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

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STATISTICAL ANALYSIS PLAN

MO28047

A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY OF PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AND A TAXANE IN FIRST-LINE TREATMENT OF PATIENTS WITH HER2- POSITIVE ADVANCED (METASTATIC OR LOCALLY RECURRENT) BREAST CANCER

AUTHOR: [redacted]

VERSION NUMBER AND DATE: FINAL VERSION 2.0, 25NOV2019

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final Version 2.0 (Dated 25NOV2019) for Protocol MO28047 amendment version 6.0 (Dated 21NOV2018).

	Name	Signature	Date
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Position:	[redacted]		
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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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2.0	25NOV2019	[redacted]	Updated to final version 2.0 for final signatures prior to database lock

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LIST OF ABBREVIATIONS

Abbreviation	Definition
aPTT	Activated partial thromboplastin time
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGPT)	Alanine aminotransferase
AST (SGOT)	Aspartate aminotransferase
BOR	Best (confirmed) overall response
BPM	Beats per minute
CBR	Clinical benefit rate
CHF	Congestive heart failure
CI	Confidence interval
CM	Centimeter
CR	Complete response
CT	Computed tomography
CTC	Common terminology criteria
DBL	Database lock
DFI	Disease-free interval
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
ER	Estrogen receptor
FACT	Functional assessment of cancer therapy
FACT-B	Functional assessment of cancer therapy for patients with breast cancer
FDA	Food and drug administration
GGT	Gamma-glutamyl transpeptidase
HER2	Human epidermal growth factor receptor 2
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INN	International non-proprietary name
ISH	In situ hybridization
ITT	Intent-to-treat
IxRS	Interactive voice response system
KG	Kilogram
KM	Kaplan-Meier
LDH	Lactate dehydrogenase

Abbreviation	Definition
LFT	Liver function test
LLQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
Min	Minimum
mm	Millimeter
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
msec	Millisecond
NCI-CTC	National cancer institute common terminology criteria
NCI-CTCAE	National cancer institute common terminology criteria for adverse events
NE	Not evaluable
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDMS	Project deviation management system
PFS	Progression-free survival
PgR	Progesterone receptor
PP	Per-protocol
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
PTT	Partial thromboplastin time
PV	Protocol violation
QoL	Quality of life
RECIST	Response evaluation criteria in solid tumors
RBC	Red blood cells
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SCR	Screened population
SD	Stable disease
SMQ	Standardized MedDRA query
SOC	System organ class

Abbreviation	Definition
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TTR	Time to response
ULN	Upper limit of normal
ULQ	Upper limit of quantification
WBC	White blood cells

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol MO28047. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol MO28047 amendment version 6.0, 21NOV2018.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective for this study is to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane.

2.2. SECONDARY OBJECTIVES

The secondary objectives are 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 (DOR)
- Time to response (TTR)
- Quality of life (QoL) (Functional Assessment of Cancer Therapy-Breast [FACT-B] questionnaire for female patients only).

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This study is an open-label, single-arm, multicenter Phase IIIb trial to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane. 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 are eligible to participate in the study.

Approximately 1500 patients will be enrolled into the study in approximately 250-300 centers worldwide over approximately 18 months.

Pertuzumab is considered to be the investigational medicinal product (IMP) in this study. Trastuzumab and taxane chemotherapy (docetaxel, paclitaxel or nab-paclitaxel) are considered to be non-IMPs in this study.

Patients will receive study treatment until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurs first. 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, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

3.1.1. STUDY DESIGN

The study design is presented in Figure 1:

Figure 1: Study Design

3.1.2. Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- PFS, defined as the time from the date of enrollment until the first radiographically documented progression of disease or death from any cause, whichever occurs first. Clinical progression in the absence of radiographic progression will also be considered as a sensitivity analyses.
- 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 (confirmed) overall response (BOR) recorded from the date of first dose of study treatment until disease progression/recurrence or death and confirmed ≥ 4 weeks later.
- CBR includes patients whose BOR was PR or CR or stable disease (SD) that lasts at least 6 months.
- DOR defined as the period from the date of initial confirmed PR or CR until the date of progressive disease (PD) or death from any cause.
- TTR for patients with a BOR of CR or PR, defined as the time from the date of enrollment to the date of first CR or PR.

3.1.3. Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity by National Cancer Institute Common Terminology Criteria (NCI-CTC) for AEs (NCI-CTCAE) version 4.0 of adverse events (AEs) and serious AEs (SAEs)
- Incidence of congestive heart failure (CHF)
- Left ventricular ejection fraction (LVEF) over the course of the study
- Laboratory test abnormalities (hematology, biochemistry and coagulation)

3.1.4. Patient-Reported Outcome Measures

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

- QoL, which will be assessed using the FACT-B questionnaire for female patients only (see Appendix 6 in the protocol).

3.1.5. 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 1:).

Table 1: 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%

3.1.6. SCHEDULE OF ASSESSMENTS

Schedule of assessments can be found in Appendix 1 of the protocol.

3.2. CHANGES TO ANALYSIS FROM PROTOCOL

- The protocol states that a subgroup analysis by country will be performed. However, due to the low number of events within certain countries, this subgroup of interest within analysis will be dropped entirely

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analysis for Independent Data Monitoring Committee (IDMC)
- Final analysis
- Additional summaries and analyses may be created for the purposes of publications; further details will not be covered in this SAP but may be provided in a separate document

This is an open-label single arm study, hence there will be no blinding for the entire study team

4.1. INDEPENDENT DATA MONITORING COMMITTEE (IDMC) REVIEW

An IDMC has been established for the study and specific policies on the operation of the IDMC have been documented in an IDMC Charter. The IDMC is 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.

Data cut-offs for the IDMC review will be defined for each reporting event during the study and displayed in the header of each statistical output. The data cut-off will keep all data which occurs on or before the data cut-off date and will use visit dates and start dates as references. The cut-off dates of the IDMCs are defined as the time when at least 100, 350, 700, 1100 and 1500 patients have been enrolled and received at least 2 cycles of study treatment. All data will be cleaned and checked for completeness in respect to safety events (SAEs, deaths, withdrawals, AEs of special interest [AESI] and study treatment exposure) and other data of interest. Efficacy summaries will be provided to the IDMC only if requested by the IDMC members. There will also be review of safety data by the IDMC approximately once per year following completion of enrollment.

Full details of the IDMC can be found in the IDMC charter.

4.2. INTERIM ANALYSIS

This is a single arm study with primary safety endpoints. There will be no formal interim analyses planned for this study, other than the IDMC analyses described above.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by [redacted] Biostatistics following Sponsor authorization of this SAP, Database Lock (DBL) and Sponsor authorization of the analysis populations.

The final analysis will be done at least 60 months after the last patient has been enrolled into the study or when all patients in the study have withdrawn consent, are lost to follow up or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first. All data available in the database until the date of clinical cut-off will be included in the analysis.

5. ANALYSIS POPULATIONS

The patients included/excluded from each analysis population will be agreed upon prior to study database lock and authorized by the sponsor immediately following database lock, before any analysis is done.

5.1. SCREENED [SCR] POPULATION

The screened (SCR) population will contain all patients who provide informed consent for this study.

Screen failure patients will be defined as patients who provide informed consent but who were reported as not fulfilling the inclusion or exclusion criteria according to the final protocol. These patients will be included in the SCR population but will be excluded from all other populations.

5.2. SAFETY [SAF] POPULATION

The safety (SAF) population will contain all enrolled patients who receive at least one dose of study treatment (pertuzumab and/or trastuzumab and/or taxane). The SAF will be the primary analysis population and will be used for all safety analysis.

5.3. INTENT-TO-TREAT [ITT] POPULATION

The intent-to-treat (ITT) population will contain all patients enrolled in the study. The ITT will be used for all efficacy analysis.

5.4. PER-PROTOCOL [PP] POPULATION

The per-protocol (PP) population will contain all ITT patients who did not have any major protocol deviations (see section 5.4.1). The PP will be used for supportive analyses of PFS and OS as described in section 17.

5.4.1. MAJOR PROTOCOL DEVIATIONS

Major protocol deviations are those which could severely impact patient safety, efficacy of the treatment regimen and the study analysis. These will be documented and explained by investigators in the final protocol deviations manual.

Major protocol deviations will include the following:

- Patient entered the study but did not satisfy the eligibility criteria (see section 4.1.1 and 4.1.2 in the protocol)
- Patient developed criteria for withdrawal from study treatment or from the overall study but was not withdrawn
- Patient received the wrong treatment dose
- Patient received a prohibited concomitant medication
- Patient received trastuzumab biosimilar

Protocol deviations will be collected using the PD99 form according to the old process and the PDMS (Project Deviation Management System) according to the new process. The two different sources of protocol deviations data will be imported into the analysis datasets separately, before output programming begins. See APPENDIX 7 for full details on the derivations. The list of inclusion and exclusion criterion that a patient did not fulfil will be provided by the IxRS vendor, [redacted].

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

The reference start date (Study Day 1) is defined as the day of the first dose of study treatment (pertuzumab and/or trastuzumab and/or taxane).

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Study Day will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference start date, then:

- Study Day = (date of event – reference start date) + 1

If the date of the event is prior to the reference start date, then:

- Study Day = (date of event – reference start date)

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear partial or missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Measurements taken on the date of first dose of study treatment will be considered as pre-dose, with the exception of AEs and non-study treatments, which will be considered as post-dose.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the worst-case value where required (e.g. shift table).

In the case of a retest (same visit/cycle number assigned), the worst assessment will be used in the summaries.

Listings will include scheduled, unscheduled and retest data.

6.4. WINDOWING CONVENTIONS

Unscheduled visits are not used within any visit-based summaries, so no windowing will be applied to these assessments.

If the date of assessment is before the date of first study treatment (pertuzumab and/or trastuzumab and/or taxane) administration, the analysis visit will be assigned as follows:

- 'Baseline' if the assessment will be used for baseline
- 'Screening' otherwise

6.5. STATISTICAL TESTS

There are no formal statistical hypothesis tests to be performed. There are no type 1 error (alpha error) adjustments for multiplicity of endpoints or within-subgroups comparisons.

6.6. COMMON CALCULATIONS

The following calculations apply for this study:

For quantitative measurements, change from baseline will be calculated as:

- Test value at visit X – Baseline value

Duration of events in days will be calculated as follows:

- End date of event – start date of event + 1

Duration of events in weeks will be calculated as follows:

- (End date of event – start date of event + 1) / 7

Duration of events in months will be calculated as follows:

- (End date of event – start date of event + 1) *12 / 365.25

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina) or later.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No adjustment for covariates and factors will be applied for the primary and secondary analysis of this study. Exploratory analyses may use covariates and factors, and these will be detailed in the appropriate sections as applicable.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. A subgroup analysis on geographic region will be performed as described in section 7.5.

Geographic region will be categorized as follows:

Geographic Region	Country
Europe	Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine
Asia	China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates
North America	Canada
South America	Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela
Africa	Algeria, Egypt, Morocco
Other	Australia

7.3. MISSING DATA

Missing safety data will not be imputed except for the missing dates to identify treatment emergent adverse events (see APPENDIX 2).

Missing efficacy data will be handled as described in section 17.

Missing data for FACT-B (Functional Assessment of Cancer Therapy for patients with Breast cancer) questionnaire will be handled according to the calculation rules of the 'FACIT Administration and Scoring Guidelines' document (see APPENDIX 5).

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

There is no adjustment for multiplicity of endpoints or within-subgroups comparisons.

7.5. EXAMINATION OF SUBGROUPS

The following subgroups will be defined for this study:

- Geographic region (see section 0): Europe, Asia, North America, South America, Africa, Other
- Age: >65 vs. ≤65 years
- Eastern Cooperative Oncology Group (ECOG) performance status at baseline: ECOG 0, 1 vs. ECOG 2
- Type of taxane: Docetaxel, paclitaxel or nab-paclitaxel. In case of switch of taxane during the study, the first taxane received will be considered
- Visceral disease at baseline: Yes vs. No. The disease will be considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue is observed during baseline tumor assessment. The disease will be considered as "non-visceral" if all lesions observed at baseline are localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue
- Prior (neo) adjuvant chemotherapy: Yes vs. No
- Hormone receptor status: Positive, Negative, Unknown
- Previous trastuzumab: Yes vs. No

Subgroup analyses will be performed for AEs Grade 3 or higher and other selected safety and efficacy variables. The subgroup analyses for primary and secondary outcomes are presented in Table 2:

Table 2: Subgroup analysis

Subgroup	Disposition	Demographics and Baseline Characteristics	Study Drug Exposure	PFS, OS	ORR, CBR, DOR, TTR, QOL	TEAE Grade ≥3	TEAE Grade ≥3 related to pertuzumab	SAE	Other TEAE	LVEF
Region	Y	Y	Y	Y		Y	Y	Y		
Age	Y	Y	Y	Y	ORR	Y	Y	Y	Related to pertuzumab, Grade 5 (Death), TEAE to Monitor	Y
ECOG performance status at baseline	Y	Y	Y	Y		Y	Y	Y		
Type of taxane	Y	Y	Y	Y	ORR	Y	Y	Y	Related to pertuzumab, Grade 5 (Death), TEAE to Monitor	Y
Visceral disease at baseline	Y	Y	Y	Y		Y	Y	Y		
Prior (neo) adjuvant chemotherapy	Y	Y	Y	Y		Y	Y	Y		
Hormone receptor status	Y	Y	Y	Y		Y	Y	Y		
Previous trastuzumab	Y	Y	Y	Y		Y	Y	Y		

Note: AE to monitor is defined in SAP section 19.1.8.

Note: Exploratory logistic regression analyses for ORR and CBR will use all subgroups. See section 17.3.2 for details.

8. OUTPUT PRESENTATIONS

APPENDIX 1 details conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by [redacted] Biostatistics.

Continuous variables will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum and maximum). For baseline and disease characteristics data, 25th and 75th percentiles will also be presented.

Categorical variables will be summarized by counts and percentages for each category or subcategory where the number of missing counts will be presented where necessary. Percentages will be calculated based on the N values (the number of patients within the analysis population) within the outputs, unless otherwise stated. Note that missing counts will only be presented for categorical variables.

Kaplan-Meier methods will be used to calculate statistics for time to event data. Summaries for the time-to-event data will include the number of patients included in the analysis, number of patients with events, number of patients censored, median, 95% CI for median, minimum, maximum, 25th and 75th percentiles.

Further details are described within each analysis section in this SAP.

9. DISPOSITION AND WITHDRAWALS

Patient disposition and withdrawals will be presented for the screened (SCR) population and all subgroups defined in section 7.5. For the subgroups, only age and region will be presented for the SCR population. All other subgroups will be presented for the SAF population as the subgroup data was not planned to be collected for screen failures.

The patient disposition table will summarize the number of screened patients and screening failure patients (where applicable). It will also summarize the number and percentage of ITT patients, SAF patients, patients receiving each of pertuzumab/trastuzumab and taxane, discontinuation from each study treatment including combinations of pertuzumab/trastuzumab and taxane, reasons for discontinuation of pertuzumab/trastuzumab and taxane, patients who have discontinued from the study, the primary reason for study discontinuation, ongoing patients and patients in follow-up. Cycle 1 information will also be summarized for trastuzumab and taxane including the total number of patients receiving each treatment (for taxane this will be split by docetaxel, paclitaxel and nab-paclitaxel as well), whether all study treatments were discontinued before administration and whether that study treatment was started at a later cycle.

The duration of follow-up will also be summarized using a Kaplan-Meier approach. Duration of follow-up will be calculated as the time in months between the date of first study treatment (pertuzumab and/or trastuzumab and/or taxane) and the date of the last follow-up assessment.

Last follow-up date will be derived as follows:

- Patients who have ended the study
  - For patients who have completed follow-up, the end of study date will be used
  - For patients who have died, the date of death will be used
  - For patients who did not participate in follow-up, the end of treatment date will be used
- Patients who are ongoing in the study
  - The most recent visit date from the 'Date of Visit' forms will be used

Event information will be based on patients who are alive, patients who die will be censored. Refer to section 6.6 for the calculation.

The following disposition information will be derived for each patient:

- Received pertuzumab: patient has at least one pertuzumab administration date available
- Received trastuzumab: patient has at least one trastuzumab administration date available
- Received taxane: patient has at least one taxane administration date available
- Discontinuation from pertuzumab: patient has a last pertuzumab dose date available on the end of study treatment form on the electronic Case Report Form (eCRF)
- Discontinuation from trastuzumab: patient has a last trastuzumab dose date available on the end of study treatment form on the eCRF
- Discontinuation from taxane: patient has a last taxane dose date available on the end of study treatment form on the eCRF
- Discontinuation from all the study treatments: patient has discontinued from all initiated study drugs (i.e. patient received at least one dose of this drug). This includes patients discontinued before administration of trastuzumab and taxane or taxane only
- Ongoing on study treatment: patient has started study treatment and study treatment is not permanently discontinued
- In follow-up: patient has stopped all the study treatments and did not die, nor withdrew consent, nor was lost to follow-up and the study is not stopped by the sponsor
- Discontinued from the study: patient has withdrew consent or was lost to follow-up at the end of treatment visit, or the end of study date is available on the eCRF

The following will also be presented for the number and percentage of patients:

- ITT patients by region, country and center/investigator
- Patients in each analysis population (using ITT patients as the denominator for percentages)
- ITT patients having major and minor protocol deviations

All patients disposition, study treatment discontinuation, analysis population, major protocol deviation and subgroup (as defined in section 7.5) data will also be listed.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT population.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported as categorical variables for this study:

- Age (years)
  - ≤65 versus >65
  - 10-year classes (<30 years, 30 - <40 years, ..., >=80 years)
- Gender (Males, Female)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Other, Not applicable as per local regulations)
- Ethnicity (Hispanic/Latino, Chinese, Japanese, Mixed ethnicity, Other, Not applicable as per local regulations)
- Child bearing potential (only females)
- ECOG performance status at baseline (0, 1, 2)
- Visceral disease at baseline
- Prior (neo) adjuvant chemotherapy

The following demographic and other baseline characteristics will be reported as continuous variables and presented as described in section 8:

- Age (years)
- Height (cm)

For baseline value calculation please refer to section 6.2.

All demographic and other baseline characteristics data will also be listed.

10.1. DERIVATIONS

Age will be calculated based on the value at baseline:

- Age (years) = year part of the reference start date – birth year

11. SURGICAL AND MEDICAL HISTORY

Surgical and medical history information will be presented for the ITT population.

- Surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The latest version available at the time of reporting will be used. Data captured on the "Surgery and Procedures History (Cancer and Non-Cancer Related)" page of the eCRF (only General surgeries and procedures) will be presented by system organ class (SOC) and preferred term (PT).
- Medical history will be coded using the latest version of MedDRA available at the time of reporting. Data captured on the "Medical History" page of the eCRF will be presented by SOC and PT.

All surgical and non-breast cancer medical history data will also be listed. A separate listing for disease history of HER2, PgR and ER will also be presented.

12. DISEASE HISTORY OF BREAST CANCER

Disease history of breast cancer will be presented for the ITT population.

For breast cancer at initial diagnosis, the following will be reported as categorical variables for this study:

- Stage (I, II, III, IV)
- Site (Left Breast, Right breast, R and L breast, Unknown)
- How breast cancer was diagnosed (Cytologically, Histologically, Both)
- Histology of primary tumor (Infiltrating ductal carcinoma, Infiltrating lobular carcinoma, Inflammatory breast carcinoma, Other)
- HER2 status (HER2-positive is defined as either immunohistochemistry (IHC) 3+ or in situ hybridization (ISH) positive result) (Positive, Negative, Unknown)
- Progesterone receptor (PgR) score (Positive, Negative, Unknown)
- Estrogen receptor (ER) score (Positive, Negative, Unknown)
- Disease-free interval (DFI) (<=12 months, >12 months)

Time since primary diagnosis of breast cancer (months) will be derived and summarized as a continuous variable (see section 12.1).

For metastatic or locally recurrent breast cancer, the following data will be summarized categorically:

- Diagnosis (Locally recurrent, Locally advanced, Metastatic)
- HER2 status (HER2-positive is defined as either IHC 3+ or ISH positive result) (Positive, Negative, Unknown)
- PgR score (Positive, Negative, Unknown)
- ER score (Positive, Negative, Unknown)

Time since diagnosis of metastatic or locally recurrent breast cancer (months) will be derived and summarized as a continuous variable (see section 12.1).

The following combined status (primary tumor and metastatic disease, see section 12.1) will also be summarized categorically:

- HER2 status combined (Positive, Negative, Unknown)
- Hormone receptor status (ER positive, PgR positive, ER positive and/or PgR positive, ER negative, PgR negative, ER negative and PgR negative, Unknown) (see section 12.1)

The number and percentage of patients with at least one positive ER or PgR for the primary tumor will be presented by ER / PgR status for metastatic disease.

All disease history of breast cancer data will be listed.

12.1. DERIVATIONS

The time since diagnosis of an event is described below:

- Time since primary diagnosis of breast cancer (months): Reference start date - Date of primary diagnosis of breast cancer (in months)
- Time since diagnosis of metastatic or locally recurrent breast cancer (months): Reference start date - Date of diagnosis of metastatic or locally recurrent breast cancer (in months)

The HER2 status combined will be defined as:

- HER2-positive is defined as at least one positive result among HER2 status for primary tumor and HER2 status for metastatic disease, negative otherwise. If assessed by immunohistochemistry, only '3+' result is considered as positive.

The hormone receptor status will be defined as:

- ER positive: if at least one positive among ER status for primary tumor and ER status for metastatic disease
- PgR positive: if at least one positive among PgR status for primary tumor and PgR status for metastatic disease
- ER positive and/or PgR positive: if at least one of ER or PgR is positive
- ER negative: if ER is not positive and at least one negative ER status for primary tumor or metastatic disease
- PgR negative: if PgR is not positive and at least one negative PgR status for primary tumor or metastatic disease
- ER negative and PgR negative: if both ER and PgR are negative

Note that if both the ER and PgR status is unknown, the patient will be included as an 'Unknown' category.

Disease-free interval in months will be derived as:

- Disease-free interval (months) = (date of diagnosis of metastatic/recurrent disease – date of initial diagnosis + 1)/30.4375

Note: If it is possible to classify a patient's DFI to either <=12 or >12 without doubt based on partial dates then partial dates will be used to determine DFI, otherwise the derivation will be set to missing. If the stage at initial diagnosis is stage IV (as DFI is not applicable due to the patient already having metastatic disease at initial diagnosis) then DFI will also be set to missing.

13. PREVIOUS ANTICANCER THERAPY FOR BREAST CANCER

Previous anticancer therapy information will be presented for the ITT population, and coded using International Non-proprietary Name (INN).

The following data entered on the eCRF pages "Previous Systemic Cancer Therapy for Breast Cancer", "Previous Radiotherapy for Breast Cancer" and "Surgery and Procedures History (Cancer and Non-Cancer Related)" (excluding non-cancer related data) will be summarized as categorical variables:

- Patients who received systemic cancer therapy prior to study. This will also include the number of patients by the therapy purpose (Adjuvant, Neo-adjuvant, Metastatic or advanced disease, Other)
- Patients who received radiotherapy for breast cancer prior to study. This will also include the number of patients by the reason for administration (Adjuvant, Neo-adjuvant, Palliative) and the number of patients by site (Abdomen, Brain, Chest, Extremities, Head and neck, Pelvis, Vertebra(e)).
- Patients who received surgery/procedure for breast cancer prior to study (only breast cancer related surgeries and procedures will be selected)
- Patients in the following categories will also be presented:
    - Received systemic therapy only
    - Received radiotherapy only
    - Received surgery only
    - Received systemic therapy and radiotherapy only
    - Received systemic therapy and surgery only
    - Received radiotherapy and surgery only
    - Received systemic therapy and radiotherapy and surgery
    - Received no therapy

Previous trastuzumab will be summarised by the therapy purpose (Adjuvant, Neo-adjuvant, Metastatic or advanced disease, Other) and reason for discontinuation (Achieve optimal response, Complete regimen, Toxicity, Disease progression, Other).

Previous systemic therapies will be classified to the below categories based on therapeutic class and PT which will be updated on a continuos basis and provided by the sponsor (see APPENDIX 4):

- Chemotherapy
- Endocrine therapy with or without mammalian target of rapamycin (mTOR) inhibitors
- Monoclonal antibodies
- Small molecules
- Other

For each category, the number of patients by the therapy purpose (Adjuvant, Neo-adjuvant, Metastatic or advanced disease, Other) and reason for discontinuation (Achieve optimal response, Complete regimen, Toxicity, Disease progression, Other) will be presented. The number and percentage of patients previously treated will also be summarized by therapeutic class and PT.

All previous anticancer therapy for breast cancer and previous radiotherapy for breast cancer data will also be listed.

14. MEDICATIONS AND THERAPIES

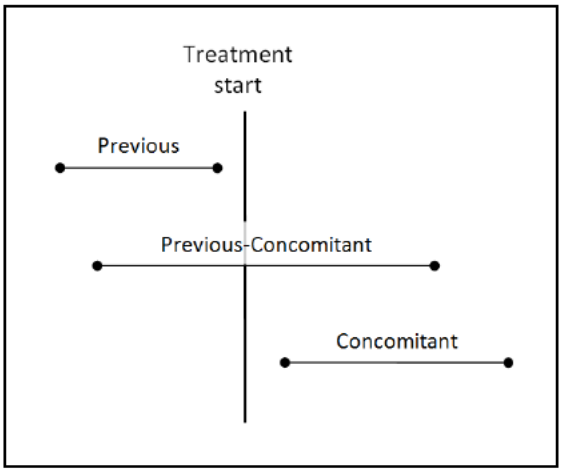
Previous medications or therapies, previous-concomitant medications or therapies and concomitant medications or therapies will be presented for the ITT population and coded using INN. Data captured on the "Concomitant Medications and Therapies" page of the eCRF will be summarized.

These medications will be classified as follows:

- Previous medications or therapies are defined as all medications or therapies with an end date occurring before the date of first dose of study treatment
- Previous-concomitant medications or therapies are defined all medications or therapies that started before the date of first dose of study treatment and ending on or after the date of first dose of study treatment, or ongoing as indicated on the eCRF
- Concomitant medications or therapies are defined as all medications or therapies that started on or after the date of first dose of study treatment

See APPENDIX 2 for handling of partial dates for treatments. In the case where it is not possible to define a medication or therapy as previous, previous-concomitant or concomitant, the treatment will be classified by the worst case; i.e. concomitant.

Figure 2: Definition of Previous, Previous-Concomitant and Concomitant Medication or Therapies Relative to Treatment Start



Previous, previous-concomitant and concomitant medications or therapies will be listed and summarized by therapeutic class and PT.

The previous surgeries and procedures recorded on the "Surgery and Procedures History (Cancer and Non-Cancer Related)" eCRF page will be listed for the ITT population and coded using INN, as will the concomitant procedures recorded on the "Concomitant procedures" eCRF page.

15. FURTHER ANTICANCER THERAPY FOR BREAST CANCER BEYOND DISEASE PROGRESSION

The anticancer therapies for breast cancer beyond progressive disease will be presented for the ITT population and coded using INN. Data captured on the "Subsequent Medical Therapy (after study chemotherapy discontinues) log" page of the eCRF will be summarized.

See APPENDIX 2 for handling of partial dates.

These therapies will be listed and summarized by therapeutic class and PT.

16. STUDY TREATMENT EXPOSURE

Exposure to study treatment will be presented for the safety population. Exposure will be summarized for the following categories:

- Any study treatment (duration of exposure only, see parameters below)
- Pertuzumab
- Trastuzumab

- Taxane – overall
- Taxane – Docetaxel
- Taxane – Paclitaxel
- Taxane – Nab-paclitaxel

The following parameters will be summarized:

- Total number of study treatment cycles
- Duration of exposure (months)
- Number of patients with at least one cycle with infusion interruption

This will also be presented by subgroups, as described in section 7.5.

The date of first study treatment administration and infusion interruptions will be taken from the eCRF forms: "Administration of treatment (PERTUZUMAB)", "Administration of treatment (TRASTUZUMAB)" and "Administration of treatment (TAXANES)" for pertuzumab, trastuzumab and taxane respectively.

The date of last study treatment will be taken from the eCRF form "End of Study Treatment". In the case of missing data, the last available date from eCRF forms "Administration of treatment" will be used in order to determine the last date of study medication.

The number of study treatment cycles will be taken from the eCRF form "Administration of treatment".

Interruptions and dose changes are not taken into account for duration of exposure and number of cycles.

The number and percentage of patients who received pertuzumab, trastuzumab and a taxane at each cycle will also be summarized.

The number and percentage of patients who crossed over from a taxane to another taxane will also be summarized. This will be presented as a total and by taxane and cycle.

All exposure data for each of the study treatments will also be listed. Cumulative exposure data will also be listed for each study treatment.

16.1. DERIVATIONS

Total number of study treatment cycles = the number of cycles where a confirmed dose was given (non-missing date of administration and non-zero dose)

Duration of exposure (month) for each study treatment = (date of last study treatment administration – date of first study treatment administration + 1) *12/ 365.25.

17. EFFICACY OUTCOMES

All efficacy parameters will be summarized and presented in tables and graphs based on the ITT population. Analysis of PFS and OS will be repeated for the PP population as described in sections 17.1.1 and 17.2.1. Subgroup analyses of efficacy data will be performed as specified in section 7.5 and summarized in Table 2:. Sensitivity analyses will not be performed for the subgroup analyses.

When is it not possible for the site to confirm the full death date, the following imputation will be applied:

1. If only year is known, then the date will be imputed as 01 June of that year e.g. if death date is collected as 2018 then the imputed death date would be 01 June 2018
2. If only the year and month is known, then the day will be imputed to the 15th of that month e.g. if the death date is collected as June 2018 then the imputed death date would be 15 June 2018

   Note: The imputed death dates would only be used within any analysis if the imputed dates are after the last known alive date, as decribed for overall survival in Section 17.2. Otherwise the death date will be imputed as the date after the last known alive date.

17.1. PROGRESSION-FREE SURVIVAL (PFS)

PFS is defined as time between the date of enrollment and date of first radiographically documented progressive disease (by RECIST) or death, whichever occurs first. Patients who have neither progressed nor died at the time of clinical cut-off or who are lost to follow-up are censored at the date of the last evaluable tumor assessment; if no post-baseline tumor assessments are available, such patients will be censored at day 1. The last evaluable tumor assessment is defined as the overall assessment with the latest end date and where a response is given and is not equal to "UNABLE TO ASSESS". If a patient misses 2 or more consecutive visits, defined as an interval of 19 weeks (133 days) or more between visits, then the patient will be censored at the last evaluable visit prior to the missed visits. The interval of 19 week is calculated as 2 scheduled scans of 9 weeks plus an extra week for a potential late scan.

Progressive disease can be documented on the eCRF either as overall tumor response or as a reason for the study treatment discontinuation. For overall tumor response the date of disease progression will be taken from the corresponding eCRF page with the response “Disease Progression (as evidenced by RECIST assessments)”. For the reason of study treatment discontinuation, the date of disease progression will be the date of the individual study treatment discontinuation with the reason “Same as Overall Reason for withdrawal" and overall withdrawal reason “Disease Progression (as evidenced by RECIST assessments)”. If both dates are provided and are not consistent the earliest date will be used.

17.1.1. ANALYSIS OF PFS

The number of patients included in the analysis, number of patients with events, number of patients censored, estimates of the median PFS and the corresponding 95% CI will be presented along with estimates for the 25th and 75th percentiles and the associated ranges (Min-Max). This will also be repeated for the PP population. The survivor function will be displayed graphically using a Kaplan-Meier (KM) curve. This will also be repeated for the subgroup analysis specified in section 7.5. Subgroup will be added as a stratification variable.

All PFS data will be listed.

17.1.2. SENSITIVITY ANALYSIS OF PFS

As a sensitivity analysis, the definition of PFS will be expanded to include clinical progression (reason for the study treatment discontinuation “Clinical progression”) for patients who do not record radiographic

progression. Note that in cases where both radiographic and clinical progression are recorded for a patient, the date of radiographic progression will be used for the calculation of PFS. The analysis will be the same as for the primary PFS definition.

17.2. OVERALL SURVIVAL (OS)

OS is defined as time from the date of enrollment until death due to any cause. Any patient not known to have died at the time of analysis will be right-censored based on the last recorded date on which the patient was known to be alive. This will be derived using the latest date from the following forms of the eCRF: Demography, electrocardiogram (ECG), administration of treatment, imaging, ECOG, LVEF, laboratory values, medical history, physical examination, FACT-B, tumor responses, subject characteristics, subject visits (for post-treatment follow-up the patients status must be known), vital signs, concomitant medications and therapies, adverse events and disposition.

17.2.1. ANALYSIS OF OS

The number of patients included in the analysis, number of patients with events, number of patients censored, estimates of the median OS and the corresponding 95% CI will be presented along with estimates for the 25th and 75th percentiles and the associated ranges (Min-Max). This will also be repeated for the PP population. The survivor function will be displayed graphically using a KM curve. This will be repeated for the subgroup analysis specified in section 7.5. Subgroup will be added as a stratification variable.

All overall survival data will be listed.

17.3. OVERALL RESPONSE RATE (ORR)

Tumor response will be assessed by the investigator using RECIST 1.1 (see APPENDIX 3).

17.3.1. BEST OVERALL RESPONSE (CONFIRMED) (BOR)

Best overall response (BOR) is defined as the best response recorded from the date of first dose of study treatment until disease progression/recurrence or death in the absence of disease progression.

The hierarchy used to determine BOR is CR>PR>SD>PD>NE (not evaluable). Note that for CR or PR confirmation is required at least 4 weeks (28 days) later.

The following algorithm describes how BOR is determined from the overall tumor assessments:

- A patient is assigned a BOR of CR if they have a response assessment of CR at two consecutive evaluable assessments at least 28 days apart
- A patient is assigned a BOR of PR if they have a response assessment of PR or CR at two consecutive evaluable assessments at least 28 days apart, without being a CR
- Patients need to have two consecutive assessments of PR or CR to be a responder (note: a

sequence of CR-NE-CR or PR-NE-PR would be considered as confirmed CR and PR respectively)

- A patient is assigned a BOR of SD if they have a response assessment of SD at least 42 days (6 weeks) after the date of first dose of study treatment. The 6-week interval was chosen in order to be consistent with the Cleopatra study (Baselga, et al., 2012). A patient is also assigned a BOR of SD if they have a response assessment of SD followed by PR, or CR but are not a confirmed CR or PR
- A patient is assigned a BOR of PD if they have a response assessment of PD at any visit or if a patient has died within the first 19 weeks (2 scheduled visits plus a week for a potential late visit), and not a BOR of CR, PR or SD before that
- Patients without any post baseline tumor assessments, or an assessment of SD, PR or CR in the first 42 days (six weeks) after the date of first dose of study treatment and either no further tumor assessments or have insufficient data after the 42 days will be assigned a BOR of NE. Patients who die after the first 19 weeks without any post-baseline tumor assessments will also be assigned a BOR of NE
- Patients who were enrolled and did not receive any study treatment will have a BOR of missing

17.3.2. Analysis of ORR

The ORR is defined as the proportion of patients (responders) with a confirmed BOR of either CR or PR (as defined in section 17.3.1). Only patients with measurable disease at baseline will be included in the denominator for the calculation of the rate. Patients without post-baseline tumor assessments will be considered non-responders.

The number and percentage of patients in all BOR categories will be summarized. The ORR together with two-sided exact 95% Clopper-Pearson CI will also be presented. This will also be summarized for the subgroups specified in section 7.5.

Logistic regression analysis will be used to assess the influence of baseline covariates on ORR, in an exploratory manner. The number of patients in each factor used in the analysis and the number and percentage of responders within each factor will be summarized. A univariate logistic regression analysis will be performed to evaluate the relationship between the ORR and each prognostic factor (see section 7.5). The univariate odds ratio (OR) with a two-sided 95% CI (calculated using profile likelihood) and p-value will be presented. A multiple logistic regression analysis will then be performed only on factors with an overall univariate p-value <0.15 (based on twice the change in log-likelihood resulting from the addition of the selected factor to the model). A stepwise selection strategy will be used to select significant prognostic factors (significance level for entry in the model will be 0.15, while the significance level to stay in the model will be 0.20). The stepwise selection process will terminate if no further variables can be added to the model or if the latest variable entered into the model is the only variable removed in the subsequent backward elimination. The final model will be interpreted with an OR, two-sided 95% CI (calculated using profile likelihood) and p-value for each predictive covariate selected. The p-value will be calculated based on twice the change in log-likelihood resulting from the addition of the selected factor to the model.

All tumor assessment data and BOR will also be listed.

17.4. CLINICAL BENEFIT RATE (CBR)

The CBR is defined as the proportion of patients (responders) whose BOR was PR, CR or SD lasting at least 6 months from the date of first dose of study treatment, where 6 months is defined as 183 days. The date of PD, death, or censoring (where censor date is the last evaluable tumor assessment) will be used as the reference date when calculating the number of days (i.e. date of PD or death or censoring date – date of first study treatment administration +1 ≥ 183 days). For example, if a patient had a sequence of SD – SD – SD – PD, the date of the assessment of PD would be used in the above calculation.

If a patient has a response of NE at an intermediate assessment between two assessments of SD or CR or PD (in whatever combination) then this assessment is included when computing the duration of clinical benefit. For example, if a patient had a sequence of SD – NE – SD – PD, the date used within the calculation would be the date of the PD assessment. If the date of PD - date of first study treatment administration +1 >=183 days, the patient is considered to have had clinical benefit.

Only patients with measurable disease at baseline will be included in the analysis of the CBR.

17.4.1. ANALYSIS OF CBR

The analysis of CBR will be same as those described for ORR in section 17.3.2. Subgroup analysis will not be performed for CBR, apart from the logistic regression specified in section 17.3.2. The number and percentage of patients with and without a clinical benefit will also be summarized.

17.5. DURATION OF RESPONSE (DOR)

Tumor response will be assessed by the investigator using RECIST 1.1 (see APPENDIX 3 and section 17.3.1 for details).

DOR is defined as the time from when a confirmed response (CR or PR) was first documented (date of the latest scan associated with the initial response) to first documented disease progression (See section 17.1) or death from any cause (whichever occurs first). Patients who do not progress or die after they have had a confirmed response are censored at the date of their last tumor measurement.

Duration of response (months) = [(Date of disease progression/death/censor – Date of first recorded CR/PR) + 1] / 30.4375

Only patients who have a BOR of CR or PR (i.e. responders) and with measurable disease at baseline will be included in the analysis of DOR.

17.5.1. ANALYSIS OF DOR

The analysis of DOR will be the same as those described for PFS in section 17.1.1. Subgroup analysis and Kaplan-Meier plots will not be summarized for DOR.

All duration of response data will be listed.

17.6. TIME TO RESPONSE (TTR)

Tumor response will be assessed by the investigator using RECIST 1.1 (see APPENDIX 3 and section 17.3.1 for the details).

Time to response for patients with a BOR of CR or PR is defined as the time from the date of enrollment to the date of first confirmed CR or PR (date of the latest scan associated with the initial response). Patients who do not have CR or PR will be censored at the date of the last evaluable tumor assessment. Patients for whom no post-baseline tumor assessments are available are censored at day 1. Only patients with measurable disease at baseline will be included in the analysis of the TTR.

17.6.1. ANALYSIS OF TTR

The analysis of TTR will be the same as those described for PFS in section 17.1.1. Subgroup analysis and Kaplan-Meier plots will not be summarized for TTR.

All time to response data will be listed.

18. PATIENT-REPORTED OUTCOMES: QUALITY OF LIFE (QOL) ANALYSIS

QoL will be assessed using the FACT-B (Brady et al., 1997) questionnaires completed by the patient (female patients only). 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 subscale scores for physical well-being, social/family well-being, emotional well-being, functional well-being, and additional concerns. FACT-B provides supplemental domain evaluative ratings or utility weights thus providing an estimate of the relative importance of each quality of life domain to an individual patient.

For calculated FACT-B total score as well as subscales, a higher score indicates a better quality of life.

The FACT-B questionnaire for female patients only (Version 4) will be administered at baseline (pre-dose), every 3 cycles of monoclonal antibodies, at 1-month post-treatment follow-up and at 3-montly post-treatment follow-up visits.

The FACT-B questionnaire should be completed prior to any other assessments, treatment administration, or physician/investigator consultation, and prior to the patient being informed of his/her disease status.

18.1.1. VARIABLES & DERIVATIONS

See APPENDIX 5 for details of total QoL score and sub-score calculations.

18.1.2. MISSING DATA METHODS

No missing data imputation methods will be used in this study. See APPENDIX 5 for details of QoL score

calculation when items or subscales scores are missing.

18.1.3. Analysis of QOL Variables

FACT-B results will be summarized at baseline and over time for the ITT population. Mean changes from baseline will be summarized using descriptive statistics including 95% CI.

Total and subscale scores for quality of life data will be listed.

19. Safety Outcomes

All outputs for safety analyses will be based on the safety population. In addition, for specific safety parameters, summaries for subgroups will be produced (see section 7.5).

The safety variables are all AEs, AEs Grade ≥3, 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 treatment-emergent AEs (TEAEs) Grade ≥3 related to pertuzumab.

19.1. Adverse Events

AEs will be coded using the latest available version of MedDRA at the time of DBL.

TEAEs are defined as AEs that started or worsened in severity on or after the date of first dose of study treatment, up to and including 28 days after the date of last dose of study treatment. SAEs related to study drug will have an increased cutoff of 7 months (214 days). See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the "worst case"; i.e. treatment emergent.

AEs will be graded using the Common Terminology Criteria (CTC) system version 4.0. The grades will be assigned by the investigator.

A patient with more than one occurrence of the same AE in a particular SOC/PT will only be counted once under the SOC/PT. If a patient experiences the same AE at more than one CTC grade level, or with more than one relationship to study treatment, the most severe rating or the stronger causal relationship to study treatment will be given precedence. Any missing CTC grade, causality, or outcome will not be imputed and classed as unknown.

Adverse events will be summarized as described in the following sub-sections.

19.1.1. Overview of TEAEs

The number and percentage of patients within each of the following categories will be presented overall:

- All TEAEs
- TEAEs CTC Grade 3 or higher
- Treatment emergent SAEs
- TEAEs leading to death
- TEAEs related to study treatment (by study treatment)
- TEAEs Grade 3 or higher related to study treatment (by study treatment)
- TEAEs leading to treatment interruption (by study treatment)
- TEAEs leading to treatment discontinuation (by study treatment)
- TEAEs to monitor
- TEAEs to monitor CTC Grade 3 or higher
- TEAEs of special interest
- TEAEs with onset within 28 days of study treatment discontinuation

Listings will be presented for each of the above subsections. These will include all AEs (the treatment emergent AEs will be flagged within the listings).

19.1.2. ALL TEAEs

Incidence of TEAEs will be presented by SOC and PT. A separate summary of the most common TEAEs (i.e. those TEAEs occurring in 10% or more patients within the preferred term) will also be presented.

19.1.3. TEAEs BY CTC GRADE

AEs will be graded using the CTC system v4.0. NCI-CTC grades, as indicated by the Investigator, are graded from 1 to 5 with increasing severity (CTC Grade 1 = Mild, CTC Grade 2 = Moderate, CTC Grade 3 = Severe, CTC Grade 4 = Life threatening/disabling, CTC Grade 5 = Death). TEAEs with a missing grade will not be summarized. If a patient reports the same AE more than once within that SOC/PT, the AE with the worst grade will be used in the corresponding summaries.

The number and percent of patients reporting TEAEs by NCI-CTC grade will be presented by SOC and PT. The incidence of TEAEs with grades 3 or higher will also be presented by SOC and PT. This summary will also be presented by the subgroups specified in section 7.5.

19.1.4. TREATMENT EMERGENT SAEs (TESAEs)

TESAEs are those TEAEs recorded as "Serious" on the "Adverse Events" page of the eCRF. An SAE is any AE that meets any of the criteria specified in section 5.2.2 of the protocol.

The incidence of TESAEs will be presented by SOC and PT. This summary will also be presented by the

subgroups specified in section 7.5. The number and percentage of patients with TESAEs will also be presented by toxicity grade.

19.1.5. TEAEs Leading to Death

TEAEs leading to death are those events which are recorded as "Fatal" on the "Adverse Events" page of the eCRF ('Died' as outcome or CTC grade 5). The incidence of TEAEs leading to death will be presented by SOC and PT, this summary will also be presented by the subgroups specified in section 7.5.

19.1.6. TEAEs Related to Study treatment

Relationship, as indicated by the Investigator, is classed as "Related", "Not related" and "Not applicable". If a patient reports the same AE more than once within that SOC/PT, the AE with the worst relationship to study treatment will be used in the corresponding relationship summaries. TEAEs with a missing relationship to study treatment will not be presented.

The incidence of TEAEs related to the study treatment will be presented separately for pertuzumab, trastuzumab and taxane, by SOC and PT. This summary will also be presented by the subgroups specified in section 7.5 for pertuzumab. The number and percentage of patients with TEAEs related to study treatment will also be presented separately for pertuzumab, trastuzumab and taxanes, by toxicity grade. The incidence of TEAEs with CTC grade 3 or higher and related to each study treatment will also be presented by SOC and PT. This summary will also be presented by the subgroups specified in section 7.5 for pertuzumab.

19.1.7. TEAEs Leading to Interruption or Discontinuation of Study treatment

TEAEs leading to permanent discontinuation of study treatment will be identified by using the questions "Action taken regarding study treatment" on the eCRF AE page. Pertuzumab and trastuzumab can be interrupted or permanently stopped. Taxanes can be interrupted (options selected "Drug interrupted" or "Drug interrupted and dose reduced") or permanently stopped.

For each treatment, the incidence of the following will summarized by SOC and PT:

- TEAEs leading to each study treatment interruption
- TEAEs leading to each study treatment discontinuation

19.1.8. TEAEs to Monitor

TEAEs to monitor will be defined according to medical review and their definition will be regularly updated as the version of the coding dictionary changes. A list of TEAEs to monitor with SOC and PT will be continuously updated and provided by the sponsor (see APPENDIX 6).

The categories for TEAEs to monitor are as follows:

- Anaphylaxis and hypersensitivity

- Cardiac dysfunction
- Diarrhoea grade >=3
- Exposure during pregnancy / Exposure during breast feeding / Pregnancy complications / Oligohydramnios / Congenital abnormalities
- Interstitial lung disease (ILD)
- Infusion-related reactions (IRR) / administration-related reactions (ARR)
- Mucositis
- Neutropenia / febrile neutropenia
- Rash / skin reactions
- Suspected transmission of infectious agent

The incidence of TEAEs to monitor will be presented by SOC and PT. This summary will also be presented by the subgroups specified in section 7.5. The incidence of TEAEs to monitor of CTC grade 3 or higher will also be presented by SOC and PT.

19.1.9. TEAEs Of Special Interest

The incidence of AESIs will be presented by SOC and PT. AESIs include the following (as shown on the eCRF AE page):

- LVEF decrease = an asymptomatic decline in LVEF (measurements of less than 50% or a change from baseline of >=10%) or requiring treatment or leading to discontinuation of study treatment
- Liver enzymes increase = an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either elevated bilirubin or clinical jaundice
- Suspected transmission of an infectious agent by the study treatment

19.1.10. TEAEs Starting on Day 1 or 2 of Cycle 1

The incidence of TEAEs with a start date on Cycle 1 Day 1, and TEAEs with a start date on Cycle 1 Days 1 or 2 will be presented by SOC and PT.

19.1.11. TEAEs Starting after Discontinuation from Study Treatment

The incidence of AEs that started within 28 days of the last dose of each study treatment (pertuzumab, trastuzumab and taxane) will be presented by SOC and PT.

19.1.12. Time to Onset of Congestive Heart Failure (CHF)

CHF is defined using the standardized MedDRA query (SMQ) 'Cardiac failure (wide)' from the latest available version of MedDRA. The time to onset of the first episode of CHF in months is ((start date of

CHF – first dose of study treatment +1) * 12 / 365.25), where CHF must be treatment emergent as described in Section 19.1.

If the date is partial, a conservative approach was taken to impute to the earliest possible date. This is applied as follows:

- If only year is known, then impute to 01 January of that year e.g. if date is 2018, then impute to 01 Jan 2018
- If only month and year is known, then impute to the first of the month e.g. if date is March 2018, then impute to 01 March 2018

  Note: If the imputed date is prior to first dose, then impute to first dose date.

The incidence of partial dates will be reviewed based on AE listings of CHF events so that the potential effect of including imputed dates in these analyses can be considered.

A KM analysis will be performed to analyze the time to first episode of CHF. For the KM analysis, the patients who did not experience any CHF at the time of data-cut will be censored at the date of the last attended visit whist on-treatment (including visits up to and including 28 days after last dose of study treatment). The number and percentage of patients with an event and those that are censored, estimates of the median time to onset and the corresponding 95% CI will be presented along with estimates for the 25th and 75th percentiles and the associated ranges (Min-Max).

19.2. DEATHS

If any patients die during the study as recorded on the "End of Treatment", "Survival Status" and "End of Study" pages of the eCRF, the information will be coded using MedDRA and presented in a summary table and a data listing.

The following data will be presented in the table:

- The number and percentage of patients who died
- The number and percentage of patients by cause of death (including other reasons) as reported by the investigator. In the case of deaths reported due to an AE, the number and percentage of patients by SOC and PT will be presented (see section 19.1.5).

The above summary will be repeated for deaths occurring within six months of the date of first study treatment administration.

19.3. LABORATORY EVALUATIONS

Clinical laboratory tests for hematology, biochemistry and coagulation will be performed at local laboratories. Laboratory toxicities will be defined based on local laboratory normal ranges and NCI-CTC grades, Version 4.0. Local laboratory data will be converted to the System International (SI) units by data management.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (LLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purposes of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Applicable laboratory measurements will be graded using the NCI-CTC system version 4.0. Some laboratory parameters can be bi-dimensional (i.e. can be graded in both the low and high direction). These parameters will be split and presented in both directions for the shift tables. For example, glucose can be graded as both hypoglycemia and hyperglycemia. If the value was classed as a grade 2 for hyperglycemia it would also be graded as grade 0 for hypoglycemia.

The following summaries for the laboratory data (hematology, biochemistry and coagulation) will be produced:

- Absolute values and change from baseline summarized by laboratory parameter and visit
- Number and percentage of patients with each NCI-CTC grade per laboratory parameter and visit. Bi-dimensional parameters will present the worst grade (e.g. if we have grade 0 in the low direction and grade 2 in the high, then we would only present "Grade 2 (High)")
- Shift from baseline to worst post-baseline value according to NCI-CTC Grade (for parameters with NCI-CTC grade defined). Bi-dimensional parameters will be split as described above.
- Shift from baseline to worst post-baseline value according to normal ranges (for parameters with NCI-CTC grade not defined). Bi-dimensional parameters based on the normal ranges (i.e. have values above the upper boundary and below the lower boundary) will be split as described above

For each laboratory test, individual patient values will be listed in chronological order and values outside the normal range will be flagged and if applicable, the NCI-CTC grades will be shown.

Plots of the mean change from baseline over time with 95% CI will be presented for the following parameters:

- **Hematology:** Hemoglobin, hematocrit, platelet count, red blood cells (RBC), white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and other cells)
- **Biochemistry:** Sodium, potassium, calcium, chloride, magnesium, blood urea nitrogen, uric acid, total protein, albumin, alkaline phosphatase, SGPT (ALT), SGOT (AST), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin, creatinine, and blood glucose and calculated creatinine clearance at baseline
- **Coagulation:** All patients will have international normalized ratio (INR) and activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) testing at baseline. Tests should be repeated at each treatment cycle in all patients receiving therapeutic doses of anti-coagulants

The last value will also be summarized, where the last value is the last non-missing value carried over from the patients last timepoint.

19.3.1. Liver Function Tests (LFTs)

Potential hepatic dysfunction will be investigated by evaluation of the laboratory data, with specific reference to the assessments of AST, ALT and Total Bilirubin.

In-line with the FDA guidance document on drug-induced liver injury, patients meeting the following criteria will be included in a listing of ALT, AST and total bilirubin results:

- ALT and/or AST >3 x upper limit of normal (ULN) in combination with a total bilirubin >2 x ULN.

Scatterplots will be produced for total bilirubin vs. AST and total bilirubin vs. ALT. The data presented in the scatterplot will represent post-baseline values for each patient's worst (highest xULN) total bilirubin and their worst (highest xULN) AST/ALT.

19.4. LEFT VENTRICULAR EJECTION FRACTION (LVEF) EVALUATION

The following LVEF parameters will be summarized at baseline and each planned visit (every 3 cycles of the study treatment and at one month post-treatment safety follow-up):

- LVEF value (%) (absolute and change from baseline)
- LVEF by category (>=45% vs <45%)

The quantitative parameters will be summarized using descriptive statistics, including a 95% CI.

The changes in LVEF will also be classified at each planned visit as:

- Increase, no change, decrease from baseline <10% points
- Absolute value <45% and decrease from baseline ≥10% to <15% points
- Absolute value <45% and decrease from baseline ≥15% points
- Absolute value >=45% and decrease from baseline ≥10% points
- No baseline value (to account for patients who have a visit value but no baseline meaning the change cannot be calculated)

In addition to the individual visits, the summary tables will include the 'Final Treatment Value', 'Worst Treatment Value' and 'Maximum decrease':

- The final treatment value is defined as the last value observed before all study treatment discontinuation.
- The worst treatment value is defined as the lowest value observed before all study treatment discontinuation.
- The maximum decrease is defined as the largest decrease of LVEF value from baseline, or minimum increase if patients' post-baseline LVEF measures are all larger than the baseline value.

The number (%) of patients whose worst treatment LVEF is >=50%, >=45% and <50%, >=40% and <45%, <40%, will be presented. All of the summary above will also be presented by the subgroups specified in section 7.5.

The time (weeks) from date of first study treatment administration to first decrease in LVEF value to <45% and decrease from baseline of ≥10% points will be summarized using a KM approach. The date of event will be the assessment date associated with the LVEF on the first occasion the patient's LVEF fell to <45%, with a decrease from baseline of ≥10% points. Patients without the event will be censored in the analysis at their last LVEF assessment date.

In order to account for possible differences in length of follow-up or completion of cardiac evaluations over time between subgroups a competing risk analysis will be performed on the time to first decrease in LVEF value to <45% and decrease from baseline of ≥10% points, including death as a competing event. Patients alive and with no decrease in LVEF value to <45% and decrease from baseline of ≥10% points are

censored at the date last known to be alive. The results will be summarised descriptively for the number and percentage of patients with an event, competing event (death) and those patients that are censored. A cumulative incidence table displaying the cumulative indence (%) at month 6, year 1 and each following year as well as a cumulative incidence plot will also be produced.

A plot of mean change in LVEF from baseline over time with 95% CI will be presented. The last value will also be summarized, where the last value is the last non-missing value carried over from the patients last timepoint.

A listing of LVEF measures will be presented. A listing of patients with an LVEF absolute value <45% that is a decrease from baseline of ≥10% points will also be presented.

19.5. ELECTROCARDIOGRAM (ECG) EVALUATIONS

The following ECG parameters will be presented at baseline and each planned visit (every 3 cycles of the study treatment and at one month post-treatment safety follow-up):

- Heart rate (beats/min)
- QRS duration (msec)
- PR interval (msec)
- QT interval (msec)
- QTc interval (msec)
- QTcB interval (msec)
- QTcF interval (msec)
- Overall evaluation of ECG (investigator's judgment):
    - Normal
    - Abnormal, not clinically significant
    - Abnormal, clinically significant
    - Not done

For quantitative parameters, the values at each visit as well as changes from baseline will be summarized using descriptive statistics (including 95% CI).

For the overall evaluation of ECG, the counts and percentages at each visit will be presented.

Plots of the mean change from baseline over time with 95% CI will be presented for the selected ECG parameters heart rate, PR interval, QT interval, QRS duration and QTc interval.

All ECG data will be listed.

19.5.1. DERIVATIONS

If at a visit there are non-missing results for PR and HR, but either QTcB or QTcF are missing, then derive

the value for these as follows:

- $\mathrm{QTcB} = \mathrm{QT} / (60/\mathrm{HR})^{1/2}$
- $\mathrm{QTcF} = \mathrm{QT} / (60/\mathrm{HR})^{1/3}$

Round derived value to nearest integer

19.6. VITAL SIGNS

The following vital signs measurements will be reported for this study:

- Sitting systolic blood pressure (mmHg)
- Sitting diastolic blood pressure (mmHg)
- Sitting pulse rate (bpm)
- Temperature (°C)
- Weight (kg)

The absolute and change from baseline values will be summarized by visit using descriptive statistics. All vital signs data will be listed.

19.7. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

The ECOG performance status is quoted from grade 0 to 5:

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

ECOG performance status will be summarized (frequency and percentage) at baseline and each planned visit (every 3 cycles of the study treatment and at one month post-treatment safety follow-up). The worst (highest) post-baseline ECOG performance status will also be summarized.

The shift from baseline to the worst (highest) post-baseline ECOG performance status will also be presented.

All ECOG performance status will also be listed.

19.8. PHYSICAL EXAMINATION

Abnormal findings on physical examination will be listed by patient and visit.

19.9. OTHER SAFETY ASSESSMENTS

Brain CT/ magnetic resonance imaging (MRI) data will be listed by patient and visit.

REFERENCES

Baselga, J., Cortes, J., Kim, S.-B., Im, S.-A., Hegg, R., Im, Y.-H., . . . Swain, S. M. (2012). Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *The New England Journal of Medicine, 366*(2). Retrieved 2 27, 2019, from https://nejm.org/doi/full/10.1056/nejmoa1113216

Brady, M. J., Cella, D., Mo, F., Bonomi, A. E., Tulsky, D. S., Lloyd, S., . . . Shiomoto, G. (1997). Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *Journal of Clinical Oncology, 15*(3), 974-986. Retrieved 2 27, 2019, from https://ncbi.nlm.nih.gov/pubmed/9060536

Eisenhauer EA, T. P. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, 45(2):228-47.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

[redacted] Output Conventions

Outputs will be presented according to the following [redacted] output conventions.

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-dd.

Spelling Format

English US will be used.

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Patient ID
- Visit (where applicable)
- Date (where applicable)

Presentation of subgroups

Subgroups	Category
Region	Europe
	Asia
	North America
	South America
	Other
Age	Age <=65
	Age >65
ECOG performance status at baseline	ECOG 0, 1
	ECOG 2
Taxane	Docetaxel
	Paclitaxel
	Nab-Paclitaxel
Visceral Disease	Yes (Visceral)
	No (Non-visceral)
Prior (neo) adjuvant chemotherapy	Yes (Prior Chemo)
	No (No Prior Chemo)
Hormone receptor status	Positive
	Negative
	Unknown
Previous trastuzumab	Yes
	No

APPENDIX 2. PARTIAL DATE CONVENTIONS

Any imputation will not be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date and <= study med end date +28 days (+214 days for SAEs related to study drug), then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date and <= study med end date +28 days (+214 days for SAEs related to study drug), then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date and <= study med end date +28 days (+214 days for SAEs related to study drug), then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute start date as the earliest possible date (i.e. If date could be the same as treatment start date then impute to treatment start date. Otherwise the first day of month if day unknown or 1st January if day and month are unknown), then: If start date <= study med end date +28 days (+214 days for SAEs related to study drug), then TEAE

START DATE	STOP DATE	ACTION
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown or date of death if this is before the above 2 dates), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant Start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

To allow for the calculation of study day or any duration, partial end dates and missing or partial start dates will need to be temporarily imputed.

For missing or partial start dates;

- Impute start date equal to treatment start date, if either the start date is completely missing, or the partial components indicate it may have started on the treatment start date.
- Otherwise impute the earliest possible start date based on known components.

For partial end dates;

- Impute the latest possible end date, based on known components.

For missing end dates;

- No imputation performed, Study Day and Duration in these instances will remain missing.

APPENDIX 3. TUMOR ASSESSMENTS (RECIST)

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 computed tomography (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 ≥10mm 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. 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, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm· 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm 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 <10mm 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-~D	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 4. SPREADSHEET OF PREVIOUS SYSTEMIC THERAPIES

PREVIOUS_SYSTEMIC_THERAPIES.xlsx

APPENDIX 5. CALCULATION OF FACT-B SCORES

The FACT-B consists of four general health subscales (Physical Well-Being [PWB], Social Well-Being [SWB], Emotional Well-Being [EWB], and Functional Well-Being [FWB]) and the Breast Cancer Score (BCS).

The questionnaire consists in 37 items ranged from 0 (not at all) to 4 (very much). Negatively stated items are reversed by subtracting the response from 4. These include:

- Physical Well-Being: GP1, GP2, GP3, GP4, GP5, GP6, GP7
- Emotional Well-Being: GE1, GE3, GE4, GE5, GE6
- Additional concerns: B1, B2, B3, B5, B6, B7, B8, P2

Then the subscale scores are computed (only if at least 50% of items within the subscale have been answered) as follows:

- Subscale Score = (Σ items) x (n_subscale) ÷ (n_answered), where
  n_subscale is the number of items in each subscale and
  n_answered is the number of items answered in each subscale.

The Total FACT-B score is derived as the sum of the individual subscale scores, provided that at least 80% of the items have been answered.

Total FACT-B score = PWB + EWB + SWB + FWB + BCS

If any of the 5 subscale scores are missing the Total FACT-B is also set to missing.

APPENDIX 6. SPREADSHEET OF ADVERSE EVENTS TO MONITOR

SMQAEGT_PERTUZUMAB_V221.xlsx

APPENDIX 7. PROTOCOL VIOLATIONS (PV) AND PER-PROTOCOL POPULATION

Method for the derivation of minor PV

This section describes the method used to derive that a subject has had a minor PV.

PD99

Any subject who has a record in the "Minor Deviations" tab.

PDMS

Any subset within the PDMS spreadsheet where the deviation_status column contains "minor".

Method for the derivation of a major PV

This section describes the method used to derive each major PV.

PD99

Using the "Protocol violations" tab:

- Assign the following to major PVs based on CATEGORY IF MAJOR and SUBCATEGORY columns:
  - "Patient entered the study but did not satisfy the eligibility criteria" if CATEGORY IF MAJOR column contains inclusion criteria or exclusion criteria.
  - "Patient developed criteria for withdrawal from study treatment or from the overall study but was not withdrawn" if SUBCATEGORY column contains "WITHDR1" or "WITHDR2".
  - "Patient received the wrong treatment dose" if SUBCATEGORY column contains "SA02" "SA03" "SA04" "SA06" "SA08" "SA12" or "SA14".
  - "Patient received a prohibited concomitant medication" if SUBCATEGORY column contains "CONMED1 PROHIBITED MEDICATION".
  - "Patient received trastuzumab biosimilars" if SUBCATEGORY column contains "SA16".

PDMS

- Assign the following to major PVs based on category and subcategory columns:
  - "Patient entered the study but did not satisfy the eligibility criteria" if category column contains inclusion criteria or exclusion criteria.
  - "Patient developed criteria for withdrawal from study treatment or from the overall study but was not withdrawn" if subcategory column contains "WITHDR1" or "WITHDR2".
  - "Patient received the wrong treatment dose" if subcategory column contains "SA02" "SA03" "SA04" "SA06" "SA08" "SA12" or "SA14".
  - "Patient received a prohibited concomitant medication" if subcategory column contains "CONMED1 PROHIBITED MEDICATION".
  - "Patient received trastuzumab biosimilars" if subcategory column contains "SA16".

Assigning patients to PP population

Patients are defined as being within the PP population if they are within the intent-to-treat population, defined as all patients enrolled in the study, and do not have a major PV as described above.