Official Title: A Multicenter, Open-Label, Single-Arm Study of Pertuzumab in Combination With Trastuzumab and a Taxane in First Line Treatment of Patients With HER2- Positive Advanced (Metastatic or Locally Recurrent) Breast Cancer

NCT Number: NCT01572038

Document Date: Protocol Version 6: 21-November-2018

PROTOCOL

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY OF PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AND A TAXANE IN FIRST LINE TREATMENT OF PATIENTS WITH HER2- POSITIVE ADVANCED (METASTATIC OR LOCALLY RECURRENT) BREAST CANCER**
PROTOCOL NUMBER:	MO28047
VERSION NUMBER:	6.0
EUDRACT NUMBER:	2011-005334-20
TEST PRODUCT:	Pertuzumab (RO 43-68451)
MEDICAL MONITOR:	[redacted], MD
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 28 November 2011
DATES AMENDED:	Version 2: 02 January 2012 Version 3: 30 August 2012 Version 4: 09 May 2014 Version 5: 20 November 2015 Version 6: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	21-Nov-2018 15:10:22

PROTOCOL AMENDMENT, VERSION 6.0: RATIONALE

Protocol MO28047 has been amended to allow for less frequent response assessment in long-term responders, less frequent IDMC meetings, and to update the policy on post-trial access to pertuzumab. Several sections in Section 5 (Safety Assessments) have been updated to include language from the current Roche protocol template and a new section (5.8) added. Changes to the protocol, along with a rationale for each change, are summarized below:

- Following discussions at the last IDMC meeting for the study (28th June, 2018), the IDMC members recommended that the frequency of imaging procedures for response assessment could be reduced in patients with long-term responses. Previously, the protocol mandated tumor assessment should be conducted every six cycles (approximately 4.5 months) in patients who remained progression free after 36 months. The IDMC recommended that for patients who are progression free for > 5 years a frequency of every 6 months would be acceptable and that for patients who are progression free for > 7 years, the frequency could be reduced to once a year unless clinically indicated otherwise. However, not all study sites will be able to reduce the frequency of imaging due to their local routine practice. The protocol text was therefore reworded to state that imaging should be performed *at least every 12 cycles,* or more frequently as dictated by patient needs and/or routine practice or local requirements/policy. Sections 4.5.1.4, 4.5.2.2, and Appendix 1 have been updated with this information.
- In line with Roche's decision to reduce the frequency of PDMA study IDMCs for drugs that have a well-known safety profile (e.g. Perjeta), Sections 3.1.1, 6, and 6.7 have been updated to indicate that IDMC meetings may be held 'approximately once per year, rather than annually.
- Section 4.3.4 (Continued access to pertuzumab) has been revised to now allow patients the option to continue to receive pertuzumab after the PERUSE study is closed.
- Section 5.8 (Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees) has been added to the protocol. This section is present in the current Roche protocol template but was not present at the time of writing of the PERUSE protocol.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 6.0: SUMMARY OF CHANGES

GLOBAL CHANGES

- Several instances of '*infusion-associated symptoms*' / '*infusion-associated AEs*' have been replaced with the more common term: '*infusion-related reactions (IRRs)*'.
- Whenever the Investigator Brochure is referred to (seven instances), it has been clarified that this means the *Perjeta* Investigator Brochure
- Several instances of 'adverse event(s)', 'serious adverse event(s)', and 'adverse events of special interest' have been abbreviated for consistency.

These changes are not summarized below.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

TITLE PAGE

[redacted] has replaced [redacted] as the Medical Monitor for this study.

SECTION 3.1.1: Independent Data Monitoring Committee

There will also be ~~an annual~~ review of safety data by the IDMC *approximately once per year* following completion of enrollment.

SECTION 4.3.4: *Continued*~~Post Trial~~ Access to Pertuzumab

The Sponsor will offer continued access to pertuzumab (the Roche IMP) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive the Roche IMP (pertuzumab) after completing the study if all of the following conditions are met:

- *The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being*
- *There are no appropriate alternative treatments available to the patient*
- *The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

A patient will not be eligible to receive the Roche IMP (pertuzumab) after completing the study if any of the following conditions are met:

- *The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)*
- *The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for HER2-positive advanced (metastatic or locally recurrent) breast cancer*

- *The Sponsor has reasonable safety concerns regarding the IMP as treatment for HER2-positive advanced (metastatic or locally recurrent) breast cancer*
- *Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country*

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

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

SECTION 4.5.1.4: Tumor and Response Evaluations

Consistency of consecutive CT scans, X-rays or MRIs should be ensured during all assessments for each patient, with the same *imaging* technique being used for evaluating lesions throughout the treatment period *and follow-up* (use of spiral CT or MRI is required for baseline lesions <20 mm and must be documented in medical records and used consistently throughout the study)….

Scheduling of tumor assessments

Baseline total tumor burden must be assessed within a maximum of 28 days before first dose of study drug treatment. Post-baseline assessments are to be performed every three treatment cycles up to 36 months, and *at least* every ~~six~~*12* cycles *(or more frequently as dictated by patient needs and/or routine practice or local requirements/policy)* thereafter for patients who remain progression free after 36 months.

SECTION 4.5.2.2: Assessments during Treatment

During the treatment period, the following assessments must be performed

…

- Tumor evaluation: every 3 cycles of monoclonal antibody up to 36 months and *at least* every *12*~~6~~ cycles *(or more frequently as dictated by patient needs and/or routine practice or local requirements/policy)* thereafter in those who remain progression free

…

Section 4.6.1.1 Discontinuation from Study Drug

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

- Clinical signs and symptoms suggesting CHF.
- Dyspnea or clinically significant hypotension (defined per investigator discretion).

- Symptomatic left ventricular dysfunction (NCI-CTCAE version 4.0 Grade 3 or 4) with a drop in LVEF consistent with cardiac failure.
- *Pregnancy.*

Section 5.2: SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and ~~non-SAEs~~*adverse events* of special interest *(AESI)*;…

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

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

Section 5.3.1: Adverse Event Reporting Period

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting SAEs).~~After informed consent has been obtained but prior to initiation of study drug, only SAEs considered to be related to a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies).~~

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

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

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

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

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

Section 5.3.5.1: Diagnosis versus Signs and Symptoms*Infusion-Related Reactions*
~~Infusion Associated Reactions~~

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms *on the Adverse Event eCRF* rather than *an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction anaphylactic reaction*~~a diagnosis of allergic reaction or infusion reaction~~.

Section 5.3.5.2: Diagnosis versus Signs and Symptoms~~Other Adverse Events~~

...

Section 5.3.5.4: Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. *The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.*~~The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.~~

Section 5.3.5.5: Abnormal Laboratory Values

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

- ~~Accompanied~~ *Is 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.
- *Is clinically significant in the investigator's judgment*

  Note: For oncology trials, certain abnormal values may not qualify as AEs.~~Clinically significant in the investigator's judgment.~~

...

Observations of the same clinically significant laboratory abnormality from visit to visit should *only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent AEs).*~~not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.~~

Section 5.3.5.8: Deaths

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

…

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6. ~~If the cause of death is disease progression, this should be recorded on the Study Completion/Early Discontinuation eCRF.~~

Section 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- SAEs *(defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)*.
- AESI *(defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)*.
- Pregnancies (see Section 5.4.3 for details on reporting requirements).

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, SAEs and AESI will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event 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, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax

number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting SAEs that occur >28 days after the final dose of study treatment are provided in Section 5.6.~~For reports of SAEs and non-SAEs of special interest, investigators should record all case details that can be gathered within 24 hours on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to The Sponsor Safety Risk Management by the EDC system.~~

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

Section 5.5.2 Sponsor Follow-Up

For SAEs, ~~non-SAEs of special interest~~*AESI*, 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.

Section 5.6: *Adverse Events That Occur After The Adverse Event Reporting Period*~~Post-Study Adverse Events~~

After the end of the AE reporting period (defined as 28 days after the final dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a SAE that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.~~The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period/completion of the study, which is at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first. However, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period/end of the study.~~

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

SECTION 5.8: ***Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees***

The Sponsor will promptly evaluate all SAEs and AESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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

- *Perjeta Investigator Brochure*

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.

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

…

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

SECTION 6.7: Interim Analyses

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

APPENDIX 1: Schedule of Activities

The schedule of activities has been revised to reflect the changes to the protocol.

SAMPLE INFORMED CONSENT FORM{S}

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY OF PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AND A TAXANE IN FIRST LINE TREATMENT WITH HER2- POSITIVE ADVANCED (METASTATIC OR LOCALLY RECURRENT) BREAST CANCER**
PROTOCOL NUMBER:	MO28047
VERSION NUMBER:	6.0
EUDRACT NUMBER:	2011-005334-20
TEST PRODUCT:	Pertuzumab (RO 43-68451)
MEDICAL MONITOR:	[redacted], MD
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

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

_____

PROTOCOL SYNOPSIS

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

Objectives

Primary Objective

The primary objective for this study is as follows:

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

Secondary Objectives

The secondary objectives for this study are as follows:

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

Study Design

Description of Study

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

Number of Patients

Approximately 1500 patients will be enrolled in the study.

Target Population

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

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

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

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

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

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

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

Length of Study

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

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

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

End of Study

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

Efficacy Outcome Measures

- PFS
- OS
- ORR
- CBR

- Duration of response
- Time to response

Safety Outcome Measures

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

Patient-Reported Outcome Measures

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

Investigational Medicinal Products

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

Pertuzumab (intravenous infusion)

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

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

Non-Investigational Medicinal Products

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

Trastuzumab

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

Taxane Chemotherapy

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

Statistical Methods

Primary Analysis

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

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

Safety Data Analysis

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

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

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

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

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

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

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

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

Efficacy analyses

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

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

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

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

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

Other analyses

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

Quality of Life

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

Subgroups analyses

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

Determination of Sample Size

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

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

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

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

Interim Analyses

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

There will also be a review of safety data by the Independent Data Monitoring Committee (IDMC) *approximately once per year* following completion of enrollment.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

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

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

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

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

1.2 BACKGROUND ON STUDY TREATMENTS

1.2.1 Human Epidermal Growth Factor Receptors (HER)

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

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

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

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

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

1.2.1.1 Pertuzumab (RhuMAb 2C4)

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

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

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

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

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

combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

See the *Perjeta* Investigator Brochure for details on nonclinical and clinical studies.

1.2.1.2 Trastuzumab (rhuMAb HER2, Herceptin®)

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

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

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

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

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

1.2.2 Taxanes

Taxanes are anti-neoplastic agents that bind to free tubulin within the cell and promote the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This mode of action leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, blocking cells in the M-phase of the cell cycle and leading to cell death. Extensive

Phase II and III data have led to regulatory approvals for its use either in combination or as monotherapy for the treatment of breast cancer.

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

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

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

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

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

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

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

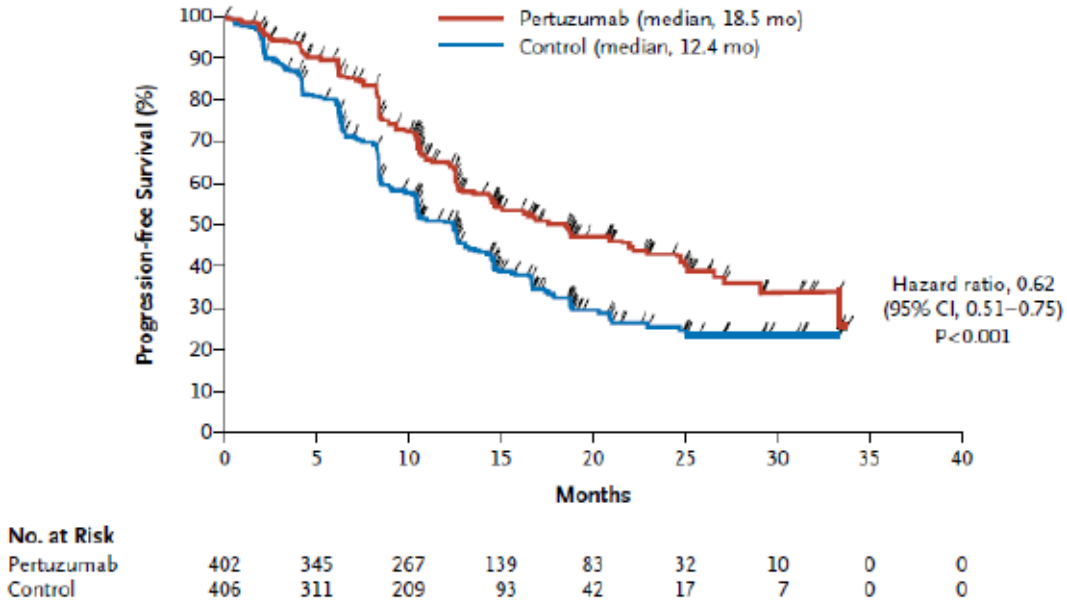


Figure 1Independently assessed progression-free survival in the CLEOPATRA trial

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

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

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

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

In CLEOPATRA, left ventricular systolic dysfunction (any grade) was reported more frequently in the control group than in the pertuzumab group (8.3% vs. 4.4%). Left

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

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

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

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

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

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective for this study is as follows:

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

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

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

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

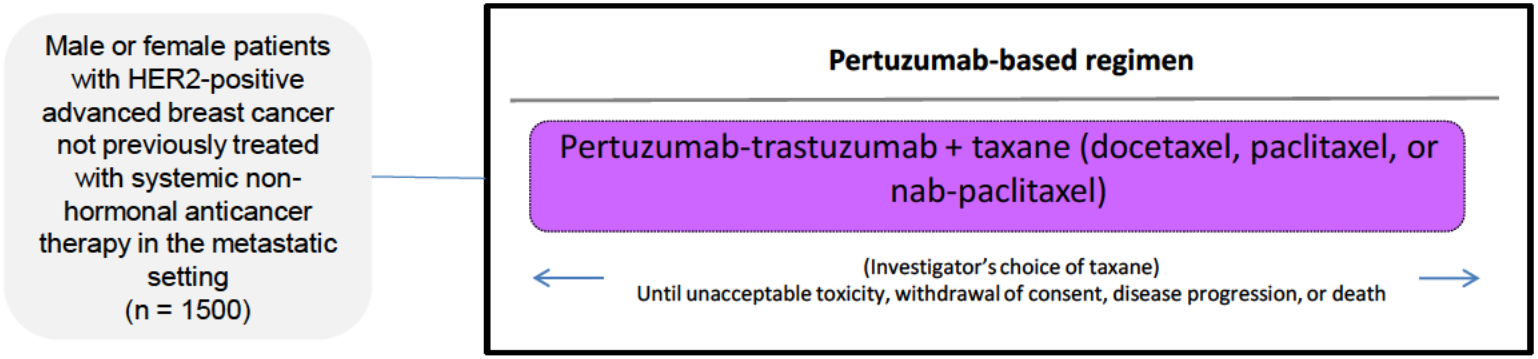
This study is an open-label, single-arm, multicenter Phase IIIb study to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane. Patients with HER2-positive advanced breast cancer (metastatic or locally recurrent) who have not previously received systemic non-hormonal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

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

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

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

Figure 2Study Design



3.1.1 Independent Data Monitoring Committee

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

There will also be a review of safety data by the IDMC approximately once per year following completion of enrollment.

3.2 END OF STUDY

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

3.3 RATIONALE FOR STUDY DESIGN

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

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

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

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

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

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

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

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

3.4.3 Patient-Reported Outcome Measures

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

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

4. MATERIALS AND METHODS

4.1 PATIENTS

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

4.1.1 Inclusion Criteria

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

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

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

4.1.2 Exclusion Criteria

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

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

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

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

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Not applicable, the study is open-label.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

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

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

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

Local packaging in some countries may be different.

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

4.3.1.1 Pertuzumab

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

For further details, see the Perjeta Investigator Brochure.

4.3.1.2 Trastuzumab

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

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

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

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

4.3.1.3 Taxanes

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

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

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Pertuzumab

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

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

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

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

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

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

4.3.2.2 Trastuzumab

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

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

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

4.3.2.3 Taxanes

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

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

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

4.3.3 Investigational Medicinal Product Accountability

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

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

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

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

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

4.3.4 Continued Access to Pertuzumab

The Sponsor will offer continued access to pertuzumab (the Roche IMP) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive the Roche IMP (pertuzumab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive the Roche IMP (pertuzumab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)

- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for HER2-positive advanced (metastatic or locally recurrent) breast cancer
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for HER2-positive advanced (metastatic or locally recurrent) breast cancer
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

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

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

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

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

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

The following treatments/procedures are permitted:

- Paracetamol (acetaminophen) or other analgesics, and diphenhydramine, chlorpheniramine, or other antihistamines can be used according to local clinical practice for the prevention and treatment of infusion reactions associated with pertuzumab and/or trastuzumab.
- Medication to treat diarrhea (e.g., loperamide).
- Granulocyte colony stimulating factor (G-CSF) may be used according to the product license and according to the currently approved prescribing information for docetaxel and ASCO clinical guidelines (Smith et al. 2006).

- Steroids for docetaxel premedication and anti-emetics according to routine practice at each clinical site.
- Steroids, antihistamines, and H2-receptor antagonists for paclitaxel premedication according to routine practice at each clinical site.
- Inhaled steroids for asthma.
- Bisphosphonates may be given according to their product license and routine clinical practice, at the investigator's discretion.
- Palliative surgical procedures. Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded including the dates, description of the procedure(s), and any clinical findings. In the case of surgery during the study, patients should have recovered from surgery and anesthesia (including liver functions) for a minimum of 14 days before antibody treatment.
- As a precautionary measure, it is recommended, but not strictly required, that if patients require placement of a central venous access device (CVAD), the procedure should be done 7 days prior to first study treatment start.
- The date of CVAD placement should be noted in the medical record and recorded in the eCRF. Episodes of CVAD replacement should be recorded, as should CVAD-related thrombosis, infection, or dysfunction.
- Anti-coagulation therapy for maintenance of patency of permanent indwelling intravenous catheters is permitted.
- Palliative radiotherapy. Radiotherapy will be allowed during the study treatment period for the indication of bone or breast lesions present at baseline as long as the lesion is not a target lesion. If a patient requires radiation therapy to a new lesion, that new lesion would, per RECIST, qualify as progressive disease. Radiotherapy will also be permitted for new brain metastases that are treatable with radiation in patients who have visceral disease control (defined as patients having received clinical benefit (i.e., PR or CR of any duration, or stable disease for ≥ 4 months). These patients will be allowed to continue to receive study therapy until they either experience systemic progression of their disease and/or further progression in the brain (based on investigator assessments). Patients must not miss more than one cycle for the treatment of their brain disease and must have an ECOG performance status of 0 or 1 to continue on therapy. For the purposes of the PFS analysis, progression will be recorded on the date when the isolated brain metastasis was documented.
- Approved endocrine therapies only after discontinuation of chemotherapy.

4.4.2 Prohibited Therapy

The following treatments are not permitted:

- Treatment with other systemic anticancer agents (e.g., chemotherapy, immunotherapy) or other treatments not part of protocol-specified anticancer

therapy. Note: Approved endocrine maintenance therapies will be permitted only after discontinuation of chemotherapy.

- Radiotherapy for unequivocal progressive disease with the exception of new brain metastases (see Section 4.4.1).
- Any oral, injected or implanted hormonal methods of contraception.
- Concurrent investigational agents of any type.
- Initiation of herbal remedies for cancer treatment. Herbal remedies initiated prior to study entry and continuing during the study are permitted and must be reported on the appropriate eCRF.

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

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

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

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

4.5.1.1 Medical History and Demographic Data

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

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

4.5.1.2 Vital Signs

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

4.5.1.3 Physical Examinations

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

At subsequent visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient

notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

4.5.1.4 Tumor and Response Evaluations

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

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

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

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

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

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

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

Scheduling of tumor assessments

Baseline total tumor burden must be assessed within a maximum of 28 days before first dose of study drug treatment. Post-baseline assessments are to be performed every three treatment cycles up to 36 months, and at least every 12 cycles (or more frequently as dictated by patient needs and/or routine practice or local requirements/policy) thereafter for patients who remain progression free after 36 months. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.

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

Instructions for scans in the event of isotope shortage

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

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

4.5.1.5 Left Ventricular Ejection Fraction Assessment

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

4.5.1.6 Performance Status

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

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

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

4.5.1.7 Laboratory Assessments

Samples for laboratory tests will be assessed locally.

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

Specifically:

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

4.5.1.8 Electrocardiograms

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

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

4.5.1.9 Patient-Reported Outcomes

PRO data will be elicited from the patients in this study to more fully characterize the clinical profile of pertuzumab. The PRO instruments (FACT-B), translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

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

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

will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

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

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

4.5.2.2 Assessments during Treatment

During the treatment period, the following assessments must be performed

- Vital signs and weight: every treatment cycle prior to administration of study drug with pulse rate, body temperature and blood pressure again after infusion during the observation period of each study medication.
- Infusion reactions: every treatment cycle during infusion and observation period
- Hematology, biochemistry and coagulation (if indicated): every treatment cycle ≤3 days (with results available) prior to administration of study drug
- Concomitant medication and SAEs/AEs: every treatment cycle
- Pregnancy test and ECG: every 3 cycles of monoclonal antibody ≤3 days (with results available) prior to administration of study drug
- LVEF: every 3 cycles of monoclonal antibody ≤7 days (with results available) prior to administration of study drug
- ECOG performance status and quality of life: every 3 cycles of monoclonal antibody (±7 days)
- Tumor evaluation: every 3 cycles of monoclonal antibody up to 36 months and at least every 12 cycles (or more frequently as dictated by patient needs and/or routine practice or local requirements/policy) thereafter in those who remain progression free
- Physical examination and brain CT/MRI: if clinically indicated

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

4.5.2.3 Assessments at Post-treatment Safety Follow-up

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

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

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

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

4.5.2.4 Follow-Up Assessments

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

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

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

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

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

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

- Investigator or Sponsor determines it is in the best interest of the patient.

4.6.1.1 Discontinuation from Study Drug

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

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

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

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

4.6.1.2 Withdrawal from Study

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

4.6.2 Study and Site Discontinuation

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

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

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

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

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

The pertuzumab dose should not be adjusted for body weight.

5.1.1 Toxicity Management Guidelines

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

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

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

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

5.1.1.1 Cardiac Safety

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

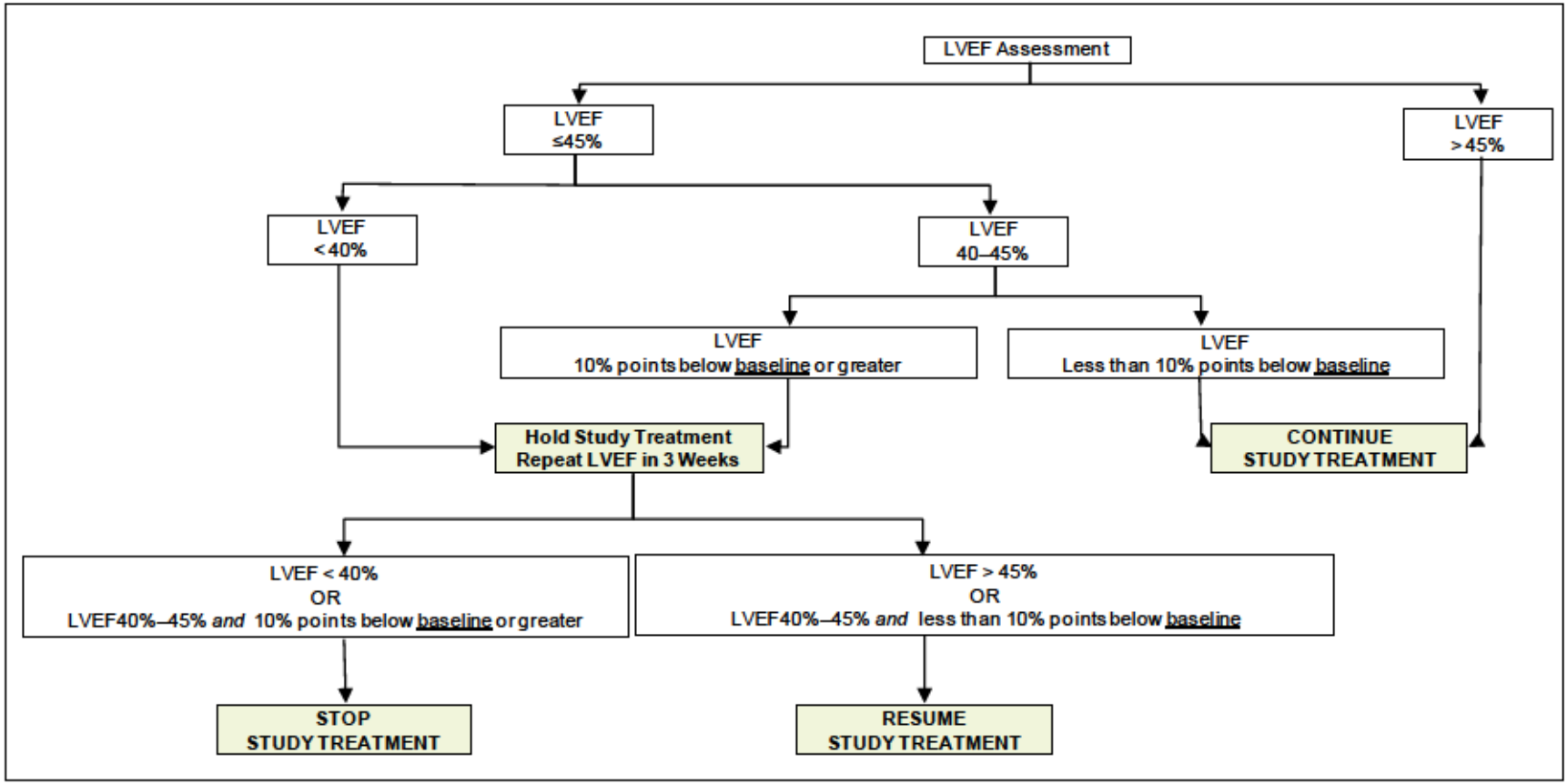
At present, there are inadequate data available to assess the prognostic significance of asymptomatic drops of LVEF. However, to ensure the safety of patients in the trial, pertuzumab and trastuzumab must be discontinued in all patients for whom a drop of LVEF to a value lower than 40% is documented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

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

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

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

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



5.1.1.2 Infusion-Related Reactions and Allergic Reactions

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

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

Patients who experience IRRs 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 IRRs occur, patients will be monitored until complete resolution of signs and symptoms.

5.1.1.3 Incomplete Loading Dose

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

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

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

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

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

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

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

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

5.1.1.4 Pertuzumab

Risk of Allergic Reactions, Including Anaphylaxis and Infusion-Related Reactions

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

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

- within 24 hours following pertuzumab infusion

were presented as IRRs, whether considered related or unrelated to pertuzumab by the investigator.

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

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

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

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

The Perjeta Investigator Brochure should be referred to for most recent data relating to risk of allergic reactions.

Risk of Cardiotoxicity

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

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

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

Monitoring of LVEF is required while patients are receiving study treatment. If symptomatic left ventricular dysfunction develops (NCI-CTCAE version 4.0 Grade 3 or 4) with a drop in LVEF consistent with cardiac failure, the patient must discontinue study treatment. Left ventricular dysfunction, whether symptomatic or not, should be treated and followed according to standard medical practice.

The Perjeta Investigator Brochure should be referred to for most recent data relating to risk of cardiotoxicity.

Risk of EGFR-Related Toxicities

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

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

Rash has also been observed with EGFR tyrosine kinase inhibitors.

The Perjeta Investigator Brochure should be referred to for most recent data relating to risk of EGFR-related toxicities.

5.1.1.5 Trastuzumab

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

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

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

Infusion Reactions, Allergic-Like Reactions, and Hypersensitivity

Serious adverse reactions to trastuzumab infusion that have been reported infrequently include dyspnea, hypotension, wheezing, bronchospasm, asthma tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, and angioedema. The majority of these events occur during or within 2.5 hours of the start of the first infusion.

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

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

Pulmonary Events

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

Cardiotoxicity

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

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

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

Most patients who developed heart failure in the Phase III trials of trastuzumab in MBC improved with standard medical treatment. This treatment included diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on weekly therapy with trastuzumab without additional clinical cardiac events.

5.1.1.6 Taxanes

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

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

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

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

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

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

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

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

5.1.2 Management of Specific Adverse Events

5.1.2.1 Pregnancy

See Section 5.4.3 for details of pregnancy during the study.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and adverse events of special interest (AESI); 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 5.3.5.10.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.2.2 Serious Adverse Events (Immediately Reportable to The Sponsor)

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

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

  This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11).
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

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

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

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

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

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

AESI for this study include the following:

- Asymptomatic declines in LVEF requiring treatment or leading to discontinuation of monoclonal antibodies
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7).
- Suspected transmission of an infectious agent by the study drug, as defined below

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting SAEs).

After initiation of study drug, all AEs will be reported until 28 days after the last dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in 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 timepoints. Examples of non-directive questions include the following:

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

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

5.3.3 Assessment of Severity of Adverse Events

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

Table 1 Adverse Event Severity Grading Scale

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

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

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a 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 Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction anaphylactic reaction.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events Occurring Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at

the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

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

5.3.5.5 Abnormal Laboratory Values

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

- Is 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.
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as AEs.

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the 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 only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent AEs).

5.3.5.6 Abnormal Vital Sign Values

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

- *Is 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.
- *Is c*linically significant in the investigator's judgment.

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should *only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent AEs).*

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

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

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

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

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Breast Cancer

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care.

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

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

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

5.3.5.12 Overdoses

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

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

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

5.3.5.13 Patient-Reported Outcome Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- SAEs (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements).
- AESI (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements).
- Pregnancies (see Section 5.4.3 for details on reporting requirements).

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

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

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

5.4.1 Emergency Medical Contacts

MEDICAL MONITOR (SPONSOR MEDICAL RESPONSIBLE) CONTACT INFORMATION

Primary Contact

Medical Monitor: [redacted] MD

Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: [redacted] MD

Telephone No.: [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 (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

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

5.4.2.1 *Events That Occur prior to Study Drug Initiation*

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, SAEs and AESI will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event 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, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting SAEs that occur >28 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

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

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

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

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

5.4.3.2 Pregnancies in Female Partners of Male Patients

Experimental studies have reported that IgGs are present in both the pre-ejaculate and the seminal plasma (Moldoveanu et al. 2005). To date, there have been no clinical studies to assess the IgG profile in the pre-ejaculate and seminal plasma in male patients receiving pertuzumab or trastuzumab. Therefore, as a precaution, male patients with female partners of childbearing potential are required to use to use one highly effective form of contraception (such as surgical sterilization) or use two effective forms of contraception (such as a barrier method of contraception in conjunction with spermicidal jelly).Similarly, vaginal absorption of pertuzumab is unknown and therefore male patients with pregnant partners are required to use condoms for the duration of the pregnancy, and then revert to contraceptive methods as outlined above. This is to ensure that the fetus is not exposed to the study medication through vaginal absorption. Similarly, sperm donation should not occur for at least 7 months after the last dose of study treatment.

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

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

5.4.3.3 Abortions

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow-Up

For SAEs, AESI, 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 Adverse Events That Occur After The Adverse Event Reporting Period

After the end of the AE reporting period (defined as 28 days after the final dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a SAE that is believed to be related to prior exposure to study drug, the event should be reported through use of the

Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 REVIEW OF SAFETY BY AN INDEPENDENT DATA MONITORING COMMITTEE

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

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

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

The Sponsor will promptly evaluate all SAEs and AESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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

- Perjeta Investigator Brochure

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

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

Further details will be provided in the statistical analysis plan.

6.1 DETERMINATION OF SAMPLE SIZE

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

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

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

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

6.2 SUMMARIES OF CONDUCT OF STUDY

The major protocol deviations will be summarized by frequency tables.

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

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

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

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

6.4 EFFICACY ANALYSES

Analysis of efficacy is a secondary endpoint in this study.

6.4.1 Efficacy Endpoints

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

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

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

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

6.5 SAFETY ANALYSES

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

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

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

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

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

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

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

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

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

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

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

6.6 PATIENT-REPORTED OUTCOME ANALYSES

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

6.7 INTERIM ANALYSES

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

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the Roche policy for retention of records.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB or IEC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; Appendix 2). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB or IEC submission. The final IRB or IEC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB or IEC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB or IEC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was

obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INDEPENDENT ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB or IEC by the Principal Investigator and reviewed and approved by the IRB or IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB or IEC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB or IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB or IEC. Investigators are also responsible for promptly informing the IRB or IEC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB or IEC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities,

Sponsor monitors, representatives, and collaborators, and the IRB or IEC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (where study completion is defined as at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB or IEC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by The Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB or IECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

An IxRS system will be used for enrollment of patients into the study.

A CRO will be used for data management (see Section 7.1).

Assessment of laboratory test results will be performed locally.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Investigators are responsible for promptly informing the IRB or IEC of any amendments to the protocol. Approval must be obtained from the IRB or IEC before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Assessments

	Screening	Baseline* (Enrolment)	Treatment period (all visits within ± 7 days of scheduled treatment day)	Post-treatment follow-up after study treatment termination	
	Day -28 to Day 1	Day -7 to Day 1	Each Treatment Cycle**	One month post-treatment safety follow-up (28 days [±5 days] after end of study treatment)[14]	~3-monthly post-treatment follow-up visits
Informed consent	X				
Demographics & medical history[1]	X				
Concomitant medication[2]	X	X	X	X	
Physical examination[3]		X	If clinically indicated	X	
Vital signs and blood pressure[3]		X	X	X	X
Height		X			
Weight[3]		X	X		
Pregnancy test[4]		X	Every 3 cycles of monoclonal antibody ≤3 days (with results available) prior to administration of study drug	X	4 and 7 months after treatment discontinuation

	Screening	Baseline* (Enrolment)	Treatment period (all visits within ± 7 days of scheduled treatment day)	Post-treatment follow-up after study treatment termination	
	Day -28 to Day 1	Day -7 to Day 1	Each Treatment Cycle**	One month post-treatment safety follow-up (28 days [±5 days] after end of study treatment)[14]	~3-monthly post-treatment follow-up visits
HER2 [5]	If positive HER2 result not available				
Tumor evaluation[6]	X		Every 3 cycles of monoclonal antibody up to 36 months, and at least every 12 cycles (or more frequently as dictated by patient needs and/or routine practice or local requirements/policy) thereafter for patients who remain progression free after 36 months	If disease progression not yet established	At least every 36 weeks if progression free after 36 months (or more frequently as dictated by patient needs and/or routine practice or local requirements/policy)
Hematology[7]		X	≤3 days (with results available) prior to administration of study drug	X	

	Screening	Baseline* (Enrolment)	Treatment period (all visits within ± 7 days of scheduled treatment day)	Post-treatment follow-up after study treatment termination	
	Day -28 to Day 1	Day -7 to Day 1	Each Treatment Cycle**	One month post-treatment safety follow-up (28 days [±5 days] after end of study treatment)[14]	~3-monthly post-treatment follow-up visits
Biochemistry[7]		X	≤3 days (with results available) prior to administration of study drug	X	
Coagulation[7]		X	If clinically indicated: ≤3 days (with results available) prior to administration of study drug	X	
Standard 12-lead ECG[8]	X		Every 3 cycles of monoclonal antibody ≤3 days (with results available) prior to administration of study drug	X	
LVEF[9]	X		Every 3 cycles of monoclonal antibody ≤7 days (with results available) prior to administration of study drug	X	

	Screening	Baseline* (Enrolment)	Treatment period (all visits within ± 7 days of scheduled treatment day)	Post-treatment follow-up after study treatment termination	
	Day -28 to Day 1	Day -7 to Day 1	Each Treatment Cycle**	One month post-treatment safety follow-up (28 days [±5 days] after end of study treatment)[14]	~3-monthly post-treatment follow-up visits
Brain CT/MRI[10]	X		If clinically indicated	If clinically indicated	If clinically indicated
ECOG performance status		X	Every 3 cycles of monoclonal antibody	X	
SAEs and AEs[11]	X	X	X	X	X
Quality of life (FACT-B)[12]		X	Every 3 cycles of monoclonal antibody	X	X
Administration of study medication			X		
Infusion reactions during infusion and observation period			X		
Survival[13]	X	X	X	X	X
Record anticancer medical or surgical procedures and therapies					X

* Baseline/ Screening assessments are allowable on Day 1 of first treatment cycle pre-dose as long as the results are available prior to enrolment

** Cycle = 3 weeks for monoclonal antibodies

Notes

1. Complete medical history and demographics (i.e. age, sex, race, and ethnicity, if applicable) and all medications taken the last 28 days prior to 1st study drug administration (dosing) will be collected.

2. Current concomitant medication will be recorded at baseline and on an ongoing basis.

3. Physical examination, including vital signs will be performed prior to enrolment with particular care taken with regard to cardiovascular signs and symptoms (e.g. elevated jugular venous pressure, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.). Vital signs will be assessed before treatment on Day 1 of every treatment cycle (pertuzumab, trastuzumab, and chemotherapy), with blood pressure, pulse rate, and body temperature recorded again after infusion during the observation period of each study medication.

4. Pregnancy tests must be performed for all WOBP (premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization). Baseline pregnancy test must be performed by serum β-HCG. Urine or serum pregnancy test must be performed every 3rd cycle within 3 days (with results available) prior to the administration of study medication, at the 1-month post-treatment safety FU visit, and at four and seven months after last dose of study medication. Any positive urine pregnancy test to be confirmed by serum β-HCG.

5. Demonstrated evidence of HER2 positive status from previous testing is acceptable, otherwise HER2-positive status on fixed tissue blocks from the primary tumor (and/or metastatic site, if primary tumor not available) to be assessed locally by IHC and/or ISH according to institutional criteria.

6. A CT or MRI and (if indicated) isotope bone scan (evaluation according to RECIST criteria) should be performed at screening and as clinically indicated. Scans at screening should not be older than 28 days prior to first study medication administration. To be performed post-study treatment only if disease progression has not yet been established. NB: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.

7. Assessment must be performed within 3 days (with results available) prior to the administration of study medication. Hematology will include hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, other cells). Biochemistry will include sodium, potassium, calcium, chloride, magnesium, BUN (or urea), uric acid, total protein, albumin, alkaline phosphatase, ALT, AST, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin, creatinine, and blood glucose. Calculated creatinine clearance to be determined at baseline only. All patients will have INR and aPTT or PTT testing at baseline. Tests will be repeated at each treatment cycle in all patients receiving therapeutic doses of anti-coagulants. Assessment of coagulation must be performed within 3 days (with results available) prior to the administration of study medication.

8. Two ECG recordings, taken two minutes apart, must be obtained at the screening visit, and every three cycles of monoclonal antibody therapy during the treatment period, ≤3 days (with results available) prior to administration of study drug (where possible at the time of LVEF measurement). ECG at safety follow-up visit to mirror ECHO/MUGA.

9. LVEF ≥ 50% at Screening period to be determined by either ECHO or MUGA scan (with ECHO as the preferred method). The same method of LVEF assessment (ECHO or MUGA) must be used for the same patient throughout the study and, to the extent possible, be obtained at the same institution. All pre-study LVEF values during and following trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrolment into the study will be collected. LVEF assessment (ECHO or MUGA) done within 42 days prior to screening does not need to be repeated. To be performed every three cycles of monoclonal antibody therapy ≤7 days (with results available) prior to administration of study drug during the treatment period and at safety follow-up. If the previous assessment showed any abnormality, assessments should be performed until resolved.

10. A CT or MRI brain scan is to be performed at screening only in patients with clinical suspicion of brain metastases, and during the study if clinically indicated. If the patient has had recent radiotherapy (within 28 days prior to 1st study drug administration (dosing), the existing CT scan can be used for baseline.

11. After informed consent, but prior to initiation of study medications, only SAEs considered to be related to a protocol-mandated intervention will be collected. Adverse events to be monitored continuously during the treatment period. All AEs occurring during the study and until the treatment discontinuation visit 28 days after last study medication are to be recorded with grading according to NCI-CTCAE, Version 4.0, and thereafter all study drug-related SAEs should continue to be collected.

12. Quality of life will be assessed using the FACT-B questionnaires completed by the patient (FACT-B only by female patients). FACT-B has a 28-item generic score for all patients, plus nine items specific to breast cancer. Patients rate items on a five-point scale ranging from 'not at all' to 'very much'. FACT-B provides a total QoL score as well as information about physical well-being, social/family well-being, functional well-being, and disease-specific concerns. FACT-B provides supplemental domain valuative ratings or utility weights thus providing an estimate of the relative importance of each quality of life domain to an individual patient.

13. Survival status will be recorded during the treatment period and every 3 months after the one month post-treatment safety follow-up visit until at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by Roche, whichever occurs first.

14. The visit at which response assessment shows progressive disease may be used as the post-treatment safety follow-up visit.

Appendix 2 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- Is fatal; [results in death] [NOTE: death is an outcome, not an event].
- Is life-threatening [NOTE: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe].
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For SAEs, possible causes of the event **are** indicated by selecting one or more options. (Check all that apply)

- Preexisting/underlying disease - specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g. accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

Such preliminary reports will be followed by detailed descriptions later, which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For SAEs, the following must be assessed and recorded on the AEs page of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the IRB or IEC of an SAE in writing as soon as is practical and in accordance with international and local laws and regulations.

SPONSOR LOCAL COUNTRY CONTACT for SAEs: Local Monitor.

SPONSOR HEADQUARTERS CONTACT for SAEs and other medical emergencies: Contact information for the Contract Research Organization responsible for drug safety will be provided separately.

24 HOUR MEDICAL COVERAGE

Identification of a contact for 24 Hour Medical Coverage is mandatory to be compliant with worldwide Regulatory Agencies and to ensure the safety of study patients.

An Emergency Medical Call Center Help Desk will access the Sponsor Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with the Sponsor medical contact for this study and track all calls. The Emergency Medical Call Center Help Desk will be manned 24 hours 7 days a week. Toll-free numbers will be distributed to all investigators participating in this clinical trial. The Help Desk will be used for medical emergencies outside regular business hours, or when the regular International Medical Leader cannot be reached.

See the Protocol Administrative and Contact Information & List of Investigators form for details of administrative, contact information, and Emergency Medical Call Center Help Desk toll-free numbers. This information will be provided separately.

Appendix 3 ECOG Performance Status

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 4 NYHA Classification and Left Ventricular Systolic Dysfunction NCI CTCAE version 4.0 Grading

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

Oxford textbook of internal medicine. Vol 2, pp 2228. Oxford University Press. 1997

Left Ventricular Systolic Dysfunction NCI-CTCAE Version 4.0 Grading

Grade 1	-
Grade 2	-
Grade 3	Symptomatic due to drop in ejection fraction responsive to intervention.
Grade 4	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated.
Grade 5	Death.

Common Terminology Criteria for Adverse Events. Version 4.0. Published May 28, 2009 (v4.03: June 14, 2010). US Department of Health and Human Services, National Institutes of Health, National Cancer Institute (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE-4.03-2010-06-14-QuickReference-5x7.pdf).

Appendix 5 Tumor Assessments (RECIST) version 1.1 (Eisenhauer et al. 2009)

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot accurately be measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease-specific, instructions for their measurement should be incorporated into protocols on a disease-specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease: To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above). In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is

restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm·x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

Evaluation of target lesions:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation.

The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Appendix 6 FACT-B

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4