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| **Official Title:** | **A PHASE IV, MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY OF PERTUZUMAB (IN COMBINATION WITH TRASTUZUMAB AND DOCETAXEL) IN FIRST LINE TREATMENT OF INDIAN PATIENTS WITH HER2-POSITIVE ADVANCED (METASTATIC OR LOCALLY RECURRENT) BREAST CANCER** |
| **NCT Number:** | **NCT02445586** |
| **Document:** | **STATISTICAL ANALYSIS PLAN** |
| **Version & Date:** | **Version 1.0: 20-June-2016** |

# STATISTICAL ANALYSIS PLAN

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| **PROTOCOL TITLE** | **:** | A PHASE IV, MULTICENTER, OPEN–LABEL, SINGLE-ARM STUDY OF PERTUZUMAB (IN COMBINATION WITH TRASTUZUMAB AND DOCETAXEL) IN FIRST LINE TREATMENT OF INDIAN PATIENTS WITH HER2-POSITIVE ADVANCED (METASTATIC OR LOCALLY RECURRENT) BREAST CANCER |
| **PROTOCOL NO.** | **:** | ML29282 |
| **STUDY DRUG** | **:** | Pertuzumab RO 43-68451 |
| **VERSION NUMBER** | **:** | Version 1.0 |
| **IND NUMBER** | **:** | **--** |
| **EUDRACT Number** | **:** | **--** |
| **SPONSOR** | **:** | Roche Products (India) Pvt. Ltd. |
| **PLAN PREPARED BY** | **:** | [redacted] |
| | | [redacted] |
| **DATE FINAL** | **:** | 20 Jun 2016 |
| **DATE AMENDED** | **:** | NA |

**SPONSOR Sign off**

I hereby declare that I have reviewed the statistical analysis plan and agree to its form and content. In addition, I confirm that the outlined statistical analysis plan contains all relevant information for the data analysis to be performed in the Protocol No. - **ML29282** study by the Biostatistics Department.

Represented by:

[redacted]
Designation: [redacted]
Role: Study Manager
Signature : [redacted]
Date: 16 Jun 2016

**Dr.** [redacted]
Designation: [redacted]
Role: Scientific Responsible
Signature : [redacted]
Date: [redacted]ne 2016

**Dr.** [redacted]
Designation: [redacted]
Role: Medical Monitor
Signature : [redacted]
Date: [redacted]

CRO Sign off :

| | | | |
|---|---|---|---|
| [redacted] | [redacted] | [redacted] | 20th June 2016 |
| Author | Designation | Signature | Date |
| for [redacted] | [redacted] | [redacted] | 21/6/2016 |
| Reviewer | Designation | Signature | Date |
| Dr. [redacted] | [redacted] | [redacted] | 20/6/2016 |
| Reviewer | Designation | Signature | Date |
| [redacted] | [redacted] | [redacted] | 21/6/2016 |
| Approver | Designation | Signature | Date |

## Revision History

| Version No. | Version Date | Author | Description of Modifications from Previous Version |
|---|---|---|---|
| 1.0 | 20 Jun 2016 | [redacted] | - |
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# STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

# TABLE OF CONTENT

# 1.0 BACKGROUND

Pertuzumab (rhuMAb 2C4) is a recombinant, humanized immunoglobulin (Ig)G1 $\kappa$ monoclonal antibody, which targets HER2 (also known as c-erbB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Pertuzumab and trastuzumab bind to distinct epitopes on the HER2 receptor without competing with each other, and have complementary mechanisms for disrupting HER2 signaling. This results in augmented anti-proliferative activity in vitro and in vivo when pertuzumab and trastuzumab are given in combination.

Previously many studies of different phases-Phase I/II/III were done using single-agent and combination regimens of Pertuzumab, such as Phase III WO20698/TOC4 129g (CLEOPATRA), phase II BP27836 (JOSHUA), Phase II BO22280 (TRYPHAENA) and so on.

In Phase III, pivotal study WO20698/TOC4129g (CLEOPATRA; N = 808) in patients with previously-untreated HER2-positive mBC, a statistically significant and clinically meaningful improvement in progression-free survival (PFS), based on tumor assessments by an independent review facility (IRF), was observed in patients treated with pertuzumab (Ptz) + trastuzumab (T) + docetaxel (D) (N = 406) compared with those receiving placebo (Pla) + trastuzumab (T) + docetaxel (D) (N = 402).

# 2.0 STUDY DESIGN

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

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

Pertuzumab, trastuzumab, and docetaxel chemotherapy will be administered in line with the Prescribing Information. Docetaxel treatment will be given at least for 6 treatment cycles; thereafter decision for continuation of docetaxel treatment will be based on investigator's discretion.

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

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

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

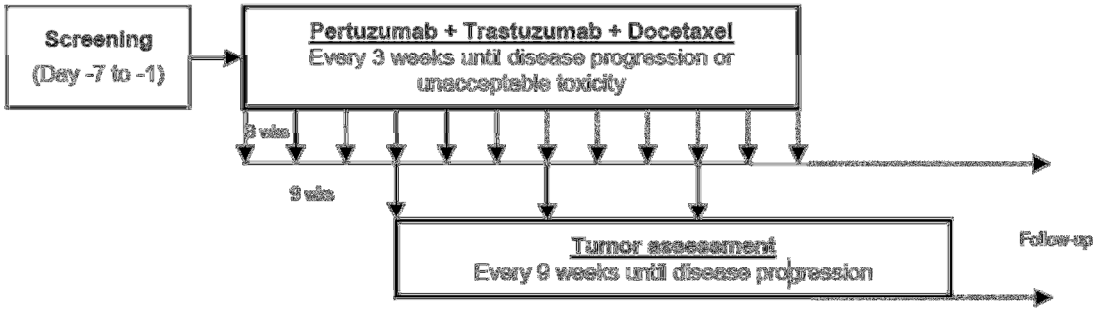


**Figure 3-1 Study Design: Patient Treatment and Assessment**

## 2.1 Protocol Synopsis

The protocol number is ML29282 titled as "A Phase IV, Multicenter, Open–Label Single-Arm Study of Pertuzumab (In Combination with Trastuzumab and Docetaxel) in First Line Treatment of Indian Patients with HER2-Positive Advanced (Metastatic or Locally Recurrent) Breast Cancer" and the Version is 1.0 amended on 6 June 2014.

## 2.2 Study Objectives and Endpoints

### 2.2.1 Study Objectives

#### 2.2.1.1 Primary Objective

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

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

#### 2.2.1.2 Secondary Objective

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

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

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

### 2.2.2 Study Endpoints

#### 2.2.2.1 Safety Endpoints

The safety endpoints of this study are as follows:

- Incidence and severity by NCI-CTCAE version 4.03 of AEs and SAEs
- Incidence of CHF and/or significant decline in LVEF

- Change in LVEF over the course of the study
- Laboratory results abnormalities
- Incidence of AEs leading to discontinuation, modification, or interruption of study medication
- Incidence and cause of death due to AEs

#### 2.2.2.2 Efficacy Endpoints

The efficacy endpoints of this study are as follows:

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

## 2.3 Determination of Sample Size

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

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

Sample size calculation for estimating proportion:

$$n = \frac{Z_{\alpha/2}^2 \quad *p \quad *(1-p)}{d^2}$$

Where,

n=Sample Size

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

d=Precision

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

## 2.4 Analysis Timing

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

There will be two interim analyses for safety and efficacy. The first interim analysis is for safety only and will take place after 50% patients have been enrolled and followed for at least 6 months of Pertuzumab therapy. The second interim analysis includes both safety and efficacy components and will take place after approximately 67% of the required deaths have been observed.

# 3.0 STUDY CONDUCT

This is a multi-centric, open-labeled, non-randomized post-marketing study, to assess the safety and efficacy of Pertuzumab in combination with Trastuzumab and Docetaxel. The study design employs standard methods for safety studies in patients with cancer. All patients will receive the active treatment. Safety will be carefully evaluated, and the type of data collected and the frequency with which patients are monitored will ensure safety of the patients.

The study team will periodically review patient eligibility and CRF data to ensure that the study is compliant with Good Clinical Practice.

The eligible patients for this study are the male or female patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer (locally recurrent, unresectable, or metastatic) who have not previously received systemic non-hormonal anticancer therapy in the metastatic setting.

The iDMC will review unblinded summaries of patient accrual, demographics and baseline characteristics, patient disposition, and eligibility violations at the interim analyses. The iDMC will alert the Sponsor if there are concerns about the appropriateness of the study population based on characteristics of enrolled patients, concerns about eligibility violations, or problems with protocol compliance.

The iDMC or the Study Clinical Scientist may request additional interim safety analyses if safety concerns arise.

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

# 4.0 STATISTICAL METHODS

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

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

All demography and baseline disease characteristics (collected at either the screening or baseline) will be summarized using the ITT population. In order to assess the conduct of the study, major protocol violations will be summarized and listed.

Overall response rate (ORR) 95% confidence intervals will be calculated using Clopper-Pearson methodology.

PFS will be analyzed by the Kaplan-Meier (KM) approach. The analysis of PFS will be based on the survivor function, which is the probability of remaining event free beyond a certain point in time. The survival function will be estimated and summarized using the 25th and 75th percentiles, median survival, and a 95% confidence interval (CI) for the median.

OS will also be analyzed by the Kaplan-Meier (KM) approach. Patients without follow-up assessment will be censored at the day of last study medication, and patients with no post-

baseline information will be censored at baseline. OS will be summarized using the 25th and 75th percentiles, median survival, and a 95% confidence interval (CI) for the median.

## 4.1 Analysis Population

### 4.1.1 Intent–to-Treat (ITT) population

Intent-to-Treat (ITT) population is defined as all the patients who are enrolled in the study.

### 4.1.2 Safety population

Safety population will include all those patients who have received at least one dose of study medication.

## 4.2 Analysis of Study Conduct

This is a multi-centric, open-labeled, non-randomized post-marketing study, to assess the safety and efficacy of Pertuzumab in combination with Trastuzumab and Docetaxel. The study design employs standard methods for safety studies in patients with cancer. All patients will receive the active treatment. Safety will be carefully evaluated, and the type of data collected and the frequency with which patients are monitored will ensure safety of the patients.

The eligible patients for this study are the male or female patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer (locally recurrent, unresectable, or metastatic) who have not previously received systemic non-hormonal anticancer therapy in the metastatic setting.

The analysis for different parameters is described below:

### 4.2.1 Demographics and Baseline Characteristics

Subject demographics include Age, Gender, Race, Ethnicity, Height, and Weight.

Variables that are measured on a continuous scale, which includes the age, weight, and height, BMI of the subject the number of non-missing observations, mean, median, SD, minimum, and maximum will be presented and variables that are measured on a categorical scale, which include gender, ethnicity the frequency count and percentages will be represented.

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

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

## 4.3 Primary And Secondary Analysis

### 4.3.1 Primary Analysis

The primary analyses are on safety and tolerability evaluation of pertuzumab (in combination with trastuzumab and docetaxel) in Indian patients. Primary safety and tolerability analysis will be summarized for the Safety population.

- **Incidence and severity of AEs and serious adverse events (SAEs)** by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03

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

  • The incidence of AEs and SAEs
    - Overall
    - By TEAEs and Non-TEAEs
    - By severity using NCI CTCAE version 4.03
    - By relationship to study drug
    - By action taken with study drug
    - By outcome

  Incidences and Severity will be summarized by frequency count and percentages. 95% confidence intervals will be calculated using Clopper-Pearson for incidences.

- **Incidence of CHF** will be summarized by frequency count and percentages.

- **Significant decline in LVEF** will be summarized by frequency count and percentages.

- **Change in LVEF** will be summarized by cycle including change from baseline summaries and frequency count and percentages.

- **Laboratory data** will be analyzed by the number of non-missing observations, mean, median, SD, minimum, and maximum. Shift table will be presented to show the change from baseline to different visits.

- **Incidence of AEs leading to discontinuation, modification or interruption of study medication** will be summarized by frequency count and percentages.

- **The incidence and cause of deaths due to AE** will be summarized by frequency count and percentages.

### 4.3.2 Secondary Analysis

Secondary Efficacy variables will be summarized for the intent-to-treat (ITT) population.
The secondary analyses are on efficacy evaluation of pertuzumab in combination with trastuzumab and docetaxel in Indian patients with respect to:

- **Overall response rate (ORR)**

  Overall response (partial response [PR] plus complete response [CR]) determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) criteria).
  The analysis of ORR is based on the best (confirmed) overall response (BOR). Best (confirmed) overall response (BOR) is defined as the best response recorded from the start of trial treatment until disease progression/recurrence or death. To be assigned a

status of PR or CR (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder.

Patients without a post-baseline tumor assessment will be considered to be non-responders.
Overall response rate (ORR) 95% confidence intervals will be calculated using Clopper-Pearson methodology.

- **Progression-free survival (PFS)**

  Progression-free survival (PFS), defined as the time from enrollment to the first occurrence of disease progression as determined by the investigator using RECIST criteria version 1.1, or death from any cause, whichever occurs first. Patients who have not progressed, died or lost to follow up at the time of the analysis will be censored on the last visit at which assessment for progression was done (two years after the last patient enrolled).

  PFS will be analyzed by the Kaplan-Meier (KM) approach.

  Patients without post baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment.

  The analysis of PFS will be based on the survivor function, which is the probability of remaining event free beyond a certain point in time. The survival function will be estimated and summarized using the 25th and 75th percentiles, median survival, and a 95% confidence interval (CI) for the median.

- **Overall Survival (OS)**

  Overall survival, defined as the time from the date of enrollment to the date of death, regardless of the cause of death. Patients who will be alive at the time of the analysis will be censored at the date of the last follow-up assessment (two years from last patient enrolled in the study).

  OS will also be analyzed by the Kaplan-Meier (KM) approach.

  Patients without follow-up assessment will be censored at the day of last study medication, and patients with no post-baseline information will be censored at baseline. OS will be summarized using the 25th and 75th percentiles, median survival, and a 95% confidence interval (CI) for the median.

## 4.4 Safety Analysis

The analysis of safety assessments in this study will include summaries of the following categories of safety data collected for each subject. It will be performed on safety population.

- Adverse event
- Concomitant medications
- Physical Examination (PE)
- Vital signs
- Pregnancy test results
- Eastern Cooperative Oncology Group (ECOG)
- Body weight

Data for continuous variables will be summarized descriptively using number of subjects (n), mean, SD, median, Range (minimum and maximum). Categorical data will be presented by number of exposed subjects along with percentage of exposed subjects in the various categories of the endpoint.

**Adverse Events**

AEs and SAEs will be coded by System organ class and preferred term, using the latest version 18.1 of MedDRA and will be summarized by frequency count and percentages.

**Concomitant Medications**

Concomitant medications will be coded by drug class and therapeutic class using the WHODD dated 1st Sep 2015 and will be summarized by frequency count and percentages.

**Physical Examinations**

Physical examination will be summarized for each body system such as head, eyes, ears, nose, and throat, and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems will be summarized by frequency count and percentages.

**Vital signs**

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position descriptively using number of subjects (n), mean, SD, median, Range (minimum and maximum) for each visit and change from screening visit to all visits will also be summarized.

**Laboratory Parameters**

Laboratory parameters will be summarized for actual values at each visit, and change from screening visit to each visit. Actual values for each parameter will also be listed by subject. Shift tables for each laboratory parameter will also be prepared to represent the shift from screening to end of study. Laboratory data will be summarized as per the descriptive statistics mentioned above for numeric data.

**ECOG**

Score for ECOG test will be summarized using frequency count with number of subjects in a particular class along with percentages of subjects.

## 4.5 Missing Data

No statistical imputation method will be applied for any missing values.

## 4.6 Interim Analyses

There will be two interim analyses for safety and efficacy. The first interim analysis is for safety only and will take place after 50% patients have been enrolled and followed for at least 6 months of Pertuzumab therapy. The second interim analysis includes both safety and efficacy components and will take place after approximately 67% of the required deaths have been observed.

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

## 4.7 Additional Analyses

If any additional statistical analyses required during the final analysis, appropriate methods will be used, and any changes, including the rationale for use, will be documented via Statistical Analysis Plan amendment. Any deviations from the planned analyses or prospective amendments to the statistical analysis plan will be documented in the Clinical Study Report (CSR).

## 4.8 Data Listings

All CRF data, as well as any outcomes derived from the data, will be summarised in detailed data listings. Patient data listings will be presented for all patients enrolled into the study.

## 4.9 Plots and Figures

The plots and graphs will be presented to illustrate the analysis of safety and efficacy.

- A K-M plot of survival probability versus time will be generated to see the overall survival profile of the patients for the single treatment group.
- A K-M plot of PFS probability versus time will be generated to see the PFS profile of the patients for the single treatment group.
- A bar chart will be generated to understand the response rate of patients as per RECIST criteria.
- A graph of LVEF over a period of time for all patients (Including mean and median)

# 5.0 REFERENCES


1. ICH E3: Structure and content of Clinical Study Reports, November 1995, Committee for Proprietary Medicinal Products.
2. ICH E9: Statistical Principles for Clinical Trials, September 1998, Committee for Proprietary Medicinal Products.

# Appendix 1 Protocol Synopsis

# Appendix 2 Schedule of Assessments

| Study Activities | Screening | Treatment period[14] | Unscheduled Visit[14] | Follow up Period[14] | | |
|---|---|---|---|---|---|---|
| | Day -7 to -1 | Each Treatment Cycle, (21 days) | | Safety Follow up visit - 28 days from Last treatment cycle[15] | 3 monthly Follow up visits - starting after safety follow-up visit | End of study visit[16] |
| Informed Consent[1] | X | | | | | |
| Demographics & medical history[2] | X | | | | | |
| Concomitant medication[3] | X | X | X | X | X | X |
| Complete physical examination[4] | X | X | X | X | X | X |
| Vital signs[5] | X | X | X | X | X | X |
| Height | X | | | | | |

| Study Activities | Screening | Treatment period[14] | Unscheduled Visit[14] | Follow up Period[14] | | |
|---|---|---|---|---|---|---|
| | Day -7 to -1 | Each Treatment Cycle, (21 days) | | Safety Follow up visit - 28 days from Last treatment cycle[15] | 3 monthly Follow up visits - starting after safety follow-up visit | End of study visit[16] |
| Weight | X | X | | X | | |
| HER2 Reports review for eligibility[5] | X | | | | | |
| Tumor evaluation[7] | X | Every 3 cycles of Monoclonal antibody * | | If disease progression not yet established | If disease progression not yet established | If disease progression not yet |
| Laboratory Investigations[8] | X | X | | X | | |
| ECOG performance status[9] | X | Every 3 cycles of monoclonal antibody | X | X | | X |
| LVEF[10] | X | Every 3 cycles of monoclonal antibody | | X | X | |

| Study Activities | Screening | Treatment period[14] | Unscheduled Visit[14] | Follow up Period[14] | | |
|---|---|---|---|---|---|---|
| | Day -7 to -1 | Each Treatment Cycle, (21 days) | | Safety Follow up visit - 28 days from Last treatment cycle[15] | 3 monthly Follow up visits - starting after safety follow-up visit | End of study visit[16] |
| SAEs and AEs[11] | | X | X | X | X | X |
| Pregnancy test[12] | X | Every 3 cycles of monoclonal antibody | | X | At 4 and 7 months after the last dose of monoclonal antibody | |
| Administration of study medication | | X | | | | |
| Infusion reactions during infusion and observation period | | X | | | | |
| Survival[13] | X | X | | X | X | X |

**Notes:**

1. Signed/dated informed consent in language comprehended by the potential ;clinical trial subject/LAR
2. Complete medical history and demographics (i.e., age, sex, race, and ethnicity, if applicable) and all medications taken during the last 28 days prior to screening visit will be collected.
3. Current concomitant medication will be recorded at Screening and on an ongoing basis.

4. Physical Examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the AE eCRF.
5. Vital signs will be assessed before treatment on Day 1 of every treatment cycle (pertuzumab, trastuzumab, and chemotherapy), recorded again after infusion during the observation period of each study medication. Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and oral or axillary temperature.
6. Documented evidence of HER2 positive status from previous testing is acceptable, otherwise HER2-positive status on fixed tissue blocks from the primary tumor (and/or metastatic site, if primary tumor not available) to be assessed locally by IHC and/or ISH according to institutional criteria and routine clinical practice. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.
7. A CT or MRI and (if indicated) isotope bone scan (evaluation according to RECIST criteria) should be performed at screening and as clinically indicated. Scans at screening should not be older than 28 days prior to first study medication administration. NB: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
8. Laboratory Assessment as per routine standard of care must be performed within 3 days (with results available) prior to the administration of study medication. Hematology, as per routine standard of care, may include hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, other cells). Serum chemistry, as per routine standard of care, may include sodium, potassium, calcium, chloride, magnesium, BUN (urea), uric acid, total protein, albumin, ALP, ALAT, ASAT, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin, creatinine, and blood glucose and calculated creatinine clearance at baseline. Coagulation tests will consist of INR and aPTT or PTT).
9. ECOG PS to be recorded every 3 cycles until PD.
10. LVEF $\geq$50% at Screening period to be determined by either ECHO or MUGA scan (with ECHO as the preferred method). The same method of LVEF assessment (ECHO or MUGA) must be used for the same patient throughout the study and, to the extent possible, be obtained at the same institution.
11. After informed consent, and prior to dosing, SAEs considered related to a study mandated procedure are reportable. As of cycle 1 all AEs and SAEs considered will be collected. AEs and SAEs to be monitored continuously collected and End-of-study visit and to be recorded with grading according to NCI-CTCAE, Version 4.03
12. For women of childbearing potential, serum $\beta$-HCG test must be performed within 7 days prior to the first dose of study treatment with the result available prior to first dosing. Urine $\beta$-HCG test must be performed within 7 days prior to every 3rd cycles (with results available prior to treatment), at

the safety follow up visit, and at 4 and 7 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

13. Overall survival is the time from the date of enrollment to the date of death, regardless of the cause of death. Patients who were alive at the time of the analysis will be censored at the date of the last follow-up assessment (two years from last patient enrolled in the study).
14. All treatment visits within ±3 days of scheduled treatment day; 28 day Safety Follow up visit within ±3 days of the scheduled visit date; 3 monthly Follow up visits (starting after safety follow-up visit) within ±14 days of the scheduled visit date(s); End of Study visit within ±14 days of the scheduled visit date. Tumour assessment ±3 days of planned scheduled visit. At the end of study visit, if patient does not fit into end of study definition, then tumour assessment to be done as per institutional criteria and routine clinical practice.
15. Patients who complete the study or discontinue from the study early will be asked to return to the hospital within 28 days after the last dose of study drug for the end-of-study visit.

## 14.1 Demographics and Baseline Characteristics

### 14.1.1 Patient Disposition

**Table 14.1.1.1 Summary of Inclusion/Exclusion Criteria – All Population (N=XXX)**

| Inclusion/Exclusion Criteria, n (%)[1] | Pertuzumab (N=XXX) |
|---|---|
| Number of Subjects Screened | XXX |
| Number of Subjects Enrolled [1] | XX (XX.X %) |
| Number of Subjects Enrolled meeting all Inclusion Criteria | XX (XX.X %) |
| Number of Subjects meeting at least one exclusion criteria | XX (XX.X %) |

**Source: Listing 16.2.3**

**Note:** [1] Percentage will be calculated by taking respective column header count as denominator.

**General Note:**

- Subjects who are meeting inclusion and exclusion criteria will be considered for eligibility analysis.
- Subjects who are eligible will be considered to enroll into the study.

**Table 14.1.1.2 Summary of Patient Disposition-All Population (N=XXX)**

| Patient Disposition, n (%) [1] | Pertuzumab (n=xxx) |
|---|---|
| **Population** | |
| Screened Population | XX |
| Intent-to-Treat Population | XX (XX.X %) |
| Safety Population | XX (XX.X %) |
| **Patients who completed the protocol** | |
| Yes | XX (XX.X %) |
| No | XX (XX.X %) |
| **Reason for discontinuation of study treatment** | |
| Withdrawal of Consent | XX (XX.X %) |
| Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study | XX (XX.X %) |
| Investigator or Sponsor determines it is in the best interest of the patient | XX (XX.X %) |
| Patient Non-compliance | XX (XX.X %) |
| Death | XX (XX.X %) |
| Death due to Disease Progression [2] | XX (XX.X %) |
| Disease Progression | XX (XX.X %) |
| Lost to follow-up | XX (XX.X %) |
| Due to AE | XX (XX.X %) |
| Other [3] | XX (XX.X %) |

**Source Data: Listing 16.2.1, 16.2.2.1 and 16.2.2.2**

**Note:**

[1] Percentages will be calculated using (N=XXX) of column header group as denominator.

[2] Percentages will be calculated using (N=XXX) of Death Count as denominator.
[3] If the reason is others, then it will be specified.

**Table 14.1.1.3 Summary of Patient Disposition by Site- ITT Population (N=XXX)**

| Site, n (%) [1] | Pertuzumab (N=XX) |
|---|---|
| **Site 1** | XX (XX.X %) |
| **Site 2** | XX (XX.X %) |
| **Site 3** | XX (XX.X %) |
| **Site 4** | XX (XX.X %) |
| **Site 5** | XX (XX.X %) |
| …… | …… |
| **Site n** | XX (XX.X %) |

**Source Data: Listing 16.2.1**

**Note:**

[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Table 14.1.1.4 Summary of Subject Follow-up Rate at each Visit- ITT Population (N=XXX)**

| Visit, n (%)[1] | Pertuzumab (N=XX) |
|---|---|
| 7 Days before Procedure | XX (XX.X %) |
| Cycle 1 | XX (XX.X %) |
| Cycle 2 | XX (XX.X %) |
| Cycle 3 | XX (XX.X %) |
| Cycle 4 | XX (XX.X %) |
| Cycle 5 | XX (XX.X %) |
| Cycle 6 | XX (XX.X %) |
| …… | …… |
| 28 Days after Last treatment cycle | XX (XX.X %) |
| 3 months Follow up visits | XX (XX.X %) |
| 6 months Follow up visits | XX (XX.X %) |
| …… | …… |
| n (every 3 months) Follow up visits | XX (XX.X %) |
| End of study | XX (XX.X %) |

**Source Data: Listing 16.2.1**

**Note:**

[1] Percentages will be calculated using column header group as denominator.

**Programming Note:**

- The same table will include the analysis for the remaining available cycle after cycle 6 and also after every 3 months follow up visits.

## 14.1.2 Demographic and Baseline Characteristics

### Table 14.1.2.1 Summary of Patient Demographics at Screening- ITT Population (N=XXX)

| Demographics | Statistics / Category, n(%)[1] | Pertuzumab (N=XX) |
|---|---|---|
| **Age (years) [2]** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| | Missing [3] | XX (XX.X %) |
| **Gender** | | |
| | Male | XX (XX.X %) |
| | Female | XX (XX.X %) |
| | Missing [3] | XX (XX.X %) |
| **Race** | | |
| | Asian | XX (XX.X %) |
| | Others | XX (XX.X %) |
| | Missing [3] | XX (XX.X %) |
| **Ethnicity** | | |
| | Indian Subcontinent | XX (XX.X %) |
| | Others | XX (XX.X %) |
| | Missing [3] | XX (XX.X %) |

**Source Data: Listing 16.2.4.1**
**Note:**
[1]Percentages will be calculated using respective column header group as denominator.

[2]If Date of Birth date is given then to calculate the Age by following formula: Age = {[Date of Informed Consent signed (Screening Date) – Date of Birth +1] /365.25

[3]If a particular parameter measurement is not captured, it will be displayed under ‘Missing’ category.

**Table 14.1.2.2 Summary of Medical History at Screening- ITT Population (N=XXX)**

| Medical History | Statistics/Category, n (%)[1] | Pertuzumab (N=XX) |
|---|---|---|
| **Any clinically significant disease other than the breast cancer** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **If Yes, Medical/ Surgical History [2]** | | |
| | History 1 | XX (XX.X %) |
| | History 2 | XX (XX.X %) |
| | History 3 | XX (XX.X %) |
| | History 4 | XX (XX.X %) |
| **History 1** | | |
| **Ongoing** | | XX (XX.X %) |
| **Subject on any Medications** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| ..... | ..... | ..... |

**Source Data: Listing 16.2.4.2**

Note:

[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

[2] Percentages will be calculated using 'Yes' category of 'Any clinically significant disease other than the breast cancer' as denominator.

**Programming Note:**

- The same table will include Medical History- History 2, History 3 and so on.

**Table 14.1.2.3 Summary of Breast Cancer Disease History at Screening- ITT Population (N=XXX)**

| Breast Cancer Disease History | Statistics/Category, n (%)[1] | Pertuzumab (N=XX) |
|---|---|---|
| **How was breast cancer diagnosed** | | |
| | Cytologically | XX (XX.X %) |
| | Histologically | XX (XX.X %) |
| | Both | XX (XX.X %) |
| **Breast cancer stage at initial diagnosis** | | |
| | I | XX (XX.X %) |
| | II | XX (XX.X %) |
| | III | XX (XX.X %) |
| | IV | XX (XX.X %) |
| **History of Primary Tumor** | | |
| **Location of Primary Tumor** | | |
| | Left | XX (XX.X %) |
| | Right | XX (XX.X %) |
| | Left and Right | XX (XX.X %) |
| | Unknown | XX (XX.X %) |
| **Was the primary tumor** | | |
| | Unifocal | XX (XX.X %) |
| | Multifocal | XX (XX.X %) |
| | Multicentric | XX (XX.X %) |
| **Primary tumor size (mm)** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Breast cancer subtype** | | |

| | | |
|---|---|---|
| | Infiltrating Ductal Carcinoma | XX (XX.X %) |
| | Infiltrating Lobular Carcinoma | XX (XX.X %) |
| | Inflammatory Breast Carcinoma | XX (XX.X %) |
| | Other | XX (XX.X %) |
| **Histological grade** | | |
| | Well Differentiated | XX (XX.X %) |
| | Moderately Differentiated | XX (XX.X %) |
| | Poorly Differentiated | XX (XX.X %) |
| | Anaplastic | XX (XX.X %) |
| | Unknown | XX (XX.X %) |
| **Nuclear grade** | | |
| | Grade 1 | XX (XX.X %) |
| | Grade 2 | XX (XX.X %) |
| | Grade 3 | XX (XX.X %) |
| | Grade 4 | XX (XX.X %) |
| **Estrogen receptor status** | | |
| | Estrogen Receptor Positive | XX (XX.X %) |
| | Estrogen Receptor Negative | XX (XX.X %) |
| **Progesterone receptor status** | | |
| | Progesterone Receptor Positive | XX (XX.X %) |
| | Progesterone Receptor Negative | XX (XX.X %) |
| **Breast cancer type** | | |
| | Operable | XX (XX.X %) |
| | Locally Advanced Inoperable | XX (XX.X %) |
| | Inflammatory | XX (XX.X %) |
| **Breast Tumor Remnants Microscopic Assessments** | | |
| | Single Focus(mm) | |
| | n | XX |
| | Mean | XX.X |

| | | |
|---|---|---|
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| | Multiple foci Largest Diameter(mm) | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| | Tumour Largest Diameter(mm) | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Macroscopic assessment** | | |
| | Gross tumor size | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) |
| **Pathological staging of breast cancer** | | |
| | Known | XX (XX.X %) |
| | Unknown | XX (XX.X %) |
| **Histology** | | |
| **Histological grade** | | |
| | Well Differentiated | XX (XX.X %) |
| | Moderately Differentiated | XX (XX.X %) |
| | Poorly Differentiated | XX (XX.X %) |

| | | |
|---|---|---|
| | Anaplastic | XX (XX.X %) |
| | Unknown | XX (XX.X %) |
| **Breast cancer subtype** | | |
| | Ductal | XX (XX.X %) |
| | Lobular | XX (XX.X %) |
| | Other | XX (XX.X %) |
| **Is DCIS (Ductal carcinoma in situ) present** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Diagnosis of metastatic or Locally recurrent Breast Cancer** | | |
| | Locally Recurrent | XX (XX.X %) |
| | Metastatic | XX (XX.X %) |
| **HER2 Confirmation If Metastatic** | | |
| **Method** | | |
| | Immunohistochemistry (IHC) | XX (XX.X %) |
| | In situ hybridization (ISH) | XX (XX.X %) |
| **Expression Score** | | |
| **IHC** | | |
| | 0 | XX (XX.X %) |
| | 1+ | XX (XX.X %) |
| | 2+ | XX (XX.X %) |
| | 3+ | XX (XX.X %) |
| **ISH** | | |
| | Negative (Non-Amplified) | XX (XX.X %) |
| | Positive (Amplified) | XX (XX.X %) |
| **Progesterone Receptor Score if Metastatic** | | |
| | Positive | XX (XX.X %) |
| | Negative | XX (XX.X %) |
| | Unknown | XX (XX.X %) |

| | | |
|---|---|---|
| **Estrogen Receptor Score if Metastatic** | | |
| | Positive | XX (XX.X %) |
| | Negative | XX (XX.X %) |
| | Unknown | XX (XX.X %) |
| **Any previous therapy for Breast Cancer prior to Study** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |

**Source Data: Listing 16.2.4.3**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Table 14.1.2.4 Summary of Previous Therapy for Breast Cancer at Screening- ITT Population (N=XXX)**

| Previous Therapy [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Has the patient received any hormone therapy** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **If Yes, Ongoing [2]** | | XX (XX.X %) |
| **Has the patient received any Immunotherapy** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **If Yes, Ongoing [3]** | | XX (XX.X %) |
| **Has the patient received any Biologic therapy** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **If Yes, Ongoing [4]** | | XX (XX.X %) |
| **Has the patient received any Radiotherapy** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **If Yes, Ongoing [5]** | | XX (XX.X %) |
| **Has the patient received any chemotherapy** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |

| | |
|---|---|
| **If Yes, Ongoing [6]** | XX (XX.X %) |

**Source Data: Listing 16.2.4.4, 16.2.4.5, 16.2.4.6, 16.2.4.7, 16.2.4.8, and 16.2.4.9**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.
[2] Percentages will be calculated using 'Yes' category of 'Patients receiving Hormone Therapy' as denominator.
[3] Percentages will be calculated using 'Yes' category of 'Patients receiving Immunotherapy' as denominator.
[4] Percentages will be calculated using 'Yes' category of 'Patients receiving Biologic Therapy' as denominator.
[5] Percentages will be calculated using 'Yes' category of 'Patients receiving Radiotherapy' as denominator.
[6] Percentages will be calculated using 'Yes' category of 'Patients receiving chemotherapy' as denominator.

**Table 14.1.2.5 Summary of Physical Examination at Screening- ITT Population (N=XXX)**

| System/Result/Significance [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **General appearance** | | |
| **Results** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| **Clinical Significance** | | |
| | NCS | XX (XX.X %) |
| | CS | XX (XX.X %) |
| **Musculoskeletal** | | |
| **Results** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| **Clinical Significance** | | |
| | NCS | XX (XX.X %) |
| | CS | XX (XX.X %) |
| **Dermatological** | | |
| **Results** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| **Clinical Significance** | | |
| | NCS | XX (XX.X %) |
| | CS | XX (XX.X %) |
| **Gastrointestinal** | | |
| **Results** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| | Not Done | XX (XX.X %) |

| | | |
|---|---|---|
| **Clinical Significance** | | |
| | NCS | XX (XX.X %) |
| | CS | XX (XX.X %) |
| **HEENT** | | |
| **Results** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| **Clinical Significance** | | |
| | NCS | XX (XX.X %) |
| | CS | XX (XX.X %) |
| **Respiratory** | | |
| **Results** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| **Clinical Significance** | | |
| | NCS | XX (XX.X %) |
| | CS | XX (XX.X %) |
| **Cardiovascular** | | |
| **Results** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| **Clinical Significance** | | |
| | NCS | XX (XX.X %) |
| | CS | XX (XX.X %) |
| **Genitourinary** | | |
| **Results** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| **Clinical Significance** | | |
| | NCS | XX (XX.X %) |
| | CS | XX (XX.X %) |

| | | |
|---|---|---|
| **Neurological** | | |
| **Results** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| **Clinical Significance** | | |
| | NCS | XX (XX.X %) |
| | CS | XX (XX.X %) |
| **Other** | | |
| **Results** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| **Clinical Significance** | | |
| | NCS | XX (XX.X %) |
| | CS | XX (XX.X %) |

**Source Data: Listing 16.4.2**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Table 14.1.2.6 Summary of Vital Signs at Screening- ITT Population (N=XXX)**

| Vital Signs [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Pulse Rate (rate/min)** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Respiratory Rate (breathes/min)** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Blood Pressure (mm/hg)** | | |
| **Systolic** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Diastolic** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Temperature (°C)** | | |
| | n | XX |
| | Mean | XX.X |

| | | |
|---|---|---|
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Height (cms.)** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Weight (kgs.)** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |

**Source Data: Listing 16.4.1**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Table 14.1.2.7 Summary of Assessment at Screening- ITT Population (N=XXX)**

| Assessment [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **HER2 Determination** | | |
| **Assessment Performed** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **IHC Result** | 0/+ | XX (XX.X %) |
| | ++ | XX (XX.X %) |
| | +++ | XX (XX.X %) |
| **ISH Result** | Negative | XX (XX.X %) |
| | Positive | XX (XX.X %) |
| **CT/MRI** | | |
| **Any clinically significant abnormalities noted in the CT/MRI** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Isotope Bone Scan** | | |
| **Result** | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |

**Source Data: Listing 16.4.3**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Table 14.1.2.8 Summary of Tumor/Disease Assessment at Screening- ITT Population (N=XXX)**

| Assessment [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Tumor/Disease Assessment** | | |
| **Any target lesions** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Lesion measurable** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Reason** | Tumour too large to accurately measure | XX (XX.X %) |
| | Tumour too small to accurately measure | XX (XX.X %) |
| | Other Reason | XX (XX.X %) |
| **Target Lesions** | | |
| **Sum of longest diameters** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Inflammatory Breast Cancer** | | |
| **Erythema** | No | XX (XX.X %) |
| | Less than 1/3 of breast | XX (XX.X %) |
| | More than 1/3 of breast | XX (XX.X %) |
| **Edema** | No | XX (XX.X %) |
| | Less than 1/3 of breast | XX (XX.X %) |
| | More than 1/3 of breast | XX (XX.X %) |

| | | |
|---|---|---|
| **Are there any non-target(non-measurable) lesions** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Method of Assessment** | CT with Contrast | XX (XX.X %) |
| | CT without Contrast | XX (XX.X %) |
| | MRI with Contrast | XX (XX.X %) |
| | MRI without Contrast | XX (XX.X %) |
| Status of Lesion | Present | XX (XX.X %) |
| | Absent | XX (XX.X %) |
| | Unequivocal Progression | XX (XX.X %) |
| | Screening/Baseline Assessment | XX (XX.X %) |
| **Number Of Non-Target Lesions Within The Organ** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |

**Source Data: Listing 16.4.3**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Table 14.1.2.9 Summary of LVEF and CHF at Screening- ITT Population (N=XXX)**

| LVEF [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Results (%)** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **LVEF done by** | | |
| | MUGA | XX (XX.X %) |
| | Echocardiography | XX (XX.X %) |
| **If Echocardiography, method [2]** | | |
| | Simpson (2-D) | XX (XX.X %) |
| | Teichholz (M-mode) | XX (XX.X %) |
| **LVEF finding** | | |
| | Normal | XX (XX.X %) |
| | Abnormal but not clinically significant | XX (XX.X %) |
| | Abnormal and clinically significant | XX (XX.X %) |
| **Any new cardiac signs and symptoms** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Any worsening cardiac signs and symptoms** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Any signs or symptoms of CHF** | | |
| | Yes | XX (XX.X %) |

| | | |
|---|---|---|
| | No | XX (XX.X %) |

**Source Data: Listing 16.2.8.7**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.
[2] Percentages should be calculated using count “Echocardiography” of “LVEF done by” as denominator.

**Table 14.1.2.10 Summary of Hematology Test at Screening- ITT Population (N=XXX)**

| Test [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Hemoglobin** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Hematocrit** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Red Blood Cells (RBC)** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |

| | | |
|---|---|---|
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **White Blood Cells (WBC)** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| … | … | … |

**Source Data: Listing 16.2.8.1**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Programming Note:**

- The same table will also include other parameters of Hematology- Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Other Cells, and Platelet Count.

**Table 14.1.2.11 Summary of Coagulation Test at Screening- ITT Population (N=XXX)**

| Test [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **International normalization ratio(INR)** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Activated Partial Thromboplastin Time (aPTT)** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Partial Thromboplastin Time (PTT)** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |

| | | |
|---|---|---|
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |

**Source Data: Listing 16.2.8.2**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Table 14.1.2.12 Summary of Serum Chemistry at Screening- ITT Population (N=XXX)**

| Test [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Sodium** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Potassium** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Calcium** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |

| | | | |
|---|---|---|---|
| | **Out of Range** | Yes | XX (XX.X %) |
| | | No | XX (XX.X %) |
| | **Clinically Significant** | Yes | XX (XX.X %) |
| | | No | XX (XX.X %) |
| … | | … | … |

**Source Data: Listing 16.2.8.3**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Programming Note:**

- The same table will also include other parameters of Serum Chemistry- Chloride, Magnesium, BUN(urea), Uric acid, Total protein, Albumin, Alkaline Phosphatase, Alanine Transaminase (ALAT), Aspartate Aminotransferase(ASAT), Gamma Glutamyl Transferase(GGT), Lactate Dehydrogenase(LDH), Total Bilirubin, Creatinine, Blood Glucose and Creatinine Clearance.

**Table 14.1.2.13 Summary of Viral Serology at Screening- ITT Population (N=XXX)**

| Test [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **HIV I** | | |
| **Result** | Reactive | XX (XX.X %) |
| | Non-Reactive | XX (XX.X %) |
| **HIV II** | | |
| **Result** | Reactive | XX (XX.X %) |
| | Non-Reactive | XX (XX.X %) |
| **Hepatitis B surface antigen (HBsAG)** | | |
| **Result** | Reactive | XX (XX.X %) |
| | Non-Reactive | XX (XX.X %) |
| **Total Hepatitis B Core antibody (HBcAB)** | | |
| **Result** | Reactive | XX (XX.X %) |
| | Non-Reactive | XX (XX.X %) |
| **Hepatitis C Virus (HCV) antibody** | | |
| **Result** | Reactive | XX (XX.X %) |
| | Non-Reactive | XX (XX.X %) |

**Source Data: Listing 16.2.8.4**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Table 14.1.2.14 Summary of ECOG Performance Status and Reproductive Status at Screening- ITT Population (N=XXX)**

| Status [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **ECOG Performance Status** | | |
| **Grade** | 0 | XX (XX.X %) |
| | 1 | XX (XX.X %) |
| | 2 | XX (XX.X %) |
| | 3 | XX (XX.X %) |
| | 4 | XX (XX.X %) |
| **Reproductive Status** | | |
| **Response** | Childbearing Potential Without Contraceptive Protection | XX (XX.X %) |
| | Surgically Sterilized | XX (XX.X %) |
| | Childbearing Potential With Contraceptive Protection | XX (XX.X %) |
| | Post-Menopausal | XX (XX.X %) |

**Source Data: Listing 16.2.8.6**
**Note:** [1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Note: In ECOG Performance Status**
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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Grade 3= Capable of only limited selfcare, 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

**Table 14.1.2.15 Summary of Serum Pregnancy Test at Screening- ITT Population (N=XXX)**

| Result [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Was Serum Pregnancy Test Done** | | |
| | Done | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| | Not Applicable | XX (XX.X %) |
| **If done, results [2]** | Positive | XX (XX.X %) |
| | Negative | XX (XX.X %) |

**Source Data: Listing 16.2.8.5**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.
[2] Percentages will be calculated using “Done” category of “Was Serum Pregnancy Test Done” as denominator.

**Table 14.1.2.16 Summary of Survival Status at Screening- ITT Population (N=XXX)**

| Status [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Survival Status** | | |
| | Alive | XX (XX.X %) |
| | Dead | XX (XX.X %) |
| | Withdrew Consent | XX (XX.X %) |
| **Did patient's disease progress since the last evaluation** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| | Not Known | XX (XX.X %) |
| **If Yes, how disease progression was assessed[2]** | Clinical | XX (XX.X %) |
| | Radiological | XX (XX.X %) |
| | Both | XX (XX.X %) |
| | Others | XX (XX.X %) |

**Source Data: Listing 16.2.6.3**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.
[2] Percentages will be calculated using "Yes" category of "Did patient's disease progress since the last evaluation" as denominator.

## 14.2 Efficacy Analysis

**Table 14.2.1.1 Summary of Evaluation of target lesions as per RECIST Criteria at Each Visit- ITT Population (N=XXX)**

| Visits, n (%) [1] | Statistics/Category, n (%) | Pertuzumab (N=XXX) |
|---|---|---|
| **Cycle 3** | | |
| | **CR** | XX (XX.X %) |
| | **PR** | XX (XX.X %) |
| | **SD** | XX (XX.X %) |
| | **PD** | XX (XX.X %) |
| | **UA** | XX (XX.X %) |
| **Cycle 6** | | |
| | **CR** | XX (XX.X %) |
| | **PR** | XX (XX.X %) |
| | **SD** | XX (XX.X %) |
| | **PD** | XX (XX.X %) |
| | **UA** | XX (XX.X %) |
| **Cycle …** | | |
| | **CR** | XX (XX.X %) |
| | **PR** | XX (XX.X %) |
| | **SD** | XX (XX.X %) |
| | **PD** | XX (XX.X %) |
| | **UA** | XX (XX.X %) |
| **After 28 Days** | | |
| | **CR** | XX (XX.X %) |

| | | |
|---|---|---|
| | **PR** | XX (XX.X %) |
| | **SD** | XX (XX.X %) |
| | **PD** | XX (XX.X %) |
| | **UA** | XX (XX.X %) |
| **After 3 Months** | | |
| | **CR** | XX (XX.X %) |
| | **PR** | XX (XX.X %) |
| | **SD** | XX (XX.X %) |
| | **PD** | XX (XX.X %) |
| | **UA** | XX (XX.X %) |
| …… | …… | …… |
| **End of Study** | | |
| | **CR** | XX (XX.X %) |
| | **PR** | XX (XX.X %) |
| | **SD** | XX (XX.X %) |
| | **PD** | XX (XX.X %) |
| | **UA** | XX (XX.X %) |

**Source Data: Listing 16.2.6.1, 16.2.6.2**

**Note:**

[1] "n" denotes the number of subjects who would have completed X months in study from the date of randomization

[2] Percentage will be calculated taking respective "n" count as denominator.

**General Note:**

- Response will be calculated using RECIST 1.1.
- UA: Unable to assess

**Programming Note:**

- The same table will include the analysis for the remaining available cycle after cycle 6 and after every 3 months follow-up visits.
- Same mock-up will be used to generate the table for summary of evaluation of non-target lesions with change in table number and table title as:

**Table 14.2.1.1.1 Summary of Evaluation of non-target lesions as per RECIST Criteria at Each Visit – ITT Population (N=XXX)**

**Table 14.2.1.1.2 Summary of Overall Response as per RECIST Criteria at Each Visit – ITT Population (N=XXX)**

| Visits, n (%) [1] | Statistics/Category, n (%) | Aggressive Disease (N=XX) | Non-Aggressive Disease (N=XX) |
|---|---|---|---|
| **Cycle 3** | | | |
| | **CR** | XX (XX.X %) | XX (XX.X %) |
| | **PR** | XX (XX.X %) | XX (XX.X %) |
| | **SD** | XX (XX.X %) | XX (XX.X %) |
| | **PD** | XX (XX.X %) | XX (XX.X %) |
| | **UA** | XX (XX.X %) | XX (XX.X %) |
| **Cycle 6** | | | |
| | **CR** | XX (XX.X %) | XX (XX.X %) |
| | **PR** | XX (XX.X %) | XX (XX.X %) |
| | **SD** | XX (XX.X %) | XX (XX.X %) |
| | **PD** | XX (XX.X %) | XX (XX.X %) |
| | **UA** | XX (XX.X %) | XX (XX.X %) |
| **Cycle …** | | | |
| | **CR** | XX (XX.X %) | XX (XX.X %) |
| | **PR** | XX (XX.X %) | XX (XX.X %) |
| | **SD** | XX (XX.X %) | XX (XX.X %) |
| | **PD** | XX (XX.X %) | XX (XX.X %) |
| | **UA** | XX (XX.X %) | XX (XX.X %) |
| **After 28 Days** | | | |
| | **CR** | XX (XX.X %) | XX (XX.X %) |
| | **PR** | XX (XX.X %) | XX (XX.X %) |
| | **SD** | XX (XX.X %) | XX (XX.X %) |

| | | | |
|---|---|---|---|
| | **PD** | XX (XX.X %) | XX (XX.X %) |
| | **UA** | XX (XX.X %) | XX (XX.X %) |
| **After 3 Months** | | | |
| | **CR** | XX (XX.X %) | XX (XX.X %) |
| | **PR** | XX (XX.X %) | XX (XX.X %) |
| | **SD** | XX (XX.X %) | XX (XX.X %) |
| | **PD** | XX (XX.X %) | XX (XX.X %) |
| | **UA** | XX (XX.X %) | XX (XX.X %) |
| ..... | ..... | ..... | ..... |
| **End of Study** | | | |
| | **CR** | XX (XX.X %) | XX (XX.X %) |
| | **PR** | XX (XX.X %) | XX (XX.X %) |
| | **SD** | XX (XX.X %) | XX (XX.X %) |
| | **PD** | XX (XX.X %) | XX (XX.X %) |
| | **UA** | XX (XX.X %) | XX (XX.X %) |

**Source Data: Listing 16.2.6.2**

**Note:**

[1] "n" denotes the number of subjects who would have completed X months in study from the date of randomization

[2] Percentage will be calculated taking respective "n" count as denominator.

**General Note:**

- NE: Not evaluated

**Programming Note:**

- The same table will include the analysis for the remaining available cycle after cycle 6 and after every 3 months follow-up visits.

**Table 14.2.1.2 Summary of Responder – ITT Population (N=XXX)**

| Response, n (%) [1] | Pertuzumab (N=XX) | 95 % CI (Clopper-Pearson) |
|---|---|---|
| **Responder** | XX (XX.X %) | XX.X – XX.X |
| **Non-Responder** | XX (XX.X %) | XX.X – XX.X |

**Note:**

[1] Percentage will be calculated taking respective header count as denominator.

**General Note:**

- Patients without a post-baseline tumor assessment will be considered to be non-responders.

**Table 14.2.1.3 Summary of Best Overall Response – ITT Population (N=XXX)**

| Response, n (%) [1] | Pertuzumab (N=XX) |
|---|---|
| **Complete Response (CR)** | XX (XX.X %) |
| **Partial Response (PR)** | XX (XX.X %) |
| **Stable Disease (SD)** | XX (XX.X %) |
| **Progression Disease (PD)** | XX (XX.X %) |
| **Unable To Assess(UA)** | XX (XX.X %) |

**Note:**

[1] Percentage will be calculated taking respective header count as denominator.

**General Note:**

- Best Overall Response will be considered to be the best response, out of all the documented responses, patient has given in the entire study period.
- Patients having response as **"UA"** will not be included in the analysis.

**Table 14.2.1.4 Summary of Overall Response Rate (CR+PR) – ITT Population (N=XXX)**

| Response, n (%) [1] | Pertuzumab (N=XX) |
|---|---|
| **ORR (CR+PR)** | XX (XX.X %) |
| **Non-ORR (SD+PD)** | XX (XX.X %) |

**Note:**

[1] Percentage will be calculated taking respective header count as denominator.

**General Note:**

- Overall response rate will be calculated by considering patients having CR or PR as response.
- Patients having response as **"UA"** will not be included in the analysis.

**Table 14.2.1.5 Summary of Disease Control (CR+PR+SD) – ITT Population (N=XXX)**

| Response, n (%) [1] | Pertuzumab (N=XX) |
|---|---|
| **Disease Control (CR+PR+SD)** | XX (XX.X %) |
| **Disease Progression (PD)** | XX (XX.X %) |

**Note:**

[1] Percentage will be calculated taking respective header count as denominator.

**General Note:**

- Patients not having disease progression will be considered under disease control category.
- Patients having response as **"UA"** will not be included in the analysis.

**Table 14.2.1.6 Summary of Duration of Overall Response – ITT Population (N=XXX)**

| Statistics | Pertuzumab (N=XXX) |
|---|---|
| n | XX |
| Mean | X.XX |
| SD | X.XX |
| Median | X.XX |
| Range (Min.: Max.) | (XX.XX:XX.XX) |

**Source Data: Listing 16.2.2.1 and 16.2.6.2**

**General Note**:

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

**Table 14.2.1.7 Summary of Duration of Stable Disease – ITT Population (N=XXX)**

| Statistics | Pertuzumab (N=XXX) |
|---|---|
| n | XX |
| Mean | X.XX |
| SD | X.XX |
| Median | X.XX |
| Range (Min.: Max.) | (XX.XX:XX.XX) |

**Source Data: Listing 16.2.6.1 and 16.2.6.2**

**General Note**:

- Duration of stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

**Table 14.2.1.8 Summary of Progression Free Survival at Each Visit - ITT Population (N=XXX)**

| Visits | Category, n (%) [1] | Pertuzumab (N=XXX) |
|---|---|---|
| **Cycle 3** | | |
| | **n** | XX |
| | **Progression Free Patients** | XX (XX.X %) |
| **Cycle 6** | | |
| | **n** | XX |
| | **Progression Free Patients** | XX (XX.X %) |
| **Cycle …** | | |
| | **n** | XX |
| | **Progression Free Patients** | XX (XX.X %) |
| **After 28 Days** | | |
| | **n** | XX |
| | **Progression Free Patients** | XX (XX.X %) |
| **After 3 Months** | | |
| | **n** | XX |
| | **Progression Free Patients** | XX (XX.X %) |
| …… | …… | …… |
| **End of Study** | | |
| | **n** | XX |
| | **Progression Free Patients** | XX (XX.X %) |

**Source Data: Listing 16.2.6.1 and 16.2.6.2**

**Note:**

[1] "n" denotes the number of subjects who would have completed "X visits" in study from the date of randomization

[2] Percentage will be calculated taking respective "n" count as denominator.

**Programming Note:**

- The same table will include the analysis for the remaining available cycle after cycle 6 and after every 3 months follow-up visits.

**Table 14.2.1.9 Summary of Progression Free Survival by K-M Analysis – ITT Population (N=XXX)**

| Category, n (%) [1] | Pertuzumab (N=XX) |
|---|---|
| **Number (%) of Patients having Progression/death** | XX (XX.X %) |
| **Number (%) of censored Patients** | XX (XX.X %) |
| **Median duration of Progression Free Survival (95 % CI) [2]** | XX.X (XX.XX : XX.XX) |
| | |
| **Probability of progression free survival** | |
| **Cycle 3** | X.XXXX |
| **Cycle 6** | X.XXXX |
| **Cycle …** | X.XXXX |
| **After 28 Days** | X.XXXX |
| **After 3 Months** | X.XXXX |
| …… | …… |
| **End of the study** | X.XXXX |

**Source Data: Listing 16.2.6.1 and 16.2.6.2**

**Note:**

[1] Percentage will be calculated taking respective column header group count as denominator.

[2] The median duration of progression free survival will be estimated by Kaplan-Meier method and also 90% confidence interval will be calculated for the median duration of progression free survival.

**General Note:**

- Events are the documented progression or death due to any cause.
- Censoring: Subjects without occurrence of progression or death during study period, drop outs and lost-to-follow up subjects are censored at the time of last follow-up visit.

**Programming Note:**

- The duration will be considered as difference between first drug administration to date of documented progression or death due to any cause.
- The probability of survival at any visit will be derived by the "OUTSERVE =" option of PROC LIFETEST. The probability from Survival Distribution Function in dataset derived by "OUTSERVE =" option will be represented at each specified time point.
- The same table will include the analysis for the remaining available cycle after cycle 6 and after every 3 months follow-up visits.
- Same mock-up will be used to generate the table for Aggressive vs. Non-aggressive by specifying "Disease Status" as STRATA in PROC LIFETEST with change in table number and table title as:

**Table 14.2.1.10 Summary of Progression Free Survival by K-M Analysis for Disease Status – ITT Population (N=XXX)**

- Same mock-up will be used to generate the table for treatment only for those patients who have prior anti-HER2 treated patients and Hormone Receptor Status with change in table number and table title as:

**Table 14.2.1.11 Summary of Progression Free Survival by K-M Analysis for Prior anti-HER2 treated patients – ITT Population (N=XXX)**

**Table 14.2.1.12 Summary of Progression Free Survival by K-M Analysis for Hormone Receptor status – ITT Population (N=XXX)**

**Table 14.2.1.13 Summary of Overall Survival at Each Visit – ITT Population (N=XXX)**

| Visits | Category, n (%) [1] | Pertuzumab (N=XXX) |
|---|---|---|
| **Cycle 3** | | |
| | **n** | XX |
| | **Alive Patients** | XX (XX.X %) |
| **Cycle 6** | | |
| | **n** | XX |
| | **Alive Patients** | XX (XX.X %) |
| **Cycle …** | | |
| | **n** | XX |
| | **Alive Patients** | XX (XX.X %) |
| **After 28 Days of last dose** | | |
| | **n** | XX |
| | **Alive Patients** | XX (XX.X %) |
| **After 3 Months** | | |
| | **n** | XX |
| | **Alive Patients** | XX (XX.X %) |
| **After 6 Months** | | |
| | **n** | XX |
| | **Alive Patients** | XX (XX.X %) |
| …… | …… | …… |

| | | |
|---|---|---|
| **End of the Study** | | |
| | **n** | XX |
| | **Alive Patients** | XX (XX.X %) |

**Source Data: Listing 16.2.6.3**

**Note:**

[1] "n" denotes the number of subjects who would have completed X months in study from the date of randomization

[2] Percentage will be calculated taking respective "n" count as denominator.

**Programming Note:**

- The same table will include the analysis for the remaining available cycle after cycle 6 and after every 3 months follow-up visits.

**Table 14.2.1.14 Summary of Overall Survival by K-M Analysis – ITT Population (N=XXX)**

| Category, n (%) [1] | Pertuzumab (N=XX) |
|---|---|
| **Number (%) of Patients having death** | XX (XX.X %) |
| **Number (%) of censored Patients** | XX (XX.X %) |
| **Median duration of Overall Survival (90 % CI) [2]** | XX.X (XX.XX : XX.XX) |
| | |
| **Probability of overall survival** | |
| **Cycle 3** | 0.XXXX |
| **Cycle 6** | 0.XXXX |
| **Cycle …** | 0.XXXX |
| **After 28 Days** | 0.XXXX |
| **After 3 Months** | 0.XXXX |
| …… | …… |
| **End of the study** | 0.XXXX |

**Source Data: Listing 16.2.6.1**

**Note:**

[1] Percentage will be calculated taking respective column header group count as denominator.

[2] The median duration of overall survival will be estimated by Kaplan-Meier method and also 90% confidence interval will be calculated for the median duration of overall survival.

**General Note:**

- Events are the documented death of the patient due to any cause.
- Censoring: Subjects without occurrence of death during study period, drop outs and lost-to-follow up subjects are censored at the time of last follow-up visit.

**Programming Note:**

- The same table will include the analysis for the remaining available cycle after cycle 6 and after every 3 months follow-up visits.
- The duration will be considered as difference between first drug administrations to date of documented death of any patient.
- The probability of survival at any visit will be derived by the "OUTSERVE =" option of PROC LIFETEST. The probability from Survival Distribution Function in dataset derived by "OUTSERVE =" option will be represented at each specified time point.
- Same mock-up will be used to generate the table for Aggressive vs. Non-aggressive by specifying "Disease Status" as STRATA in PROC LIFETEST with change in table number and table title as:

**Table 14.2.1.15 Summary of Overall Survival by K-M Analysis for Disease Status – ITT Population (N=XXX)**

- Same mock-up will be used to generate the table for treatment only for those patients who have prior anti-HER2 treated patients and Hormone Receptor Status with change in table number and table title as:

**Table 14.2.1.16 Summary of Overall Survival by K-M Analysis for Prior anti-HER2 treated patients – ITT Population (N=XXX)**

**Table 14.2.1.17 Summary of Overall Survival by K-M Analysis for Hormone Receptor status – ITT Population (N=XXX)**

## 14.3 Safety Analysis

### 14.3.1 Adverse Events

**Table 14.3.1.1 Overall Summary of Adverse Events –Safety Population (N=XXX)**

| | Pertuzumab (N=XXX) |
|---|---|
| **Total Number of AEs Reported** | XX |
| **Subjects Reporting Any AEs [1]** | XX (XX.X %) |
| Subjects Reporting 1 AE | XX (XX.X %) |
| Subjects Reporting >1 AE | XX (XX.X %) |
| **Subjects Reporting No AEs [1]** | XX (XX.X %) |
| **Number of AEs with Intensity (NCI –CTCAE v4.03): [2]** | |
| Grade 1 | XX (XX.X %) |
| Grade 2 | XX (XX.X %) |
| Grade 3 | XX (XX.X %) |
| Grade 4 | XX (XX.X %) |
| Grade 5 | XX (XX.X %) |
| **Number of AEs with Relationship to Pertuzumab:[2]** | |
| Yes | XX (XX.X %) |
| **Number of AEs with Relationship to Trastuzumab:[2]** | |
| Yes | XX (XX.X %) |
| **Number of AEs with Relationship to Docetaxel:[2]** | |
| Yes | XX (XX.X %) |
| **Number of AEs by Action taken:[2]** | |

| | |
|---|---|
| No action taken | XX (XX.X %) |
| Infusion Slow Down | XX (XX.X %) |
| Infusion Interrupted | XX (XX.X %) |
| Appropriate Medical Therapies Administered | XX (XX.X %) |
| **Number of AEs by Event Outcome:[2]** | |
| Resolved No-Sequelae | XX (XX.X %) |
| Resolved-with Sequelae | XX (XX.X %) |
| Unresolved | XX (XX.X %) |
| Death | XX (XX.X %) |
| **Number of AEs by Chemotherapy Adjustment:[2]** | |
| None | XX (XX.X %) |
| Dosage Modified/including interruptions | XX (XX.X %) |
| Discontinued | XX (XX.X %) |
| **Number of AEs of suspected cardiac origin:[2]** | |
| Yes | XX (XX.X %) |
| **Number of AEs symptomatic of left ventricular systolic dysfunction:[2]** | |
| Yes | XX (XX.X %) |
| No | XX (XX.X %) |
| **Number of AEs with NYHA Class [2]** | |
| I | XX (XX.X %) |
| II | XX (XX.X %) |
| III | XX (XX.X %) |
| IV | XX (XX.X %) |
| **Number of AEs with LVEF decreases:[2]** | |
| Yes | XX (XX.X %) |

| | |
|---|---|
| No | XX (XX.X %) |
| **Subjects Reporting AEs Leading to Withdraw [1]** | XX (XX.X %) |
| **Subjects Reporting Serious AEs [1]** | XX (XX.X %) |
| Subjects Reporting Death | XX (XX.X %) |
| **Subjects Reporting AESIs [1]** | |
| Yes | XX (XX.X %) |
| No | XX (XX.X %) |

**Source Data: Listing 16.2.7**

**Note:**

[1] Percentage will be calculated by taking respective column header group count as denominator.

[2] Percentage will be calculated by taking count of 'Total Number of AEs Reported' in corresponding treatment group as denominator.

**General Note:**

- Adverse events are coded using MedDRA version 18.1 or later.
- AEs: Adverse Events

**Table 14.3.1.1a Overall Summary of Treatment Emergent Adverse Events –Safety Population (N=XXX)**

| | Pertuzumab (N=XXX) |
|---|---|
| **Total Number of TEAEs Reported** | XX |
| **Subjects Reporting Any TEAEs [1]** | XX (XX.X %) |
| Subjects Reporting 1 TEAE | XX (XX.X %) |
| Subjects Reporting >1 TEAE | XX (XX.X %) |
| **Subjects Reporting No TEAEs [1]** | XX (XX.X %) |
| **Number of TEAEs with Intensity (NCI –CTCAE v4.03): [2]** | |
| Grade 1 | XX (XX.X %) |
| Grade 2 | XX (XX.X %) |
| Grade 3 | XX (XX.X %) |
| Grade 4 | XX (XX.X %) |
| Grade 5 | XX (XX.X %) |
| **Number of TEAEs with Relationship to Pertuzumab:[2]** | |
| Yes | XX (XX.X %) |
| **Number of TEAEs with Relationship to Trastuzumab:[2]** | |
| Yes | XX (XX.X %) |
| **Number of TEAEs with Relationship to Docetaxel:[2]** | |
| Yes | XX (XX.X %) |
| **Number of TEAEs by Action taken:[2]** | |
| No action taken | XX (XX.X %) |
| Infusion Slow Down | XX (XX.X %) |

| | |
|---|---|
| Infusion Interrupted | XX (XX.X %) |
| Appropriate Medical Therapies Administered | XX (XX.X %) |
| **Number of TEAEs by Event Outcome:[2]** | |
| Resolved No-Sequelae | XX (XX.X %) |
| Resolved-with Sequelae | XX (XX.X %) |
| Unresolved | XX (XX.X %) |
| Death | XX (XX.X %) |
| **Number of TEAEs by Chemotherapy Adjustment:[2]** | |
| None | XX (XX.X %) |
| Dosage Modified/including interruptions | XX (XX.X %) |
| Discontinued | XX (XX.X %) |
| **Number of TEAEs of suspected cardiac origin:[2]** | |
| Yes | XX (XX.X %) |
| **Number of TEAEs symptomatic of left ventricular systolic dysfunction:[2]** | |
| Yes | XX (XX.X %) |
| No | XX (XX.X %) |
| **Number of TEAEs with NYHA Class [2]** | |
| I | XX (XX.X %) |
| II | XX (XX.X %) |
| III | XX (XX.X %) |
| IV | XX (XX.X %) |
| **Number of TEAEs with LVEF decreases:[2]** | |
| Yes | XX (XX.X %) |
| No | XX (XX.X %) |

| | |
|---|---|
| **Subjects Reporting TEAEs Leading to Withdraw [1]** | XX (XX.X %) |
| **Subjects Reporting Serious TEAEs [1]** | XX (XX.X %) |
| Subjects Reporting Death | XX (XX.X %) |
| **Subjects Reporting AESIs [1]** | |
| Yes | XX (XX.X %) |
| No | XX (XX.X %) |

**Source Data: Listing 16.2.7**

**Note:**

[1] Percentage will be calculated by taking respective column header group count as denominator.

[2] Percentage will be calculated by taking count of 'Total Number of TEAEs Reported' in corresponding treatment group as denominator.

**General Note:**

- Adverse events will be coded using MedDRA version 18.1 or later.
- TEAEs: Treatment Emergent Adverse Events

**Table 14.3.1.1b Overall Summary of Non-Treatment Emergent Adverse Events -Safety Population (N=XXX)**

| | Pertuzumab (N=XXX) |
|---|---|
| **Total Number of non-TEAEs Reported** | XX |
| **Subjects Reporting Any non-TEAEs [1]** | XX (XX.X %) |
| Subjects Reporting 1 **non-TEAE** | XX (XX.X %) |
| Subjects Reporting >1 **non-TEAE** | XX (XX.X %) |
| **Subjects Reporting No non-TEAEs [1]** | XX (XX.X %) |
| **Number of non-TEAEs with Intensity (NCI -CTCAE v4.03): [2]** | |
| Grade 1 | XX (XX.X %) |
| Grade 2 | XX (XX.X %) |
| Grade 3 | XX (XX.X %) |
| Grade 4 | XX (XX.X %) |
| Grade 5 | XX (XX.X %) |
| **Number of non-TEAEs with Relationship to Pertuzumab:[2]** | |
| Yes | XX (XX.X %) |
| **Number of non-TEAEs with Relationship to Trastuzumab:[2]** | |
| Yes | XX (XX.X %) |
| **Number of non-TEAEs with Relationship to Docetaxel:[2]** | |
| Yes | XX (XX.X %) |
| **Number of non-TEAEs by Action taken:[2]** | |
| No action taken | XX (XX.X %) |
| Infusion Slow Down | XX (XX.X %) |

| | |
|---|---|
| Infusion Interrupted | XX (XX.X %) |
| Appropriate Medical Therapies Administered | XX (XX.X %) |
| **Number of non-TEAEs by Event Outcome:[2]** | |
| Resolved No-Sequelae | XX (XX.X %) |
| Resolved-with Sequelae | XX (XX.X %) |
| Unresolved | XX (XX.X %) |
| Death | XX (XX.X %) |
| **Number of non-TEAEs by Chemotherapy Adjustment:[2]** | |
| None | XX (XX.X %) |
| Dosage Modified/including interruptions | XX (XX.X %) |
| Discontinued | XX (XX.X %) |
| **Number of non-TEAEs of suspected cardiac origin:[2]** | |
| Yes | XX (XX.X %) |
| **Number of non-TEAEs symptomatic of left ventricular systolic dysfunction:[2]** | |
| Yes | XX (XX.X %) |
| No | XX (XX.X %) |
| **Number of non-TEAEs with NYHA Class [2]** | |
| I | XX (XX.X %) |
| II | XX (XX.X %) |
| III | XX (XX.X %) |
| IV | XX (XX.X %) |
| **Number of non-TEAEs with LVEF decreases:[2]** | |
| Yes | XX (XX.X %) |
| No | XX (XX.X %) |

| | |
|---|---|
| **Subjects Reporting non-TEAEs Leading to Withdraw [1]** | XX (XX.X %) |
| **Subjects Reporting Serious non-TEAEs [1]** | XX (XX.X %) |
| Subjects Reporting Death | XX (XX.X %) |
| **Subjects Reporting AESIs [1]** | |
| Yes | XX (XX.X %) |
| No | XX (XX.X %) |

**Source Data: Listing 16.2.7**

**Note:**

[1] Percentage will be calculated by taking respective column header group count as denominator.

[2] Percentage will be calculated by taking count of 'Total Number of non TEAEs Reported' in corresponding treatment group as denominator.

**General Note:**

- Non Treatment Emergent Adverse events will be coded using MedDRA version 18.1 or later.
- Non TEAEs: Non Treatment Emergent Adverse events

**Table 14.3.1.2 Summary of Adverse Events (including subjects reporting SAEs) by MedDRA System Organ Class and Preferred Term –Safety Population (N=XXX)**

| System Organ Class/Preferred Term, n (%) [1] | Pertuzumab (N=XXX) |
|---|---|
| **Total number of subjects with at least one Adverse Events(including subjects reporting SAEs)** | XX (XX.X %) |
| **Total number of Adverse Events** | XX |
| **System Organ Class 1** | XX (XX.X %) |
| Preferred Term 1 | XX (XX.X %) [XX] |
| Preferred Term 2 | XX (XX.X %) [XX] |
| …… | …… |
| **System Organ Class 2** | XX (XX.X %) |
| Preferred Term 1 | XX (XX.X %) [XX] |
| Preferred Term 2 | XX (XX.X %) [XX] |
| …… | …… |

**Source Data: Listing 16.2.7**

**Note:**
[1] Percentage will be calculated by taking respective column header group count as denominator.

**General Note:**

- Adverse events will be coded using MedDRA version 18.1 or later
- All Adverse events are presented as: number of subjects (percent of subjects) [number of events].
- Subjects may have reported more than one event per system organ class or preferred term. Subjects will be only counted once for each system organ class or preferred term.

**Table 14.3.1.2a Summary of Adverse Events (excluding subjects reporting SAEs) by MedDRA System Organ Class and Preferred Term –Safety Population (N=XXX)**

| System Organ Class/Preferred Term, n (%) [1] | Pertuzumab (N=XXX) |
|---|---|
| **Total number of subjects with at least one Adverse Events(excluding subjects reporting SAEs)** | XX (XX.X %) |
| **Total number of Adverse Events** | XX |
| **System Organ Class 1** | XX (XX.X %) |
| Preferred Term 1 | XX (XX.X %) [XX] |
| Preferred Term 2 | XX (XX.X %) [XX] |
| …… | …… |
| **System Organ Class 2** | XX (XX.X %) |
| Preferred Term 1 | XX (XX.X %) [XX] |
| Preferred Term 2 | XX (XX.X %) [XX] |
| …… | …… |

**Source Data: Listing 16.2.7**

**Note:**
[1] Percentage will be calculated by taking respective column header group count as denominator.

**General Note:**

- Adverse events will be coded using MedDRA version 18.1 or later
- All Adverse events are presented as: number of subjects (percent of subjects) [number of events].
- Subjects may have reported more than one event per system organ class or preferred term. Subjects will be only counted once for each system organ class or preferred term.

**Table 14.3.1.3 Summary of Adverse Events by MedDRA System Organ Class and Preferred Term by Intensity –Safety Population (N=XXX)**

| System Organ Class/Preferred Term, n (%) [1] | Intensity | Pertuzumab (N=XXX) |
|---|---|---|
| **Total number of subjects with at least one Adverse Events** | | XX (XX.X %) |
| **Total number of Adverse Events** | | XX |
| **System Organ Class 1** | | XX (XX.X %) |
| Preferred Term 1 | | XX (XX.X %) [XX] |
| | Grade 1 | XX (XX.X %) [XX] |
| | Grade 2 | XX (XX.X %) [XX] |
| | Grade 3 | XX (XX.X %) [XX] |
| | Grade 4 | XX (XX.X %) [XX] |
| | Grade 5 | XX (XX.X %) [XX] |
| Preferred Term 2 | | XX (XX.X %) [XX] |
| | Grade 1 | XX (XX.X %) [XX] |
| | Grade 2 | XX (XX.X %) [XX] |
| | Grade 3 | XX (XX.X %) [XX] |
| | Grade 4 | XX (XX.X %) [XX] |
| | Grade 5 | XX (XX.X %) [XX] |
| …… | …… | …… |

**Source Data: Listing 16.2.7**

**Note:**
[1] Percentage will be calculated by taking respective column header group count as denominator

**General Note:**

- Adverse events will be coded using MedDRA version 18.1 or later
- All Adverse events are presented as: number of subjects (percent of subjects) [number of events].

- Subjects may have reported more than one event per system organ class or preferred term. Subjects will be only counted once for each system organ class or preferred term.

**Table 14.3.1.4 Summary of Adverse Events by MedDRA System Organ Class and Preferred Term by Action Taken –Safety Population (N=XXX)**

| System Organ Class/Preferred Term, n (%) [1] | Action Taken | Pertuzumab (N=XXX) |
|---|---|---|
| **Total number of subjects with at least one Adverse Events** | | XX (XX.X %) |
| **Total number of Adverse Events** | | XX |
| **System Organ Class 1** | | XX (XX.X %) |
| Preferred Term 1 | | XX (XX.X %) [XX] |
| | No action taken | XX (XX.X %) [XX] |
| | Infusion Slow Down | XX (XX.X %) [XX] |
| | Infusion Interrupted | XX (XX.X %) [XX] |
| | Appropriate Medical Therapies Administered | XX (XX.X %) [XX] |
| Preferred Term 2 | | XX (XX.X %) [XX] |
| | No action taken | XX (XX.X %) [XX] |
| | Infusion Slow Down | XX (XX.X %) [XX] |
| | Infusion Interrupted | XX (XX.X %) [XX] |
| | Appropriate Medical Therapies Administered | XX (XX.X %) [XX] |
| …… | …… | …… |

**Source Data: Listing 16.2.7**

**Note:**

[1] Percentage should be calculated by taking respective column header group count as denominator.

**General Note:**

- Adverse events will be coded using MedDRA version 18.1 or later

- All Adverse events will be presented as: number of subjects (percent of subjects) [number of events].
- Subjects may have reported more than one event per system organ class or preferred term. Subjects will be only counted once for each system organ class or preferred term.

**Table 14.3.1.5 Summary of Adverse Events by MedDRA System Organ Class and Preferred Term by Event Outcome –Safety Population (N=XXX)**

| System Organ Class/Preferred Term, n (%) [1] | Event Outcome | Pertuzumab (N=XXX) |
|---|---|---|
| **Total number of subjects with at least one Adverse Events** | | XX (XX.X %) |
| **Total number of Adverse Events** | | XX |
| **System Organ Class 1** | | XX (XX.X %) |
| Preferred Term 1 | | XX (XX.X %) [XX] |
| | Resolved No-Sequelae | XX (XX.X %) [XX] |
| | Resolved-with Sequelae | XX (XX.X %) [XX] |
| | Unresolved | XX (XX.X %) [XX] |
| | Death | XX (XX.X %) [XX] |
| Preferred Term 2 | | XX (XX.X %) [XX] |
| | Resolved No-Sequelae | XX (XX.X %) [XX] |
| | Resolved-with Sequelae | XX (XX.X %) [XX] |
| | Unresolved | XX (XX.X %) [XX] |
| | Death | XX (XX.X %) [XX] |
| …… | …… | …… |

**Source Data: Listing 16.2.7**

**Note:**
[1] Percentage will be calculated by taking respective column header group count as denominator.

**General Note:**

- Adverse events will be coded using MedDRA version 18.1 or later

- All Adverse events will be presented as: number of subjects (percent of subjects) [number of events].
- Subjects may have reported more than one event per system organ class or preferred term. Subjects will be only counted once for each system organ class or preferred term.

**Table 14.3.1.6 Summary of Assessment during Adverse Event –Safety Population (N=XXX)**

| Assessment [1] | Category n (%) [1] | Pertuzumab (N=XXX) |
|---|---|---|
| **Chemotherapy adjustment** | | |
| | None | XX (XX.X %) |
| | Dosage modified/including interruptions | XX (XX.X %) |
| | Discontinued | XX (XX.X %) |
| **Is Event symptomatic of left ventricular systolic dysfunction** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **NYHA Class** | | |
| | I | XX (XX.X %) |
| | II | XX (XX.X %) |
| | III | XX (XX.X %) |
| | IV | XX (XX.X %) |
| **LVEF decrease** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |

**Source Data Listings: 16.2.7**

**Note:**

[1] Respective column header group count will be used as denominator in percentage calculation.

## 14.3.2 Serious Adverse Events

**Table 14.3.2.1 Summary of Serious Adverse Events –Safety Population (N=XXX)**

| | Pertuzumab (N=XXX) |
|---|---|
| **Total Number of SAEs Reported** | XX |
| **Subjects Reporting Any SAEs [1]** | XX (XX.X %) |
| Subjects Reporting 1 **SAEs** | XX (XX.X %) |
| Subjects Reporting >1 **SAEs** | XX (XX.X %) |
| **Subjects Reporting No SAEs [1]** | XX (XX.X %) |
| **Number of SAEs with Intensity (Initial NCI –CTCAE v4.03): [2]** | |
| Grade 1 | XX (XX.X %) |
| Grade 2 | XX (XX.X %) |
| Grade 3 | XX (XX.X %) |
| Grade 4 | XX (XX.X %) |
| Grade 5 | XX (XX.X %) |
| **Number of SAEs with Intensity ( Most Extreme NCI –CTCAE v4.03): [2]** | |
| Grade 1 | XX (XX.X %) |
| Grade 2 | XX (XX.X %) |
| Grade 3 | XX (XX.X %) |
| Grade 4 | XX (XX.X %) |
| Grade 5 | XX (XX.X %) |
| **Number of SAEs with Intensity Scale (Initial Intensity) [2]** | |
| Mild | XX (XX.X %) |
| Moderate | XX (XX.X %) |
| Severe | XX (XX.X %) |

| | |
|---|---|
| **Number of SAEs with Intensity Scale (Most Extreme Intensity) [2]** | |
| Mild | XX (XX.X %) |
| Moderate | XX (XX.X %) |
| Severe | XX (XX.X %) |
| **Number of SAEs with Relationship to Pertuzumab:[2]** | |
| Yes | XX (XX.X %) |
| **Number of SAEs with Relationship to Trastuzumab:[2]** | |
| Yes | XX (XX.X %) |
| **Number of SAEs with Relationship to Docetaxel:[2]** | |
| Yes | XX (XX.X %) |
| **Number of SAEs by Suspect Cause:[2]** | |
| Caused by drug | XX (XX.X %) |
| Disease under study | XX (XX.X %) |
| Medical History or Concurrent Illness | XX (XX.X %) |
| Concomitant Medication | XX (XX.X %) |
| Protocol Related Procedure | XX (XX.X %) |
| Others | XX (XX.X %) |
| **Number of SAEs by Action taken:[2]** | |
| Infusion of Pertuzumab Reduced | XX (XX.X %) |
| Infusion of Pertuzumab Temporarily Interrupted | XX (XX.X %) |
| Infusion of Pertuzumab Permanently Discontinued | XX (XX.X %) |
| Infusion of Trastuzumab Reduced | XX (XX.X %) |
| Infusion of Trastuzumab Reduced | XX (XX.X %) |
| Infusion of Trastuzumab Temporarily Interrupted | XX (XX.X %) |
| Infusion of Trastuzumab Permanently Discontinued | XX (XX.X %) |

| | |
|---|---|
| Infusion of Docetaxel Reduced | XX (XX.X %) |
| Infusion of Docetaxel Temporarily Interrupted | XX (XX.X %) |
| Infusion of Docetaxel Permanently Discontinued | XX (XX.X %) |
| **Number of SAEs by Event Outcome:[2]** | |
| Fatal | XX (XX.X %) |
| Recovered/Resolved | XX (XX.X %) |
| Recovered/Resolved-with Sequelae | XX (XX.X %) |
| Recovering/Resolving | XX (XX.X %) |
| Not recovered/Not resolved | XX (XX.X %) |
| Unknown | XX (XX.X %) |
| **Number of SAEs by Reasons:[2]** | |
| Results in death | XX (XX.X %) |
| Life-threatening | XX (XX.X %) |
| Requires in patient hospitalization | XX (XX.X %) |
| Requires prolongation of existing hospitalization | XX (XX.X %) |
| Persistent or significant disability / incapacity | XX (XX.X %) |
| Congenital anomaly / birth defect | XX (XX.X %) |
| Medically Significant | XX (XX.X %) |
| **Subjects Reporting SAEs Leading to Withdraw [1]** | XX (XX.X %) |
| **Subjects Reporting Serious SAEs [1]** | XX (XX.X %) |
| Subjects Reporting Death | XX (XX.X %) |

**Source Data: Listing 16.2.7**

**Note:**
[1] Percentage should be calculated by taking respective column header group count as denominator.

**General Note:**

- Serious Adverse events will be coded using MedDRA version 18.1 or later
- All Serious Adverse events will be presented as: number of subjects (percent of subjects).
- Subjects might have reported more than one event per system organ class or preferred term. Subjects will be only counted once for each system organ class or preferred term.

**Table 14.3.2.2 Summary of Serious Adverse Events by MedDRA System Organ Class and Preferred Term –Safety Population (N=XXX)**

| System Organ Class/Preferred Term, n (%) [1] | Pertuzumab (N=XXX) |
|---|---|
| **Total number of subjects with at Least one serious adverse events** | XX (XX.X %) |
| **Total number of serious adverse events** | XX |
| **System Organ Class 1** | XX (XX.X %) |
| Preferred Term 1 | XX (XX.X %) [XX] |
| Preferred Term 2 | XX (XX.X %) [XX] |
| …… | …… |
| **System Organ Class 2** | XX (XX.X %) |
| Preferred Term 1 | XX (XX.X %) [XX] |
| Preferred Term 2 | XX (XX.X %) [XX] |
| …… | …… |

**Source Data: Listing 16.2.7**

**Note:**

[1] Percentage should be calculated by taking respective column header group count as denominator.

**General Note:**

- Serious Adverse events will be coded using MedDRA version 18.1 or later
- All Serious Adverse events will be presented as: number of subjects (percent of subjects) [number of events].
- Subjects might have reported more than one event per system organ class or preferred term. Subjects will be only counted once for each system organ class or preferred term.

**Table 14.3.2.3 Summary of Adverse Event of Special Interest –Safety Population (N=XXX)**

| | Pertuzumab (N=XXX) |
|---|---|
| **Total Number of AESIs Reported** | XX |
| **Subjects Reporting Any AESIs [1]** | XX (XX.X %) |
| Subjects Reporting 1 AESIs | XX (XX.X %) |
| Subjects Reporting >1 AESIs | XX (XX.X %) |
| **Subjects Reporting No AESIs [1]** | XX (XX.X %) |
| **Number of AESIs with Intensity ( Initial NCI –CTCAE v4.03): [2]** | |
| Grade 1 | XX (XX.X %) |
| Grade 2 | XX (XX.X %) |
| Grade 3 | XX (XX.X %) |
| Grade 4 | XX (XX.X %) |
| Grade 5 | XX (XX.X %) |
| **Number of AESIs with Intensity ( Most Extreme NCI –CTCAE v4.03): [2]** | |
| Grade 1 | XX (XX.X %) |
| Grade 2 | XX (XX.X %) |
| Grade 3 | XX (XX.X %) |
| Grade 4 | XX (XX.X %) |
| Grade 5 | XX (XX.X %) |
| **Number of AESIs with Intensity Scale (Initial Intensity) [2]** | |
| Mild | XX (XX.X %) |
| Moderate | XX (XX.X %) |
| Severe | XX (XX.X %) |

| | |
|---|---|
| **Number of AESIs with Intensity Scale (Most Extreme Intensity) [2]** | |
| Mild | XX (XX.X %) |
| Moderate | XX (XX.X %) |
| Severe | XX (XX.X %) |
| | |
| **Number of AESIs with Relationship to Pertuzumab:[2]** | |
| Yes | XX (XX.X %) |
| | |
| **Number of AESIs with Relationship to Trastuzumab:[2]** | |
| Yes | XX (XX.X %) |
| | |
| **Number of AESIs with Relationship to Docetaxel:[2]** | |
| Yes | XX (XX.X %) |
| | |
| **Number of AESIs by Suspect Cause:[2]** | |
| Caused by drug | XX (XX.X %) |
| Disease under study | XX (XX.X %) |
| Medical History or Concurrent Illness | XX (XX.X %) |
| Concomitant Medication | XX (XX.X %) |
| Protocol Related Procedure | XX (XX.X %) |
| Others | XX (XX.X %) |
| | |
| **Number of AESIs by Action taken:[2]** | |
| Infusion of Pertuzumab Reduced | XX (XX.X %) |
| Infusion of Pertuzumab Temporarily Interrupted | XX (XX.X %) |
| Infusion of Pertuzumab Permanently Discontinued | XX (XX.X %) |
| Infusion of Trastuzumab Reduced | XX (XX.X %) |
| Infusion of Trastuzumab Temporarily Interrupted | XX (XX.X %) |
| Infusion of Trastuzumab Permanently Discontinued | XX (XX.X %) |
| Infusion of Docetaxel Reduced | XX (XX.X %) |

| | |
|---|---|
| Infusion of Docetaxel Temporarily Interrupted | XX (XX.X %) |
| Infusion of Docetaxel Permanently Discontinued | XX (XX.X %) |
| **Number of AESIs by Event Outcome:[2]** | |
| Fatal | XX (XX.X %) |
| Recovered/Resolved | XX (XX.X %) |
| Recovered/Resolved-with Sequelae | XX (XX.X %) |
| Recovering/Resolving | XX (XX.X %) |
| Not recovered/Not resolved | XX (XX.X %) |
| Unknown | XX (XX.X %) |
| **Number of AESIs by Reasons:[2]** | |
| Results in death | XX (XX.X %) |
| Life-threatening | XX (XX.X %) |
| Requires in patient hospitalization | XX (XX.X %) |
| Requires prolongation of existing hospitalization | XX (XX.X %) |
| Persistent or significant disability / incapacity | XX (XX.X %) |
| Congenital anomaly / birth defect | XX (XX.X %) |
| Medically Significant | XX (XX.X %) |
| **Subjects Reporting AESIs Leading to Withdraw [1]** | XX (XX.X %) |
| **Subjects Reporting AESIs[1]** | XX (XX.X %) |
| Subjects Reporting Death | XX (XX.X %) |

**Note:**

[1] Percentage should be calculated by taking respective column header group count as denominator.

**General Note:**

- Adverse events of special interest (AESIs) will be coded using MedDRA version 18.1 or later

- All Adverse events of special interest (AESIs) will will be presented as: number of subjects (percent of subjects).
- Subjects might have reported more than one event per system organ class or preferred term. Subjects will be only counted once for each system organ class or preferred term.

## 14.3.3 Concomitant Medication

### Table 14.3.3.1 Summary of Concomitant Medication Assessment –Safety Population (N=XXX)

| Therapeutic Class, n (%) [1] | Generic name, n (%) [2] | Pertuzumab(N=XXX) | Count of Ongoing [3] |
|---|---|---|---|
| Therapeutic Class 1 | | XX (XX.X %) | |
| | Generic Name 1 | XX (XX.X %) | XX (XX.X %) |
| | Generic Name 2 | XX (XX.X %) | XX (XX.X %) |
| | Generic Name 3 | XX (XX.X %) | XX (XX.X %) |
| | …… | …… | …… |

**Source Data: Listing**

**Note:**

[1] Percentages of Therapeutic class will be calculated from respective column header group count as denominator in percentage calculation.

[2] Percentages of Generic Name will be calculated from Respective Class counts.

[3] Percentages of Count of Ongoing will be calculated from respective generic name counts.

## 14.3.4 Vital Signs

**Table 14.3.4.1 Summary of Weight at all visits –Safety Population (N=XXX)**

| Visits | Statistics | Pertuzumab (N=XXX) |
|---|---|---|
| **Cycle 1** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) |
| | Missing [1] | XX |
| … | … | … |

**Source Data: Listing 16.4.1.1 and 16.4.1.2**

**Note:**

[1] If a particular parameter measurement is not captured, will be displayed under 'Missing' category

**Programming Note:**

- The same table will also include the analysis for all the other remaining available visits.

**Table 14.3.4.2 Summary of Vital Signs at different Cycles –Safety Population (N=XXX)**

| Vital Signs | Statistics | Infusion of Pertuzumab | | Infusion of Trastuzumab | | Infusion of Docetaxel | |
|---|---|---|---|---|---|---|---|
| | | Prior | After | Prior | After | Prior | After |
| **Cycle 1** | | | | | | | |
| **Pulse Rate** | | | | | | | |
| | n | XX | XX | XX | XX | XX | XX |
| | Mean | XX.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | SD | XX.XX | XX.XX | XX.XX | XX.XX | XX.XX | XX.XX |
| | Median | XX.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) |
| | Missing [1] | XX | XX | XX | XX | XX | XX |
| **Respiratory rate** | | | | | | | |
| | n | XX | XX | XX | XX | XX | XX |
| | Mean | XX.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | SD | XX.XX | XX.XX | XX.XX | XX.XX | XX.XX | XX.XX |
| | Median | XX.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) |
| | Missing [1] | XX | XX | XX | XX | XX | XX |
| **Blood Pressure(mmHg)** | | | | | | | |
| **Systolic** | | | | | | | |
| | n | XX | XX | XX | XX | XX | XX |
| | Mean | XX.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | SD | XX.XX | XX.XX | XX.XX | XX.XX | XX.XX | XX.XX |
| | Median | XX.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) |
| | Missing [1] | XX | XX | XX | XX | XX | XX |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Diastolic** | | | | | | | |
| | n | XX | XX | XX | XX | XX | XX |
| | Mean | XX.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | SD | XX.XX | XX.XX | XX.XX | XX.XX | XX.XX | XX.XX |
| | Median | XX.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) |
| | Missing [1] | XX | XX | XX | XX | XX | XX |
| **Temperature (°C)** | | | | | | | |
| | n | XX | XX | XX | XX | XX | XX |
| | Mean | XX.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | SD | XX.XX | XX.XX | XX.XX | XX.XX | XX.XX | XX.XX |
| | Median | XX.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) |
| | Missing [1] | XX | XX | XX | XX | XX | XX |
| … | … | … | … | … | … | … | … |

**Source Data: Listing 16.4.1.1 and 16.4.1.2**

**Note:**

[1] If a particular parameter measurement is not captured, will be displayed under 'Missing' category

**Programming Note:**

- The same table will also include the analysis for all other remaining available visits-Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6 and so on.

**Table 14.3.4.3 Summary of Vital Signs at different visits at follow-up Safety Population (N=XXX)**

| Vital Signs | Statistics | Pertuzumab (N=XXX) |
|---|---|---|
| **After 28 Days** | | |
| **Pulse Rate** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) |
| | Missing [1] | XX |
| **Respiratory rate** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) |
| | Missing [1] | XX |
| **Blood Pressure(mmHg)** | | |
| **Systolic** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) |
| | Missing [1] | XX |
| **Diastolic** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |

| | | |
|---|---|---|
| | Median | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) |
| | Missing [1] | XX |
| **Temperature (°C)** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min: Max) | (XX.X:XX.X) |
| | Missing [1] | XX |
| … | … | … |

**Source Data: Listing 16.4.1.1 and 16.4.1.2**

**Note:**

[1] If a particular parameter measurement is not captured, will be displayed under 'Missing' category

**Programming Note:**

- The same table will also include the analysis for all other remaining available visits-After 28 Days, After every 3 months follow-up period, and End of the study.

## 14.3.5 Physical Examination

**Table 14.3.5.1 Summary of Physical Examination at all visits- Safety Population (N=XXX)**

| Physical Examination [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Cycle 1** | | |
| **Physical examinations performed** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **If Yes, Result[2]** | | |
| | Normal | XX (XX.X %) |
| | Abnormal | XX (XX.X %) |
| … | … | … |

**Source Data: Listing 16.4.2**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.
[1] Percentages will be calculated using category "Yes" of "Physical examinations performed" as denominator.

**Programming Note:**
- Also, the same table will also include the analysis for all the remaining available visits.

## 14.3.6 Laboratory Assessments

**Table 14.3.6.1 Summary of Serum Chemistry at all visits- Safety Population (N=XXX)**

| Test [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Cycle 1** | | |
| **Sodium** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Potassium** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Calcium** | | |
| **Result** | n | XX |

| | | |
|---|---|---|
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| … | … | … |

**Source Data: Listing 16.2.8.3**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Programming Note:**

- The same table will also include other parameters of Serum Chemistry- Chloride, Magnesium, BUN(urea), Uric acid, Total protein, Albumin, Alkaline Phosphatase, Alanine Transaminase (ALAT), Aspartate Aminotransferase(ASAT), Gamma Glutamyl Transferase(GGT), Lactate Dehydrogenase(LDH), Total Bilirubin, Creatinine, Blood Glucose and Creatinine Clearance.
- Also, the same table will include the analysis for all the remaining available visits.

**Table 14.3.6.2 Summary of Hematology Test at All Visit- Safety Population (N=XXX)**

| Test [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Cycle 1** | | |
| **Hemoglobin** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Hematocrit** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Red Blood Cells (RBC)** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |

| | | |
|---|---|---|
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **White Blood Cells (WBC)** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| … | … | … |

**Source Data: Listing 16.2.8.1**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Programming Note:**

- The same table will also include other parameters of Hematology- Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Other Cells, and Platelet Count.
- Also, the same table will include the analysis for all the remaining available visits.

**Table 14.3.6.3 Summary of Coagulation Test at All Visits- Safety Population (N=XXX)**

| Test [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Cycle 1** | | |
| **International normalization ratio(INR)** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Activated Partial Thromboplastin Time (aPTT)** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **Out of Range** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Clinically Significant** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Partial Thromboplastin Time (PTT)** | | |
| **Result** | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |

| | | | |
|---|---|---|---|
| | | Median | XX.X |
| | | Range(Min:Max) | (XX.X:XX.X) |
| | **Out of Range** | Yes | XX (XX.X %) |
| | | No | XX (XX.X %) |
| | **Clinically Significant** | Yes | XX (XX.X %) |
| | | No | XX (XX.X %) |
| … | | … | … |

**Source Data: Listing 16.2.8.2**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Programming Note:**
- Also, the same table will include the analysis for all the remaining available visits.

**Table 14.3.6.4 Summary of Pregnancy Test at different Visits- Safety Population (N=XXX)**

| Result [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Cycle 3** | | |
| **Was Pregnancy Test Done** | | |
| | Done | XX (XX.X %) |
| | Not Done | XX (XX.X %) |
| | Not Applicable | XX (XX.X %) |
| **If done [2]** | | |
| **Method** | Serum | XX (XX.X %) |
| | Urine | XX (XX.X %) |
| **Results** | Positive | XX (XX.X %) |
| | Negative | XX (XX.X %) |
| **If Urinary positive[3]** | | |
| **Serum Results** | Positive | XX (XX.X %) |
| | Negative | XX (XX.X %) |
| … | … | … |

**Source Data: Listing 16.2.8.5**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.
[2] Percentages will be calculated using "Done" category of "Was Pregnancy Test Done" as denominator.
[3] Percentages will be calculated using "positive" category of "Results of Urine Pregnancy Test" as denominator.

**Programming Note:**
- Also, the same table will include the analysis for all the remaining available visits.

**Table 14.3.6.5 Summary of ECOG at different Visits- Safety Population (N=XXX)**

| Status [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Cycle 3** | | |
| **ECOG Performance Status** | | |
| **Grade** | 0 | XX (XX.X %) |
| | 1 | XX (XX.X %) |
| | 2 | XX (XX.X %) |
| | 3 | XX (XX.X %) |
| | 4 | XX (XX.X %) |
| … | … | … |

**Source Data: Listing 16.2.8.6**
**Note:** [1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Note: In ECOG Performance Status**
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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Grade 3= Capable of only limited selfcare, 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

**Programming Note:**
- Also, the same table will include the analysis for all the remaining available visits.

**Table 14.3.6.6 Summary of LVEF and CHF at different Visits- Safety Population (N=XXX)**

| LVEF [1] | Statistics/Category, n (%) | Pertuzumab (N=XX) |
|---|---|---|
| **Cycle 3** | | |
| **Results (%)** | | |
| | n | XX |
| | Mean | XX.X |
| | SD | XX.XX |
| | Median | XX.X |
| | Range(Min:Max) | (XX.X:XX.X) |
| **LVEF done by** | | |
| | MUGA | XX (XX.X %) |
| | Echocardiography | XX (XX.X %) |
| **If Echocardiography, method** | | |
| | Simpson (2-D) | XX (XX.X %) |
| | Teichholz (M-mode) | XX (XX.X %) |
| **LVEF finding** | | |
| | Normal | XX (XX.X %) |
| | Abnormal but not clinically significant | XX (XX.X %) |
| | Abnormal and clinically significant | XX (XX.X %) |
| **Any new cardiac signs and symptoms** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| **Any worsening cardiac signs and symptoms** | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |

| | | |
|---|---|---|
| **Any signs or symptoms of CHF** | | |
| | Yes | XX (XX.X %) |
| | No | XX (XX.X %) |
| … | … | … |

**Source Data: Listing 16.2.8.7**
**Note:**
[1] Percentages will be calculated using (N=XX) of corresponding column header group as denominator.

**Programming Note:**
- Also, the same table will include the analysis for all the remaining available visits.

**Table 14.3.6.7 Summary of LVEF at each visit-Safety Population (N=XXX)**

| Visits, n (%) [1] | Statistics/Category | Pertuzumab (N=XXX) |
|---|---|---|
| **Baseline** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Cycle 3** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Change from baseline to Cycle 3** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Cycle 6** | | |
| | n | XX |
| | Mean | X.XX |

| | | |
|---|---|---|
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Change from Baseline to Cycle 6** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| …… | …… | …… |
| **After 28 days** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Change from Baseline to After 28 Days** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **After 3 months** | | |
| | n | XX |

| | | |
|---|---|---|
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Change from Baseline to After 3 months** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **After 6 months** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Change from Baseline to After 6 months** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| …… | …… | …… |

**Source Data: Listing 16.2.8.7**

**Programming Note:**

- The same table will include the analysis for the remaining available cycle after cycle 6 and after every 3 months follow-up period.

**Table 14.3.6.8 Summary of Target Lesion (Sum of longest diameters) at each visit-Safety Population (N=XXX)**

| Visits, n (%) [1] | Statistics/Category | Pertuzumab (N=XXX) |
|---|---|---|
| **Baseline** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Cycle 3** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Change from baseline to Cycle 3** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Cycle 6** | | |
| | n | XX |
| | Mean | X.XX |

| | | |
|---|---|---|
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Change from Baseline to Cycle 6** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| …… | …… | …… |
| **After 28 days** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Change from Baseline to After 28 Days** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **After 3 months** | | |
| | n | XX |

| | | |
|---|---|---|
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Change from Baseline to After 3 months** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **After 6 months** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| **Change from Baseline to After 6 months** | | |
| | n | XX |
| | Mean | X.XX |
| | SD | X.XX |
| | Median | X.XX |
| | Range (Min.: Max.) | (XX.XX:XX.XX) |
| …… | …… | …… |

**Source Data:** Listing 16.2.6.1

**Programming Note:**

- The same table will include the analysis for the remaining available cycle after cycle 6 and after every 3 months follow-up period.

**Table 14.3.6.9 Summary of Mean Exposure to Study Treatment –Safety Population (N=XXX)**

| Cycle, n (%) [1] | Pertuzumab (N=XX) | Trastuzumab (N=XX) | Docetaxel (N=XX) |
|---|---|---|---|
| Length of Cycle | | | |
| n | XX | XX | XX |
| Mean | XX.X | XX.X | XX.X |
| SD | XX.XX | XX.XX | XX.XX |
| Median | XX.X | XX.X | XX.X |
| Range(Min:Max) | (XX.X:XX.X) | (XX.X:XX.X) | (XX.X:XX.X) |

## 1.2 Figures

### 14.2.1 Figures for Efficacy Analysis

**Figure 14.2.1.1 K-M Plot for Progression Free Survival by Treatment –ITT Population (N=XXX)**

| | |
|---|---|
| K-M Plot | A step diagram of K-M analysis will be generated where X-axis will represent Time (Days) and Y-axis will represent Progression Free survival probability |

**Source Data: Table 14.2.1.9**

**Programming Note:**
- Same analysis figure will be prepared for the ITT Population with an appropriate change in title and figure no.:

**Figure 14.2.1.2 K-M Plot for Progression Free Survival by Disease Status –ITT Population (N=XXX)**

**Figure 14.2.1.3 K-M Plot for Progression Free Survival for Prior anti-HER2 treated patients –ITT Population (N=XXX)**

**Figure 14.2.1.4 K-M Plot for Progression Free Survival for Hormone Receptor Status-ITT Population (N=XXX)**

**Figure 14.2.1.5 Bar Chart for Response Rate Analysis at Each Visit –ITT Population (N=XXX)**

| | |
|---|---|
| Bar chart | A multiple bar-chart will be generated to represent the response rate at each visit where X-axis will represent all the visits along with all the categories of response and Y-axis will represent percentage of patients. |

**Source Data: Table 14.2.1.1**

**Figure 14.2.1.6 K-M Plot for Overall Survival by Treatment –ITT Population (N=XXX)**

| | |
|---|---|
| K-M Plot | A step diagram of K-M analysis will be generated where X-axis will represent Time (Days) and Y-axis will represent overall survival probability |

**Source Data: Table 14.2.1.14**

**Programming Note:**
- Same analysis figure will be prepared for the ITT Population with an appropriate change in title and figure no.:

**Figure 14.2.1.7 K-M Plot for Overall Survival by Disease Status –ITT Population (N=XXX)**

**Figure 14.2.1.8 K-M Plot for Overall Survival for Prior anti-HER2 treated patients –ITT Population (N=XXX)**

**Figure 14.2.1.9 K-M Plot for Overall Survival for Hormone Receptor Status-ITT Population (N=XXX)**

**Figure 14.2.1.10 Line Diagram for LVEF over a period of time –Safety Population (N=XXX)**

| | |
|---|---|
| Line Diagram for Mean and Median | Two line diagram for LVEF will be generated where X-axis will represent Time (Days) and Y-axis will represent Mean and Median respectively for both the line diagram. |

**Source Data: Table 14.3.6.7**

## 16.2 Patient Data Listings

### Listing 16.2.1 Listing of Patient Discontinuation

| Site ID/ Subject No. | Age/Sex | The patient completed the protocol | If Yes, Date of Completion | If No, Date of Discontinuation | The primary reason for pre-mature discontinuation | If reason is death, mention date | Death Due to Disease Progression | If other reason, specify |
|---|---|---|---|---|---|---|---|---|
| NN/XXXX | NN/XXX | Yes/No | DDMMMYYYY | DDMMMYYYY | XXXX | DDMMMYYYY | Yes/No | XXXX |
| NN/XXXX | NN/XXX | Yes/No | DDMMMYYYY | DDMMMYYYY | XXXX | DDMMMYYYY | Yes/No | XXXX |
| NN/XXXX | NN/XXX | Yes/No | DDMMMYYYY | DDMMMYYYY | XXXX | DDMMMYYYY | Yes/No | XXXX |
| … | … | … | … | … | … | … | … | … |

**Listing 16.2.2.1 Listing of Protocol Deviation –Enrolled Population (N=XXX)**

| Site No./ Subject No. | Age/ Gender | Date | Reason of Deviation | Comments |
|---|---|---|---|---|
| XXX/NNN | NN/XXX | DDMMMYYYY | XXXXXXX | XXX |
| XXX/NNN | NN/XXX | DDMMMYYYY | XXXXXXX | XXX |
| XXX/NNN | NN/XXX | DDMMMYYYY | XXXXXXX | XXX |
| … | … | … | … | … |

**Listing 16.2.2.2 Listing of Analysis Population Sets –Enrolled Population (N=XXX)**

| Site No./ Subject No. | Age/Gender | Efficacy Population | Safety Population |
|---|---|---|---|
| XXX/NNN | NN/XXX | Yes/No | Yes/No |
| XXX/NNN | NN/XXX | Yes/No | Yes/No |
| XXX/NNN | NN/XXX | Yes/No | Yes/No |
| … | … | … | … |

**Listing 16.2.3 Listing of Patients who fail to meet Inclusion/Exclusion Criteria –Enrolled Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Date of Informed Consent | All Inclusion and Exclusion criteria met | If No, Inclusion Criteria Number(s) | All Exclusion criteria Satisfied | If no, Exclusion criteria number(s) |
|---|---|---|---|---|---|---|
| NN/XXXX | NN/XXX | DDMMMYYYY | Yes/No/NA | NN | NN | NN |
| NN/XXXX | NN/XXX | DDMMMYYYY | Yes/No/NA | NN | NN | NN |
| NN/XXXX | NN/XXX | DDMMMYYYY | Yes/No/NA | NN | NN | NN |
| … | … | … | … | … | … | … |

## 16.2.4 Listing of Demographics

### Listing 16.2.4.1 Listing of Patient Demographics –ITT Population (N=XXX)

| Site ID/ Subject No. | Age | Date of Visit | Sex | Date of Birth | Race | Ethnicity |
|---|---|---|---|---|---|---|
| NN/XXXX | NN | DDMMMYYYY | Male/Female | DDMMMYYYY | XXX | XXX |
| NN/XXXX | NN | DDMMMYYYY | Male/Female | DDMMMYYYY | XXX | XXX |
| NN/XXXX | NN | DDMMMYYYY | Male/Female | DDMMMYYYY | XXX | XXX |
| … | … | … | … | … | … | … |

**Listing 16.2.4.2 Listing of Medical History at Screening-ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Medical History | Start date | Stop Date | Ongoing | Is the subject on Medications |
|---|---|---|---|---|---|---|
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX | Yes/No |
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX | Yes/No |
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX | Yes/No |
| … | … | … | … | … | … | … |

**Listing 16.2.4.3 Listing of Breast Cancer Disease Therapy at Screening-ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Date of initial histological or cytological diagnosis | Breast cancer diagnosed | BC stage at initial Diagnosis | Location of Primary Tumor | Was the primary tumor | Primary tumor size | Breast cancer subtype | Histological grade | Nuclear grade | Estrogen receptor status | Progesterone receptor status | Breast cancer type |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NN/XXX | NN/XXX | DDMMMYYYY | XXX | NN | XXX | XXX | NN.N | XXX | XXX | XXX | XXX | XXX | XXX |
| NN/XXX | NN/XXX | DDMMMYYYY | XXX | NN | XXX | XXX | NN.N | XXX | XXX | XXX | XXX | XXX | XXX |
| NN/XXX | NN/XXX | DDMMMYYYY | XXX | NN | XXX | XXX | NN.N | XXX | XXX | XXX | XXX | XXX | XXX |
| … | … | … | … | … | … | … | … | … | … | … | … | … | … |

| Date of Primary surgery | Date of pathological Assessment | Breast tumor remnants | | | | Histological grade | Breast cancer subtype | DCIS present | Date of Diagnosis of Metastatic or Locally Recurrent Disease | Diagnosis of metastatic or Locally recurrent BC | Date of Last Recurrence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Microscopic assessment | | Macroscopic assessment | | | | | | | |
| | | Type of Tumor | Diameter of Tumor | Gross tumor size | Pathological staging of BC | | | | | | |
| DDMMMYYYY | DDMMMYYYY | XXX | NN.N | NN.N | NN | XXX | XXX | Yes/No | DDMMMYYYY | XXX | DDMMMYYYY |
| DDMMMYYYY | DDMMMYYYY | XXX | NN.N | NN.N | NN | XXX | XXX | Yes/No | DDMMMYYYY | XXX | DDMMMYYYY |
| DDMMMYYYY | DDMMMYYYY | XXX | NN.N | NN.N | NN | XXX | XXX | Yes/No | DDMMMYYYY | XXX | DDMMMYYYY |
| … | … | … | … | … | … | … | … | … | … | … | … |

| Date of HER2 Confirmation If Metastatic | Method | IHC Score | ISH Negative/Positive | Progesterone Receptor Score if Metastatic | Estrogen Receptor Score if Metastatic | Any previous therapy for BC prior to Study |
|---|---|---|---|---|---|---|
| DDMMMYYYY | **IHC/ISH** | NN | XXX | XXX | XXX | Yes/No |
| DDMMMYYYY | **IHC/ISH** | NN | XXX | XXX | XXX | Yes/No |
| DDMMMYYYY | **IHC/ISH** | NN | XXX | XXX | XXX | Yes/No |
| … | … | … | … | … | … | … |

**Listing 16.2.4.4 Listing of Previous Hormone Therapy for Breast Cancer at Screening –ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Has the patient received any hormone therapy | Name of Treatment | Total Dose Per Cycle | Unit | Route | Start date | End date | Ongoing at Screening |
|---|---|---|---|---|---|---|---|---|---|
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.4.5 Listing of Previous Immunotherapy for Breast Cancer at Screening –ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Has the patient received any Immunotherapy | Name of Treatment | Total Dose Per Cycle | Unit | Route | Start date | End date | Ongoing at Screening |
|---|---|---|---|---|---|---|---|---|---|
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.4.6 Listing of Previous Biologic Therapy for Breast Cancer at Screening –ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Has the patient received any Biologic Therapy | Name of Treatment | Total Dose Per Cycle | Unit | Route | Start date | End date | Ongoing at Screening |
|---|---|---|---|---|---|---|---|---|---|
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.4.7 Listing of Previous Radiotherapy for Breast Cancer at Screening –ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Has the patient received any Radiotherapy | Location | Specify location if other | Total Dose | Unit | Reason for administration | Start date | End date | Ongoing at Screening |
|---|---|---|---|---|---|---|---|---|---|---|
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| … | … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.4.8 Listing of Previous Chemotherapy for Breast Cancer at Screening –ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Has the patient received any Radiotherapy | Name of Drug Treatment | If Anthracycline | Number Cycle | Unit | Method | Start date | End date | Ongoing at Screening |
|---|---|---|---|---|---|---|---|---|---|---|
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | **Yes/No** | XXX | XXX | XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| … | … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.4.9 Listing of Previous Concomitant Therapy Log for Breast Cancer at Screening –ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Generic Name | Indication | Start date | End date | Ongoing at Screening |
|---|---|---|---|---|---|---|
| NN/XXX | NN/XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | XXX | XXX | DDMMMYYYY | DDMMMYYYY | XXX |
| … | … | … | … | … | … | … |

## 16.2.6 Listing for Efficacy

### Listing 16.2.6.1 Listing of Tumor/Disease Assessment (Target Lessions) –ITT Population (N=XXX)

| Site ID/ Subject No. | Age/Sex | Visit | Date of assessment | Are there any target lesions | Was lesion measurable | Reason | Code of Organ site | Location of lesion | How assessed | Status of Lesion | Size (mm) | Sum of longest diameters | Inflammatory Breast Cancer | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | Erythema | Edema |
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX | XXX | XXX | XXX | NN | NN | NN/XXX | NN/XXX |
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX | XXX | XXX | XXX | NN | NN | NN/XXX | NN/XXX |
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX | XXX | XXX | XXX | NN | NN | NN/XXX | NN/XXX |
| … | … | … | … | … | … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.6.2 Listing of Tumor/Disease Assessment (Non-Target Lesions) -ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Visit | Date of assessment | Are there any non-target lesions | Method of Assessment | Status of Lesion | Code of Organ site | If other organ site | Number Of Non-Target Lesions Within The Organ | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Single Lesion | Multiple Lesions |
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX | XXX | NN | NN |
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX | XXX | NN | NN |
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX | XXX | NN | NN |
| … | … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.6.3 Listing of Tumor/Disease Assessment (New Lesions –Target Lesions and Non-target Lesions) –ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Visit | Date of assessment | Are there any new lesions | Evaluation (Response) of Target Lesions | Evaluation (Response) of Non-Target Lesions | Overall Response |
|---|---|---|---|---|---|---|---|
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX |
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX |
| NN/XXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX |
| … | … | … | … | … | … | … | … |

**Listing 16.2.6.4 Listing of Survival Status-ITT Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Visit | Survival Status | | Did patient's disease progress since the last evaluation | If Yes | | If No | If Not known |
|---|---|---|---|---|---|---|---|---|---|
| | | | Status (Alive/Dead/ Withdrew consent) | Date of the status | | Date of Progressive disease | How disease progression Was assessed | Date of most recent tumor assessment | Specify |
| NN/XXX | NN/XXX | XXX | XXX | DDMMMYYYY | **Yes/No/Not Known** | DDMMMYYYY | XXX | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | XXX | XXX | DDMMMYYYY | **Yes/No/Not Known** | DDMMMYYYY | XXX | DDMMMYYYY | XXX |
| NN/XXX | NN/XXX | XXX | XXX | DDMMMYYYY | **Yes/No/Not Known** | DDMMMYYYY | XXX | DDMMMYYYY | XXX |
| … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.7 Listing of Adverse Event –Safety Population (N=XXX)**

| Site No./ Subject No. | Age/ Gender | Visit | AE Reported | SOC | Preferred Term | Event | Onset Date | Is this event considered as a related to Pertuzumab | Is this event considered as a related to Trastuzumab | Is this event related to Docetaxel | Serious AE | Is this an Adverse Event of Special Interest (AESI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XXX/NNN | NN/XXX | XXX | Yes/No | XXX | XXX | XXX | DDMMYYYY | Yes/No | Yes/No | Yes/No | Yes/No | Yes/No |
| XXX/NNN | NN/XXX | XXX | Yes/No | XXX | XXX | XXX | DDMMYYYY | Yes/No | Yes/No | Yes/No | Yes/No | Yes/No |
| XXX/NNN | NN/XXX | XXX | Yes/No | XXX | XXX | XXX | DDMMYYYY | Yes/No | Yes/No | Yes/No | Yes/No | Yes/No |
| … | … | … | … | … | … | … | … | … | | … | … | … |

| Action Taken | Intensity (NCI – CTCAE v4.0) | Chemotherapy adjustment | Treatment given for this event | Adverse events of suspected cardiac origin | Is this event symptomatic of left ventricular systolic dysfunction | If Yes, NYHA Class | LVEF decrease | If not adverse event of suspected cardiac origin, specify other cause | Is there a reasonable suspected causal relationship to study medication | If Yes, mention study medication | Outcome | Date Event Resolved | Comments on AE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XXX | XXX | XXX | Yes/No | Yes/No | Yes/No | XXX | Yes/No | XXX | Yes/No | XXX | XXX | DDMMYYYY | XXX |
| XXX | XXX | XXX | Yes/No | Yes/No | Yes/No | XXX | Yes/No | XXX | Yes/No | XXX | XXX | DDMMYYYY | XXX |
| XXX | XXX | XXX | Yes/No | Yes/No | Yes/No | XXX | Yes/No | XXX | Yes/No | XXX | XXX | DDMMYYYY | XXX |
| … | … | … | … | … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.7.1 Listing of Serious Adverse Event –Safety Population (N=XXX)**

| Site No./ Subject No. | Age/ Gender | Visit | AE Reported | SOC | Preferred Term | Event | Onset Date | Date event became serious | Study Drug Causality | Study Drug | Other Suspect Causes | Cause of Seriousness of event |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XXX/NNN | NN/XXX | XXX | Yes/No | XXX | XXX | XXX | DDMMYYYY | DDMMYYYY | Yes/No | XXX | XXX | XXX |
| XXX/NNN | NN/XXX | XXX | Yes/No | XXX | XXX | XXX | DDMMYYYY | DDMMYYYY | Yes/No | XXX | XXX | XXX |
| XXX/NNN | NN/XXX | XXX | Yes/No | XXX | XXX | XXX | DDMMYYYY | DDMMYYYY | Yes/No | XXX | XXX | XXX |
| … | … | … | … | … | … | … | … | … | | … | … | … |

| SAE/AE SI outcome | Date | AE Initial Intensity | AE most extreme intensity | AE initial NCI-CTCAE grade | AE most extreme NCI-CTCAE grade | Action taken with Pertuzumab | Date of Action taken with Pertuzumab | Action taken with Trastuzumab | Date of Action taken with Trastuzumab | Action taken with Docetaxel | Date of Action taken with Docetaxel |
|---|---|---|---|---|---|---|---|---|---|---|---|
| XXX | DDMMYYYY | XXX | XXX | XXX | XXX | XXX | DDMMYYYY | XXX | DDMMYYYY | XXX | DDMMYYYY |
| XXX | DDMMYYYY | XXX | XXX | XXX | XXX | XXX | DDMMYYYY | XXX | DDMMYYYY | XXX | DDMMYYYY |
| XXX | DDMMYYYY | XXX | XXX | XXX | XXX | XXX | DDMMYYYY | XXX | DDMMYYYY | XXX | DDMMYYYY |
| … | … | … | … | … | … | … | … | … | … | … | … |

## 16.2.8 Lab Test Evaluations

### Listing 16.2.8.1 Listing of Hematology –Safety Population (N=XXX)

| Site ID/ Subject No. | Age/Sex | Visit | Date of Collection | Test | Results | Out of Range | Units | Clinically Significant |
|---|---|---|---|---|---|---|---|---|
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | Yes/No | XXX | Yes/No |
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | Yes/No | XXX | Yes/No |
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | Yes/No | XXX | Yes/No |
| … | … | … | … | … | … | … | … | … |

**Listing 16.2.8.2 Listing of Coagulation Test –Safety Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Visit | Date of Collection | Test | NA | Results | Units | Out of Range | Clinically Significant |
|---|---|---|---|---|---|---|---|---|---|
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | Yes/No | XXX | XXX | Yes/No | Yes/No |
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | Yes/No | XXX | XXX | Yes/No | Yes/No |
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | Yes/No | XXX | XXX | Yes/No | Yes/No |
| … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.8.3 Listing of Serum Chemistry –Safety Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Visit | Date of Collection | Test | Results | Out of Range | Units | Clinically Significant |
|---|---|---|---|---|---|---|---|---|
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | Yes/No | XXX | Yes/No |
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | Yes/No | XXX | Yes/No |
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | Yes/No | XXX | Yes/No |
| … | … | … | … | … | … | … | … | … |

**Listing 16.2.8.4 Listing of Viral Serology –Safety Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Visit | Date of Collection | Test | Results |
|---|---|---|---|---|---|
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX |
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX |
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX |
| … | … | … | … | … | … |

**Listing 16.2.8.5 Listing of Pregnancy Test –Safety Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Visit | Reproductive Status | Pregnancy Test Done | If Done | | | If Urinary positive | | If Pregnancy test Not done, specify reason |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Date of pregnancy test | Method (Serum/Urine) | Results | Date of serum pregnancy test | Results | |
| NN/XXXX | NN/XXX | XXX | XXX | XXX | DDMMMYYYY | XXX | XXX | DDMMMYYYY | XXX | XXX |
| NN/XXXX | NN/XXX | XXX | XXX | XXX | DDMMMYYYY | XXX | XXX | DDMMMYYYY | XXX | XXX |
| NN/XXXX | NN/XXX | XXX | XXX | XXX | DDMMMYYYY | XXX | XXX | DDMMMYYYY | XXX | XXX |
| … | … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.8.6 Listing of ECOG Performance Status –Safety Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Visit | Response | Grade | ECOG |
|---|---|---|---|---|---|
| NN/XXXX | NN/XXX | XXX | XXX | NN | XXX |
| NN/XXXX | NN/XXX | XXX | XXX | NN | XXX |
| NN/XXXX | NN/XXX | XXX | XXX | NN | XXX |
| … | … | … | … | … | … |

**Listing 16.2.8.7 Listing of LVEF (Left ventricular ejection fraction) –Safety Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Visit | Date of Assessment | Result | By | If Echocardiography, specify calculation method | LVEF finding | Any new cardiac signs and symptoms | Any worsening cardiac signs and symptoms (since screening) | Any signs or symptoms of CHF |
|---|---|---|---|---|---|---|---|---|---|---|
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX | Yes/No | Yes/No | Yes/No |
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX | Yes/No | Yes/No | Yes/No |
| NN/XXXX | NN/XXX | XXX | DDMMMYYYY | XXX | XXX | XXX | XXX | Yes/No | Yes/No | Yes/No |
| … | … | … | … | … | … | … | … | … | … | … |

## 16.4 Individual subject data listings

### Listing 16.4.1 Listing of Vital Signs (All Enrolled Subjects)

### Listing 16.4.1.1 Listing of Vital Signs -Safety Population (N=XXX)

| Site ID/ Subject No. | Age/Sex | Visit | Weight | Pulse Rate | Respiratory Rate | Blood Pressure | | Temperature |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Systolic | Diastolic | |
| NN/XXXX | NN/XXX | XXX | NN | NN | NN | NN | NN | NN |
| NN/XXXX | NN/XXX | XXX | NN | NN | NN | NN | NN | NN |
| NN/XXXX | NN/XXX | XXX | NN | NN | NN | NN | NN | NN |
| … | … | … | … | … | … | … | … | … |

**Listing 16.4.1.2 Listing of Vital Signs during infusion of Pertuzumab, Trastuzumab and Docetaxel –Safety Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Visit | Time of capturing Vital Signs | Weight | Pulse Rate | Respiratory Rate | Blood Pressure | | Temperature |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Systolic | Diastolic | |
| NN/XXXX | NN/XXX | XXX | XXX | NN | NN | NN | NN | NN | NN |
| NN/XXXX | NN/XXX | XXX | XXX | NN | NN | NN | NN | NN | NN |
| NN/XXXX | NN/XXX | XXX | XXX | NN | NN | NN | NN | NN | NN |
| … | … | … | … | … | … | … | … | … | … |

**Programming Note:**

- Time of capturing Vital Signs will be Before and After the infusion of Pertuzumab, Trastuzumab and Docetaxel

**Listing 16.4.2 Listing of Physical Examination –Safety Population (N=XXX)**

| Site No./ Subject No. | Age/ Gender | Visit | Physical Examination Performed | Date of Physical Examination | If No, Reason | Body System /Site | Results | If abnormal ,specify | Clinical Significance |
|---|---|---|---|---|---|---|---|---|---|
| XXX/NNN | NN/XXX | XXX | Yes/No | DDMMYYYY | XXXX | XXXX | Normal/Abnormal/Not Done | XXX | Yes/No |
| XXX/NNN | NN/XXX | XXX | Yes/No | DDMMYYYY | XXXX | XXXX | Normal/Abnormal/Not Done | XXX | Yes/No |
| XXX/NNN | NN/XXX | XXX | Yes/No | DDMMYYYY | XXXX | XXXX | Normal/Abnormal/Not Done | XXX | Yes/No |
| … | … | … | … | … | … | … | … | … | … |

**Listing 16.4.3 Listing of Her-2 Determination, CT/MRI and Isotope Bone Scan -Safety Population (N=XXX)**

| Site No./ Subject No. | Age/ Gender | Visit | Her-2 Determination | | | | CT/MRI | | | Isotope Bone Scan | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Assessment performed | Sample collection date | Immunohistochemistry (IHC) Result | In situ hybridization (ISH) Result | Date CT/MRI performed | clinically significant | If Yes, specify | Date isotope bone scan performed | Result (Normal/Abnormal) | If Yes abnormal, specify |
| XXX/NNN | NN/XX | XXX | Yes/No | DDMMYYYY | XXXX | XXXX | DDMMYYYY | Yes/No | XXXX | DDMMYYYY | XXXX | XXXX |
| XXX/NNN | NN/XX | XXX | Yes/No | DDMMYYYY | XXXX | XXXX | DDMMYYYY | Yes/No | XXXX | DDMMYYYY | XXXX | XXXX |
| XXX/NNN | NN/XX | XXX | Yes/No | DDMMYYYY | XXXX | XXXX | DDMMYYYY | Yes/No | XXXX | DDMMYYYY | XXXX | XXXX |
| … | … | … | … | … | … | … | … | … | … | … | … | … |

**Listing 16.4.4 Listing of Study Drug Administration**

**Listing 16.4.4.1 Listing of Administration of Pertuzumab –Safety Population (N=XXX)**

| Site No./Subject No. | Age/Gender | Cycle No. | Date of Dose | Batch No. | Start Time | Final Stop Time | Planned Dose | Total Dose Received | Total Volume Received | Reasons, if scheduled infusion was delayed, interrupted or the dose modified | If other reason, specify | Batches used for this administration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XXX/NNN | NN/XXX | XXX | DDMMYYYY | NNN | NN:NN | NN:NN | NNN | NNN | NNN | XXX | XXX | XXX |
| XXX/NNN | NN/XXX | XXX | DDMMYYYY | NNN | NN:NN | NN:NN | NNN | NNN | NNN | XXX | XXX | XXX |
| XXX/NNN | NN/XXX | XXX | DDMMYYYY | NNN | NN:NN | NN:NN | NNN | NNN | NNN | XXX | XXX | XXX |
| … | … | … | … | … | … | … | … | … | … | … | … | … |

**Listing 16.4.4.2 Listing of Administration of Trastuzumab –Safety Population (N=XXX)**

| Site No./Subject No. | Age/Gender | Cycle No. | Date of Dose | Time of Dose | Total Dose Received | Route | Reasons, if scheduled infusion was delayed, interrupted or the dose modified | | If other reason, specify |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Adverse Event | Other | |
| XXX/NNN | NN/XXX | XXX | DDMMYYYY | NN:NN | NNN | XXX | Yes/No | Yes/No | XXX |
| XXX/NNN | NN/XXX | XXX | DDMMYYYY | NN:NN | NNN | XXX | Yes/No | Yes/No | XXX |
| XXX/NNN | NN/XXX | XXX | DDMMYYYY | NN:NN | NNN | XXX | Yes/No | Yes/No | XXX |
| … | … | … | … | … | … | … | … | … | … |

**Listing 16.4.4.3 Listing of Administration of Docetaxel –Safety Population (N=XXX)**

| Site No./Subject No. | Age/Gender | Cycle No. | Date of Dose | Time of Dose | Total Dose Received | Route | Reasons, if scheduled infusion was delayed, interrupted or the dose modified | | If other reason, specify |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Adverse Event | Other | |
| XXX/NNN | NN/XXX | XXX | DDMMYYYY | NN:NN | NNN | XXX | Yes/No | Yes/No | XXX |
| XXX/NNN | NN/XXX | XXX | DDMMYYYY | NN:NN | NNN | XXX | Yes/No | Yes/No | XXX |
| XXX/NNN | NN/XXX | XXX | DDMMYYYY | NN:NN | NNN | XXX | Yes/No | Yes/No | XXX |
| … | … | … | … | … | … | … | … | … | … |

**Listing 16.2.4.4 Listing of Concomitant Medications –Safety Population (N=XXX)**

| Site ID/ Subject No. | Age/Sex | Medication (Generic Name) | Class of Medication[1] | Indication | Regimen | Dose(per day) |
|---|---|---|---|---|---|---|
| NN/XXXX | NN/XXX | XXXX | XXXX | XXXX | XXX | NN |
| NN/XXXX | NN/XXX | XXXX | XXXX | XXXX | XXX | NN |
| NN/XXXX | NN/XXX | XXXX | XXXX | XXXX | XXX | NN |
| … | … | … | … | … | … | … |

| Unit | Frequency | Route[2] | Date started | Date stopped | Ongoing |
|---|---|---|---|---|---|
| XXX | XXX | XXXXX | DDMMMYYYY | DDMMMYYYY | Yes/No |
| XXX | XXX | XXXXX | DDMMMYYYY | DDMMMYYYY | Yes/No |
| XXX | XXX | XXXXX | DDMMMYYYY | DDMMMYYYY | Yes/No |
| … | … | … | … | … | … |