDFS at 3 years for the trastuzumab control group for this study was estimated to be 88% regardless of the chemotherapy regimen (with annual decreases in Kaplan–Meier estimates of 2% during the first year after randomization, 5% during Years 2 and 3, and 2% during Year 4 and beyond). Based on this and a projected monthly accrual rate of 0.29 patients at 700 sites, it was estimated that with 3806 patients, enrolled in approximately 27 months, 379 IDFS events would occur at around 55 months.

Revised protocol recruitment and event rate assumptions:

As of the end of September 2012, approximately 1900 patients have been enrolled in this study at a monthly recruitment rate more than 50% higher than foreseen. In these patients, the proportion with node-negative disease is nearly double that expected based on BCIRG 006, resulting in a population inconsistent with the assumptions upon which the protocol design was based. In response to this, protocol version A has been amended to reduce the overall proportion of patients with node-negative disease by only randomizing further patients to node-positive strata and to expanding the sample size by approximately 1000, to 4800 patients. This amendment is in order to bring the study population closer to the original assumptions.

As a result, the following revised sample size assumptions now apply:

The annual decrease in Kaplan–Meier estimates of the invasive disease-free survival function in the trastuzumab control group (regardless of the chemotherapy regimen) is anticipated to be 1.9% during the first year after randomization, 4.5% during Year 2, 4.4% during Year 3, and 1.8% during Year 4 and beyond. Therefore the Kaplan–Meier estimate of IDFS at 3 years for the trastuzumab control group is 89.2%. These assumptions are based on 5 year follow-up data from BCIRG 006. Under the alternative hypothesis and with the assumption that IDFS for both groups is exponentially distributed, the magnitude of treatment effect in terms of increase in IDFS at 3 years will be 2.6%, meaning a Kaplan–Meier estimate of IDFS at 3 years for the pertuzumab group of 91.8%. The smallest estimated difference detectable at a 5%, 2-sided significance level is HR = 0.818, under which the magnitude of treatment effect will be 1.9%.

As of end of September2012, approximately 1900 patients have been enrolled, at a peak rate of approximately 350 patients per month. It is estimated that following the implementation of protocol Amendment B, the enrollment rate will reduce by approximately 50%, as node-negative patients will no longer be enrolled.

Under these assumptions, it is planned that 4800 patients will be enrolled over an estimated 25 months, and assuming a 10% drop-out rate, the 379 IDFS events required for the primary analysis will have occurred at 46 months. In order to ensure sufficient data maturity (particularly in patients enrolled after the protocol amendment B), in the event that 379 IDFS events are reached sooner than 30 months after last patient enrolled (as is anticipated based on the revised IDFS assumptions), the primary analysis will be delayed until 30 months after last patient randomized.

Sample size calculations are performed using EAST v5. 4 (Cytel Inc).

9. DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Sponsors SOPs and the SOPs of the BrEAST Data Center who will be performing data collection and will hold the clinical study database.

An EDC system using eCRFs will be utilized for all data capture required for this study. Exceptions to this include radiographic tumor assessment films (including but not limited to chest X-rays, CT scans, MRI, and bone scans), ECHO/MUGA cardiac assessments, and paper quality-of-life questionnaires completed by the patients. Local clinical laboratory data, including hematology and serum chemistry, and quality of life questionnaires completed by the patients will be transcribed by the site from the paper laboratory reports onto the eCRF. In no case is the eCRF to be considered as source data for this trial.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the study monitor (source document verification), and the maintenance of a drug-dispensing log by the Investigator.

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the study database will verify the data and discrepancy reports will be

generated accordingly and transferred electronically to the eCRF at the site for resolution by the Investigator.

Throughout the study, the joint clinical science team will review data according to the Data Review Plan as described in the Data Quality Plan.

For classification purposes, preferred terms will be assigned by the BrEAST Data Center to the original terms entered on the eCRF, using the most up to date version of MedDRA for AEs and diseases and the INN (international non-proprietary name) drug terms and procedures dictionary for treatments and surgical and medical procedures.

Unblinding will not be permitted during the study, unless the central study team agree that unblinding is in the best interests of the patient, as per a request from an investigator (see Section 6.7). Planned treatment unblinding will take place immediately before the final analysis for the primary endpoint or at the time the IDMC recommends trial stopping.

10. STUDY COMMITTEES

10.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be formed to review data including those from interim analyses of overall safety including specific cardiac safety. The IDMC members will be independent of the trial and familiar with the methodology of oncology trials. The IDMC will comprise of a fixed number of permanent members with experience of clinical studies in oncology including at least one statistician. They must be aware of the implications of the conclusions based on immature data and agree with the design and objectives of this protocol.

Relevant safety data for review by the IDMC will include:

- AEs (NCI-CTC AE version 4.0) and SAEs
- AEs requiring dose reduction or modification
- Cardiac safety (see Section 8.2.4).

The first IDMC meeting will take place 6 months after the first patient is recruited and regular meetings will take place approximately every 6 months. The IDMC schedule may be modified based on the recommendation of its members or request by the sponsor. The operating procedures for the meetings will be detailed in the IDMC charter.

After each meeting, the IDMC will provide the Interface Committee with its recommendation. The Interface Committee comprises of senior team members not involved in the day-to-day running of the trial to provide a firewall to prevent the study team from being unblinded by the IDMC decisions. An Interface Committee Charter will fully detail the composition, roles, responsibilities and interactions of this committee.

An IDCC will prepare the unblinded data package for the IDMC meetings. The IDMC Charter will fully describe the communication flow and role of the IDCC.

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PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 Local Regulations/Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC). For studies conducted in the United States or under a U.S. IND, the Investigator will additionally adhere to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsor and Investigators," part 50, "Protection of Human Patients," and part 56, "Institutional Review Boards."

In other countries where "Guidelines for Good Clinical Practice" exist, the Sponsor and the Investigators will strictly ensure adherence to the stated provisions.

12.2 Informed Consent

It is the responsibility of the Investigator or a person designated by the Investigator (if acceptable by local regulations) to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, anticipated benefits, objectives, and potential hazards of the study. Appropriate forms for obtaining written informed consent will be provided by the Investigator or by the Sponsor or designee.

For patients not qualified to give or incapable of giving legal consent, written consent must be obtained from the legal representative. In the case where both the patient and his or her legal representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and/or legal representative has/have orally consented to participation in the trial, the witness's signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The eCRFs for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients, including those already being treated, should be informed of the new information, given a copy of the revised form, and give their consent to continue in the study.

12.3 Independent Ethics Committees/Institutional Review Board

Independent Ethics Committees (IEC) (non-U.S. Sites): This protocol and any accompanying material provided to the patient (such as patient information sheets or

descriptions of the study used to obtain informed consent), as well as any advertising or compensation given to the patient, will be submitted by the Investigator to an IEC, as per national legislation Approval from the committee must be obtained before starting the study and should be documented in a letter to the Investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the IEC approval must also be submitted by the Investigator to the Committee in accordance with local procedures and regulatory requirements.

Institutional Review Board (U.S. Sites): It is the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures will be reviewed and approved by an IRB. This board must operate in accordance with the current U.S. Federal Regulations. A letter or certificate of approval will be sent by the Investigator to the Sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications must be prepared by and agreed upon between the Sponsor and Breast International Group. Protocol modifications must be reviewed and approved by the Steering Committee.

The investigator shall not, on his/her own make any modifications to the protocol.

All protocol modifications must be submitted to the appropriate IEC/IRB for information and approval in accordance with local requirements, and to Regulatory Agencies, if required.

Once approved by the appropriate Independent Ethics Committee or Institutional Review Board and by the Regulatory Agencies (if required), the investigator shall implement such Protocol modifications. Protocol modifications for urgent safety matters shall however be directly implemented, as per the instructions of the Sponsor, BIG and/or BrEAST Data Center.

14. CONDITIONS FOR TERMINATING THE STUDY

Both the Sponsor and the Investigator reserve the right to terminate their participation in the study under the circumstances agreed upon in the site agreement. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patients' interests.

15. STUDY DOCUMENTATION, eCRFs, AND RECORD KEEPING

15.1 Investigator's Files/Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: (1) Investigator's study file; and (2) patient clinical source documents.

The Investigator's study file will contain the protocol and amendments, IRB/IEC and governmental approval with correspondence, sample Informed Consent Form, drug records, staff curriculum vitae, and authorization forms and other appropriate documents and correspondence, etc. In addition, at the end of the study the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the Investigator's study file.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include patient hospital/clinic records; physician's and nurse's notes; appointment book; original laboratory reports; ECG, electroencephalogram (EEG), X-ray, pathology and special assessment reports; signed Informed Consent Forms; consultant letters; and patient screening and enrollment logs.

The Investigator must keep these two categories of documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the study or for a longer period of time if required by local regulations. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator, in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made before storing outside of the site.

15.2 Source Documents and Background Data

The Investigator shall supply, upon request, any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

15.3 Audits and Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Pharma Development Quality Assurance Unit, or Genentech GCP/Quality Assurance Group or its designees, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

15.4 Electronic Case Report Forms

Data for this study will be captured via an EDC system by using an eCRF. An audit trail will maintain a record of initial entries and changes made, reasons for change, time and date of entry, and user name of person authorizing entry or change. For each patient

randomized, an eCRF must be completed and electronically signed by the principal Investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study treatment, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness, and timeliness of the data reported to the BrEAST Data Center in the eCRFs and in all required reports.

16. MONITORING THE STUDY

This protocol will be co-sponsored by F. Hoffmann-La Roche and Genentech, Inc. These Sponsors in conjunction with BIG will oversee the management of this study and will be responsible for clinical operations including site management and source data verification.

The Sponsors and BIG will identify potential sites for participation in this study. Study networks will be assessed by the Sponsors and BIG. The Sponsors and BIG Groups will perform pre-trial evaluations at individual sites. The Sponsors and BIG/BIG Groups will oversee selection, approval, and monitoring of all clinical study sites. Patient eligibility verification will be conducted on all patients identified for enrollment into the study.

Investigator site monitoring will be managed by the study Sponsors and BIG Groups. Statistical analyses will be performed by Frontier Science. Perceptive Informatics will be responsible for collection of patient screening information and for patient randomization using a web-based system.

The IWRS will be utilized for drug management.

Tissue and blood samples will be collected for this study and will be stored and assayed by a central analytical laboratory. Data from central analytical laboratories will be sent directly to BrEAST Data Centre and will not be collected via CRF. Local clinical laboratory data including hematology and serum chemistry will be transcribed by the site from the paper source documents onto the eCRF.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The Investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, patients should not be identified by their names, but by an identification code. The Investigator should keep a patient enrollment log showing codes, names, and addresses. The Investigator should maintain documents not for submission to the Sponsors, e.g., patients' written Informed Consent Forms, in strict confidence.

18. CLINICAL STUDY REPORT (CSR)

A clinical study report will be written and distributed to Health Authorities as required by applicable regulatory requirements.

19. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Publication and presentations of any results from this study shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the specific policy developed for this study. This "Publication and Presentation Policy" shall be approved by the Study Steering Committee and made available to all investigators, sites and groups participating in the study.

Appendix 1 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

– is fatal; [results in death] [NOTE: death is an outcome, not an event]

– is Life-Threatening [NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe].

– required in-patient hospitalization or prolongation of existing hospitalization

– results in persistent or significant disability/incapacity

– is a congenital anomaly/birth defect

– is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the Investigator. For SAEs, possible causes of the event are indicated by selecting one or more options. (Check all that apply)

– Pre-existing/Underlying disease - specify

– Study treatment -specify the drug(s) related to the event

– Other treatment (concomitant or previous) - specify

– Protocol-related procedure

– Other (e.g., accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

Appendix 1 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A (Cont.)

A serious adverse event occurring during the study or which comes to the attention of the Investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test "drug", should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs eForm of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The Investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor [see attached gcp_for000227 for details of administrative and contact information].

ROCHE HEADQUARTERS CONTACT for SAEs: Clinical Operations/Clinical Science [see attached gcp_for000227 for details of administrative and contact information].

Within the US, weekends, holidays and after 5:00 pm, call 1-800-526-6367 and ask for the physician on call. Outside the US, call the local emergency contact number provided by the Monitor.

Appendix 2 Radiotherapy Guidelines

I. BREAST CONSERVING THERAPY

MANDATORY: Breast radiotherapy (RT) after complete local excision

Breast RT may be contraindicated in patients with significant comorbidity (for example, scleroderma and systemic lupus erythematous). Reasons for not delivering breast RT after complete local excision of the primary breast cancer should be documented in the **eCRF.**

Target Volume

- Whole breast including the primary tumor bed
- Primary tumor bed boost in conjunction with whole breast RT may be used as per local policy declared by the center prior to local activation.
- Partial breast RT may be used as per local policy declared by the center prior to local activation.
- Regional nodal RT: Refer to Item III below.

Dose Fractionation

- Whole breast - recommended schedules:
  a) 50 Gy in 25 fractions, 5 fractions per week; or
  b) 42.5 Gy in 16 fractions, 5 fractions per week; or
  c) 40 Gy in 15 fractions, 5 fractions per week.

Other schedules may be used as per local policy declared by the center prior to local activation.

- Primary tumor bed boost in conjunction with whole breast RT: As per local policy declared by the center prior to local activation.
- Partial breast RT: As per local policy declared by the center prior to local activation.

Treatment planning

- Computer tomography (CT) based treatment planning is strongly recommended for whole breast RT and tumor bed boost.
- Computer tomography (CT) based treatment planning is mandatory for partial breast irradiation delivered using external beam RT.

II. POST MASTECTOMY RADIOTHERAPY

MANDATORY:

a) 4 or more positive axillary nodes or
b) Pathologic T4 disease.
c) 'Non-resectable' microscopic positive deep margin (invasive carcinoma or DCIS)

OPTIONAL:

a) **1-3 positive axillary nodes or**
b) **Higher risk node negative disease (for example T3 primary in the presence of high histologic grade and/or lymphovascular invasion)**

Target Volume

- Whole chest wall
- Primary tumor bed boost in conjunction with chest wall RT may be used as per local policy declared by the center prior to local activation.
- Regional nodal RT: Refer to Item III below.

Dose Fractionation

- Whole breast: Recommended schedule is 50 Gy in 25 fractions, 5 fractions per week. Other schedules may be used as per local policy declared by the center prior to local activation.
- Primary tumor bed boost in conjunction with chest wall RT: As per local policy declared by the center prior to local activation.

Treatment planning

- Computer tomography (CT) based treatment planning is strongly recommended for chest wall RT.

III. REGIONAL NODAL RT

For patients who have completed SNB alone or ALND as per protocol:

RECOMMENDED:

Any breast surgery, 4 or more positive axillary nodes

OPTIONAL:

Any breast surgery, 0-3 positive axillary nodes, pathological T4 (pT4) disease

Target volume

- Required:
  a) Supraclavicular fossa if there are 4 or more positive axillary nodes;
  b) Internal mammary nodes if tumor involvement is biopsy confirmed.
- Optional:
  a) Supraclavicular fossa if there are 0-3 positive axillary nodes;
  b) Axilla as per local policy declared by the center prior to local activation (for example, known or high risk of residual axillary disease post-surgery);

c) Internal mammary nodes if there is a high risk of tumor involvement as per local policy declared by the center prior to local activation.

Dose fractionation

- Recommended schedule: 50 Gy in 25 fractions, 5 fractions per week. Other schedules may be used as per local policy declared by the center prior to local activation. Hypofractionated schedules are not recommended.

Treatment planning

- Computer tomography (CT) based treatment planning is strongly recommended for supraclavicular fossa and/or axillary RT.
- Computer tomography (CT) based treatment planning is mandatory for internal mammary nodal RT.

Appendix 3 ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Reference:
Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

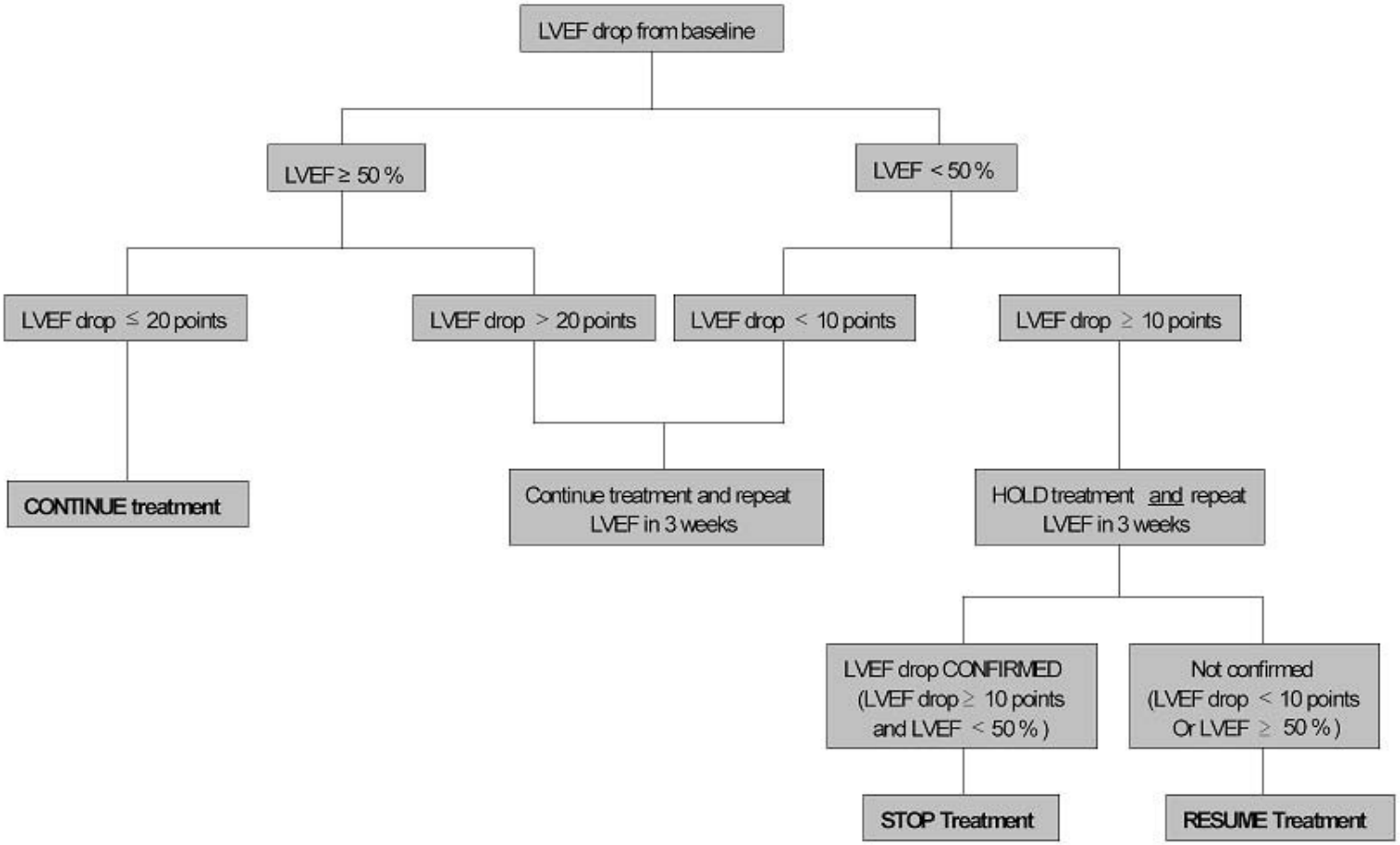
The above information will be reported in the appropriate eCRF section.

Appendix 4 Criteria for New York Heart Association Functional Classification

Functional capacity (four classes)

Class I:	No limitation of physical activity (asymptomatic) Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea
Class II:	Slight limitation of physical activity Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea
Class III:	Marked limitation of physical activity Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea
Class IV:	Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased

Appendix 5 Asymptomatic decline in LVEF: Algorithm for Continuation and Discontinuation of HER2-Targeted Study Medication



Appendix 6 Standard Procedures for the Pathological Examination of the Samples to Assess In Situ Versus Invasive Breast Cancer Recurrences

Sampling of the specimens

a) Excisional biopsy specimens (surgical specimens).

– The surgical specimen should be delivered promptly and intact to the pathology laboratory.

– The specimen should be dissected as soon as possible, and the size of any grossly identifiable lesion should be recorded in centimeters in 3 dimensions.

– Distinct lesions that appear grossly <2 cm in size should be entirely sampled for histology, and should include a margin of surrounding non-neoplastic tissue.

– Distinct lesions >2 cm should be extensively sampled with at least 2 blocks prepared per 1 cm size of tumor (i.e., for a tumor of 4 cm, at least 8 blocks should be taken), always including a margin of surrounding non-neoplastic tissue.

b) Incisional biopsy specimens, core biopsies.

– All the tissue obtained by incision or core biopsies must be submitted for histology.

c) Fine needle aspiration cytology

– Fine needle aspiration cytology does not permit differentiation of in situ disease from invasive breast cancer recurrences and as such cannot be used as a diagnostic means in the context of this trial.

Histopathological examination

The recommended section thickness for histological examination is 2-3 microns. In the vast majority of the cases, the differential diagnosis of in situ vs invasive breast cancer recurrence is straightforward. However in problematic cases, including the instances of doubtful microinvasion, the final diagnosis should be rendered according to the evaluation of the histopathological features and to the results of immunohistochemical stainings as recommended by Rosen PP, and Tavassoli FA & Devitee P.

The highlighting of the myoepithelial cell layer by immunohistochemical staining has been shown to be a very useful aid to the pathologist in the identification of in situ recurrences as opposed to invasive recurrences, where the myoepithelial cell layer is invariably absent.

Recommended markers for immunolabelling of the myoepithelial cells are p63 (nuclear antigen) and cytoplasmic markers of smooth muscle differentiation, namely smooth muscle myosin heavy chain, calponin, and caldesmon.

Smooth muscle actin is not a suitable marker, because it will stain also the myofibroblastic cells, in addition to myoepithelial cells, thus possibly leading to false-positive identification of the latter cells.

Appendix 6 Standard Procedures for the Pathological Examination of the Samples to Assess In Situ Versus Invasive Breast Cancer Recurrences (Cont.)

It should be borne in mind, however, that while the presence of myoepithelial cells rules out the possibility of an invasive recurrence, the opposite is not true, because some high-grade ductal carcinomas in situ (DCIS) may loosen identifiable myoepithelial cell layers without being invasive.

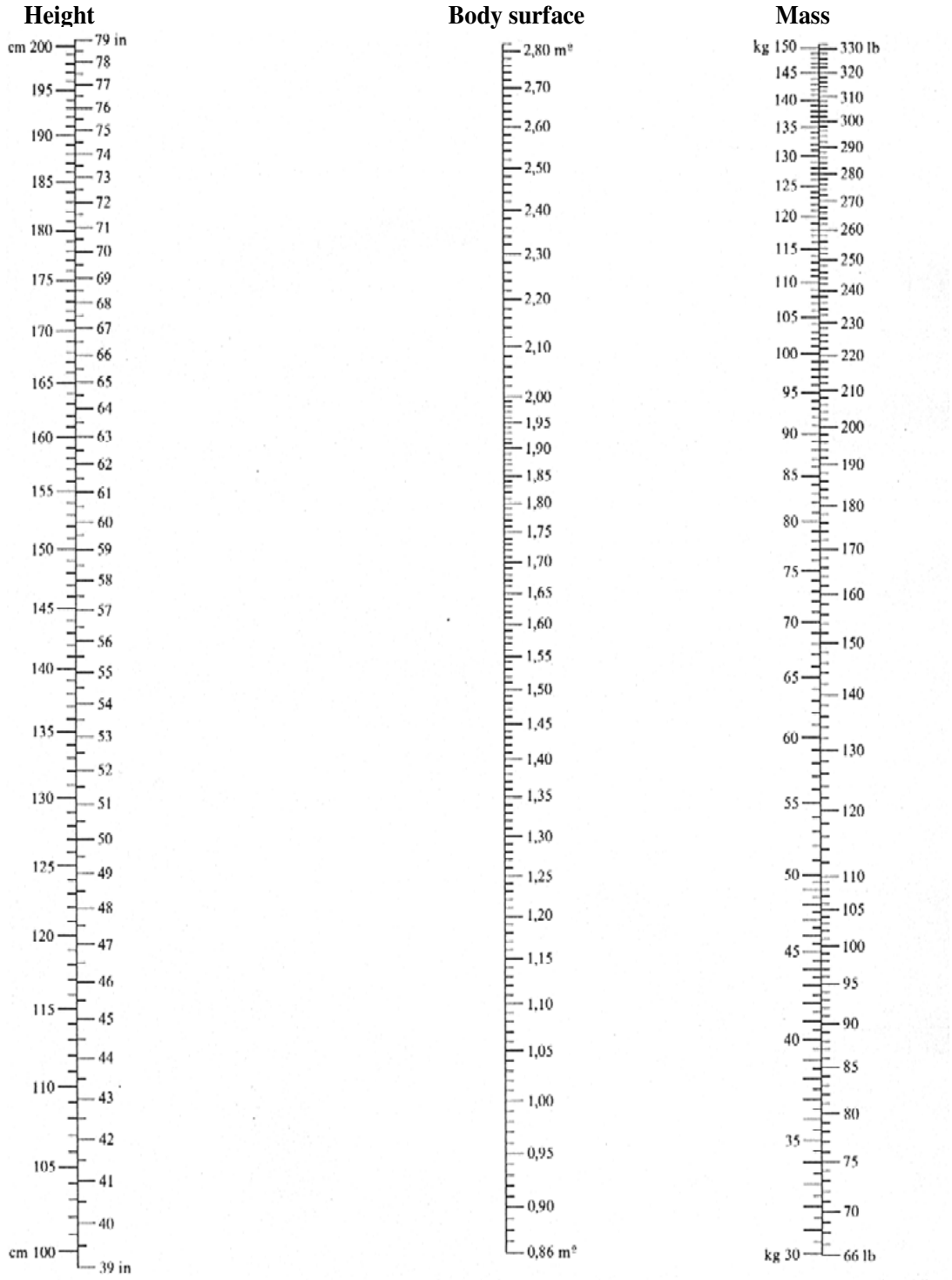
In these cases, the diagnosis must be made according to the pure morphological features of the recurrence in the original stained sections and in additional sections obtained by re-cutting.

Finally, as recommended by Tavassoli FA & Devitee P, when there is still doubt about the actual invasion even after recuts and repeat immunostaining for identification of the myoepithelial cells, the case should be diagnosed as an in situ carcinoma.

Rosen's Breast Pathology, III ed, Lippincott 2009, pp. 333-341

WHO Classification of Tumours. Tumours of the Breast and Female Genital Organs. IARC Press, Lyon, 2003. pp 74-75

Appendix 7 Suggested Nomogram for the Determination of Body Surface Area



Based on the Formula from Du Bois and Du Bois, Arch intern Med , 17, 863 (1916): $0 = M^{0,425} \times L^{0,725} + 71,84$ resp $\log 0 = \log M \times 0,425 + \log L \times 0,725 + 1,8564$
(0: Body surface [in cm2], M; Body mass [in kg]: L: Body length [in cm]

Appendix 8 EORTC QLQ—C30 Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

Appendix 8 EORTC QLQ—C30 Questionnaire (cont.)

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 9 EORTC QLQ—BR23 Questionnaire

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

Appendix 9 EORTC QLQ—BR23 Questionnaire (cont.)

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Appendix 10 EQ-5D Questionnaire

Health Questionnaire

English version for the UK
(validated for Ireland)

Appendix 10 EQ-5D Questionnaire (cont.)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

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ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Not Applicable

ANNEX 7:

OTHER SUPPORTING DATA

(INCLUDING REFERENCED MATERIAL)

ANNEX 7: OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

Not applicable

ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval date/Procedure[a]	Change
2.1	4 March 2013 (Commission Decision)/ EMEA/H/C/002547 (initial MAA)	No new safety concerns have been added to version 3 of the EU RMP.
3.0	Subject to amendment within procedure/ EMEA/H/C/002547/PSUV/006 and superceded by RMP v3.1	Version 3.0 was prepared to include the Global Enhanced PV Pregnancy Program for pregnancy monitoring. No new safety concerns added.
3.1	9 January 2014/ EMEA/H/C/002547/PSUV/0006	Prepared in response to the assessment of version 3.0 Study milestones updated. No new safety concerns added.
3.2	30 June 2014 (Commission Decision)/ EMEA/H/C/002547/II/0007	Prepared to support the amendment of the PHEREXA protocol. No new safety concerns added.
3.3	8 July 2014 (Commission Decision)/ EMEA/H/C/002547/II/0009	Prepared to support the amendment of the PERUSE protocol. No new safety concerns added.
4.0	Subject to amendment within procedure/ EMEA/H/C/002547/II/010 and superceded by RMP v5.0	Prepared to support the marketing application for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer. No new safety concerns added.
5.0	Subject to amendment within procedure/ EMEA/H/C/002547/II/010 and superceded by RMP v5.1	Change made to provide greater clarity on patient population. Missing information “Risk in male patients” changed to “Risk in male breast cancer patients.”
5.1	28 July 2015 (Commission Decision)/ EMEA/H/C/002547/II/010	Prepared to support the approval of Perjeta in the neoadjuvant setting. Addition of PASS & PAES and agreed indication wording for neoadjuvant treatment.
5.2	22 October 2015/ EMEA/H/C/002547/IB/0018	Prepared to support the request to change the study milestone for the PHEREXA study. No new safety concerns added.

Version	Approval date/Procedure[a]	Change
6.0	25 February 2015/ EMEA/H/C/002547/II/0021/G	Prepared to support the request to change the study protocol and milestone for the PERUSE study. RMP aligned with PBRER #1064561 and approved SmPC. No new safety concerns added.
7.0	15 September 2016/ EMEA/H/C/002547/II/0026	Prepared to include data from the Study MO22324 (PHEREXA) Primary CSR. No new safety concerns added.
8.0	23 February 2017/ EMEA/H/C/002547/II/0028	Prepared to include final safety data from the Study BO22280 (TRYPHAENA) Final CSR. No new safety concerns added.
9.0	18 December 2017 (Commission Decision)/ EMEA/H/C/002547/II/0029	Prepared to include primary safety data from the Study WO29217 (BERENICE) Primary CSR. No new safety concerns added.
10.0	Subject to amendment within procedure/ EMEA/H/C/002547/II/034 and superceded by RMP v10.1	Submitted to support a label extension for adjuvant treatment in patients with HER2-positive EBC. Submission of data from Study BO25126 (APHINITY). No new safety concerns added.
10.1	Subject to amendment within procedure/ EMEA/H/C/002547/II/034 and superceded by RMP v10.2	RMP 10.0 was transitioned into the new EU RMP template and is being submitted as part of the ongoing procedure for the adjuvant treatment of patients with HER2-positive EBC (EMEA/H/C/002547/II/0034). No new safety concerns added.

Version	Approval date/Procedure[a]	Change
10.2	31 May 2018 (Commission Decision)/ EMEA/H/C/002547/II/0034	Submitted as part of the ongoing procedure for the adjuvant treatment of patients with HER2-positive EBC (EMEA/H/C/002547/II/0034). Based on feedback from the PRAC assessment for Procedure EMEA/H/C/002547/II/0034 the following safety concerns previously considered as missing information were reclassified as important potential risks: Risk in fertility in humans, Risk in patients aged 75 years or older and Risk of lack of efficacy due to immunogenicity. The PRAC agreed with the removal of the following safety concerns from the RMP: Exacerbation of chemotherapy/docetaxel associated neutropenia, Mucositis, Interstitial lung disease, Risk in male breast cancer patients, Risk in patients with hepatic impairment and Risk in patients with severe renal impairment. No new safety concerns added.
11.0	17 January 2019 (Commission Decision)/ EMEA/H/C/002547/II/0041	The 2018 Annual Data Summary report (ADS) of the MotHER Registry (reporting interval of 1 February 2017 through 31 January 2018) was considered the final report for patients exposed to Perjeta in the MotHER Registry and was provided in support of the marketing authorization holder's (MAH's) request to close out this RMP commitment of MotHER Registry relating to Perjeta. RMP version 11.0 was prepared to reflect this, and to support the EU Type II variation. This proposal was also accepted by the Committee of Medicinal Products for Human Use (CHMP), as indicated in a positive opinion dated 17 January 2019 (Procedure EMEA/H/C/002547/II/0041)

Version	Approval date/Procedure[a]	Change
12.0	9 July 2020 EMEA/H/C/002547/IB/0050	Submitted to address PRAC request to remove safety concern Grade ≥3 Diarrhea from EU-specific list of safety concerns (request was received as part of assessment report for Perjeta PSUR/PBRER Report No. 1094402 covering reporting interval 8 June 2018 to 7 June 2019; Procedure no.: EMEA/H/C/PSUSA/00010125/201906). This version also removes all existing and ongoing pharmacovigilance activities for the MotHER Registry (Study H4621g) relating to Perjeta in order to fulfill RMP commitments regarding the potential risk of Oligohydramnios. Clinical and post-marketing exposure in the RMP was updated to align with information presented in the 2019 Perjeta PSUR/PBRER (Report No. 1094402; reporting interval 8 June 2018 to 7 June 2019). The epidemiology section in this version was also updated to include more recent information. No new safety concerns were added.

Version	Approval date/Procedure[a]	Change
13.0	10 July 2020	Prepared to include data from the Study MO28047 (PERUSE) final CSR. Clinical and post-marketing exposure in the RMP was updated to align with information presented in the 2020 Perjeta PSUR/PBRER (Report No. 1101895; reporting interval 8 June 2019 to 7 June 2020). Details of Important Identified Risks, Important Potential Risks, And Missing Information was updated with PERUSE information. No new information was obtained for the safety concern (Congestive heart failure / Left ventricular dysfunction and Risk in patients with cardiovascular impairment). Any reference to H4621g/GE28099 (MotHER Pregnancy Registry) has been removed from the RMP as MotHER Registry (H4621g/GE28099) is now closed. No further additional PV activity will be conducted within the MotHER Registry for the safety concern of oligohydramnios
13.1	Current Submission	Within this RMP update, the references to PERUSE study from the pharmacovigilance plan has been removed and have been indicated as not applicable. The information regarding the APHINITY study was updated for the study status. The references made to the PERUSE study was deleted from additional pharmacovigilance section since the study is no longer ongoing. The references made to the PERUSE study were removed from Part VI Modules II.B and II.C of current EU RMP.

[a] Note that not all versions of the EU RMP are approved by the EMA.