Official Title:	**A PHASE IV, MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY OF PERTUZUMAB (IN COMBINATION WITH TRASTUZUMAB AND DOCETAXEL) IN FIRST LINE TREATMENT OF INDIAN PATIENTS WITH HER2-POSITIVE ADVANCED (METASTATIC OR LOCALLY RECURRENT) BREAST CANCER**
NCT Number:	**NCT02445586**
Document:	**PROTOCOL**
Version & Date:	**Version 1.0: 06-June-2014**

PROTOCOL

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PROTOCOL NUMBER:	ML29282
VERSION NUMBER:	1.0
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
TEST PRODUCT:	Pertuzumab RO 43-68451
MEDICAL MONITOR:	Dr. [redacted]
SPONSOR:	Roche Products (India) Pvt. Ltd
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Signature with Date: [redacted] 6 JUN 2014
Name: Dr. [redacted]
Designation: [redacted]

Signature with Date: [redacted] 6 Jun 2014
Name: Dr. [redacted]
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Signature with Date: [redacted] UN 2014.
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PROTOCOL ACCEPTANCE FORM

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form as instructed by your local study monitor at Roche Products (India) Pvt. Ltd. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

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PHASE:	IV
INDICATION:	HER2-Positive Advanced (Metastatic or Locally Recurrent) Breast Cancer
SPONSOR:	Roche Products (India) Pvt. Ltd.

Objectives

Primary Objectives

The primary objectives for this study are to evaluate safety and are as follows:-

- To evaluate the safety of pertuzumab (in combination with trastuzumab and docetaxel) in Indian patients
- To evaluate the tolerability of pertuzumab (in combination with trastuzumab and docetaxel) in Indian patients

Secondary Objectives

The secondary objectives for this study are to evaluate efficacy and are as follows:-

To evaluate the efficacy of pertuzumab in combination with trastuzumab and docetaxel in Indian patients with respect to:-

- Overall response rate (ORR)
- Progression-free survival (PFS)
- Overall survival (OS)

Study Design

Description of Study

Multicenter, open-label, single-arm, Phase IV study

Number of Patients

Approximately 52 patients will be enrolled in the study.

Target Population

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

Patients who have been considered being eligible for pertuzumab (in combination with trastuzumab, and docetaxel) therapy by the treating physician as per the prescribing information.

Patients must meet the following criteria for study entry:-

1. Male or female patients aged ≥18 years
2. Signed written informed consent approved by the relevant Institutional Review Board/Ethics Committee,prior to any study procedure
3. Histologically or cytologically confirmed and documented adenocarcinoma of the breast with metastatic or locally recurrent disease not amenable to curative resection; patients with measurable and/or non-measurable disease are eligible
4. Known and documented HER2-positive (defined as either immunohistochemistry [IHC] 3+ or *in situ* hybridization [ISH] positive) as assessed on primary tumor and/or metastatic site as determined in a local laboratory that is experienced/certified in HER2-expression testing using an accurate and validated assay
5. Known and documented left ventricular ejection fraction (LVEF) of at least 50%
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1
7. A negative serum β-HCG test for women of childbearing potential (premenopausal, or <12 months of amenorrhea post-menopause, and women who have not undergone surgical sterilization [i.e., absence of ovaries and/or uterus]) within 7 days prior to the first dose of study treatment with the result available prior to first dosing
8. For women of childbearing potential and men with partners of childbearing potential, agreement 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 use must continue for the duration of study treatment and for at least 7 months after the last dose of study treatment. Male patients whose partners are pregnant should use condoms for the duration of the pregnancy.

   (for women of childbearing potential: agreement to remain abstinent (only if it is in line with the preferred and usual lifestyle) or use single or combined non-hormonal contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of study drug)

9. Adequate organ function, as determined by the following laboratory results, within 3 days prior to study treatment:
    - Absolute neutrophil count >1,500 cells/mm^3
    - Platelet count >100,000 cells/mm^3
    - Hemoglobin >9 g/dL (patients may receive transfused red blood cells to obtain this level)
    - Albumin >2.5 g/dL
    - Total bilirubin ≤1.5 times 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 for patients with liver metastases)
    - Alkaline phosphatase >2.5 × ULN (>5 × ULN in patients with liver metastases or >10 × ULN for patients with bone metastases)
    - Serum creatinine > 2.0 mg/dL or 177 µmol/L
    - International normalized ratio (INR), activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) <1.5 × ULN (unless on therapeutic anti-coagulation)

Patients who meet any of the following criteria will be excluded from study entry:

1. Previous systemic non-hormonal anti-cancer therapy for the metastatic or locally recurrent disease
2. Previous approved or investigative anti-HER2 agents in any breast cancer treatment setting, except trastuzumab and/or lapatinib in the adjuvant or neoadjuvant setting
3. Disease progression while receiving or within 12 months of completion of trastuzumab and/or lapatinib treatment in the adjuvant or neoadjuvant setting
4. History of persistent Grade 2 or higher (NCI-CTC, Version 4.03) hematological toxicity resulting from previous adjuvant or neoadjuvant therapy
5. Current, known peripheral neuropathy of Grade 3 or greater (National Cancer Institute [NCI]-Common Toxicity Criteria [CTC], Version 4.03)
6. 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

7. Serious uncontrolled concomitant disease that would contraindicate the use of any drug used in this study or that would put the patient at high risk for treatment-related complications
8. Uncontrolled hypertension (systolic >150 mmHg and/or diastolic >100 mmHg) *or* clinically significant (i.e. active and/or requiring medication) cardiovascular disease, including but not limited to cerebrovascular accident (CVA)/stroke *or* myocardial infarction within 6 months prior to first study medication, unstable angina, CHF of New York Heart Association (NYHA) grade II or higher, *or* serious cardiac arrhythmia requiring medication, *or* other cardiovascular problem that is uncontrolled or is currently controlled with medication
9. Current known infection with HIV, Hepatitis B virus, or Hepatitis C virus
10. Dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
11. 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
12. Known hypersensitivity to any of the study medications or to excipients of recombinant human or humanized antibodies
13. History of receiving any investigational treatment within 28 days prior to 1st study drug administration (dosing) and/or concurrent participation in any interventional clinical trial
14. Pregnant or lactating women
15. Current clinical or radiographic evidence of central nervous system (CNS) metastases
16. History of LVEF decline to below 50% during or after prior trastuzumab adjuvant or neo-adjuvant therapy

Length of Study

1. Enrollment period will be of approx. 12 months or till achievement of enrollment target of approx. 52 patients
2. Patients will receive study medication till disease progression or unacceptable toxicity or withdrawal of consent or death, whichever occurs first

End of Study

The study will end when all patients have been followed up for at least 24 months after the last patient in, unless they have been lost to follow-up, withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

Roche will continue to provide study medication to all the patients

- who are still receiving the study medication and have not progressed on study medication at the end of the study
- and who are willing to continue study medication
- and are considered suitable by the investigator to continue receiving study medication till progression of the disease

Primary Outcome Measures:

The primary outcome measures for this study are on safety evaluation and are as follows:

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03
- Incidence of congestive heart failure (CHF) and/or significant decline in LVEF over the course of the study
- Laboratory results abnormalities
- Incidence of AEs leading to discontinuation, modification, or interruption of study medication
- Incidence and cause of death due to AEs

Secondary Outcome Measures:

The secondary outcome measures for this study are on efficacy evaluation and are as follows:

- Overall response rate (ORR)
- Progression-free survival (PFS)
- Overall survival rate (OS)

Investigational Medicinal Products

Pertuzumab will be considered as investigational medicine product in this study. Pertuzumab, Trastuzumab and docetaxel chemotherapy will be administered in line with approved local Product Information.

Test Product

Pertuzumab will be administered in line with approved local Product Information.

Non-Investigational Medicinal Products

Trastuzumab and docetaxel chemotherapy will be considered as non-investigational medicine in this study and will be administered in line with approved local Product Information. After Cycle 6, continuation of docetaxel treatment will be at the discretion of the investigator.

Statistical Methods

Primary Analysis

Safety Analysis

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

- The incidence of AEs and SAEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Summaries will include: the incidence of AEs and SAEs (overall, by severity using NCI CTCAE version 4.03, by relationship to study drug, by action taken with study drug)
- Incidence of CHF and/or significant decline in LVEF: The incidence of CHF and/or significant decline in LVEF will be summarized using number (n) and percentage
- LVEF will be summarized by cycle including change from baseline summaries where appropriate
- All laboratory data will be analyzed with appropriate summary statistics and also, shift tables will be presented for the laboratory test results
- Incidence of AEs leading to discontinuation, modification or interruption of study medication: This event will be summarized using number (n) and percentage (%)
- The incidence and cause of deaths due to AE: The number of deaths due to AEs will be summarized using number and percentage

Efficacy analyses

Efficacy variables (PFS and ORR) will be summarized for the intent-to-treat (ITT) population defined as a population that includes all patients enrolled in the study. PFS will be obtained by the Kaplan-Meier (KM) approach. There are no formal statistical hypothesis tests to be performed in this study.

Determination of Sample Size

A total of approximately 52 patients will be enrolled in this study.

For the purpose of the estimation of sample size, the incidence of all grade AEs related to Pertuzumab in combination with Trastuzumab and Docetaxel was chosen as a safety endpoint of primary interest. If the observed incidence of all grade AEs related to Pertuzumab in combination with Trastuzumab and Docetaxel is 97.3% and assuming level of significance 5% and precision 5%, 52 enrolled patients are planned for this study.

Sample size calculation for estimating proportion:

$$n = \frac{Z^2_{\alpha/2} \cdot p \cdot (1 \cdot p)}{d^2}$$

Where,

P = Incidence of AE related to Pertuzumab in combination with Trastuzumab and Docetaxel.

d: Precision

$Z_{\alpha/2}$ value: 1.96 for 95% confidence level

Interim Analysis

In addition to the final analysis, there will be interim analysis for safety once approximately 50% patients complete 6 months investigational medicinal product therapy.

An iDMC will be formed and composed of 3 members, including a statistician. An iDMC will perform the review of this interim analysis of efficacy and safety and subsequent safety reviews as described in the iDMC Charter.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alkaline transaminase
aPTT	activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
CHF	Congestive heart failure
CL	Clearance
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CVAD	Central venous access device
DDI	Drug-drug interactions
DMC	Data monitoring committee
DSMB	Data safety monitoring board
EC	Ethics committee
ECG	Electrocardiography
ECOG	Eastern cooperative oncology group
eCRF	electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
ePRO	electronic Patient-reported outcome
FDA	Food and drug administration
G-CSF	Granulocyte-colony stimulating factor
GD	Gestation day
HBV	Hepatitis B virus
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HER	Human epidermal growth factor receptor
HIPAA	Health insurance portability and accountability act

HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
ICMR	Indian Council of Medical Research
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IRF	Independent review facility
ISH	In situ hybridization
LDH	Lactate dehydrogenase
LPLV	Last patient, last visit
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
mBC	Metastatic breast cancer
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall survival
ORR	Overall response rate
PD	Progressive disease
PFS	Progression-free survival
PI	Prescribing information
PK	Pharmacokinetic
PR	Partial response
PRO	Patient-reported outcome
PTT	Partial thromboplastin time
RBC	Red blood cell
RCR	Roche Clinical Repository
RECIST	Response evaluation criteria in solid tumours
SAEs	Serious adverse events
SPC	Summary of product characteristics
SS	Steady state
ULN	Upper limit of normal
Vc	Central volume of distribution
WBC	White blood cell

1. `BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

Breast cancer is by far the most frequent cancer among women worldwide 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) (Ferlay et al., 2010). Breast cancer is a cause of concern in developed as well as developing regions of the world and India is no exception. Although the overall incidence of breast cancer in India is comparatively lower than in western world, the burden remains high. Data recorded from urban registries in India showed breast cancer incidence ranging from 19.3 % to 27.5% (ICMR 2001-2004).

A study conducted over 30 years in Mumbai, India showed that the annual rate of breast cancer significantly increased during the period 1976 and 2005. The rates of breast cancer among women aged 30–64 had risen gradually over the 30-year study period, with the mean increase estimated at 1.1% per year, and representing 32% of the female cancer burden in 2001-2005 (Dhillon et al., 2011).

Surgery is the main modality of local treatment for breast cancer. Where ever possible isolated loco-regional recurrence should be treated with curative intent. If feasible, excision of recurrent tumor is recommended. In patients not suitable for local treatment with curative intent (e.g. inoperable), systemic therapies remain the mainstay of treatment. Their choice mainly depends on tumor biology and previous systemic treatments.

Less than 10% of breast cancers are metastatic at diagnosis across developed and developing nations of the world; of these approximately one-fifth patients survive for five years (Cardoso et al., 2012; Hagberg et al., 2013; Barinoff et al., 2013; Lord et al., 2012). In contrast, a higher proportion of breast cancer patients, i.e., about 6% to 25% have metastatic disease at presentation in India. (Agarwal et al., 2007; Nair et al., 1993)

In a study from New Delhi, 80% of the patients treated for breast cancer over a period of a decade had metastatic disease in the axillary lymph nodes. (Saxena et al., 2005)

The primary goals of treatment of advance stage cancer are maximizing the patient's survival and preserving quality of life. Treatment options for these patients have become more numerous, with the option to use sequential single agents or combination regimens. Additional considerations to use therapies directed to specific molecular subtypes of breast cancer also serve to maximize the benefit for an individual patient. Several targeted drugs with different molecular pathways have been approved for metastatic breast cancer (mBC).

1.1.1 The HER family receptors

The members of human epidermal growth factor receptor (HER) family of receptor tyrosine kinases are important mediators of cell growth, survival, and differentiation.

The HER family comprises of four receptors: HER1 (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 exit as inactive monomers. Activation of HER receptors occurs following ligand binding, leading to receptor dimerization and cell signaling through the P13-kinase/AKT pathway for promotion of tumor cell survival and through the mitogen-activated protein kinase (MAPK) pathway for cellular proliferation.

Although 11 ligands are known to bind to various HER family members, none of these ligands binds directly to HER2. Instead, HER2 is frequently activated by forming dimers with another HER family receptor, when activated in HER ligand-dependent manner. This ligand-driven heterodimerization of HER2 with another HER family member is likely to play an important role in neoplastic transformation and/or progression. The HER2-HER3 dimer produces the most potent signaling for activation of the P13-kinase/AKT pathway. (Lee-Hoeflich et al., 2008; Olayioye et al., 2000)

Overexpression of HER2 in breast cancer has been correlated with high histologic grade, increased mitotic activity, p53 mutation, negative estrogen receptor (ER), 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 (DFS) and overall survival (OS) compared with tumors that do not overexpress HER2 (Pauletti et al. 2000; Ménard et al, 2001)

The validation of the prognostic significance of HER2 gene amplification and protein overexpression in the absence of anti-HER2 targeted therapy is discussed in a review of 107 published studies involving 39,730 patients, which reported an overall HER2 positivity rate of 22.2% (Ross et al., 2009). The HER2 positivity rate in breast cancer varies among Indian studies, i.e., from 29% to 43.2% by IHC (Vaidyanathan et al., 2010; Munjal et al., 2009).

Trastuzumab IV has proven clinical benefits in HER2-positive mBC patients and most importantly improved survival. It is currently the standard of care for this patient population. Pertuzumab is approved by Food and Drug Administration (FDA) and European Medicinal Agency (EMA) for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive mBC, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease (Prescribing Information [PI], 2013; Summary of Product Characteristics [SPC], 2013). In addition, pertuzumab in combination with trastuzumab and docetaxel is approved by EMA for use in adult patients with locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy (SPC, 2013). Combination of pertuzumab with trastuzumab and docetaxel has been categorized as preferred first-line treatment (Category 1) for HER2-positive recurrent and mBC (NCCN Guidelines, 2014).

1.2 BACKGROUND ON STUDY TREATMENT

1.2.1 Pertuzumab

Pertuzumab (rhuMAb 2C4) is a recombinant, humanized immunoglobulin (Ig)G1κ monoclonal antibody, which targets HER2 (also known as c-erbB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Pertuzumab is the first in a new class of targeted cancer treatments called HER2 dimerization inhibitors. By binding to the subdomain 2 epitope of the extracellular domain of HER2, it prevents heterodimerization of HER2 with other members of the HER family (HER1, HER3, and HER4). As a result, ligand-activated downstream signaling is blocked by pertuzumab. Pertuzumab is also capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) in cell-based assays. (Cho et al., 2003; Franklin et al., 2004)

Pertuzumab and trastuzumab bind to distinct epitopes on the HER2 receptor without competing with each other, and have complementary mechanisms for disrupting HER2 signaling. This results in augmented anti-proliferative activity *in vitro* and *in vivo* when pertuzumab and trastuzumab are given in combination.

1.2.1.1 Nonclinical Studies

The combination of pertuzumab and trastuzumab has been shown to synergistically inhibit the growth of xenografts derived from HER2-overexpressing KPL-4 breast cancer. (Scheuer et al., 2009)

The synergistic action of pertuzumab and trastuzumab may be explained by their complementary modes of action; while pertuzumab prevents the ligand-activated formation of HER2 heterodimers, trastuzumab can block the shedding of HER2 extracellular domain that would result in constitutively activated truncated receptors. Trastuzumab is thought to be effective in disrupting ligand independent HER2-HER3-PI3K complexes, whilst pertuzumab prevents ligand-induced HER2-HER3 dimerization. (Junttila et al., 2009)

1.2.1.1.1 Nonclinical Toxicology

Pertuzumab administered weekly by intravenous injection was generally well tolerated in primates at doses up to 150 mg/kg. Treatment-related diarrhea was noted at doses of 15 mg/kg and higher. More chronic dosing (>12 weeks of weekly dosing) resulted in diarrhea related dehydration in monkeys.

Reproductive toxicology studies have been conducted in cynomolgus monkeys and no adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six months duration.

In an embryo-fetal development reproductive toxicity study, pertuzumab administered to pregnant cynomolgus monkeys, twice weekly, during the period of fetal organogenesis (gestation day [GD] 19 to 50), at clinically relevant exposure levels, caused a dose related increase in embryo-fetal death. In addition, low amniotic fluid volume (oligohydramnios) and microscopic evidence of delayed renal development (renal hypoplasia) were observed in all pertuzumab-treated groups.

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of pertuzumab. Studies have not been performed to evaluate the mutagenic potential of pertuzumab. No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. (Prescribing Information, US)

1.2.1.2 Clinical Studies

Phase I/II/III studies conducted using single-agent and combination regimens of pertuzumab have been summarized in Table 1-1.

Table 1-1 Overview of Pertuzumab Clinical Studies

Study	Phase	Indication	Dose[a]/regimens	No of patients Treated	Status[b]
Phase I Dose Escalation Single Agent Studies					
TOC2297g	Ia	Advanced solid tumors	0.5, 2.0, 5.0, 10.0, and 15 mg/kg	21	Completed, published
JO17076[c]	I	Advanced solid tumors	5, 10, 15 and 25 mg/kg	18	Completed
Phase II					
TOC2689g[d]	II	Advanced ovarian cancer	Cohort 1: 420 mg Cohort 2: 1050 mg	61 62	Completed, published
BO16934	II	mBC with low expression of HER2	Arm A: 420 mg Arm B: 1050 mg	41 37	Completed, published
BO17004	II	Hormone refractory prostate cancer (HRPC) chemotherapy naïve	Cohort 1: 420 mg Cohort 2: 1050 mg	35 33	Completed, published
TOC2682g[d]	II	Castration resistant PC pretreated with docetaxel	420 mg	41	Completed
TOC2572g[d]	II	Advanced recurrent non-small cell lung cancer (NSCLC)	420 mg	43	Completed
Phase I Combination Therapy Studies					
BO17003	Ib	Advanced solid tumors	Pertuzumab 1050 mg q3w Capecitabine (825, 1000, 1250 mg/m^2)	18	Completed, published
BO17021	Ib	Advanced solid tumors	Pertuzumab 1050 mg q3w Docetaxel (60, 75 mg/m^2) Pertuzumab 420 mg q3w Docetaxel (75, 100 mg/m^2)	19	Completed, published

WO20024	Ib	Advanced NSCLC	Pertuzumab 420 mg q3w Erlotinib (100,150 mg/day)	15	Completed, CSR published
Phase II Non-Randomized, Single-Arm Studies					
BO17929	II	HER2 positive mBC	Pertuzumab 420 mg q3w Trastuzumab (either 2 mg/kg qw or 6 mg/kg q3w)	66 in Cohorts 1 and 2 29 in Cohort 3	Ongoing, (primary analysis Cohorts 1 & 2 CSR published, primary analysis Cohort 3 CSR published)
TOC4603g	II	NSCLC	Pertuzumab 420 mg q3w Erlotinib 150 mg/day	41	Study closed Nov 2011
Phase II Randomized Studies					
TOC3258g	II	Platinum-resistant ovarian, peritoneal or fallopian tube cancer	Gemcitabine 800 mg/m^2 ± Pertuzumab/ 420 mg q3w	Gem + per: 65 Gem: 65	Completed; CSR published
BO17931	II	Platinum-sensitive ovarian cancer	Carboplatin-based chemo[e] ± Pertuzumab 420 mg q3w	Pertuzumab+ chemo: 75 chemo: 74	Completed, published
WO20697 (NEOSPHERE)	II	HER2-positive early breast cancer (EBC)	Arm A: trastuzumab, docetaxel[f] Arm B: trastuzumab, docetaxel, pertuzumab[f] Arm C: trastuzumab, pertuzumab[f] Arm D: pertuzumab, docetaxel[f] Pertuzumab 420 mg q3w, Trastuzumab 6mg/kg, Docetaxel 75 mg/m^2 to 100 mg/m^2	Arm A: 107 Arm B: 107 Arm C: 108 Arm D: 94	Ongoing, primary analysis CSR (neoadjuvant phase) and update CSR (adjuvant phase) completed
MO22324 (PHEREXA)	II	HER2-positive mBC	Pertuzumab 420 mg q3w Trastuzumab 6	271 recruited, 134	Ongoing

			mg/kg q3w Arm A (no pertuzumab): Capecitabine 1250 mg/m² twice-daily for 14 days followed by 7 days rest q3w. Arm B (with pertuzumab): Capecitabine 1000 mg/m² as above	received pertuzumab (as of 7 Nov 2012)	
BO22280 (TRYPHAENA)	II	HER2-positive EBC	Neoadjuvant: All q3w Pertuzumab 420 mg Trastuzumab 6 mg/kg FEC: 5-FU 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 600 mg/m^2 Carboplatin AUC 6 Docetaxel 75 mg/m^2 initially, 100 mg/m^2 if no DLT (patients on carboplatin and docetaxel with trastuzumab + pertuzumab stay on 75 mg/m^2)	Arm A: 72 Arm B: 75 Arm C: 76	Completed, published
BP27836 (JOSHUA)	IIa	HER2-positive adenocarcinoma of the stomach or gastroesophageal junction	All q3w: Pertuzumab 420 mg (Arm A) or 840 mg (Arm B) Trastuzumab 6 mg/kg Capecitabine 1000 mg/m^2 Cisplatin 80 mg/m^2	Arm A: 15 Arm B: 15	Ongoing; Primary analysis for PK conducted (data memo available) and ongoing for safety
Phase III randomized studies					
WO20698/TOC4129g (CLEOPATRA)	III	HER2 positive mBC	Pertuzumab or placebo plus trastuzumab, docetaxel: Pertuzumab 420 mg q3w Trastuzumab 6 mg/kg q3w Docetaxel 75 mg/m^2 to 100 mg/m^2	Pertuzumab + trastuzumab + docetaxel: 407 Placebo + trastuzumab+ docetaxel	Completed, published

				: 397	

a pertuzumab given q3w – the 420 mg dose is given following an initial 840 mg loading dose, trastuzumab given either as 2 mg/kg weekly (loading dose: 4 mg/kg) or 6 mg/kg q3w (loading dose 8 mg/kg);
b "Completed" indicates end of trial (as defined in protocol) has been reached;
c Japanese studies sponsored by Chugai Pharmaceutical Co Ltd;
d An extension study (TOC2664g) was initiated to follow up patients from these studies opting to continue pertuzumab treatment. Three patients were enrolled before the parent studies closed. This study has been completed;
e either paclitaxel (175 mg/m2 q3w)/carboplatin (AUC 5/q3w) or gemcitabine (1000 mg/m2 day 1 and day 8 q3w)/carboplatin (AUC 4/q3w);
f Arms A-D all receive 5-fluorouracil (600 mg/m2), epirubicin (90 mg/m2), cyclophosphamide (600 mg/m2), and Arm C receives docetaxel 75 mg/m2 to 100 mg/m2 in the adjuvant setting

1.2.1.3 Clinical Pharmacokinetics

Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2-25 mg/kg. The population PK (popPK) analysis was done for the concentration data available for 481 patients. The median clearance (CL) and half-life of pertuzumab was 0.24 L/day and 18 days respectively. The steady state (SS) concentration of pertuzumab was reached after first maintenance dose (with an initial dose of 840 mg followed by a maintenance dose of 420 mg). (Prescribing Information, US)

Pertuzumab was administered by intravenous infusion (every 3 weeks) either as a weight-based dose (0.5-15 mg/kg) or a fixed dose (420 or 1050 mg). It was reported that weight- and BSA-based dosing reduced the population variability of C (SS, trough) moderately as compared to fixed dosing. (Ng CM et al., 2006)

The popPK analysis suggested that there were no differences observed based on age, gender, and ethnicity (Japanese vs. non-Japanese) in PK parameters. Baseline serum albumin level and lean body weight as covariates only exerted a minor influence on PK parameters. Therefore, no dose adjustments based on body weight or baseline albumin level are needed. (Prescribing Information, US)

No drug interactions were observed between pertuzumab and trastuzumab. There were no relationship between CLcr (27 to 244 mL/min) and pertuzumab exposure was observed. (Prescribing Information, US)

Phase III study WO20698/TOC4129g (CLEOPATRA), demonstrated that there is no evidence of drug-drug interactions between pertuzumab and trastuzumab, or between pertuzumab and docetaxel. (Cortés et al., 2013)

1.2.1.4 Efficacy of Pertuzumab

In Phase III, pivotal study WO20698/TOC4129g (CLEOPATRA; N = 808) in patients with previously-untreated HER2-positive mBC, a statistically significant and clinically meaningful improvement in progression-free survival (PFS), based on tumor assessments by an independent review facility (IRF), was observed in patients treated with pertuzumab (Ptz) + trastuzumab (T) + docetaxel (D) (N = 406) compared with those receiving placebo (Pla) + trastuzumab (T) + docetaxel (D) (N = 402). PFS was prolonged at the median by 6.1 months and the risk of disease progression or death was reduced by 38% (Hazard ratio [HR] = 0.62; 95% CI = 0.51, 0.75; p

<0.0001) with an improvement in median PFS from 12.4 months to 18.5 months. (Baselga et al., 2011)

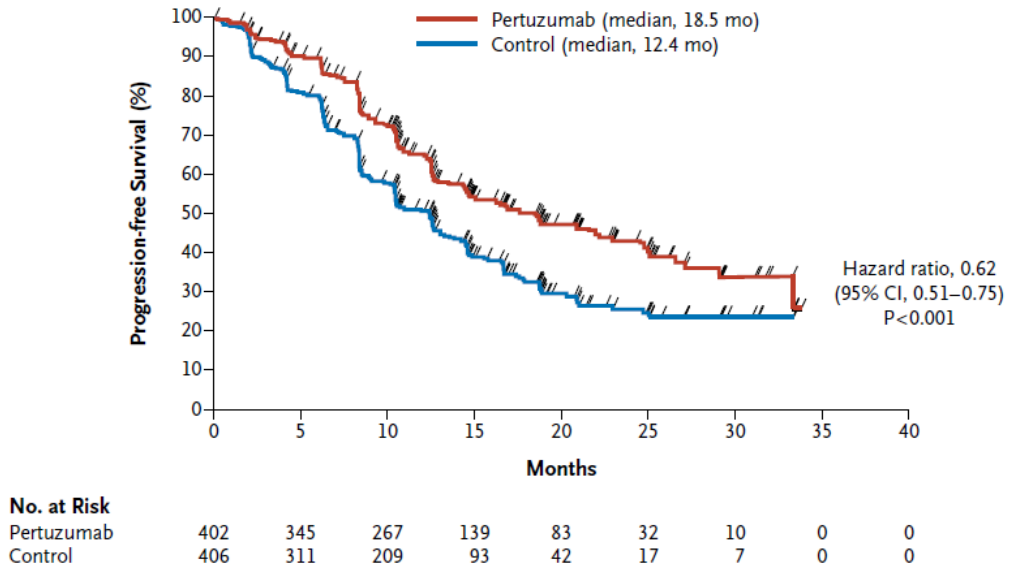

Figure 1-1 Independently Assessed Progression-free Survival Results from CLEOPATRA study (Baselga et al., 2011)

Results of the investigator-assessed PFS analysis were consistent with those observed for IRF-assessed PFS.

A second interim analysis of overall survival (OS) (performed one year after the primary analysis of efficacy) crossed the predefined stopping boundary for statistical significance (p ≤0.0138), demonstrating that treatment with Ptz+T+D significantly improved OS when compared with Pla+T+D (HR = 0.66; 95% CI = 0.52, 0.84; p = 0.0008). (Swain et al., 2013)

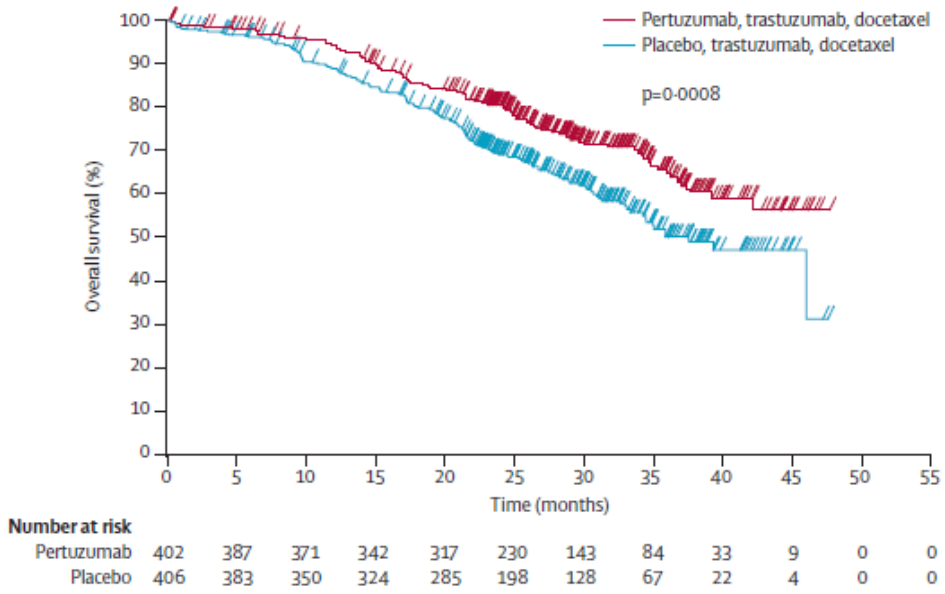

Figure 1-2 Overall Survival – Results from CLEOPATRA study (Swain et al., 2013)

1.2.1.5 Safety of Pertuzumab

Safety data are available from 2195 cancer patients treated with pertuzumab in company-sponsored pertuzumab trials and from an additional 175 patients treated with pertuzumab in combination studies with trastuzumab emtansine. (Pertuzumab IB, 2013)

Overall, data indicate that pertuzumab is well-tolerated as monotherapy and that it can be given in combination with trastuzumab and a range of other therapeutic agents with manageable additional toxicity. No unexpected toxicities were encountered other than those that are known for agents that target the HER family of receptors. Serious or severe infusion-associated symptoms have been rarely observed in patients receiving pertuzumab. Low levels of cardiac toxicities, predominantly asymptomatic decline in left ventricular ejection fraction (LVEF), have been reported. (Lenihan et al., 2011; Portera et al., 2008)

In the pivotal Phase III CLEOPATRA study, the rates of symptomatic and asymptomatic left ventricular systolic dysfunction (LVSD) were not higher in patients receiving Ptz+T+D (1.2%) than in those receiving Pla+T+D (1.8%). The safety profile of Ptz+T+D (at the time of clinical cut-off of 14 May 2012) was generally similar to that of Pla+T+D. The most common adverse event (AE) in both arms was alopecia (Pla+T+D [60.6%]) vs. Ptz+T+D [60.8%]) (an AE associated with docetaxel), followed by diarrhea (Pla+T+D [48.2%]) vs. Ptz+T+D [68.1%]), neutropenia (Pla+T+D [49.7%]) vs. Ptz+T+D [52.9%]), nausea (Pla+T+D [42.4%]) vs. Ptz+T+D [43.9%]), fatigue (Pla+T+D [37.4%]) vs. Ptz+T+D [38.0%]) and rash (Pla+T+D [24.0%]) vs. Ptz+T+D [36.5%]). (Swain et al., 2013)

1.2.2 Trastuzumab

Trastuzumab is a recombinant humanized anti-HER2 monoclonal antibody that binds specifically and with high affinity to the extracellular domain of HER2. Trastuzumab has been shown to inhibit the proliferation of human tumor cells overexpressing HER2 both *in vitro* and *in vivo*. *In vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2. (Sliwkowski et al., 1999)

The clinical data in breast cancer are derived from more than 10 trials in women with HER2-overexpressing mBC. Table 1-2 below presents summary of these studies.

Table 1-2 Key Clinical Studies of Trastuzumab for Metastatic Breast Cancer

Study No.	Phase	N	Disease	Treatment Plan	Trastuzumab Efficacy (p-value vs. control)	Reference
Phase III Combination Regimens						
H0648g	III	469	mBC	[AC or paclitaxel] ± trastuzumab	↑ORR, ↑DR, ↑TTP, ↑OS	Slamon et al., 2001
H2223g (TAnDEM)	III	207	mBC	anastrazole ± trastuzumab	↑ORR, ↑TTP, ↑PFS	Mackey et al., 2006 Kaufman et al., 2009
WO16437 (BCIRG007)	III	263	mBC	[trastuzumab + docetaxel] ± carboplatin	=ORR, =DR, =TTP, =OS	Pegram et al., 2007
Phase II Monotherapy						
H0649g	II	222	mBC	trastuzumab 4 mg/kg × 1→2 mg/kg qW	ORR 15%	Cobleigh et al., 1999
H0650g	II	114	mBC	trastuzumab 4 mg/kg × 1→2 mg/kg qW vs. trastuzumab 8 mg/kg × 1→4 mg/kg qW	ORR 25% ORR 27%	Vogel et al., 2002
WO16229	II	105	mBC	trastuzumab 8 mg/kg × 1→6 mg/kg q3W	ORR 20% cont	Clinical Study Report – WO16229
Phase I or II Combination Regimens						
M77001	rand. II	186	mBC	docetaxel vs. [trastuzumab→docetaxel]	ORR: 61% (p = 0.0002) DR: 11.7 mo (p = 0.009) TTP: 11.7 mo (p = 0.0001) OS: 31.2 mo (p = 0.0325)	Clinical Study Report M77001 Marty et al., 2005
BO15935	I-II	32	mBC	trastuzumab 8 mg/kg × 1→6 mg/kg q3W + paclitaxel, then trastuzumab until progressive disease	ORR: 59% DR: 10.5 mo TTP: 12.2 mo	Leyland et al., 2003
M77003 (Hercules)	II	180	mBC	epirubicin 90 mg/m² vs. epirubicin 60 mg/m² + trastuzumab vs. epirubicin 90 mg/m² + trastuzumab	↑ORR, ↑TTP, ↑PFS	Clinical Study Report – M77003

Study No.	Phase	N	Disease	Treatment Plan	Trastuzumab Efficacy (p-value vs. control)	Reference
MO16419 (CHAT)	rand. II	225	LABC/ mBC	[trastuzumab + docetaxel] (HT) vs. HT + capecitabine (HTX)	HT vs. HTX ORR: 73% vs. 71% PFS: 12.8 mo vs. 17.9 mo (p = 0.045) TTP: 13.6 mo vs. 18.6 mo (p = 0.033) OS: 47.3 mo vs. 43.5 mo (p = 0.476)	Clinical Study Report – MO16419 Wardley et al., 2010

AC: anthracycline + cyclophosphamide; CMF: cyclophosphamide + methotrexate + fluorouracil; DR: duration of response; EBC: early breast cancer; LABC: locally advanced breast cancer; mBC: metastatic breast cancer; ORR: objective response rate; rand: randomized; PFS: progression-free survival; TTP: time to disease progression

The most relevant adverse reactions related to trastuzumab include cardiac dysfunction, administration-related reactions, pulmonary AEs, and neutropenia/febrile neutropenia (both in combination with chemotherapy).

Patients who receive trastuzumab for HER2-positive cancer may experience signs and symptoms of cardiac dysfunction, such as dyspnea, orthopnea, increased cough, pulmonary edema, S3 gallop, or ejection fraction decreased. For the complete list of adverse reactions and guidance regarding their management refer to the IB of trastuzumab.

For details please refer the IB/local PI of trastuzumab.

1.2.3 Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxoid family. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5• -20epoxy-1,2• ,4,7• ,10• ,13• -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.

Docetaxel acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

Clinical studies including docetaxel treatment with trastuzumab and/or pertuzumab are summarized in Table 1-1 and 1-2. For details on clinical studies please refer to the local PI of docetaxel.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The synergistic action of combination of pertuzumab and trastuzumab has been observed in several pre-clinical studies ([redacted] 2005; Friess et al., 2006). The synergistic action of pertuzumab and trastuzumab may be explained by their complementary modes of action; while pertuzumab prevents the ligand-activated formation of HER2 heterodimers and homodimers, trastuzumab can block the shedding of HER2 extracellular domain that would result in constitutively activated truncated receptors. Furthermore, as the two antibodies are not competing for the same binding epitope on HER2, their combination may lead to a higher antibody load, resulting in increased tumor-cell killing via ADCC.

In a Phase II (NEOSPHERE) study, addition of pertuzumab to the neoadjuvant treatment regimen of trastuzumab plus docetaxel significantly improved CR rate (45.8% vs. 29.0%). Also, the incidence of AEs and SAEs was comparable between the two treatments.

Furthermore, results of Phase III (CLEOPATRA) study have shown a significant efficacy benefit with a manageable tolerability profile and no new safety signals with a regimen consisting of pertuzumab, trastuzumab, and docetaxel.

The benefit/risk of the combination of pertuzumab, trastuzumab and taxanes is therefore anticipated to be favorable in Indian patients. This provides a strong rationale to further explore and better characterize the safety and tolerability profiles of the combination in Indian patients.

It is a post-marketing requirement to gain an understanding of safety and efficacy of pertuzumab in Indian patients. Therefore, this Phase IV, single-arm, open-label, multicenter study is aimed to assess the safety and efficacy of pertuzumab in combination with trastuzumab and docetaxel for the treatment of Indian patients with HER2-positive advanced (metastatic or locally recurrent) breast cancer.

A low level of cardiac toxicities, predominantly asymptomatic declines in LVEF, have been reported with pertuzumab/trastuzumab treatment, therefore this study will include regular cardiac LVEF monitoring of all patients and will implement treatment stopping algorithm for LVEF decline.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objectives for this study are on safety evaluation and are as follows:

- To evaluate the safety of pertuzumab (in combination with trastuzumab and docetaxel) in Indian patients
- To evaluate the tolerability of pertuzumab (in combination with trastuzumab and docetaxel) in Indian patients

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are on efficacy evaluation and are as follows:

To evaluate pertuzumab in combination with trastuzumab and docetaxel in Indian patients with respect to:

- Overall response rate (ORR)
- Progression-free survival (PFS)
- Overall survival (OS)

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase IV, single-arm, open-label, multicenter study to assess the safety and efficacy of pertuzumab in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive advanced (locally recurrent, unresectable, or metastatic) breast cancer. Patients must not have received systemic non-hormonal anticancer therapy for their locally recurrent, unresectable, or metastatic disease.

3.1.1 Overview of Study Design

A total of 52 patients will be enrolled over duration of approximately 12 months.

Pertuzumab, trastuzumab, and docetaxel chemotherapy will be administered in line with the PI. Docetaxel treatment will be given at least for 6 treatment cycles; thereafter decision for continuation of docetaxel treatment will be based on investigator's discretion (Figure 3-1).

For details on dose regimen refer Section 4.3.2.

Patients will receive study medication till disease progression or unacceptable toxicity or withdrawal of consent or death, whichever occurs first.

All patients will be followed-up for at least 2 years after the last patient is enrolled; unless they have been lost to follow up, withdrawn consent, or died, or the study has been prematurely terminated by the Sponsor.

Tumor assessments will be conducted every 9 weeks from the Day 1 of first treatment cycle, i.e., every 3 cycles of monoclonal antibody treatment. Tumor assessments will be conducted during the follow-up period until progressive disease (PD) has been established, even if treatment has been discontinued due to unacceptable toxicity (Figure 3).

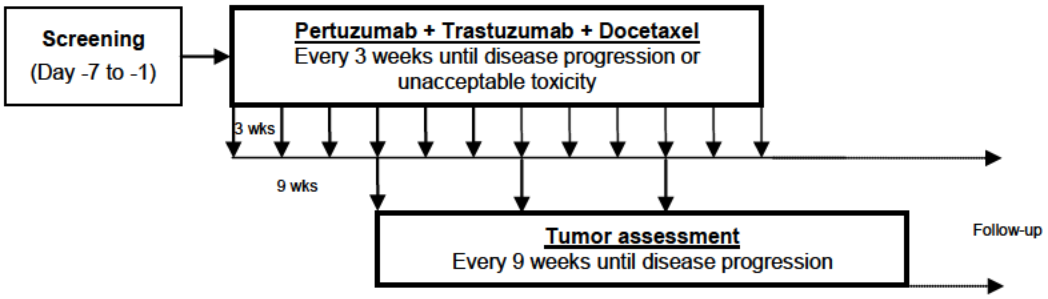

Figure 3-1 Study Design: Patient Treatment and Assessment

A schedule of assessments is provided in Appendix 1.

3.1.2 Data Monitoring Committee

In addition to the final analysis, there will be interim analysis for safety once approximately 50% patients complete 6 months investigational medicinal product therapy with further review of accumulating safety data every 6 months.

An iDMC will be formed and composed of 3 members, including a statistician. An iDMC will perform the review of this interim analysis of efficacy and safety as described in the iDMC Charter.

3.2 END OF STUDY

The end of study is defined as the date when all patients have been followed up for at least 24 months after the last patient is enrolled; unless they have been lost to follow-up, 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 the multi-centric, open-labeled, non-randomized post-marketing study, to assess the safety and efficacy of pertuzumab in combination with trastuzumab and docetaxel to fulfill Indian regulatory requirement. The study design employs standard methods for safety studies in patients with cancer. All patients will receive the active treatment. Safety will be carefully evaluated, and the type of data collected and the frequency with which patients are monitored will ensure safety of the patients.

3.3.1 Rationale for Combination Therapy

The use of the combination of pertuzumab with trastuzumab may be explained by their complementary mode of action, while pertuzumab prevents the ligand-activated formation of HER2 heterodimers and homodimers, trastuzumab can block the shedding of HER2 extracellular domain that would result in constitutively activated truncated receptors. Furthermore, as the two antibodies are not competing for the same binding epitope on HER2, their combination may lead to a higher antibody load, resulting in increased tumor-cell killing via ADCC.

Phase III (CLEOPATRA) study has shown a significant efficacy and reasonable safety profile of the combination of pertuzumab, with trastuzumab and docetaxel over placebo with trastuzumab and docetaxel. Ptz+T+D significantly improved overall survival (OS) compared with Pla+T+D (HR = 0.66; 95% CI: 0.52, 0.84; p = 0.0008). The overall safety profile, including the cardiac toxicity profile, of the pertuzumab combination regimen was generally comparable with that of the placebo-controlled arm, apart from a higher incidence ($\geqslant$5% difference) of Grade 1-2 diarrhea, rash, mucosal inflammation, dry skin and Grade 3-4 febrile neutropenia. (Swain et al., 2013)

In this study, efficacy, safety, and tolerability of pertuzumab (in combination with trastuzumab and docetaxel) will be explored further to gain a better understanding of the use of this combination in treatment of Indian patients with HER2-positive advanced breast cancer.

3.3.2 Rationale for Test Product Dosage

Pertuzumab, trastuzumab and docetaxel chemotherapy will be administered in line with the PI. The efficacy and safety of the doses being administered in present study have been established in the pivotal Phase III CLEOPATRA study; aimed to compare the efficacy and safety of pertuzumab, trastuzumab, and docetaxel with placebo, trastuzumab, and docetaxel in patients with HER2-positive first-line metastatic breast cancer (Swain et al, 2013).

3.3.3 Rationale for Patient Population

The patient population for this study includes patients with HER2-positive advanced breast cancer (metastatic or locally recurrent) presentation which is not amenable to curative resection. Only patients who had previously not received systemic non-hormonal anticancer therapy for their metastatic or locally recurrent disease will be included. Good efficacy and a manageable safety profile have been demonstrated in clinical trials of pertuzumab in this patient population.

3.4 OUTCOME MEASURES

3.4.1 Primary Outcome Measures

The primary outcome measures for this study are on safety evaluation and are as follows:

- Incidence and severity of AEs and serious adverse events (SAEs) by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03
- Incidence of congestive heart failure (CHF) and/or significant decline in LVEF
- LVEF over the course of the study
- Laboratory results abnormalities
- Incidence of AEs leading to discontinuation, modification, or interruption of study medication
- Incidence and cause of death due to AEs

3.4.2 Secondary Outcome Measures

The secondary outcome measures for this study are on efficacy evaluation and are as follows:

- Overall response rate (ORR)

Overall response (partial response [PR] plus complete response [CR]) determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1. ORR is defined as best response recorded from the start of study treatment until disease progression/recurrence or death and confirmed ≥4 weeks later.

- Progression-free survival (PFS)

Progression free survival is defined as the time from enrollment to the first radiographically documented disease progression as determined by the investigator using RECIST criteria version 1.1, or death from any cause, whichever occurs first.

- Overall Survival (OS)

Overall survival is 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 (two years from last patient enrolled in the study).

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population for this study is male or female patients with HER2-positive advanced breast cancer (locally recurrent, unresectable, or metastatic). These patients must be eligible for treatment with pertuzumab (in combination with trastuzumab and docetaxel) as per the PI in the opinion of the treating physician.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Male or female patients age ≥18 years
2. Signed, written informed consent (approved by the relevant Institutional Review Board [IRB]/ Ethics Committee[EC]), prior to any study procedure
3. Histologically or cytologically confirmed and documented adenocarcinoma of the breast with metastatic or locally recurrent disease not amenable to curative resection; patients with measurable and/or non-measurable disease are eligible
4. Known and documented HER2-positive (defined as either immunohistochemistry [IHC] 3+ or in situ hybridization [ISH] positive) as assessed 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) as determined in a local laboratory that is experienced/certified in HER2-expression testing using an accurate and validated assay
5. Known and documented LVEF of at least 50%
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1
7. A negative serum β-HCG test for women of childbearing potential (premenopausal, or <12 months of amenorrhea post-menopause, and women who have not undergone surgical sterilization [i.e., absence of ovaries and/or uterus]) within 7 days prior to the first dose of study treatment with the result available prior to first dosing
8. For women of childbearing potential and men with partners of childbearing potential, agreement 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 use must continue for the duration of study treatment and for at least 7 months after the last dose of study treatment. Male patients whose partners are pregnant should use condoms for the duration of the pregnancy.

   (for women of childbearing potential: agreement to remain abstinent (only if it is in line with the preferred and usual lifestyle) or use single or combined non-hormonal contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of study drug)
9. Adequate organ function, as determined by the following laboratory results, within 3 days prior to study treatment:
   - Absolute neutrophil count >1,500 cells/mm^3

- Platelet count >100,000 cells/mm^3
- Hemoglobin >9 g/dL. (patients may receive transfused red blood cells to obtain this level)
- Albumin >2.5 g/dL
- Total bilirubin ≤1.5 times 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 for patients with liver metastases)
- Alkaline phosphatase (ALP) >2.5 × ULN (>5 × ULN in patients with liver metastases or >10 × ULN for patients with bone metastases)
- Serum creatinine >2.0 mg/dL or 177 • mol/L
- International normalized ratio (INR), activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) <1.5 × ULN (unless on therapeutic anti-coagulation)

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Previous systemic non-hormonal anticancer therapy for the metastatic or locally recurrent disease
2. Previous approved or investigative anti-HER2 agents in any breast cancer treatment setting, except trastuzumab and/or lapatinib in the adjuvant or neo-adjuvant setting
3. Disease progression while receiving or within 12 months of completion of trastuzumab and/or lapatinib treatment in the adjuvant or neo-adjuvant setting
4. History of persistent Grade 2 or higher (NCI-CTCAE, Version 4.03) hematologic toxicity resulting from previous adjuvant or neo-adjuvant therapy
5. Current, known peripheral neuropathy of Grade 3 or greater (NCI-CTCAE, Version 4.03)
6. 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
7. Serious uncontrolled concomitant disease that would contraindicate the use of any drug used in this study or that would put the patient at high risk for treatment-related complications
8. Uncontrolled hypertension (systolic >150 mmHg and/or diastolic >100 mmHg) *or* clinically significant (i.e. active and/or requiring medication) cardiovascular disease, including but not limited to cerebrovascular accident (CVA)/stroke *or* myocardial infarction within 6 months prior to first study medication, unstable angina, CHF of New York Heart Association (NYHA) grade II or higher, *or* serious cardiac arrhythmia requiring medication, *or* other cardiovascular problem that is uncontrolled or is currently controlled with medication
9. Current known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV)
10. Dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy

11. 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

12. Known hypersensitivity to any of the study medications or to excipients of recombinant human or humanized antibodies
13. History of receiving any investigational treatment within 28 days prior to 1st study drug administration (dosing) and/or concurrent participation in any interventional clinical trial
14. Pregnant or lactating women
15. Current clinical or radiographic evidence of central nervous system (CNS) metastases
16. History of LVEF decline to below 50% during or after prior trastuzumab adjuvant or neo-adjuvant therapy

4.2 STUDY TREATMENT

4.2.1 Formulation, Packaging, and Handling

4.2.1.1 Pertuzumab

Pertuzumab, the Investigational Medicinal Product (IMP) for the study will be manufactured and supplied by the Sponsor.

Pertuzumab will be provided as a single use formulation containing 30 mg/mL pertuzumab in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20. Each vial will contain 420 mg/14.0 mL (30 mg/mL) of pertuzumab.

Study drug packaging and labeling will be overseen by the Sponsor and will be in accordance with the Sponsor's standards and local regulatory requirements.

Pertuzumab vials must be shipped at temperature ranging from 2°C to 8°C (36°F to 46°F) and should be maintained at this temperature until use. Vials must not be frozen. Vials must be kept in outer carton in order to protect from light. Vials must not be shaken. For further details, see the PI.

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, any deviations or product complaints are to be reported to the Monitor upon discovery.

4.2.1.2 Trastuzumab

Commercial trastuzumab will be provided to the site for intravenous use during this study.

For further details, see the local PI for trastuzumab.

4.2.1.3 Docetaxel

Commercial docetaxel will be obtained locally by the investigational sites. Sponsor will reimburse for the same.

For further details, see the local PI for docetaxel.

4.2.2 Dosage, Administration, and Compliance

4.2.2.1 Pertuzumab

Each treatment cycle is 3 weeks (21 days) in duration. The initial dose (Cycle 1, Day 1) of pertuzumab will be 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks by a dose of 420 mg administered as an intravenous infusion over 30 to 60 minutes.

Pertuzumab must be administered as an intravenous infusion only, not as an intravenous push or bolus.

For preparation of pertuzumab solution for infusion, using aseptic technique, following steps are to be followed:

- The formulation must be inspected visually for particulates and discoloration prior to administration
- Appropriate volume of pertuzumab should be withdrawn from the vial(s), and diluted into a 250 mL 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag
- Mixing of diluted solution should be done by gentle inversion. Not to be shaken
- Administration to be done immediately once prepared. If the diluted infusion solution is not used immediately, it can be stored at 2°C to 8°C for up to 24 hours

Dilution must be done with 0.9% sodium chloride injection only, not with dextrose (5%) solution.

For delayed or missed doses, if the time between two sequential infusions is less than 6 weeks, the 420 mg dose of pertuzumab should be administered. Do not wait until the next planned dose. If the time between two sequential infusions is 6 weeks or more, the initial dose of 840 mg pertuzumab should be re-administered as a 60-minute intravenous infusion followed every 3 weeks thereafter by a dose of 420 mg administered as an intravenous infusion over 30 to 60 minutes.

No dose reductions are to be made for pertuzumab.

Pertuzumab to be discontinued, if trastuzumab treatment is discontinued.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 4.2 and 4.5.

For further information on drug interactions, storage conditions, etc., please refer to the PI.

4.2.2.2 Trastuzumab and Docetaxel

The initial dose of trastuzumab will be 8 mg/kg administered as a 90-minute intravenous infusion, followed every 3 weeks by a dose of 6 mg/kg administered as an intravenous infusion over 30 to 90 minutes.

Pertuzumab, trastuzumab, and docetaxel will be administered sequentially in line with the prescribing information. Docetaxel should be administered after pertuzumab and trastuzumab. Patient must be observed for a period of 30 to 60 minutes after each pertuzumab infusion and before commencement of any subsequent infusion of trastuzumab.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

4.2.3 Dose Delays and Modifications

If any of the individual study medications must be delayed for 1 day or more, all three agents (pertuzumab, trastuzumab, and docetaxel) 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. Pertuzumab dose should not be adjusted for body weight.

4.2.4 Investigational Medicinal Product Accountability

Pertuzumab, the IMP required for completion of this study will be provided by the Sponsor. The investigational site will acknowledge receipt of IMP; 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 IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.2.5 Post-Trial Access to Pertuzumab

The Sponsor will provide pertuzumab to the patients who will be:

- receiving the study medication till the end of the study, and will have not progressed on study medication till the end of the study;
- willing to continue study medication;

- considered suitable by the investigator to continue receiving study medication till progression of the disease.

4.3 CONCOMITANT THERAPY

4.3.1 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 study completion/early termination 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 according to standard of care when necessary.

The following list of allowed medications is provided as guidance. 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 local clinical practice and according to the currently approved PI for docetaxel
- Steroids for docetaxel premedication and anti-emetics according to routine clinical practice
- 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
- 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 i.e. radiotherapy is only allowed during the study treatment period for the indication of bone lesions present at baseline. If a patient requires radiation therapy to a new lesion, that new lesion would, per RECIST, qualify as progressive disease.

4.3.2 Prohibited Therapy

Use of the following therapies is prohibited:

- Any other systemic anticancer agent or other treatments not part of protocol-specified anticancer therapy
- Any oral, injected, or implanted hormonal methods of contraception
- Any other investigational agent
- 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 (TNF)-α inhibitors
    - Anti-T cell antibodies

4.4 STUDY ASSESSMENTS

4.4.1 Description of Study Assessments

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

4.4.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies including trastuzumab treatment and procedures), reproductive status, cardiovascular history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to the screening visit.

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

4.4.1.2 Physical Examinations

At Baseline, a complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems; however particular attention should be given to cardiovascular system.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF.

4.4.1.3 Vital Signs

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

4.4.1.4 Tumor and Response Evaluations

RECIST criteria version 1.1 will be used to evaluate response and assess progressive disease (Eisenhauer et al., 2009). A summary of RECIST criteria version 1.1 is provided in Appendix 3.

All measurable and non-measurable lesions must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of physical examinations, computed tomography (CT) scans, and magnetic resonance imaging (MRI), using RECIST criteria version 1.1. An objective response should be confirmed by repeat assessments 4 weeks after initial documentation. The same radiographic procedure used to define measurable disease sites at screening must be used throughout the study (e.g., the same contrast protocol for CT scans). Assessments should be preferably performed by the same evaluator to ensure internal consistency across visits.

At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected. This unscheduled assessment should be documented in the eCRF.

4.4.1.5 Other Disease-Specific Assessments

LVEF assessments

LVEF assessments will be performed within 42 days of enrollment and every three treatment cycles by either ECHO or MUGA scan. For being eligible for this study, LVEF ≥50% is required at Screening. ECHO should be the method of choice for these assessments. The same method of LVEF assessment 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 all patients will be collected.

Performance Status

Performance status will be measured using the ECOG performance status scale (see Appendix 2). 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.

4.4.1.6 Laboratory Assessments

Samples for the following standard laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (red blood cell [RBC] count, hemoglobin, hematocrit, platelet count, white blood cell [WBC] with differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells])

- Serum chemistry (sodium, potassium, chloride, bicarbonate, magnesium, blood glucose, blood urea nitrogen [BUN] or urea, creatinine, total protein, albumin, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, lactate dehydrogenase [LDH])
- Coagulation (INR, aPTT, and PTT)

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.

- Viral serology at screening (human immunodeficiency virus [HIV], hepatitis B surface antigen [HBsAg], total hepatitis B core antibody [HBcAb], hepatitis C virus [HCV] antibody)
- Pregnancy test

For women of childbearing potential, serum *β*-HCG test must be performed within 7 days prior to the first dose of study treatment with the result available prior to first dosing. Urine β-HCG test must be performed within 7 days prior to every 3rd cycles (with results available prior to treatment), at the safety follow-up visit, and at 4 and 7 months after the last dose of study treatment. All positive urine pregnancy tests must be confirmed by a serum *β*-HCG test.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.4.2 Timing of Study Assessments

4.4.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled subjects and for subjects who are not subsequently enrolled will be maintained at the study site. Also, audio-visual recordings of informed consent process prior to enrollment if required as per regulations at the time of consenting must be arranged while preserving the confidentiality of the subjects.

Documented 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) to be assessed by IHC and/or ISH at a local laboratory that is experienced/certified in HER2-expression testing using an accurate and validated assay.

Women with child bearing potential and male patients with partners of child bearing potential 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.

Screening tests and evaluations will be performed within 7 days prior to the first study medication administration (dosing), unless otherwise specified.

CT or MRI scans performed prior to obtaining informed consent and within 28 days prior to the first study medication administration (dosing) may be used; these tests do not need to be repeated for screening. In patients with signs and symptoms suggesting CNS involvement or other unexplained neurological symptoms, CT or MRI brain scan is to be performed at screening.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. 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.

Pretreatment tests and evaluations will be performed within 3 days prior to the first study medication administration (dosing), after confirmation of other eligibility criteria, unless otherwise specified.

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

4.4.2.2 Assessments during Treatment

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 1). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments.

The following assessments must be performed every three treatment cycles: tumor assessment, ECOG performance status, and LVEF.

Samples for hematology and blood chemistry will be collected and submitted to a local laboratory within 3 days prior to treatment administration in each cycle; the results must be available prior to dosing.

For women of childbearing potential, serum β-HCG test must be performed within 7 days prior to the first dose of study treatment with the result available prior to first dosing. Urine β-HCG test must be performed within 7 days prior to every 3rd cycle (with results available prior to treatment), at the safety follow-up visit, and at 4 and 7 months after the last dose of study treatment. All positive urine pregnancy tests must be confirmed by a serum β HCG test.

Please see Appendix 1 for the Schedule of Assessments performed during the treatment period.

4.4.2.3 Assessments at Post-treatment Safety Follow-up

Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, or death. All patients will continue to be followed up for 24 months after the last patient enrolled in study, unless they have been lost to follow-up, withdrawn consent, or died. 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.

4.4.2.4 Assessments at Study Completion/Early Termination Visit

Patients who complete the study or discontinue from the study early will be asked to return to the clinic 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 study completion/early termination visit.

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

4.4.2.5 Follow-Up Assessments

After the study completion/early termination 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 all patients have been followed up for at least 24 months after the last patient enrolled in the study, unless they have been lost to follow-up, withdrawn consent, or died, whichever occurs first.

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

4.4.2.6 Assessments at Unplanned Visits

Please see Appendix 1 for assessments that are required to be performed in case of an unplanned visit.

4.5 PATIENT, STUDY, AND SITE DISCONTINUATION

4.5.1 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
- Patient non-compliance, specifically defined as non-compliance with the study procedures, the schedule of assessments, or the protocol defined timelines

4.5.1.1 Discontinuation from Study Drug

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

- Pregnancy

- Serious hypersensitivity reaction/anaphylaxis
- Clinical signs and symptoms suggesting CHF
- Changes in LVEF (see Appendix 4) Dyspnea or clinically significant hypotension (defined per investigator discretion)
- 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 study completion/early termination 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.

4.5.1.2 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. Patients who withdraw from the study will not be replaced.

4.5.2 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 replace a site at any time. Reasons for replacing 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 Harmonisation (ICH) guideline for Good Clinical Practice

In addition, the study may be discontinued on the recommendation of the Indian Licensing Authority.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 Toxicity Management Guidelines

The NCI-CTCAE version 4.03 will be used to grade toxicity. Pertuzumab, trastuzumab, and docetaxel will be administered 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 by ECHO or MUGA 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, 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 lower than 45% (50% is required for entry into the study), the decision to stop or continue study treatment is based on the algorithm shown in Appendix 4. The incidence of CHF will also be recorded throughout the study.

See Appendix 5 for details of the NYHA classification and left ventricular systolic dysfunction NCI-CTCAE version 4.03 grading.

5.1.1.2 Infusion-associated Reactions, Hypersensitivity Reactions and Anaphylaxis

Pertuzumab has been associated with infusion associated reactions, such as chills, diarrhea, fatigue, headache, nausea, and pyrexia, and with hypersensitivity reactions. Close observation of the patient during administration, for 60 minutes after the first infusion and, if well tolerated, for 30 minutes following subsequent infusions.

If a significant infusion-associated reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Since there is the potential for a delayed onset of infusion-associated reactions, patients should be instructed to contact the treating physician with any concerns.

Permanent discontinuation should be considered in patients with severe infusion reactions. This clinical assessment should be based on the severity of the preceding reaction and response to the administered treatment for the adverse reaction.

Patients who experience an NCI-CTCAE version 4.03 Grade 4 allergic reactions, 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), the initial loading dose of 840 mg pertuzumab should be re-administered as a 60-minute infusion followed by cycles of 420 mg administered over 30-60 minutes.

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 (i.e., pertuzumab).

5.1.1.4 Risk of Cardiotoxicity with Pertuzumab

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 4.03 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.

IB should be referred to for most recent data relating to risk of cardiotoxicity.

5.1.1.5 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. IB should be referred to for most recent data relating to risk of EGFR-related toxicities.

5.1.1.6 Respiratory Events

In the pivotal study CLEOPATRA, respiratory events (i.e., dyspnea, cough) were reported in >10% in pertuzumab-treated patients, which are unspecific symptoms of various conditions, including infusion associated reaction or hypersensitivity/anaphylaxis, cardiac dysfunction, and respiratory disease. Although pertuzumab targets the HER2 receptor it inhibits heterodimerization with other members of the HER family (e.g., epidermal growth factor receptor [EGFR] [HER1]). Accordingly, it may cause toxicities associated with the use of EGFR inhibitors, such as interstitial lung disease.

5.1.1.7 Warnings and Precautions for Docetaxel

Docetaxel 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. 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. In the case of neutropenia, patients should not be re-treated 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. 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. 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 PI for docetaxel.

5.1.2 Management of Specific Adverse Events

Withhold pertuzumab and trastuzumab dosing for at least 3 weeks for either:

- a drop in LVEF to less than 45% or
- LVEF of 45% to 49% with a 10% or greater absolute decrease below pretreatment values

Pertuzumab may be resumed if the LVEF has recovered to greater than 49% or to 45% to 49% associated with less than a 10% absolute decrease below pretreatment values.

If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, pertuzumab and trastuzumab should be discontinued, unless the benefits for the individual patient are deemed to outweigh the risks.

Refer Appendix 4.

5.1.3 Dose Modification and Discontinuation for Trastuzumab and Docetaxel

For Trastuzumab

- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Discontinue trastuzumab for severe or life-threatening infusion reactions

For Docetaxel

Refer local approved PI for dose modification and discontinuation of docetaxel.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AEs 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
- AEs 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 criteria version 4.03; 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.

SAEs are required to be reported by the investigator/Sponsor to the Licensing Authority immediately (i.e., no more than 24 hours after occurrence 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 AEs of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). AEs of special interest for this study include the following:

- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment
- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6
- Suspected transmission of an infectious agent by the study drug (defined as 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.)

[Note: In general, 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 to a value 10% points below baseline or lower, and <50% must be reported as an AE
- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment must be reported in an expedited manner by using the SAE form and classifying the event as Non-Serious Event of Special Interest

In both cases, it should be reported as left ventricular systolic dysfunction and graded according to NCI-CTCAE, Version 4.03.]

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 AE 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 AE 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 AE eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by 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 end of the study (as defined in Section 3.2). After this period, investigators should report any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation time points. 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 AE severity grading scale for the NCI CTCAE (v4.03) will be used for assessing adverse AE severity. Table 1 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 5-1 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 AE [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the NCI CTCAE (v4.03), 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 SAE (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 5.4.2 for reporting instructions), per the definition of SAE 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 AE eCRF. Avoid colloquialisms and abbreviations.

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

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

AEs 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-related reactions, a diagnosis (if known) should be recorded on the AE 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 AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one 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 AE 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 an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the AE 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 AE 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 AE 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 AE eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must 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., ALP and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the AE eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE 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 AE. 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 AE 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 must 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 AE eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the AE 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 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. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST >3 • baseline in combination with total bilirubin >2 • ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST >3 • baseline 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 AE eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after occurrence or learning of the event, as applicable), either as a SAE or a non-serious AE of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the AE eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of breast cancer.

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 AE 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 death is attributed to progression of breast cancer, "breast cancer progression" should be recorded on the AE eCRF.

During post-study survival follow-up, deaths attributed to progression of breast cancer should be recorded only on the Survival 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 AE 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 criteria version 1.1. 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 an 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 and observation after 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 AE associated with an overdose or incorrect administration of study drug should be recorded on the AE eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after occurrence of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the event occurs or investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after occurrence/learning (whichever is applicable) of the event, regardless of relationship to study drug:

- SAEs
- Non-serious AEs of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 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/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information

Primary Contact

Medical Monitor: Dr. [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: Dr. [redacted]

Telephone No.: [redacted]

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, 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").

Drug Safety: Contact Information

To ensure the safety reporting, following contact information will be available to all investigators.

Telephone No.: +91-9820163752

Direct: +91-22-3394 1422

Fax: +91-22-3394 1054

E-mail: india.drugsafety@roche.com

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

For reports of SAEs and non-serious AEs of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours after occurrence or learning of the event, as applicable) on the AE eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper SAE/Non-Serious AE of Special Interest CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after occurrence/learning of the event, as applicable), 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

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become 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 immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the AE eCRF. The investigator should discontinue study drug 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. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE eCRF.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

Roche will collect additional follow-up information at the end of the 1st and 2nd trimester, after delivery and at 3, 6, and 12 months of the infant's life.

5.4.3.2 Pregnancies in Female Partners of Male Patients

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 immediately (i.e., no more than 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 AE eCRF, and reported to the Sponsor immediately (i.e., no more than 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 AE eCRF, and reported to the Sponsor immediately (i.e., no more than 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 AE 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 AE 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-serious AEs 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

At the study completion/early termination visit, the investigator should instruct each patient to report to the investigator any subsequent AEs that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any death, SAE, or other AE of concern occurring at any time after a patient has discontinued study participation if the event is believed to be related

to prior study drug treatment or study procedures. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The investigator should report these events to Roche Safety Risk Management on the AE eCRF. If the AE eCRF is no longer available, the investigator should report the event directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information & List of Investigators").

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

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non-serious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, IECs, and applicable health authorities based on applicable regulations.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Prescribing information for Pertuzumab

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The following is an outline of the statistical methodology that will be used to report and analyze this study. A more detailed description will be provided in a separate statistical analysis plan (SAP).

All baseline summaries and efficacy analyses will be based on the intent-to-treat (ITT) population. This will be defined as all enrolled patients. All safety summaries and analysis will be based on the safety population, defined as all enrolled patients who receive at least one dose of study medication.

Where it is stated that data will be summarized, unless alternative methods are given, the following will apply:

- continuous data will be summarized using: n, mean, median, range, standard deviation, minimum and maximum.
- discrete data will be summarized using frequency counts (n) and percentages (%)

6.1 DETERMINATION OF SAMPLE SIZE

A total of approximately 52 patients will be enrolled in this study.

For the purpose of the estimation of sample size, the incidence of all grade AEs related to Pertuzumab in combination with Trastuzumab and Docetaxel was chosen as a safety endpoint of primary interest. If the observed incidence of all grade AEs related to Pertuzumab in combination with Trastuzumab and Docetaxel is 97.3% and assuming level of significance 5% and precision 5 % 52 enrolled patients are planned for this study.

Sample size calculation for estimating proportion:

$$n = \frac{Z^2_{\alpha/2} \cdot p \cdot (1 \cdot p)}{d^2}$$

Where,

P = Incidence of AE related to Pertuzumab in combination with Trastuzumab and Docetaxel.

d = Precision

$Z_{\alpha/2}$ value = 1.96 for 95% confidence level

6.2 SUMMARIES OF CONDUCT OF STUDY

All demography and baseline disease characteristics (collected at either the screening or baseline) will be summarized using the ITT population.

In order to assess the conduct of the study, major protocol violations will be summarized and listed.

6.3 EFFICACY ANALYSES

The analysis of ORR is based on the best (confirmed) overall response (BOR). Best (confirmed) overall response (BOR) is defined as the best response recorded from the start of trial treatment until disease progression/recurrence or death. To be assigned a status of PR or CR (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder.

Patients without a post-baseline tumor assessment will be considered to be non-responders. 95% confidence intervals (calculated using Clopper-Pearson methodology) for this will be provided.

Progression-free survival (PFS), defined as the time from enrollment to the first occurrence of disease progression as determined by the investigator using RECIST criteria version 1.1, or death from any cause, whichever occurs first. Patients who have neither progressed nor died or who are lost to follow-up at the time of analysis will be documented or the last date of follow-up for progression of disease, whichever is last. Patients without post baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment.

The analysis of PFS is based on the survivor function, which is the probability of remaining event free beyond a certain point in time. The survival function will be estimated using Kaplan-Meier methodology and summarized using the 25^{th} and 75^{th} percentiles, median survival, and a 95% confidence interval (CI) for the median. The plot of Kaplan-Meier estimates for the single treatment group will be presented.

Overall survival is 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 (two years from last patient enrolled in the study). Patients without follow-up assessment will be censored at the day of last study medication, and patients with no post-baseline information will be censored at baseline. Analysis methods for OS will be the same as those described for the PFS.

A listing will be provided for all efficacy data.

6.3.1 Efficacy Endpoints

The efficacy outcome measures for this study are as follows:

- Overall response rate (ORR)
- Progression-free survival (PFS)
- Overall Survival (OS)

6.4 SAFETY ANALYSES

The incidence of AEs and SAEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

Summaries will include:

- The incidence of AEs and SAEs
    - overall
    - by severity using NCI CTCAE version 4.03
    - by relationship to study drug
    - by action taken with study drug

Summaries will include the incidence of AEs and SAEs, Summaries will include frequency counts and percentages. 95% confidence intervals (calculated using Clopper-Pearson methodology) for incidences will be provided.

A subject with multiple AEs within a body system is only counted once towards the total of this body system. AEs and SAEs will be coded by System Organ Class (SOC) and preferred term using the latest Medical Drug Dictionary for Regulatory Activities (MedDRA) version 15.1.

- Incidence of CHF and/or significant decline in LVEF: The incidence of CHF and/or significant decline in LVEF will be summarized using number (n) and percentage (%). A listing will be provided for incidence of CHF and/or significant decline in LVEF. A graph will also be provided for changes in Incidence of CHF and/or significant decline in LVEF over the study period.
- LVEF will be summarized by cycle including change from baseline summaries where appropriate.
- All laboratory data will be analyzed with appropriate summary statistics and also, shift table will be presented for the laboratory test results. A listing of the lab test results will be presented. The values below and above the normal ranges will be flagged with L (below the lower limit) and H (above the upper limit).
- Incidence of AEs leading to discontinuation, modification or interruption of study medication: This event will be summarized using number (n) and percentage (%). A listing will be provided for this event. A graph will also be provided for changes in Incidence of AEs leading to discontinuation, modification, or interruption of study medication over the study period.
- The incidence and cause of deaths due to AE: The number of deaths due to AEs will be summarized using number and percentage (%). A listing will be provided for the number of deaths due to AEs.

6.4.1 Safety Endpoints

The safety outcome measures for this study are as follows:

- Incidence and severity by NCI-CTCAE version 4.03 of AEs and SAEs
- Incidence of CHF and/or significant decline in LVEF
- LVEF over the course of the study
- Laboratory results abnormalities
- Incidence of AEs leading to discontinuation, modification, or interruption of study medication
- Incidence and cause of death due to AEs

6.5 INTERIM ANALYSIS

One interim analysis for safety and efficacy will be done once approximately 50% patients will complete 6 months of Pertuzumab therapy.

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.

The Sponsor will perform oversight of the data management of this study. The Sponsor/ designee will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Laboratory data will be sent directly to the CRO, using the CRO's standard procedures 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 by the Sponsor/ designee and records retention for the study data will be consistent with the Sponsor'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 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.

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, 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 policy for retention of records described in Section 7.6.

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/EC 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

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 (India) 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) and local requirements of India.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as 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/EC submission. The final IRB/EC-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.

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/EC 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. The audio-visual recording of discussion between the patient and the study doctor regarding the patient's decision whether to or not to participate in this study will be performed as per regulations. This recording should be kept confidential to an extent permissible by law. It may be viewed by the investigator or any other person authorized by him, sponsoring company and/or its representatives. It may also be viewed by people from regulatory authorities and ethics committees to check that the study is being carried out correctly.

8.3 INSTITUTIONAL REVIEW BOARD OR 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/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC 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 IRB/EC. Investigators may receive written Investigational New Drug (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/EC, 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/EC 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 (as defined in Section 3.2).

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/EC 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.

Protocol waivers will not be granted, except in circumstances impacting the clinical subjects' health/ health management

All protocol waivers will be approved by the Medical Monitor or Medical Director.

All Protocol violations have to reported to the sponsor and to the institutional ethics committee

9.2 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 IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

Table 9-1 Study Administrative Structure

Sponsor	Roche Products India Pvt. Ltd.
Clinical Supplies	Local warehouse, Site Pharmacy, etc., as applicable
Clinical Laboratory	Institutional laboratories and/or external laboratories
Study Monitoring	Roche Products India Pvt. Ltd., designated CRO, as applicable
Project Management	Roche Products India Pvt. Ltd.
List of Investigators	List will be included in the clinical trial application dossier to local health authorities

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. 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.

The Sponsor will comply with the requirements for publication of study results. 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.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) 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).

Changes that involve logistical or administrative aspects only may also be documented via a Protocol Clarification Memo alone.

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Appendix 1
Schedule of Assessments

Appendix 1
Schedule of Assessments

Study Activities	Screening	Treatment period[14]	Unscheduled Visit[14]	Follow up Period[14]		
	Day -7 to -1	Each Treatment Cycle, (21 days)		Safety Follow up visit - 28 days from Last treatment cycle[15]	3 monthly Follow up visits - starting after safety follow-up visit	End of study visit[15]
Informed Consent[1]	X					
Demographics & medical history[2]	X					
Concomitant medication[3]	X	X	X	X	X	X
Complete physical examination[4]	X	X	X	X	X	X
Vital signs[5]	X	X	X	X	X	X
Height	X					
Weight	X	X		X		
HER2 Reports review for eligibility[6]	X					

Appendix 1
Schedule of Assessments (cont.)

Study Activities	Screening	Treatment period[14]	Unscheduled Visit[14]	Follow up Period[14]		
	Day -7 to -1	Each Treatment Cycle, (21 days)		Safety Follow up visit - 28 days from Last treatment cycle[15]	3 monthly Follow up visits - starting after safety follow-up visit	End of study visit[15]
Tumor evaluation[7]	X	Every 3 cycles of Monoclonal antibody *		If disease progression not yet established	If disease progression not yet established	If disease progression not yet
Laboratory Investigations[8]	X	X		X		
ECOG performance status[9]	X	Every 3 cycles of monoclonal antibody	X	X		X
LVEF[10]	X	Every 3 cycles of monoclonal antibody		X	X	
SAEs and AEs[11]		X	X	X	X	X
Pregnancy test[12]	X	Every 3 cycles of monoclonal antibody		X	At 4 and 7 months after the last dose of monoclonal antibody	
Administration of study medication		X				
Infusion reactions during infusion and observation period		X				

Appendix 1
Schedule of Assessments (cont.)

Study Activities	Screening	Treatment period[14]	Unscheduled Visit[14]	Follow up Period[14]		
	Day -7 to -1	Each Treatment Cycle, (21 days)		Safety Follow up visit - 28 days from Last treatment cycle[15]	3 monthly Follow up visits - starting after safety follow-up visit	End of study visit[15]
Survival[13]	X	X		X	X	X

Notes:

1. Signed/dated informed consent in language comprehended by the potential ;clinical trial subject/LAR
2. Complete medical history and demographics (i.e., age, sex, race, and ethnicity, if applicable) and all medications taken during the last 28 days prior to screening visit will be collected.
3. Current concomitant medication will be recorded at Screening and on an ongoing basis.
4. Physical Examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the AE eCRF
5. Vital signs will be assessed before treatment on Day 1 of every treatment cycle (pertuzumab, trastuzumab, and chemotherapy), recorded again after infusion during the observation period of each study medication. Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and oral or axillary temperature.

Appendix 1
Schedule of Assessments (cont.)

6. Documented 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 and routine clinical practice. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.
7. 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. NB: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
8. Laboratory Assessment as per routine standard of care must be performed within 3 days (with results available) prior to the administration of study medication. Hematology, as per routine standard of care, may include hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, other cells). Serum chemistry, as per routine standard of care, may include sodium, potassium, calcium, chloride, magnesium, BUN (urea), uric acid, total protein, albumin, ALP, ALAT, ASAT, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin, creatinine, and blood glucose and calculated creatinine clearance at baseline. Coagulation tests will consist of INR and aPTT or PTT).
9. ECOG PS to be recorded every 3 cycles until PD.
10. 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.
11. After informed consent, and prior to dosing, SAEs considered related to a study mandated procedure are reportable. As of cycle 1 all AEs and SAEs considered will be collected. AEs and SAEs to be monitored continuously collected and End-of-study visit and to be recorded with grading according to NCI-CTCAE, Version 4.03

Appendix 1
Schedule of Assessments (cont.)

12. For women of childbearing potential, serum β-HCG test must be performed within 7 days prior to the first dose of study treatment with the result available prior to first dosing. Urine β-HCG test must be performed within 7 days prior to every 3rd cycles (with results available prior to treatment), at the safety follow-up visit, and at 4 and 7 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
13. Overall survival is 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 (two years from last patient enrolled in the study).
14. All treatment visits within ±3 days of scheduled treatment day; 28 day Safety Follow up visit within ±3 days of the scheduled visit date; 3 monthly Follow up visits (starting after safety follow-up visit) within ±14 days of the scheduled visit date(s); End of Study visit within ±14 days of the scheduled visit date. Tumour assessment ±3 days of planned scheduled visit. At the end of study visit, if patient does not fit into end of study definition, then tumour assessment to be done as per institutional criteria and routine clinical practice.
15. Patients who complete the study or discontinue from the study early will be asked to return to the hospital within 28 days after the last dose of study drug for the end-of-study visit.

Appendix 2

Appendix 2
Eastern Cooperative Oncology Group (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

As published in:

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. 1982;5:649-55.

Appendix 3
RECIST Criteria Version 1.1

Response Evaluation Criteria in Solid Tumors (RECIST): An Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1,[1] are presented below, with the addition of explanatory text as needed for clarity.[2]

1. Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as discussed below.

i. Measurable

Tumor Lesions

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 size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately 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 the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

See also notes below on “Baseline Documentation of Target and Non-Target Lesions” for information on lymph node measurement.

ii. Non-Measurable Tumor Lesions

Non-measurable tumor lesions include small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis • 10 but < 15 mm) 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, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

iii. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as given below.

Bone Lesions

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been

demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

iv. Specifications by Methods of Measurements

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

b. 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 the follow-up visits. Imaging-based evaluation should always be preferred over clinical examination.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and • 10 mm in 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.

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. 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).

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be

discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward.

Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology: The utilization of these techniques for objective tumor evaluation cannot generally be advised. However, these techniques can be used to confirm the complete pathological response.

2. Tumor Response Evaluation

i. 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. Measurable disease is defined by the presence of at least one measurable lesion, as described above.

ii. 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 that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$ 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should 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 that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that 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 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 that is reported as being 20 mm × 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 of < 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 of 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 of diameters will be used as a 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 Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

iii. Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

a. 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 of diameters
- Progressive disease (PD): At least a 20%, the sum must also demonstrate an absolute increase of at least 5mm.
- The appearance of one or more new lesions is also considered progression.

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure: During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

Lesions That Split or Coalesce on Treatment: When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits

PD: Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread, or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the

identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease.

If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

iv. Evaluation of 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. 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’.

a. Time point Response

It is assumed that at each protocol-specified time point, a response assessment occurs.

Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, **Table 2** is to be used.

Table 1 Time point Response: Patients with Target Lesions (with or without Non-Target Lesions)

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	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Time point Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.
[a]"Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for

target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess” except where this is clear evidence of progression, as this equates with the case being not evaluable at that time point.

c. Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient’s best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in **Table 3.**

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Time point	Overall Response at Subsequent Time point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a]If a CR is truly met at the first time point, any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

d. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in **Table 1**, **2** and **3**.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

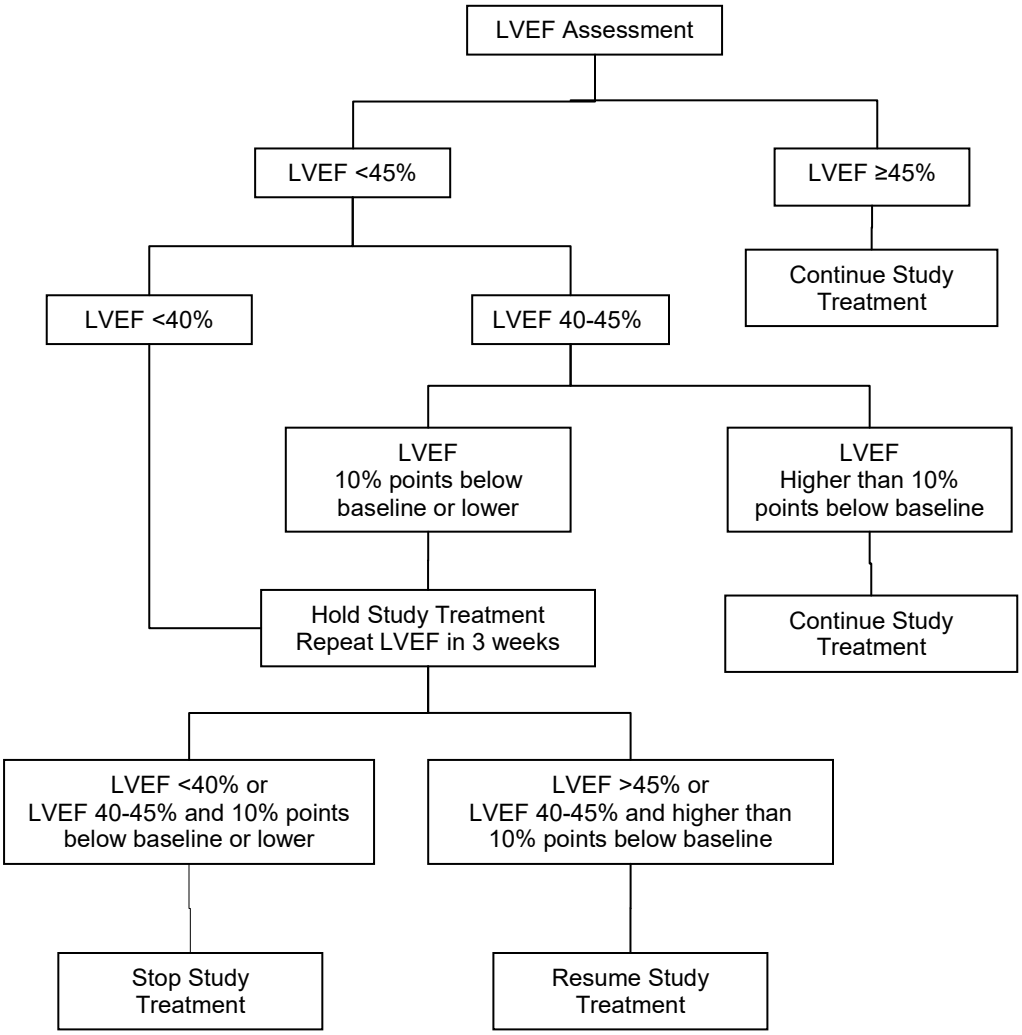
v. Frequency of tumor re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

Appendix 4

Appendix 4

Algorithm for Continuation and Discontinuation of Pertuzumab based on LVEF assessment



Appendix 5
NYHA Classification of Heart Failure and Left Ventricular Systolic Dysfunction NCI-CTCAE Version 4.03 Grading

NYHA Classification of Heart Failure

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.

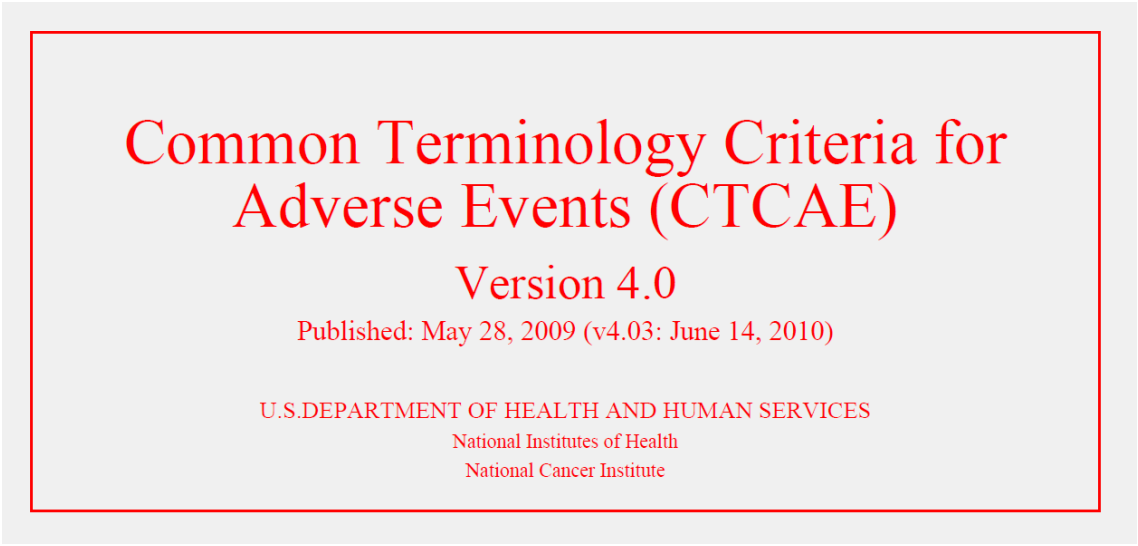
Left Ventricular Systolic Dysfunction NCI-CTCAE Version 4.03 Grading

Grade	
3	Symptomatic due to drop in ejection fraction responsive to intervention
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
5	Death

A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

Appendix 6
Common Terminology Criteria For Adverse Events (CTCAE) Version 4.03

A copy will be provided to each study site


Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

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